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Total Synthesis of Virgatolide B

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

Doctor of Philosophy

By

Paul Alexander Hume

School of Chemical Sciences
University of Auckland
July 2014
Preface

All of the work described was carried out by the author of this thesis, except for the work of others in which case due reference has been made to this in the text.

Parts of this thesis have been published:


“Why, what’s going to happen on Thursday?” asked Rabbit, and when Pooh had explained, and Rabbit, whose life was made up of Important Things, said, “Oh, I thought you’d really come by about something,” they sat down for a little… and by-and-by Pooh and Piglet went on again.

The wind was behind them now, so they didn’t have to shout.

“Rabbit’s clever,” said Pooh thoughtfully.
“Yes,” said Piglet, “Rabbit’s clever.”
“And he has Brain.”
“Yes,” said Piglet, “Rabbit has Brain.”
There was a long silence.
“I suppose,” said Pooh, “that that’s why he never understands anything.”

~A. A Milne, *The House at Pooh Corner*

To my family, I love you all so much.
Abstract

This thesis describes the first, enantioselective synthesis of the natural product virgatolide B (2). Virgatolides A-C (1-3) are a family of polyketide metabolites isolated from the endophytic fungus Pestalotiopsis virgatula, cultured from the leaves of Dracontomelon duperreanum. The compounds were discovered during a biological screening programme aimed at identifying fungal metabolites with cytotoxicity against HeLa (cervical epithelium) cells. Isolation of compounds 1-3 (IC$_{50}$ 19.0, 22.5, and 20.6 μM respectively) from an active extract enabled structural elucidation, revealing that the compounds share a common tetracyclic core, differing from one another only at C-4 and C-13.

A convergent and flexible strategy was developed to provide access to the 6,6-benzannulated spirotetal in an efficient manner. Three key fragments: trifluoroboratoamide 158, bromide 261 and aldehyde 245, were synthesised using readily available starting materials. In particular, trifluoroboratoamide 158 was obtained from the chiral pool reagent (R,R)-pseudoephedrine, thus enabling the synthesis to be conducted in an enantioselective manner. Trifluoroboratoamide 158 and bromide 261 were successfully united using an sp$^3$-sp$^2$ Suzuki cross-coupling reaction, providing the challenging α-chiral β-arylated carbonyl motif. A 1,3-anti selective Mukaiyama aldol reaction between methyl ketone 300 and aldehyde 245 afforded spiroketalisation precursor 299.
Initial attempts to construct the spiroketal core employed an EOM-protected cyclisation precursor. However, the acidic conditions required for deprotection resulted in elimination of the β-hydroxyl group. A revised protecting group strategy was therefore devised in order to employ pH-neutral deprotection conditions.

Exchange of the EOM protecting groups for BOM and incorporation of the alkene side chain prior to the Suzuki coupling increased the convergence of the synthesis, enabling the synthesis of spiroketal precursor 299. Global deprotection under hydrogenolysis, concomitant spiroketalisation and a mild equilibration procedure furnished virgatolide B (2). The regioselectivity of the spirocyclisation was governed by intramolecular hydrogen-bonding.

In addition to the total synthesis of virgatolide B (2) this thesis also describes investigations towards the synthesis of virgatolide A (1). Four synthetic strategies for the synthesis of virgatolide A (1) via intermediates readily accessible from the synthesis of virgatolide B (2) were evaluated on model systems: carbene insertion, cross-metathesis, hydroalkoxylation and a ketone-ketone aldol reaction. Although unsuccessful, these investigations provide important synthetic insights relevant to future attempts towards virgatolide A (1).
Acknowledgements

First, I would like to thank my supervisor Prof. Margaret Brimble for the opportunity to work on this project and for all her help over these past years. You have supported me the entire time, even when I am certain that it would have been easier not to. I truly appreciate it Margaret. Dr Dan Furkert, thank you so much for always being so generous with your time and for all the help you have given me. Thank you for being such a great friend as well as a mentor.

A big thank you everyone who helped me with proofreading or even just suggestions for my thesis: Margaret, Dan, Jono, Briar, Rachelle, Freda, Sarah and Harry. I would also like to thank all the technical staff for their tireless help. Janice and Tim for the millions of things you do to ensure that our group doesn’t grind to a halt. Michael, Raissa, and Nick for your support with NMR and mass spectrometry.

For want of space I would like to thank the Brimble group as a whole, you guys are awesome! Jono, it has been a privilege to work alongside you. You are a true friend and I can’t wait to see what the future holds for you, I hold you in very high esteem. Briar, thanks for your down-to-earth attitude and for helping me to keep things in perspective when I started frequenting crazytown. Tsz, I know you will probably never read this, but thank you so much for your patience and for all that you taught me. Andrew, thanks for being a great lab bro and for hilarious fumehood conversations. Rachelle, thanks for scouring my experimental for mistakes and for putting up with my endless teasing. “You doin’ alright ‘arry?” I hope so because I have really enjoyed our important discussions from “OBC!” to “Oh ja!” I’m going to miss seeing you every day (you know what I mean). James, it has been awesome getting to know you and having someone to talk to about how great Wilco are. Wilco is an essential part of life. Thanks for all the laughs, now that I have the facebook we can all keep in touch!

Now, my wonderful family. Thank you so much for loving me unconditionally and for your support over this time, I love you all. Dad, I can’t say what it means to still have you to call for help when I need it. Mum, you continually remind me of what is important in life. Sam and Emma, for teaching me the importance of looking for beauty in life. Carl and Fleur, for the encouragement you give me and for settling the island nation of Catan. Celeste, thank you for always being so happy to see me, I love being your brother.
To Celia, thank you so much for marrying me. It is the best thing that has ever happened to me. I can’t believe that I get to live my life with you. I love you with all my heart.

Finally, my Lord God. Thank you for helping me achieve this and for all the wonderful people you have put in my life. I know I don’t understand the extent of your love very well, but thank you. Though it pales in comparison, I love you.

Paul Alexander Hume

June 2014
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<tr>
<td>δ</td>
<td>chemical shift</td>
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<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>*</td>
<td>chiral centre</td>
</tr>
<tr>
<td>Å</td>
<td>Ångström</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
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<tr>
<td>2D</td>
<td>two-dimensional</td>
</tr>
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<tr>
<td>a.u.</td>
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<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
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<tr>
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<td>ddd</td>
<td>doublet of doublet of doublets</td>
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<td>ED₅₀</td>
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<td>e.e.</td>
<td>enantiomeric excess</td>
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<td>electron impact</td>
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<td>ESI</td>
<td>electrospray ionisation</td>
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<tr>
<td>et al.</td>
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<td>fMLP</td>
<td>formyl-methionyl-leucyl-phenylalanine</td>
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<td>heat shock protein 90</td>
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<td>HSQC</td>
<td>heteronuclear single quantum correlation</td>
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<td>IBX</td>
<td>2-iodobenzoic acid</td>
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<tr>
<td>IC₅₀</td>
<td>half maximal inhibitory concentration</td>
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<td>isopinocampheyl</td>
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<tr>
<td>i-Pr</td>
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<td>Abbreviation</td>
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<td>-----------</td>
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<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
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<td>rate constant</td>
</tr>
<tr>
<td>L</td>
<td>litre, large or unspecified ligand</td>
</tr>
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<td>Lewis acid</td>
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<td>LDA</td>
<td>lithium diisopropylamide</td>
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<td>lit.</td>
<td>literature</td>
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<td>M</td>
<td>molar, medium or unspecified metal</td>
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<td>multiplet or milli</td>
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<td>meta</td>
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<tr>
<td>MAP</td>
<td>mitogen-activated protein</td>
</tr>
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<td>mCPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
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<td>m.p.</td>
<td>melting point</td>
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<td>m/\text{z}</td>
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<td>nOe</td>
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<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
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<td>pH</td>
<td>power of hydrogen</td>
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<td>pin</td>
<td>pinacolato</td>
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<tr>
<td>PMB</td>
<td>\textit{para}-methoxybenzyl</td>
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<tr>
<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>PPTS</td>
<td>pyridinium \textit{para}-toluenesulfonate</td>
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<tr>
<td>PTSA</td>
<td>\textit{para}-toluenesulfonic acid</td>
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<td>quartet</td>
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<tr>
<td>R</td>
<td>unspecified alkyl group</td>
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<tr>
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<tr>
<td>T</td>
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<tr>
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</tr>
<tr>
<td>(t)</td>
<td>\textit{tert} (tertiary)</td>
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<tr>
<td>TAK-1</td>
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<td>TMEDA</td>
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<td>TPAP</td>
<td>\textit{tetra}-\textit{n}-propylammonium perruthenate</td>
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<td>(\nu)</td>
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<td>X</td>
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Chapter One

Introduction
1.1 The Virgatolides – Isolation, Structure and Biosynthesis

Virgatolides A-C (1-3, Figure 1.1) are a family of three 6,6-benzannulated spiroketals, isolated and characterised in 2011 by Che et al.1 The compounds were discovered during an investigation into fungal metabolites produced by the genus Pestalotiopsis, conducted in Beijing. An ethyl acetate extract of a fermentation culture of the endophytic fungus Pestalotiopsis virgatula (L147), isolated from the leaves of Dracontomelon duperreanum, exhibited cytotoxicity towards HeLa (cervical epithelium) cells during preliminary biological screening. Separation of the constituents furnished virgatolides A-C (1-3, IC\textsubscript{50} 19.0, 22.5, and 20.6 μM respectively) together with previously described pestaphthalides A and B (4 and 5): natural products that share common hypothetical biosynthetic precursors with the virgatolides.1-2

![Figure 1.1. Structures of virgatolides A-C (1-3) and pestaphthalides A (4) and B (5).](image)

Virgatolides A-C (1-3) contain two key structural motifs: a 6,6-benzannulated spiroketal and a chiral phthalide ring system. Benzannulated spiroketals\textsuperscript{3} and phthalides\textsuperscript{4,5} are both moieties found in large numbers of natural products, displaying broad and potent biological activities. Compounds 1-3 share a common tetracyclic core and differ from one another only in their stereochemistry and substitution at C-4 and C-13. Significantly, virgatolide A (1) contains an additional spiro γ-lactone centred on C-13, which is not present in the remaining members; virgatolides B (2) and C (3) display hydroxyl groups at this position. The structure and relative stereochemistry of virgatolide A (1) was unambiguously secured by X-ray crystallography and the absolute stereochemistry then
determined by comparison of the CD-spectrum to those of pestaphthalides A (4) and B (5) (Figure 1.2). The structures of virgatolides B (2) and C (3), including their relative and absolute stereochemistry, were established by NMR and HRMS analysis and by comparison of their CD-spectra with compounds 1, 4 and 5. Importantly, the stereochemical information at C-4 and C-5 in compounds 2 and 3 could not be directly correlated with that of the spiroketal moiety. The absolute configuration of the stereocentres within the spiroketal ring system in virgatolides B (2) and C (3) was therefore assumed to be analogous to that of virgatolide A (1) in view of the likely biosynthetic connection between compounds 1-3.

The X-ray crystal structure of virgatolide A (1) provides valuable information concerning both the configuration and conformation of the spiroketal ring system. In particular, the spiroketal adopts an anomerically-stabilised conformation, placing the phenolic oxygen atom axial relative to the chair conformation of the non-fused ring of the spiroketal. It should also be noted that the oxygen atom contained within the spiro-γ-lactone resides in the equatorial position, placing the methylene unit of the γ-lactone in the axial position.

**Figure 1.2.** X-ray crystal structure of virgatolide A (1) and CD-spectra of 1-3.¹
The proposed biosynthesis of the virgatolides occurs *via* a polyketide pathway and involves 3,6-dimethyl-4-hydroxy-2-pyrone (8) as a common intermediate (Scheme 1.1). Pyrone 8 is formed by the condensation of acetyl-CoA (6) with two molecules of malonyl-CoA (7). Further reaction of pyrone 8 with malonyl-CoA (7) to form compound 9, followed by coupling with phthalide 10 and subsequent intramolecular cyclisation generates the tetracyclic framework. Further enzymatic modifications produce virgatolide B (2). Virgatolide A (1) is thought to be derived *via* elaboration of virgatolide B (2). Virgatolide C (3) is produced in an analogous manner to virgatolide B (2) by reaction of compound 9 with a phthalide containing the required stereochemistry.

![Scheme 1.1](image-url)
1.2 Benzannulated 6,6-Spiroketals in Nature

The virgatolides (1-3) each contain a 6,6-benzannulated spiroketal core, a structural motif uncommon among natural products. The only other known examples are chaetoquadrins A-C (13-15), citreoviranol (16), demethylcitreoviranol (17), the dimeric cyandiones, dehydrocollatolic acid (18), citreoviranol (16), demethylcitreoviranol (17), the dimeric cyandiones, dehydrocollatolic acid (18), peniphenone A (19) and the peniciketals (20-22).

1.2.1 The Chaetoquadrins

Isolation of the chaetoquadrins (13-15) from a strain of the ascomycete Chaetomium quadrangulatum was reported in 2002 and the compounds have also subsequently been isolated from Chaetomium aureus (Figure 1.3). It should be noted that the substitution pattern of the spiroketal core of the chaetoquadrins (13-15) is analogous to that of the virgatolides (1-3), although different in relative configuration. The chaetoquadrins exhibit mouse liver monoamine oxidase inhibitory activity.

![Figure 1.3. Structures of chaetoquadrins A-C (13-15).](image)

1.2.2 Citreoviranol

Citreoviranol (16) and demethylcitreoviranol (17) were isolated in 1988 from the mycelium of Penicillium citreoviride B (IFO 4692) after incubation on polished rice. Compounds 16 and 17 contain a spiroketal ring system in which the benzannulated ring is a δ-lactone (Figure 1.4). In addition to the spiroketal core, compounds 16 and 17 contain the characteristic resorcylic lactone moiety present in the resorcylic acid family of natural products, which are known to exhibit potent bioactivity against several medically relevant enzyme targets, including HSP90, MAP kinase and TAK-1.
Introduction

Figure 1.4. Structures of citreoviranol (16) and demethylcitreoviranol (17).³

1.2.3 The Cynandiones

Cynandione B (24) is a member of a family of four dimeric 6,6-bisbenzannulated spiroketsls formed via self-condensation of cynandione A (23) (Figure 1.5).³ Additionally, cynantetrone (25), a tetrameric adduct of cynandione A has also been isolated.⁵ Cynandione B (24) exhibits dose-dependent inhibition of β-glucoronidase and lysozyme release in rat neutrophils stimulated by formyl-methionyl-leucyl-phenylalanine (fMLP, IC₅₀ 1.5 ± 0.2 and 1.6 ± 0.2 μM respectively).³,⁴ Cynandione B (24) also inhibits the formation of superoxide anion in rat neutrophils that have been stimulated with 3 nM phorbol 12-myristate 13-acetate (PMA, IC₅₀ 78.0 ± 8.1 μM).³,⁴ These effects indicate that 24 may exhibit anti-inflammatory activity via inhibition of neutrophil activation.³,⁴ The cynandiones also exhibit anti-tumour activity: cynandione B (24) is active against human hepatoma PLC/PRF/5 cell lines (ED₅₀ 2.7 μg/mL) and both cynandione B (24) and cynantetrone (25) exhibit in vitro cytotoxicity against human bladder carcinoma T-24 cell lines (ED₅₀ 3.5 and 2.5 μg/mL respectively).³,⁵

Figure 1.5. Representative structures of the cynandiones.³
1.2.4 Dehydrocollatolic Acid

Dehydrocollatolic acid (18) was isolated as a minor constituent from the lichen *Parmotrema nilgherrense* (Figure 1.6). Compound 18 was isolated together with major quantities of the related natural products alectoronic acid (26) and α-collatolic acid (27). Compounds 18, 26 and 27 share a common carbon skeleton, but only dehydrocollatolic acid (18) contains the 6,6-spiroketal moiety. The structure of dehydrocollatolic acid (18) was determined by a combination of NMR and HRMS analysis. However, the configuration of the two chiral centres was not determined.

![dehydrocollatolic acid (18)](image)

![R=H, alectoronic acid (26)](image)

![R=Me, α-collatolic acid (27)](image)

**Figure 1.6.** Dehydrocollatolic acid (18) and related natural products 26 and 27.

1.2.5 Peniphenone A

Peniphenones A-D (19, 28-30) were isolated from a strain of the filamentous fungi *Penicillium dipodomyicola*, from the mangrove plant *Acanthus ilicifolius* (Figure 1.7). Interestingly, although compounds 19, 28-30 are thought to share a common biosynthetic precursor, only (±)-peniphenone A (19) contains the 6,6-benzannulated spiroketal ring system. Furthermore, (±)-peniphenone A (19) was not isolated as a single enantiomer and was instead obtained as a racemic mixture. The biological activity of (±)-19 was not tested, due to limitations in the quantities that could be obtained from the natural source. However, peniphenones B (28) and C (29) displayed strong inhibitory activity against *Mycobacterium tuberculosis* protein tyrosine...
phosphatase B (IC\textsubscript{50} 0.16 ± 0.02 and 1.37 ± 0.05 μM respectively) indicating the potential of these natural products as lead compounds for the development of new anti-tuberculosis therapeutics.\textsuperscript{10}

**Figure 1.7. Peniphenones A-D (19, 29-30).\textsuperscript{10}**

### 1.2.6 Peniciketals A-C

Peniciketals A-C (20-22) were isolated from the saline soil derived fungi *Penicillium raistrickii* (Figure 1.8).\textsuperscript{11} Sharing a common framework, the compounds contain both a benzannulated 6,6-spiroketal ring system and a 2,8-dioxabicyclo[3.3.1]nonane moiety. Peniciketals A-C (20-22) exhibit potent cytotoxicity against A549, HL-60 and K562 cancer cell lines (IC\textsubscript{50} 0.31, 0.085 and 0.23 μM respectively).\textsuperscript{11} In addition to their impressive cytotoxicity, compounds 20-22 display considerable selectivity towards HL-60 cells compared to control cells.\textsuperscript{11} Due to their promising bioactivity, the researchers who isolated peniciketals A-C (20-22) have sought patent protection.\textsuperscript{11}

**Figure 1.8. Peniciketals A-C (20-22).\textsuperscript{11}**
1.3 The Chemistry of Spiroketals

Although 6,6-benzannulated spiroketals such as the virgatolides (1-3) are rare, the spiroketal moiety is a structural motif common to many natural products, many of which exhibit interesting biological activity.\textsuperscript{16,17} Spiroketal-containing natural products display a large breadth of structural diversity and have been isolated from a variety of sources, including insects, plants, microorganisms and marine sources.\textsuperscript{16-18} Among naturally-occurring spiroketals 5,5-(31), 5,6-(32) and 6,6-spiroketals (33) are the structural frameworks most frequently encountered (Figure 1.9).\textsuperscript{16}

The biological relevance and structural aesthetics displayed by spiroketal-containing natural products have resulted in significant investigative efforts towards their synthesis.\textsuperscript{16-22}

![Fig 1.9](image-url)  
**Figure 1.9.** Spiroketal frameworks commonly observed in natural products.\textsuperscript{16}

In all but the simplest cases, the acetal carbon contained within a spiroketal is a stereogenic centre. Consideration of the factors governing the configuration at this centre is essential in any synthetic endeavour towards a spiroketal-containing structure. Of key importance is the anomeric effect (Figure 1.10).\textsuperscript{17,23} Originally discovered in carbohydrates,\textsuperscript{24} the anomeric effect refers to the preference of heteroatom substituents at the anomeric centre of a pyranose ring system (or any 6-membered ring system containing a suitable heteroatom) to reside in the axial rather than equatorial position.\textsuperscript{17}

![Fig 1.10](image-url)  
**Figure 1.10.** The anomeric effect in spiroketals.\textsuperscript{17}
The origins of the anomeric effect have been the subject of some debate, with two generally accepted explanations offered: a hyperconjugative model (Figure 1.11)\textsuperscript{17} and an electrostatic model (Figure 1.12).\textsuperscript{25-27}

**Figure 1.11.** Hyperconjugative model of the anomeric effect.\textsuperscript{17}

The hyperconjugative model rationalises the anomeric effect as due to a stabilising interaction between a lone pair on the oxygen atom contained in the pyranose ring and the $\sigma^*$ orbital of the axial C-O bond.\textsuperscript{17} The orbital overlap required for this interaction to be significant is achieved when the C-O bond is antiperiplanar to the oxygen lone pair. This occurs when the C-O bond resides in the axial position, but not when it is placed equatorial.\textsuperscript{17} The hyperconjugative model has been criticised on theoretical grounds\textsuperscript{27} and also with respect its agreement with experimental data\textsuperscript{25-26} but is still commonly invoked as an explanation for the anomeric effect.\textsuperscript{17}

**Figure 1.12.** Electrostatic model of the anomeric effect.\textsuperscript{25-27}

The electrostatic model explains the anomeric effect in terms of dipole-dipole interactions between the two oxygen atoms.\textsuperscript{25-27} In this model, placement of the exocyclic oxygen axial is favoured because the resultant structure contains the two dipoles approximately opposing one another, rather than aligned in the same direction as the equatorial arrangement requires. The electrostatic penalty associated with the alignment of the two dipoles in the equatorial conformer is more significant than the steric hindrance imposed by 1,3-diaxial interactions when the C-O bond is placed axial.\textsuperscript{25-27} A more sophisticated extension of this model explicitly examines the lone pair orbital interactions.\textsuperscript{25,27}
In the absence of other factors, the configuration at the anomeric centre of 6,6-spiroketalts such as virgatolides A-C (1-3) is most often governed by the anomeric effect. In principle, for a given stereochemical configuration at the anomeric centre, 6,6-spiroketalts can exist in four possible structures (Figure 1.13).\(^\text{17}\)

![Diagram showing possible structures for 6,6-spiroketalts.](image)

**Figure 1.13.** Possible structures for 6,6-spiroketalts.\(^\text{17}\)

The structures possible for a 6,6-spiroketal ring system are often referred to as “configurations”.\(^\text{17}\) Strictly speaking this is incorrect, as there are only two possible configurations at the anomeric centre. Structures 34-37 are different conformations of the same molecular structure and can be obtained from one another *via* conversion between the different chair conformations of each of the six-membered rings. Under equilibrating conditions, one configuration at the anomeric centre will allow the maximum number of substituents to reside in the equatorial position when the molecule adopts the anomerically-stabilised conformation, thus leading to preferential formation of a single spiroketal isomer.

It should be noted that not all naturally-occurring spiroketalts adopt the structure with the maximum number of anomic relationships. This occurs when other factors (such as steric and chelation effects) result in a non-anomerically stabilised structure possessing lower total energy than an anomerically stabilised structure.
1.4 Synthesis of Spiroketalts

There are many different methods available for the synthesis of spiroketalts.\textsuperscript{28-37} Spiroketalts can be prepared from a diverse range of spiroketalisation precursors, providing flexibility in the design of a synthetic strategy (Figure 1.14). Common methods for the construction of spiroketalts include: dehydrative spiroketalisation of dihydroxyketones, hydroalkoxylation of internal alkynes, addition of oxygen nucleophiles \textit{via} an oxonium ion, oxa-Michael addition, cycloadditions such as hetero Diels-Alder reactions, ring closing metathesis, and a variety of oxidative methods.\textsuperscript{28} Many of these processes can be conducted under transition metal catalysis.\textsuperscript{29} The methods available for the synthesis of 3-substituted phthalides such as those present in virgatolides A-C (1-3) have been reviewed elsewhere.\textsuperscript{38}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure14}
\caption{Overview of the methods available for the construction of spiroketalts.\textsuperscript{28}}
\end{figure}
1.4.1 Synthesis of Benzannulated Spiroketal-Containing Natural Products

Benzannulated spiroketals possess an aryl moiety fused to the spiroketal substructure. Among spiroketal-containing natural products, benzannulated spiroketals such as virgatolides A-C (1-3) are uncommon. The synthesis of natural products containing a benzannulated spiroketal moiety has been reviewed by our group, covering the literature until late 2009. A concise summary of the syntheses prior to 2010, indicating the key steps employed is given in Figure 1.15.

The first total synthesis of berkelic acid (38) was reported by Snider et al. in 2009, confirming the absolute stereochemistry which had previously been uncertain. The spiroketal framework was established via an oxa-Pictet-Spengler reaction between acetal 39 and aromatic alcohol 40. Later in the same year, a second synthesis of 38 was reported by De Brabander, which employed a biomimetic [4+2] cycloaddition to assemble the tetracyclic core.

The first total synthesis of the human telomerase inhibitor (±)-γ-rubromycin (43) was accomplished by Kita et al. in 2007, using a Pummerer-type reaction between aryl sulfonium species 45 and enol ether 46 to unite the two halves of the molecule. Intercepting the final stages of this synthesis, Brimble et al. published a formal total synthesis of (±)-γ-rubromycin (43) in 2009 employing a dehydrative spirocyclisation to construct the spiroketal core. Also, related to the synthesis of γ-rubromycin (43) is the construction of the aglycon of (±)-heliquinomycin 44 by Danishefsky using an unusual Mitsunobu strategy for the formation of the spiroketal from hemiacetal 48-44.

The first total synthesis of the fungal metabolite papulacandin D (49) was reported by Barrett in 1995. The synthesis utilised nucleophilic addition of the lithiate of bromide 51 to lactone 50 followed by acid-catalysed spirocyclisation. A second synthesis of papulacandin D (49) was achieved by Denmark in 2007, forming the spiroketal framework via an intramolecular epoxide-opening reaction.

Finally, the total synthesis of (±)-terreinol (53) was achieved by Yao in 2005 using an intramolecular iodoetherification strategy.
Figure 1.15. Synthesis of naturally-occurring benzannulated spiroketals.\textsuperscript{39-48}
There have been a number of syntheses of benzannulated spiroketal natural products after the publication of the 2009 review.\textsuperscript{1,2,3} In particular, a number of new syntheses of berkelic acid (38) and members of the rubromycin family have been reported (Figure 1.16).

In 2010, Fürstner reported a total synthesis of berkelic acid (38).\textsuperscript{49} This work was a continuation of earlier work which had resulted in the synthesis of berkelic acid methyl ester in 2008, an endeavour which led to the revision of the relative stereochemistry possessed by naturally-occurring berkelic acid (38).\textsuperscript{50} The key spiroketalisation step was accomplished utilising an intramolecular oxa-Michael addition followed by dehydrative spirocyclisation.\textsuperscript{49} In 2011, Brimble et al. reported a formal synthesis of berkelic acid (38), intercepting the latter stages of the synthesis by Snider.\textsuperscript{39,51} Assembly of the carbon framework was achieved by addition of silyl enol ether 56 to oxonium ion 57.\textsuperscript{51} Subsequent dehydrative spirocyclisation provided the spiroketal core. Another formal total synthesis of berkelic acid (38) was published in 2011 by Pettus et al. utilising a [4+2] cycloaddition reaction to assemble the tetracyclic core, in analogy to the work of De Brabander.\textsuperscript{40,52} Finally, in 2012, Fañanás and Rodríguez reported a highly scalable, protecting-group free strategy for the synthesis of berkelic acid (38), allowing the preparation of all synthetic intermediates on a gram scale.\textsuperscript{53} This synthesis also utilised a [4+2] cycloaddition strategy similar to the earlier syntheses reported by De Brabander\textsuperscript{40} and Pettus.\textsuperscript{52}

Following the publication of our 2009 review, four new syntheses of members of the rubromycin family have been reported. In 2011, Pettus published the synthesis of (±)-γ-rubromycin (43) using a [3+2] cycloaddition strategy for the union of intermediates 62 and 63.\textsuperscript{54} This was followed by a formal synthesis of (±)-γ-rubromycin (43) by Li et al. in 2012.\textsuperscript{55} Li conducted an oxidative cyclisation on advanced intermediate 64 to establish the spirocyclic framework of (±)-γ-rubromycin (43). In 2013, Li also published a synthesis of the related compound (±)-δ-rubromycin (65), which is structurally identical to 43 except that it lacks a single hydroxyl group.\textsuperscript{56} Despite the structural similarity, this synthesis employed a different strategy for the assembly of the spiroketal moiety. Oxypalladation of alkyne 66 furnished the corresponding enol ether, which was followed by acid-catalysed deprotection/cyclisation to generate the spiroketal motif.\textsuperscript{56} Finally, in 2014 Reissig reported a synthesis of (±)-γ-rubromycin (43) \textit{via} dehydrative spirocyclisation of advanced intermediate 67.\textsuperscript{57} Ketone 67 was in turn accessed \textit{via} an aryl Grignard addition to an α,β-unsaturated ketone.
Figure 1.16. Recent syntheses of naturally-occurring benzannulated spiroketalts.49,51-57
In addition to syntheses of berkelic acid (38) and members of the rubromycin family, the first total synthesis of the benzannulated spiroketalts paecilospirone (68) and chaetoquadrin C (15) have also been reported (Figure 1.17). The total synthesis of paecilospirone (68) was published by Brimble et al. in 2011. Attempted synthesis of paecilospirone (68) via acid-catalysed deprotection/spirocyclisation was plagued by elimination of the sensitive β-hydroxy moiety present in paecilospirone (68). This necessitated the use of a pH-neutral deprotection/spirocyclisation procedure for the assembly of the spiroketal substructure. In 2013, Brimble et al. published the synthesis of chaetoquadrin C (15), together with ent-chaetoquadrians A and B. Installation of the carbon backbone of spiroketalisation precursor 70 was achieved via a diastereoselective aldol reaction. Subsequent dehydrative spirocyclisation of ketone 70 afforded chaetoquadrin C (15).

The 5,5-benzannulated spiroketal natural products cryptoacetalide (71) and danshenspiroketallatone (73) were synthesized by Deiters in 2010 and Brimble in 2011 respectively. Both syntheses employed an oxidative radical cyclisation for the construction of the spiroketal moiety, although the methods used to assemble spiroketalisation precursors 72 and 74 differed significantly.

**Figure 1.17.** Recent syntheses of naturally-occurring benzannulated spiroketals.
1.5 Previous Syntheses of Structural Motifs Related to the Virgatolides

1.5.1 Total Synthesis of Chaetoquadrins A-C by Brimble et al.

In 2013, Brimble et al. reported the synthesis of chaetoquadrin C (15) and ent-chaetoquadtrins A (ent-13) and B (ent-14) using an acid-catalysed spiroketalisation strategy (Scheme 1.2). Given the similarity between the spiroketal subunits of virgatolides A-C (1-3) and chaetoquadtrins A-C (13-15), this synthesis provides an important case study relevant to this work.

Key intermediate, benzyl bromide 76 was prepared in 27% yield over eight steps from readily available noreugenin (75). Diastereoselective alkylation of amide 77 with bromide 76 furnished amide 78 and subsequent conversion to methyl ketone 81 was then achieved in 69% yield over four steps. Aldol reaction of ketone 81 and aldehyde 82 employing Paterson’s conditions furnished aldol 70 with moderate diastereoselectivity. Deprotection followed by acid-mediated spirocyclisation, completed the synthesis of chaetoquadrin C (15). Syntheses of ent-chaetoquadtrin A (ent-13) and B (ent-14) were achieved via an analogous procedure utilising the enantiomer of aldehyde 82 in the key aldol reaction.

Although successful, the synthesis is highly linear, requiring eighteen consecutive reactions beginning with noreugenin (75), which in turn had to be prepared from commercially available 2,4,6-trihydroxyacetophenone. In particular, it should be noted that benzylic halide 76 required significant prior functionalisation. Also, the use of an oxazolidinone chiral auxiliary demanded a four step conversion to methyl ketone 81, as opposed to the corresponding pseudoephedrine auxiliary which would facilitate direct alkylation to furnish methyl ketone 81.
Scheme 1.2. Reagents and conditions: a) 77, NaHMDS, THF −78 °C, 1 h then 76, 30 min, 51%; b) LiBH₄, Et₂O, MeOH, rt, 1.5 h, 97%; c) IBX, DMSO, rt, 2 h, 94%; d) MeMgBr, LiCl, Et₂O, −78 °C, 30 min, 80%; e) IBX, DMSO, rt, 2 h, 94%; f) 81, (−)-Ipc₂BCl, NEt₃, Et₂O, then 82, −78 °C, 2 h, 43% over two steps; g) TBAF, THF, rt, 50 min; h) H₂, Pd/C, EtOAc, rt, 2 h; i) PPTS, CH₂Cl₂, rt, 12 h, 33% over three steps.²⁹

1.5.2 Total Synthesis of Pestaphhalides A and B by Koert et al.

As noted in Section 1.1, pestaphhalides A (4) and B (5) are thought to be involved in the biosynthesis of virgatolides A-C (1-3) and share a common phthalide framework.¹ In particular, pestaphhalide A possesses the same stereochemical configuration as virgatolides A (1) and B (2).

In 2011, Koert et al. reported the first total synthesis of (+)-pestaphthalide A (4) and (−)-pestaphthalide B (5) using a meta-selective CH-borylation/Suzuki cross-coupling strategy (Scheme 1.3).⁶⁵ The synthesis began from 2-methylresorcinol dimethyl ether (83), which was subjected to iridium-catalysed meta borylation, affording boronate 84 in good yield. Suzuki cross-coupling of boronate 84 with (Z)-1-bromoprop-1-ene (85) delivered Z-alkene 86 in high yield as a single stereoisomer. Formation of the E-alkene using similar conditions was also attempted.
but generated an inseparable mixture of E/Z-alkene products. Jacobsen epoxidation, followed by acid-catalysed epoxide opening afforded a diastereomeric mixture of diols 88 and 89 in a 3:1 ratio. Conversion of diols 88 and 89 to the corresponding cyclic carbonates 90 and 91 enabled separation of the diastereomers. The syntheses of pestaphthalides A (4) and B (5) then continued in parallel from carbonates 90 and 91 respectively. Bromination of the aromatic ring proceeded smoothly, affording bromides 92 and 93. Treatment of bromides 92 and 93 with tert-butyllithium triggered an intramolecular rearrangement to generate the phthalide scaffold and subsequent demethylation afforded pestaphthalides A (4) and B (5).

**Scheme 1.3.** *Reagents and conditions:* a) B$_2$pin$_2$, [Ir(cod)OMe]$_2$, dtbpy, octane, 125 °C, 93%; b) Pd(PPh$_3$)$_4$, K$_2$CO$_3$, EtOH, H$_2$O, toluene, 45 °C, 91%; c) mCPBA, NMO, (R,R)-salen-Mn(II) catalyst, CH$_2$Cl$_2$, −78 °C to rt, 95%, 93% e.e.; d) aq. HClO$_4$, acetone, −20 °C, 60%, 3:1, 88/89; e) triphosgene, pyridine, CH$_2$Cl$_2$, −78 °C to rt, 77% 90, 18% 91; f) NBS, MeCN, 0 °C, 85% 92, 85% 93; g) t-BuLi, THF, −78 °C to rt, 50% from 92, 74% from 93; h) BBr$_3$, CH$_2$Cl$_2$, rt, 75% 4, 78% 5.65
1.5.3 Total Synthesis of Acetophthalidin by Kitahara et al.

In 1997, Kitahara et al. reported the total synthesis of both enantiomers of the phthalide natural product acetophthalidin (95, Scheme 1.4). In addition to acetophthalidin (95), several structural analogues sharing the phthalide core structure present in virgatolides A (1) and B (2) were also prepared. The synthesis was motivated by the desire to biologically evaluate both enantiomeric forms of compound 95, which was isolated only as a racemic mixture from the natural source. The isolation procedure effected hydrolysis of compound 95 to inactive trihydroxymellein (94). This meant that acetophthalidin (95) could only be obtained by heating isolated 94 under acidic conditions, a process which also resulted in racemisation via keto-enol tautomerisation.

Scheme 1.4. Hydrolytic racemisation of acetophthalidin (95).

Kithara’s synthesis of acetophthalidin (95) began from methyl 2,4,6-trihydroxybenzoate (96) which was protected as the dibenzyl ether 97 and the remaining phenolic hydroxyl group then converted to the triflate (Scheme 1.5). Stille coupling of triflate 98 with tri-n-butyl(1-propenyl)tin (1:1 E/Z mixture) afforded alkene (E/Z)-99 in good yield as a 3:1 mixture of stereoisomers. Recrystallisation from hexanes/ethyl acetate then allowed preparation of nearly isomerically pure alkene (E)-99 (E/Z ratio 50:1). Sharpless asymmetric dihydroxylation of 99 using either AD-mix α or AD-mix β with concomitant lactonisation afforded both enantiomers of 100 with high enantioselectivity (>99% e.e.). Dess-Martin oxidation of the secondary alcohol followed by hydrogenolysis of the benzyl groups with palladium hydroxide on carbon afforded both enantiomers of acetophthalidin (95). Importantly, intermediate 100 has a chiral hydroxyethyl-substituted phthalide framework analogous to that contained in virgatolides A (1) and B (2). The preparation of both enantiomers of hydroxyl analogue 10 from benzyl ether 100 was also reported. Phthalide 10 shares the same core phthalide structure and relative stereochemistry as pestalphthalide A (4) and virgatolides A (1) and B (2).
Scheme 1.5. Reagents and Conditions: a) BnBr, $\text{K}_2\text{CO}_3$, NaI, DMF, rt, 12 h, 47%; b) $\text{Tf}_2\text{O}$, pyridine, $\text{CH}_2\text{Cl}_2$, $-40^\circ\text{C}$ to $0^\circ\text{C}$, 4 h, 77%; c) MeCH=CHSnBu$_3$, Pd(PPh$_3$)$_4$, LiCl, THF, 90 $^\circ\text{C}$, 7 d, 59%; d) AD-mix α, MeSO$_2$NH$_2$, t-BuOH, H$_2$O, 4 $^\circ\text{C}$, 3 d, 79%; e) Dess-Martin periodinane, $\text{CH}_2\text{Cl}_2$, rt, 1 h, 99.5%; f) H$_2$, Pd(OH)$_2$/C, 10 wt%, EtOAc, rt, 15 min, 87%; g) H$_2$, Pd(OH)$_2$/C, EtOAc, rt, 85%.

1.5.4 Total Synthesis of Herbaric Acid by Brimble et al.

In 2010, Brimble et al. reported the first total synthesis of the fungal metabolite (−)-herbaric acid (109) using a heteroatom-directed reverse Wacker oxidation as a key step (Scheme 1.6). Herbaric acid (109) possesses a resorcinol-derived aromatic core analogous to that contained in virgatolides A-C (1-3). The synthesis began from readily accessible aldehyde 102, which was treated with vinylmagnesium bromide to furnish racemic alcohol (±)-103. Chiral material was accessed via a microwave-assisted chemoenzymatic resolution, which provided enantioenriched alcohol (S)-103 with 84% e.e. Compound (S)-103 was then treated with 1,1’-carbonyldimidazole and diethylamine to provide carbamate 104. Lithium-halogen exchange of 104 was effected with tert-butyllithium, triggering an intramolecular acylation reaction. Further treatment with anhydrous hydrochloric acid resulted in the formation of vinylphthalide 105. Heteroatom-directed Wacker oxidation of compound 105 showed complete selectivity for the anti-Markovnikov product, affording aldehyde 106 as a single regioisomer. Further oxidation of aldehyde 106 and subsequent esterification provided enantioenriched lactone ester 108.
Demethylation with boron tribromide, followed by saponification of the methyl ester afforded \((-\)-herbaric acid (109).

Scheme 1.6. Reagents and conditions: a) vinylmagnesium bromide, THF, \(-78 \, ^\circ\, \text{C}\), 12 h, 85%; b) \(p\)-chlorophenyl acetate, Novozyme 435\(^\circ\), toluene, 48 h, 50%, 84% e.e.; c) CDI, HN\(\text{Et}_2\), CH\(_2\)Cl\(_2\), 24 h, 90%; d) \(n\)-BuLi, THF, \(-78 \, ^\circ\, \text{C}\), 1 h; e) anhydrous HCl (1M), dioxane, 12 h, 74% over two steps; f) PdCl\(_2\), CuCl, O\(_2\), DMF/H\(_2\)O (3:1), r.t., 2 h, 86%; g) Oxone, DMF, rt, 6 h, 89%; h) H\(_2\)SO\(_4\), MeOH, rt, 12 h, 82%; i) BBr\(_3\), CH\(_2\)Cl\(_2\), 0 \, ^\circ\, \text{C}\), 2 h, then r.t. 72 h; j) NaOH, MeOH/H\(_2\)O, 12 h, 65% over two steps.\(^{68}\)
1.6 Aims of the Present Research

Virgatolides A-C (1-3) constitute a recent addition to the collection of naturally occurring 6,6-benzannulated spiroketals. The novel molecular structures displayed by these metabolites make them attractive targets for total synthesis. Furthermore, prior to this work, no total synthesis of a member of the virgatolides had been reported. Although virgatolides A-C (1-3) display only moderate growth inhibitory activity towards HeLa cells, an efficient method for their synthesis would provide the basis for a more thorough investigation of the biological profile of this novel class of natural products and analogues thereof. To this end, virgatolide B (2) was chosen as the structural prototype of the virgatolides and a synthetic strategy devised with the expectation that a successful synthesis would also enable access to the remaining two congeners.

Retrosynthetically, virgatolide B (2) was to be constructed by dehydrative spirocyclisation (Scheme 1.7, see also Section 1.4). Disconnection of the spiroketal ring system in virgatolide B (2) provides ketone 110. The diastereoselectivity obtained from the spirocyclisation step was envisioned to be controlled by the existing chirality in precursor 110. As noted earlier, examination of the X-ray structure of virgatolide A (1) indicates that the configuration of the spiroketal centre is influenced by anomeric stabilisation.¹

![Scheme 1.7. Retrosynthetic analysis of virgatolide B (2).](image-url)

The acyclic spiroketal precursor 110 would be accessed via a diastereoselective aldol reaction between methyl ketone 112 and aldehyde 111. Aldehyde 111 is readily available from commercially available ethyl (S)-3-hydroxybutyrate via known chemistry,⁶⁹-⁷⁰ whilst methyl ketone 112 requires further disconnection. The key structural feature in 112 is the α-chiral β-arylated ketone side chain.
It was noted that following deprotection of ketone 110, cyclisation of ketone 113 could possibly give rise to two different spiroketal regioisomers, depending on which phenolic oxygen atom was incorporated in the spiroketal ring system. It was postulated that intramolecular hydrogen bonding between the phthalide carbonyl and the neighbouring phenol would result in an energetic differential between 2 and the spiroketal regioisomer 114 formed upon spirocyclisation of the alternate phenolic oxygen (Figure 1.18).

The nature of the substitution pattern of phthalide 112 requires the consideration of molecular symmetry. If intramolecular hydrogen bonding between the adjacent carbonyl group and the peri phenol in virgatolide B (2) is sufficient to control the regioselectivity of spirocyclisation then P\(^3\) and P\(^3\) may be chosen as identical, due to the free rotation of the aromatic nucleus. However, if this effect is not capable of providing sufficient regiocontrol, then the two phenolic oxygen atoms must be orthogonally protected in order to ensure production of 2 as opposed to the undesired regioisomer 114.
1.7 Aldol Reactions of Methyl Ketones

The aldol reaction is one of the most thoroughly studied reactions in the field of organic synthesis. In its most general form, the reaction occurs between an enolate nucleophile and a carbonyl electrophile (usually an aldehyde), resulting in the formation of a \( \beta \)-hydroxy carbonyl product (Scheme 1.8). The reaction generates either one or two new stereocentres, depending on whether or not the enolate is substituted at the \( \alpha \)-position.

![Scheme 1.8. The aldol reaction.](image)

The construction of ketone 110 via aldol reaction of methyl ketone 112 and aldehyde 111 imposes several constraints on what aldol methodology can be used to control the stereoselectivity of the newly generated chiral centre (see Scheme 1.7). In particular, an auxiliary-mediated approach cannot be adopted since the structure of virgatolide B (2) requires the use of a ketone which contains both the \( \alpha \)-chiral \( \beta \)-arylated moiety and a methyl substituent, such as ketone 112. The approaches that remain viable for the construction of 2 are ligand-mediated asymmetric induction and substrate-mediated asymmetric induction.

1.7.1 Ligand-Mediated Asymmetric Induction

The most common ligands used to induce stereoselectivity in aldol reactions are boron-derived (Figure 1.19). In this variant of the aldol reaction, deprotonation in the presence of a chiral Lewis acid facilitates the formation of an enolate species in which the oxygen atom is directly bonded to a chiral reagent. This chiral group differentiates the two diastereotopic \( \pi \)-faces of the enolate and thus results in selective reaction at one face.
The diastereoselectivity of an aldol reaction depends on the enolate geometry, provided that the reaction proceeds according to the Zimmerman-Traxler model.\textsuperscript{73} This is normally the case for Paterson-type aldol reactions.\textsuperscript{74} In this model, both the enolate nucleophile and carbonyl electrophile are bound to a Lewis acid (e.g. boron, M\(^+\)), forming a six-membered, chair-like transition state. The absolute stereochemistry is governed by the nature of the ligands on the boron/metal. The presence of chirality in the ligands results in an energy difference between the two diastereomeric transition states generated by attack of the electrophile by either face of the enolate.

The most highly developed approach to ligand-mediated aldol reactions is the work reported by Paterson, which uses isopinocampheyl substituents on boron.\textsuperscript{72,74-75} In this approach, facial selectivity is controlled by steric interactions between the axial enolate substituent and the isopinocampheyl ligands, in particular the methyl group adjacent to boron on the axial ligand (Figure 1.20). For an enolate derived from \((-\text{Ipc}_2\text{BOTf})\), nucleophilic attack of the \(si\) face of the aldehyde is favoured. The enantioselectivity of the reaction can be reversed by instead using \((+\text{-Ipc}_2\text{BOTf})\).
There is an exception to this model in the case of Paterson aldol reactions employing methyl ketones (R²=H). In these cases, the facial selectivity is the reverse of that expected upon applying the above model. It has been proposed that these reactions instead proceed through a twist-boat transition state 120 (Figure 1.21). In this model, the twist-boat conformation avoids the 1,3-diaxial interaction between R¹ and the axial isopinocampheyl ligand present in the chair transition state (c.f. Figure 1.20).

Only methyl ketones proceed via this transition state, because when R²≠H, the steric interactions between R² and the proximal Ipc ligand in the twist-boat conformation 122 are greater than the
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1,3-diaxial strain between R¹ and the axial Ipc ligand in the chair conformation 116. This results in the chair transition state being operative when R²≠H.⁷⁶ Although the twist-boat conformation when employing methyl ketones explains why the enantioselectivity differs substantially from the general case, a convincing rationalisation of the facial selectivity in the twist-boat conformation has yet to be offered.⁷⁶ The levels of enantioselectivity of Paterson aldol reactions employing methyl ketones (53-78% e.e.) are lower than those observed when R²≠H (66-91% e.e.).⁷⁶ This indicates that the factors influencing enantioselectivity in the twist-boat transition state are likely to be subtle.

1.7.2 Substrate-Mediated Asymmetric Induction

Chirality present in either the aldehyde or ketone substrates of an aldol reaction can often confer facial selectivity without the use of chiral ligands or auxiliaries. Most commonly, the chiral centre that is α to one (or both) of the reacting centres. When an α-chiral aldehyde is employed, facial selectivity is, in general, governed by the Felkin-Ahn model.⁷²,⁷⁷ The use of α-chiral ketones is less common and is dependent on a number of factors, including the enolisation conditions and the choice of protecting groups when present.⁷⁸

Although aldehyde 111 lacks an α-chiral centre, a substrate-controlled aldol reaction is still feasible. In particular, Mukaiyama aldol reactions of chiral β-alkoxy aldehydes such as 111, facilitated by boron trifluoride, are known to favour the formation of the 1,3-anti diastereomer (Scheme 1.9).⁷⁹-⁸¹

![Scheme 1.9. Substrate-controlled Mukaiyama aldol reaction.](image)

The selectivity of these reactions cannot be explained on the basis of chelation-control because boron trifluoride is a monodentate Lewis acid.⁸¹ Evans et al. have proposed a model for the 1,3-stereoinduction observed in these reactions based on electrostatic and steric interactions within the boron trifluoride-complexed aldehyde (Figure 1.22).
Evans’ model is built on two assumptions. First, in the transition state, the aldehyde adopts a staggered conformation with respect to the newly-forming bond (123a) and the aldehyde α substituents (123b). Second, the transition state places the newly-forming bond anti to the Cα-Cβ bond in order to minimise repulsive interactions between the nucleophile and the α-substituent, in an analogous manner to the Felkin-Ahn model. Following these two assumptions, the preferred conformation according to semi-empirical calculations is 123, which minimises the torsional strain by placing Rβ and the carbonyl group anti across the Cα-Cβ bond. Conformation 123 lacks the destabilising dipole-dipole repulsions present in conformation 125, which results from rotation of the carbonyl group about the Cα-Cβ bond. Attack of the nucleophile yields the 1,3-anti adduct.

The selectivity of the addition accords with the strength of the dipole moment of the protected alcohol functionality, and hence the nature of the protecting group is a key consideration for such transformations. Experimentally the levels of stereoinduction decrease in the order OPMB > OTBS > OAc.
1.8 The Chemistry of α-Chiral β-Arylated Carbonyl Compounds

α-Chiral β-arylated carbonyl compounds such as methyl ketone 112 represent a significant challenge in the field of organic chemistry. The common methods employed to access these motifs have been summarised by Molander et al. (Scheme 1.10). These methods include: benzylation of chiral enolates, conjugate addition of aryl organometallics, catalytic asymmetric hydrogenation of α,β-unsaturated carbonyls or cross-coupling of chiral β-metallo carbonyls with compatible aryl halide coupling partners.

![Scheme 1.10](image)

**Scheme 1.10.** Common methods for the synthesis of α-chiral β-arylated carbonyls.

1.8.1 Benzylation of Chiral Enolates

The addition of chiral enolates to benzyl halides is commonly achieved by the use of chiral auxiliaries, for example the well-known Evans or Myers auxiliaries (Scheme 1.11). The benzylation approach is thus a subset of the more general asymmetric alkylation methodology provided by such auxiliaries. The chiral auxiliary ensures diastereoselectivity during the course of the reaction and provides the desired enantio- or diastereoenriched α-chiral carbonyl compound upon cleavage.

The oxazolidinone auxiliaries developed by Evans selectively form (Z)-enolates upon deprotonation. Bidentate chelation of the metal cation confers conformational rigidity to the enolate and ensures steric blockage of a single face by the bulky alkyl/aryl substituent of the
oxazolidinone. Selective alkylation of the unhindered face thus provides diastereoenriched products.\textsuperscript{85}

**Evans' auxiliary**

**Myers' auxiliary**

Scheme 1.11. Examples of asymmetric alkylation using chiral auxiliaries.\textsuperscript{64,85}

The origin of stereoselectivity in pseudoephedrine amide enolate alkylation is less well understood. It has been proposed that the reactive conformation of the preferred (Z)-enolate in solution places the pseudoephedrine side chain in a staggered conformation such that the CH bond α to the nitrogen atom is coplanar with the enolate oxygen (Figure 1.23).\textsuperscript{64} In this conformation, the lithium alkoxide and possibly the lithium-associated solvent molecules prevent the approach of an electrophile to the β-face of the enolate and hence result in selective alkylation of the α-face.\textsuperscript{64} This leads to the observed 1,4-\textit{syn} product. As noted earlier, pseudoephedrine auxiliaries can be cleaved directly by the addition of organolithium nucleophiles, providing the corresponding ketones in high yields.\textsuperscript{64,84} This is possible because the addition of the organolithium reagent generates a stable tetrahedral intermediate which does not form the ketone prior to work-up, thus preventing an undesired second nucleophilic attack.\textsuperscript{64}
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Figure 1.23. Proposed reactive conformation of pseudoephedrine amide enolates.64

1.8.2 Conjugate Addition of Aryl Organometallics

Conjugate additions of aryl-organometallics followed by enantioselective protonation of the enolate or oxa-\(\pi\)-allyl intermediate have been utilised for the synthesis of \(\alpha\)-chiral esters86-87 and amino acids.88-90 These transformations are typically achieved using aryl-boron species under rhodium catalysis86-90 (Scheme 1.12) but variants employing Grignard reagents,91 magnesium organocuprates91 and aryl-stannanes92 are also known.

Scheme 1.12. General mechanism of chiral rhodium-catalysed conjugate addition.86

The selectivity of the protonation in the rhodium-catalysed reaction is governed by several factors, including the nature of the organometallic species, the choice of ligand and the proton source.86-90 In general, high levels of enantioselectivity can be achieved for a range of aryl-boronic acid or aryl-trifluoroborate substrates (selected examples are given in Scheme 1.13). With respect to the synthesis of virgatolide B (2), it should be noted however, that the presence of a methoxy substituent ortho to boron can significantly reduce the yield of the reaction.87 Commonly employed ligands for chiral rhodium-catalysed conjugate additions include BINAP86 and DIFLUORPHOS.90
Scheme 1.13. Reagents and conditions: a) $[\text{Rh(cod)}_2]\text{PF}_6$, (R)-BINAP, benzene/H$_2$O (20:1), 110 °C; b) $[\text{Rh(acac})(\text{C}_2\text{H}_4)_2]$, (S)-BINAP, B(OH)$_3$, dioxane, 100 °C, microwave (110 W), 1 h; c) $[\text{Rh(cod)}_2]\text{PF}_6$, (R)-BINAP, guiacol, toluene, 110 °C.

1.8.3 Catalytic Asymmetric Hydrogenation

Enantioselective hydrogenation of trisubstituted $\alpha,\beta$-unsaturated carbonyl compounds is a viable route to both $\alpha$-chiral ketones and carboxylic acids and can be achieved by a variety of catalytic systems (Scheme 1.14). Asymmetric hydrogenation utilising cinchonine/cinchonidine (133/134) modified palladium as a catalyst is highly substrate dependent, providing optimal enantioselectivity when the carboxylic acid substrate contains both a sterically demanding $\alpha$-substituent and an electron donating $\beta$-aryl substituent. However, when the substrate lacks either of these structural requirements, the enantioselectivity declines markedly.
Scheme 1.14. Palladium-catalysed enantioselective hydrogenation of $\alpha,\beta$-unsaturated carbonyl compounds.$^{92}$

In contrast, enantioselective hydrogenation of $\alpha,\beta$-unsaturated ketones$^{93-94}$ and carboxylic acids$^{95}$ using iridium catalysis, while expensive, proceeds with high enantioselectivity and improved substrate scope, tolerating a range of aliphatic and aromatic substituents (Scheme 1.15). The stereochemical outcome of the reaction shows significant substrate dependence and can be difficult to accurately predict.$^{93-95}$ A potential disadvantage of this method is that it can require the construction of a stereodefined trisubstituted alkene substrate.

Scheme 1.15. Reagents and conditions: a) $\text{H}_2$ (6 atm), 135 (0.25 mol %), NEt$_3$, MeOH, rt, 89-99%; b) $\text{H}_2$ (2 atm), 136 (1 mol %), toluene, rt, 86-97%.$^{94-95}$
Cross-coupling of α-chiral β-metallo carbonyl compounds with aryl halides can be achieved using both Negishi and Suzuki cross-coupling methodologies. In 1977, Negishi reported the development of a procedure for the Ni/Pd-catalysed cross-coupling of organozinc reagents and aryl halides. This methodology has since been extended to the construction of α-chiral esters. The Nakamura reagent (137, Scheme 1.16) reported in 1987 was developed with the aim of providing an optically active homoenolate equivalent. The primary challenge in this endeavour was to suppress the known racemisation pathway of α-chiral homoenolates. Racemisation of the α-centre occurs via addition of the β-anion to the carbonyl group, generating cyclopropane intermediate 139. Fragmentation of 139 to 140, followed by anion inversion coupled with the reverse process culminates in racemisation of the α-centre. However, the Nakamura reagent displays retention of configuration at the α-centre, indicating that the right hand side of this equilibrium system is not operative for 137.

Cross-coupling of homoenolate 137 can be performed using a variety of electrophiles including aryl, acyl, allyl and vinyl halides (Scheme 1.17). The use of aryl halide coupling partners with non-halogen ortho substituents is tolerated. Yields are generally moderate to good (60-80%), but the instability of 137 to both moisture and oxygen requires that it be generated in situ under an inert atmosphere. Like the previous methods summarised, this methodology has been successfully applied to the synthesis of amino acids.
Scheme 1.17. Reagents and conditions: a) 137, HMPA, CuBr₂·SMe₂, Et₂O, 0 °C, 4 h.²⁸-⁹⁹

Recently, following related work on achiral systems, Molander reported the development of a new α-chiral homoenolate equivalent using an auxiliary-based approach (Scheme 1.18). In this work, a series of chiral potassium trifluoroboratoamide salts 158-161 were prepared by alkylation of the respective chiral amides 149-152 with iodomethylpinacolboronate (153), followed by conversion to the trifluoroborate salts with potassium bifluoride. These trifluoroborate salts were able to undergo Suzuki cross-coupling with a variety of aryl- and hetaryl chlorides. The catalytic system employed palladium (II) diacetate as the palladium source and RuPhos/SPhos as ligands. It should be noted that Evans’ oxazolidinone and Oppolzer’s sultam auxiliaries were also trialled, but the auxiliaries underwent cleavage when exposed to the conditions required for cross-coupling.²²
Scheme 1.18. Reagents and conditions: a) LDA, LiCl, THF, −78 °C to rt, 90 min, then 153, 0 °C, 30 min, 83-95%; b) KHF$_2$, MeCN/H$_2$O (1:1), 0 °C to rt, 30 min, 51-90%; c) ArCl/HetArCl, Pd(OAc)$_2$, RuPhos/SPhos, K$_2$CO$_3$, toluene/H$_2$O (4:1), 85 °C, 22 h, 38-82%.\textsuperscript{82}

Reaction of trifluoroboratoamide 158 with a range of aryl halides helped to elucidate the dependence of the reaction on the structural features of the aryl chloride coupling partner. Optimal yields were achieved when utilising electron-poor aryl halides and steric hindrance at the ortho positions, although tolerated, resulted in decreased yields.\textsuperscript{82} The reaction permitted a wide range of functionality on the aryl chloride, including alkyl, ether, ester, nitro and aldehyde substituents.

One of the key advantages of utilising trifluoroborate salts, as opposed to the corresponding boronic acids or boronate esters, is their stability to both ambient moisture and oxygen, meaning that preparation of trifluoroboratoamides 158-161 can be conducted \textit{en masse}, followed by long term storage if required. Trifluoroborate salts have very low toxicity and have a reduced propensity to undergo protodeboronation during the course of the Suzuki coupling when compared with boronic acids and boronate esters.\textsuperscript{82,106} This allows cross-coupling reactions to be carried using near stoichiometric amounts of the coupling partners as opposed to the excess boron species required when using other boron sources (20-50% for boronic acids).\textsuperscript{107}
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1.9 Retrosynthesis of Methyl Ketone 112

Upon investigation of the various methodologies available for the construction of α-chiral β-arylated carbonyls it was decided to construct ketone 112 via a cross-coupling approach (Scheme 1.19).

![Scheme 1.19. Retrosynthetic analysis of ketone 112.]

This decision was in part motivated by the perceived difficulties of other methods. For example, benzylolation of a chiral enolate would require the construction of a highly substituted, electron-rich benzylic halide while the conjugate addition approach would require the use of an ortho-disubstituted aryl-boron reagent. In particular, our synthetic approach to ketone 112 makes use of the Suzuki methodology developed by Molander, because it allows rapid conversion of the cross-coupling product to the desired methyl ketone 112 as opposed to the ester adduct obtained with the Nakamura reagent.

The key α-chiral β-aryl substructure is to be constructed by Suzuki cross-coupling of trifluoroboratoamide 158 and halo-phthalide 162. The use of Br or I in place of Cl in 162 is intended to increase the reactivity of 162 towards oxidative insertion and overcome the steric hindrance imparted by the ortho disubstituted aromatic framework. Accordingly, the choice of the phenol protecting groups is to be informed by steric considerations.
Chapter Two

Discussion
2.1 Synthesis of Phthalides (±)-177 and (±)-178 via a Stille Cross-Coupling Approach

2.1.1 Overview

The initial focus of the present research was to construct virgatolide B (2) from fully elaborated spiroketal precursor 163 (Scheme 2.1). Dihydroxyketone 163 would in turn be derived from an asymmetric aldol reaction between methyl ketone 164 and aldehyde 111. The α-chiral β-arylated carbonyl moiety present in ketone 164 would be installed via sp³-sp² Suzuki cross-coupling of differentially protected halo-phthalide 165/166 and known trifluoroboratoamide 158. The use of orthogonal protecting groups on the phenolic oxygen atoms would ensure regiocontrol during the spirocyclisation process. By analogy to the approach adopted by Kitahara et al. in the synthesis of acetophthalidin (95, see Section 1.5.3), the chirality present in phthalide 165/166 would be installed by Sharpless asymmetric dihydroxylation of alkene 167. In turn, alkene 167 would be derived from Stille cross-coupling of aryl triflate 168 and allyltributylstannane with subsequent double bond isomerisation. Triflate 168 was to be constructed from commercially available 2,4,6-trihydroxybenzoic acid (169).

Scheme 2.1. Retrosynthetic analysis of virgatolide B (2).
2.1.2 Synthesis of Phthalides (±)-177 and (±)-178

The synthesis of aryl triflate 168 required three selective protection steps to be carried out sequentially (see Scheme 2.1). Selective esterification of 2,4,6-trihydroxybenzoic acid (169) to give methyl ester 96 can be achieved by employing a single equivalent of dimethyl sulfate in acetone at room temperature.\(^\text{110}\) Pleasingly, the use of this procedure on commercially available 2,4,6-dihydroxybenzoic acid monohydrate was successful, providing synthetically useful quantities of methyl ester 96 (Table 2.1, entry 1). The undesired dimethylation product 170 was also generated in low levels (14\%) but was readily separable from monomethylated 96 by flash chromatography. It was found that the use of DMF as a solvent increased the yield of undesired dimethylated product 170 and also generated trace amounts (<5\%) of the trimethylated species 171 (entry 2).

Because of the known toxicity of dimethyl sulfate,\(^\text{110}\) alternative procedures for the preparation of methyl ester 96 were investigated. These approaches included: classical esterification with methanol and concentrated sulfuric acid (entry 3), conversion to the acyl chloride (entry 4),\(^\text{111}\) Steglich esterification (entry 5)\(^\text{112}\) and the use of dimethyl carbonate as a low-toxicity alternative to dimethyl sulfate (entry 6).\(^\text{113}\) Surprisingly, none of these alternative approaches provided comparable results to the use of dimethyl sulfate, which was thus selected as the reagent of choice, in spite of its toxicity.

\[
\begin{align*}
\text{OH} & \quad \text{OH} & \quad \text{OH} \\
\text{HO} & \quad \text{CO} & \quad \text{OMe} \\
\text{HO} & \quad \text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{CO} & \quad \text{OMe} \\
\text{HO} & \quad \text{CO} & \quad \text{OMe}
\end{align*}
\]

\(\text{169} \xrightarrow{a} \text{96} + \text{170} + \text{171}\)

<table>
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<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
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</thead>
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<tr>
<td>1</td>
<td>(\text{Me}_2\text{SO}_4, \text{K}_2\text{CO}_3, \text{acetone, rt, 16 h})</td>
<td>56% \text{96}, 14% \text{170}</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Me}_2\text{SO}_4, \text{K}_2\text{CO}_3, \text{DMF, rt, 21 h})</td>
<td>3 component mixture</td>
</tr>
<tr>
<td>3</td>
<td>(\text{MeOH, H}_2\text{SO}_4 (95%, \text{cat.}, \text{reflux, 24 h}))</td>
<td>no product</td>
</tr>
<tr>
<td>4</td>
<td>(\text{SOCl}_2, \text{MeOH, reflux, 24 h})</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>(\text{DMAP, EDC, MeOH, rt, 18 h})</td>
<td>20%</td>
</tr>
<tr>
<td>6</td>
<td>(\text{Me}_2\text{CO}_3, \text{H}_2\text{SO}_4 (95%, \text{cat.}, \text{reflux, 18 h}))</td>
<td>no product</td>
</tr>
</tbody>
</table>

Table 2.1. Preparation of methyl ester 96.
Selective benzylation of the para-phenol of methyl ester 96 was effected with benzyl bromide in acetone (Scheme 2.2). The use of one equivalent of benzyl bromide afforded benzyl ether 172 as the major product. It was found that heating of the reaction mixture to reflux was required in order to attain sufficient conversion of starting material. Minor quantities of dibenzylated ester 97 and unreacted methyl ester 96 were observed but both were easily separable by flash chromatography. When DMF was probed as an alternative solvent, the reaction rate was reduced and more side-products were observed by TLC and the 1H NMR spectrum of the crude product mixture.

Scheme 2.2. Reagents and conditions: a) BnBr, K$_2$CO$_3$, NaI, acetone, reflux, 3 h, 62% 172, 17% 97, 16% 96.

Selective methylation of one of the two remaining hydroxyl groups present in benzyl ether 172 was now required (Scheme 2.3). Treatment of benzyl ether 172 with TMS-diazomethane and stoichiometric methanol in diethyl ether or THF resulted in moderate yields of the desired product 173 (55-60%). However, as this method required reaction times of up to 48 hours a more expedient route was sought. It was found that methylation of benzyl ether 172 with methanol under Mitsunobu conditions provided methylated product 173 in better yields with significantly shorter reaction times (2 hours). Conversion of 173 to triflate 168 was then achieved in high yield using N phenyltriflimide.

Scheme 2.3. Reagents and conditions: a) DIAD, PPh$_3$, MeOH, THF, rt, 2 h, 64%; b) PhNTf$_2$, NEt$_3$, CH$_2$Cl$_2$, reflux, 48 h, 96%.
Attention now turned to the installation of the alkenyl side-chain by Stille cross-coupling of triflate 168 with allyltributyltin (Scheme 2.4). It was found that Pd(PPh3)4 efficiently catalysed the cross-coupling reaction in the presence of three equivalents of lithium chloride. Analysis of the TLC and 1H NMR spectrum of the crude product mixture indicated that cross-coupling product 174 underwent partial isomerisation under the reaction conditions to form the thermodynamically favoured alkene 167. The olefinic resonances in the 1H NMR spectrum of alkene 167 revealed a vinylic coupling constant of 15.6 Hz, indicating that the double bond possesses E-stereochemistry.

In view of this, it was decided to conduct the cross-coupling and the subsequent isomerisation reaction in tandem, without isolating cross-coupling adduct 174. Upon completion of the Stille coupling reaction, treatment of the crude reaction mixture with potassium tert-butoxide with mild heating effected full conversion to alkene 167 in 85% yield over two steps.

Dihydroxylation of alkene 167 with osmium tetroxide and N-methylmorpholine-N-oxide in acetone/water proceeded with concomitant lactonisation affording cis phthalide (±)-175 in high yield. At this stage, phthalide (±)-175 was generated as a racemate for the purpose of investigating subsequent transformations. This procedure was carried out with the knowledge that Sharpless asymmetric dihydroxylation would provide access to enantioenriched 175 when required. Neither the intermediate diol nor the isochromanone (±)-176 derived from lactonisation of the alternate alcohol functionality were observed.

Scheme 2.4. *Reagents and conditions:* a) allylSnBu3, Pd(PPh3)4, LiCl, THF, reflux, 48 h; b) t-BuOK, THF, 40 °C, 24 h, 83% over two steps; c) OsO4, NMO, acetone/water (10:1), rt, 16 h, 90%.
The free alcohol present in phthalide (±)-175 was protected both as an ethoxymethyl (EOM) ether and a tert-butyldimethylsilyl (TBS) ether in order to probe the effects of the protecting group on the regioselectivity of subsequent halogenation (Scheme 2.5). EOM ether (±)-177 was prepared by reaction of alcohol (±)-175 with chloromethyl ethyl ether and diisopropylethylamine in dichloromethane, while TBS ether (±)-178 was generated using tert-butyldimethylsilyl triflate and 2,6-lutidine. It was postulated that the increased steric demand of the TBS group might improve selectivity for the C-6 position by partially blocking the C-4 position. It is of note that attempted use of sodium hydride as base during the TBS protection resulted in degradation of phthalide (±)-175 due to deprotonation at the benzylic position, followed by elimination to give alkene 179.

Scheme 2.5. *Reagents and conditions:* a) EOMCl, DIPEA, DMAP, CH₂Cl₂, rt, 48 h, quant.; b) TBSOTf, 2,6-lutidine, CH₂Cl₂, −78 °C, 4 h, quant.

2.1.3 Attempted Halogenation of Phthalides (±)-177 and (±)-178

Selective halogenation of phthalides (±)-177, and (±)-178 at C-6 was required to generate the correct carbon framework upon cross-coupling with trifluoroboratoamide 158 (Scheme 2.6). However, prediction of the preferred site for electrophilic aromatic substitution based on simple substituent-directing considerations was challenging for these substrates. Relative to each of the aromatic substituents, both C-4 and C-6 are favoured positions for substitution to occur.

Scheme 2.6. Desired regioselectivity for halogenation of phthalides (±)-177, and (±)-178.
Precedent for the desired regioselectivity was reported by Shimizu et al. during the total synthesis of mycophenolic acid and a series of structural analogues (Scheme 2.7).\textsuperscript{121} In this work, treatment of phthalide 180 with iodine and silver trifluoroacetate in dichloromethane provided iodide 181 in good yield with complete selectivity for C-6.\textsuperscript{121} Another example demonstrating precedent for selective halogenation at C-6 was the bromination of benzoate 182 to exclusively afford aryl bromide 183, reported by Li et al.\textsuperscript{122}

![Diagram of chemical structures](image)

**Scheme 2.7.** *Reagents and conditions:* a) I$_2$, F$_3$CO$_2$Ag, CH$_2$Cl$_2$, rt, 21 h, 85\%;\textsuperscript{121} b) NBS, benzoyl peroxide, CCl$_4$, reflux, 5 h, 79\%.\textsuperscript{122}

Encouraged by these examples, halogenation of phthalides (±)-177 and (±)-178 with both N-bromosuccinimide (NBS) and iodine was probed (Scheme 2.8). Unfortunately, in all cases halogenation occurred exclusively at the undesired C-4 position.
Scheme 2.8. **Reagents and conditions:** a) NBS, CH₂Cl₂, 0 °C to rt, 16 h, 93%; b) I₂, AgO₂CF₃, CH₂Cl₂, rt, 1 h, 96%; c) NBS, CH₂Cl₂, 0 °C to rt, 3 d, 93%; d) I₂, F₃CCO₂Ag, CH₂Cl₂, rt, 3 h, 88%.

Structural assignment of the halogenation products was determined by analysis of the HMBC and NOESY spectra. Halides 184-187 exhibited NOESY correlations between the remaining aromatic proton H-6 and the methoxy and benzyl substituents, indicating that halogenation had taken place at C-4 rather than C-6. In addition, NOESY correlations between H-6 and the phthalide methine protons were absent in the NOESY spectra of halides 184-187. Furthermore, HMBC analysis showed no correlations between the aromatic proton H-6 and the phthalide methine protons, except in the case of iodide (±)-185 (discussed below).

Interestingly, although the aromatic proton in iodide (±)-185 correlated with both protecting group resonances, the HMBC spectrum showed a correlation between the aromatic proton H-6 and C-1'. A derivative was therefore prepared in order to secure an unambiguous structural assignment. Palladium diacetate catalysed Stille cross-coupling of iodide (±)-185 with allyltributyltin furnished phthalide (±)-188 good yield (Scheme 2.9). The NOESY spectrum of phthalide (±)-188 displayed correlations between the aromatic proton H-6 and both protecting group resonances. NOESY correlations were also observed between the allyl group and the phthalide methine protons. The HMBC spectrum lacked any correlation between the aromatic proton (or the associated carbon resonance) with the methine resonances, indicating that the structure of iodide (±)-185 had been correctly assigned.
Reagents and conditions: a) allylSnBu₃, Pd(OAc)₂, PPh₃, DMF, 110 °C, 24 h, 84%.

2.1.4 Halogenation of Structural Derivatives of Alkene 167 and Phthalide (±)-177

Realising that an extensive screen of halogenation conditions was unlikely to overturn the regiochemical preference inherent in phthalides (±)-177 and (±)-178, it was decided to change the structure of the halogenation substrate. In an attempt to change the electronic character of the aromatic ring, the benzyl group was removed and the resultant phenol (±)-189 investigated as a halogenation candidate (Scheme 2.10).

Phenol (±)-189 was readily accessible from benzyl ether (±)-177 via removal of the benzyl group. Pd-catalysed hydrogenolysis of benzyl ether (±)-177 under hydrogen afforded phenol (±)-189 in high yield. However, halogenation with both NBS and iodine once again took place at the undesired C-4 position. In addition to the undesired halides (±)-190 and (±)-192, low levels of dihalogeneration (<25%) were also observed. These results are easily rationalised by the greater activating ability of phenol substituents compared to phenolic ethers and the decrease in steric hindrance resulting from loss of the benzyl protecting group.
Scheme 2.10. Reagents and conditions: a) H$_2$, Pd/C, MeOH, rt, 24 h, 89%; b) NBS, CH$_2$Cl$_2$, 0 °C to rt, 24 h, 62% (±)-190, 15% (±)-191; c) I$_2$, F$_3$CCO$_2$Ag, CH$_2$Cl$_2$, 0 °C to rt, 16 h, 56% (±)-192, 21% (±)-193.

Following these results, the effect of the phthalide moiety on the regioselectivity of the halogenation step was investigated by halogenation of alkene 167 and several derivatives. Two alkene variants were prepared: unprotected alkene 194 and mono-protected alkene 195 (Scheme 2.11). Alkene 194 was constructed by deprotection of methyl ester 167 with boron tribromide in dichloromethane at −78 °C. Preparation of benzyl ether 195 from phenol 194 was achieved using benzyl bromide in acetone. Although significant levels (20-30%) of the dibenzyl ether 99 were observed, the reaction provided sufficient quantities of benzyl ether 99 for our studies and was therefore not fully optimised.

Scheme 2.11. Reagents and conditions: a) BBr$_3$, CH$_2$Cl$_2$, −78 °C, 2 h, 87%; b) BnBr, acetone, reflux, 24 h, 69% 195, 21% 99.
Compounds 167, 194 and 195 were now subjected to halogenation with NBS. Unfortunately, bromination of alkene 167 resulted in selective formation of the undesired bromide 196 (Scheme 2.12). Bromination of 194 resulted in the formation of a separable mixture of starting material, monobrominated and dibromo compounds. Once more, halogenation was selective for the undesired position. Finally, bromination of alkene 195 led to a three-component mixture of bromination products with no clear regiochemical preference as determined by analysis of the \(^1\)H NMR spectrum. Structural assignment of all halogenation adducts was achieved by analysis of the \(^1\)H and \(^{13}\)C NMR spectra. In particular, the regioselectivity of halogenation was deduced from the NOESY and HMBC correlations analogous to the assignment of halides 184-187 and 190, 192.

\[
\begin{align*}
167, P^1 = &\text{Me, } P^2 = \text{Bn} \\
194, P^1 = &\text{H, } P^2 = \text{H} \\
195, P^1 = &\text{H, } P^2 = \text{Bn} \\
196, P^1 = &\text{Me, } P^2 = \text{Bn} \\
197, P^1 = &\text{H, } P^2 = \text{H} \\
198, P^1 = &\text{H, } P^2 = \text{Bn} \\
199, P^1 = &\text{Me, } P^2 = \text{Bn} \\
200, P^1 = &\text{H, } P^2 = \text{H} \\
201, P^1 = &\text{H, } P^2 = \text{Bn}
\end{align*}
\]

\textbf{Scheme 2.12.} Reagents and conditions: a) NBS, CH\(_2\)Cl\(_2\), 0 \(^\circ\)C to rt, 20 h.

Although a complete survey of halogenation methods on each substrate was not conducted, these results indicated that selective halogenation at the C-6 position was likely to be difficult to achieve. A revised retrosynthetic strategy employing a simplified aryl halide coupling partner for the key sp\(^3\)-sp\(^2\) Suzuki cross-coupling was therefore developed.

\subsection{2.1.5 Summary of the Attempted Synthesis of Halides (±)-165 and (±)-166}

Selective protection and functionalisation of 2,4,6-tri hydroxybenzoic acid (169), followed by Stille cross-coupling with allyltributyltin and subsequent isomerisation installed the requisite carbon framework for phthalide formation (Scheme 2.13). Dihydroxylation of the double bond with concomitant lactonisation, followed by protection of the free alcohol provided halogenation precursors (±)-177 and (±)-178. Modulation of the protecting groups present in alkene 167 and phthalide (±)-177 provided access to a range of differentially protected alkenes: 167, 194 and 195, and phthalide (±)-189. Unfortunately, all attempts at halogenation either resulted in the exclusive
halogenation of the undesired C-4 position, or the formation of product mixtures in which the desired C-6 halide was not a major constituent.

Scheme 2.13. Reagents and conditions: a) BnBr, K2CO3, Nal, acetone, reflux, 3 h, 62%; b) DIAD, PPh3, MeOH, THF, rt, 2 h, 64%; c) PhNTf2, NEt3, CH2Cl2, reflux, 48 h, 96% d) AllylSnBu3, Pd(PPh3)4, LiCl, THF, reflux, 48 h; e) t-BuOK, THF, 40 °C, 24 h, 83% over two steps; f) OsO4, NMO, acetone/water (10:1), rt, 16 h, 90%; g) EOMCl, DIPEA, DMAP, CH2Cl2, rt, 48 h, quant.; h) TBSOTf, 2,6-lutidine, CH2Cl2, −78 °C, 4 h, quant.; i) NBS, CH2Cl2, 0 °C to rt, 20 h; j) I2, F3CCO2Ag, CH2Cl2, 0 °C to rt, 16 h.
2.2 Synthesis of Spiroketal Precursor 247 via Suzuki Cross-Coupling

2.2.1 Revised Retrosynthetic Strategy

In view of the difficulties encountered in constructing a fully substituted halo-phthalide coupling partner, our retrosynthetic strategy for virgatolide B (2) was modified (Scheme 2.14). In particular, we sought to preserve the rotational symmetry of the aromatic ring. This new strategy provides flexibility in the sequence of the final transformations to generate virgatolide B (2). Retrosynthetically, virgatolide B (2) could be derived either from deprotection/spirocyclisation of ketone 202 (Path A) or sequential dihydroxylation and carboalkoxylation of halo-spiroketal 203 (Path B).

Ketone 202 (Path A) would be available from halo-alkene 204 via dihydroxylation/carboalkoxylation. Halo-alkene 204 would in turn be accessed from aldol precursor 206 by meta-selective iridium-catalysed CH borylation and Suzuki cross-coupling to install the alkene side-chain, followed by halogenation of the aromatic ring.\textsuperscript{17,25,71,82}

The alkene side-chain present in halo-spiroketal 203 (Path B) would be installed by meta-borylation of spiroketal 205 and subsequent Suzuki cross-coupling.\textsuperscript{17,25,71,82} The halide substituent would then be introduced by ortho-directed halogenation of the aromatic ring. Spiroketal 205 would in turn be derived from aldol 206 by deprotection/cyclisation.

Common intermediate 206 would be constructed by a diastereoselective aldol reaction between methyl ketone 207 and aldehyde 111. Methyl ketone 207 would be assembled via sp\textsuperscript{3}-sp\textsuperscript{2} Suzuki cross-coupling of rotationally symmetric aryl halide 208/209 and trifluoroboratoamide 158.

The rotational symmetry of the aromatic nucleus ensures that either spiroketalisation or functionalisation of the aromatic ring is not required to be regioselective, depending on which transformation is conducted earlier in the synthesis. This delays the requirement for regioselective functionalisation until it can be governed by either ortho-directed electrophilic aromatic substitution or intramolecular hydrogen bonding interactions.
2.2.2 Synthesis of Trifluoroboratoamide 158

The key sp²-sp³ Suzuki cross-coupling required the preparation of trifluoroboratoamide 158, which was to be prepared by alkylation of readily available pseudoephedrine amide 149⁶⁴,⁸⁴ with iodomethylpinacolboronate (153), followed by conversion of boronate 154 to trifluoroboratoamide 158 (Scheme 2.15).⁸²

![Scheme 2.15](image)

**Scheme 2.15.** Intended synthesis of trifluoroboratoamide 158.⁸²

Access to gram quantities of iodomethylpinacolboronate (153) was required in order to prepare trifluoroboratoamide 158 on sufficient scale (Scheme 2.16). Initially iodide 153 was prepared via treatment of triisopropylborate (210) with pinacol, providing the corresponding boronate species 211.¹⁰¹,¹²⁴ Alkylation of boronate 211 with the lithiate of diiodomethane afforded iodide 153 in moderate yield.¹²⁴

![Scheme 2.16](image)

**Scheme 2.16.** Reagents and conditions: a) pinacol, 120 °C, 48 h, 75%; b) CH₂I₂, n-BuLi, −78 °C to rt, 16 h, 61%.

Although this method provided access to synthetically useful quantities of iodide 153, up to three purification steps were required: distillation of boronate 211 and purification of 153 by both flash chromatography and distillation under reduced pressure. It was found that reversal of the order of the two transformations as reported by Brown resulted in an operationally simpler procedure (Scheme 2.17).¹²⁵-¹²⁶ Alkylation of borate 210 afforded intermediate iodide species 212 in moderate yield following distillation under reduced pressure. Reaction of iodide 212 with pinacol in pentane, removal of excess pinacol by extraction of the pentane layer with water and concentration in vacuo provided iodide 153 in quantitative yield without the need for further purification.¹²⁶ Pleasingly,
the isolated yields of this simplified procedure were higher than those achieved using the previous method.

\[
\begin{align*}
B(O'Pr)_3 & \quad \text{a} \quad \rightarrow \quad B(O'Pr)OPr^+ \quad \text{b} \quad \rightarrow \quad B(O'Pr)OPr + I^- \\
210 & \quad \rightarrow \quad 212 & \quad \rightarrow \quad 153
\end{align*}
\]

Scheme 2.17. Reagents and conditions: a) CH\(_3\)I, n-BuLi, −78 °C to rt, 16 h, 55%; b) pinacol, n-pentane, rt, 16 h, quant.

With useful quantities of iodide 153 in hand, attention turned to the preparation of pseudoephedrine amide 149 (Scheme 2.18).\(^{64,84}\) Treatment of (R,R)-pseudoephedrine 213 with propionic anhydride and triethylamine in dichloromethane afforded amide 149 in 94% yield.\(^{64}\) Alkylation of amide 149 with iodide 153 was achieved using Molander’s procedure.\(^{82}\) Double deprotonation of amide 149 with lithium diisopropylamide in the presence of excess lithium chloride, followed by the addition of iodide 153 furnished boronate 154 in a pleasing 73% yield. Initially, it appeared that boronate 154 was unstable to silica gel: early attempts at purification failed to provide boronate 154 and yielded large quantities of pinacol indicating cleavage of the boronate ester. However, when higher grade silica was used for the chromatographic separation (Merck\(^\text{©}\), silica gel 60, 0.040-0.063mm) no decomposition was observed. Treatment of boronate 154 with potassium hydrogen fluoride in acetonitrile/water gave the desired potassium trifluoroboratoamide salt 158 in good yield. In agreement with the work of Molander, trifluoroboratoamide 158 could be stored for extended periods of time without appreciable decomposition and was stable to ambient moisture and oxygen.\(^{82}\)

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \quad \text{OH} \quad \text{a} \quad \rightarrow \quad \text{Ph} & \quad \text{O} \quad \text{OH} \quad \text{b} \quad \rightarrow \quad \text{Ph} & \quad \text{O} \quad \text{OH} & \quad \text{Bpin} & \quad \text{c} \quad \rightarrow \quad \text{Ph} & \quad \text{O} \quad \text{OH} & \quad \text{BF}_3K^+ \\
213 & \quad \rightarrow \quad 149 & \quad \rightarrow \quad 154 & \quad \rightarrow \quad 158
\end{align*}
\]

Scheme 2.18. Reagents and conditions: a) propionic anhydride, NEt\(_3\), CH\(_2\)Cl\(_2\), rt, 30 min, 94%; b) LDA, LiCl, THF, −78 °C to 0 °C then 153, 30 min, 73%; c) KHF\(_2\), MeCN/H\(_2\)O (1:1), 0 °C, 30 min, 77%. 

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2.2.3 The Suzuki Cross-Coupling Reaction

Attention now turned to the key cross-coupling of trifluoroboratoamide 158 and halides 208/209 to set up the key α-chiral β-aryl moiety (Scheme 2.19).

Scheme 2.19. Intended construction of amide 214.

The palladium-catalysed cross-coupling of an organohalide with an organoboron compound is known as the Suzuki reaction (Scheme 2.20). In addition to a catalytically active Pd(0) species, the reaction requires the presence of a stoichiometric base.\(^{127}\)

Scheme 2.20. The Suzuki cross-coupling reaction.\(^{127}\)

The seminal report by Suzuki et al. in 1979 described the union of alkenylboranes with either 1-alkenyl or 1-alkynyl bromides, providing the corresponding conjugated dienes in high yields (Scheme 2.21).\(^{127}\)

Scheme 2.21. Original report by Suzuki et al.\(^{127}\)
Following this work, the Suzuki cross-coupling reaction has become one of the most versatile and widely used reactions in organic synthesis, allowing the successful cross-coupling of a variety of organoboron compounds with a range of halide coupling partners.\textsuperscript{128-130} The organoboron species required for the reaction can be prepared by a variety of methods, including substitution of the corresponding organolithium or organomagnesium reagents, hydroboration of alkenes/alkynes or haloboration of terminal alkynes.\textsuperscript{130}

The mechanism of the Suzuki reaction has been extensively studied\textsuperscript{128,131-132} and conforms well to the general catalytic cycle for palladium-catalysed cross-coupling of organometallics and halides (or halide equivalents).\textsuperscript{130} A generalised cross-coupling mechanism is illustrated in Scheme 2.22. The catalytic cycle consists of three key processes: oxidative addition, transmetalation and reductive elimination.

\textbf{Scheme 2.22.} General catalytic cycle for the cross-coupling of organometallics and halides.\textsuperscript{130}

\textbf{A. Oxidative Addition}

Following generation of a coordinatively unsaturated palladium(0) species \textit{215} (either via ligand dissociation or \textit{in situ} catalyst generation), the first step in the catalytic cycle of the Suzuki reaction consists of oxidative addition of the organohalide to the active palladium species forming a thermodynamically stable \textit{trans}-\(\sigma\)-palladium(II) complex \textit{216}. The oxidative addition is often the rate-determining step in Suzuki-cross-coupling reactions.\textsuperscript{128,131}
B. Transmetalation

The details of the transmetallation step of the Suzuki cross-coupling have been studied recently by several groups with a key focus on the role of the base required by the reaction.\textsuperscript{131-133} The transmetallation process exhibits a strong dependence on the reaction conditions.\textsuperscript{133} Because of this, the precise mechanism of transmetalation has not yet been fully elucidated and is the subject of some debate (Scheme 2.23).\textsuperscript{131-133} The two most prominent mechanisms differ in the nature of the boron species which undergoes transmetallation: “ate” complex \textsuperscript{219} (Path A) or boronic acid \textsuperscript{218} (Path B).

\textbf{Scheme 2.23.} Proposed mechanisms for transmetallation in Suzuki cross-coupling reactions.\textsuperscript{133}

Following the discovery of the reaction, it was postulated that nucleophilic addition of a negatively charged base to the organoboron was required in order to activate the organoboron reagent towards transmetallation (Path A).\textsuperscript{130} This was proposed because although the boron atom in an organoboron compound is highly electrophilic, the attached organic group (i.e. \( R^1 \)) is only weakly nucleophilic in comparison with other organometallic reagents. Nucleophilic addition of a negatively charged base to the boronic acid species would generate the corresponding “ate” complex \textsuperscript{219}, thus increasing the electron density on the attached carbon atom, rendering it more nucleophilic and facilitating transmetallation. A recent study on the role of the base in Suzuki cross-couplings supports this mechanism.\textsuperscript{133}

In support of path B, it has been well documented that organopalladium halides (such as oxidative addition product \textsuperscript{216}) readily undergo nucleophilic displacement by hydroxy, alkoxy or acetoxy anions, providing the corresponding Pd-OR complexes \textsuperscript{220} (Scheme 2.24).\textsuperscript{134-136} These oxygenated palladium complexes have been observed to facilitate transmetallation of organoboron compounds.
under neutral (i.e. non-basic) conditions, providing an alternative process by which transmetallation can occur.

\[
\begin{align*}
&\text{Scheme 2.24. Formation of hydroxy palladium species 220 and transmetalation.} \\
&\text{A recent study of the base in Suzuki cross-couplings (supporting path B) has indicated that the base is involved in three key processes.}^{132}\text{ First, the base displaces the halide present in complex 216 generating the reactive hydroxy complex 220 (Scheme 2.25). This complex reacts directly with the organoboron coupling partner 218, undergoing a transmetalation process which is favoured due to the oxophilicity of boron.}^{132}\text{ Second, it was shown that although the presence of base did induce the production of the “ate” complex 219, this complex appeared unable to participate in transmetalation. High concentrations of base were therefore deemed to inhibit the reaction due to increased production of 219. Third, the base was unexpectedly discovered to increase the rate of reductive elimination (see following section).}
\end{align*}
\]

\[
\begin{align*}
&\text{Scheme 2.25. Proposed mechanism of base-induced transmetalation.}^{132}\text{ Due to these considerations, the exact nature of the reacting boron and palladium species in the transmetallation step of Suzuki cross-coupling reactions is an area of ongoing research.}^{133}
\end{align*}
\]
C. Reductive Elimination

As previously mentioned, it has been shown that the presence of base accelerates the rate of reductive elimination in Suzuki cross-coupling reactions. Normally, reductive elimination of complex 217 is understood to take place following a cis/trans isomerisation process facilitated by ligand dissociation/association (Scheme 2.26). Reductive elimination can then occur via the cis complex 221, producing coupled product and regenerating the catalytically active palladium species.

![Scheme 2.26. Isomerisation of 217 followed by reductive elimination.]

However, as noted earlier, the reductive elimination step is accelerated by the presence of base. This is rationalised by nucleophilic addition of the base to complex 217, producing a pentacoordinate, anionic palladium complex 222 in which R¹ and R² are close together in space. The increased proximity of R¹ and R² promotes the reductive elimination process thus rendering prior isomerisation unnecessary (Scheme 2.27).

![Scheme 2.27. Base-accelerated reductive elimination.]

D. Overall Mechanism

An overall mechanism for the Suzuki coupling can be represented by incorporating the details of these three steps (Scheme 2.28). This mechanism takes into account the three roles of the base whilst reserving judgement on the nature of the reacting species in the transmetallation step.


Scheme 2.28. Integrated mechanism of the Suzuki cross-coupling.\textsuperscript{132}

2.2.4 Suzuki Cross-Coupling of Trifluoroboratoamide 158 and Bromide 208

Prior to investigation of the key Suzuki cross-coupling reaction, it was acknowledged that the required aryl halide coupling partner 208/209 was both electron-rich and ortho-disubstituted. Both of these features were reported by Molander to result in decreased yields of coupled product.\textsuperscript{82} Noting that this work had been conducted exclusively on aryl and hetaryl chlorides, it was postulated that the decrease in yield observed when employing these substrates may be the result of inefficient oxidative addition of the aryl chlorides to the palladium catalyst. If so, then the use of more reactive aryl halides may improve the yields obtained with these types of coupling partners. Therefore, a series of four symmetric aryl halides was prepared: two bromides (224 and 208) and two iodides (225 and 209), a protected and unprotected variant of each (Scheme 2.29). Tri-bromination of resorcinol (223) followed by selective debromination afforded bromide 224 in
good yield,\textsuperscript{137} which was subsequently protected as the ethoxymethyl ether \textbf{208}. Similarly, regioselective iodination of \textbf{223} furnished the desired iodide \textbf{225} which was also protected, providing EOM ether \textbf{209} in high yield.\textsuperscript{138}

![Scheme 2.29](image)

\textbf{Scheme 2.29. Reagents and conditions:} a) \(\text{Br}_2\), CHCl\(_3\), reflux, 2 h, then Na\(_2\)SO\(_3\), NaOH, MeOH/H\(_2\)O (5:1), rt, 16 h, 93\%; b) EOMCl, DIPEA, CH\(_2\)Cl\(_2\), rt, 48 h, quant.; c) I\(_2\), NaHCO\(_3\), H\(_2\)O, 0 \(\circ\)C to rt, 3.5 h, 75\%; d) EOMCl, DIPEA, CH\(_2\)Cl\(_2\), rt, 16 h, 89\%.

With halides \textbf{208}, \textbf{209}, \textbf{224}, \textbf{225} and trifluoroboratoamide \textbf{158} in hand, attention turned to the Suzuki cross-coupling reaction (Table 2.2). Attempted cross-coupling of trifluoroboratoamide \textbf{158} with bromide \textbf{224} resulted in the formation of a by-product identified by NMR and HRMS analysis as protodeboronated amide \textbf{227} (Entry 1). Reaction of iodide \textbf{225} resulted in the formation of a complex mixture (Entry 2). Pleasingly, the use of protected aryl bromide \textbf{208} as the coupling partner resulted in a 60\% yield of coupled product \textbf{214} together with low levels (10-20\%) of oxidised amide \textbf{226}, also a product of cross-coupling (Entry 3). Amide \textbf{226} co-eluted with a catalyst-derived species and therefore could not be obtained in an analytically pure form, but was identified by a combination of NMR and HRMS analysis. Coupling of iodide \textbf{209} with \textbf{158} provided amide \textbf{214} in low yield together with appreciable quantities of recovered iodide \textbf{209} even after extended reaction times (Entry 4).
Table 2.2. Suzuki cross-coupling of trifluoroboratoamide 158.

Given the successful cross-coupling of trifluoroboratoamide 158 and bromide 208 we were interested in increasing the efficiency of the synthesis of trifluoroboratoamide 158. The possibility of converting boronate ester 154 into trifluoroborate 158 without prior purification by flash chromatography was therefore considered. It was proposed that following aqueous work-up of the alkylation reaction generating boronate 154, any organic impurities remaining would be removed during the precipitation of trifluoroborate salt 158 with diethyl ether. Unfortunately, although the spectral data of the sample of trifluoroboratoamide 158 thus prepared was identical with the literature, use of this material in Suzuki cross-coupling reactions was unsuccessful, presumably due to the presence of an unidentified impurity.

---

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halide&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time</th>
<th>Yield (%)</th>
<th>214</th>
<th>226</th>
<th>227</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>224, X=Br, P=H</td>
<td>3 h</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>225, X=I, P=H</td>
<td>19 h</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>208, X=Br, P=EOM</td>
<td>3 h</td>
<td>60</td>
<td>10-20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>209, X=I, P=EOM</td>
<td>22 h</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reagents and conditions: 158, RuPhos, K₂CO₃, toluene/H₂O, 85 °C
2.2.5 Synthesis of Aldol 247

Having achieved success in the key Suzuki cross-coupling reaction, elaboration of the carbon framework was now required. The carbon backbone was to be installed via aldol reaction of methyl ketone 207 and chiral aldehyde 111 (Scheme 2.30).

![Scheme 2.30](image)

**Scheme 2.30.** Intended synthesis of aldol 206.

A. Synthesis of Ketone 207

Replacement of the pseudoephedrine auxiliary in coupled product 214 with a methyl group was required to construct the methyl ketone for the aldol reaction. Pseudoephedrine amides can be cleaved directly by treatment with alkyllithium reagents in a manner similar to Weinreb amides (see Section 1.8.1). This represents a synthetic advantage over other auxiliaries such as oxazolidinones, which generally require conversion to the aldehyde, followed by addition of the desired organometallic reagent and oxidation of the resulting secondary alcohol. Addition of an organometallic reagent to a carboxylic acid derivative (such as an ester or amide) generates an anionic tetrahedral intermediate. In the absence of stabilising interactions this intermediate collapses, generating the corresponding ketone which can then act as an electrophile with a second equivalent of the organometallic reagent. Tertiary carboxamides facilitate direct cleavage upon treatment with organometallic reagents via the formation of a stabilised tetrahedral intermediate which only breaks down to generate the ketone upon work-up, thus preventing further nucleophilic addition. In a typical reaction of an alkyllithium with a pseudoephedrine amide, quenching of the reaction is conducted in two steps. First, diisopropylamine is added in order to scavenge excess lithium reagent and then a dilute solution of acetic acid in ether promotes decomposition of the tetrahedral intermediate, producing the desired ketone product.
Pleasingly, treatment of the coupled product 214 with methyl lithium generated the corresponding methyl ketone 207 in good yield (Scheme 2.31).

Scheme 2.31. Reagents and conditions: a) MeLi, Et₂O, −78 °C to 0 °C, 30 min then DIPA, AcOH, 80%.

B. Synthesis of Aldehydes 233, 234 and 82

Having successfully synthesised α-chiral β-methyl ketone 207, the aldehyde coupling partner for the aldol reaction was required (Scheme 2.32). We sought to prepare aldehydes with a range of different protecting groups in order to investigate the effect of the steric bulk of the protecting group on the diastereoselectivity of the reaction. Kinetic resolution of racemic ethyl hydroxybutyrate (±)-228 using Candida antarctica Lipase B (CAL-B, Novozym-435) proceeded smoothly, giving ethyl (S)-3-hydroxybutyrate (S)-228 in high yield and enantioselectivity. The optical rotation compared well with the literature value for enantiomerically enriched material ([α]_D^{25} +41.7 (c 0.36 in CHCl₃), lit. +42, (c 1.0 in CHCl₃), e.e. = 95%). A series of protected derivatives 230-232 was then prepared, varying the protecting group. Esters 230-232 were then converted to the respective aldehydes via reduction with disobutylaluminium hydride in dichloromethane, furnishing compounds 233, 234 and 82 in good yields.

Scheme 2.32. Reagents and conditions: a) isopropenyl acetate, CAL-B, rt, 24 h, 46% (S)-228; b) EOMCI, DIPEA, 0 °C to rt, 16 h, 92%; c) BOMCI, DIPEA, 0 °C to rt, 24 h, 98%; d) TBSCI, imidazole, 0 °C to rt, 24 h, 95%; e) DIBAL-H, CH₂Cl₂, −78 °C, 1 h, 84% 233, 96% 234, 75% 82.
C. Aldol Reaction of Methyl Ketone 207 with Aldehydes 233, 234 and 82

Given that the Paterson aldol reaction had previously proven successful with similar substrates within our group (Section 1.5.1), an investigation into this methodology on the current system was conducted. The use of EOM-protected aldehyde 233 provided the desired aldol adduct 235 in good yield (Scheme 2.33). However, aldol 235 could not be fully characterised due to the presence of inseparable isopinocampheol produced by hydrolysis of the diisopinocampheylboron chloride employed in the reaction. For this reason aldol 235 was protected as the TBS ether 236, enabling separation of the by-product and characterisation of TBS ether 236. The diastereoselectivity of the reaction could not be precisely quantified by $^1$H NMR spectra due to the overlap of resonances resulting from the two diastereomers. However, inspection of the $^{13}$C NMR data clearly revealed the presence of two diastereomers in a ratio of approximately 2:1 (Figure 2.1). The carbonyl resonance at approximately 212 ppm was particularly diagnostic for the presence of diastereomers, showing clear signal separation between the resonances derived from each isomer.

![Scheme 2.33](image)

**Scheme 2.33.** Reagents and conditions: a) (+)-Ipc$_2$-BCl, NEt$_3$, −78 °C to 0 °C, 1 h then 233, −78 °C to 0 °C, 3 h; b) TBSCI, imidazole, DMF, rt, 16 h, 55% over two steps, d.r. = 2:1.
Figure 2.1. $^{13}$C NMR spectrum of aldol 236 revealing the presence of two diastereomers.
It was proposed that the poor stereoselectivity observed when using aldehyde 233 may be due to the lack of steric bulk afforded by the ethoxymethyl group, leading to a lack of facial differentiation in the transition state. However, use of more hindered aldehydes 234 and 82 showed no improvement in facial selectivity. The use of BOM-protected aldehyde 234 provided no diastereoselectivity, producing aldol adduct 237 in a 1:1 diastereomeric ratio and moderate yield (Scheme 2.34). Once more, the diastereoselectivity of the reaction was determined by inspection of the $^{13}$C NMR data.

\[ \text{BOMO} \quad \overset{234}{\text{H}} \quad + \quad \overset{O}{\text{EOM}} \quad \overset{207}{\text{O}} \quad \overset{\text{a}}{\text{OH}} \quad \text{BOMO} \quad \overset{237}{\text{EOM}} \]

**Scheme 2.34. Reagents and conditions:** a) (+)-(Ipc)$_2$-BCl, NEt$_3$, $-78 \, ^\circ\text{C}$ to 0 $^\circ\text{C}$, 1 h then $-78 \, ^\circ\text{C}$ to $-20 \, ^\circ\text{C}$, 16 h, 60%, d.r. = 1:1.

Interestingly, when TBS-protected aldehyde 82 was employed, aldol 238 was produced as a single diastereomer, albeit in poor yield (~30%). Additionally, TLC analysis revealed the formation of a new product during the work-up procedure. Analysis of the $^1$H NMR spectrum of this compound indicated that it was alkene 239, generated by the elimination of aldol adduct 238. In an effort to suppress this degradation, the reaction was repeated and quenched with pH 7 buffer solution. Pleasingly, this procedure resulted in an improved 60% yield of aldol 238, whilst elimination product 239 was not observed (Scheme 2.35). However, NMR analysis revealed that the product 238 was not diastereomerically pure as had previously been observed. Instead, a 1:1 mixture of isomers was obtained. This was rationalised by preferential elimination of one diastereomer under unbuffered aqueous work-up, leading to a 30% yield of diastereomerically pure 238, contrasted with a two-fold higher yield of a diastereomeric mixture of aldol 238 when elimination was suppressed by the use of buffer solution.

\[ \text{TBSO} \quad \overset{82}{\text{H}} \quad + \quad \overset{O}{\text{EOM}} \quad \overset{207}{\text{OEOM}} \quad \overset{\text{a}}{\text{OH}} \quad \text{TBSO} \quad \overset{238}{\text{EOM}} \quad \overset{239}{\text{EOM}} \]

**Scheme 2.35. Reagents and conditions:** a) (+)-(Ipc)$_2$-BCl, NEt$_3$, $-78 \, ^\circ\text{C}$ to 0 $^\circ\text{C}$, 1 h then $-78 \, ^\circ\text{C}$ to $-50 \, ^\circ\text{C}$, 16 h, 60%, d.r. = 1:1.
D. Synthesis of Aldol 247

Realising that modification of the protecting groups on the aldehyde was unlikely to significantly improve the diastereoselectivity of the aldol reaction, an alternative method was sought. In particular, the 1,3-anti selective Mukaiyama aldol reaction studied by Reetz and Evans appeared promising (Table 2.3, also see discussion in Section 1.7.2).\textsuperscript{79-81} The stereochemistry required by virgatolide B (2) is consistent with the selectivity exhibited by this reaction. Studies of this reaction have shown that the highest levels of 1,3-anti diastereoselectivity are achieved when the alcohol functionality on aldehyde 241 is protected with a para-methoxybenzyl (PMB) group.

![Mukaiyama aldol reaction](attachment:image)

\[ \text{OTMS} + \text{H}X \xrightarrow{\text{BF}_3\text{OEt}_2} \text{R}^1\text{R}^2 + \text{R}^3\text{R}^4 \]

<table>
<thead>
<tr>
<th>X</th>
<th>Yield (%)</th>
<th>242:243</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPMB</td>
<td>87</td>
<td>81:19</td>
</tr>
<tr>
<td>OTBS</td>
<td>90</td>
<td>73:27</td>
</tr>
<tr>
<td>OAc</td>
<td>79</td>
<td>43:57</td>
</tr>
<tr>
<td>Cl</td>
<td>84</td>
<td>83:17</td>
</tr>
</tbody>
</table>

Table 2.3. Effect of β-substituent in Mukaiyama aldol reactions.\textsuperscript{81}

Motivated by this precedent, PMB-protected aldehyde 245 was prepared from ethyl (S)-hydroxybutyrate (228) in two steps (Scheme 2.36). Treatment of (S)-228 with PMB-trichloroacetimidate and catalytic camphorsulfonic acid in dichloromethane furnished protected ester 244.\textsuperscript{69} Separation of ester 244 from a PMB-derived side-product proved difficult. Ester 244 was therefore not fully characterised but instead employed directly in the next reaction. Reduction of ester 244 with disobutylaluminium hydride provided the desired aldehyde 245\textsuperscript{70} in a satisfying 83% yield over two steps and enabled removal of the contaminant by flash chromatography.
Scheme 2.36. Reagents and conditions: a) PMB-trichloroacetimidate, CSA, CH₂Cl₂, rt, 24 h; b) DIBAL-H, CH₂Cl₂, −78 °C, 2.5 h, 83% over two steps.

Attention now turned to the Mukaiyama aldol reaction (Scheme 2.37). It was found that regioselective formation of silyl enol ether 246 from methyl ketone 207 could be effected by treatment with trimethylsilyl triflate using triethylamine as the base. Although stable to aqueous work-up, silyl enol ether 246 was not chromatographically purified prior to use in the Mukaiyama aldol reaction. Formation of the silyl enol ether was monitored by TLC and the crude product analysed by 1H NMR to confirm complete consumption of starting material. Traces of water were removed by azeotropic distillation with toluene. Next, a solution of aldehyde 245 in dichloromethane was pre-complexed with boron trifluoride diethyl etherate at −78 °C for two minutes, followed by addition of a solution of silyl enol ether 246 in dichloromethane. TLC analysis indicated that decomposition occurred upon warming of the reaction mixture. The reaction mixture was therefore maintained at −78 °C for 90 minutes and then quenched with saturated aqueous sodium bicarbonate at this temperature, providing aldol 247 in 82% yield over two steps as a single diastereomer by 1H and 13C NMR. The configuration of the newly generated stereocentre was not conclusively determined as it was expected that formation of the spiroketal core would facilitate assignment of the new chiral centre via NOESY analysis. However, based on considerable literature precedent, it was tentatively assumed that aldol 247 possessed the 1,3-anti configuration as shown in Scheme 2.37.79-81,142

Scheme 2.37. Reagents and conditions: a) TMSOTf, NEt₃, CH₂Cl₂, 0 °C, 30 min; b) 245, BF₃·OEt₂, CH₂Cl₂, −78 °C, 2 min then 246, 1.5 h, 82% over two steps.
2.2.6 Attempted Spiroketalisation of Aldol 247

With the carbon framework required for the spiroketal core of virgatolide B (2) in place, removal of the EOM and PMB protecting groups prior to spiroketalisation was investigated. It was noted that the aldol functionality in 247 may be prone to elimination under the acidic conditions required to remove the EOM protecting groups. It was therefore decided to remove the PMB protecting group first, allowing formation of the monocyclic acetal, hopefully minimising the propensity for acid-catalysed elimination. Attempted removal of the PMB group by oxidation with DDQ\textsuperscript{143} resulted in the formation of complex mixtures. Instead, cleavage of the PMB ether was achieved by hydrogenolysis in methanol, utilising palladium(II) hydroxide as catalyst (Scheme 2.38).\textsuperscript{142} Upon deprotection, cyclisation of the liberated alcohol functionality onto the carbonyl group resulted in the formation of methoxy acetal 248. Analysis of the $^1$H NMR spectrum indicated that acetal 248 was generated as a 3:1 mixture of epimers at the anomeric carbon. A conclusive assignment of the configuration at the anomeric centre was not secured since the spiroketalisation step requires rehybridisation of the anomeric centre. The stereochemical configuration of acetal 248 therefore does not determine the configuration of the spiroketal product.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme238.png}
\caption{Reagents and conditions: a) H$_2$, Pd(OH)$_2$/C, MeOH, rt, 1 h, 90\%.

Methoxy acetal 248 was not purified by column chromatography in order to avoid decomposition of the sensitive acetal functionality. Filtration of the reaction mixture through Celite\textsuperscript{®} followed by removal of the volatiles \textit{in vacuo} provided acetal 248 in high purity without the need for further purification. Although not conclusively determined, the stereochemistry at the epimeric centre of the major isomer was provisionally assigned as S, corresponding to the thermodynamically stabilised diastereomer, in which the methoxy group adopts an axial position due to the anomeric effect (Figure 2.2).}
All that remained in order to achieve spiroketalisation was deprotection of the phenolic EOM groups. Ethoxymethyl ethers are known to be labile under similar reaction conditions as methoxymethyl (MOM) ethers, in particular Brønsted and Lewis acidic reagents.\textsuperscript{144} A survey of acidic deprotection conditions was therefore undertaken in order to elucidate optimal reaction conditions that would result in the formation of spiroketal 249 (Table 2.4).

The use of sodium bisulfate on silica\textsuperscript{145} is known to be a relatively mild method for the deprotection of EOM and MOM ethers and has previously proven successful in our group.\textsuperscript{42,146} Unfortunately, application of these conditions to acetal 248 resulted in the formation of a complex mixture as assessed by both TLC and NMR (Entry 1). The presence of olefinic peaks in the $^1$H NMR spectrum ($\delta$ 6.17-6.12 and 5.73-5.70 ppm) indicated partial elimination of the hydroxyl group. Another comparatively benign deprotection procedure known to our group\textsuperscript{147} was the use of catalytic pyridinium para-toluenesulfonate in tert-butanol under reflux.\textsuperscript{148} However, exposure of acetal 248 to these conditions led to the formation of a complex mixture, unidentifiable by NMR (Entry 2). Although complete removal of the EOM groups was demonstrated by this protocol, the complexity of the product mixture meant that the formation of spiroketal 248 could not be proven. These conditions were also attempted at a lower temperature, yielding similar results (Entry 3). Treatment of acetal 248 with 1 M aqueous hydrochloric acid in either tetrahydrofuran or methanol (Entries 4 and 5) also effected cleavage of the EOM groups, but NMR analysis gave no clear indication of product formation. The use of camphorsulfonic acid in dichloromethane resulted in elimination of the alcohol functionality within several minutes (Entry 6). NMR analysis of the crude product mixture formed upon treatment with Amberlyst$^\text{®}$-15 in methanol indicated the exchange of the hydroxyl functionality with a methoxy group, presumably via elimination followed by addition of methanol (Entry 7).\textsuperscript{144} Finally, the use of bismuth triflate in tetrahydrofuran/water mixtures has been reported as a mild method for the deprotection of MOM ethers.\textsuperscript{149} Unfortunately, application of this method to the deprotection of acetal 248 once more resulted in the generation of a complex.
product mixture (Entry 8). $^1$H NMR analysis of a repeat experiment employing anhydrous tetrahydrofuran revealed significant levels of elimination products (Entry 9).

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na$_2$SO$_4$·SiO$_2$, CH$_2$Cl$_2$, rt, 2.5 h</td>
<td>Elimination</td>
</tr>
<tr>
<td>2</td>
<td>PPTS, $t$-BuOH, reflux, 2.5 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>PPTS, $t$-BuOH, 30 °C, 2.5 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>1M HCl/THF (1:1), rt, 48 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>1M HCl/MeOH (1:1), rt, 48 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>CSA, CH$_2$Cl$_2$, rt, 5 min</td>
<td>Elimination</td>
</tr>
<tr>
<td>7</td>
<td>Amberlyst, MeOH, rt to 30 °C, 6 h</td>
<td>Elimination, addition</td>
</tr>
<tr>
<td>8</td>
<td>Bi(OTf)$_3$, THF/H$_2$O (1:1), rt to 40 °C, 48 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>9</td>
<td>Bi(OTf)$_3$, THF, rt to 40 °C, 48 h</td>
<td>Elimination</td>
</tr>
</tbody>
</table>

Table 2.4. Unsuccessful removal of EOM protecting groups.

Olefinic resonances could only be observed in the $^1$H NMR spectra of product mixtures generated by acid-catalysed deprotection in non-nucleophilic solvents. It therefore appeared probable that in all cases elimination was occurring, but was not directly observable when nucleophilic solvents capable of interacting with a newly formed double bond were present. In an attempt to overcome this problem, methoxy acetal 248 was protected as triisopropylsilyl (TIPS) ether 250 in the hope that this would suppress elimination and lead to cleaner product distributions (Scheme 2.39). The TIPS group was chosen as it is known to exhibit greater stability toward acid-catalysed hydrolysis than the tert-butyldimethylsilyl group.\textsuperscript{144}
Scheme 2.39. Reagents and conditions: TIPSOTf, 2,6-lutidine, CH$_2$Cl$_2$, $-78^\circ$C, 40 min, 75%.

A selection of conditions for the deprotection of acetal 250 was investigated (Table 2.5). The use of PPTS in tert-butanol at reflux resulted in removal of the EOM groups and loss of the TIPS group with accompanying elimination (Entry 1). The same reaction conditions at room temperature revealed that the rate of cleavage of the TIPS group was faster than the rate of EOM deprotection (Entry 2). Interestingly, treatment with Amberlyst-15$^\circledR$ in methanol gave a crude product mixture with an identical NMR spectrum to that produced upon exposure of the unprotected methoxy acetal 248 to the same reaction conditions. It was clear that acid-catalysed elimination had occurred, followed by conversion to the corresponding methoxy compound (Entry 3). Treatment of a solution of acetal 250 in tetrahydrofuran with three drops of 1 M aqueous hydrochloric acid resulted in the total loss of the TIPS group prior to EOM deprotection (Entry 4). Finally, the use of catalytic para-toluenesulfonic acid in ethanol resulted in the formation of a complex mixture (Entry 5).
Discussion

Table 2.5. Unsuccessful removal of EOM protecting groups.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPTS, t-BuOH, reflux, 4 h</td>
<td>Silyl deprotection, elimination</td>
</tr>
<tr>
<td>2</td>
<td>PPTS, t-BuOH, 30 °C, 2.5 h</td>
<td>Silyl deprotection</td>
</tr>
<tr>
<td>3</td>
<td>Amberlyst, MeOH, rt, 24 h</td>
<td>Silyl deprotection, elimination, addition</td>
</tr>
<tr>
<td>4</td>
<td>1M HCl/THF (1:1), rt, 96 h</td>
<td>Silyl deprotection</td>
</tr>
<tr>
<td>5</td>
<td>PTSA·H₂O, EtOH, rt, 24 h</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Although we had originally hypothesised that elimination of the free alcohol might be suppressed by conversion of the carbonyl group to a monocyclic acetal, it had become clear that acetals 248 and 250 were highly prone to elimination. This can be understood by noting that under acidic conditions, acetals are known to equilibrate with their open-chain forms via oxonium ion intermediates (Figure 2.3).

![Equilibration of acetals under protic conditions.](image)

Figure 2.3. Equilibration of acetals under protic conditions.

Deprotonation of either an oxonium ion intermediate generated from acetal 248 under acidic conditions or the completely open keto form would thus lead to elimination products, consistent
with our experimental observations. A proposed mechanism for the deprotonation of an oxonium ion intermediate is illustrated in Scheme 2.40.

![Scheme 2.40. Proposed elimination pathway of \( \text{248} \) under acidic conditions.](image)

Realising that masking the ketone as an acetal may not reduce the tendency of the \( \beta \)-hydroxy group to undergo elimination, the deprotection sequence of the PMB and EOM groups was reversed. Attempts were made to remove the two EOM groups in aldol product \( \text{247} \) first. Unfortunately, the use of sodium hydrogen sulfate on silica, pyridinium \( \text{para} \)-toluenesulfonate and dilute aqueous acid all resulted in the formation of complex mixtures (Scheme 2.41).

![Scheme 2.41. Unsuccessful deprotection of aldol \( \text{247} \).](image)

The problems encountered in the deprotection of compounds \( \text{247} \), \( \text{248} \) and \( \text{250} \) mirrored those reported earlier by our group during the development of the first total synthesis of paecilospirone (\( \text{68} \), see Section 1.4.1).\(^{58}\) In this work, removal of the MOM groups from spiroketal precursor \( \text{256} \)...
was accompanied by significant β-elimination, generating undesired spiroketalts 257 and 258 (Scheme 2.42). Interestingly, elimination of the β-oxygenated substituent is believed to occur after the spiroketalisation event.\textsuperscript{19} Unable to overcome the propensity of this system to undergo elimination under acidic conditions, the total synthesis of paecilospirone (68) was ultimately accomplished using a pH-neutral double deallylation/spirocyclisation strategy. Acknowledging this precedent, and realising that a change of protecting groups could provide an expedient solution to this problem, it was decided that revision of the synthetic strategy was in order. Although it is conceivable that modification of the protecting group used on the β-oxygen could provide access to spiroketal 249 from precursor 248, such a procedure would add 1-2 steps to the overall sequence and decrease the efficiency of our synthesis of virgatolide B (2).

Scheme 2.42. Unsuccessful acid-mediated deprotection \textit{en route} to paecilospirone (68).\textsuperscript{58}

2.2.7 Summary of the Attempted Synthesis of Spiroketal 249

The synthesis of spirocyclisation precursors 247, 248 and 250 relied on a key sp\textsuperscript{2}-sp\textsuperscript{3} Suzuki cross-coupling of trifluoroboratoamide 158 and bromide 208 (Scheme 2.43). Bromide 208 was accessed from commercially available resorcinol (223) whilst trifluoroboratoamide 158 was constructed using the asymmetric alkylation approach described in the literature.\textsuperscript{82} The key sp\textsuperscript{2}-sp\textsuperscript{3} Suzuki cross-coupling of chiral trifluoroboratoamide 158 and rotationally symmetric aryl bromide 208 provided access to the challenging α-chiral β-arylated carbonyl motif present in virgatolide B (2). Treatment with methyllithium afforded the key aldol reaction precursor 207. Substrate-controlled Mukaiyama aldol reaction of methyl ketone 207 and aldehyde 245 proceeded smoothly, providing excellent yields and diastereoselectivity. Unfortunately, treatment of spiroketal precursors 247, 248, and 250 with any acid capable of effecting removal of the EOM protecting groups resulted in degradation of the starting material.
Scheme 2.43. Reagents and conditions: a) 149, LDA, LiCl, THF, −78 °C to 0 °C then 153, 30 min, 73%; b) KHF₂, MeCN/H₂O (1:1), 0 °C, 30 min, 77%; c) Pd(OAc)₂, RuPhos, K₂CO₃, toluene/H₂O (4:1), 85 °C, 3 h, 60%; d) MeLi, Et₂O, −78 °C to 0 °C, 30 min then DIPA, AcOH, 80%; e) TMSOTf, NEt₃, CH₂Cl₂, 0 °C, 30 min; f) 245, BF₃·OEt₂, CH₂Cl₂, −78 °C, 2 min then 246, 1.5 h, 82% over two steps.
2.3 Attempted Synthesis of Virgatolide B (2) via a pH-neutral Deprotection Approach

2.3.1 Revised Protecting Group Strategy

Our original approach to virgatolide B (2) was based upon an acid-catalysed deprotection/spirocyclisation strategy. Although spiroketalisation precursors 247 and 248 were readily accessible, all attempts at removal of the EOM groups were unsuccessful, resulting in the formation of complex mixtures in almost all cases. Rather than exploring different protecting groups on the β-oxygen as a means of suppressing degradation, we instead opted to change the phenolic protecting groups so that acid-mediated deprotection was no longer required. This led us to a revised synthetic strategy for virgatolide B (2).

Retrosynthetically, virgatolide B (2) would be derived from aldol 259 following spiroketalisation and phthalide formation via dihydroxylation/carbonylation (Scheme 2.44). Importantly, the order in which the spiroketal and phthalide structures are constructed remains flexible in this strategy, enabling late stage adaptation. Aldol 259 would be constructed using the Mukaiyama aldol reaction employed for aldol 247. Methyl ketone 260 would be assembled via Suzuki coupling of trifluoroboratoamide 158 and revised aryl bromide coupling partner 261. Bromide 261 was to be derived from aldehyde 262 via Wittig reaction with ethyltriphenylphosphonium iodide. Aldehyde 262 would be accessible from commercially available 3,5-dihydroxybenzoic acid 263 via bromination, global BOM protection and subsequent manipulation of the oxidation state at the benzylic position.

The revised synthetic strategy incorporates two key changes to the aryl bromide coupling partner 261, the use of benzyloxymethyl (BOM) protecting groups and the presence of an E-alkene side chain. BOM was chosen as the desired protecting group because it possesses similar electronic properties to EOM and would provide a comparable local steric environment. Based on these considerations, we predicted that BOM groups were likely to be tolerated in the key Suzuki cross-coupling reaction. BOM ethers are able to be cleaved via hydrogenolysis and thus the problems associated with acid-mediated cleavage would be obviated. It was envisioned that incorporation of the alkene side-chain prior to the Suzuki coupling would increase the simplicity and convergence of the synthesis.
Still key to this strategy was the preservation of the rotational symmetry of the aryl halide coupling partner. The rotational symmetry of the aromatic nucleus ensures that either spiroketalisation or functionalisation of the aromatic ring is not required to be regioselective, depending on which transformation is conducted first (see Section 1.6).

Scheme 2.44. Revised retrosynthetic analysis of virgatolide B (2).

2.3.2 Synthesis of Aldehyde 262

The synthesis of aldehyde 262 began with halogenation of 3,5-dihydroxybenzoic acid (263, Scheme 2.45). Treatment with bromine in 20% aqueous hydrochloric acid according to the literature procedure afforded bromide 264 in a pleasing 99% yield.\textsuperscript{150} Next, triple BOM protection was achieved by treatment with BOMCl and diisopropylethylamine as the base, furnishing BOM ester 265 in high yield.\textsuperscript{151} It was hoped that reduction with diisobutylaluminium hydride (DIBAL-H) would provide direct access to aldehyde 262. However, despite maintaining the reaction temperature at $-78 \, ^\circ\text{C}$ and quenching the reaction at the same temperature, significant quantities (>50%) of benzylic alcohol 266 were produced. As a result, a two-step reduction/oxidation sequence was adopted. The number of equivalents of DIBAL-H was increased in order to provide 266 as the sole product of the reaction in an excellent 95% yield. Originally, oxidation of alcohol 266 to aldehyde 262 was achieved using pyridinium chlorochromate (PCC) in dichloromethane. However, an alternative was sought due to the toxicity of PCC and the cumbersome work-up procedure required. The operationally simple Parikh-Doering oxidation proved a far more reasonable method.\textsuperscript{152} Reaction of alcohol 266 with dimethylsulfoxide, sulfur...
troide-pyridine complex and diisopropylethylamine generated desired aldehyde 262 in quantitative yield with a pleasing fifteen minute reaction time followed by a simple work-up procedure.

Scheme 2.45. Reagents and conditions: a) Br₂, 20% aq. HCl, reflux, 2 h, 99%; b) BOMCl, DIPEA, CH₂Cl₂, rt, 16 h, 87%; c) DIBAL-H, CH₂Cl₂, −78 °C to 0 °C, 20 min, 95%; d) SO₃·Py, DIPEA, DMSO, 0 °C, 15 min, quant.

2.3.3 Wittig Olefination of Aldehyde 262

Despite the documented preference for Wittig reactions of unstabilised ylids to generate the kinetically favoured Z-alkene products,¹⁵³⁻¹⁵⁵ we investigated the Wittig reaction as a means of installing the E-alkene side-chain present in aryl bromide 261 (Scheme 2.46). Although the reaction proceeded cleanly, providing alkene (E/Z)-261 in quantitative yield, the stereoselectivity of the olefination was moderate, furnishing an inseparable 3:1 mixture of E/Z-stereoisomers. The major isomer (E)-261 and minor isomer (Z)-261 were assigned based on the magnitudes of the coupling constants of the olefinic proton resonances using the Karplus relation.¹⁵⁶⁻¹⁵⁷ Isomer (E)-261 exhibited olefinic resonances with a coupling constant of 15.6 Hz whilst isomer (Z)-261 displayed a lower value of 11.6 Hz. Since the geometry of the double bond would be a key factor in the stereochemical outcome of the Sharpless asymmetric dihydroxylation to install the chiral centres present in the phthalide subunit of virgatolide B (2), the possibility of isomerisation of the undesired Z-isomer was investigated.
Scheme 2.46. Reagents and conditions: a) EtPPh₃I, KO'Bu, 18-crown-6, CH₂Cl₂, rt, 89%; b) double bond isomerisation.
2.3.4 Ruthenium-Catalysed Isomerisation

Ruthenium hydride complexes are known to catalyse the isomerisation of oleins. A catalyst often used for this purpose is carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) (267). The catalyst can either mediate a simple \( E/Z \) isomerisation or can alter the location of the double bond. Thermodynamically favoured products are often, but not exclusively obtained. The mechanism of the isomerisation involves hydroruthenation of the double bond, followed by \( \beta \)-hydride elimination (Scheme 2.47). As the elimination product itself can interact with the catalyst, this catalytic system can be used to establish an equilibrium favouring the formation of the most thermodynamically stable olefin isomer.

\[ \text{Scheme 2.47. Ruthenium-catalysed double bond isomerisation.} \]

An illustrative example of the use of complex 267 for the isomerisation of \( E/Z \) mixtures is given by the isomerisation of \((E/Z)-1\)-phenylbut-1-ene (268) (Scheme 2.48). Treatment of alkene \((E/Z)-268\) with complex 267 (3 mol%) in refluxing tetrahydrofuran for 45 minutes resulted in a product distribution consisting of 88\% \((E)-268\), together with 4\% \((Z)-268\). The remaining constituents of the product mixture were isomeric alkenes \((E)-269\) and \((Z)-269\).

\[ \text{Scheme 2.48. Reagents and conditions: a) Ru(CO)ClH(PPh\(_3\))\(_3\), THF, reflux, 45 min, 88\%.} \]

This methodology has also been employed by our group during the total synthesis of palmyrolide A (272). In this work, the final transformation required was migration of the double bond in...
alkene 271 (Scheme 2.49). Treatment of alkene 271 with catalyst 267 in refluxing toluene for 24 hours provided palmyrolide A (272) as a single regioisomer.

Scheme 2.49. Reagents and conditions: a) Grubbs-II, CH$_2$Cl$_2$, 60 °C, 48 h; b) Ru(CO)ClH(PPh$_3$)$_3$, toluene, reflux, 24 h, 64% over two steps.\textsuperscript{162}

Given the success in the case of palmyrolide A (272) and the relatively innocuous reaction conditions offered by this catalytic system, the isomerisation of \((E/Z)-261\) in was attempted. \((E/Z)-261\) was exposed to complex 267 in refluxing toluene for 24 hours. Because isomers \((E)-261\) and \((Z)-261\) were indistinguishable by TLC, aliquots of the reaction mixture were concentrated \textit{in vacuo} and then analysed by $^1$H NMR spectroscopy in order to monitor the progress of the isomerisation. Pleasingly, this method proved successful, effecting almost total conversion (\~95\%) to the thermodynamically favoured isomer \((E)-261\), which lacks the unfavourable steric interactions between the alkene substituents present in \((Z)-261\) (Scheme 2.50).

Scheme 2.50. Reagents and conditions: a) Ru(CO)ClH(PPh$_3$)$_3$, toluene, reflux, 24 h, 90%.

The diagnostic resonances in the $^1$H NMR spectrum allowing assessment of the extent of isomerisation were those arising from the olefinic protons and the chemically equivalent protons on the aromatic core. Figure 2.4 shows the $^1$H NMR spectrum of isomeric \((E/Z)-261\) compared to that of the isomerically enriched product \((E)-261\). It should be noted that the multiplet centred at $\delta$ 6.25 ppm contains contributions from both olefinic protons of the major isomer \((E)-261\) and one of the olefinic resonances from the minor isomer \((Z)-261\).
Figure 2.4. $^1$H NMR spectra indicating isomerisation of alkene 261.
2.3.5  Suzuki Coupling with Bromide 261

Having successfully prepared BOM-protected bromide 261, attention turned once more to the key Suzuki cross-coupling. It was hoped that the properties of the BOM group would be similar to that of EOM, allowing us to retain our successful cross-coupling protocol. Gratifyingly, cross-coupling of trifluoroboratoamide 158 and bromide 261 proceeded smoothly under identical conditions to those utilised previously (Scheme 2.51, also see Section 2.2.4). Once more, mass spectrometry indicated the presence of the oxidised side-product 275 present in low quantities (~10%). Also isolable from the reaction mixture was arene 274, the product of protodehalogenation of bromide 261. Arene 274 was indistinguishable from bromide 261 by TLC analysis.

Scheme 2.51.  Reagents and conditions: a) Pd(OAc)$_2$, RuPhos, K$_2$CO$_3$, toluene/H$_2$O (4:1), 85 °C, 1.5 h, 55% 273, ~10% 275.

Although this transformation was successful and capable of providing sufficient quantities of coupled product 273 to continue the synthesis of aldol 259, we were interested in investigating the formation of oxidised side-product 275. The effect of changing the reaction temperature was therefore examined. As noted in Section 2.2.3, the oxidative addition process is commonly the rate-limiting step in Suzuki cross-coupling reactions. Therefore, since this work employs an aryl bromide rather than the less reactive aryl chlorides used in the work of Molander, we hypothesised that successful cross-coupling may be possible at lower temperatures. In addition, if the pathways leading to the formation of side-products 274 and 275 require greater activation
energy than the cross-coupling reaction itself, lowering the reaction temperature might allow suppression of their formation.

Interestingly, cross-coupling of trifluoroboratoamide 158 and bromide 261 did proceed at 55 °C, albeit more slowly. Work-up of the reaction after four hours provided a 22% yield of coupled product 273 together with unreacted bromide 261 (Table 2.6, Entry 1). Pleasingly, the formation of oxidised side-product 275 was not observed by TLC. Extension of the reaction time at this temperature did not result in an appreciable increase in conversion (Entry 2). After 21 hours, the starting material had not been consumed and no further reaction took place upon increased heating to 85°C for three hours. The reaction was therefore stopped, providing amide 273 in 40% yield. Increasing the initial temperature to 65°C provided a 41% yield of coupled product together with recovered bromide 261 after 3 hours (Entry 3). Extension of the reaction time at 65°C led to the production of oxidised product 275 (Entry 4). Under these conditions, coupled product 273 was obtained in 55% yield and uncoupled bromide 261 was isolated as a 2.7:1 mixture with arene 274.

![Chemical structure](image)

**Table 2.6.** Variation of reaction time and temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>273:275</th>
<th>Oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>4</td>
<td>22</td>
<td>1:0</td>
<td>Not observed</td>
</tr>
<tr>
<td>2</td>
<td>55→85</td>
<td>21</td>
<td>40</td>
<td>1:0</td>
<td>Not observed</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>3</td>
<td>41</td>
<td>1:0</td>
<td>Not observed</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>22</td>
<td>55</td>
<td>1:3</td>
<td>Observed by TLC</td>
</tr>
</tbody>
</table>

*aReagents and conditions: 158, 261, RuPhos, K$_2$CO$_3$, toluene/H$_2$O (4:1).
Given that lowering the reaction temperature had resulted in extended reaction times without improving the yield of coupled product 273, and noting that re-optimisation of the catalytic system was likely to prove time consuming, the 55% yield afforded by the original reaction conditions was deemed sufficient and focus returned to the synthesis of aldol 259.

### 2.3.6 Synthesis of Aldol 259

Following successful coupling of trifluoroboratoamide 158 and bromide 261, displacement of the pseudoephedrine auxiliary with methyllithium was required in order to conduct the aldol reaction. Treatment of amide 273 with methyllithium afforded methyl ketone 260 in a pleasing 85% yield. However, the reaction suffered from poor reproducibility because of the variable quality of commercially available methyllithium. Due to the extended shipping times to New Zealand, solutions of methyllithium often suffer significant losses in activity by the time of arrival. Exchange of the solvent from diethyl ether to tetrahydrofuran offered some improvement in reactivity, presumably via increased solvent donating ability causing the breakdown of methyllithium aggregates. However, the transformation was still difficult to perform on a large scale, requiring multiple additions of methyllithium and cooling of the reaction mixture to −78 °C for each addition followed by warming to 0 °C. For this reason, we opted to prepare fresh methyllithium in order to guarantee a sufficient concentration of reactive species. Methyllithium was prepared by addition of lithium metal to a solution of methyl iodide in ether. The exothermic reaction caused reflux of the solvent. Reaction was deemed complete once the mixture had been stable at room temperature for one hour. Filtration under nitrogen, followed by storage in a Schlenk flask afforded methyllithium solutions that retained activity for several months. The concentration was determined by hydrolysis of an aliquot of methyllithium followed by acid-base titration with 0.1 M hydrochloric acid. The use of this freshly prepared methyllithium allowed the conversion of amide 273 to methyl ketone 260 to be conducted much more efficiently and consistently (Scheme 2.52).

![Scheme 2.52](image)

**Scheme 2.52.** *Reagents and conditions: a) MeLi, THF, −78 °C to 0 °C, 30 min, 85%.*
Attention now turned to the aldol reaction of methyl ketone 260 with chiral aldehyde 245. Motivated by our previous success with a Mukaiyama aldol reaction, we aimed to employ an analogous procedure with methyl ketone 260. Formation of silyl enol ether 276 was achieved by treatment with trimethylsilyl triflate, triethylamine and N,N-dimethylaminopyridine. The Lewis acid-mediated aldol reaction proceeded smoothly once more, although full conversion to aldol 259 could not be attained. Reaction of 276 with aldehyde 245 at −78 °C in the presence of two equivalents of boron trifluoride diethyl etherate provided aldol 259 in 58% yield over two steps together with 38% recovered methyl ketone 260 (Scheme 2.53). The aldol reaction was difficult to monitor since the temperature increase involved in removing an aliquot for TLC analysis led to degradation of both the product and starting material. Therefore, in an effort to increase the conversion of the reaction, the reaction time was extended to three hours. Interestingly, this did not result in any improvement in the yield of aldol 259, obtained in a comparable 56% yield. This result seems to indicate that competitive desilylation was occurring in conjunction with the desired reaction.

Scheme 2.53. Reagents and conditions: a) TMSOTf, NEt₃, DMAP, CH₂Cl₂, 0 °C, 30 min; b) 245, BF₃·OEt₂, CH₂Cl₂, −78 °C, 2 min, then 276, −78 °C, 3 h, 58% over two steps.

Analogous to the earlier series of aldol reactions conducted on methyl ketone 207 (Section 2.2.5) the diastereoselectivity of the reaction was inferred from the lack of any diastereomeric resonances in either the ¹H or ¹³C NMR spectra. The stereochemical configuration at the newly generated chiral centre was tentatively assigned as R, noting that this assignment would be readily confirmed by NOESY correlations upon formation of the spiroketal core.
2.3.7 Attempted Halogenation of Alkene 259

Following the successful elaboration of the carbon framework by the Mukaiyama aldol reaction, our focus turned to the final carbon-carbon bond formation required to provide access to the phthalide framework (Figure 2.5). This was envisioned to take place via halogenation, Sharpless asymmetric dihydroxylation of the olefin and carboalkoxylation.

![Comparison of the carbon framework of virgatolide B (2) and (259).](image)

Attempted halogenation of aldol 259 with N-bromosuccinimide led to the formation of a complex mixture (Scheme 2.54). Although no specific products were identifiable, $^1$H NMR analysis of the crude product mixture indicated loss of the double bond. The use of N-iodosuccinimide provided only 50% recovered starting material 259 after reaction for 24 hours at room temperature. Treatment of aldol 259 with iodine and silver trifluoroacetate also resulted in the formation of a complex mixture, accompanied by loss of the olefinic resonances.

![Scheme 2.54. Reagents and conditions: a) NBS, DMF, 0 °C to rt, 24 h, complex mixture; b) NIS, CH$_2$Cl$_2$, rt, 24 h, 50% 259; c) I$_2$, AgO$_2$CCF$_3$, CH$_2$Cl$_2$, rt, 2 h, complex mixture.](image)

Surprised by these results, especially recalling the successful bromination of alkene 167 (Section 2.1.4), we proposed that removal of the double bond would facilitate halogenation of the aromatic core without degradation. Attention therefore turned to the Sharpless asymmetric dihydroxylation of alkene 259.
2.3.8 **Sharpless Asymmetric Dihydroxylation**

The Sharpless asymmetric dihydroxylation (SAD) allows the selective formation of stereodefined 1,2-diols (Scheme 2.55).\(^{109,165}\) The reaction was developed following the observation that tertiary amines were capable of accelerating the stoichiometric reaction between osmium tetroxide and olefins.\(^{166}\) This led to an investigation into the dihydroxylation of alkenes accelerated by chiral tertiary amines, with a view toward developing a chiral variant of the already well known racemic dihydroxylation.\(^{166-168}\) Because of the toxicity of osmium tetroxide, development of a catalytic process was highly desirable. An asymmetric, catalytic process was elucidated by Sharpless in 1992 after substantial development.\(^{108}\) The standard catalytic system utilises potassium osmate as an osmium source, amine ligands derived from dihydroquinine (DHQ) or dihydroquinidine (DHQD), potassium ferricyanide as a co-oxidant to regenerate the osmium catalyst and potassium carbonate.\(^{108}\) The facial selectivity of the reaction is governed by the choice of ligand. Addition of methanesulfonamide improves the rate of the reaction for non-terminal olefins.

A variety of ligands have been employed in order to achieve high enantioselectivities on different substrates. However, the most commonly employed ligands are those constructed from two molecules of DHQ or DHQD separated by a phthalazine (PHAL) linker (Figure 2.6).

**Scheme 2.55.** Sharpless asymmetric dihydroxylation.\(^{108}\)

**Figure 2.6.** Ligands commonly employed for the Sharpless asymmetric dihydroxylation.\(^{109}\)
The mechanism of the SAD has been extensively studied. The accepted mechanism for the SAD in a biphasic solvent system with potassium ferricyanide as a co-oxidant is outlined in Scheme 2.56. The catalytic cycle begins with the reaction of the olefin and osmium tetroxide (278) in a [3+2] cycloaddition to generate an osmium glycolate intermediate 277 in the organic phase. Hydrolytic breakdown of this intermediate liberates the product diol and an Os(VI) species 279. Oxidation of Os(VI) to Os(VIII) in the aqueous phase then regenerates the catalytically active species. As noted earlier, the use of methanesulfonamide accelerates the reaction by increasing the rate of hydrolysis of the osmium glycolate intermediate 277, allowing more rapid catalytic turnover.

Scheme 2.56. Mechanism of the Sharpless asymmetric dihydroxylation.\textsuperscript{109}

The facial selectivity of the reaction arises due to the rapid and reversible formation of a three component ligand-OsO\textsubscript{4}-olefin complex prior to formation of the [3+2] cycloaddition transition state (Figure 2.7).\textsuperscript{169} The ligand and OsO\textsubscript{4} form a U-shaped, “enzyme-like” binding pocket, favouring one binding orientation of the olefin over the other. Dihydroxylation of the accessible alkene face generates the enantioenriched product.\textsuperscript{109}
Although difficult to visualise, the favoured face for dihydroxylation can be readily predicted by application of the so-calledSharpless mnemonic (Figure 2.8). In this mnemonic, the substituents on the alkene are classified by their steric bulk as R_L, R_M, and R_S: the largest, medium-sized and smallest substituents respectively. After orientation of the reacting olefin according to the mnemonic as shown in Figure 2.8, dihydroxylation accelerated by DHQ derivatives leads to dihydroxylation of the bottom (α) face, whilst DHQD derivatives cause dihydroxylation of the top (β) face. For this reason, pre-blended mixtures of potassium osmate, potassium ferricyanide, potassium carbonate and (DHQ)_2PHAL or (DHQD)_2PHAL are referred to as AD-mix α and AD-mix β, respectively.
2.3.9 Synthesis of Spiroketal 282

Application of the Sharpless mnemonic to alkene 259 indicated that the use of AD-mix α ((DHQ)$_2$PHAL) was required in order to install the desired ($S,S$) stereochemistry for the phthalide subunit (Scheme 2.57).

Scheme 2.57. Reagents and conditions: a) K$_2$OsO$_2$(OH)$_4$, (DHQ)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, MeSO$_2$NH$_2$, $t$-BuOH/H$_2$O (1:1), 0 °C, 18 h, 90%.
Pleasingly, exposure of alkene 259 to standard dihydroxylation conditions\textsuperscript{165} provided diol 281 in 90\% yield. Inspection of the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra did not reveal any resonances attributable to the undesired isomer derived from dihydroxylation of the \(\beta\)-face. However, the aromatic nucleus separates the two chiral portions of the molecule and therefore it was unclear whether or not the diol diastereomers would be distinguishable by \textsuperscript{1}H NMR analysis. Given the value of this late stage intermediate, we were interested in investigating the final transformations to virgatolide B (2). The diastereoselectivity was therefore not confirmed at this stage, and the structure tentatively assigned as diol 281.

Given the difficulties encountered in constructing the spiroketal core from protected dihydroxyketone 247 (Section 2.2.6), our top priority was to ascertain whether the change to BOM groups enabled this transformation. Hydrogenolysis in methanol catalysed by palladium hydroxide on carbon proved unsuccessful, resulting in the formation of a complex mixture. NMR analysis of the crude product mixture revealed that although both BOM groups and the PMB group had been removed, spiroketal 282 had not been formed in any appreciable quantity. When ethyl acetate was used as a solvent instead, spiroketal 282 was isolated in 45\% yield together with a 50\% yield of by-product 283, identified by mass spectrometry (Scheme 2.58). By-product 283 was believed to have been formed by elimination of the hydroxyl group and subsequent hydrogenation of the double bond. Realising that the Pd(OH)\textsubscript{2} was causing base-catalysed degradation of the aldol moiety, the hydrogenation was conducted with palladium on carbon. Spiroketal 282 was generated in a moderate 55\% yield.

\textbf{Scheme 2.58. Reagents and conditions:} a) \textsuperscript{2}H, Pd(OH)\textsubscript{2}/C, EtOAc, rt, 4 h, 45\% 282, 50\% 283; b) \textsuperscript{2}H, Pd/C, EtOAc, rt, 4 h, 55\% 282.

Successful formation of the spiroketal moiety was confirmed by \textsuperscript{13}C NMR. The resonance arising from the anomeric carbon was clearly observed at \(\delta\) 101.2 ppm, while the carbonyl resonance observed at \(\delta\) 215.6 ppm in cyclisation precursor 281 was no longer visible.
Successful formation of the spiroketal core meant that the absolute configuration of the chiral centre generated in the aldol reaction could now be unambiguously assigned. Pleasingly, the NOESY spectrum revealed a clear nOe correlation between the methine protons H-4’ and H-6’, indicating a cis relationship across the ring system (Figure 2.9). Since the S configuration at C-6’ was derived from chiral pool reagent (S)-228, the configuration at C-4’ could be assigned as R.

Figure 2.9. Key through-space correlation allowing structural assignment of C-4’.

The key H-3↔H-3’ correlation was required for an unambiguous assignment of the configuration of the anomeric centre (Figure 2.10). Unfortunately, this correlation was not observed in the NOESY spectrum of spiroketal 282 due to signal overlap. However, conversion of spiroketal 282 to the natural product would enable assignment by comparison of the NMR spectra to that of naturally-occurring virgatolide B (2).\(^1\) Furthermore, the absence of nOe correlations between H-11 and H-4’/H-6’ indicated that spiroketal 282 did not possess the alternative configuration at the anomeric centre. The structure of spiroketal 282 was therefore provisionally assigned as shown in Figure 2.10, as this configuration is analogous to that of virgatolide B (2) and allows the substituents on the spiroketal ring system to be placed equatorial when the anomerically stabilised conformation is adopted.
In order to form the final carbon-carbon bond, functionalisation of the aromatic nucleus was required. Attempted iodination with N-iodosuccinimide at 0 °C furnished a mixture of products difficult to analyse by NMR. However, lowering of the temperature to −20 °C followed by quenching at this temperature after three hours provided an inseparable mixture of C-6 and C-8 iodination products 284/285 in 47% yield together with 30% recovered spiroketal 282. A further decrease in the temperature to −40 °C, coupled with an extended reaction time increased the yield of iodides 284/285 to 60% in a 1:1 ratio (Scheme 2.59).

Although spiroketal 285 contains the iodine atom in the undesired C-8 position, we reasoned that successful carbonylation, followed by acid-catalysed equilibration of the spiroketal may allow rotation of the aromatic core, facilitating interchange between the two regioisomeric carbonylation products 2 and 114 (Scheme 2.60).
Scheme 2.60. Proposed acid-catalysed interconversion of regioisomers 2 and 114.

With this in mind, isomers 284 and 285 were subjected to carbonylation (Scheme 2.61). Attempted carbonylation of 284/285 with carbon monoxide, bis(triphenylphosphine)palladium(II) dichloride, hydrazine hydrate and potassium carbonate\(^{170}\) led to the formation of a complex mixture after three hours. As this reaction was conducted at 60 °C we reasoned that lowering the reaction temperature might provide better results. Unfortunately, exposure of iodides 284/285 to the same reaction conditions at room temperature resulted in incomplete reaction after 24 hours. Analysis of the crude product mixture by \(^1\)H and \(^{13}\)C NMR revealed a mixture of unreacted iodides 284/285 and spiroketal 282, the product of protodehalogenation. Disappointingly, no trace of the desired carbonylated products 2 and 114 could be detected.

Scheme 2.61. Reagents and conditions: a) CO, PdCl\(_2\)(PPh\(_3\))\(_2\), N\(_2\)H\(_2\)H\(_2\)O, K\(_2\)CO\(_3\), 60 °C or rt, 3 h or 24 h.
Although the options for construction of the phthalide moiety were by no means extinguished, the loss of synthetically valuable iodides 284/285 encouraged us to consider our approach more carefully. It was likely that the free phenol group present in the molecule was contributing to the protodehalogenation pathway operative for iodides 284 and 285. We therefore sought to change the order of synthetic events, conducting the carbonylation process prior to unmasking of the phenolic oxygen atoms.

It was decided that a carbonylation study on a model system would allow us to investigate the best method for the final carbon-carbon bond formation, avoiding the need to use valuable late stage intermediates.

### 2.3.10 Summary of the Attempted Total Synthesis of Virgatolide B (2)

Preparation of BOM-protected aryl bromide 261 was achieved in six steps from 3,5-dihydroxybenzoic acid (263, Scheme 2.62). Suzuki cross-coupling of trifluoroboratoamide 158 and bromide 261 was successful, tolerating both the change of protecting groups and the introduction of the alkene side-chain. Coupled product 273 was then readily elaborated to methyl ketone 260 which underwent smooth aldol reaction with aldehyde 245, providing aldol 259 with the desired 1,3-anti stereochemistry. Asymmetric dihydroxylation of alkene 259 appeared stereoselective, with none of the subsequent intermediates indicating the presence of diastereomers by NMR analysis. Formation of spiroketal 282 was achieved by triple deprotection and concomitant spirocyclisation. Iodination of the aromatic ring was non-selective, forming a regioisomeric mixture of iodides 284/285, although this was deemed to be easily remedied by acid-catalysed equilibration. Attempted carbonylation of iodides 284/285 resulted in protodehalogenation. For this reason, a carbonylation model system was to be developed in order to provide access to virgatolide B (2).
Scheme 2.62. Reagents and conditions: a) 158, Pd(OAc)$_2$, RuPhos, K$_2$CO$_3$, toluene/H$_2$O (4:1), 85 °C, 1.5 h, 55%; b) MeLi, THF, −78 °C to 0 °C, 30 min, 85%; c) TMSOTf, NEt$_3$, DMAP, CH$_2$Cl$_2$, 0 °C, 30 min; d) 245, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, −78 °C, 2 min, then 276, −78 °C, 3 h, 58% over two steps; e) K$_2$OsO$_2$(OH)$_4$, (DHQ)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, MeSO$_2$NH$_2$, t-BuOH/H$_2$O (1:1), 0 °C, 18 h, 90%; f) H$_2$, Pd/C, EtOAc, rt, 4 h, 55%; g) NIS, DMF, −40 °C, 24 h, 60%; h) CO, PdCl$_2$(PPh$_3$)$_2$, N$_2$H$_4$·H$_2$O, K$_2$CO$_3$, 60 °C or rt, 3 h or 24 h.
2.4 Development of a Carbonylation Model System

2.4.1 Construction of the Phthalide Framework

Following a brief attempt at the carbonylation of iodides 284/285, we decided that a more economical approach toward virgatolide B (2) would be to optimise this final transformation on a model system, rather than utilising advanced intermediates requiring lengthy preparations. The two approaches to install the carbonyl group we sought to investigate were palladium-catalysed carboalkoxylation and hydrolysis of an aromatic nitrile (Scheme 2.63).

Scheme 2.63. Construction of the phthalide moiety.

In order to be a useful tool, the chosen model system needed to contain the hydroxyethyl substituent present at C-4 of virgatolide B (2). For this reason aryl iodide (±)-287 was selected as the carbonylation/cyanation precursor (Scheme 2.64). We hoped that either carbonylation or nitrile hydrolysis would be accompanied by spontaneous ring-closure. It was therefore essential that the model system contain the dihydroxylated side-chain. Inclusion of this moiety also meant that the potential formation of the six-membered isochromanone could be monitored.

Retrosynthetically, iodide (±)-287 would be constructed analogously to bromide 261. The cis diol moiety would be installed via osmium catalysed dihydroxylation of alkene (E)-288, which would in turn be available from Wittig reaction of 2-iodobenzaldehyde (289) with ethyltriphenylphosphonium iodide. Aldehyde 289 would then simply be derived from commercially available 2-iodobenzyl alcohol (290).
**2.4.2 Synthesis of Diol (±)-287**

Pleasingly, preparation of diol (±)-287 proved unproblematic (Scheme 2.65). Parikh-Doering oxidation\textsuperscript{152} of alcohol 290 provided aldehyde 289 in 90\% yield after a brief fifteen minute reaction time. Wittig reaction of aldehyde 289 with ethyltriphenylphosphonium iodide provided alkene 288 in 80\% yield as an inseparable mixture of \textit{E}/\textit{Z} isomers. Isomerisation of (\textit{E}/\textit{Z})-288 to isomerically pure (\textit{E})-288 using an analogous procedure to that used for (\textit{E}/\textit{Z})-261, followed by racemic \textit{cis}-dihydroxylation afforded diastereomERICALLY pure diol (±)-287 in 60\% yield over two steps.

**Scheme 2.65.**  \textit{Reagents and conditions:} a) DMSO, SO\textsubscript{3}·Py, DIPEA, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 15 min, 90\%; b) EtPPh\textsubscript{3}I, 18-crown-6, \textit{t}-BuOK, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 1 h, 80\%; c) Ru(CO)ClH(PPh\textsubscript{3})\textsubscript{3} toluene, reflux, 3 h; d) OsO\textsubscript{4}, NMO, acetone/water (1:1), rt, 2 h, 60\% over two steps.
2.4.3 Palladium-Catalysed Carboalkoxylation

Several related procedures for the tandem carbonylation/alkoxylation (carboalkoxylation) of aryl halides in the presence of carbon monoxide and an alcoholic solvent were developed in the 1970s.\textsuperscript{171-173} The intramolecular variant, which generates benzo-fused lactones as products, was a straightforward adaptation of this methodology (Scheme 2.66).\textsuperscript{170} This methodology proved particularly useful for the synthesis of phthalides.\textsuperscript{121,174-175} However, isochromanones and other higher order ring systems can also be readily constructed with this methodology.\textsuperscript{170,176}

![Scheme 2.66. Palladium-catalysed alkoxylation of aryl halides.](image)

Mechanistic studies\textsuperscript{176-178} have indicated that the catalytic cycle is initiated by oxidative addition of the halide species to palladium(0), generating adduct \textsuperscript{292} (Scheme 2.67). Next, insertion of carbon monoxide into the palladium-carbon bond generates a labile aroyl intermediate \textsuperscript{293}. Coordination of the alcohol functionality to the metal centre followed by deprotonation is likely to generate oxapalladacycle \textsuperscript{294}, although the presence of this species has not yet been confirmed.\textsuperscript{176} Subsequent reductive elimination then liberates the lactonised product \textsuperscript{295} and regenerates the active catalyst.
Unable to find any examples of carboalkoxylation of substrates containing dihydroxylated appendages, we were interested to see whether the six-membered isochromanone (±)-298 would be formed alongside the desired phthalide (±)-297 upon carboxylation (Table 2.7). The iodide species was chosen in the hope that the increased reactivity toward oxidative addition (commonly the rate-determining step in palladium-catalysed coupling reactions) would obviate the requirement for elevated reaction temperatures, thus maximising the kinetic preference for five-membered ring formation over the thermodynamically favoured six-membered ring. The carboxylation reaction was trialled on both 2-iodobenzyl alcohol (295) and iodide (±)-286. Yields for these reactions were not determined, instead the percentage conversion was monitored by $^1$H and $^{13}$C NMR of aliquots of the crude reaction mixture. In all cases the conversion was simple to determine as the formation of side-products was minimal.

Initial attempts at carboxylation of iodide 290 were plagued by poor conversion. The use of bis(triphenylphosphine)palladium(II) dichloride, hydrazine hydrate and potassium carbonate in tetrahydrofuran at room temperature resulted in an unacceptable 43% conversion after 24 hours (Entry 1). Similarly, the use of palladium tetrakis(triphenylphosphine) in tetrahydrofuran provided only 23% conversion after 24 hours (Entry 2). Pleasingly, the use of DMF as a solvent allowed room temperature carboalkoxylation of iodide 290 to be achieved within two hours when
Discussion

bis(triphenylphosphine)palladium(II) dichloride was employed as catalyst (Entry 3). While successful, application of this methodology to iodide (±)-287 required extended reaction times to achieve adequate conversion (Entry 4). Having avoided the formation of the undesired isochromanone (±)-298 thus far, we were interested in exploring the possibility of using elevated reaction temperatures. It was found that carbonylation catalysed by palladium tetrakis(triphenylphosphine) in dimethylformamide at 100 °C effected quantitative conversion of iodide (±)-287 to phthalide (±)-297, with no isochromanone observed by $^1$H NMR analysis (Entry 5). Although higher temperatures were required when using palladium tetrakis(triphenylphosphine), the reaction proved more operationally consistent than using PdCl$_2$ in the presence of a reductant. Satisfied that we had two successful systems for carbonylation, work on the model system was concluded in the knowledge that the full range of carbonylation options had by no means been fully probed.

![Reaction Scheme]

**Table 2.7.** Carboalkoxylation of iodides 290 and (±)-287.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>290, CO, PdCl$_2$(PPh$_3$)$_2$, N$_2$H$_4$$\cdot$H$_2$O, K$_2$CO$_3$, THF, rt, 24 h</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>290, CO, Pd(PPh$_3$)$_4$, K$_2$CO$_3$, rt, 24 h</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>290, CO, PdCl$_2$(PPh$_3$)$_2$, N$_2$H$_4$$\cdot$H$_2$O, K$_2$CO$_3$, DMF, rt, 2 h</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>(±)-287, CO, PdCl$_2$(PPh$_3$)$_2$, N$_2$H$_4$$\cdot$H$_2$O, K$_2$CO$_3$, DMF, rt, 2 d</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>(±)-287, CO, Pd(PPh$_3$)$_4$, DIPEA, 100 °C, 24 h</td>
<td>100</td>
</tr>
</tbody>
</table>
2.4.4 Cyanation and Nitrile Hydrolysis

Although successful installation of the carbonyl moiety had already been achieved via carboalkoxylation, we also opted to briefly test the viability of nitrile hydrolysis to achieve the same purpose. Noting the recent precedent for the construction of phthalides by osmium-catalysed dihydroxylation of species containing an aromatic nitrile and ortho alkene moiety (Scheme 2.68),\textsuperscript{179} we hoped that this process could be achieved in the reverse order: installation of the nitrile after dihydroxylation.

![Scheme 2.68](image)

**Scheme 2.68.** Synthesis of 3-substituted phthalides via dihydroxylation/nitrile hydrolysis.\textsuperscript{179}

Pleasingly, application of the method of Sargent\textsuperscript{180} provided success on this front: treatment of iodide (±)-287 with copper(I) cyanide in dimethylformamide at 100 °C followed by alkaline hydrolysis provided quantitative conversion within 24 hours (Scheme 2.69). However, analysis of the crude \textsuperscript{1}H NMR revealed that phthalide (±)-297 was formed together with the undesired isochromanone (±)-298, in an 8:1 ratio. Despite the minor quantities of isochromanone (±)-298 formed, this method was still considered a viable entry for the formation of the final carbon-carbon bond. With several possible methods for the construction of virgatolide B (2) available, attention turned to the completion of the total synthesis.

![Scheme 2.69](image)

**Scheme 2.69.** Reagents and conditions: a) CuCN, DMF, 100 °C, 24 h, 100% conversion, 8:1 297/298.
2.5 Total Synthesis of Virgatolide B (2)

2.5.1 Revised Retrosynthesis

Considering the successful carbonylation of iodide ($\pm$)-287, and noting that initial attempts to convert iodides 284/285 to virgatolide B (2) using the same conditions\textsuperscript{170} had led to protodehalogenation (Section 2.3.9), we now re-evaluated our strategy towards virgatolide B (2). The protodehalogenation of iodides 284/285 was postulated to have been induced by the presence of the free ortho phenol liberated during the deprotection/cyclisation process. Accordingly, we decided instead to conduct installation of the carbonyl moiety at an earlier stage, prior to deprotection. Because it was undesirable to expose aldot 259 to base at elevated temperatures, the carbonylation would also precede the key aldol reaction. Fully substituted aldot 299 would be derived from the aldol reaction of phthalide 300 and aldehyde 245 in analogy to our earlier strategy (Scheme 2.70). Phthalide 300 would in turn be constructed via dihydroxylation, iodination and carboalkoxylation of previously synthesised methyl ketone 260, available from the Suzuki coupling of trifluoroboratoamide 158 and bromide 261.

![Scheme 2.70. Retrosynthesis of virgatolide B (2).](#)
Chapter Two

The final step in the construction of virgatolide B (2) is deprotection with concomitant formation of the spiroketal core. Because carbonylation is to be conducted prior to this, the aromatic nucleus no longer contains rotational symmetry and thus two possible regioisomeric spiroketals can be formed (Scheme 2.71). However, we reasoned that acid-catalysed equilibration of the spiroketal moiety in an aprotic solvent would be accompanied by transient rotation of the aromatic ring, facilitating inter-conversion of regioisomers 2 and 114. The presence of an intramolecular hydrogen bond between the free phenol peri to the carbonyl group in virgatolide B (2) would lower the energy of regioisomer 2 relative to 114, meaning that 2 would predominate in the equilibrium distribution.

Scheme 2.71. Proposed acid-catalysed inter-conversion of regioisomers 2 and 114.

Density functional theory calculations supported our hydrogen-bonding hypothesis. Structural optimisations of regioisomers 2 and 114 were conducted, followed by calculation of the associated energy values. The calculations indicated that virgatolide B (2) possessed a 22.5 kJ/mol stabilisation relative to regioisomer 114, corresponding to an equilibrium composition heavily favouring 2 (Figure 2.11). In addition to regioisomers 2 and 114, the structures and energies of the respective epimers differing in configuration at the spiroketal centre were also calculated. As expected, the energies of these spiroketal epimers were significantly higher than 2 and 114. This was due to the inability of these spiroketals to adopt a conformation possessing anomeric stabilisation whilst placing the other substituents in equatorial positions. The energy calculations and geometry optimisations were performed with GAUSSIAN 09 using restricted DFT. The non-local B3LYP functional hybrid method was employed. The standard 6-31(d,p) basis set was used for the geometry optimisation and frequency analysis. Subsequent single-point electronic energy calculations were performed with the larger 6-311 (2df,p) basis set. The Gibbs energy of each structure was then taken as the sum of the single-point electronic energy and the thermal correction to the Gibbs free energy.
2.5.2 Synthesis of Iodide 301

The synthesis of phthalide 300 began from methyl ketone 260 (Scheme 2.72). In order to avoid interference of the olefin moiety with halogenation of the aromatic ring, asymmetric dihydroxylation was conducted first. Treatment of alkene 260 with AD-mix α in tert-butanol/water (1:1) at 0 °C before allowing the temperature to rise slowly to room temperature provided diol 302 in a pleasing 87% yield. Inspection of the $^1$H and $^{13}$C NMR spectra did not indicate the presence of a diastereomeric mixture. However, although alkene 260 is structurally well-suited to the Sharpless mnemonic, we thought it pertinent to ensure that diol 302 was indeed
a single diastereoisomer. Towards this end, a sample of alkene 260 was employed in a non-selective cis-dihydroxylation reaction utilising N-methylmorpholine-N-oxide (NMO). Interestingly, the $^1$H NMR spectra of the two samples were indistinguishable. The $^{13}$C NMR showed some differences between samples, but nothing conclusive enough to pronounce the Sharpless dihydroxylation selective. This is relatively unsurprising as the aromatic ring spatially separates the dihydroxylated side-chain and the α-chiral methyl ketone, thus minimising magnetic interactions between the two groups. Hoping that this would change upon installation of the iodide or carbonyl group, both samples were carried forward to be analysed by NMR at a later stage.

![Scheme 2.72](image)

**Scheme 2.72. Reagents and conditions:** a) K$_2$OsO$_2$(OH)$_4$, (DHQ)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, MeSO$_2$NH$_2$, r-BuOH/H$_2$O (1:1), 0 °C to rt, 18 h, 87% 302; b) OsO$_4$, NMO, acetone/water (1:1), rt, 2 h, 90% 302/303, (1:1).

Next, monoiiodination of one of the two equivalent aromatic positions was required. The sample of diol 302 from the Sharpless asymmetric dihydroxylation and the sample of isomeric 302/303 produced by non-selective cis-dihydroxylation were both subjected to halogenation. The use of iodine and silver trifluoroacetate$^{[121]}$ provided desired iodiode 301 in 72% yield with minor quantities of starting material and the di-iodide species isolable from the reaction mixture (Scheme 2.73).

![Scheme 2.73](image)

**Scheme 2.73. Reagents and conditions:** a) 302, I$_2$, CF$_3$CO$_2$Ag, 0 °C, 1, h, 72% 301; b) 302/303, I$_2$, CF$_3$CO$_2$Ag, 0 °C, 1, h, 70% 301/304 (1:1).

Pleasingly, introduction of the iodide to the aromatic ring allowed clear differentiation of the diastereomers in the isomeric sample obtained from treatment of alkene 260 with osmium tetroxide and NMO. Resonances in the $^1$H NMR spectrum showed the presence of two closely related
compounds, but unfortunately baseline separation of the signals was not observed. However, the $^{13}$C NMR spectrum contained several resonances derived from an isomeric product that were clearly separated from those of the desired product 301, although complete separation was still not achieved. In contrast, the $^{13}$C NMR spectrum of the sample of iodide 301 derived from the Sharpless asymmetric dihydroxylation contained peaks from a single isomer. Comparison of the $^{13}$C NMR spectra of the two samples enabled us to conclude that the Sharpless asymmetric dihydroxylation had indeed been highly diastereoselective (Figure 2.12).

![Figure 2.12](image1.png)  
**Figure 2.12.** Selected examples of $^{13}$C NMR peaks of iodide 301 compared to the isomeric mixture.
2.5.3 Synthesis of Phthalide 300

Attention now turned to the installation of the carbonyl moiety. First, carbonylation of iodide 301 with bis(triphenylphosphine)palladium(II) dichloride and hydrazine at 60 °C was investigated (Entry 1, Table 2.8). After 30 minutes, the starting material had been fully consumed, furnishing a low yield of an unidentifiable product, potentially formed via reaction of hydrazine with the carbonyl moiety. In contrast, application of the high temperature carboalkoxylation conditions developed during the model study was successful (Entry 2). Carboalkoxylation with carbon monoxide catalysed by palladium tetrakis(triphenylphosphate) with diisopropylethylamine as base provided phthalide 300 in 75% yield, with no isochromanone formation observed by NMR (Entry 2). In an attempt to improve the yield of this reaction, an alternative carboalkoxylation procedure employing carbon monoxide, bis(triphenylphosphine)palladium(II) dichloride and triethylamine in a mixture of dimethylformamide and methanol was attempted. Unfortunately these conditions failed to effect significant conversion after 24 hours at 65 °C (Entry 3). Finally, attempted cyanation with copper(I) cyanide in DMF at 90 °C resulted in the formation of a complex mixture (Entry 4).

![Chemical structure 300](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO, PdCl2(PPh3)2, N2H4·H2O, K2CO3, THF, 60 °C, 24 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CO, Pd(PPh3)4, DIPEA, 100 °C, 18 h</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>CO, PdCl2(PPh3)2, NEt3, DMF-MeOH, 65 °C, 24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>CuCN, DMF, 90 °C, 18 h</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

**Table 2.8. Synthesis of phthalide 300.**
2.5.4 Final Elaboration to Virgatolide B (2)

With phthalide 300 in hand, the final carbon-carbon bond forming reaction required was the aldol reaction between methyl ketone 300 and aldehyde 245. Although phthalide 300 contains a free alcohol capable of interfering with the aldol reaction, we reasoned that treatment with two equivalents of trimethylsilyl triflate would simultaneously protect the alcohol as the trimethylsilyl ether whilst effecting formation of the silyl enol ether. This would avoid unnecessary introduction of a protecting group near the end of the synthesis. Pleasingly, this was borne out in practice: treatment of 300 with trimethylsilyl triflate and triethylamine in dichloromethane afforded the disilylated species 306 (Scheme 2.74). Silyl enol ether 306 was characterised only by $^1$H NMR analysis of the crude product mixture following aqueous work-up and immediately employed in the subsequent aldol reaction. Addition of a solution of 306 to a pre-complexed mixture of aldehyde 245 and boron trifluoride diethyl etherate at $-78^\circ$ C produced crude aldol adduct 307 with the trimethylsilyl protecting group still intact. Dissolution of the crude reaction mixture in methanol followed by addition of several drops of saturated aqueous potassium carbonate effected cleavage of the trimethylsilyl protecting group within 30 minutes.

![Scheme 2.74](image)

Scheme 2.74. Reagents and conditions: a) TMSOTf, NE$_3$ DMAP, CH$_2$Cl$_2$, 0°C, 15 min; b) 245, BF$_3$-OEt$_2$, CH$_2$Cl$_2$, $-78^\circ$ C, 1.5 h; c) sat. aq. K$_2$CO$_3$ (5 drops), MeOH, rt, 30 min, 65% 299, 25-30% 300 over three steps.

As before, analysis of the $^1$H and $^{13}$C NMR spectra of aldol 299 showed no indication of the presence of diastereomers and the subsequent deprotection-cyclisation sequence would allow unambiguous assignment of the configuration at the newly generated chiral centre.
All that remained in order to access virgatolide B (2) was removal of the protecting groups and formation of the spiroketal core. The deprotection was first conducted on a small scale (~5 mg) in order to avoid the loss of advanced intermediate 299. Hydrogenolysis catalysed by palladium on carbon in ethyl acetate furnished a mixture of two major products as assessed by TLC and crude NMR analysis. Separation of these products by preparative TLC followed by $^1$H NMR analysis indicated the formation of virgatolide B (2) and an isomeric product, presumably either the epimer at the spiroketal centre or the regioisomer derived from cyclisation of the undesired phenolic oxygen. Dissolution of the isomeric product in dichloromethane and addition of a catalytic quantity of camphorsulfonic acid effected conversion to 2 as observed by TLC and NMR of the crude product mixture. The reaction was then repeated on a larger scale in order to provide greater quantities of 2. Pleasingly, hydrogenolysis followed by treatment of the crude product mixture with camphorsulfonic acid provided virgatolide B (2) in 55% yield over two steps (Scheme 2.75).

![Scheme 2.75](image)

**Scheme 2.75.** Reagents and conditions: a) H$_2$, Pd/C, EtOAc, rt, 3 h; b) CSA, CH$_2$Cl$_2$, 16 h, 55% over 2 steps.

The $^1$H and $^{13}$C NMR spectra and mass spectrometric data of synthetically prepared virgatolide B (2) were identical that reported in the literature (Table 2.9, Figure 2.14). Gratifyingly, the optical rotation value of synthetic 2 was also in good agreement with the literature value ($[\alpha]_D^{25}$ +19.1 (c 0.25 in MeOH), lit. +25.0, (c 0.07 in MeOH)). In order to confirm the configuration at C-13, which was derived from the diastereoselective Mukaiyama aldol reaction, the NOESY spectrum was analysed. A correlation was observed between the protons on C-13 and C-15, indicating that the relative stereochemistry of these protons is syn with respect to the six-membered ring (Figure 2.13). Since the stereochemistry at C-15 was derived from ethyl (S)-3-hydroxybutyrate the C-13 stereocentre can be unambiguously assigned as R, in full agreement with the 1,3-anti asymmetric induction model.81
Figure 2.13. Correlations observed in the NOESY spectrum of synthetic virgatolide B (2).

Table 2.9. $^1$H NMR (methanol-$d_4$) spectroscopic data of natural virgatolide B (2) compared to synthetic virgatolide B (2) prepared herein.
Figure 2.14. $^1$H NMR (methanol-$d_4$) spectroscopic data of synthetic virgatolide B (2, top) prepared herein compared to natural virgatolide B (2, bottom).
2.5.5 Overall Summary and Conclusion

In summary, the first total synthesis of virgatolide B (2) has been achieved in 16 steps (longest linear sequence) from commercially available 3,5-dihydroxybenzoic acid (263). The key reaction in this synthesis was an sp^3-sp^2 Suzuki cross-coupling reaction between chiral trifluoroboratoamide 158 and aryl bromide 261, efficiently constructing the challenging α-chiral β-arylated carbonyl motif. To our knowledge this is the first use of this methodology outside the initial report and in a total synthesis. Also of importance was the use of a palladium-catalysed carbonylation of iodide 301 with concomitant intramolecular alkoxylation to selectively form phthalide 300. A highly selective 1,3-anti Mukaiyama aldol reaction then provided the spiroketal framework with the requisite stereochemical configuration. The present study has exploited the presence of rotational symmetry within the molecule, delaying the requirement for regioselective functionalisation until control could be governed by intramolecular hydrogen bonding. The overall approach is enantioselective, scalable and should be readily amenable to the synthesis of analogues. The successful strategy employed to construct virgatolide B (2) is illustrated in Scheme 2.76 and Scheme 2.77.

Scheme 2.76. Reagents and conditions: a) Br_2, 20% aq. HCl, reflux, 2 h, 99%; b) BOMCl, DIPEA, CH_2Cl_2, rt, 16 h, 87%; c) DIBAL-H, CH_2Cl_2, −78 °C to 0 °C, 20 min, 95%; d) SO_3-Py, DIPEA, DMSO, 0 °C, 15 min, quant.; e) EtPPh_3I, KO'Bu, 18-crown-6, CH_2Cl_2, rt, 89%; f) Ru(CO)ClH(PPh_3)_3, toluene, reflux, 24 h, 90%; g) propionic anhydride, NEt_3, CH_2Cl_2, rt, 30 min, 94%; h) CH_3I_2, n-BuLi, −78 °C to rt, 16 h, 55%; i) pinacol, n-pentane, rt, 16 h, quant.; j) 149, LDA, LiCl, THF, −78 °C to 0 °C then 153, 30 min, 73%; k) KHF_2, MeCN/H_2O (1:1), 0 °C, 30 min, 77%.
Scheme 2.77. Reagents and conditions: a) Pd(OAc)$_2$, RuPhos, K$_2$CO$_3$, toluene/H$_2$O, (4:1), 85 °C, 1.5 h, 55%; b) MeLi, THF, −78 °C to 0 °C, 30 min, 85%; c) K$_2$OsO$_2$(OH)$_4$, (DHQ)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, MeSO$_2$NH$_2$, t-BuOH/H$_2$O (1:1), 0 °C to rt, 18 h, 87%; d) I$_2$, CF$_3$CO$_2$Ag, 0 °C, 1 h, 72%; e) CO, Pd(PPh$_3$)$_4$, DIPEA, 100 °C, 18 h, 75%; f) PMB-trichloroacetimidate, CSA, CH$_2$Cl$_2$, rt, 24 h; g) DIBAL-H, CH$_2$Cl$_2$, −78 °C, 2.5 h, 83% over two steps; h) TMSOTf, NEt$_3$ DMAP, CH$_2$Cl$_2$, 0 °C, 15 min; i) 245, BF$_3$-OEt$_2$, CH$_2$Cl$_2$, −78 °C, then 306, 1.5 h; j) sat. aq. K$_2$CO$_3$ (5 drops), MeOH, rt, 30 min, 65% over three steps; k) H$_2$, Pd/C, EtOAc, rt, 3 h; b) CSA, CH$_2$Cl$_2$, 16 h, 55% over 2 steps.
2.6 Towards the Total Synthesis of Virgatolide A (1)

2.6.1 Overview

Following the successful synthesis of virgatolide B (2), we were interested in investigating the synthesis of virgatolide A (1). Virgatolide A (1) contains a challenging spiro \(\gamma\)-lactone centred on C-13, not present in virgatolide B (2). However, given the shared core structure of the two compounds, it was postulated that functionalisation of a compound closely related to virgatolide B (2) would enable us to access virgatolide A (1). Such a transformation would require a carbon-carbon bond formation to the C-13 stereocentre, whilst either retaining or selectively reintroducing chirality (Figure 2.15). The X-ray crystal structure of virgatolide A (1) reveals that the oxygen atom attached to C-13 resides in the equatorial position, placing the methylene bridge of the spiro \(\gamma\)-lactone axial.

![Figure 2.15. X-ray crystal structure of virgatolide A (1).](image)

Retrosynthetically, several options for the construction of virgatolide A (1) were available (Scheme 2.78). The most direct method would involve formation of diazo ester 308 from protected virgatolide B (2) followed by carbene insertion into the axial C-H bond (route A). Such a process, although highly speculative, would efficiently provide 1 following stereoselective reduction of the resultant \(\alpha\)-keto lactone. Ketone 309 (route B) and epoxide 310 (route C) represent more conservative candidates for the synthesis of 1, allowing installation of the remaining carbon framework by nucleophilic addition of suitable organometallic reagents.
2.6.2 Attempted Synthesis of γ-Lactone 312 via Carbene Insertion

Despite the lack of precedent for C-H insertions of carbenes derived from α-keto β-diazo esters such as diazocarbonyl 308, these species have been employed in transition-metal catalysed carbenoid type processes such as cyclopropanations,\textsuperscript{186} formal 1,3-cycloadditions\textsuperscript{187,189} and ring expansions.\textsuperscript{190} It was decided to investigate this method first, as it offered the most direct route to virgatolide A (1). However, rather than trial this reaction directly on a fully elaborated diazocarbonyl, we opted to investigate a simple model system 311 (Scheme 2.79). Diazo compound 311 was readily prepared by reaction of cyclohexanol with oxalyl chloride and trimethylsilyldiazomethane.\textsuperscript{191}

\begin{center}
\textbf{Scheme 2.78.} Retrosynthetic analysis of virgatolide A (1).
\end{center}

\begin{center}
\textbf{Scheme 2.79.} Reagents and conditions: a) (COCl)$_2$, CH$_2$Cl$_2$, 0 °C, 2 h, then TMSCH$_2$N$_2$, THF, 0 °C, 3 h, 95%.
\end{center}
Hypothetically, C-H insertion of carbene $\text{313}$, generated by transition metal-catalysed decomposition of $\text{311}$ could generate either a five- or six-membered lactone (Scheme 2.80). It was hoped that reaction would be selective for the five-membered lactone via reaction with the most activated C-H bond. A kinetic preference for five-membered ring formation might also be invoked.

Scheme 2.80. C-H Insertion of carbene $\text{313}$. 
Unfortunately, a screen of rhodium\textsuperscript{186-190,194} copper\textsuperscript{190,195-196} and silver\textsuperscript{190} catalysts commonly employed for the generation of metallocarbenes proved unsuccessful using dichloromethane as solvent at a range of temperatures (Table 2.10).

![Chemical structure](image)

**Table 2.10.** Attempted intramolecular C-H insertion of diazo compound 311.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, reflux, 1.5 h</td>
</tr>
<tr>
<td>2</td>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, rt, 4 h</td>
</tr>
<tr>
<td>3</td>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, (-25) °C, 1.5 h</td>
</tr>
<tr>
<td>4</td>
<td>AgOTf, CH\textsubscript{2}Cl\textsubscript{2}, rt, 3 h</td>
</tr>
<tr>
<td>5</td>
<td>AgOTf, CH\textsubscript{2}Cl\textsubscript{2}, (-25) °C, 3 h</td>
</tr>
<tr>
<td>6</td>
<td>Cu(acac)\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, rt, 24 h</td>
</tr>
<tr>
<td>7</td>
<td>Cu(acac)\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, (-78) °C to rt 16 h (slow warm-up)</td>
</tr>
</tbody>
</table>

In each case, analysis of the crude product distribution by \textsuperscript{1}H and \textsuperscript{13}C NMR indicated complete consumption of diazo carbonyl 311, presumably via generation of the corresponding metallocarbene. However, all attempted reaction conditions resulted in the formation of a complex mixture with no easily discernable major product(s). Our attention therefore turned to the more conservative strategies that hinge on ketone 309 or epoxide 310 (see Scheme 2.78).
2.6.3 Synthesis of Spiro γ-Lactone (±)-317 via Cross-Metathesis

Although synthesis of virgatolide A (1) via ketone 309 or epoxide 310 was considerably less speculative than the proposed carbene route, these strategies were likely to require multiple steps and therefore needed to be highly efficient in order to provide a viable synthetic route to virgatolide A (1). The construction of virgatolide A (1) via nucleophilic addition to ketone 309 was investigated first (see Scheme 2.78).

In order to construct virgatolide A (1), strict stereochemical control is required during the installation of the C-13 stereocentre. This poses a problem for the use of ketone 309 as a synthetic intermediate. Presumably, preferential equatorial delivery of a nucleophile to ketone 309 would furnish alcohol 315 with the undesired S configuration at C-13, placing the alcohol functionality in the axial position (Scheme 2.81). This issue could in principle be remedied either by axial delivery of a nucleophile, or by equatorial attack, followed by inversion of the resultant tertiary alcohol 315.

![Scheme 2.81. Equatorial addition of a nucleophile to ketone 309.](image)

In order to test the feasibility of the construction of virgatolide A (1) in this manner, we decided to attempt the synthesis of racemic spiro γ-lactone (±)-316 as a model system (Scheme 2.82). Retrosynthetically, γ-lactone (±)-316 would be derived from α-oxygenation of γ-lactone (±)-317. Formation of the spiro γ-lactone moiety would be achieved via hydrogenation of alkene precursor (±)-318 and subsequent intramolecular lactonisation. Alkene 318 would be constructed via cross-metathesis of alkene 319 and ethyl acrylate. Alkene (±)-319 would in turn be accessed
by inversion of the tertiary alcohol present in alkene (±)-320, the product of equatorial nucleophilic addition to ketone (±)-321. Ketone (±)-321 contains a phenyl substituent in order to confer a degree of conformational rigidity to the cyclohexane ring system, allowing assessment of the diastereoselectivity of the nucleophilic addition. The phenyl group would also enable us to avoid volatile synthetic intermediates.

Scheme 2.82. Retrosynthesis of model γ-lactone (±)-316.

Ketone (±)-321 was prepared via rhodium-catalysed conjugate addition of phenylboronic acid to cyclohexenone, affording (±)-321 in quantitative yield (Scheme 2.83). Reaction of ketone (±)-321 with vinylmagnesium bromide furnished separable alcohols (±)-320 and (±)-319 in high yield. As expected, NOESY correlations indicated the major product to be alcohol (±)-320, arising from nucleophilic attack via an equatorial trajectory. The relatively low diastereoselectivity in this example (~2:1) may be attributed to the lack of any axial substituents prior to addition, meaning that the 1,3-diaxial interactions with a nucleophile approaching from an axial trajectory are minimised. These interactions would be present during nucleophilic addition to ketone 309 due to the presence of the axial spiroketal oxygen (see Scheme 2.81).

Scheme 2.83. Reagents and conditions: a) PhB(OH)$_2$, [Rh(COD)Cl]$_2$, NEt$_3$, dioxane/H$_2$O (4:1), rt, 15 min, quant.; b) vinylMgBr, THF, −78 °C to rt, 3 h, 56% (±)-320, 33% (±)-319.
Before attempting to invert the quaternary stereocentre, we were eager to investigate the formation of the spiro \( \gamma \)-lactone, in order to validate the overall strategy (Scheme 2.84). Cross-metathesis of alkene \((\pm)-319\) and ethyl acrylate was conducted using Hoveyda-Grubbs second generation catalyst, providing alkene \((\pm)-318\) in moderate yield. Gratifyingly, hydrogenation of \((\pm)-318\) catalysed by palladium on carbon with concomitant spirolactonisation afforded \(\gamma\)-lactone \((\pm)-317\) in 93\% yield over two steps.

![Scheme 2.84](image)

**Scheme 2.84.** *Reagents and conditions:* a) ethyl acrylate, Hoveyda-Grubbs 2\textsuperscript{nd} generation, CH\(_2\)Cl\(_2\), rt, 16 h, 50\%; b) H\(_2\), Pd/C, EtOAc, rt, 24 h, 93\% over two steps.

Having secured a route to the spiro \(\gamma\)-lactone framework, the inversion of tertiary alcohol \((\pm)-320\) was now investigated. Since nucleophilic attack of ketone \((\pm)-321\) is expected to proceed *via* an equatorial trajectory, this method for the construction of the \(\gamma\)-lactone would only be applicable to the synthesis of virgatolide A (1) if inversion were successful.

Mitsunobu inversion of tertiary alcohols remains a challenge in organic synthesis, with few examples in the literature.\(^{198-199}\) In 2003, Mukaiyama et al. developed an inversion sequence capable of transforming tertiary alcohols to the corresponding tert-alkyl carboxylates (Scheme 2.85).\(^{199}\) The reaction proceeds *via* deprotonation of the tertiary alcohol 322 followed by trapping of the alkoxide anion with chlorodiphenylphosphine. Next, nucleophilic addition of phosphinite intermediate 323 to 2,6-dimethylbenzoquinone (324) generates zwitterionic intermediate 325. \(S_N2\) displacement of the activated hydroxyl group by a carboxylate anion then affords the inverted tert-alkyl carboxylate 327.
We aimed to apply this methodology to tertiary alcohol \((\pm)-320\), using acrylic acid as a nucleophile (Table 2.11). If successful, this would lead to the formation of alkene \((\pm)-328\) which could easily be converted to spiro \(\gamma\)-lactone \((\pm)-317\) via ring closing metathesis and hydrogenation of the double bond. Unfortunately, attempted inversion of alcohol \((\pm)-320\) did not provide any desired product, leading instead to the formation of a non-polar by-product unable to be fully purified by flash chromatography. Analysis of the \(^1\)H NMR spectrum revealed olefinic resonances inconsistent with product \((\pm)-328\). Use of standard Mitsunobu conditions conducted at a range of temperatures also proved ineffective to achieve the desired transformation, resulting only in recovered alcohol \((\pm)-320\). Noting the dearth of examples of tertiary alcohol inversion in the literature, an alternative approach for the synthesis of virgatolide A (1) was sought.
Since attempts to invert alcohol (±)-320 had proven unsuccessful, construction of the lactone subunit via epoxide (±)-331 was investigated (Scheme 2.86). In this strategy, spiro γ-lactone (±)-316 would be accessed via α-oxygenation of lactone (±)-317. Formation of the lactone would be achieved by gold-catalysed intramolecular hydroalkoxylation of bromoalkyne (±)-329. Bromoalkyne (±)-329 would be generated upon nucleophilic addition of lithium acetylide to epoxide (±)-331 and subsequent bromination.
The stereochemical configuration of epoxide 310 at C-13 is critical to the success of this strategy. In order to be a viable intermediate for the synthesis of virgatolide A (1), the configuration at C-13 must be R, placing the oxygen atom in the equatorial position (Scheme 2.87). We intended to construct the epoxide with the desired stereochemistry by Corey-Chaykovsky epoxidation of ketone 309, exploiting the known preference of sulfonium ylides to attack via an axial trajectory.

\[ \text{Scheme 2.87. Epoxidation of ketone 309.} \]

Unfortunately, attempts to construct model epoxide (±)-331 diastereoselectively via Corey-Chaykovsky epoxidation were unsuccessful.\(^{201-202}\) The reaction provided only moderate quantities of (±)-331 (34-43\%) with poor facial selectivity for delivery of the sulfur ylide, perhaps due to the conformational flexibility of the mono-substituted ring system. Noting that optimisation of the epoxidation could be conducted later, provided that the rest of the synthetic route was acceptable, we determined to forge ahead and investigate the construction of the γ-lactone subunit. Wittig methylenation followed by non-selective epoxidation was conducted, providing epoxides (±)-331/333 in good yield as an inseparable mixture of diastereomers (Scheme 2.88).
Scheme 2.88. Reagents and conditions: a) MePPh$_3$T, t-BuOK, 18-crown-6, 0 °C to rt, 48 h; b) m-CPBA, CH$_2$Cl$_2$, 0 °C, 2 h, 94% over two steps.

Treatment of epoxides (±)-331/333 with lithium acetylide-ethylenediamine complex furnished the two separable diastereomeric alcohols (±)-334 and (±)-330 (Scheme 2.89). Although separable, the relative stereochemical configurations of diastereomers (±)-334/330 were not determined at this stage. The structures in Scheme 2.89 were confirmed retrospectively (see below).

Scheme 2.89. Reagents and conditions: a) LiC≡CH∙en, DMSO, 0 °C, 4 h, 62% (±)-334, 23% (±)-330.

In 2012, Reddy et al. reported a series of intramolecular hydroalkoxylations of bromoalkynes to form the corresponding γ-lactones, catalysed by either gold(III) chloride or mercury(II) salts (Scheme 2.90). A similar method was published in the same year by Ye et al. who reported the gold-catalysed oxidation/cycloisomerisation of a series of alkynes. The advantage of the former method is that unmodified gold(II) chloride can be used as a catalyst, rather than the modified gold catalyst employed in the work of Ye et al. The mechanistic rationale for this transformation hinges on the formation of cyclic intermediate 336 following electrophilic activation of the triple bond by coordination to the metal catalyst and subsequent intramolecular nucleophilic attack. Hydrolysis followed by protodeauration yields the hemiacetal species 337 which then collapses to generate the corresponding lactone 338. However it should be noted that this pathway was not proven, and only represents a mechanistic hypothesis.
We now sought to apply this methodology to the synthesis of spiro \( \gamma \)-lactone (±)-340 (Scheme 2.91). Since greater quantities of alkyne isomer (±)-334 were available from the epoxide opening reaction, the cyclisation was investigated using this diastereomer as the substrate, despite possessing the undesired stereochemical configuration. Treatment of major isomer (±)-334 with \( N \)-bromosuccinimide afforded the corresponding bromoalkyne (±)-339 in good yield. Treatment of (±)-339 with gold (III) chloride in toluene/water furnished \( \gamma \)-lactone (±)-340 in a disappointing 36% yield. Pleasingly, when premixed chloro(triphenylphosphine) gold(I) and silver(V) hexafluoroantimonate was employed as a catalytic system, lactone (±)-340 was isolated in an improved 58% yield. Analysis of the NOESY NMR spectrum of lactone (±)-340 enabled assignment of the relative stereochemistry. In contrast to previously prepared lactone (±)-317 (see Section 2.6.3), no NOESY correlation was observed between H-3 and H-7, indicating that these substituents are trans to one another with respect to the cyclohexane ring. This analysis enabled retrospective assignment of alcohols (±)-330 and (±)-334 (see Scheme 2.89).

**Scheme 2.90.** Gold-catalysed hydroalkoxylation of bromoalkynes.\(^{200}\)

**Scheme 2.91.** *Reagents and conditions:* a) NBS, acetone, rt, 2 h, 94%; b) AuClPPh\(_3\), AgSbF\(_6\), toluene/H\(_2\)O, (10:1), rt, 24 h, 58%.

Having established a viable route to \( \gamma \)-lactone (±)-340 that was applicable to the synthesis of virgatolide A (1), provided that epoxidation could be conducted diastereoselectively, attention turned to the installation of the \( \alpha \)-hydroxyl functionality at C-2' of 1 (Scheme 2.92). The \( \alpha \)-hydroxyl group was to be installed \( \text{via} \) generation of the ester enolate and subsequent reaction with an oxaziridine reagent.\(^{204-205}\) Unfortunately, attempted
oxygenation of γ-lactone (±)-340 with either (E)-2-(para-methyl-phenylsulfonyl)-3-phenyloxaziridine or (+)-(10-camphorsulfonfyl)oxaziridine using lithium diisopropylamide or potassium bis(trimethylsilyl)amide as the base was unsuccessful. Use of lithium diisopropylamide as the base did not result in significant conversion of γ-lactone (±)-340 at either −78 °C or 0 °C, whilst the use of potassium bis(trimethylsilyl)amide resulted in the formation of a complex mixture. Finally, attempted oxidation of bromoalkyne (±)-339 to α-ketolactone (±)-342 with potassium permanganate according to the method of Wu et al. also proved unsuccessful.

\[ \text{O} \quad \text{O} \]
\[ \text{Ph} \quad \text{Ph} \]
\[ (±)-340 \]
\[ \text{a, b or c} \]
\[ \text{O} \quad \text{OH} \]
\[ \text{O} \quad \text{Br} \]
\[ \text{HO} \quad \text{HO} \]
\[ \text{Ph} \quad \text{Ph} \]
\[ (±)-341 \]
\[ \text{Br} \]
\[ (±)-339 \]
\[ \text{d} \]
\[ \text{O} \quad \text{O} \]
\[ \text{Ph} \quad \text{Ph} \]
\[ (±)-342 \]

**Scheme 2.92.** Reagents and conditions: a) LDA, (E)-2-(p-methyl-phenylsulfonyl)-3-phenyloxaziridine, THF, −78 °C, 4 h, no reaction; b) LDA, (+)-(10-camphorsulfonfyl)oxaziridine, THF, −78 °C to 0 °C, 4 h, no reaction; c) KHMDS, (E)-2-(p-methyl-phenylsulfonyl)-3-phenyloxaziridine, THF, −78 °C, 2 h, complex mixture; d) KMnO₄, NaHCO₃, MgSO₄, MeOH/H₂O (1:1), 0 °C to rt, 2 h, complex mixture.
2.6.5 Evaluation of Synthetic Routes to (±)-312 and (±)-316

Although all possible routes to γ-lactone (±)-316 had by no means been extinguished, we felt that given the difficulties encountered with our model system, a critical examination of our synthetic strategy was now warranted. If successful, the carbene-insertion strategy (Section 2.6.2), would have provided rapid access to virgatolide A (1) from virgatolide B (2) and preserved the stereochemical information at C-13. However, all attempts to perform this transformation on a model system proved unsuccessful. The use of ketone (±)-309 and epoxide (±)-310 as electrophilic intermediates both suffer from the drawback that the C-13 stereocentre, established earlier by the Mukaiyama aldol reaction, must be removed and reintroduced by other means. Direct installation of the three-carbon backbone by nucleophilic addition to ketone (±)-321 proceeded via an equatorial trajectory to provide tertiary alcohol (±)-320 (Section 2.6.3). Unfortunately, (±)-320 could not be inverted, rendering this approach inapplicable to the synthesis of virgatolide A (1). Finally, we deemed synthesis of virgatolide A (1) via epoxide 310 to be too inefficient to pursue further. Work on model epoxide (±)-334 (Section 2.6.4) had revealed that construction of virgatolide A (1) from 310 would increase the length of the synthetic strategy by six to seven steps. In addition to the lengthened reaction sequence, the epoxidation procedure would have to be optimised in order to improve the diastereoselectivity, the yield of the gold-catalysed spirolactonisation would have to be significantly improved, and a functional method for the α-oxidation of the resultant spiro γ-lactone would need to be established. For these reasons, an alternative synthetic strategy was sought.
2.6.6 Revised Synthetic Strategy

As none of the approaches devised in order to access virgatolide A (1) from a derivative of virgatolide B (2) appeared promising when tested on model systems, an alternative retrosynthetic strategy for the synthesis of virgatolide A (1) was developed. Still seeking to capitalise on the successful synthesis of virgatolide B (2), we aimed to employ an advanced intermediate from this synthesis. The revised synthetic strategy was based on a modified ketone-ketone aldol reaction (Scheme 2.93).

Retrosynthetically, virgatolide A (1) would be accessed via global deprotection and concomitant spiroketalisation of ketone 343, once more exploiting intramolecular hydrogen bonding in order to control regioselectivity. Spiro γ-lactone 343 would in turn be derived from lactonisation of the open-chain tertiary alcohol 344. Key intermediate 344 would be assembled by the aldol reaction between ketone 345 and previously synthesised methyl ketone 300. Chiral ketone 345 would be constructed by a diastereoselective aldol reaction between methyl ketone 346 and ethyl glyoxylate (347).

Scheme 2.93. Revised retrosynthetic analysis of virgatolide A (1).
2.6.7 Synthesis of Aldol 352

It was envisaged that required methyl ketone 346 could be synthesised from previously synthesised ester 244 (Section 2.2.5) by conversion to the Weinreb amide and subsequent alkylation (Scheme 2.94).211 This was borne out in practice: treatment of ester 244 with N,O-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in tetrahydrofuran at –20 °C provided amide 348 in 72% yield. Reaction of amide 348 with methylmagnesium bromide afforded methyl ketone 346 in 89% yield.

Scheme 2.94. Reagents and conditions: a) MeNHOMe·HCl, i-PrMgCl, THF, –20 °C, 2 h, 72%; b) MeMgBr, Et₂O, 0 °C to rt, 4 h, 89%.

With methyl ketone 346 in hand, attention turned to the aldol reaction of methyl ketone 346 and ethyl glyoxylate (347). In 2011, Loh et al. reported the development of an enantioselective Mukaiyama aldol reaction between glyoxylates and silyl enol ethers using indium tribromide and PyBox-type ligands (Scheme 2.95).212 In this work, silyl enol ethers derived from methyl ketones were heavily represented. Impressive enantioselectivity (90-98%) was observed in all cases, however all the examples employed aryl ketone-derived nucleophiles.212 Although the precise nature of the reactive intermediates involved are not known, the reaction is thought to proceed via the formation of an indium(III)-PyBox complex. Chelation by glyoxylate then generates a facially discriminated complex prior to nucleophilic addition of the silyl enol ether nucleophile.212

Scheme 2.95. Enantioselective Mukaiyama aldol reaction by Loh et al.212
We now sought to apply this methodology to the construction of aldol 345. Methyl ketone 346 was converted to the corresponding triisoproplysilyl enol ether 350 by treatment with triisoproplysilyl triflate and triethylamine in dichloromethane (Scheme 2.96). The key aldol reaction could now be attempted. When this reaction was first investigated, we did not have immediate access to indium tribromide. However, during optimisation of this methodology, Loh et al. employed indium trichloride in the reaction to similar effect.\textsuperscript{212} Interestingly, reaction of silyl enol ether 350 with ethyl glyoxylate (347) in the presence of indium trichloride, PyBox ligand (±)-349 and silver hexafluoroantimonate afforded a mixture of three products: aldol 352, alkene 353 and silyl enol ether 351. Aldol 352 and alkene 353 were inseparable by column chromatography, therefore the stereocchemical configurations of these compounds could not be conclusively determined at this stage.

Scheme 2.96. Reagents and conditions: a) ethyl glyoxylate, InCl\textsubscript{3}, AgSbF\textsubscript{6}, PyBox (+)-349, MeCN, \textasciitilde 40 °C, 16 h, 40\% 351, 24\% 352, 12\% 353.

The unexpected formation of silyl enol ether 351 is thought to be due to a competitive ene reaction between silyl enol ether 350 and ethyl glyoxylate (Scheme 2.97). Such a transformation has considerable precedent under the reaction conditions employed.\textsuperscript{213-216}

Scheme 2.97. Formation of silyl enol ether 351 via competitive ene reaction.
The stereochemical configuration of the newly generated chiral centre in silyl enol ether 351 was determined by $^{19}$F NMR analysis of the corresponding (R)-Mosher’s ester. Esterification of silyl enol ether 351 with (R)-(+)-$\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetic acid in dichloromethane afforded ester 354 (Scheme 2.98).

![Scheme 2.98. Reagents and conditions: a) (R)-MTPA-OH, DCC, DMAP, CH$_2$Cl$_2$, rt, 36 h, 55%, 88% d.e.](image)

Analysis of the $^{19}$F NMR spectrum of ester 354 according to the model proposed by Mosher enabled assignment of the configuration of the newly generated stereogenic centre as R (Figure 2.16). The TIPS-containing substituent was assigned as the more sterically demanding substituent (R$_L$) and the ester functionality as the less bulky substituent (R$_S$). In accordance with the model, the CF$_3$ group and the hydrogen atom attached to the stereocentre were assumed to be coplanar. When the configuration of the chiral centre is R this conformation places R$_L$ proximal to the phenyl ring. In order to minimise the steric penalty associated with this conformation, R$_L$ and the phenyl group rotate away from one another. This rotation moves the CF$_3$ substituent into the shielding zone associated the carbonyl group. In contrast, if the configuration at the chiral centre is S, the CF$_3$ group remains in the deshielding zone of the carbonyl group. The chemical shift of the CF$_3$ resonance of the R isomer of 354 is therefore expected to appear upfield relative to the corresponding signal from the S isomer.
Pleasingly, the major $\text{CF}_3$ resonance in the $^{19}\text{F}$ NMR spectrum of ester 354 was observed at $\delta = -71.5$ ppm, upfield relative to the signal due to the minor diastereomer at $\delta = -71.3$ ppm, confirming the stereochemistry of the newly generated stereogenic centre as $R$ (Figure 2.17).
selectivity of the reaction should be the same in both cases, forming the aldol product 352 with the desired $R$ configuration at the newly generated stereogenic centre.

It was proposed that the steric bulk of the TIPS group may be preventing the desired aldol reaction from occurring, thus allowing the ene reaction to become competitive. We were therefore interested in investigating the aldol reaction of the corresponding TMS enol ether (Scheme 2.99). Conversion of methyl ketone 346 to silyl enol ether 355 was effected by treatment with trimethylsilyl triflate and triethylamine. Silyl enol ether 355 was used in the Mukaiyama aldol reaction without prior purification. Pleasingly, the use of less-hindered silyl enol ether 355 afforded aldol 352 in excellent yield over two steps as a single diastereomer as observed by NMR analysis.

\[
\begin{align*}
\text{Scheme 2.99. Reagents and conditions:} & \quad \text{a) TMSOTf, NEt}_3, \text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C}, 15 \text{ min;} \\
& \quad \text{b) ethyl glyoxylate, InCl}_3, \text{AgSbF}_6, \text{PyBox (+)-349, MeCN, } -40 \, ^\circ\text{C}, 16 \text{ h, 81$\%$ over two steps.}
\end{align*}
\]

Although it was clear that aldol 352 had been formed with very high diastereoselectivity, the configuration of the newly generated stereocentre required confirmation. Formation of the Mosher’s ester was inconclusive due to the comparable steric bulk of the two substituents flanking the chiral centre. Attempted formation of the para-bromobenzoate ester in order to obtain a crystalline solid to enable acquisition of an X-ray crystal structure resulted only in elimination of the aldol moiety.

Following the failure of these two methods, we devised an alternative strategy to determine the configuration at the unknown stereocentre using the known stereocentre present in the molecule (Scheme 2.100). It was envisioned that tethering the two alcohol groups together to form a cyclic structure would enable assignment of the unknown stereocentre via analysis of the NOESY NMR spectrum. Removal of the PMB group by hydrogenolysis afforded diol 356 in 50$\%$ yield following purification. Reaction of diol 356 with dichlorodimethylsilane in dichloromethane afforded the corresponding siloxane 357 in good yield.
Assignment of the stereochemistry of the new chiral centre was now achieved by analysis of the NOESY spectrum of siloxane 357 (Figure 2.18). The H-2 and H-6 methine resonances both correlated to those of H-3 and H-5. The H-2 resonance correlated to both H-3 protons but only H-5a, the proton on the same side of the ring. Conversely, H-6 correlated only to H-3b and H-5b, the protons on the opposite side of the ring. These observations, together with the absence of any correlation between H-2 and H-6 confirmed that the C-2 stereocentre possessed the desired R stereochemistry.
Figure 2.18. Key nOe correlations observed in the NOESY spectrum of siloxane 357.

2.6.7 Attempted Synthesis of Aldol 364

Having successfully synthesised ketone 352, attention turned to the key aldol reaction with methyl ketone 300 in order to construct the carbon framework required by virgatolide A (1). To investigate the aldol reaction, three differently protected derivatives of ketone 352 were prepared (Scheme 2.101). Treatment of aldol 352 with para-methoxybenzyl trichloroacetimidate in the presence of catalytic camphorsulfonic acid afforded ketone 358 in a pleasing 77% yield. Realising that the pseudosymmetric nature of ketone 358 may reduce the stereoselectivity in the subsequent aldol reaction, differentially protected ketones 359 and 360 were prepared by reaction of aldol 352 with triisopropylsilyl triflate and triethylsilyl triflate respectively. During the silyl protection reactions it was found that the reaction temperature had to be strictly maintained at 0 °C in order to avoid
competitive silyl enol ether formation. Despite the moderate yields of these reactions, sufficient quantities of material could be obtained to investigate the key ketone-ketone aldol reaction.

**Scheme 2.101.** Reagents and conditions: a) PMB-trichloroacetimidate, CSA, CH₂Cl₂, rt, 48 h, 77% 358; b) TIPSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C to rt, 16 h, 54% 359; c) TESOTf, 2,6-lutidine, CH₂Cl₂, 16 h, 64% 360.

Realising the challenge posed by a diastereoselective ketone-ketone aldol reaction, we decided to investigate the transformation using a model nucleophile. The enol species derived from acetophenone (362) was chosen for this purpose, given that this nucleophile has been employed extensively in aldol reactions.⁷⁵-⁷⁶,²¹²,²¹⁹-²²⁰

We first investigated the reaction conditions successfully employed for the aldol reaction between methyl ketone 300 and aldehyde 245. Reaction of the trimethylsilyl enol ether derived from acetophenone 361 with ketone 358 using boron trifluoride as a Lewis acid resulted in decomposition of the starting materials within two hours at −78 °C (Table 2.12, Entry 1).¹⁴² The use of trifluoromethanesulfonimide as a Lewis acid resulted in incomplete conversion of ketone 358 at −78 °C (Entry 2).²²¹ Upon gradual warming of the reaction mixture, complete decomposition of the starting materials was observed.

Following these results, and realising that differential protection of ketone 352 was more likely to result in facial discrimination, we investigated the use of TIPS-protected ketone 359 as the electrophilic coupling partner in the aldol reaction. Attempted Mukaiyama aldol reaction with silyl enol ether 361 in the presence of boron trifluoride resulted only in recovered starting material, even after extended reaction times at 0 °C (Entry 3). The use of iodine as a Lewis acid, according to the method of Villano et al. also resulted in recovered starting material (Entry 4).²²² Employing the lithium enolate of acetophenone generated with lithium diisopropylamide resulted in complete decomposition (Entry 5).
Noting that attempted Mukaiyama aldol reactions of ketone 359 had resulted only in recovered starting material, the aldol reaction was investigated with a less sterically hindered ketone. Triethylsilyl-protected ketone 360 served this purpose. The decrease in steric bulk rendered ketone 360 more prone to degradation, generating a complex mixture upon attempted boron trifluoride-mediated Mukaiyama aldol reaction (Entry 6). Boron-mediated aldol reactions conducted at 0 °C and room temperature, using either acetophenone (362) or acetone (363) both failed to effect any conversion of ketone 360 to desired aldol 364 (Entries 7-9). Application of the aldol reaction conditions used for the synthesis of aldol 352 to this system also proved ineffective (Entry 10). An organocatalytic aldol reaction employing acetone as the nucleophile was unsuccessful, resulting only in recovered starting material after 24 hours (Entry 11).

Next, minimisation of the steric bulk was investigated by employing mono-protected ketone 352 as an electrophile. Interestingly, attempted Mukaiyama aldol reaction using boron trifluoride resulted only in cleavage of the PMB group upon gradual increase of the reaction temperature to 0 °C (Entry 12). No formation of coupled product was observed. Boron-mediated aldol reaction on this substrate resulted only in recovered starting material (Entry 13). Finally, reaction of cyclic ketone 357 with silyl enol ether 361 resulted in cleavage of the dimethylsilyl group, generating unprotected ketone 356 (Entry 14).
Table 2.12. Attempted aldol reaction of ketones 358-360 and 352.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>358, BF₃·OEt₂, −78 °C, 3 min then 361, 2 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>358, 361, HNTf₂, −78 °C to 0 °C, 16 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>359, BF₃·OEt₂, −78 °C, 3 min, then 361, −78 °C to 0 °C, 16 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>359, 361, I₂, CH₂Cl₂, 0 °C, 2 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>acetophenone, LDA, THF, 0 °C, 1 h, then −78 °C, 359, 2 h then 0 °C, 16 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>360, BF₃·OEt₂, −78 °C, 3 min, then −78 °C, 361, 4 h, then 0 °C, 16 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>acetophenone, n-Bu₂Bcl, NEt₃, 0 °C, 1 h, then 360, 16 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>acetophenone, n-Bu₂Bcl, NEt₃, rt, 1 h, then 360, 16 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>acetone, n-Bu₂Bcl, NEt₃, rt, 1 h, then 360, 16 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>360, 361, InCl₃, PyBox (+)-349, −20 °C, 16 h, then rt, 24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>360, acetone, (S)-proline, DMSO, rt, 24 h, then 40 °C, 8 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>352, BF₃·OEt₂, −78 °C, 3 min, then 361, −78 °C to 0 °C, 4 h</td>
<td>356</td>
</tr>
<tr>
<td>13</td>
<td>acetophenone, n-Bu₂Bcl, NEt₃, rt, 1 h, then 352, 16 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>14</td>
<td>357, BF₃·OEt₂, −78 °C, 3 min, then 361, −78 °C to 0 °C, 8 h.</td>
<td>356</td>
</tr>
</tbody>
</table>
2.6.8 Summary of the Attempted Synthesis of Virgatolide A (1)

In summary, four approaches for the construction of virgatolide A (1) that would employ intermediates readily available from the successful synthesis of virgatolide B (2) have been investigated (Scheme 2.102). Construction of the spiro γ-lactone present in virgatolide A (1) via carbene C-H insertion was tested on model diazo compound 311 (route A). Unfortunately, a survey of common transition metal catalysts for the generation of carbenes was unsuccessful, generating complex mixtures in all cases.

Successful formation of γ-lactone (±)-317 could be achieved following nucleophilic addition of vinylmagnesium bromide to ketone (±)-321 and subsequent cross-metathesis with ethyl acrylate (route B). However, this approach was not applicable to the synthesis of virgatolide A (1) since all attempts to invert tertiary alcohol (±)-320, the product of equatorial nucleophilic addition to ketone (±)-321, were unsuccessful.

In order to install the correct stereochemistry at C-13 of virgatolide A (1), the formation of γ-lactone (±)-340 via epoxides (±)-331/333 was examined (route C). The formation of epoxide (±)-331 did not exhibit appreciable selectivity for axial delivery of the sulfur ylide. However, the formation of γ-lactone (±)-340 was investigated in order to evaluate the overall synthetic strategy. Alkyne addition to epoxides (±)-331/333, followed by bromination of alkyne (±)-334 and gold-catalysed lactonisation afforded γ-lactone (±)-340 in moderate yield. Attempted α-oxygenation of γ-lactone (±)-340 with oxaziridine reagents was unsuccessful when using either lithium diisopropylamide or potassium bis(trimethylsilyl)amide as the base. Synthesis of virgatolide A (1) via this method would necessitate significant improvements in the epoxidation, lactonisation and oxygenation steps and would also require an additional six to seven steps to be conducted on an advanced intermediate. This route was therefore abandoned and a more elegant approach sought.

Towards this end, the preparation of virgatolide A (1) by the aldol reaction of previously synthesised methyl ketone 300 and ketones 358-360 was studied. Diastereoselective aldol reaction of readily accessible methyl ketone 346 and ethyl glyoxylate (347) proceeded in high yield, affording aldol 352 as a single diastereomer (route D). However, all attempts to conduct an aldol reaction of ketones 358-360 with simple methyl ketones were unsuccessful, indicating that ketones 358-360 were unsuitable as substrates for aldol addition.
Scheme 2.102. a) vinylMgBr, THF, −78 °C to rt, 3 h, 56% (±)-320, 33% (±)-319; b) ethyl acrylate, Hoveyda-Grubbs 2nd generation, CH₂Cl₂, rt, 16 h, 50%; c) H₂, Pd/C, EtOAc, rt, 24 h, 93% over two steps; d) LiC≡CH-en, DMSO, 0 °C, 4 h, 62% (±)-334, 23% (±)-330; e) NBS, acetone, rt, 2 h, 94%; f) AuClPPh₃, AgSbF₆, toluene/H₂O, (10:1), rt, 24 h, 58%; g) TMSOTf, NEt₃, CH₂Cl₂, 0 °C, 15 min; h) ethyl glyoxylate, InCl₃, AgSbF₆, PyBox (+)-349, MeCN, −40 °C, 16 h, 81% over two steps.
2.6.9 Future Work

Following the successful synthesis of virgatolide B (2), it remains to execute the total synthesis of the other two members of this family of natural products: virgatolide A (1) and virgatolide C (3). The synthesis of virgatolide C (3) is expected to be readily achievable via adaptation of the successful synthesis employed for virgatolide B (2). In particular, disconnection of the spiroketal moiety present in virgatolide C (3) provides ketone 365, which would in turn be accessed via the aldol reaction between methyl ketone 366 and aldehyde 245 (Scheme 2.103). Methyl ketone 366 would be accessed from trans-diol 367 following iodination and carboalkoxylation. Diol 367 would be derived from epoxide 368 by hydrolytic epoxide opening. Epoxide 368 would be accessed from previously synthesised alkene 260 using an asymmetric epoxidation reaction.223

Scheme 2.103. Retrosynthetic analysis of virgatolide C (3).

Virgatolide A (1) poses a greater synthetic challenge. A proposed synthesis of virgatolide A (1) involves Prins cyclisation224-226 of alkene 371 and ortholactone 369 (Scheme 2.104). Retrosynthetically, alkene 371 would be accessed by a Wittig olefination of ketone 372. Ortholactone 369 would be constructed from ester 370 by dihydroxylation and phthalide formation.
followed by removal of the phenolic protecting groups. Scheme 2.104 outlines a proposed mechanism for the Prins cyclisation process. Generation of oxonium ion 373 from ortholactone 369 followed by nucleophilic addition of alcohol 371 would generate coupled intermediate 374. Formation of a second oxonium ion 375 would be followed by nucleophilic attack by the double bond, generating tertiary carbocation 376. Intramolecular trapping of the carbocation by the free acid functionality would then complete the formation of the spiro γ-lactone moiety. Deprotection of the resultant product 377 would provide virgatolide A (1).

Scheme 2.104. Retrosynthetic analysis of virgatolide A (1).
Chapter Three

Experimental
3.1 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 (1H 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 CDCl3, CD3OD, (CD3)3CO, C8D6 or (CD3)SO solutions on either a Bruker DRX300 spectrometer operating at 300 MHz for 1H nuclei and 75 MHz for 13C nuclei or using a Bruker DRX-400 spectrometer operating at 400 MHz for 1H nuclei and 100 MHz for 13C nuclei. Chemical shifts are reported in parts per million (ppm) from tetramethylsiane (δ = 0) and were measure 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.
3.2 Synthesis of Phthalides (±)-177, (±)-179 and Alkenes 167, 194 and 195

Methyl 2,4,6-trihydroxybenzoate (96)

To a stirred solution of 2,4,6-trihydroxybenzoic acid monohydrate 169 (10 g, 53 mmol) in acetone (300 mL) was added K$_2$CO$_3$ (7.4 g, 53 mmol) and dimethyl sulfate (5.5 mL, 59 mmol) at room temperature. The solution was stirred for 16 h and then quenched with conc. aq. NH$_3$ (40 mL) and stirred for a further 20 min. The reaction mixture was acidified to pH ~ 5 by the addition of aq. 2M HCl, concentrated in vacuo and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the title compound 96 (5.6 g, 30 mmol, 57%) as a white solid; m.p. 175–179 °C (lit. 177–178 °C)$^{110}$; $^1$H NMR (400 MHz, ((CD$_3$)$_2$SO): $\delta$ 10.40 (2H, s, OH $\times 2$), 10.18 (1H, s, OH), 5.85 (2H, s, H-3 and H-5), 3.84 (3H, s, OCH$_3$); $^{13}$C NMR (100 MHz, (CD$_3$)$_2$SO): $\delta$ 170.4 (C=O), 163.7 (C), 161.9 (C $\times 2$), 95.1 (Ar-CH $\times 2$), 94.3 (C), 52.0 (CH$_3$). The spectroscopic data were in agreement with those reported in the literature.$^{110}$

Methyl 4-(benzylxy)-2,6-dihydroxybenzoate (172)

To a stirred solution of ester 96 (0.25 g, 1.4 mmol) in anhydrous acetone (6.8 mL) was added K$_2$CO$_3$ (0.19 g, 1.4 mmol), NaI (70 mg, 0.43 mmol) and benzyl bromide (0.16 mL, 1.4 mmol). The resultant mixture was heated at reflux for 3 h, cooled to room temperature and quenched with H$_2$O (10 mL). The reaction mixture was extracted with EtOAc (3 × 15 mL), the combined organic extracts dried over MgSO$_4$ and then concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the title compound 172 (0.23 g, 0.84 mmol, 62%) as a white solid; m.p. 110-112 °C (lit. 117-118 °C)$^{227}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41-7.31 (5H, m, Ar-H $\times 5$),
6.13 (2H, s, H-3 and H-5), 5.04 (2H, s, OCH$_2$), 4.00 (3H, s, OCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 169.5 (C), 165.4 (C × 2), 162.4 (C=O), 135.9 (C), 128.5 (Ar-CH × 2), 128.1 (Ar-CH), 127.4 (Ar-CH × 2), 95.1 (Ar-CH × 2), 94.0 (C), 69.9 (CH$_2$), 52.4 (CH$_3$). The spectroscopic data were in agreement with those reported in the literature.$^{227}$

**Methyl 4-(benzyloxy)-2-hydroxy-6-methoxybenzoate (173)**

![Chemical structure](image)

To a stirred solution of ester 172 (4.4 g, 16 mmol), PPh$_3$ (4.3 g, 16 mmol) and MeOH (0.98 mL, 24 mmol) in THF (120 mL) at 0 °C was added DIAD (3.2 mL, 16 mmol) dropwise. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with sat. aq. NH$_4$Cl (40 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 8:1) afforded the *title compound* 173 (3.0 g, 10 mmol, 63%) as a colourless solid; m.p. 116-117 °C (lit. 106 °C)$^{228}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 12.03 (1H, s, OH), 7.44-7.35 (5H, m, Ar-H × 5), 6.20 (1H, d, $J = 2.4$ Hz, Ar-H), 6.06 (1H, d, $J = 2.4$ Hz, Ar-H), 5.06 (2H, s, OCH$_2$), 3.92 (3H, s, OCH$_3$), 3.82 (3H, s, OCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.7 (C=O), 165.9 (C), 164.5 (C), 162.2 (C), 136.0 (C), 128.7 (Ar-CH × 2), 128.3 (Ar-CH), 127.7 (Ar-CH × 2), 96.8 (C), 94.4 (Ar-CH), 92.2 (Ar-CH), 70.2 (CH$_2$), 56.1 (CH$_3$), 52.2 (CH$_3$). The spectroscopic data were in agreement with those reported in the literature.$^{228}$
Methyl 4-(benzyloxy)-6-methoxy-2-(((trifluoromethyl)sulfonyl)oxy)benzoate (168)

To a stirred solution of phenol 173 (1.4 g, 5.0 mmol) in CH₂Cl₂ (20 mL) was added NEt₃ (1.3 mL, 9.9 mmol) and N-phenyltriflimide (2.5 g, 7.0 mmol). The resultant mixture was heated to reflux for 48 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (20 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL), the combined organic extracts dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the title compound 168 (2.1 g, 5.0 mmol, 99%) as a pale amber solid; m.p. 57-58 °C (lit. 71 °C); ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.26 (5H, m, Ar-H × 5), 6.52 (1H, d, J = 2.0 Hz, Ar-H), 6.48 (1H, d, J = 2.0 Hz, Ar-H), 5.02 (2H, s, OC₂H₂), 3.85 (3H, s, OCH₃), 3.75 (3H, s, OCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 163.5 (C=O), 161.7 (C), 159.7 (C), 148.1 (C), 135.4 (C), 128.8 (Ar-CH × 2), 128.5 (Ar-CH), 127.6 (Ar-CH × 2), 125.1 (CF₃, J = 315 Hz), 110.0 (C), 100.2 (Ar-CH), 99.2 (Ar-CH), 70.7 (CH₂), 56.3 (CH₃), 52.4 (CH₃). The spectroscopic data were in agreement with those reported in the literature.²²⁸

(E)-Methyl 4-(benzyloxy)-6-methoxy-2-(prop-1-en-1-yl)benzoate (167)

To a solution of triflate 168 (1.9 g, 4.5 mmol) and LiCl (0.58 g, 14 mmol) in degassed THF (8 mL) was added Pd(PPh₃)₄ (0.26 g, 0.2 mmol) and allyltributylstannane (1.6 mL, 5.1 mmol). The reaction mixture was heated to 80 °C, stirred for 48 h and then allowed to cool to room temperature. THF (40 mL) and tBuOK (1.5 g, 13 mmol) were added and the reaction mixture heated to 45 °C with stirring for 8 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (100 mL). The layers were separated and the combined organic extracts washed successively with aq. NH₃ (25% v/v, 25 mL), aq. HCl (1 M, 25 mL) and sat. aq. NaHCO₃ (25 mL). The organic extract was dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography
Experimental

(hexanes/EtOAc 5:1) afforded the title compound 167 (1.2 g, 3.8 mmol, 84%) as a colourless oil; \( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.43-7.31 (5H, m, Ar-H \( \times 5 \)), 6.67 (1H, d, \( J = 2.0 \) Hz, Ar-H), 6.42 (1H, d, \( J = 2.0 \) Hz, Ar-H), 6.36 (1H, dd, \( J = 15.6, 1.6 \) Hz, H-1'), 6.18 (1H, dq, \( J = 15.6, 6.5 \) Hz, H-2'), 5.10 (2H, s, OCH\(_2\)), 3.89 (3H, s, OCH\(_3\)), 3.76 (3H, s, OCH\(_3\)), 1.85 (3H, dd, \( J = 6.5, 1.6 \) Hz, H-3'); \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 168.4 (C=O), 160.3 (C), 157.8 (C), 137.7 (C), 136.4 (C), 129.0 (CH), 128.4 (Ar-CH \( \times 2 \)), 127.9 (CH), 127.5 (Ar-CH), 127.3 (Ar-CH \( \times 2 \)), 115.3 (C), 102.4 (Ar-CH), 97.9 (Ar-CH), 69.9 (CH\(_2\)), 55.7 (CH\(_3\)), 52.0 (CH\(_3\)), 18.5 (CH\(_3\)); IR (film) \( \nu \)max 2950, 1724, 1599, 1427, 1260, 1155, 1097, 1039, 961, 700 cm\(^{-1}\); HRMS (ESI+) for C\(_{19}\)H\(_{20}\)O\(_4\) [M+Na]\(^+\) requires 335.1254 found 335.1240.

5-(Benzyloxy)-3-(1-hydroxyethyl)-7-methoxyisobenzofuran-1(3H)-one ((\(\pm\))-175)

To a solution of alkene 167 (370 mg, 1.2 mmol) in acetone/H\(_2\)O (1:1, 9.5 mL) was added NMO (150 mg, 1.3 mmol) and OsO\(_4\) (2.5% w/w in \( t \)BuOH, 0.31 mL, 0.024 mmol) and the resultant mixture stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (30 mL), the layers separated and the organic layer washed successively with sat. aq. Na\(_2\)S\(_2\)O\(_4\) (5 mL), H\(_2\)O (5 mL) and sat. aq. NaCl (5 mL). The organic extract was dried over MgSO\(_4\) and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the title compound (\(\pm\))-175 (310 mg, 0.98 mmol, 82%) as a white solid; m.p. 75-78 °C; \( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.49-7.31 (5H, m, Ar-H \( \times 5 \)), 6.64 (1H, s, Ar-H), 6.47 (1H, s, Ar-H), 5.19 (1H, d, \( J = 4.0 \) Hz, H-3), 5.08 (2H, ABq, \( \Delta \delta_{AB} = 0.02, J_{AB} = 11.5 \) Hz, OCH\(_2\)), 4.15-4.13 (1H, m, H-1'), 3.85 (3H, s, OCH\(_3\)), 2.65 (1H, br s, OH), 1.23 (3H, d, \( J = 6.4 \) Hz, H-2'); \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 168.3 (C=O), 165.6 (C), 159.4 (C), 151.9 (C), 135.5 (C), 128.6 (Ar-CH \( \times 2 \)), 128.3 (Ar-CH), 127.5 (Ar-CH \( \times 2 \)), 107.3 (C), 99.7 (Ar-CH), 99.3 (Ar-CH), 82.5 (CH), 70.6 (CH\(_2\)), 68.2 (CH), 55.8 (CH\(_3\)), 18.1 (CH\(_3\)); IR (film) \( \nu \)max 3452, 2935, 1716, 1603, 1347, 1317, 1213, 1161, 1064, 762, 689 cm\(^{-1}\); HRMS (ESI+) for C\(_{18}\)H\(_{19}\)O\(_5\) [M+Na]\(^+\) requires 337.1046 found 337.1060.
To a stirred solution of phthalide (±)-175 (250 mg, 0.80 mmol) and DIPEA (1.1 mL, 6.4 mmol) in THF (7 mL) at 0 °C was added EOMCl (0.75 mL, 8.0 mmol). The resultant solution was allowed to warm to room temperature and stirred for 48 h. The reaction was quenched with sat. aq. NaHCO₃ (7 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the title compound (±)-177 (290 mg, 0.77 mmol, 96%) as a colourless oil; ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.30 (5H, m, Ar-H × 5), 6.65 (1H, s, Ar-H), 6.48 (1H, s, Ar-H), 5.27 (1H, d, J = 3.6 Hz, H-3), 5.10 (2H, s, OCH₂), 4.63 (2H, ABq, ΔδAB = 0.06, JAB = 7.0 Hz, OCH₂O), 4.18-4.14 (1H, m, H-1'), 3.87 (3H, s, OCH₃), 3.48-3.39 (2H, m, OCH₂), 1.12 (3H, t, J = 6.8 Hz, CH₃), 1.01 (3H, d, J = 6.4 Hz, H-2'); ¹³C NMR (100 MHz, CDCl₃): δ 167.9 (C=O), 165.3 (C), 159.3 (C), 151.8 (C), 135.5 (C), 128.5 (Ar-CH × 2), 128.2 (Ar-CH), 127.4 (Ar-CH × 2), 107.6 (C), 99.7 (Ar-CH), 99.5 (Ar-CH), 93.8 (CH₂), 80.5 (CH), 72.4 (CH), 70.5 (CH₂), 63.3 (CH₂), 55.8 (CH₃), 14.8 (CH₃), 14.7 (CH₃); IR (film) νmax 2976, 2934, 1756, 1604, 1450, 1326, 1211, 1157, 1019, 840 cm⁻¹; HRMS (ESI+) for C₂₁H₂₄O₆ [M+Na]⁺ requires 395.1465 found 395.1467.
5-(Benzyloxy)-3-(1-((tert-butyldimethylsilyl)oxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one ((±)-178)

To a stirred solution of phthalide (±)-175 (100 mg, 0.32 mmol) in CH$_2$Cl$_2$ (2 mL) at −78 °C was added 2,6-lutidine (0.15 mL, 1.3 mmol) and tert-butyldimethylsilyl triflate (0.20 mL, 0.95 mmol). The resultant solution was stirred at −78 °C for 4 h, and then quenched by the addition of sat. aq. NaHCO$_3$ (2 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography afforded the title compound (±)-178 (140 mg, 0.32 mmol, 100%) as a colourless oil; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36-7.31 (5H, m, Ar-H × 5), 6.68 (1H, d, $J = 2.0$ Hz, Ar-H), 6.49 (1H, d, $J = 2.0$ Hz, Ar-H), 5.15 (1H, d, $J = 3.7$ Hz, H-3), 5.09 (2H, s, OCH$_2$), 4.25-4.18 (1H, m, H-1’), 3.87 (3H, s, OCH$_3$), 0.96 (3H, d, $J = 6.6$ Hz, H-2’), 0.82 (9H, s, CH$_3$ × 3), 0.04 (3H, s, SiCH$_3$), −0.02 (3H, s, SiCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.2 (C=O), 165.3 (C), 159.4 (C), 152.2 (C), 135.7 (C), 128.7 (Ar-CH × 2), 128.3 (Ar-CH), 127.4 (Ar-CH × 2), 108.0 (C), 99.9 (Ar-CH), 99.5 (Ar-CH), 81.6 (CH), 70.4 (CH$_2$), 68.2 (CH), 55.8 (CH$_3$), 25.5 (CH$_3$ × 3), 17.8 (C), 17.6 (CH$_3$), −4.6 (CH$_3$), −5.1 (CH$_3$); IR (film) $\nu_{\text{max}}$ 2953, 2929, 2856, 1755, 1602, 1471, 1322, 1210, 1154, 1021, 957, 833, 732 cm$^{-1}$; HRMS (ESI+) for C$_{24}$H$_{32}$O$_5$Si [M+Na]$^+$ requires 451.1911, found 451.1897.
To a stirred solution of phthalide (±)-177 (60 mg, 0.16 mmol) and silver trifluoracetate (53 mg, 0.24 mmol) in CH$_2$Cl$_2$ (3.2 mL) was added I$_2$ (61 mg, 0.24 mmol) in CH$_2$Cl$_2$ (1.7 mL) over 30 min. The reaction mixture was stirred at room temperature for 30 min, then filtered through Celite®.
Experimental

Sat. aq. Na₂S₂O₃ (1 mL) and NaOH (1M, 1 mL) were added to the filtrate with stirring. The layers were separated and the aqueous layer further extracted with CH₂Cl₂ (2 × 3 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash column chromatography (hexanes/EtOAc 2:1) afforded the title compound (±)-185 (77 mg, 0.15 mmol, 96%) as a colourless solid; m.p. 146-148 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.49-7.32 (5H, m, Ar-H × 5), 6.45 (1H, s, H-6), 5.24 (2H, s, OCH₂), 5.06 (1H, d, J = 1.0 Hz, H-3), 4.82 (1H, qd, J = 6.5 Hz, 1.0 Hz, H-1’), 4.43 (1H, d, J = 7.6 Hz, OCH₂O), 4.25 (1H, d, J = 7.6 Hz, OCH₂O), 3.94 (3H, s, OCH₃), 3.20-3.16 (1H, m, OCH₂), 2.97-2.93 (1H, m, OCH₂), 1.47 (3H, d, J = 6.5 Hz, H-2’), 1.00 (3H, t, J = 7.0 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 167.6 (C=O), 162.8 (C), 159.9 (C), 153.9 (C), 128.8 (Ar-CH × 2), 128.4 (Ar-CH), 127.0 (Ar-CH × 2), 110.3 (C), 97.0 (Ar-CH), 96.8 (CH₂), 84.9 (CH), 71.6 (CH₂), 68.8 (C), 68.7 (CH), 63.0 (CH₂), 56.2 (CH₃), 17.4 (CH₃), 14.9 (CH₃); IR (film) v max 2969, 2928, 1744, 1592, 1439, 1241, 1199, 1181, 1021, 974, 743 cm⁻¹; HRMS (ESI+) for C₂₁H₂₃O₆I [M+Na]+ requires 521.0432 found 521.0427.

5-(Benzyloxy)-4-bromo-3-((tert-butyldimethylsilyl)oxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one (±)-186

To a stirred solution of phthalide (±)-178 (35 mg, 0.082 mmol) in CH₂Cl₂ (1 mL) at 0 °C was added NBS (16 mg, 0.090 mmol) in three portions over 30 min. The resultant solution was allowed to warm to room temperature and stirred for 18 h. The reaction was quenched by the addition of H₂O (1 mL) and the layers separated. The aqueous layer was further extracted with CH₂Cl₂ (3 × 3 mL), the combined organic extracts dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound (±)-186 (38 mg, 0.075 mmol, 93%) as a colourless solid; m.p. 150-154 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.47-7.34 (5H, m, Ar-H × 5), 6.48 (1H, s, H-6), 5.26 (2H, ABq, ΔδAB = 0.03, JAB = 12.2 Hz, OCH₂), 5.14 (1H, d, J = 1.0 Hz, H-3), 4.72 (1H, qd, J = 6.4, 1.0 Hz, H-1’), 3.89 (3H, s, OCH₃), 1.44 (3H, d, J = 6.4 Hz, H-2’), 0.57 (9H, s, CH₃ × 3), −0.06 (3H, s, CH₃), −0.39 (3H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 167.8 (C=O), 160.8 (C), 158.9 (C), 150.7 (C), 135.5 (C), 128.9 (Ar-CH × 2), 128.5 (Ar-CH),
To a stirred solution of phthalide (±)-177 (25 mg, 0.058 mmol) and silver trifluoroacetate (19 mg, 0.088 mmol) in CH$_2$Cl$_2$ (1.2 mL) was added I$_2$ (22 mg, 0.088 mmol) in CH$_2$Cl$_2$ (0.6 mL) over 30 min. The resultant suspension was stirred at room temperature for 3 h and then filtered through Celite®. Excess I$_2$ was scavenged by the addition of sat. aq. Na$_2$S$_2$O$_3$ (0.5 mL). The layers were separated and the aqueous layer further extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography afforded the title compound (±)-187 (29 mg, 0.052 mmol, 90%) as a colourless solid; m.p. 170-173 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.49-7.35 (5H, m, Ar-CH × 5), 6.43 (1H, s, H-6), 5.26 (2H, ABq, $\Delta\delta_{AB} = 0.02$, $J_{AB} = 12.3$ Hz, OCH$_2$), 5.02 (1H, s, H-3), 4.79 (1H, q, $J = 6.5$ Hz, H-1'), 3.90 (3H, s, OCH$_3$), 1.45 (3H, d, $J = 6.5$ Hz, H-2'), 0.57 (9H, s, CH$_3$ × 3), −0.06 (3H, s, CH$_3$), −0.41 (3H, s, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 168.0 (C=O), 162.8 (C), 160.1 (C), 154.5 (C), 153.5 (C), 128.9 (Ar-CH × 2), 128.5 (Ar-CH), 127.1 (Ar-CH × 2), 111.0 (C), 97.3 (Ar-CH), 85.7 (CH), 71.8 (CH$_2$), 69.1 (C), 65.6 (CH), 56.5 (CH$_3$), 25.4 (CH$_3$ × 3), 21.1 (CH$_3$), 17.6 (C), −4.3 (CH$_3$), −5.4 (CH$_3$); IR (film) $\nu_{\text{max}}$ 2928, 2855, 1760, 1594, 1358, 1180, 1043, 957, 837, 776 cm$^{-1}$; HRMS (ESI+) for C$_{24}$H$_{31}$IO$_5$Si [M+H]$^+$ requires 555.1058 found 555.1058.
4-Allyl-5-(benzyloxy)-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one
((±)-188)

To a stirred solution of iodide (±)-187 (30 mg, 0.060 mmol), Pd(OAc)$_2$ (1.1 mg, 5.8 μmol), PPh$_3$ (3.0 mg, 11 μmol) in degassed DMF (0.5 mL) under argon was added allyltributylstannane (23 μL, 0.070 mmol) and the resultant solution heated to 110 °C for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with CH$_2$Cl$_2$ (10 mL) and the layers separated. The organic extract was sequentially washed with H$_2$O (2 × 3 mL) and sat. aq. NaCl (3 mL), then dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the title compound (±)-188 (21 mg, 0.051 mmol, 84%) as a colourless solid; m.p. 126-132 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.42-7.33 (5H, m, Ar-H × 5), 6.50 (1H, s, H-6), 5.93-5.84 (1H, m, H-2”), 5.30 (1H, d, $J = 1.2$ Hz, H-3), 5.17 (2H, s, OCH$_2$), 5.06-4.95 (2H, m, H-3”), 4.51 (1H, d, $J = 7.5$ Hz, OCH$_2$O), 4.36 (1H, d, $J = 7.5$ Hz, OCH$_2$O), 4.33-4.27 (1H, m, H-1”), 3.93 (3H, s, OCH$_3$), 3.60-3.54 (1H, m, H-1”a), 3.44-3.38 (1H, m, H-1”b), 3.30 (1H, dq, $J = 9.5, 7.0$ Hz, OCH$_2$) 3.10 (1H, dq, $J = 9.5, 7.0$ Hz, OCH$_2$), 1.35 (3H, d, $J = 6.4$ Hz, H-2”), 1.05 (3H, t, $J = 7.0$ Hz, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 168.7 (C=O), 162.8 (C), 158.4 (C), 149.6 (C), 136.1 (C), 135.4 (CH), 128.8 (Ar-CH × 2), 128.5 (Ar-CH), 127.3 (Ar-CH × 2), 115.8 (CH$_2$), 114.9 (C), 107.5 (C), 96.4 (Ar-CH), 93.5 (CH$_2$), 82.0 (CH), 71.3 (CH), 71.0 (CH$_2$), 63.3 (CH$_2$), 56.1 (CH$_3$), 29.9 (CH$_2$), 17.4 (CH$_3$), 15.0 (CH$_3$); IR (film) $\nu_{\text{max}}$ 2975, 2927, 1751, 1601, 1501 1443, 1198, 1144, 1025, 913, 740 cm$^{-1}$; HRMS (ESI+) for C$_{24}$H$_{28}$O$_6$ [M+Na]$^+$ requires 435.1778 found 435.1772.
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3-(1-(Ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one ((±)-189)

To a stirred solution of phthalide (±)-177 (110 mg, 0.29 mmol) in MeOH (6 mL) was added Pd/C (11 mg, 10 wt%) and stirred under H₂ at room temperature for 24 h. The reaction mixture was filtered through Celite® and concentrated in vacuo. Purification by flash chromatography afforded the title compound (±)-189 (74 mg, 0.26 mmol, 89%) as a colourless solid; m.p. 134-137 ºC; ¹H NMR (400 MHz, CDCl₃): δ 7.76 (1H, br s, OH), 6.63 (1H, s, Ar-H), 6.49 (1H, s, Ar-H), 5.31 (1H, d, J = 3.6 Hz, H-3), 4.66 (2H, ABq, ΔδAB = 0.06, JAB = 7.0 Hz, OCH₂O), 4.20-4.17 (1H, m, H-1'), 3.88 (3H, s, OCH₃), 3.50-3.44 (2H, m, OCH₂), 1.15 (3H, t, J = 7.2 Hz, CH₃), 1.10 (3H, d, J = 6.4 Hz, H-2'); ¹³C NMR (100 MHz, CDCl₃): δ 169.6 (C=O), 164.4 (C), 159.9 (C), 152.0 (C), 106.5 (C), 101.9 (Ar-CH), 99.5 (Ar-CH), 94.0 (CH₂), 81.3 (CH), 72.5 (CH₂), 63.6 (CH), 55.8 (CH₃), 15.1 (CH₃), 14.9 (CH₃); IR (film) νmax 3274, 2976, 2927, 1708, 1599, 1439, 1169, 966, 845, 689 cm⁻¹; HRMS (ESI+) for C₁₄H₁₈O₆ [M+Na]⁺ requires 305.0996 found 305.0997.

4-Bromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one ((±)-190) and
4,6-Dibromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one ((±)-191)

To a stirred solution of phthalide (±)-189 (30 mg, 0.11 mmol) in CH₂Cl₂ (2.0 mL) at 0 ºC was added NBS (21 mg, 0.12 mmol) in 3 portions over 30 min. The reaction mixture was stirred at room temperature for 24 h and then concentrated in vacuo. Purification by flash chromatography
Experimental

(hexanes/EtOAc 1:1) afforded the title compounds \((\pm)-190\) (24 mg, 0.07 mmol, 62%) and \((\pm)-191\) (7 mg, 0.02 mmol, 15%) as colourless solids.

4-Bromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one
\((\pm)-190\)

Contains 14% starting material and \(N\)-hydroxysuccinimide by NMR.

m.p. 145-150 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.66 (1H, s, H-6), 5.19 (1H, d, \(J = 1.0\) Hz, H-3), 4.70-4.66 (1H, m, H-1'), 4.49 (1H, d, \(J = 7.5\) Hz, OCH\(_2\)O), 4.32 (1H, d, \(J = 7.5\) Hz, OCH\(_2\)O), 3.92 (3H, s, OCH\(_3\)), 3.27-3.19 (1H, m, OCH\(_2\)), 3.07-2.99 (1H, m, OCH\(_2\)), 1.47 (3H, d, \(J = 6.5\) Hz, H-2'), 1.04 (3H, t, \(J = 7.0\) Hz, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 177.5 (C=O), 168.1 (C), 159.7 (C), 159.2 (C), 150.3 (C), 109.7 (C) 100.2 (Ar-CH), 93.2 (CH\(_2\)), 83.3 (CH), 69.0 (CH), 63.4 (CH\(_2\)), 56.4 (CH\(_3\)), 17.6 (CH\(_3\)), 15.0 (CH\(_3\)); IR (film) \(\nu_{\text{max}}\) 3171, 1975, 2932, 1709, 1594, 1360, 1211, 1070, 976, 836 cm\(^{-1}\); HRMS (ESI+) for BrC\(_{14}\)H\(_{17}\)O\(_6\) [M+Na]\(^+\) requires 383.0101 found 383.0102.

4,6-Dibromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one
\((\pm)-191\)

m.p. 118-121 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.22 (1H, d, \(J = 1.6\) Hz, H-3), 4.69 (1H, qd, \(J = 6.4, 1.6\) Hz, H-1'), 4.50 (1H, d, \(J = 7.0\) Hz, OCH\(_2\)O), 4.32 (1H, d, \(J = 7.0\) Hz, OCH\(_2\)O), 4.18 (3H, s, OCH\(_3\)), 3.27-3.20 (1H, m, OCH\(_2\)), 3.02-2.95 (1H, m, OCH\(_2\)), 1.49 (3H, d, \(J = 6.4\) Hz, H-2'), 1.03 (3H, t, \(J = 6.9\) Hz, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 166.2 (C=O), 156.3 (C), 155.1 (C), 148.8 (C), 113.4 (C), 106.4 (C), 97.3 (C), 93.3 (CH\(_2\)), 83.5 (CH), 69.1 (CH\(_2\)), 63.5 (CH\(_3\)), 63.3 (CH), 17.6 (CH\(_3\)), 15.0 (CH\(_3\)); IR (film) \(\nu_{\text{max}}\) 3223, 2927, 1732, 1586, 1364, 1159, 1089, 1017, 772 cm\(^{-1}\); HRMS (ESI+) for Br\(_2\)C\(_{14}\)H\(_{16}\)O\(_6\) [M+Na]\(^+\) requires 460.9206 found 460.9198.
To a stirred solution of phthalide \((\pm)\)-189 (37 mg, 0.13 mmol) and silver trifluoroacetate (43 mg, 0.19 mmol) in \(\text{CH}_2\text{Cl}_2\) (2.6 mL) was added \(\text{I}_2\) (29 mg, 0.19 mmol), in \(\text{CH}_2\text{Cl}_2\) (1.5 mL) over 30 min. The reaction mixture was stirred at room temperature for 16 h and filtered through Celite®. Sat. aq. \(\text{Na}_2\text{S}_2\text{O}_3\) (1.0 mL) was added to the filtrate. The layers were separated, the aqueous layer further extracted with \(\text{CH}_2\text{Cl}_2\) (2 × 3 mL), the combined organic extracts dried over \(\text{Na}_2\text{SO}_4\) and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the title compounds \((\pm)-192\) (30 mg, 0.070 mmol, 56%) and \((\pm)-193\) (14 mg, 0.030 mmol, 20%) as colourless solids.

\[3-\left(1-\text{Ethoxymethoxy}\right)\text{ethyl}-5\text{-hydroxy}-4\text{-iodo}-7\text{-methoxyisobenzofuran-1(3H)}\text{-one}\]
\((\pm)-192\)

Contains 15% starting material by NMR.

m.p. 149-151 °C (Some trace material did not melt until 169 °C); \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.68 (1H, s, H-6), 5.08 (1H, d, \(J = 1.0\) Hz, H-3), 4.78 (1H, qd, \(J = 6.6\) Hz, 1.0 Hz, H-1'), 4.47 (1H, d, \(J = 7.2\) Hz, OCH\(_2\)O), 4.28 (1H, d, \(J = 7.2\) Hz, OCH\(_2\)O), 3.91 (3H, s, OCH\(_3\)), 3.22-3.18 (1H, m, OCH\(_2\)), 3.00-2.97 (1H, m, OCH\(_2\)), 1.47 (1H, d, \(J = 6.6\) Hz, H-2'), 1.03 (3H, t, \(J = 7.2\) Hz, CH\(_3\)), \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 168.6 (C=O), 162.3 (C), 160.1 (C), 154.1 (C), 109.9 (C), 99.2 (Ar-CH), 93.0 (CH\(_2\)), 85.1 (CH), 68.5 (CH), 67.1 (C), 63.3 (CH\(_2\)), 56.2 (CH\(_3\)), 17.4 (CH\(_3\)), 15.0 (CH\(_3\)); IR (film) \(\nu_{\text{max}}\) 3172, 2975, 2926, 1708, 1586, 1447, 1362, 1212, 1070, 980, 834, 732 cm\(^{-1}\); HRMS (ESI+) for C\(_{14}\)H\(_{17}\)IO\(_6\) [M+Na]\(^+\) requires 430.9962 found 430.9966.
3-(1-(Ethoxymethoxy)ethyl)-5-hydroxy-4,6-diiodo-7-methoxyisobenzofuran-1(3H)-one (±)-193

m.p. 119-121 °C; ¹H NMR (400 MHz, CDCl₃): δ 5.10 (1H, d, J = 1.5 Hz, H-3), 4.77 (1H, qd, J = 6.5, 1.5 Hz, H-1'), 4.48 (1H, d, J = 7.5 Hz, OCH₂O), 4.29 (1H, d, J = 7.5 Hz, OCH₂O), 4.17 (3H, s, OCH₃), 3.24-3.16 (1H, m, OCH₂), 2.96-2.88 (1H, m, OCH₂), 1.51 (3H, d, J = 6.5 Hz, H-2'), 1.02 (3H, t, J = 7.2 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 166.1 (C=O), 159.7 (C), 159.3 (C), 154.4 (C), 113.2 (C), 93.3 (CH₂), 91.0 (C), 85.3 (CH), 83.0 (C), 68.9 (CH), 63.5 (CH₂), 63.3 (CH₃), 17.6 (CH₃), 15.1 (CH₃); IR (film) νmax 3365, 2983, 2928, 1748, 1574, 1401, 1170, 1068, 1012, 730 cm⁻¹; HRMS (ESI+) for C₁₄H₁₆I₂O₆ [M+Na]⁺ requires 556.8928 found 556.8932.

(E)-Methyl 4,6-dihydroxy-2-(prop-1-en-1-yl)benzoate (194)

To a stirred solution of alkene 167 (100 mg, 0.32 mmol) in CH₂Cl₂ (1.6 mL) under argon at −78 °C was added BBr₃ (1M in CH₂Cl₂, 1.6 mL) over 20 min. The solution was stirred at −78 °C for a further 20 min and then quenched by the addition of H₂O (1.0 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with CH₂Cl₂ (2 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the title compound 194 (67 mg, 0.28 mmol, 87%); m.p. 117-119 °C; ¹H NMR (400 MHz, CDCl₃): δ 11.63 (1H, s, OH), 6.92 (1H, dq, J = 15.5, 1.8 Hz, H-1'), 6.40 (1H, d, J = 2.5 Hz, Ar-H), 6.33 (1H, s, J = 2.5 Hz, Ar-H), 5.93 (1H, dq, J = 15.5, 6.5 Hz, H-2'), 5.63 (1H, s, OH), 3.92 (3H, s, OCH₃), 1.87 (3H, dd, J = 6.5, 1.8 Hz, H-3'); ¹³C NMR (100 MHz, CDCl₃): δ 171.8 (C=O), 164.6 (C), 160.5 (C), 144.4 (C), 131.8 (CH), 128.3 (CH), 108.4 (Ar-CH), 104.2 (C), 102.2 (Ar-CH), 52.2 (CH₃), 18.7 (CH₃); IR (film) νmax 3342, 1911, 1644, 1577, 1325, 1267, 1178, 1018, 832, 690 cm⁻¹; HRMS (ESI+) for C₁₁H₁₂O₄ [M+Na]⁺ requires 231.0628 found 231.0631.
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(E)-Methyl 4-(benzyloxy)-6-hydroxy-2-(prop-1-en-1-yl)benzoate (195)

\[ \begin{align*} 
\text{OH} & \quad \text{OMe} \\
194 & \quad \rightarrow \\
\text{BnO} & \quad \text{OMe} \\
195 
\end{align*} \]

A stirred suspension of alkene 194 (42 mg, 0.19 mmol), K$_2$CO$_3$ (27 mg, 0.19 mmol) and benzyl bromide (27 μL, 0.23 mmol) in acetone (1.0 mL) was heated under reflux for 16 h. The reaction mixture was allowed to cool to room temperature, H$_2$O (2.0 mL) added and the resultant solution extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography afforded the title compound 195 (41 mg, 0.14 mmol, 68%) as a colourless solid; m.p. 82-85 ºC; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 11.63 (1H, s, OH), 7.39-7.27 (5H, m, Ar-H × 5), 6.92 (1H, dq, $J = 15.4$, 1.6 Hz, H-1'), 6.53 (1H, d, $J = 2.5$ Hz, Ar-H), 6.42 (1H, d, $J = 2.5$ Hz, Ar-H), 5.91 (1H, dq, $J = 15.4$, 6.5 Hz, H-2'), 4.99 (2H, s, OCH$_2$), 3.86 (3H, s, OCH$_3$), 1.85 (3H, dd, $J = 6.5$, 1.6 Hz, H-3'); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.7 (C=O), 164.9 (C), 163.1 (C), 143.5 (C), 136.2 (C), 132.0 (CH), 128.6 (Ar-CH×2), 128.1 (Ar-CH), 127.7 (CH), 127.5 (Ar-CH×2), 108.5 (Ar-CH), 103.8 (C), 100.6 (Ar-CH), 69.9 (CH$_2$), 51.9 (CH$_3$), 18.6 (CH$_3$); IR (film) $\nu_{max}$ 2916, 1646, 1607, 1568, 1430, 1328, 1252, 1168, 1029, 962, 731, 692 cm$^{-1}$; HRMS (ESI+) for C$_{18}$H$_{18}$O$_4$ [M+Na]$^+$ requires 321.1097 found 321.1099.

(E)-Methyl 4-(benzyloxy)-3-bromo-6-methoxy-2-(prop-1-en-1-yl)benzoate (196)

\[ \begin{align*} 
\text{OMe} & \quad \text{OMe} \\
167 & \quad \rightarrow \\
\text{BnO} & \quad \text{OMe} \\
196 
\end{align*} \]

To a stirred solution of alkene 167 (50 mg, 0.16 mmol) in CH$_2$Cl$_2$ at 0 ºC was added NBS (31 mg, 0.18 mmol) in three portions over 30 min. The reaction mixture was stirred at 0 ºC for 3 h and stored at 0 ºC overnight. The solution was allowed to warm to room temperature and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the title compound 196 as a colourless solid; m.p. 89-91 ºC; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.48-7.29 (5H, m, Ar-H × 5), 6.47 (1H, d, $J = 16.0$ Hz, H-1'), 6.41 (1H, s, Ar-H), 5.86 (1H, dq, $J = 16.0$, 6.4 Hz, H-2'), 5.16 (2H, s, OCH$_2$), 3.80 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$), 1.85 (1H, d,
Experimental

$J = 6.4 \text{ Hz}, H-3')$; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.1 (C=O), 156.1 (C), 156.3 (C), 138.5 (C), 136.1 (C), 131.8 (CH), 128.8 (CH), 128.7 (Ar-CH $\times 2$), 128.1 (Ar-CH), 127.0 (Ar-CH $\times 2$), 117.2 (C), 104.8 (C), 96.8 (Ar-CH), 71.2 (CH$_2$), 56.1 (CH$_3$), 52.3 (CH$_3$), 18.8 (CH$_3$); IR (film) $\nu_{\text{max}}$ 2947, 1729, 1585, 1570, 1336, 1218, 1202, 1067, 974, 738 cm$^{-1}$; HRMS (ESI+) for BrC$_{19}$H$_{19}$O$_4$ [M+Na]$^+$ requires 413.0359 found 413.0361.

(E)-Methyl 3,5-dibromo-4,6-dihydroxy-2-(prop-1-en-1-yl)benzoate (200)

![Diagram of compounds 194 and 200](image)

To a stirred solution of alkene 194 (30 mg, 0.14 mmol) in toluene (1.3 mL) at 0 °C under nitrogen was added NBS (28 mg, 0.16 mmol) in three portions over 30 min. The resultant mixture was stirred at room temperature for 16 h and then concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1 to 5:1) afforded the title compound 200 (30 mg, 0.088 mmol, 56%) as a colourless solid; m.p. 93-96 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.44 (1H, dq, $J = 16.0, 2.0$ Hz, H-1'), 5.55 (1H, dq, $J = 16.0, 6.6$ Hz, H-2'), 3.90 (3H, s, OCH$_3$), 1.89 (3H, dd, $J = 6.6, 2.0$ Hz, H-3'); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.1 (C=O), 158.8 (C), 153.9 (C), 141.6 (C), 131.4 (CH), 129.5 (CH), 107.4 (C), 103.8 (C), 97.2 (C), 52.7 (CH$_3$), 18.4 (CH$_3$); IR (film) $\nu_{\text{max}}$ 3412, 2956, 2853, 1637, 1580, 1395, 1318, 1243, 952, 795 cm$^{-1}$; HRMS (ESI+) for Br$_2$C$_{11}$H$_{10}$O$_4$ [M+Na]$^+$ requires 386.8838 found 386.8837.
3.3 Synthesis of Trifluoroboratoamide 158

Diisopropyl(iodomethyl)boronate (212)

To a stirred solution of B(O\(^{\text{Pr}}\)\(_3\)) \(_{210}\) (11.5 mL, 50 mmol) and diiodomethane (4.0 mL, 50 mmol) in THF (25 mL) at \(-78^\circ\text{C}\) was added \(^{\text{^6}}\text{BuLi}\) (1.6 M in hexane, 31 mL, 50 mmol) over 30 min and the resultant solution stirred for a further 30 min. The reaction was quenched by the addition of HCl (4M in dioxane, 13 mL, 52 mmol) and allowed to warm to room temperature with stirring over 1 h. The reaction mixture was filtered through oven-dried Celite\(^\circ\) under nitrogen and concentrated in vacuo. Distillation under reduced pressure afforded the title compound \(_{212}\) (7.5 g, 28 mmol, 55%) as a pale yellow liquid; b.p. 92 \(^\circ\text{C}/40 \text{mbar};\) \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 4.39 (2H, septet, \(J = 6.3 \text{ Hz}, \text{CH} \times 2\)), 2.13 (2H, s, CH\(_2\)), 1.19 (12H, d, \(J = 6.3 \text{ Hz}, \text{CH}_3 \times 4\)); The spectroscopic data were in agreement with those reported in the literature.\(^{125,126}\)

Iodomethylpinacolboronate (153)

A solution of iodide \(_{212}\) (7.5 g, 28 mmol) and anhydrous pinacol (3.9 g, 33 mmol) in \(n\)-pentane (10 mL) was stirred at room temperature overnight. The reaction mixture was washed with H\(_2\)O (2 \(\times\) 5 mL), dried over MgSO\(_4\) and the organic layer concentrated in vacuo to afford the title compound \(_{153}\) (7.4 g, 28 mmol, 100%) as a pale yellow liquid; \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.13 (2H, s, CH\(_2\)), 1.24 (12H, s, CH\(_3\) \(\times\) 4); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 84.3 (C \(\times\) 2), 24.5 (CH\(_3\) \(\times\) 4); The signal arising from the methylene carbon was not observed. The spectroscopic data were in agreement with those reported in the literature.\(^{82,125-126}\)
Experimental

(R,R)-N-(1-Hydroxy-1-phenylpropan-2-yl)-N-methylpropionamide (149)

![Chemical structure](image)

To a solution of pseudoephedrine 213 (9.4 g, 57 mmol) and triethylamine (9.5 mL, 68 mmol) in CH₂Cl₂ (110 mL) in a room temperature bath was added propionic anhydride (7.8 mL, 61 mmol) in 1.0 mL portions and the resultant solution stirred at for 30 min. The reaction mixture was quenched with H₂O (20 mL) and the layers separated. The organic layer was washed with sat. aq. NaHCO₃ (2 × 30 mL), 1M HCl (2 × 30 mL), dried over Na₂SO₄ and concentrated in vacuo. Recrystallization from boiling toluene (38 mL) afforded the title compound 149 (11.5 g, 52.0 mmol, 91%) as white crystals; m.p. 113-115 °C (lit. 113-114 °C)⁶⁴,⁸⁴; [α]ᵣᵣ¹⁰ = −103.0 (c 0.65 in MeOH), lit. −100.0 (c 0.57 in MeOH)⁶⁴,⁸⁴; ¹H NMR (400 MHz, C₆D₆): δ 7.32-7.06 (5H, m Ar-H × 5), 4.86 (1H, br s, OH), 4.53-4.49 (1H, m, J = 7.3 Hz, H-1'), 4.31-4.23 (1H, m, H-2'), 4.22* (1H, dd, J = 8.7, 3.0 Hz, H-1*), 3.71* (1H, m, H-2*), 3.46* (1H, br s, OH*), 2.81* (3H, s, NCH₃*), 2.49-2.42* (1H, m, H-2a*), 2.12 (3H, s, NCH₃), 2.12-2.05* (1H, m, H-2b*), 1.83-1.69 (2H, m, H-2), 1.19* (3H, t, J = 7.3 Hz, H-3*), 0.93 (3H, d, J = 7.1 Hz, H-3'), 0.57* (3H, d, J = 6.6 Hz, H-3'); ¹³C NMR (100 MHz, C₆D₆): δ 175.3 (C=O), 174.4* (C=O), 143.8 (C), 142.9* (C), 128.6* (Ar-CH × 2), 128.4 (Ar-CH × 2), 128.2* (Ar-CH), 127.5 (Ar-CH), 127.4* (Ar-CH × 2), 127.0 (Ar-CH × 2), 76.5 (CH), 75.4* (CH), 59.0 (CH), 58.5* (CH), 32.6 (CH₃), 27.5 (CH₂), 27.0* (CH₂), 26.6* (CH₃) 15.3* (CH₃), 14.4 (CH₃), 10.0* (CH₃), 9.4 (CH₃); The spectroscopic data were in agreement with those reported in the literature.⁶⁴,⁸⁴
(S)-N-((1R,2R)-1-Hydroxy-1-phenylpropan-2-yl)-N-2-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl)propanamide (154)

To a stirred solution of anhydrous LiCl (3.0 g, 72 mmol) in THF (27 mL) was added
diisopropylamine (3.2 mL, 23 mmol) and the resultant solution cooled to −78 °C. n-BuLi (1.6 M
in hexane, 14 mL, 22 mmol) was added. The solution was stirred at −78 °C for 5 min and then at
0 °C for 5 min. The reaction mixture was cooled to −78 °C and a solution of amide 149 (2.0 g, 9.1 mmol) in THF (30 mL) added via cannula. The solution was stirred at −78 °C for 1 h, 0 °C for
15 min and room temperature for 5 min. The reaction mixture was then cooled to 0 °C and iodide 153 (3.6 g, 14 mmol) added. The solution was stirred at 0 °C for 30 min, quenched with sat. aq.
NH₄Cl (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were
washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by
flash chromatography (hexanes/EtOAc 3:1 to 1:1) afforded the title compound 154 (2.3 g, 6.2 mmol, 67%) as a colourless oil; ¹H NMR (400 MHz, C₆D₆, 1.2:1 rotamer ratio):  7.39-7.08
(5H, m, Ar-H), 4.73-4.71* (1H, m, H-1*), 4.42 (1H, d, J = 9.1 Hz, H-1'), 4.18* (1H, s, H-2''),
4.18-4.08* (1H, br s, OH*), 4.02-3.95 (1H, m, H-2'), 3.35-3.26 (1H, m, H-2), 2.78 (3H, s, NCH₃),
2.70-2.63* (1H, m, H-2*), 2.39* (3H, s, NCH₃*), 1.67 (1H, dd, J = 15.8, 9.7 Hz, H-3a), 1.24 (1H,
 dd, J = 15.8, 7.3 Hz, H-3b), 1.15* (15H, s, CH₃* × 5), 1.13 (15H, m, CH₃ × 5), 1.04 (3H, d,
J = 7.0 Hz, CH₃), 0.61* (3H, d, J = 6.7 Hz, CH₃); The spectroscopic data were in agreement with
those reported in the literature. ²

Sample contained both pinacol and EtOAc that could not be removed. For this reason only a
¹H NMR spectrum was obtained. An optical rotation was not run for this reason. Yields were
calculated based on the ¹H NMR.
Potassium (S)-3-(trifluoroborato)-N-((1R,2R)-1-hydroxy-1-phenylpropan-2-yl)-N-2-dimethylpropanamide (158)

To a stirred solution of 154 (2.3 g, 6.4 mmol) in acetonitrile (13 mL) at 0 °C was added KHF₂ (2.6 g, 32 mmol) in H₂O (8.0 mL). The reaction mixture was stirred for 30 min, concentrated in vacuo, and dried under vacuum for 18 h. The residue was extracted with acetone (3 × 11 mL) and the combined extracts concentrated in vacuo. Et₂O (15 mL) was added to precipitate the product and the resultant solid filtered and dried under vacuum to furnish the title compound 158 (1.7 g, 4.9 mmol, 77%) as a white solid; m.p. 133-138 °C (lit. 124-129 °C); [α]D²⁵ = −51.2 (c 1.28 in MeOH), lit. +48.2 (c 1.42 in MeOH) for opposite enantiomer; ¹H NMR (400 MHz, DMSO-d₆, 2:1 rotamer ratio, less than 3% pinacol by weight): δ 7.44-7.21 (5H, m, Ar-H), 5.33-5.31 (1H, m, OH), 5.03-5.00* (1H, m, OH*), 4.68-4.45 (3H, m, H-1', H-2' and H-1*), 4.23-4.17* (1H, m, H-2*''), 2.80 (3H, s, NCH₃), 2.70* (3H, s, NCH₃*), 2.54-2.49 (1H, m, H-2*), 2.64-2.59 (1H, m, H-2), 0.92* (3H, d, J = 6.5 Hz, CH₃*), 0.86 (3H, d, J = 6.5 Hz, CH₃), 0.78 (3H, d, J = 6.7 Hz, CH₃), 0.64-0.58* (1H, m, H-3a*), 0.16-0.09 (1H, m, H-3a), 0.01-0.13 (1H, m, H-3b and H-3b*); ¹³C NMR (100 MHz, DMSO-d₆), δ 179.5 (C=O), 179.4* (C=O), 143.9 (C), 143.8* (C), 127.9* (Ar-CH × 2), 127.8 (Ar-CH × 2), 127.4* (Ar-CH × 2), 127.2* (Ar-CH), 126.9 (Ar-CH), 126.8 (Ar-CH × 2), 74.2* (CH), 73.9 (CH), 56.1 (CH), 53.4* (CH), 32.3 (CH), 31.9* (CH), 29.4 (CH₃), 25.9* (CH₃), 24.9 (CH₂ and CH₃*), 19.9* (CH₃), 18.8 (CH₃), 15.4* (CH₃), 13.9 (CH₃); The spectroscopic data were in agreement with those reported in the literature.
3.4 Synthesis of Halides 208 and 209

2-Bromoresorcinol (224)

To a suspension of resorcinol 223 (2.0 g, 18 mmol) in CHCl₃ (31 mL) was added Br₂ (3.1 mL, 61 mmol) dropwise and the resultant mixture stirred at room temperature for 30 min. The reaction was then heated to reflux for 2 h, allowed to cool to room temperature and quenched with sat. aq. Na₂SO₃ (50 mL). The reaction mixture was extracted with EtOAc (3 × 50 mL), the combined organic extracts dried over MgSO₄ and concentrated in vacuo. The crude product was then dissolved in a mixture of H₂O (46 mL) and MeOH (9.0 mL). A solution of NaOH (1.5 g, 37 mmol) and Na₂SO₃ (4.7 g, 37 mmol) in H₂O (54 mL) was added and the resultant solution stirred at room temperature for 18 h. The reaction mixture was acidified to pH ~ 4 by addition of 1 M aq. HCl and extracted with Et₂O (3 × 100 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the title compound 224 (3.2 g, 17 mmol, 93%) as a colourless solid; m.p. 100-102 °C (lit. 102-103 °C)¹³⁷; ¹H NMR (400 MHz, CDCl₃): δ 7.10 (1H, t, J = 8.0 Hz, H-5), 6.61 (2H, d, J = 8.0 Hz, H-4 and H-6), 5.44 (2H, s, OH); ¹³C NMR (100 MHz, CDCl₃): δ 153.0 (C × 2), 129.1 (Ar-CH), 108.1 (Ar-CH × 2), 99.4 (C); The spectroscopic data were in agreement with those reported in the literature.¹³⁷
2-Iodoresorcinol (225)

To a stirred solution of resorcinol 223 (1.0 g, 9.1 mmol) and I$_2$ (2.5 g, 9.7 mmol) in H$_2$O (6.8 mL) at 0 °C was added NaHCO$_3$ (0.85 g, 10 mmol) portionwise over 30 min. The reaction mixture was stirred at room temperature for 1 h, and then extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo to afford the title compound 225 (1.6 g, 6.8 mmol, 75%) as a colourless solid; m.p. 85-87 °C (lit. 90 °C); $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.10 (1H, t, $J$ = 8.4 Hz, H-5), 6.55 (2H, d, $J$ = 8.4 Hz, H-4 and H-6), 5.47 (2H, br s, OH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.8 (C × 2), 130.4 (Ar-CH), 107.4 (Ar-CH × 2), 77.6 (C); The spectroscopic data were in agreement with those reported in the literature.$^{138}$

2-Bromo-1,3-bis(ethoxymethoxy)benzene (208)

To a stirred solution of bromide 224 (2.0 g, 11 mmol) and diisopropylethylamine (11 mL, 64 mmol) in CH$_2$Cl$_2$ (13 mL) at 0 °C was added chloromethylethyl ether (3 mL, 32 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound 208 (3.2 g, 11 mmol, 99%) as a colourless oil; $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.16 (1H, t, $J$ = 8.4 Hz, H-5), 6.84 (2H, d, $J$ = 8.4 Hz, H-4 and H-6), 5.28 (4H, s, OCH$_2$O × 2), 3.77 (4H, q, $J$ = 6.8 Hz, OCH$_2$ × 2), 1.22 (6H, t, $J$ = 6.8 Hz, CH$_3$ × 2); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.2 (C × 2), 128.2 (Ar-CH), 109.4 (Ar-CH × 2), 103.8 (C), 93.9 (CH$_2$ × 2), 64.7 (CH$_2$ × 2), 15.1 (CH$_3$ × 2); IR (film) $\nu$_max 2977, 2902, 1593, 1466, 1242, 1028, 890, 771 cm$^{-1}$; HRMS (ESI+) for BrC$_{12}$H$_{17}$NaO$_4$ [M+Na]$^+$ requires 327.0202 found 327.0211.
2-Iodo-1,3-bis(ethoxymethoxy)benzene (209)

To a stirred solution of iodide 225 (0.77 g, 3.3 mmol) and diisopropylethylamine (3.4 mL, 20 mmol) in CH₂Cl₂ (5.2 mL) at 0 °C was added chloromethylethyl ether (0.91 mL, 9.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of H₂O (10 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound 209 (1.0 g, 2.9 mmol, 89%) as a colourless oil; ¹H NMR (400 MHz, CDCl₃): δ 7.19 (1H, t, J = 8.0 Hz, H-5), 6.76 (2H, d, J = 8.0 Hz, H-4 and H-6), 5.28 (4H, s, OCH₂ × 2), 3.76 (4H, q, J = 7.2 Hz, OCH₂ × 2), 1.22 (6H, t, J = 7.2 Hz, CH₃ × 2); ¹³C NMR (100 MHz, CDCl₃): δ 157.6 (C × 2), 129.7 (Ar-CH), 108.5 (Ar-CH × 2), 93.8 (CH₂ × 2), 80.7 (C), 64.7 (CH₂ × 2), 15.1 (CH₃ × 2); IR (film) ν_max 2976, 2902, 1587, 1461, 1240, 1115, 1034, 888, 771 cm⁻¹; HRMS (ESI+) for C₁₂H₁₇INO₄ [M+Na]^+ requires 375.0064 found 375.0071.
3.5 Synthesis of Aldol 247

(S)-3-(2,6-Bis(ethoxymethoxy)phenyl)-N-((1R,2R)-1-hydroxy-1-phenylpropan-2-yl)-N,2-dimethylpropanamide (214)

A flask was charged with trifluoroboratoamide 158 (400 mg, 1.2 mmol), bromide 208 (390 mg, 1.3 mmol), Pd(OAc)$_2$ (13.0 mg, 0.06 mmol, 10 mol %), RuPhos (55 mg, 0.12 mmol, 20 mol %) and K$_2$CO$_3$ (490 mg, 3.5 mmol) and purged with N$_2$ three times. A degassed mixture of toluene (4 mL) and H$_2$O (1 mL) was then added. The reaction mixture was heated at 85 °C with stirring for 1.5 h and then allowed to cool to room temperature. A solution of pH 7 buffer (2 mL), prepared from NaHPO$_4$ (1.7 g) and NaH$_2$PO$_4$·2H$_2$O (1.2 g) in H$_2$O (50 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic extracts dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 4:1 to 1:1) afforded the title compound 214 (330 mg, 0.72 mmol, 60%) as a colourless oil; [α]$_D^{25}$ = −26.4 (c 0.73 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$, 5:1 rotamer ratio): δ 7.36-7.22 (5H, m, Ar- H × 5), 7.15-7.08 (1H, m, H-4' and H-4'*), 6.85* (2H, d, $J = 8.4$ Hz, H-3'* and H-5'*), 6.78 (2H, d, $J = 8.4$ Hz, H-3' and H-5'), 5.20 (4H, s, OCH$_2$O × 2), 4.84 (1H, br s, OH), 4.65-4.61 (1H, m, H-1"), 4.55* (1H, d, $J = 8.2$ Hz, H-1"*), 4.32-4.30 (1H, m, H-2'"), 4.20-4.15* (1H, m, H-2'"*), 3.72-3.66 (4H, m, OCH$_2$ × 2 and OCH$_2$* × 2), 3.30-3.26* (1H, m, H-2'"*), 3.15-2.99* (2H, m, H-3*), 3.04-2.99 (1H, m, H-2), 2.92-2.86 (1H, m, H-3, + NCH$_3$*), 2.82 (3H, s, NCH$_3$), 2.67 (1H, dd, $J = 12.8$, 4.6 Hz, H-3b), 1.23-1.17 (6H, m, CH$_3$ × 2), 1.14 (3H, d, $J = 7.0$ Hz, H-3"), 1.03 (3H, d, $J = 6.6$ Hz, H-4), 0.96* (3H, d, $J = 6.7$ Hz, H-3'"*); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 179.5 (C=O), 178.3* (C=O), 156.9* (C × 2), 156.7 (C × 2), 142.9 (C), 141.2* (C), 128.7* (Ar-CH × 2), 128.4 (Ar-CH × 2), 127.6 (Ar-CH), 127.5 (Ar-CH), 127.3* (Ar-CH × 2), 126.4 (Ar-CH × 2), 118.3* (C), 117.7 (C), 107.9* (Ar-CH × 2), 107.6 (Ar-CH × 2), 93.4* (CH$_2$ × 2), 93.3 (CH$_2$ × 2), 76.8 (CH), 75.4* (CH), 64.5 (CH$_2$ × 2), 60.1 (CH), 58.2* (CH), 36.3 (CH), 35.5* (CH), 33.5 (CH$_3$), 27.5 (CH$_2$), 26.8* (CH$_2$), 17.0* (CH$_3$), 16.1 (CH$_3$), 15.4* (CH$_3$), 15.2 (CH$_3$ × 2), 14.6 (CH$_3$); IR (film) v$_{max}$ 3379, 2951, 1614, 1469, 1251, 1073, 1029, 703 cm$^{-1}$; HRMS (ESI+) for C$_{28}$H$_{37}$NO$_6$ [M+Na]$^+$ requires 482.2513 found 482.2519.
Chapter Three

**((S)-4-(2,6-Bis(ethoxymethoxy)phenyl)-3-methylbutan-2-one (207))**

To a stirred solution of amide 214 (100 mg, 0.22 mmol) in Et₂O (2.2 mL) at −78 °C was added MeLi (0.5 M in Et₂O, 1.1 mL, 0.55 mmol). The resultant suspension was warmed to 0 °C and stirred for 15 min. Excess MeLi was scavenged by the addition of diisopropylamine (0.25 mL, 1.8 mmol) and the reaction mixture stirred for a further 15 min at 0 °C. A solution of acetic acid (0.25 mL) in Et₂O (1.5 mL) was added, followed by H₂O (10 mL). The reaction mixture was extracted with Et₂O (3 × 10 mL), the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 7:1) afforded the *title compound* 207 (59 mg, 0.19 mmol, 88%) as a colourless oil; [α]₂⁵D = +45.9 (c 1.07 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.19 (1H, t, J = 8.4 Hz, H-4'), 6.79 (2H, d, J = 8.4 Hz, H-3' and H-5'), 5.21 (4H, s, OCH₂×2), 3.71 (4H, q, J = 7.2 Hz, OCH₂×2), 2.88 (1H, dd, J = 12.0, 5.0 Hz, H-4a), 2.83-2.75 (1H, m, H-3), 2.72 (1H, dd, J = 12.0, 8.4 Hz, H-4b), 2.14 (3H, s, H-1), 1.17 (6H, t, J = 7.2 Hz, CH₃×2), 0.96 (3H, d, J = 6.7 Hz, H-5); ¹³C NMR (100 MHz, CDCl₃): δ 212.9 (C=O), 156.6 (C×2), 127.6 (Ar-CH), 117.8 (C), 107.7 (Ar-CH×2), 93.4 (CH₂×2), 64.5 (CH₂×2), 47.0 (CH), 28.4 (CH₃), 26.7 (CH₂), 15.7 (CH₃), 15.3 (CH₃×2); IR (film) νmax 2976, 2931, 1711, 1594, 1467, 1251, 1097, 1030 cm⁻¹; HRMS (ESI+) for C₁₇H₂₆O₅ [M+Na]⁺ requires 333.1672 found 333.1684.

**((S)-3-(Ethoxymethoxy)butanal (233))**

To a stirred solution of ethyl (S)-3-hydroxybutyrate 228 (310 mg, 2.3 mmol) and diisopropylethylamine (1.6 mL, 9.2 mmol) in CH₂Cl₂ (6 mL) at 0 °C was added chloromethylethyl ether (0.64 mL, 6.9 mmol). The reaction mixture was stirred at room temperature for 18 h and then quenched by the addition of pH 7 buffer (5 mL). The layers were separated and the aqueous layer further extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried over Na₂SO₄...
and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded ester 230 which was used directly in the next step without complete removal of the solvent.

To a stirred solution of ester 230 in CH₂Cl₂ (21 mL) at −78 °C was added diisobutylaluminium hydride (1M in toluene, 2.3 mL, 2.3 mmol) over 1 h. The reaction was quenched by the addition of MeOH (6 mL) and allowed to warm to room temperature. Sat. aq. potassium sodium tartrate (12 mL) was added and the resultant mixture stirred vigorously for 2 h. The layers were separated and the aqueous layer extracted with CH₂Cl₂ (4 × 15 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/Et₂O, 4:1) afforded the title compound 233 (270 mg, 1.9 mmol, 83% over two steps) as a colourless oil; [α]D²⁵ +30.2 (c 1.15 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.80-9.79 (1H, m, H-1), 4.71 (2H, ABq, ΔδAB = 0.05, JAB = 7.3 Hz, OCH₂O), 4.30-4.22 (1H, m, H-3), 3.63-3.54 (2H, m, OCH₂), 2.67 (1H, ddd, J = 16.4, 7.4, 3.0 Hz, H-2a), 2.51 (1H, ddd, J = 16.4, 5.0, 2.0 Hz, H-2b), 1.27 (3H, d, J = 6.2 Hz, H-4), 1.21 (3H, t, J = 7.0 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 201.3 (C=O), 93.7 (CH₂), 68.6 (CH), 63.5 (CH₂), 50.9 (CH₂), 20.7 (CH₃), 15.1 (CH₃); IR (film) νmax 2936, 1726, 1383, 1106 1037 cm⁻¹; HRMS (ESI+) for C₇H₁₄O₃ [M+Na]⁺ requires 169.0835 found 169.0839.

(S)-Ethyl 3-((benzyloxy)methoxy)butanoate (231)

To a stirred solution of ethyl (S)-3-hydroxybutyrate 228 (200 mg, 1.5 mmol) and diisopropylethylamine (1.1 mL, 6.2 mmol) in CH₂Cl₂ (4 mL) at 0 °C was added chloromethylbenzyl ether (0.64 mL, 4.6 mmol). The reaction mixture was stirred at room temperature for 24 h and then quenched by the addition of H₂O (5 mL). The layers were separated and the aqueous layer further extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded ester 231 (380 mg, 1.5 mmol, 98%) as a colourless oil; [α]D²⁵ +9.2 (c 1.02 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.25 (5H, m, Ar-H × 5), 4.81 (2H, ABq, ΔδAB = 0.02, JAB = 7.1 Hz, OCH₂O), 4.63-4.57 (2H, m, OCH₂), 4.28-4.20 (1H, m, H-3), 4.13 (2H, d, J = 6.9 Hz, OCH₃), 2.61 (1H, dd, J = 15.4, 7.5 Hz, H-2a), 2.43 (1H, dd, J = 15.4, 5.5 Hz, H-2b), 1.27-1.23 (6H, m, H-4 and CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 171.4 (C=O), 138.0 (C), 128.5 (Ar-CH × 2), 128.0 (Ar-CH × 2), 127.8 (Ar-CH), 93.4 (CH₂), 70.5 (CH), 69.5 (CH₂), 60.5 (CH₂),

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42.5 (CH₂), 20.6 (CH₃), 14.3 (CH₃); The spectroscopic data were in agreement with those reported in the literature.²²⁹

(S)-3-((Benzyloxy)methoxy)butanal (234)

To a stirred solution of ester 231 (190 mg, 0.73 mmol) in CH₂Cl₂ (7.5 mL) at −78 °C was added diisobutylaluminium hydride (1 M in toluene, 0.8 mL, 0.80 mmol) over 30 min. The reaction was quenched with MeOH (2.5 mL) and allowed to warm to room temperature. Sat. aq. potassium sodium tartrate (5 mL) was added and the resultant mixture stirred vigorously for 2 h. The layers were separated and the aqueous layer further extracted with CH₂Cl₂ (4 × 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the title compound 234 (130 mg, 0.62 mmol, 87%) as a colourless oil; [α]D²⁵ +29.7 (c 1.13 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.78-9.76 (1H, m, H-1), 7.34-7.24 (5H, m, Ar-H × 5), 4.80 (2H, ABq, ΔδAB = 0.05, JAB = 7.0 Hz, OCH₂O), 4.58 (2H, ABq, ΔδAB = 0.02, JAB = 11.7 Hz, OCH₂), 4.34-4.27 (1H, m, H-3), 2.66 (1H, ddd, J = 16.5, 7.3, 2.6 Hz, H-2a), 2.50 (1H, ddd, J = 16.5, 5.0, 1.8 Hz, H-2b), 1.28 (3H, d, J = 6.2 Hz, H-4); ¹³C NMR (100 MHz, CDCl₃): δ 201.1 (C=O), 137.8 (C), 128.5 (Ar-CH × 2), 127.9 (Ar-CH × 2), 127.8 (Ar-CH), 93.1 (CH₂), 69.7 (CH₂), 68.7 (CH), 50.8 (CH₂), 20.6 (CH₃); IR (film) v max 2971, 2890, 1724, 1379, 1104, 1035, 1025, 739, 698 cm⁻¹; HRMS (ESI+) for C₁₂H₁₆O₃ [M+Na]⁺ requires 231.0992 found 231.0990. The spectroscopic data were in agreement with those reported in the literature.²²⁹
Experimental

(S)-Ethyl 3-((tert-butyldimethylsilyl)oxy)butanoate (232)

\[
\begin{align*}
\text{(S)-228} & \quad \text{O} \quad \text{OEt} \\
\text{232} & \quad \text{O} \quad \text{OEt}
\end{align*}
\]

To a stirred solution of ethyl (S)-3-hydroxybutyrate 228 (200 mg, 1.5 mmol) and tert-butyldimethylsilyl chloride (280 mg, 1.9 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added imidazole (120 mg, 1.7 mmol) and the resultant solution stirred at room temperature for 24 h. The reaction was quenched by the addition of H$_2$O (3 mL), the layers separated and the aqueous layer further extracted with CH$_2$Cl$_2$ (3 × 3 mL). The combined organic extracts were washed with H$_2$O (4 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound 232 (360 mg, 1.5 mmol, 95%) as a colourless oil; [α]$_{D}^{25}$ +30.6 (c 1.17 in CHCl$_3$), lit. +22 (c 0.97 in CHCl$_3$)$^{230}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 4.31-4.21 (1H, m, H-$\text{CH}_3$), 4.15-4.05 (2H, m, OCH$_2$), 2.49-2.31 (2H, m, H-$\text{CH}_2$), 1.25 (H, t, J = 7.1 Hz, CH$_3$), 1.18 (3H, d, J = 6.1 Hz, H-$\text{CH}_3$), 0.85 (9H, s, CH$_3$ × 3), 0.05 (3H, s, SiCH$_3$), 0.03 (3H, s, SiCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.8 (C=O), 65.9 (CH), 60.4 (CH$_2$), 45.1 (CH$_2$), 25.9 (CH$_3$ × 3), 24.0 (CH$_3$), 18.1 (C), 14.3 (CH$_3$), −4.4 (CH$_3$), −4.3 (CH$_3$); The spectroscopic data were in agreement with those reported in the literature.$^{230}$

(S)-3-((tert-Butyldimethylsilyl)oxy)butanal (82)

\[
\begin{align*}
\text{232} & \quad \text{O} \quad \text{OEt} \\
\text{82} & \quad \text{O} \quad \text{H}
\end{align*}
\]

To a stirred solution of ester 232 (360 mg, 1.5 mmol) in CH$_2$Cl$_2$ (15 mL) at −78 °C was added diisobutylaluminium hydride (1M in toluene, 1.8 mL, 1.8 mmol) dropwise. The resultant mixture was stirred at this temperature for 5 min, warmed to −50 °C for 5 min and then quenched by the addition of methanol (5 mL). The reaction mixture was warmed to room temperature, sat. aq. potassium sodium tartrate (20 mL) was added and the resultant mixture stirred vigorously for 20 min. The layers were separated and the aqueous layer further extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/Et$_2$O 25:1 to 10:1) afforded the title compound 82 (240 mg, 1.2 mmol, 75%) as a colourless oil; [α]$_{D}^{25}$ +18.0 (c 0.54 in CHCl$_3$), lit. +14.0 (c 1.0 in CHCl$_3$)$^{230}$;
\textit{Chapter Three}

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.81-9.80 (1H, m, H-1), 4.39-4.33 (1H, m, H-3), 2.60-2.42 (2H, m, H-2), 1.24 (3H, d, $J = 6.2$ Hz, H-4), 0.88 (9H, s, CH$_3 \times 3$), 0.08 (3H, s, SiCH$_3$), 0.07 (3H, s, SiCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.3 (C=O), 64.7 (CH), 53.1 (CH$_2$), 25.9 (CH$_3 \times 3$), 24.3 (CH$_3$), 18.3 (C), $-4.2$ (CH$_3$), $-4.8$ (CH$_3$); The spectroscopic data were in agreement with those reported in the literature.$^{230}$

(2S,7S)-1-(2,6-Bis(ethoxymethoxy)phenyl)-5-((tert-butyldimethylsilyl)oxy)-7-(ethoxymethoxy)-2-methyloctan-3-one (236)

A flame-dried flask was charged with (+)-DIP-chloride (92 mg, 0.14 mmol) and placed under vacuum for 30 min to remove traces of HCl. The flask was placed under a nitrogen atmosphere and Et$_2$O (1.5 mL) added. The resultant solution was cooled to $-78$ °C and triethylamine (55 μL, 0.39 mmol) and a solution of ketone 207 (32 mg, 0.10 mmol) in Et$_2$O (1.5 mL) were added sequentially. The resultant solution was stirred for 1 h at 0 °C and cooled to $-78$ °C once more. A solution of aldehyde 233 (19 mg, 0.13 mmol) in Et$_2$O (1 mL) was added dropwise and the reaction mixture stirred for 3 h. The reaction mixture was warmed to 0 °C for 15 min, then quenched by the addition of H$_2$O (5 mL). The layers were separated, and the aqueous layer further extracted with EtOAc (3 $\times$ 5mL). The combined organic extracts were dried over MgSO$_4$ and concentrated \textit{in vacuo}. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded an inseparable mixture of aldol 235 and IpcoH.

Imidazole (13 mg, 0.18 mmol) and \textit{tert}-butylidemethylsilyl chloride (17 mg, 0.11 mmol) were added to a solution of aldol 235 prepared above in DMF (0.5 mL). The resultant mixture was stirred at room temperature overnight and then quenched by the addition of pH 7 buffer (5 mL). The reaction mixture was extracted with CH$_2$Cl$_2$ (3 $\times$ 5 mL). The combined organic extracts were washed with H$_2$O (3 $\times$ 3 mL), dried over MgSO$_4$ and concentrated \textit{in vacuo}. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the \textit{title compound} 236 (32 mg, 0.056 mmol, 56\% over two steps) as a mixture of diastereomers (d.r. $\sim 2:1$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.08 (1H, t, $J = 8.2$ Hz, H-4'), 6.79 (2H, d, $J = 8.2$ Hz, H-3' and H-5'), 5.21 (4H, s, OCH$_2$O $\times$ 2), 4.72-4.62 (2H, m, OCH$_2$O), 4.36-4.28 (1H, m, H-5), 3.83-3.74 (1H, m, H-7), 3.70 (4H, q, $J = 7.1$ Hz, OCH$_2$ $\times$ 2), 3.64-3.52 (2H, m, OCH$_2$), 2.90 (1H, dd, \textit{Chapter Three})
Experimental

$J = 12.0, 3.9 \text{ Hz}, H-1_a, 2.84-2.76 \text{ (1H, m, H-2)}, 2.76-2.70 \text{ (2H, m, H-1_b and H-4_a), 2.60-2.54 \text{ (1H, m, H-4_b), 1.80-1.70 \text{ (1H, m, H-6_a), 1.56-1.48 \text{ (1H, m, H-6_b), 1.24-1.16 \text{ (12H, m, H-8 and CH}_3 \times 3)}, 0.97-0.95 \text{ (3H, m, H-9)}, 0.84* \text{ (9H, s, CH}_3^* \times 3), 0.83 \text{ (9H, s, CH}_3 \times 3), 0.08* \text{ (3H, s, SiCH}_3^*), 0.06 \text{ (3H, s, SiCH}_3), 0.02* \text{ (3H, s, SiCH}_3^*), 0.00 \text{ (3H, s, SiCH}_3); ^{13}C \text{ NMR (100 MHz, CDCl}_3): \delta 212.9 \text{ (C=O), 212.5* (C=O), 156.5 (C \times 2), 127.4 (Ar-CH), 117.8 (C), 107.5 (Ar-CH \times 2), 77.4* (CH_2), 93.1 (CH}_2 \times 3), 71.2* (CH), 69.9 (CH), 66.3 (CH), 64.4 (CH}_2 \times 2), 63.2 (CH_2), 49.3* (CH_2), 48.8 (CH_2), 47.0 (CH), 46.8* (CH), 45.9* (CH_2), 45.3 (CH_2), 25.8 (CH_2 and CH}_3 \times 3), 21.4* (CH_3), 20.4 (CH_3), 18.0* (C), 17.9 (C), 15.1 (CH}_3 \times 3), 14.9* (CH_3), 14.7 (CH_3), -4.3* (CH}_3 \times 2), -4.6 (CH}_3 \times 2); \text{ HRMS (ESI+ for C}_{30}H_{54}NaO_8Si [M+Na]^+ requires 593.3480 found 593.3480.}

(25,7S)-7-((Benzyloxy)methoxy)-1-(2,6-bis(ethoxymethoxy)phenyl)-5-hydroxy-2-methyloctan-3-one (237)

\[
\begin{align*}
\text{BOMO} & \quad \overset{\text{H}}{\text{O}} \\
\text{234} & \quad + \\
\overset{\text{EOMO}}{\text{O}} \quad \overset{\text{EOMO}}{\text{O}} \quad \text{OEOM} \\
\text{207} & \quad \rightarrow \\
\overset{\text{HO}}{\text{O}} \quad \overset{\text{EOMO}}{\text{O}} \quad \text{OEOM}
\end{align*}
\]

A flame-dried flask was charged with (+)-DIP-chloride (100 mg, 0.31 mmol) and placed under vacuum for 30 min to remove traces of HCl. The flask was placed under a nitrogen atmosphere and Et\(_2\)O (0.9 mL) added. The resultant solution was cooled to −78 °C and triethylamine (50 μL, 0.36 mmol) and a solution of ketone 207 (28 mg, 0.090 mmol) in Et\(_2\)O (0.9 mL) were added sequentially. The resultant solution was stirred for 1 h at 0 °C and cooled to −78 °C once more. A solution of aldehyde 234 (36 mg, 0.17 mmol) in Et\(_2\)O (0.9 mL) was added dropwise and the reaction mixture stirred for 3 h, warmed to −20 °C and stirred overnight. The reaction was quenched by the addition of H\(_2\)O (5 mL). The layers were separated, and the aqueous layer further extracted with EtOAc (3 × 5mL). The combined organic extracts were dried over MgSO\(_4\) and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the title compound 237 (28 mg, 0.054 mmol, 60%) as an inseparable mixture of diastereomers (d.r. ~ 1:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.36-7.26 (5H, m, Ar-H \times 5), 7.10 (1H, t, $J = 8.3 \text{ Hz}, H-4^{'})$, 6.79 (2H, d, $J = 8.3 \text{ Hz, H-3^{'}}$ and H-5^{'}), 5.21 (4H, s, OCH\(_2\)O \times 2), 4.87-4.69 (2H, m, OCH\(_2\)O), 4.69-4.57 (2H, m, OCH\(_2\)), 4.35-4.28* (1H, m, H-5*), 4.23-4.16 (1H, m, H-5), 4.13-4.06* (1H, m, H-7*), 4.07-4.00 (1H, m, H-7), 3.71 (4H, q, $J = 7.0 \text{ Hz, OCH}_2 \times 2), 3.52 (1H, br s, OH), 3.38* (1H, br s, OH*), 2.95-2.72 (3H, m, H-2 and H-1), 2.68-2.54 (2H, m, H-4), 2.43-2.33 (3H, m, H-3).
A flame-dried flask was charged with (+)-DIP-chloride (60 mg, 0.19 mmol) and placed under vacuum for 30 min to remove traces of HCl. The flask was placed under a nitrogen atmosphere and Et₂O (1.2 mL) added. The resultant solution was cooled to −78 °C and triethylamine (30 μL, 0.21 mmol) and a solution of ketone 207 (25 mg, 0.081 mmol) in Et₂O (0.8 mL) were added sequentially. The resultant solution was stirred for 1 h at 0 °C and cooled to −78 °C once more. A solution of aldehyde 82 (28 mg, 0.14 mmol) in Et₂O (0.8 mL) was added dropwise and the reaction mixture stirred for 45 min, warmed to −50 °C and stirred for 2 h. The reaction was quenched by the addition of pH 7 buffer solution (5 mL). The layers were separated, and the aqueous layer further extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 20:1 to 10:1) afforded the title compound 238 (28 mg, 0.055 mmol, 68%) as an inseparable mixture of diastereomers (d.r. ~ 1:1); ¹H NMR (400 MHz, CDCl₃, data reported for pure diastereomer, see discussion in Section 2.2.5, D): δ 7.01 (1H, t, J = 8.4 Hz, H-4'), 6.71 (2H, d, J = 8.4 Hz, H-3' and H-5'), 5.13 (4H, s, OCH₂O × 2), 4.25-4.19 (1H, m, H-5), 4.10-4.03 (1H, m, H-7), 3.62 (4H, q, J = 7.1 Hz, OCH₂ × 2), 3.47 (1H, br s, OH), 2.86-2.81 (1H, m, H-1ₐ), 2.80-2.73 (1H, m, H-2), 2.71-2.65 (1H, m, H-1ₜ), 2.53-2.51 (2H, m, H-4), 1.52-1.45 (1H, m, H-6ₐ), 1.38-1.32 (1H, m, H-6ₜ), 1.17-1.10 (9H, m, H-8 and CH₃ × 2), 0.92 (3H, d, J = 6.8 Hz, H-9), 0.80 (9H, s, CH₃ × 3), 0.00 (3H, s, SiCH₃), −0.01 (3H, s, SiCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 215.3 (C=O), 156.4 (C × 2), 127.5 (Ar-CH), 117.5 (C), 107.5 (Ar-CH × 2), 93.2 (CH₂ × 2), 66.2 (CH), 64.5 (CH), 64.3
(CH₂ × 2), 48.2 (CH₂), 46.4 (CH), 45.1 (CH₂), 26.3 (CH₂), 25.8 (CH₃ × 3), 23.7 (CH₃), 18.0 (C), 15.3 (CH₃), 15.1 (CH₃ × 2), −4.5 (CH₃) −4.9 (CH₃); HRMS (ESI+) for C₂₇H₄₈NaO₇Si [M+Na]⁺ requires 535.3062 found 535.3052.

(S)-3-((4-Methoxybenzyl)oxy)butanal (245)

To a stirred solution of ethyl (S)-3-hydroxybutyrate 228 (1.4 g, 11 mmol) in CH₂Cl₂ (53 mL) was added 4-methoxybenzyl trichloroacetimidate (6.1 g, 21 mmol) and CSA (250 mg, 1.1 mmol). The resultant solution was stirred at room temperature for 48 h. H₂O (50 mL) was added and the layers separated. The aqueous layer was further extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (25 mL), dried over MgSO₄ and concentrated in vacuo.

Purification by flash chromatography (hexanes/EtOAc 10:1) afforded 244 as a mixture with PMB₂O which was used in the next step without further purification.

Ester 244 was dissolved in CH₂Cl₂ (64 mL) and cooled to −78 °C. DIBAL-H (1M in toluene, 7.5 mL, 7.5 mmol) was added over 30 min and the solution stirred at −78 °C for a further 30 min. The reaction was quenched by the addition of MeOH (6 mL) and allowed to warm to room temperature. Sat. aq. potassium sodium tartrate (100 mL) was added and the mixture stirred vigorously for 2 h. The layers were separated and the aqueous layer further extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo.

Purification by flash chromatography (hexanes/EtOAc 10:1 to 5:1) afforded the title compound 245 (1.2 g, 5.9 mmol, 56% over two steps) as a pale yellow oil; [α]D²⁵ = +39.1 (c 1.30 in CHCl₃), lit. −40.0 (c 0.975 in CHCl₃), for opposite enantiomer;¹ H NMR (400 MHz, CDCl₃): δ 9.78-9.77 (1H, m, H-1), 7.26-7.22 (2H, m, Ar-H × 2), 6.90-6.86 (2H, m, Ar-H × 2), 4.48 (2H, ABq, ΔδAB = 0.12, JAB = 11.1 Hz, OCH₂), 4.09-4.03 (1H, m, H-3), 3.82 (3H, s, OCH₃), 2.69 (1H, ddd, J = 16.5, 7.4, 2.6 Hz, H-2), 2.50 (1H, ddd, J = 16.5, 5.0, 1.9 Hz, H-2a), 1.29 (3H, d, J = 6.2 Hz, H-4);¹³C NMR (100 MHz, CDCl₃): δ 201.6 (C=O), 162.5 (C), 130.2 (C), 129.4 (Ar-CH × 2), 114.0 (Ar-CH × 2), 70.4 (CH₂), 70.0 (CH), 55.4 (CH₃), 50.6 (CH₂), 19.9 (CH₃); The spectroscopic data were in agreement with those reported in the literature.²³²
(2S,5R,7S)-1-(2,6-Bis(ethoxymethoxy)phenyl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyloctan-3-one (247)

To a stirred solution of ketone 207 (160 mg, 0.51 mmol) and triethylamine (0.21 mL, 1.5 mmol) in CH$_2$Cl$_2$ (3.2 mL) at 0 °C was added trimethylsilyl triflate (0.14 mL, 0.76 mmol) dropwise. The resultant mixture was stirred for 30 min and then quenched by addition of sat. aq. NH$_4$Cl (3 mL). The layers were separated, and the aqueous layer further extracted with Et$_2$O (2 × 5 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude silyl enol ether 246 was azeotropically dried with toluene and used directly in the next step without further purification.

Boron trifluoride diethyl etherate (0.16 mL, 1.2 mmol) was added to a solution of aldehyde 245 (130 mg, 0.61 mmol) in CH$_2$Cl$_2$ (10 mL) at −78 °C and the resultant solution stirred for 2 min. A solution of silyl enol ether 246 prepared above in CH$_2$Cl$_2$ (2 mL) was added dropwise. The resultant solution was stirred at −78 °C for 90 min and then quenched by the addition of sat. aq. NaHCO$_3$ (5 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 4:1 to 1:1) afforded the title compound 247 (220 mg, 0.42 mmol, 82%) as a colourless oil; $[\alpha]_D^{25} +39.5$ (c 0.74 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.28-7.23 (2H, m, Ar-H × 2), 7.10 (1H, t, $J =$ 8.4 Hz, H-4'), 6.88-6.85 (2H, m, Ar-H × 2), 6.78 (2H, d, $J =$ 8.4 Hz, H-3' and H-5'), 5.22-5.19 (4H, m, OCH$_2$O × 2), 4.55 (1H, d, $J =$ 11.0 Hz, OCH$_2$), 4.38 (1H, d, $J =$ 11.0 Hz, OCH$_2$), 4.37-4.29 (1H, m, H-5), 3.87-3.82 (1H, m, H-7), 3.79 (3H, s, OCH$_3$), 3.70 (4H, q, $J =$ 6.9 Hz, OCH$_2$ × 2), 3.42 (1H, br s, OH), 2.94-2.90 (1H, m, H-1), 2.87-2.82 (1H, m, H-2), 2.79-2.74 (1H, m, H-1), 2.67-2.53 (2H, m, H-4), 1.64-1.50 (2H, m, H-6), 1.22 (3H, d, $J =$ 6.2 Hz, H-8), 1.22 (6H, t, $J =$ 6.9 Hz, CH$_3$ × 2), 1.01 (3H, d, $J =$ 6.7 Hz, H-9); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 215.8 (C=O), 159.3 (C), 156.5 (C × 2), 130.9 (C), 129.5 (Ar-CH × 2), 127.7 (Ar-CH), 117.6 (C), 113.9 (Ar-CH × 2), 107.6 (Ar-CH × 2), 93.4 (CH$_2$ × 2), 71.9 (CH), 70.7 (CH$_2$), 64.9 (CH), 64.5 (CH$_2$ × 2), 55.4 (CH$_3$), 48.0 (CH$_2$), 46.6 (CH), 43.7 (CH$_2$), 26.5 (CH$_2$), 19.9 (CH$_3$), 15.5 (CH$_3$), 15.2 (CH$_3$ × 2); IR (film)
Experimental

$\nu_{\text{max}}$ 3489, 2971, 2926, 1704, 1594, 1514, 1469, 1248, 1151, 1095, 1032, 821 cm$^{-1}$; HRMS (ESI+) for C$_{29}$H$_{42}$NaO$_8$ [M+Na]$^+$ requires 541.2772 found 541.2754.

(4$R$,6$S$)-2-((S)-1-(2,6-Bis(ethoxymethoxy)phenyl)propan-2-yl)-2-methoxy-6-methyltetrahydro-2H-pyran-4-ol (248)

A mixture of aldon 247 (100 mg, 0.20 mmol) and palladium hydroxide on carbon (80 mg) in MeOH (44 mL) under an atmosphere of hydrogen was stirred at room temperature for 1 h. The reaction mixture was filtered through Celite® and concentrated in vacuo to give the title compound 248 (77 mg, 0.19 mmol, 95%) as a colourless oil; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.09-7.04 (1H, m, H-4”), 6.79-6.75 (2H, m, H-3” and H-5”), 4.21 (4H, s, OCH$_2$O × 2), 4.15-4.07 (1H, m, H-4), 3.78-3.66 (5H, m, H-6 and OCH$_2$ × 2), 3.12* (3H, s, OCH$_3$*), 3.08 (3H, s, OCH$_3$), 2.95-2.89 (1H, m, H-1’a), 2.59-2.51 (1H, m, H-1’b), 2.35-2.26 (1H, m, H-2’), 2.24-2.19* (1H, m, H-2*b), 2.04-1.97 (1H, m, H-3’a) 1.96-1.91 (1H, m, H-5’a), 1.48-1.43 (1H, m, H-3b), 1.23 (6H, t, $J = 7.0$ Hz, CH$_3$ × 2), 1.17 (3H, d, $J = 6.3$ Hz, H-7), 1.15-1.09 (1H, m, H-5b), 1.11* (3H, d, $J = 5.9$ Hz, H-7*), 0.76 (3H, d, $J = 7.0$ Hz, H-3’), 0.73* (3H, d, $J = 7.1$ Hz, H-3’*); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.7* (C × 2), 156.6 (C × 2), 126.9 (Ar-CH), 126.7* (Ar-CH), 120.5* (C), 120.2 (C), 107.9* (Ar-CH × 2), 107.8 (Ar-CH × 2), 103.8 (C), 101.9* (C), 93.5* (CH$_2$ × 2), 93.4 (CH$_2$ × 2), 66.1* (CH), 65.5 (CH), 65.0 (CH), 64.3 (CH$_2$ × 2), 46.4 (CH$_3$), 42.6 (CH$_3$), 37.4* (CH), 36.8 (CH), 36.5 (CH$_2$), 32.9* (CH$_2$), 25.4 (CH$_2$), 22.1* (CH$_3$), 21.6 (CH$_3$), 15.3 (CH$_3$ × 2), 13.3 (CH$_3$); IR (film) $\nu_{\text{max}}$ 2971, 2933, 1594, 1469, 1381, 1251, 1151, 1095, 1079, 1034, 922, 779 cm$^{-1}$; HRMS (ESI+) for C$_{22}$H$_{36}$NaO$_7$ [M+Na]$^+$ requires 435.2353 found 435.2344. The optical rotation of 248 was not measured because the sample was not diastereomERICally pure.
To a stirred solution of methoxy acetal 248 (10 mg, 0.024 mmol) and 2,6-lutidine (7 μL, 0.061 mmol) in CH₂Cl₂ (0.5 mL) at −78 °C under nitrogen was added triisopropyl triflate (8 μL, 0.029 mmol). The resultant solution was stirred at −78 °C for 1 h then quenched by the addition of sat. aq. NaHCO₃ (1 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with Et₂O (3 × 2 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (1 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 40:1 with 0.25% v/v NEt₃) afforded the title compound 250 (9.6 mg, 0.017 mmol, 70%) as a colourless oil; [α]_D²⁵⁻⁹.₃ (c 0.74 in MeOH); ¹H NMR (400 MHz, CDCl₃): 7.07 (1H, t, J = 8.3 Hz, H-4″), 6.77 (2H, d, J = 8.3 Hz, H-3″ and H-5″), 5.22 (4H, s, OCH₂O × 2), 4.23-4.14 (1H, m, H-4), 3.79-3.71 (4H, m, OCH₂ × 2), 3.69-3.61 (1H, m, H-6), 3.07 (3H, s, OCH₃), 2.92 (1H, dd, J = 12.4, 3.6 Hz, H-1″a), 2.57 (1H, dd, J = 12.4, 10.8 Hz, H-1″b), 2.32-2.23 (1H, m, H-2″), 1.96 (1H, ddd, J = 12.7, 1.7 Hz, H-3″), 1.90-1.86 (1H, m, H-5″a), 1.47 (1H, dd, J = 12.7, 10.6 Hz, H-3″b), 1.24 (3H, t, J = 7.0 Hz, CH₃ × 2), 1.24-1.17 (1H, m, H-5″b), 1.16 (3H, d, J = 6.2 Hz, H-7), 1.09 (21H, s, CH₃ × 6 and SiCH × 3), 0.75 (3H, d, J = 7.0 Hz, H-3″); ¹³C NMR (100 MHz, CDCl₃): δ 156.7 (C × 2), 126.8 (Ar-CH), 120.6 (C), 107.9 (Ar-CH × 2), 103.8 (C), 93.4 (CH₂ × 2), 66.1 (CH), 64.9 (CH), 64.3 (CH₂ × 2), 46.4 (CH₃), 43.3 (CH₂), 37.1 (CH₂), 36.9 (CH), 25.4 (CH₂), 21.7 (CH₃), 18.3 (CH₃ × 6), 15.3 (CH₃ × 2), 13.4 (CH₃), 12.5 (CH × 3); IR (film) ν_max 2939, 2867, 1731, 1594, 1467, 1384, 1154, 1095, 1037, 850, 681 cm⁻¹; HRMS (ESI+) for C₃₁H₅₆NaO₇Si [M+Na]⁺ requires 591.3688 found 591.3686.
3.6 Synthesis of Amide 273

4-Bromo-3,5-dihydroxybenzoic acid (264)

To a stirred suspension of 3,5-dihydroxybenzoic acid 263 (5.0 g, 32 mmol) in 20% aq. HCl (55 mL) was added Br₂ (1.7 mL, 32 mmol) at room temperature. The resultant suspension was heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature then extracted with Et₂O (3 × 150 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo affording the title compound 264 (7.5 g, 32 mmol, 99%) as a pale brown solid; m.p. 245-250 °C; ¹H NMR (400 MHz, (CD₃)₂CO): δ 9.06 (2H, br s, OH × 2), 7.21 (2H, s, H-2 and H-6); ¹³C NMR (100 MHz, (CD₃)₂CO): δ 167.2 (C=O), 156.1 (C × 2), 131.4 (C), 109.0 (Ar-CH × 2), 104.5 (C); The spectroscopic data were in agreement with those reported in the literature.¹⁵⁰

(Benzyloxy)methyl 3,5-bis((benzyloxy)methoxy)-4-bromobenzoate (265)

To a stirred solution of 264 (3.9 g, 17 mmol) and diisopropylethylamine (17 mL, 98 mmol) in CH₂Cl₂ (45 mL) at 0 °C was added BOMCl (9.5 mL, 68 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was quenched with sat. aq. NH₄Cl (50 mL), the layers separated and the aqueous layer extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1 to 1:1) afforded the title compound 265 (8.7 g, 15 mmol, 87%) as a colourless solid; m.p. 46-48 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.58 (2H, s, H-2 and H-6), 7.37-7.27 (15H, m, Ar-H × 15), 5.57 (2H, s, OCH₃O), 5.41 (4H, s,
OCH₂O × 2), 4.78 (4H, s, OCH₂ × 2), 4.73 (2H, s, OCH₂); \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta\) 165.3 (C), 162.3 (C), 155.0 (C × 2), 136.9 (C × 2), 130.2 (C), 128.6 (Ar-CH × 6), 128.2 (Ar-CH × 4), 128.1 (Ar-CH × 3), 128.0 (Ar-CH × 2), 110.5 (ArCH × 2), 110.2 (C), 93.0 (CH₂ × 2), 89.3 (CH₂), 72.2 (CH₂), 70.6 (CH₂ × 2); IR (film) \(\nu_{\text{max}}\) 3032, 2901, 1725, 1588, 1378, 1324, 1098, 1048, 938, 903, 729, 692 cm⁻¹; HRMS (ESI+) for BrC\(_{31}\)H\(_{29}\)NaO\(_7\) [M+Na\(^+\)] requires 615.0989 found 615.0981.

(3,5-Bis((benzyloxy)methoxy)-4-bromophenyl)methanol (266)

To a stirred solution of ester 265 (10 g, 17 mmol) in CH\(_2\)Cl\(_2\) (130 mL) at −78 °C was added DIBAL-H (1M in cyclohexane, 50 mL, 50 mmol). The reaction mixture was warmed to 0 °C, stirred for 15 min and then quenched with MeOH (20 mL). Sat. aq. potassium sodium tartrate (200 mL) was added and the resultant mixture was stirred vigorously for 4 h. The layers were separated and the aqueous layer extracted with CH\(_2\)Cl\(_2\) (3 × 100 mL). The combined organic extracts were dried over MgSO\(_4\) and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 2:1) afforded the title compound 266 (7.3 g, 16 mmol, 95%) as a colourless solid; m.p. 54-56 °C; \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 7.37-7.31 (10H, m, Ar-H × 10), 6.92 (2H, s, H-2 and H-6), 5.39 (4H, s, OCH₂O × 2), 4.79 (4H, s, OCH₂ × 2), 4.61 (2H, s, CH₂); \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta\) 155.1 (C × 2), 142.0 (C), 137.0 (C × 2), 128.6 (Ar-CH × 4), 128.3 (Ar-CH × 4), 128.1 (Ar-CH × 2), 108.0 (Ar-CH × 2), 102.8 (C), 92.9 (CH₂ × 2), 70.5 (CH₂ × 2), 65.0 (CH₂); IR (film) \(\nu_{\text{max}}\) 3403, 3032, 2908, 1488, 1439, 1158, 1040, 904, 741, 698 cm⁻¹; HRMS (ESI+) for BrC\(_{23}\)H\(_{23}\)NaO\(_5\) [M+Na\(^+\)] requires 481.0621 found 481.0632.
3,5-Bis((benzyloxy)methoxy)-4-bromobenzaldehyde (262)

To a stirred solution of alcohol 266 (4.6 g, 10 mmol), SO$_3$-Py (3.2 g, 20 mmol) and diisopropylethylamine (6.0 mL, 34 mmol) in CH$_2$Cl$_2$ (130 mL) at 0 °C was added DMSO (13 mL, 185 mmol) and the reaction mixture stirred for 15 min. H$_2$O (100 mL) was added, the layers separated and the organic layer washed with H$_2$O (2 × 50 mL). The organic extract was dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the title compound 262 (3.4 g, 7.4 mmol, 74%) as a colourless oil; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.87 (1H, s, CHO), 7.38-7.23 (12H, m, H-2, H-6, and Ar-H × 10), 5.42 (4H, s, OCH$_2$O × 2), 4.77 (4H, s, OCH$_2$ × 2); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 190.9 (C=O), 155.7 (C × 2), 136.7 (C × 2), 136.5 (C), 128.6 (Ar-CH × 4), 128.2 (Ar-CH × 4), 128.2 (Ar-CH × 2), 111.2 (C), 109.7 (Ar-CH × 2), 92.9 (CH$_2$ × 2), 70.7 (CH$_2$ × 2); IR (film) $\nu_{max}$ 3031, 2905, 1698, 1583, 1440, 1376, 1314, 1224, 1156, 1043, 903, 740 cm$^{-1}$; HRMS (ESI+) for BrC$_{23}$H$_{21}$NaO$_5$ [M+Na]$^+$ requires 479.0465 found 479.0462.

3,5-Bis((benzyloxy)methoxy)-4-bromo-1-(E)-prop-1-en-1-ylbenzene (261)

To a stirred solution of aldehyde 262 (4.3 g, 9.4 mmol), ethyltriphenylphosphonium iodide (4.5 g, 11 mmol) and 18-crown-6 (25 mg, 0.07 mmol) in CH$_2$Cl$_2$ (50 mL) at 0 °C was added KOtBu (1.2 g, 10 mmol). The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was filtered through Celite® and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 20:1) afforded the title compound (E/Z)-261 (3.7 g, 8.0 mmol, 85%) as an inseparable mixture of E/Z isomers (d.r. approx 6:1).
To a solution of \((E/Z)-261\) in toluene (250 mL), was added Ru(CO)HCl(PPh\(_3\))\(_3\) (210 mg, 0.22 mmol) and the resultant suspension heated under reflux with stirring for 16 h. The reaction mixture was allowed to cool to room temperature and concentrated \textit{in vacuo}. Purification by flash chromatography (hexanes/EtOAc 20:1) afforded the \textit{title compound} 261 (3.6 g, 7.7 mmol, 96%) as a colourless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.40-7.31 (10H, m, Ar-H \times 10), 6.92 (2H, s, H-2 and H-6), 6.34 (1H, dq, \(J = 15.6, 1.3\) Hz, H-1'), 6.24 (1H, dq, \(J = 15.6, 6.4\) Hz, H-2'), 5.39 (4H, s, OCH\(_2\)O \times 2), 4.81 (4H, s, OCH\(_2\) \times 2), 1.88 (3H, dd, \(J = 6.4, 1.3\) Hz, H-3'); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 155.0 (C \times 2), 138.7 (C), 137.1 (C \times 2), 130.4 (C\(\text{H}\)), 128.6 (Ar-CH \times 4), 128.3 (Ar-CH \times 4), 128.0 (Ar-CH \times 2), 127.3 (CH), 107.4 (Ar-CH \times 2), 102.1 (C), 93.0 (CH\(_2\) \times 2), 70.4 (CH\(_2\) \times 2), 18.5 (CH\(_3\)); IR (film) \(\nu_{\text{max}}\) 3030, 2917, 1576, 1430, 1379, 1232, 1158, 1100, 1037, 903, 736, 696 cm\(^{-1}\); HRMS (ESI+) for BrC\(_{25}\)H\(_{25}\)NaO\(_4\) [M+Na\(^+\)] requires 491.0828 found 491.0837.

\((S)-3-(2,6-\text{Bis((benzyloxy)methoxy)-4-((E)-prop-1-en-1-yl)phenyl})-N-((1R,2R)-1-hydroxy-1-phenylpropan-2-yl})-N,2-dimethylpropanamide\) (273)

A flask was charged with trifluoroboratoamide 158 (410 mg, 1.2 mmol), bromide 261 (550 mg, 1.2 mmol), Pd(OAc)\(_2\) (13 mg, 0.06 mmol, 10 mol %), RuPhos (55 mg, 0.12 mmol, 20 mol %) and K\(_2\)CO\(_3\) (490 mg, 3.5 mmol) and purged with N\(_2\) three times. A degassed mixture of toluene (4 mL) and H\(_2\)O (1 mL) was then added. The reaction mixture was heated at 85 °C with stirring for 1.5 h and then allowed to cool to room temperature. A solution of pH 7 buffer (2 mL, prepared from NaHPO\(_4\) (1.7 g) and NaH\(_2\)PO\(_4\)·\(2\)H\(_2\)O (1.2 g) in H\(_2\)O (50 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (3 \times 10 mL), the combined organic extracts dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification by flash column chromatography afforded the \textit{title compound} 273 (380 mg, 0.61 mmol, 52%) as a colourless oil; \([\alpha]^{25}_{D} = -17.4 (c 0.95 \text{ in CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\), 5:1 rotamer ratio): \(\delta\) 7.35-7.19 (15H, m, Ar-H \times 15), 6.92* (2H, s, H-3'* and H-5'*), 6.86 (2H, s, H-3' and H-5'), 6.35-6.30 (1H, m, H-1'''), 6.21-6.16 (1H, m, H-2'''), 5.28 (4H, s, OCH\(_2\)O \times 2), 4.84 (1H, br s, OH), 4.69 (4H, s, OCH\(_2\) \times 2), 4.63-4.61 (1H, m, H-1'''), 4.57-4.51* (1H, m, H-1'''), 4.34-4.29 (1H, m, H-2''), 4.18-4.14* (1H, m, H-2''), 3.29-3.26* (1H, m, H-2'''), 3.16-3.08* (1H, m, H-3''), 3.00-2.95 (1H, m, H-2), 2.92-2.86 (1H, m, H-3a), 2.79 (3H, s, NCH\(_3\)), 2.68 (1H, dd, \(J = 12.6, 4.1\) Hz, 194
Experimental

H-3b), 1.84 (3H, dd, J = 6.5, 1.2 Hz, H-3’’), 1.13 (3H, d, J = 7.0 Hz, H-3’’), 1.05 (3H, d, J = 6.5 Hz, H-4), 0.95* (3H, d, J = 6.5 Hz, H-3’’); 13C NMR (100 MHz, CDCl3): δ 179.4 (C=O), 156.9* (C × 2), 156.6 (C × 2), 142.9 (C), 137.9 (C), 137.3 (C × 2), 131.0 (CH), 128.6 (Ar-CH × 4), 128.4 (Ar-CH × 2), 128.0 (Ar-CH × 4), 128.0 (Ar-CH × 2), 127.5 (Ar-CH), 126.4 (Ar-CH × 2), 126.1 (CH), 116.5 (C), 105.6* (Ar-CH × 2), 105.5 (Ar-CH × 2), 92.5 (CH × 2), 76.7 (CH), 75.3* (CH), 70.2 (CH × 2), 60.1 (CH), 58.2* (CH), 36.7 (CH), 35.8* (CH), 33.6 (CH3), 27.5 (CH2), 26.8* (CH2), 18.4 (CH3), 17.1* (CH3), 16.2 (CH3), 15.4* (CH3), 14.6 (CH3); IR (film) νmax 3384, 2929, 1614, 1576, 1454, 1207, 1071, 1036, 742, 700 cm⁻¹; HRMS (ESI+) for C39H45N6NaO6 [M+Na]+ requires 646.3139 found 646.3150.

(S,E)-4-(2,6-Bis((benzyloxy)methoxy)-4-(prop-1-en-1-yl)phenyl)-3-methylbutan-2-one (260)

![Chemical structure of 273](image)

![Chemical structure of 260](image)

To a stirred solution of 273 (380 mg, 0.61 mmol) in THF (7.0 mL) at −78 °C was added MeLi (1.2 M in Et2O, 1.3 mL, 1.6 mmol). The resultant suspension was warmed to 0 °C and stirred for 15 min. Excess MeLi was scavenged by the addition of diisopropylamine (1.0 mL, 7.14 mmol) and the reaction mixture stirred for a further 15 min at 0 °C. A solution of acetic acid (0.5 mL) in Et2O (2.5 mL) was added, followed by H2O (10 mL). The reaction mixture was extracted with Et2O (3 × 10 mL), the combined organic extracts dried over MgSO4 and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound 260 (0.24 g, 0.51 mmol, 84%) as a colourless oil; [α]D25 = +16.7 (c 0.27 in MeOH); 1H NMR (400 MHz, CDCl3): δ 7.43-4.30 (10H, m, Ar-H × 10), 6.89 (2H, s, H-3 and H-5'), 6.35 (1H, dq, J = 15.5, 1.3 Hz, H-1”), 6.21 (1H, dq, J = 15.5, 6.4 Hz, H-2”), 5.31 (4H, s, OCH2O × 2), 4.74 (4H, s, OCH2 × 2), 2.98-2.76 (3H, m, H-3 and H-4), 2.15 (3H, s, H-1), 1.86 (3H, dd, J = 6.4, 1.3 Hz, H-3’’), 1.06 (3H, d, J = 6.5 Hz, H-5’); 13C NMR (100 MHz, CDCl3): δ 212.8 (C=O), 156.5 (C × 2), 137.9 (C), 137.4 (C × 2), 131.0 (CH), 128.6 (Ar-CH × 4), 128.1 (Ar-CH × 4), 128.0 (Ar-CH × 2), 126.1 (CH), 116.5 (C), 105.5 (Ar-CH × 2), 92.6 (CH × 2), 70.3 (CH × 2), 47.1 (CH), 28.5 (CH3), 26.8 (CH2), 18.5 (CH3), 15.7 (CH3); IR (film) νmax 2931, 1710, 1577, 1454, 1432, 1213, 1161, 1124, 1037, 741, 698 cm⁻¹; HRMS (ESI+) for C39H45N6NaO6 [M+Na]+ requires 497.2298 found 497.2300.
To a stirred solution of methyl ketone 260 (26 mg, 0.055 mmol), triethylamine (23 μL, 0.17 mmol) and N,N-dimethylaminopyridine (1 mg, 8.2 μmol) in CH₂Cl₂ (0.5 mL) at 0 °C under nitrogen was added trimethylsilyl triflate (15 μL, 0.083 mmol). The resultant solution was stirred for 10 min, and then quenched by the addition of sat. aq. NH₄Cl (2 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude 260 was azeotropically dried with toluene and used directly in the next step without further purification.

Boron trifluoride diethyl etherate (21 μL, 0.17 mmol) was added to a solution of aldehyde 245 (17 mg, 0.083 mmol) in CH₂Cl₂ (1.4 mL) at −78 °C and the resultant solution stirred for 2 min. A solution of silyl enol ether 276 in CH₂Cl₂ (0.6 mL) was added dropwise. The resultant solution was stirred at −78 °C for 3 h and quenched by the addition of sat. aq. NaHCO₃ (1 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 4:1) afforded the title compound 259 (22 mg, 0.032 mmol, 58%) as a colourless oil; [α]D²⁵ = +44.8 (c 0.58 in CHCl₃);

¹H NMR (400 MHz, CDCl₃): δ 7.34-7.24 (12H, m, Ar-H × 12), 6.86-6.84 (4H, m, H-3’, H-5’ and Ar-H × 2), 6.32 (1H, dq, J = 15.7, 1.3 Hz, H-1’), 6.18 (1H, dq, J = 15.7, 6.3 Hz, H-2’), 5.28 (4H, s, OCH₂O × 2), 4.70 (4H, s, OCH₂ × 2), 4.52 (1H, d, J = 11.1 Hz, OCH₂), 4.36 (1H, d, J = 11.1 Hz, OCH₂), 4.36-4.29 (1H, m, H-5), 3.85-3.80 (1H, m, H-7), 3.76 (3H, s, OCH₃), 3.42 (1H, br s, OH), 2.92 (1H, dd, J = 11.8, 4.4 Hz, H-1a), 2.84-2.72 (2H, m, H-2 and H-1s), 2.64-2.53 (2H, m, H-4), 1.84 (3H, dd, J = 6.7, 1.3 Hz, H-3”), 1.63-1.49 (2H, m, H-6), 1.21 (3H, d, J = 6.1 Hz, H-8), 1.02 (3H, d, J = 6.5 Hz, H-9); ¹³C NMR (100 MHz, CDCl₃): δ 215.7 (C=O), 159.3 (C), 156.4 (C × 2), 138.0 (C), 137.4 (C × 2), 131.0 (CH), 130.9 (C), 129.5 (Ar-CH × 2), 128.6 (Ar-CH × 4), 128.1 (Ar-CH × 4), 128.0 (Ar-CH × 2), 126.1 (CH), 116.3 (C), 113.9 (Ar-CH × 2), 105.5 (Ar-CH × 2), 92.5 (CH₂ × 2), 71.9 (CH), 70.6 (CH₂), 70.3 (CH₂ × 2), 64.9
Experimental

(CH), 55.3 (CH₃), 48.0 (CH₂), 46.7 (CH), 43.6 (CH₂), 26.1 (CH₂), 19.9 (CH₃), 18.4 (CH₃), 15.5 (CH₃); IR (film) νₚ 3511, 2923, 1704, 1609, 1512, 1455, 1377, 1247, 1037, 930, 742, 699 cm⁻¹; HRMS (ESI+) for C₄₂H₃₈NaO₈ [M+Na]⁺ requires 705.3398 found 705.3395.

(2⁵S,5⁷R,7S)-1-(2,6-Bis((benzyloxy)methoxy)-4-(((1⁵S,2⁵S)-1,2-dihydroxypropyl)phenyl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methylcyclohexan-3-one (281)

A solution of K₂OsO₄(OH)₄ (0.08 mg, 0.2 μmol), (DHQ)₂PHAL (0.9 mg, 1.2 μmol) K₃Fe(CN)₆ (110 mg, 0.34 mmol), K₂CO₃ (47 mg, 0.34 mmol) and MeSO₂NH₂ (11 mg, 0.11 mmol) in t-BuOH (1.1 mL) and H₂O (0.55 mL) was added to alkene 259 (78 mg, 0.11 mmol) at 0 °C with stirring. The resultant mixture was stirred at 0 °C for 16 h. Sat. aq. Na₂SO₃ (1 mL) was added and the reaction mixture stirred for a further 30 min at room temperature. The reaction mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the title compound 281 (72 mg, 0.10 mmol, 91%) as a colourless oil; [α]D²⁵ = +43.7 (c 0.83 in CHCl₃);

¹H NMR (400 MHz, CDCl₃): δ 7.34-7.25 (12H, m, Ar-H × 12), 6.88-6.86 (4H, m, H₃', H₅' and Ar-H × 2), 5.30 (4H, ABq, ΔδAB = 0.02, JAB = 7.0 Hz, OCH₂O × 2), 4.71 (4H, ABq, ΔδAB = 0.02, JAB = 11.9 Hz, OCH₂), 4.55 (1H, d, J = 11.1 Hz, OCH₂), 4.38 (1H, d, J = 11.1 Hz, OCH₂), 4.34-4.26 (2H, m, H₅ and H-1'), 3.86-3.75 (2H, m, H-7 and H-2'), 3.78 (3H, s, OCH₃), 3.42 (1H, br s, OH), 3.04 (1H, br s, OH), 2.94 (1H, d, J = 11.9, 4.7 Hz, H-1₁), 2.88-2.71 (3H, m, H-2, H₁₁ and OH), 2.58 (2H, m, H-4), 1.63-1.41 (2H, m, H-6), 1.22 (3H, d, J = 6.2 Hz, CH₃), 1.07 (3H, d, J = 6.3 Hz, CH₃), 1.04 (3H, d, J = 6.6 Hz, H-9); ¹³C NMR (100 MHz, CDCl₃): δ 215.6 (C=O), 159.3 (C), 156.2 (C × 2), 141.4 (C), 137.3 (C × 2), 130.8 (C), 129.5 (Ar-CH × 2), 128.6 (Ar-CH × 4), 128.0 (Ar-CH × 6), 117.2 (C), 113.9 (Ar-CH × 2), 106.3 (Ar-CH × 2), 92.5 (CH₂ × 2), 79.4 (CH), 72.1 (CH), 71.9 (CH), 70.6 (CH₂), 70.3 (CH₂ × 2), 64.8 (CH), 55.3 (CH₃), 48.1 (CH₂), 46.4 (CH), 43.5 (CH₂), 26.5 (CH₂), 19.8 (CH₃), 18.9 (CH₃), 15.7 (CH₃); IR (film) νₚ 3396, 2967, 2923, 1701, 1586, 1513, 1330, 1247, 1154, 1035, 1026, 819, 742, 699 cm⁻¹; HRMS (ESI+) for C₄₂H₃₈NaO₈ [M+Na]⁺ requires 739.3453 found 739.3442.
(2R,3S,4'R,6'S)-7-((1S,2S)-1,2-Dihydroxypropyl)-3,6'-dimethyl-3',4',5',6'-tetrahydrospiro[chroman-2,2'-pyran]-4',5-diol (282)

A mixture of ketone 281 (35 mg, 0.049 mmol) and Pd/C (10 wt%, 50 mg) in EtOAc (2 mL) was stirred under an atmosphere of H₂ at room temperature for 3 h. The reaction mixture was filtered through Celite® and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 1:4) afforded the title compound 282 (9 mg, 0.027 mmol, 55%) as a colourless oil. \([\alpha]_{D}^{25} = -12.1 (c 0.70 \text{ in MeOH})\); ¹H NMR (400 MHz, (CD₃)₂CO): δ 8.12 (1H, br s, OH), 6.47 (1H, d, \(J = 1.4 \text{ Hz, Ar-H}\)), 6.31 (1H, d, \(J = 1.4 \text{ Hz, Ar-H}\)), 4.30-4.24 (1H, m, H-4'), 4.16 (1H, br s, OH), 4.12 (1H, d, \(J = 7.0 \text{ Hz, H-1''}\)), 3.86-3.81 (2H, m, H-6' and OH), 3.68-3.65 (2H, m, H-2'' and OH), 2.63 (1H, dd, \(J = 16.5, 5.8 \text{ Hz, H-4 a}\)), 2.36 (1H, dd, \(J = 16.5, 12.0 \text{ Hz, H-4 b}\)), 2.04-1.94 (2H, m, H-3'a and H-5'a), 1.92-1.84 (1H, m, H-3), 1.61 (1H, dd, \(J = 12.5, 11.1 \text{ Hz, H-3'' b}\)), 1.15-1.07 (1H, m, H-5'b), 1.10 (3H, d, \(J = 6.7 \text{ Hz, H-11}\)), 1.02 (3H, d, \(J = 6.2 \text{ Hz, H-7'}\)), 0.95 (3H, d, \(J = 6.3 \text{ Hz, H-3''}\)); ¹³C NMR (100 MHz, CDCl₃): δ 153.1 (C), 142.4 (C) 110.6 (C), 107.7 (Ar-CH), 106.9 (C), 106.3 (Ar-CH), 101.2 (C), 79.8 (CH), 72.5 (CH), 66.5 (CH), 64.4 (CH), 43.7 (CH₂), 41.2 (CH₂), 35.2 (CH), 25.3 (CH₂), 21.8 (CH₃), 19.4 (CH₃), 16.4 (CH₃); IR (film) ν max 3345, 2970, 2928, 1626, 1594, 1435, 1378, 1141, 1062, 1030, 993, 912, 799 cm⁻¹; HRMS (ESI+) for C₁₈H₂₆NaO₆ [M+Na]⁺ requires 361.1622 found 361.1632.
Experimental

(2R,3S,4'R,6'S)-7-(((1S,2S)-1,2-Dihydroxypropyl)-6-iodo-3,6'-dimethyl-3',4',5',6'-tetrahydrospiro[chroman-2,2'-pyran]-4',5-diol (284) and (2R,3S,4'R,6'S)-7-(((1S,2S)-1,2-Dihydroxypropyl)-8-iodo-3,6'-dimethyl-3',4',5',6'-tetrahydrospiro[chroman-2,2'-pyran]-4',5-diol (285)

To a stirred solution of spiroketal 282 (10 mg, 0.030 mmol) in DMF (0.5 mL) at −40 °C was added N-iodosuccinimide (7 mg, 0.030 mmol) and the reaction mixture stirred for 24 h. The reaction was quenched by the addition of sat. aq. Na$_2$S$_2$O$_3$ (1 mL) and allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 2:1) afforded the title compounds 284 and 285 (8.4 mg, 0.018 mmol, 60%) as an inseparable mixture. For this reason the $^1$H NMR spectrum could not be fully assigned. The regioisomeric mixture was employed in subsequent reactions; HRMS (ESI+) for C$_{18}$H$_{25}$INO$_6$ [M+Na]$^+$ requires 487.0588 found 487.0597.
3.7 Carbonylation Model Study

2-Iodobenzaldehyde (289)

To a stirred solution of 2-iodobenzyl alcohol 290 (1.0 g, 4.3 mmol), sulfur trioxide pyridine complex (2.7 g, 17 mmol) and diisopropylethylamine (5.2 mL, 30 mmol) in CH$_2$Cl$_2$ (40 mL) at 0 °C was added dimethylsulfoxide (4.3 mL, 60 mmol). The resultant solution was stirred for 15 min, and then quenched by the addition of H$_2$O. The layers were separated and the organic layer washed with H$_2$O (2 × 10 mL). The organic layer was dried over MgSO$_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the title compound 289 (0.90 g 3.9 mmol, 90%) as a colourless oil; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.08 (1H, d, $J$ = 1.0 Hz, CHO), 7.96 (1H, dd, $J$ = 8.0, 1.0 Hz, Ar-H); 7.89 (1H, dd, $J$ = 7.7, 1.8 Hz, Ar-H), 7.50-7.44 (1H, m, Ar-H), 7.32-7.26 (1H, m, Ar-H); The spectroscopic data were in agreement with those reported in the literature.\textsuperscript{233}

1-(2-Iodophenyl)propane-1,2-diol (±-287)

To a stirred solution of aldehyde 289 (1.0 g, 4.3 mmol), ethyltriphenylphosphonium iodide (2.0 g, 4.7 mmol) and 18-crown-6 (11 mg, 0.043 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 °C was added potassium tert-butoxide (0.53 g, 4.7 mmol) portionwise over 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was filtered through silica (eluting with CH$_2$Cl$_2$) and the filtrate concentrated in vacuo. Purification by flash chromatography (n-pentane) afforded the title compound (±)-287 (0.83 g, 3.4 mmol, 80%) as an inseparable mixture of stereoisomers.
RuClH(CO)(PPh$_3$)$_3$ (60 mg, 0.22 mmol) was added to a solution of alkene (±)-288 (0.83 g, 3.4 mmol) in toluene (10 mL) in a sealed tube and heated at 130 °C with stirring for 3 h. The reaction mixture was allowed to cool to room temperature, and purified by flash chromatography (pentane) affording the title compound (E)-288 as a colourless oil. Because of the volatility of alkene (E)-288, it was used directly in the next step without complete removal of the solvent or characterisation.

To a stirred solution of alkene (E)-288 in acetone (20 mL) and H$_2$O (5 mL) was added N-methylmorpholine-N-oxide (0.55 g, 4.7 mmol) and OsO$_4$ (2.5% w/w in t-BuOH, 1.1 mL). The resultant mixture was stirred at room temperature for 2 h, and then quenched by the addition of sat. aq. Na$_2$S$_2$O$_4$ (5 mL). The reaction mixture was stirred for a further 30 min, then extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with H$_2$O (5 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 2:1) afforded the title compound (±)-287 (0.68 g, 2.2 mmol, 65% over two steps) as a colourless solid; m.p. 68-72°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (1H, dd, $J = 7.9$, 1.0 Hz, Ar-H), 7.42-7.34 (2H, m, Ar-H), 7.01-6.97 (1H, m, Ar-H), 4.78-4.76 (1H, m, H-1), 3.98-3.91 (1H, m, H-2), 2.92 (1H, d, $J = 4.5$ Hz, OH), 2.41 (1H, d, $J = 4.1$ Hz, OH), 1.23 (3H, d, $J = 6.4$ Hz, H-3); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.5 (C), 139.7 (Ar-CH), 129.8 (Ar-CH), 128.7 (Ar-CH), 128.2 (Ar-CH), 98.9 (C), 80.9 (CH), 71.7 (CH), 19.2 (CH$_3$); The spectroscopic data were in agreement with those reported in the literature.$^{214}$

3-(1-Hydroxyethyl)isobenzofuran-1(3H)-one ((±)-297)

(i) Using PdCl$_2$(PPh$_3$)$_2$ and Hydrazine

Degassed DMF (1 mL) was added to a mixture of diol (±)-287 (50 mg, 0.16 mmol), PdCl$_2$(PPh$_3$)$_2$ (30 mg, 0.043 mmol) and potassium carbonate (60 mg, 0.43 mmol) under an atmosphere of carbon monoxide. Hydrazine hydrate (10 μL, 0.21 mmol) was added and the resultant mixture heated at 60 °C with stirring for two days. The reaction mixture was allowed to cool to room temperature,
H₂O (5 mL) added and then extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 2:1 to 1:1) afforded the title compound (±)-297 (26 mg, 0.15 mmol, 93%) as a colourless oil.

(ii) Using Pd(PPh₃)₄

A solution of diol (±)-287 (30 mg, 0.095 mmol), Pd(PPh₃)₄ (15 mg, 0.048 mmol) and diisopropylethylamine (33 μL, 0.19 mmol) in degassed DMF (0.5 mL) was heated to 100 °C under an atmosphere of carbon monoxide for 24 h. The reaction mixture was allowed to cool to room temperature and sat. aq. NaCl (2 mL) added. The reaction mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts dried over MgSO₄ and concentrated in vacuo. Analysis of the crude product mixture by ¹H NMR indicated 100% conversion of starting material to the title compound (±)-297; m.p. 68-72 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.91 (1H, d, J = 7.6 Hz, Ar-H), 7.71-7.66 (1H, m, Ar-H), 7.57-7.53 (2H, m, Ar-H), 5.37 (1H, d, J = 4.3 Hz, H-3), 4.21-4.14 (1H, m, H-1'), 2.31 (1H, br s, OH), 1.36 (3H, d, J = 6.5 Hz, H-2'); ¹³C NMR (100 MHz, CDCl₃): δ 170.5 (C=O), 146.9 (C), 134.2 (Ar-CH), 129.6 (Ar-CH), 126.8 (C), 125.9 (Ar-CH), 122.8 (Ar-CH), 84.3 (CH), 68.8 (CH), 18.7 (CH₃); The spectroscopic data were in agreement with those reported in the literature.²³⁵
Synthesis of Virgatolide B (2)

(S)-4-(2,6-Bis((benzoyl)methoxy)-4-((15,25)-1,2-dihydroxypropyl)phenyl)-3-methylbutan-2-one (302)

To a stirred solution of K$_2$OsO$_4$(OH)$_4$ (1 mg, 0.003 mmol), (DHQ)$_2$PHAL (10 mg, 0.013 mmol), K$_3$Fe(CN)$_6$ (250 mg, 0.76 mmol), K$_2$CO$_3$ (105 mg, 0.76 mmol) and MeSO$_2$NH$_2$ (24 mg, 0.25 mmol) in t-BuOH/H$_2$O (1:1, 2.5 mL) was added 260 (120 mg, 0.25 mmol) and the reaction mixture stirred at room temperature for 18 h. Sat. aq. Na$_2$S$_2$O$_3$ (1 mL) was added and the reaction mixture stirred for 30 min. The reaction mixture was extracted with EtOAc (3 × 2 mL), the combined organic extracts dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the title compound 302 (104 mg, 0.20 mmol, 84%) as a colourless oil; $[\alpha]^{25}_D = +35.0$ (c 0.3 in MeOH); $^1$H NMR (400 MHz, CDCl$_3$, contains less than 10 wt% MeSO$_2$NH$_2$): $\delta$ 7.35-7.32 (10H, m, Ar-H × 10), 6.88 (2H, s, H-3' and H-5'), 5.32 (4H, s, OCH$_2$O × 2), 4.72 (4H, s, OCH$_2$ × 2), 4.31 (1H, d, $J = 7.0$ Hz, H-1”), 3.86-3.80 (1H, m, H-2”), 2.98-2.94 (1H, m, H-4a), 2.86-2.74 (2H, m, H-3 and H-4b), 2.15 (3H, s, H-1), 1.08 (3H, d, $J = 6.3$ Hz, H-3”), 1.05 (3H, d, $J = 6.7$ Hz, H-5); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 212.9 (C=O), 156.3 (C × 2), 141.2 (C), 137.2 (C × 2), 128.6 (Ar-CH × 4), 128.0 (Ar-CH × 6), 117.5 (C), 106.2 (Ar-CH × 2), 92.5 (CH$_2$ × 2), 79.5 (CH), 72.2 (CH), 70.3 (CH$_2$ × 2), 46.9 (CH), 28.3 (CH$_3$), 26.7 (CH$_2$), 19.0 (CH$_3$), 15.7 (CH$_3$); IR (film) $\nu_{max}$ 3416, 2977, 2935, 1706, 1588, 1459, 1130, 1043, 739, 701 cm$^{-1}$; HRMS (ESI+) for C$_{30}$H$_{36}$NaO$_7$ [M+Na]$^+$ requires 531.2353 found 531.2356.
To a stirred solution of diol 302 (104 mg, 0.20 mmol) and silver trifluoroacetate (47 mg, 0.21 mmol) in CHCl₃ (4 mL) at 0 °C was added I₂ (55 mg, 0.21 mmol) in CHCl₃ (2 mL) portionwise over 30 min. The reaction mixture was stirred at room temperature for 1 h, quenched with sat. aq. Na₂S₂O₃ (0.5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography afforded the title compound 301 (93 mg, 0.15 mmol, 72%) as a colourless oil; [α]D²⁵ = +16.7 (c 0.27 in MeOH); ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.25 (10H, m, Ar-H × 10), 7.13 (1H, s, H-5'), 5.29 (2H, ABq, ΔδAB = 0.04, JAB = 6.9 Hz, OCH₂O), 5.16 (2H, ABq, ΔδAB = 0.03, JAB = 5.9 Hz, OCH₂O), 4.88 (2H, ABq, ΔδAB = 0.02, JAB = 11.8 Hz, OCH₂), 4.83 (1H, d, J = 5.1 Hz, H-1''), 4.69 (2H, s, OCH₂), 3.93-3.87 (1H, m, H-2''), 3.14 (1H, br s, OH), 3.08-3.03 (1H, m, H-4a), 2.91-2.85 (2H, m, H-3 and H-4b), 2.53 (1H, br s, OH), 2.09 (3H, s, H-1), 1.21 (3H, d, J = 6.5 Hz, H-3''), 1.02 (3H, d, J = 6.5 Hz, H-5); ¹³C NMR (100 MHz, CDCl₃): δ 212.4 (C=O), 156.9 (C), 156.7 (C), 144.0 (C), 137.2 (C), 128.6 (Ar-CH × 4), 128.1 (Ar-CH × 2), 128.0 (Ar-CH × 4), 124.1 (C), 110.2 (Ar-CH), 98.6 (CH₂), 92.5 (CH₂), 88.6 (C), 81.0 (CH), 72.1 (CH₂), 71.6 (CH), 70.5 (CH₂), 46.9 (CH), 28.3 (CH₂), 28.1 (CH₃), 19.4 (CH₃), 16.0 (CH₃); IR (film) νmax 3423, 2935, 1708, 1590, 1455, 1373, 1158, 1082, 1031, 1000, 742 cm⁻¹; HRMS (ESI+) for C₃₀H₃₅I-KO⁺ requires 673.1059 found 673.1063.
(S)-5,7-Bis((benzyloxy)methoxy)-3-((S)-1-hydroxyethyl)-6-((S)-2-methyl-3-oxobutyl)isobenzofuran-1(3H)-one (300)

A stirred solution of iodide 301 (45 mg, 0.07 mmol), Pd(PPh₃)₄ (40 mg, 0.03 mmol) and diisopropylethylamine (25 μL, 0.14 mmol) in degassed DMF (0.5 mL) was placed under an atmosphere of CO (1 atm, balloon) and heated at 100 °C for 24 h. The reaction mixture was allowed to cool to room temperature and sat. aq. NaCl (3 mL) was added. The layers were separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 2:1 to 1:1) afforded the title compound 300 (33 mg, 0.06 mmol, 75%, 10% remaining starting material, inseparable by chromatography) as a pale yellow oil; [α]D²⁵ = +42.0 (c 0.35 in CDCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.28 (10H, m, Ar-H × 10), 7.05 (1H, s, H-4), 5.53 (2H, s, OCH₂O), 5.37 (2H, ABq, ΔδAB = 0.04, JAB = 7.0 Hz, OCH₂O), 5.18 (1H, d, J = 4.0 Hz, H-3), 4.82 (2H, s, OCH₂), 4.62 (2H, ABq, ΔδAB = 0.03, JAB = 11.8 Hz, OCH₂), 4.12-4.08 (1H, m, H-1”), 3.08-3.03 (1H, m, H-1”), 2.93-2.85 (2H, m, H-2’ and H-1’b), 2.14 (3H, s, H-4’), 1.89 (1H, d, J = 6.0 Hz, OH), 1.34 (3H, d, J = 6.5 Hz, H-2”), 1.05 (3H, d, J = 6.6 Hz, H-5’); ¹³C NMR (100 MHz, CDCl₃): δ 212.1 (C=O), 168.3 (C=O), 161.9 (C), 156.0 (C), 149.1 (C), 137.2 (C), 136.7 (C), 128.7 (Ar-CH × 2), 128.6 (Ar-CH × 2), 128.4 (Ar-CH), 128.2 (Ar-CH × 2), 128.1 (Ar-CH), 128.0 (Ar-CH × 2), 123.5 (C), 110.9 (C), 103.0 (Ar-CH), 99.5 (CH₂), 92.6 (CH₂), 83.1 (CH), 72.1 (CH₂), 71.0 (CH₂), 68.9 (CH), 46.8 (CH), 28.3 (CH₃), 26.9 (CH₂), 19.0 (CH₃), 15.9 (CH₃); IR (film) νmax 3436, 2933, 1753, 1708, 1604, 1453, 1228, 1089, 1029, 921, 742, 699 cm⁻¹; HRMS (ESI+) for C₃₁H₃₄NaO₈ [M+Na]⁺ requires 557.2146 found 557.2133.
To a stirred solution of phthalide 300 (10 mg, 0.018 mmol) in CH₂Cl₂ (0.5 mL) was added N,N'-dicyclohexylcarbodiimide (6 mg, 0.028 mmol), DMAP (1 mg, 8 μmol) and (R)-(+) α-methoxy-α-trifluoromethylphenylacetic acid (4 mg, 0.022 mmol). The resultant solution stirred at room temperature for 24 h. The reaction was quenched by the addition of sat. aq. NaHCO₃ (1 mL), the layers separated and the aqueous layer further extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound 378 (10 mg, 0.014 mmol, 75%) as a colourless oil; [α]ᵢ₀⁵⁺ = +53.8 (c 0.74 in CDCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.25 (15H, m, Ar-H×15), 6.91 (1H, s, H-4), 5.62 (1H, qd, J = 6.5, 2.6 Hz, H-1'''), 5.41 (2H, ABq, Δδₐₘ = 0.17, Jₐₘ = 6.5 Hz, OCH₂O), 5.31-5.26 (3H, m, H-3 and OCH₂O), 4.81 (2H, s, OCH₂), 4.70 (2H, ABq, Δδₐₘ = 0.03, Jₐₘ = 4.7 Hz, OCH₂), 3.34 (3H, s, OMe), 3.04-3.00 (1H, m, H-1ₐ'''), 2.89-2.82 (2H, m, H-2' and H-1ₐ'''), 2.14 (3H, s, H-4''), 1.48 (3H, J = 6.5 Hz, H-2''). 1.02 (3H, d, J = 6.6 Hz, H-5''); ¹³C NMR (100 MHz, CDCl₃): δ 212.0 (C=O), 167.6 (C), 165.7 (C), 162.0 (C), 156.0 (C), 147.6 (C), 137.3 (C), 136.7 (C), 131.7 (C), 129.8 (Ar-CH), 128.7 (Ar-CH × 2), 128.6 (Ar-CH × 2), 128.5 (Ar-CH × 2), 128.4 (Ar-CH), 128.2 (Ar-CH × 2), 128.1 (Ar-CH) 127.9 (Ar-CH × 2), 127.2 (Ar-CH × 2), 123.8 (C), 110.9 (C), 102.6 (Ar-CH) 99.5 (CH₂), 92.7 (CH₃), 80.0 (CH), 72.0 (CH₂), 71.5 (CH), 71.1 (CH₂), 55.3 (CH₃), 46.8 (CH), 28.2 (CH₃), 26.8 (CH₂), 15.9 (CH₃), 15.7 (CH₃), CF₃ signal not observed; IR (film) νₘₐₓ 2937, 2753, 1710, 1605, 1453, 1359, 1229, 1165, 1026, 916, 736 cm⁻¹; HRMS (ESI+) for C₄₁F₄₁H₄₁NaO₁₀ [M+Na]⁺ requires 773.2544 found 773.2544.

Comparison of the ¹H, ¹³C and ¹⁹F NMR spectra of ester 378 to the mixture of esters generated by reaction of 300 with (R/S)-MTPA confirmed the stereochemistry of C-1'' as S.
(S)-5,7-Bis((benzyl oxy)methoxy)-6-((2S,5R,7S)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyl-3-oxooctyl)-3-((S)-1-hydroxyethyl)isobenzofuran-1(3H)-one (299)

To a stirred solution of ketone 300 (20 mg, 0.037 mmol), triethylamine (26 μL, 0.19 mmol) and DMAP (5 mg, 0.041 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added TMSOTf (20 μL, 0.11 mmol). The reaction mixture was stirred for 15 min, and then quenched with sat. aq. NH$_4$Cl (1 mL). The layers were separated, and the aqueous layer extracted with Et$_2$O (2 × 1 mL). The combined organic extracts were dried over MgSO$_4$, concentrated in vacuo and then azeotropically dried with toluene to give crude enol ether 306 which was used without further purification.

To a stirred solution of aldehyde 245 (28 mg, 0.13 mmol) in CH$_2$Cl$_2$ (1 mL) at −78 °C was added BF$_3$·OEt$_2$ (20 μL, 0.14 mmol) and the solution stirred for 3 min. A solution of silyl enol ether 306 in CH$_2$Cl$_2$ (1 mL) was added dropwise and the reaction mixture stirred at −78 °C for 1.5 h. Sat. aq. NaHCO$_3$ (1 mL) was added and the reaction mixture allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo to give crude aldol 307 which was used without further purification.

Aldol 307 was dissolved in MeOH (1 mL), sat. aq. K$_2$CO$_3$ (0.1 mL) added and the reaction mixture stirred at room temperature for 15 min. MgSO$_4$ was added and the reaction mixture filtered, then concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 2:1 to 1:1) afforded the title compound 299 (18 mg, 0.024 mmol, 65% over 3 steps) as a colourless oil; [α]$_D^{25}$ = +40.3 (c 0.37 in CDCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.38-7.24 (12H, m, Ar-H × 12), 7.02 (1H, s, H-4), 6.87-6.84 (2H, m, Ar-H × 2), 5.54 (2H, s, OCH$_2$O), 5.37 (2H, ABq, $\Delta$$\delta_{AB}$ = 0.03, $J_{AB}$ = 7.2 Hz, $\gamma$-H × 2, $\delta$-H × 2).
OCH\textsubscript{2}O), 5.17 (1H, d, J = 3.5 Hz, H-3), 4.82 (2H, ABq, \Delta\delta_{AB} = 0.01, J_{AB} = 12.0 Hz, OCH\textsubscript{2}), 4.72 (2H, ABq, \Delta\delta_{AB} = 0.03, J_{AB} = 11.8 Hz, OCH\textsubscript{2}), 4.54-4.52 (1H, m, OCH\textsubscript{2}), 4.37-4.34 (1H, m, OCH\textsubscript{2}), 4.33-4.27 (1H, m, H-5'), 4.11-4.07 (1H, m, H-1''), 3.82-3.78 (4H, m, H-7' and OCH\textsubscript{3}), 3.27 (1H, d, J = 3.0 Hz, OH), 3.08-3.01 (1H, m, H-1''), 2.93-2.85 (2H, m, H-2' and H-1''), 2.57 (1H, dd, J = 17.5, 14.0 Hz, H-4''), 2.46 (1H, dd, J = 17.5, 8.5 Hz, H-4''), 1.97 (1H, br s, OH), 1.58-1.46 (2H, m, H-6'), 1.35 (3H, d, J = 6.5 Hz, H-2''), 1.20 (3H, d, J = 6.2 Hz, H-8''), 1.04 (3H, d, J = 6.4 Hz, H-9'); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \delta 214.9 (C=O), 168.3 (C=O), 161.8 (C), 159.3 (C), 156.0 (C), 149.3 (C), 137.2 (C), 136.8 (C), 130.9 (C), 129.4 (Ar-CH \times 2), 128.6 (Ar-CH \times 2), 128.5 (Ar-CH \times 2), 128.2 (Ar-CH), 128.0 (Ar-CH \times 2), 127.9 (Ar-CH), 127.8 (Ar-CH \times 2), 123.2 (C), 113.8 (Ar-CH \times 2), 110.9 (C), 103.0 (Ar-CH), 99.5 (CH\textsubscript{2}), 92.7 (CH\textsubscript{2}), 83.1 (CH), 71.9 (CH\textsubscript{2}), 71.8 (CH), 70.9 (CH\textsubscript{2}), 70.4 (CH\textsubscript{2}), 68.6 (CH), 64.7 (CH), 55.4 (CH\textsubscript{3}), 48.5 (CH\textsubscript{2}), 46.2 (CH), 43.4 (CH\textsubscript{2}), 27.0 (CH\textsubscript{2}), 19.8 (CH\textsubscript{3}), 19.1 (CH\textsubscript{3}), 15.9 (CH\textsubscript{3}); IR (film) \nu_{\text{max}} 3465, 2930, 1755, 1608, 1514, 1455, 1249, 1035, 743, 699 cm\textsuperscript{-1}; HRMS (ESI+) for C\textsubscript{43}H\textsubscript{50}NaO\textsubscript{11}[M+Na]\textsuperscript{+} requires 765.3245 found 765.3260.

Virgatolide B (2)

\begin{align*}
\textbf{299} & \quad \rightarrow \quad \textbf{2}
\end{align*}

A mixture of ketone \textbf{299} (18 mg, 0.024 mmol) and Pd/C (10 wt%, 40 mg) in EtOAc (1 mL) was stirred under an atmosphere of H\textsubscript{2} at room temperature for 3 h. The reaction mixture was filtered through Celite\textsuperscript{®} and concentrated \textit{in vacuo}. The crude residue was then dissolved in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) and CSA (1 mg) added. The reaction mixture was stirred at room temperature for 16 h, and then quenched with sat. aq. NaHCO\textsubscript{3} (0.5 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 \times 1 mL). The combined organic extracts were dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. Purification by flash chromatography (hexanes/EtOAc 1:2) afforded the \textit{title compound} \textbf{2} (5 mg, 0.014 mmol, 55%) as a colourless oil; [\alpha]_D^{25} = +19.1 (c 0.25 in MeOH), lit. +25.0 (c 0.07 in MeOH); \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}OD): \delta 6.53 (1H, s, H-2), 5.28 (1H, d, J = 3.0 Hz, H-4), 4.28 (1H, ddt, J = 15.7, 11.2, 4.5 Hz, H-13), 4.13 (1H, qd, J = 6.5, 3.0 Hz, H-16), 3.88-3.80 (1H, m, H-15), 2.71 (1H, dd, J = 16.6, 5.9 Hz, H-9\textsubscript{a}), 2.41 (1H, dd, J = 16.6, 12.3 Hz, H-9\textsubscript{b}), 2.04-1.98 (2H, m, H-12\textsubscript{a} and H-14\textsubscript{a}), 1.92 (1H, ddq, J = 12.3, 6.5, 5.9 Hz, H-10), 1.66 (1H,
Experimental

dd, J = 12.7, 11.2 Hz, H-12α), 1.23 (3H, d, J = 6.5 Hz, H-17), 1.17-1.13 (1H, m, H-14α), 1.14 (3H, d, J = 6.5 Hz, H-18), 1.06 (3H, d, J = 6.0 Hz, H-19); 13C NMR (100 MHz, CD3OD): δ 173.0 (C=O), 160.1 (C), 155.6 (C), 148.3 (C), 112.7 (C), 105.9 (C), 104.0 (C-2), 102.9 (C-11), 85.5 (C-4), 68.8 (C-16), 67.6 (C-15), 65.0 (C-13), 43.3 (C-14), 40.8 (C-12), 35.2 (C-10), 24.9 (C-9), 21.6 (C-19), 18.7 (C-17), 16.2 (C-18); IR (film) ν max 3421, 2925, 1727, 1608, 1456, 1387, 1240, 1112, 1064, 988, 960, 911, 870 cm\(^{-1}\); HRMS (ESI+) for C\(_{19}\)H\(_{24}\)NaO\(_7\) [M+Na]\(^+\) requires 387.1414 found 387.1408. The spectroscopic data were in agreement with those reported in the literature.\(^1\)
3.9 Synthesis of Spiro γ-Lactones (±)-317 and (±)-340

Cyclohexyl 3-diazo-2-oxopropanoate (311)

\[
\text{OH} \quad \rightarrow \quad \begin{array}{c}
\text{N}_2\text{O} \\
\text{311}
\end{array}
\]

To a stirred solution of oxalyl chloride (0.7 mL, 7.9 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 °C was added cyclohexanol (0.83 mL, 7.9 mmol) in CH$_2$Cl$_2$ (20 mL) over 30 min. The resultant solution was then allowed to warm to room temperature, stirred for 90 min and concentrated in vacuo. The crude residue was dissolved in THF (40 mL) and TMS-diazomethane (2 M in hexane 12 mL) added. The resultant solution was stirred at room temperature for 3 h, and then quenched by the addition of aqueous hydrochloric acid (1 M, 20 mL). The reaction mixture was extracted with Et$_2$O (2 × 40 mL), the combined organic extracts dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 4:1) afforded the title compound 311 (1.5 g, 7.4 mmol, 95%) as a pale yellow solid; m.p. 101-103 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.14 (1H, s, H-3'), 4.93-4.86 (1H, m, H-1), 1.94-1.90 (2H, m, H-2a and H-6a), 1.81-1.76 (2H, m, H-3a and H-5a), 1.60-1.51 (4H, m, H-4, H-2b and H-6b), 1.44-1.31 (2H, m, H-3b and H-5b); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.5 (C), 159.9 (C), 76.2 (CH), 56.9 (CH), 31.4 (CH$_2$ 2), 25.3 (CH$_2$), 23.9 (CH$_2$ 2); IR (film) $\nu_{\text{max}}$ 3082, 2941, 2861, 2156, 2098, 1730, 1619, 1602, 1454, 1358, 1234, 1122, 1036, 1006, 947, 891, 811, 781 cm$^{-1}$; HRMS (ESI+) for C$_9$H$_{12}$N$_2$NaO$_3$ [M+Na]$^+$ requires 219.0740 found 219.0743.

(±)-3-Phenylcyclohexanone ((±)-321)

\[
\text{O} \quad \rightarrow \quad \begin{array}{c}
\quad \text{O} \\
\text{(±)-321}
\end{array}
\]

To a stirred solution of [RhCl(COD)]$_2$ (64 mg, 0.13 mmol) and phenylboronic acid (1.3 g, 11 mmol) in dioxane/H$_2$O (10:1, 13 mL) was added cyclohexenone (500 mg, 5.2 mmol) and
triethylamine (0.73 mL, 5.2 mmol). The resultant solution was stirred at room temperature for 3 h and the reaction mixture concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 20:1 to 5:1) afforded the title compound (±)-321 (0.89 g, 5.1 mmol, 98%) as a colourless oil; 1H NMR (400 MHz, CDCl3): δ 7.35-7.21 (5H, m, Ar-H × 5), 3.06-2.97 (1H, dddd, J = 11.7, 11.7, 3.9, 3.9 Hz, H-3), 2.63-2.34 (4H, m, CH of C2H × 4), 2.17-2.07 (2H, m, CH of C2 × 2), 1.91-1.74 (2H, m, CH of C2 × 2); The spectroscopic data were in agreement with those reported in the literature.22

(±)-(1R*,3R*)-3-Phenyl-1-vinylcyclohexanol ((±)-320) and
(±)-(1S*,3R*)-3-phenyl-1-vinylcyclohexanol ((±)-319)

To a stirred solution of ketone (±)-321 (100 mg, 0.57 mmol) in THF (4.4 mL) at −78 °C was added vinylmagnesium bromide (1 M in Et2O, 2.0 mL) and the resultant solution stirred for 1 h. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 h, and then quenched with sat. aq. NH4Cl (1 mL). The reaction mixture was extracted with Et2O (3 × 5 mL), the combined organic extracts dried over Na2SO4 and concentrated in vacuo. Purification by flash chromatography afforded the title compounds (±)-320 (65 mg, 0.32 mmol, 56%) and (±)-319 (39 mg, 0.19 mmol, 33%) as colourless solids.

(±)-(1R*,3R*)-3-Phenyl-1-vinylcyclohexanol ((±)-320)

1H NMR (400 MHz, CDCl3): δ 7.29-7.15 (5H, m, Ar-H × 5), 5.96 (1H, dd, J = 17.4, 10.8 Hz, H-7), 5.24 (1H, dd, J = 17.4, 1.3 Hz, H-8a), 5.00 (1H, dd, J = 10.8, 1.3 Hz, H-8b), 3.01 (1H, dddd, J = 12.5, 12.5, 3.3, 3.3 Hz, H-3), 1.90-1.37 (8H, m, CH2 × 4); 13C NMR (100 MHz, CDCl3): δ 147.0 (C), 146.8 (CH), 128.5 (Ar-CH × 2), 127.0 (Ar-CH × 2), 126.1 (Ar-CH), 111.1 (CH2), 72.4 (C), 44.7 (CH2), 39.1 (CH), 36.7 (CH2), 33.3 (CH2), 21.8 (CH2); IR (film) νmax 3398, 2929, 1494, 1447, 1265, 1133, 968, 918, 738 cm−1; HRMS (ESI+) for C14H18NaO [M+Na]+ requires 225.1250 found 225.1246.
(±)-(1S*,3R*)-3-Phenyl-1-vinylcyclohexanol ((±)-319)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.29-7.19\) (5H, m, Ar-H \(\times 5\)), 6.16 (1H, dd, \(J = 17.7, 10.8\) Hz, H-7), 5.39 (1H, dd, \(J = 17.7, 1.0\) Hz, H-8\(_a\)), 5.24 (1H, dd, \(J = 10.8, 1.0\) Hz, H-8\(_b\)), 2.66 (1H, dddd, \(J = 12.6, 12.6, 3.3, 3.3\) Hz, H-3), 2.06-1.38 (8H, m, CH\(_2\) \(\times 4\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 146.3\) (C), 142.9 (CH), 128.6 (Ar-CH \(\times 2\)), 126.9 (Ar-CH \(\times 2\)), 126.3 (Ar-CH), 114.6 (CH\(_2\)), 72.8 (C), 46.2 (CH\(_2\)), 41.5 (CH), 38.4 (CH\(_2\)), 33.8 (CH\(_2\)), 23.7 (CH\(_2\)); IR (film) \(\nu_{\text{max}}\) 3370, 2931, 2856, 1450, 1041, 998, 951, 924, 736 cm\(^{-1}\); HRMS (ESI+) for C\(_{14}\)H\(_{18}\)NO \([M+Na]^+\) requires 225.1250 found 225.1256.

To a stirred solution of (±)-319 (25 mg, 0.12 mmol) and ethyl acrylate (56 μL, 0.62 mmol) in CH\(_2\)Cl\(_2\) (0.6 mL) was added Hoveyda-Grubbs 2\(^{nd}\) generation catalyst (8 mg, 12 μmol) and the resultant solution stirred at room temperature for 16 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1 to 5:1) afforded the title compound (±)-318 (13 mg, 0.060 mmol, 50%) as a colourless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.34-7.17\) (6H, m, H-3' + Ar-H \(\times 5\)), 6.17 (1H, d, \(J = 16.0\) Hz, H-2'), 4.23 (2H, q, \(J = 7.1\) Hz, OCH\(_2\)), 2.72 (1H, dddd, \(J = 12.6, 12.6, 3.4, 3.4\) Hz, H-3), 2.05-1.40 (8H, CH\(_2\) \(\times 4\)), 1.31 (3H, t, \(J = 7.1\) Hz, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 167.0\) (C=O), 151.5 (CH), 145.7 (C), 128.6 (Ar-CH \(\times 2\)), 126.9 (Ar-CH \(\times 2\)), 126.5 (Ar-CH), 120.5 (CH), 72.7 (C), 60.7 (CH\(_2\)), 46.4 (CH\(_2\)), 41.2 (CH), 38.7 (CH\(_2\)), 33.6 (CH\(_2\)), 23.5 (CH\(_2\)), 14.4 (CH\(_3\)); IR (film) \(\nu_{\text{max}}\) 3438, 2933, 1730, 1701, 1651, 1452, 1368, 1306, 1269, 1181, 1034, 986, 757 cm\(^{-1}\); HRMS (ESI+) for C\(_{17}\)H\(_{22}\)NaO \([M+Na]^+\) requires 297.1461 found 297.1460.
(±)-(5R*,7R*)-7-Phenyl-1-oxaspiro[4.5]decan-2-one ((±)-317)

![Chemical Structure of 317](image)

A mixture of alkene (±)-318 (29 mg, 0.11 mmol) and Pd/C (10 mg, 10 wt%) in EtOAc (2 mL) was stirred at room temperature under a hydrogen atmosphere for 24 h and then the reaction mixture concentrated in vacuo. Purification by flash chromatography afforded the title compound (±)-317 (26 mg, 0.11 mmol, 93%) as a colourless solid; ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.11 (5H, m, Ar-H × 5), 2.61-2.47 (3H, m, H-3 and H-7), 2.11 (2H, dd, J = 8.4, 8.4 Hz, H-4), 1.92-1.66 (6H, m, CH of CH₂ × 6), 1.48-1.27 (2H, m, CH of CH₂ × 2); ¹³C NMR (100 MHz, CDCl₃): δ 176.5 (C=O), 145.1 (C), 128.7 (Ar-CH × 2), 126.8 (Ar-CH × 2), 126.7 (Ar-CH), 87.3 (C), 43.9 (CH₂), 41.4 (CH), 36.2 (CH₂), 33.3 (CH₂), 30.8 (CH₂), 28.8 (CH₂), 23.2 (CH₂); IR (film) νmax 2935, 2960, 1756, 1494, 1452, 1293, 1179, 1036, 956, 908 cm⁻¹; HRMS (ESI+) for C₁₅H₁₈NaO₂ [M+Na]⁺ requires 253.1199 found 253.1202.

(±)-(3R*,5R*)-5-phenyl-1-oxaspiro[2.5]octane ((±)-333) and (±)-(3S*,5R*)-5-phenyl-1-oxaspiro[2.5]octane ((±)-331)

![Chemical Structure of 321 to 333](image)

To a stirred solution of ketone (±)-321 (1.8 g, 11 mmol), methyltriphenylphosphonium iodide (4.7 g, 12 mmol) and 18-crown-6 (26 mg, 0.10 mmol) in CH₂Cl₂ (53 mL) at 0 °C was added t-BuOK (1.3 g, 12 mmol). The resultant solution was allowed to warm to room temperature, stirred for 24 h and then concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 20:1) afforded the intermediate alkene (±)-332 as a volatile liquid that was used directly in the next step without full characterisation.

m-CPBA (2.0 g, 12 mmol) was added to a solution of alkene (±)-332 in CH₂Cl₂ (50 mL) at 0 °C and the reaction mixture stirred at 0 °C for 2 h. Purification by flash chromatography
(hexanes/EtOAc 10:1) afforded the title compound (±)-331/333 (1.9 g, 10 mmol, 94% over two steps); 1H NMR (400 MHz, CDCl₃): δ 7.31-7.16 (5H, m, Ar-H × 5), 2.95 (1H, dddd, J = 12.5, 12.5, 3.6, 3.6 Hz, H-5), 2.75* (1H, dddd, J = 12.2, 12.2, 3.4, 3.4 Hz, H-5*), 2.68-2.63 (2H, m, H-2), 2.07-1.77 (5H, m, CH of CH₂ × 5), 1.61-1.28 (3H, m, CH of CH₂ × 3); 13C NMR (100 MHz, CDCl₃): δ 146.4 (C), 145.7* (C), 128.6* (Ar-CH × 2), 128.5 (Ar-CH × 2), 126.8 (Ar-CH × 2), 126.8* (Ar-CH × 2), 126.4* (Ar-CH), 126.2 (Ar-CH), 59.5* (C), 58.6 (C), 54.9* (CH₂), 54.0 (CH₂), 44.0* (CH), 41.9* (CH₂), 41.3 (CH), 41.0 (CH₂), 33.6* (CH₂), 33.5* (CH₂), 32.9 (CH₂), 32.6 (CH₂), 25.3* (CH₂), 23.9 (CH₂); IR (film) νmax 2932, 2858, 1493, 1449, 1265, 910, 734 cm⁻¹; HRMS (ESI+) for C₁₃H₁₆NaO [M+Na]⁺ requires 211.1093 found 211.1099.

(±)-(1R*,3R*)-3-Phenyl-1-(prop-2-yn-1-yl)cyclohexanol ((±)-334) and (±)-(1S*,3R*)-3-Phenyl-1-(prop-2-yn-1-yl)cyclohexanol ((±)-330)

\[
\begin{align*}
\text{To a stirred solution of epoxide (±)-331/333 (500 mg, 2.7 mmol) in DMSO (4 mL) at 0 °C was added lithium acetylide-ethylenediamine complex (370 mg, 4.1 mmol). The resultant suspension was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by the addition of H₂O (4 mL) and extracted with Et₂O (3 × 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the title compounds (±)-334 (360 mg, 1.7 mmol, 62%) and (±)-330 (130 mg, 0.61 mmol, 23%) as colourless solids.}
\end{align*}
\]

(±)-(1R*,3R*)-3-Phenyl-1-(prop-2-yn-1-yl)cyclohexanol ((±)-334)

1H NMR (400 MHz, CDCl₃): δ 7.33-7.19 (5H, m, Ar-H × 5), 3.00 (1H, dddd, J = 12.5, 12.5, 3.5, 3.5 Hz, H-3), 2.45-2.36 (2H, m, H-1'), 2.11-2.10 (1H, m, H-3'), 2.01-1.75 (6H, m, CH of CH₂ × 6), 1.61-1.37 (2H, m, CH of CH₂ × 2); 13C NMR (100 MHz, CDCl₃): δ 146.9 (C), 128.5 (Ar-CH × 2), 127.1 (Ar-CH × 2), 126.2 (Ar-CH), 80.4 (C), 71.9 (CH), 70.9 (C), 44.3 (CH₂), 39.3 (CH), 36.2 (CH₂), 34.8 (CH₂), 33.6 (CH₂), 21.9 (CH₂); IR (film) νmax 3453, 3297, 2931, 2852,
Experimental

1602, 1494, 1449, 1133, 994, 942, 758 cm⁻¹; HRMS (ESI+) for C₁₅H₁₈NaO [M+Na]⁺ requires
237.1250 found 237.1247.

(±)-(1S*,3R*)-3-Phenyl-1-(prop-2-yn-1-yl)cyclohexanol ((±)-330)

¹H NMR (400 MHz, CDCl₃); δ 7.34-7.19 (5H, m, Ar-H × 5), 2.62-2.54 (3H, m, H-1’ and H-3),
2.17-2.09 (4H, m, H-3' and CH of CH₂), 2.00-1.85 (3H, m, CH of CH₂× 3), 1.71-1.36 (4H, m, CH
of CH₂× 4); ¹³C NMR (100 MHz, CDCl₃); δ 146.0 (C), 128.6 (Ar-CH × 2), 126.9
(Ar-CH × 2), 126.4 (Ar-CH), 80.4 (C), 72.1 (CH), 71.7 (C), 44.8 (CH₂), 41.6 (CH), 37.2 (CH₂),
33.7 (CH₂), 28.7 (CH₂), 23.7 (CH₂); IR (film) νmax 3411, 3295, 2931, 2858, 1602, 1494, 1448,
1063, 959, 749 cm⁻¹; HRMS (ESI+) for C₁₅H₁₈NaO [M+Na]⁺ requires 237.1250 found 237.1246.

(±)-(1R*,3R*)-1-(3-Bromoprop-2-yn-1-yl)-3-phenylcyclohexanol ((±)-339)

To a stirred solution of alkyne (±)-334 (360 mg, 1.7 mmol) in acetone (7 mL) was added NBS
(350 mg, 2.0 mmol) and AgNO₃ (23 mg, 0.13 mmol). The resultant solution was stirred at room
temperature for 2 h, then quenched with H₂O (15 mL). The reaction mixture was extracted with
Et₂O (3 × 30 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated
in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound
(±)-339 (460 mg, 1.6 mmol, 94%) as a colourless solid; ¹H NMR (400 MHz, CDCl₃); δ 7.34-7.20
(5H, m, Ar-H × 5), 3.00 (1H, dddd, J = 12.6, 12.6, 3.5, 3.5 Hz, H-3), 2.44-2.43 (2H, m, H-1’),
1.99-1.74 (5H, m, CH of CH₂ × 5), 1.59-1.38 (3H, m, CH of CH₂ × 3); ¹³C NMR (100 MHz,
CDCl₃); δ 146.8 (C), 128.5 (Ar-CH × 2), 127.1 (Ar-CH × 2), 126.2 (Ar-CH), 76.5 (C), 71.2 (C),
44.3 (CH₂), 41.4 (C), 39.3 (CH), 36.2 (CH₂), 36.0 (CH₂), 33.6 (CH₂), 21.9 (CH₂); IR (film)
νmax 3428, 2928, 2852, 1777, 1600, 1494, 1448, 1132, 1068, 991, 944, 758 cm⁻¹; HRMS (ESI+) for
A mixture of chlorotriphenylphosphine gold(I) (5 mg, 16 μmol) and silver hexafluoroantimonate (5 mg, 16 μmol) in toluene-H₂O (10:1, 0.7 mL) was stirred at room temperature for 1 h and then bromide (±)-339 (50 mg, 0.17 mmol) added. The resultant mixture was stirred at room temperature for 16 h, filtered through Celite® and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound (±)-340 (23 mg, 0.10 mmol, 58%) as a colourless oil; 1H NMR (400 MHz, CDCl₃): δ 7.33-7.19 (5H, m, Ar-H × 5), 3.02 (1H, dddd, J = 12.6, 12.6, 3.5, 3.5 Hz, H-7), 2.64-2.59 (2H, m, H-3), 2.08-1.81 (7H, m, CH of CH₂ × 7), 1.69-1.45 (3H, m, CH of CH₂ × 3); 13C NMR (100 MHz, CDCl₃): δ 176.8 (C=O), 146.1 (C), 128.6 (Ar-CH × 2), 126.9 (Ar-CH × 2), 126.4 (Ar-CH), 86.3 (C), 44.7 (CH₂), 39.9 (CH), 36.7 (CH₂), 34.7 (CH₂), 32.9 (CH₂), 28.6 (CH₂), 22.5 (CH₂); IR (film) v<sub>max</sub> 2931, 1765, 1451, 1222, 1180, 964, 924, 757 cm⁻¹; HRMS (ESI+) for C₁₅H₁₈NaO [M+Na]<sup>+</sup> requires 253.1199 found 253.1206.
3.10 Synthesis of Aldol 352

(S)-N-Methoxy-3-((4-methoxybenzyl)oxy)-N-methylbutanamide (348)

To a stirred solution of ester 244 (0.44 g, 1.7 mmol) and N,O-dimethylhydroxylamine hydrochloride (260 mg, 2.7 mmol) in THF (5 mL) at −20 °C under nitrogen was added isopropylmagnesium chloride (2 M in Et₂O, 2.7 mL) and the resultant solution stirred for 2 h. The reaction was quenched by the addition of sat. aq. NH₄Cl (5 mL) and extracted with Et₂O (3 × 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the title compound 348 (340 mg, 1.3 mmol, 72%) as a colourless oil; [α]D²⁵ = −3.6 (c 1.11 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.23 (2H, d, J = 8.6 Hz, Ar-H × 2), 6.84 (2H, d, J = 8.6 Hz, Ar-H × 2), 4.46 (2H, ABq, ΔδAB = 0.07, JAB = 12.0 Hz, OCH₂), 4.11-4.00 (1H, m, H-3), 3.77 (3H, s, OCH₃), 3.63 (3H, s, OCH₃), 3.17 (3H, s, NCH₃), 2.86 (1H, dd, J = 15.2, 6.8 Hz, H-2a), 2.42 (1H, dd, J = 15.2, 6.0 Hz, H-2b), 1.25 (3H, d, J = 6.1 Hz, H-4); ¹³C NMR (100 MHz, CDCl₃): δ 162.4 (C), 159.1 (C), 131.0 (C), 129.3 (Ar-CH × 2), 113.8 (Ar-CH × 2), 72.0 (CH), 70.8 (CH₂), 61.3 (CH₃), 55.3 (CH₃), 39.4 (CH₂), 32.1 (CH₃), 20.3 (CH₃); IR (film) νmax 2969, 2937, 2837, 1655, 1613, 1513, 1463, 1383, 1301, 1247, 1174, 1088, 1033, 822 cm⁻¹; HRMS (ESI+) for C₁₄H₂₁NNaO₄ [M+Na]+ requires 290.1363 found 290.1352.

(S)-4-((4-Methoxybenzyl)oxy)pentan-2-one (346)

To a stirred solution of amide 348 (330 mg, 1.2 mmol) in Et₂O (3.2 mL) at 0 °C was added methylmagnesium bromide (3 M in Et₂O, 0.6 mL) and the resultant mixture allowed to warm to room temperature over 4 h. The reaction was quenched by the addition of sat. aq. NH₄Cl (5 mL) and extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried over MgSO₄ and
concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound 346 (240 mg, 1.1 mmol, 89%) as a colourless oil; $[\alpha]_{D}^{25} = +29.7$ (c 1.1 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.26-7.21 (2H, m, Ar-H × 2), 6.87-6.84 (2H, m, Ar-H × 2), 4.51-4.36 (2H, ABq, $\Delta\delta_{AB} = 0.11$, $J_{AB} = 12.0$ Hz, OCH$_2$), 4.05-3.95 (1H, m, H-4), 3.79 (3H, s, OCH$_3$), 2.76 (1H, dd, $J = 15.7$, 7.4 Hz, H-3a), 2.49-2.42 (1H, dd, $J = 15.7$, 5.2 Hz, H-3b), 2.14 (2H, s, H-1), 1.22 (3H, m, J = 6.1 Hz, H-5); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 207.6 (C=O), 159.3 (C), 130.7 (C), 129.4 (Ar-CH × 2), 113.9 (Ar-CH × 2), 71.3 (CH), 70.6 (CH$_2$), 55.3 (CH$_3$), 50.9 (CH$_2$), 31.1 (CH$_3$), 19.9 (CH$_3$); IR (film) $\nu_{max}$ 2969, 2935, 1712, 1612, 1513, 1372, 1236, 1172, 1082, 1032, 820 cm$^{-1}$; HRMS (ESI+) for C$_{13}$H$_{18}$NaO$_3$ [M+Na]$^+$ requires 245.1148 found 245.1142.

(S)-Triisopropyl((4-((4-methoxybenzyl)oxy)pent-1-en-2-yl)oxy)silane (350)

To a stirred solution of ketone 346 (140 mg, 0.63 mmol) and triethylamine (220 μL, 1.6 mmol) in CH$_2$Cl$_2$ (1.3 mL) at 0 °C was added triisopropylsilyl trifluoromethanesulfonate (190 μL, 0.69 mmol) and the resultant solution stirred for 1 h. The reaction was quenched by the addition of sat. aq. NaHCO$_3$ (1 mL) and the volatiles removed in vacuo without heating. Purification by flash chromatography (hexanes/EtOAc 20:1) afforded the title compound 350 (240 mg, 0.63 mmol, 100%) as a colourless oil; $[\alpha]_{D}^{25} = +4.05$ (c 1.34 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.28 (2H, d, $J = 8.5$ Hz, Ar-H × 2), 6.87 (2H, d, $J = 8.5$ Hz, Ar-H × 2), 4.49 (2H, s, OCH$_2$), 4.09 (2H, d, $J = 3.0$ Hz, H-1), 3.89-3.80 (1H, m, H-4), 3.81 (3H, m, OCH$_3$), 2.51 (1H, dd, $J = 13.6$, 5.7 Hz, H-3a), 2.09 (1H, dd, $J = 13.6$, 7.6 Hz, H-3b), 1.24 (3H, d, $J = 6.1$ Hz, H-5), 1.10-1.08 (21H, m, CH$_3$ × 6 + SiCH × 3); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.2 (C), 156.9 (C), 131.3 (C), 129.3 (Ar-CH × 2), 113.9 (Ar-CH × 2), 91.1 (CH$_2$), 72.7 (CH), 70.4 (CH$_2$), 55.4 (CH$_3$), 44.5 (CH$_2$), 19.9 (CH$_3$), 18.2 (CH$_3$ × 6), 12.8 (CH × 3); IR (film) $\nu_{max}$ 2944, 2866, 1614, 1513, 1463, 1302, 1246, 1082, 1015, 881, 817 cm$^{-1}$; HRMS (ESI+) for C$_{22}$H$_{38}$NaO$_3$Si [M+Na]$^+$ requires 401.2482 found 401.2493.
(2R,6S,Z)-Ethyl 2-hydroxy-6-((4-methoxybenzyl)oxy)-4-((triisopropylsilyl)oxy)hept-4-enoate (351)

To a stirred suspension of activated 4 Å molecular sieves (200 mg, powder) in acetonitrile (1.6 mL) was added indium (III) chloride (6.0 mg, 26 μmol) and (+)-PyBox 349 (11 mg, 30 μmol) and the resultant mixture stirred at room temperature for 30 min. Silver(I) hexafluoroantimonate (18 mg, 53 μmol) was added and the mixture stirred for a further 30 min at room temperature. Ethyl glyoxylate (50% v/v in toluene, 105 μL, 0.53 mmol) was added and the reaction mixture stirred for 16 h at −40 °C. A solution of silyl enol ether 350 (100 mg, 0.26 mmol) in acetonitrile (1 mL) was added dropwise and the reaction mixture stirred for 16 h at −40 °C. The reaction was quenched by the addition of sat. aq. NaHCO₃ (1 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1 to 1:1) afforded the title compound 351 (31 mg, 0.064 mmol, 25%) as a colourless oil and an inseparable mixture of aldol 352 (32 mg, 0.077 mmol, 30%) with elimination product 353 (6 mg, 0.032 mmol, 12%). The yields of 352 and 353 were calculated based upon the NMR ratio; [$\alpha$]$_D^{25}$ = +9.5 (c 0.25 in CHCl₃); $^1$H NMR (400 MHz, CDCl₃): δ 7.26-7.24 (2H, m, Ar-H × 2), 6.87-6.84 (2H, m, Ar-H × 2), 4.64 (1H, d, J = 8.6 Hz, H-5), 4.52-4.45 (2H, m, H-6 and CH of OCH₂), 4.40-4.32 (2H, m, H-2 and CH of OCH₂), 4.28-4.18 (2H, m, OCH₂), 3.79 (3H, s, OCH₃), 2.79 (1H, d, J = 5.6 Hz, OH), 2.62 (1H, dd, J = 14.8, 4.2 Hz, H-3a), 2.39 (1H, dd, J = 14.8, 8.1 Hz, H-3b), 1.31-1.25 (6H, m, H-7 and CH₃), 1.11-1.08 (21H, m, CH₃ × 6 and SiCH × 3); $^{13}$C NMR (100 MHz, CDCl₃); δ 174.3 (C=O), 159.1 (C), 148.2 (C), 131.4 (C), 129.3 (Ar-CH × 2), 114.1 (Ar-CH × 2), 113.3 (CH), 69.5 (CH and CH₂), 69.0 (CH), 61.9 (CH₂), 55.4 (CH₃), 41.7 (CH₃), 21.5 (CH₃), 18.1 (CH₃ × 6), 14.3 (CH₃), 13.4 (CH × 3); IR (film) $\nu_{max}$ 3455, 2944, 2867, 1736, 1513, 1465, 1300, 1245, 1180, 1071, 1035, 988, 882 cm⁻¹; HRMS (ESI+) for C₇₆H₄₄NaO₆Si [M+Na]$^+$ requires 503.2799 found 503.2786.
(2R,6S,Z)-Ethyl 6-((4-methoxybenzyl)oxy)-2-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)-4-(((triisopropylsilyl)oxy)hept-4-enoate (354)

To a stirred solution of silyl enol ether 351 (20 mg, 0.041 mmol) in CH$_2$Cl$_2$ (1 mL) was added N,N'-dicyclohexylcarbodiimide (13 mg, 0.063 mmol), DMAP (1 mg, 8 μmol) and (R)-(+) α-methoxy-α-trifluoromethylphenylacetic acid (12 mg, 0.051 mmol) and the resultant solution stirred at room temperature for 24 h. The reaction was quenched by the addition of sat. aq. NaHCO$_3$ (1 mL), the layers separated and the aqueous layer further extracted with CH$_2$Cl$_2$ (3 × 2 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated _in vacuo_. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the _title compound_ 354 (16 mg, 0.022 mmol, 55%) as a colourless oil; [α]$^\text{D}_25 = +12.8$ (c 0.71 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.64-7.62 (2H, m, Ar-H × 2), 7.40-7.37 (3H, m, Ar-H × 3), 7.21-7.19 (2H, m, Ar-H × 2), 6.86-6.83 (2H, m, Ar-H × 2), 5.36 (1H, dd, J = 8.5, 4.6 Hz, H-2), 4.54 (1H, d, J = 8.5 Hz, H-5), 4.41-4.33 (2H, m, H-6 and CH of OCH$_2$), 4.28-4.21 (3H, m, OCH$_3$ and CH of OCH$_2$), 3.79 (3H, s, OCH$_3$), 3.61 (3H, s, OCH$_3$), 2.70-2.60 (2H, m, H-3), 1.27 (3H, t, J = 7.0 Hz, CH$_3$), 1.07-1.04 (24H, m, H-$7$, CH$_3$ × 6 and SiCH × 3); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 168.9 (C), 166.5 (C), 159.1 (C), 146.1 (C), 132.1 (C), 131.4 (C), 129.8 (Ar-CH), 129.2 (Ar-CH × 2), 128.5 (Ar-CH × 2), 127.7 (Ar-CH × 2), 124.7 (C), 114.1 (CH), 113.8 (Ar-CH × 2), 72.2 (CH), 70.7 (CH and CH$_2$), 62.1 (CH$_2$), 55.7 (CH$_3$), 55.4 (CH$_3$), 38.5 (CH$_2$), 21.0 (CH$_3$), 18.1 (CH$_3$ × 6), 14.2 (CH$_3$), 13.5 (CH × 3), CF$_3$ signal not observed; IR (film) $\nu_{\text{max}}$ 2946, 2868, 1749, 1670, 1513, 1464, 1372, 1246, 1185, 1080, 1037, 883 cm$^{-1}$; HRMS (ESI+) for C$_{36}$F$_3$H$_{51}$NaO$_8$Si [M+Na]$^+$ requires 719.3198 found 719.3216.
(2R,6S)-Ethyl 2-hydroxy-6-((4-methoxybenzyl)oxy)-4-oxoheptanoate (352)

To a stirred solution of ketone 346 (130 mg, 0.58 mmol) and triethylamine (0.19 mL, 1.4 mmol) in CH₂Cl₂ (2.8 mL) at 0 °C was added trimethylsilyl triflate (0.12 mL, 0.67 mmol) dropwise. The resultant mixture was stirred for 30 min then quenched by addition of sat. aq. NH₄Cl (1 mL). The layers were separated, and the aqueous layer further extracted with Et₂O (3 × 4 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude silyl enol ether 355 was used directly in the next step without further purification.

To a stirred suspension of activated 4 Å molecular sieves (200 mg, powder) in acetonitrile (3.4 mL) was added indium(III) chloride (13 mg, 0.058 mmol) and (+)-PyBox 349 (25 mg, 0.064 mmol) and the resultant mixture stirred at room temperature for 30 min. Silver(I) hexafluoroantimonate (40 mg, 0.12 mmol) was added and the mixture stirred for a further 30 min at room temperature. Ethyl glyoxylate (50% v/v in toluene, 250 μL, 1.2 mmol) was added and the solution cooled to −40 °C. A solution of silyl enol ether 355 prepared above in acetonitrile (1 mL) was added dropwise and the reaction mixture stirred for 16 h at −40 °C. The reaction was quenched by the addition of sat. aq. NaHCO₃ (1 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 3:1 to 1:1) afforded the title compound 352 (160 mg, 0.49 mmol, 83% over two steps) as a colourless oil; [α]D²⁵ = +23.4 (c 1.2 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.24-7.22 (2H, m, Ar-H × 2), 6.88-6.84 (2H, m, Ar-H × 2), 4.50-4.47 (2H, m, H-2 and CH of OC₆H₅), 4.39-4.36 (1H, m, CH of OC₆H₅), 4.28-4.20 (2H, m, OCH₂), 4.05-3.95 (1H, m, H-6), 3.79 (3H, s, OCH₃), 3.30 (1H, d, J = 5.4 Hz, OH), 3.01-2.85 (2H, m, H-3), 2.77 (1H, dd, J = 15.8, 7.4 Hz, H-5a), 2.49 (1H, dd, J = 15.8, 5.1 Hz, H-5b), 1.27 (3H, t, J = 7.0 Hz, CH₃), 1.22 (3H, d, J = 6.3 Hz, H-7); ¹³C NMR (100 MHz, CDCl₃): δ 207.1 (C=O), 173.8 (C=O), 159.3 (C), 130.5 (C), 129.4 (Ar-CH × 2), 113.9 (Ar-CH × 2), 71.2 (CH), 70.6 (CH₂), 66.9 (CH), 61.9 (CH₂), 55.3 (CH₃), 50.5 (CH₂), 47.2 (CH₂), 19.9 (CH₃), 14.2 (CH₃); IR (film) νmax 3479, 2930, 1737, 1613, 1514, 1373, 1247, 1108, 1032, 822 cm⁻¹; HRMS (ESI+) for C₁₇H₂₄NaO₆ [M+Na]+ requires 347.1465 found 347.1460.
(2R,6S)-Ethyl 2,6-dihydroxy-4-oxoheptanoate (356)

A mixture of ketone 352 (80 mg, 0.24 mmol) and Pd/C (10 wt%, 20 mg) in EtOAc (1.2 mL) was stirred under an atmosphere of H₂ at room temperature for 4 h. The reaction mixture was filtered through Celite® and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 1:4) afforded the title compound 356 (25 mg, 0.12 mmol, 50%) as a colourless oil; [α]D²⁵ = +56.5 (c 0.29 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 4.52-4.47 (1H, m, H-2), 4.30-4.23 (3H, m, H-6 and OCH₂), 3.20 (1H, br s, OH), 3.01-2.85 (2H, m, H-3), 2.66-2.53 (2H, m, H-5), 1.30 (3H, t, J = 7.1 Hz, CH₃), 1.20 (3H, d, J = 6.4 Hz, H-7); ¹³C NMR (100 MHz, CDCl₃): δ 209.0 (C=O), 173.8 (C=O), 67.0 (CH), 63.9 (CH), 62.1 (CH₂), 51.7 (CH₂), 46.8 (CH₂), 22.6 (CH₃), 14.2 (CH₃); IR (film) νmax 3452, 2962, 1740, 1468, 1369, 1211, 1071, 1025, 944, 817 cm⁻¹; HRMS (ESI+) for C₉H₁₆NaO₅ [M+Na]⁺ requires 227.0890 found 227.0897.

(4R,8S)-Ethyl 2,2,8-trimethyl-6-oxo-1,3,2-dioxasilocane-4-carboxylate (357)

To a stirred solution of diol 356 (20 mg, 0.098 mmol) in CH₂Cl₂ (0.5 mL) at 0 °C was added triethylamine (30 μL, 0.22 mmol), DMAP (1 mg, 9.8 μmol) and dichlorodimethylsilane (13 μL, 0.11 mmol). The reaction was stirred for 15 minutes, then diluted with Et₂O (1 mL) and the reaction mixture filtered through silica and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound 357 (18 mg, 0.069 mmol, 71%) as a colourless oil; [α]D²⁵ = +39.7 (c 0.37 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 4.77 (1H, dd, J = 10.0, 3.0 Hz, H-4), 4.51-4.46 (1H, m, H-8), 4.25-4.18 (2H, m, OCH₂), 2.96-2.82 (2H, m, H-5), 2.69 (1H, dd, J = 12.6, 10.0 Hz, H-7a), 2.52 (1H, dd, J = 12.6, 2.5 Hz, H-7b), 1.30-1.25 (6H, m, H-9 and CH₃), 0.18 (3H, s, SiCH₃), 0.13 (3H, s, SiCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 208.4 (C=O), 171.4 (C=O), 68.7 (CH), 66.1 (CH), 61.6 (CH₂), 53.4 (CH₂), 48.2 (CH₂), 24.6 (CH₃), 14.3 (CH₃), −3.1 (CH₃), −3.1 (CH₃); IR (film) νmax 2973, 1713, 1378, 1260, 1189, 1131, 1059, 1005, 943, 804 cm⁻¹; HRMS (ESI+) for C₁₁H₂₀NaO₅Si [M+Na]⁺ requires 283.0972 found 283.0968.
(2R,6S)-Ethyl 2,6-bis((4-methoxybenzyl)oxy)-4-oxoheptanoate (358)

To a stirred solution of aldol 352 (25 mg, 0.077 mmol) in CH₂Cl₂ (0.4 mL) was added 4-methoxybenzyl trichloroacetimidate (44 mg, 0.15 mmol) and CSA (2 mg, 0.07 mmol). The resultant solution was stirred at room temperature for 48 h. H₂O (1 mL) was added and the layers separated. The aqueous layer was further extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (1 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5:1 to 1:1) afforded the title compound 358 (26 mg, 0.059 mmol, 77%) as a colourless oil; [α]D²⁵ = +32.0 (c 0.27 in CHCl₃);

¹H NMR (400 MHz, CDCl₃): δ 7.27-7.20 (2H, m, Ar-H × 4), 6.89-6.83 (2H, m, Ar-H × 4), 4.64 (1H, d, J = 10.8 Hz, CH of OCH₂), 4.48-4.35 (4H, m, H-2, OCH₂ and CH of OCH₂), 4.22-4.15 (2H, m, OCH₂), 4.03-3.98 (1H, m, H-6), 3.78 (6H, s, OCH₃ × 2), 2.93-2.80 (2H, m, H-3), 2.76 (1H, dd, J = 16.0, 7.4 Hz, H-5a), 2.46 (1H, dd, J = 16.0, 5.3 Hz, H-5b), 1.27 (3H, t, J = 7.1 Hz, CH₃), 1.19 (3H, d, J = 6.1 Hz, H-7); ¹³C NMR (100 MHz, CDCl₃): δ 205.5 (C=O), 172.1 (C=O), 159.5 (C), 159.2 (C), 130.6 (C), 129.9 (Ar-CH × 2), 129.5 (C), 129.3 (Ar-CH × 2), 113.8 (Ar-CH × 4), 73.8 (CH), 72.8 (CH₂), 71.1 (CH), 70.6 (CH₂), 61.2 (CH₂), 55.3 (CH₃ × 2), 50.7 (CH₂), 46.5 (CH₂), 19.9 (CH₃), 14.3 (CH₃); IR (film) νmax 2923, 1718, 1612, 1511, 1464, 1301, 1275, 1174, 1109, 1031, 820 cm⁻¹; HRMS (ESI+) for C₂₅H₃₂NaO₇ [M+Na]^+ requires 467.2040 found 467.2050.
(2R,6S)-Ethyl 6-((4-methoxybenzyl)oxy)-4-oxo-2-((triisopropylsilyl)oxy)heptanoate (359)

To a stirred solution of aldol 352 (25 mg, 0.077 mmol) and 2,6-lutidine (18 μL, 0.15 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C was added triisopropylsilyl trifluoromethanesulfonate (32 μL, 0.12 mmol) and the resultant solution stirred for 16 h. The reaction was quenched by the addition of sat. aq. NaHCO₃ (0.5 mL) and the reaction mixture loaded directly onto silica gel. Purification by flash chromatography (hexanes/EtOAc 20:1) afforded the title compound 359 (20 mg, 0.042 mmol, 54%) as a colourless oil; [α]D⁰₂⁵ = +30.8 (c 0.76 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.24-7.22 (2H, m, Ar-H × 2), 6.87-6.83 (2H, m, Ar-H × 2), 4.77 (1H, t, J = 5.9 Hz, H-2), 4.49-4.37 (2H, ABq, ΔδAB = 0.08, JAB = 11.1 Hz, OCH₂), 4.16 (2H, q, J = 7.2 Hz, OCH₂), 4.03-3.98 (1H, m, H-6), 3.79 (3H, s, OCH₃), 2.96-2.77 (3H, m, H-3 and H-5a), 2.50 (1H, dd, J = 16.2, 5.7 Hz, H-5b), 1.26 (3H, t, J = 7.1 Hz, CH₃), 1.21 (3H, d, J = 6.2 Hz, H-7), 1.06-1.03 (21H, m, CH₃ × 6 and SiCH × 3); ¹³C NMR (100 MHz, CDCl₃): δ 206.1 (C=O), 172.9 (C=O), 159.3 (C), 130.8 (C), 129.4 (Ar-CH × 2), 113.9 (Ar-CH × 2), 71.1 (CH), 70.6 (CH₂), 68.9 (CH), 61.2 (CH₂), 55.4 (CH₃), 51.1 (CH₂), 49.1 (CH₂), 20.1 (CH₃), 18.1 (CH₃ × 6), 14.2 (CH₃), 12.4 (CH × 3); IR (film) νmax 2943, 2867, 1753, 1719, 1613, 1514, 1464, 1372, 1247, 1134, 1035, 883 cm⁻¹; HRMS (ESI+) for C₂₆H₄₄NaO₆Si [M+Na⁺] requires 503.2799 found 503.2803.

(2R,6S)-Ethyl 6-((4-methoxybenzyl)oxy)-4-oxo-2-((triethylsilyl)oxy)heptanoate (360)

To a stirred solution of aldol 352 (50 mg, 0.15 mmol) and 2,6-lutidine (27 μL, 0.23 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C was added triethylsilyl trifluoromethanesulfonate (49 μL, 0.21 mmol) and stirred for 16 h. The reaction was quenched by the addition of sat. aq. NaHCO₃ (0.5 mL) and the reaction mixture loaded directly onto silica gel. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the title compound 360 (42 mg, 0.096 mmol, 64%) as a colourless oil; [α]D⁰₂⁵ = +50.5 (c 0.39 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.24-7.21 (2H, m, Ar-H × 2), 6.87-6.84 (2H, m, Ar-H × 2), 4.68 (1H, dd, J = 6.9, 5.3 Hz, H-2), 4.43 (2H, ABq, ΔδAB = 0.09,
$J_{AB} = 11.1$ Hz, OCH$_2$), 4.20-4.14 (2H, m, OCH$_2$), 4.04-3.99 (1H, m, H-6), 3.79 (3H, s, OCH$_3$), 2.85-2.82 (2H, m, H-3), 2.80 (1H, dd, $J = 16.1, 6.9$ Hz, H-5$_a$), 2.48 (1H, dd, $J = 16.1, 5.6$ Hz, H-5$_b$), 1.27 (3H, t, $J = 7.0$ Hz, CH$_3$), 1.21 (CH$_3$, d, $J = 6.1$ Hz, H-7), 0.94 (9H, t, $J = 8.0$ Hz, CH$_3 \times 3$), 0.65-0.59 (6H, m, SiCH$_2 \times 3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 206.1 (C=O), 173.0 (C=O), 159.3 (C), 130.8 (C), 129.4 (Ar-CH $\times 2$), 113.9 (Ar-CH $\times 2$), 71.1 (CH), 70.6 (CH$_2$), 68.3 (CH), 61.2 (CH$_2$), 55.4 (CH$_3$), 51.2 (CH$_2$), 48.7 (CH$_2$), 20.1 (CH$_3$), 14.2 (CH$_3$), 6.8 (CH$_3 \times 3$), 4.7 (CH$_2 \times 3$); IR (film) $\nu_{\text{max}}$ 2956, 2877, 1751, 1718, 1613, 1514, 1463, 1374, 1249, 1173, 1131, 1034, 821, 743 cm$^{-1}$; HRMS (ESI+) for C$_{23}$H$_{38}$NaO$_6$Si [M+Na]$^+$ requires 461.2330 found 461.2343.
Appendix
NMR Spectra of Novel Compounds

*(E)*-Methyl 4-(benzyloxy)-6-methoxy-2-(prop-1-en-1-yl)benzoate (167)

$^1$H NMR (400 MHz, CDCl$_3$):

$^1$C NMR (100 MHz, CDCl$_3$):
5-(Benzyloxy)-3-(1-hydroxyethyl)-7-methoxyisobenzofuran-1(3H)-one ((±)-175)

$^1$H NMR (400 MHz, CDCl$_3$):

$^1$C NMR (100 MHz, CDCl$_3$):
5-(Benzyloxy)-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one ((±)-177)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
5-(Benzyloxy)-3-((tert-butyldimethylsilyl)oxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one ((±)-178)

1H NMR (400 MHz, CDCl₃):

13C NMR (100 MHz, CDCl₃):
5-(Benzyloxy)-4-bromo-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one ((±)-184)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds

5-(Benzyloxy)-3-(1-(ethoxymethoxy)ethyl)-4-iodo-7-methoxyisobenzofuran-1(3H)-one ((±)-185)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
5-(Benzyloxy)-4-bromo-3-((tert-butyldimethylsilyl)oxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one (±-186)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds

5-(Benzyloxy)-3-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-7-methoxyisobenzofuran-1(3H)-one (±)-187

$^1$H NMR (400 MHz, CDCl$_3$):

$^13$C NMR (100 MHz, CDCl$_3$):
4-Allyl-5-(benzylxylo)-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one ((±)-188)

\[ \text{Formula Image} \]

\(^1\text{H NMR (400 MHz, CDCl}_3\):\]

\[^{13}\text{C NMR (100 MHz, CDCl}_3\):\]
3-(1-(Ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one ((±)-189)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
4-Bromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one ((±)-190)

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3): \\
\text{1H NMR (400 MHz, CDCl}_3): \\
\text{13C NMR (100 MHz, CDCl}_3): \\
\end{align*}
\]
4,6-Dibromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one ((±)-191)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
3-(1-(Ethoxymethoxy)ethyl)-5-hydroxy-4-iodo-7-methoxyisobenzofuran-1(3H)-one ((±)-192)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds

3-(1-(Ethoxymethoxy)ethyl)-5-hydroxy-4,6-diodo-7-methoxyisobenzofuran-1(3H)-one (±-193)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(E)-Methyl 4,6-dihydroxy-2-(prop-1-en-1-yl)benzoate (194)

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{5} & \quad \text{6} \\
\text{1} & \quad \text{2} \\
\text{3} & \quad \text{4} \\
\text{Me} & \quad \text{y} \\
\end{align*}
\]

\[1^H\text{ NMR (400 MHz, CDCl}_3\):

\[13^C\text{ NMR (100 MHz, CDCl}_3\):

\[18.6 \quad 52.1 \quad 76.7 \quad 77.0 \quad 77.3 \quad 102.1 \quad 104.1 \quad 108.3 \quad 128.1 \quad 131.7 \quad 144.3 \quad 160.4 \quad 164.5 \quad 171.7 \]
(E)-Methyl 4-(benzylxylo)-6-hydroxy-2-(prop-1-en-1-yl)benzoate (195)

\[ \text{NMR Spectra of Novel Compounds} \]

\[ \text{OH} \]
\[ \text{O} \]
\[ \text{OMe} \]
\[ \text{BnO} \]

\[ \text{1H NMR (400 MHz, CDCl}_3\text{):} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{):} \]

244
(E)-Methyl 4-(benzylloxy)-3-bromo-6-methoxy-2-(prop-1-en-1-yl)benzoate (196)

\[ \text{\textsuperscript{1}}H \text{ NMR (400 MHz, CDCl\textsubscript{3})}: \]

\[ \text{\textsuperscript{13}}C \text{ NMR (100 MHz, CDCl\textsubscript{3})}: \]
(E)-Methyl 3,5-dibromo-4,6-dihydroxy-2-(prop-1-en-1-yl)benzoate (200)

\[\text{HO} \quad \text{O} \quad \text{OMe} \]
\[\text{Br} \quad \text{Br} \quad \text{O} \quad \text{Br} \]

\(^1^H\) NMR (400 MHz, CDCl\(_3\)):

- \(7.26\) ppm
- \(6.40\) ppm
- \(6.42\) ppm
- \(6.28\) ppm
- \(6.46\) ppm
- \(6.44\) ppm
- \(3.88\) ppm
- \(5.51\) ppm
- \(5.53\) ppm
- \(5.54\) ppm
- \(5.55\) ppm
- \(5.56\) ppm
- \(5.57\) ppm
- \(5.58\) ppm
- \(5.60\) ppm
- \(6.41\) ppm
- \(6.42\) ppm
- \(6.45\) ppm
- \(6.46\) ppm

\(^1^C\) NMR (100 MHz, CDCl\(_3\)):

- \(171.2\) ppm
- \(153.9\) ppm
- \(158.7\) ppm
- \(171.0\) ppm
- \(141.5\) ppm
- \(77.3\) ppm
- \(77.0\) ppm
- \(76.7\) ppm
- \(129.4\) ppm
- \(131.3\) ppm
- \(141.5\) ppm
- \(107.3\) ppm
- \(103.7\) ppm
- \(97.1\) ppm
- \(18.3\) ppm
- \(52.6\) ppm
- \(160\) ppm
- \(150\) ppm
- \(140\) ppm
- \(130\) ppm
- \(120\) ppm
- \(110\) ppm
- \(100\) ppm
- \(90\) ppm
- \(80\) ppm
- \(70\) ppm
- \(60\) ppm
- \(50\) ppm
- \(40\) ppm
- \(30\) ppm
- \(20\) ppm
- \(10\) ppm
2-Bromo-1,3-bis(ethoxymethoxy)benzene (208)

\[ \text{OEOM} \]

^1^H NMR (400 MHz, CDCl$_3$):

\[ \begin{align*}
7.10 & & 7.06 \\
6.85 & & 5.28 \\
3.74 & & 3.79 \\
1.20 & & 1.23 \\
\end{align*} \]

^1^C NMR (100 MHz, CDCl$_3$):

\[ \begin{align*}
15.1 & & 155.2 \\
64.7 & & 128.2 \\
76.8 & & 103.8 \\
77.2 & & 109.4 \\
77.5 & & 93.9 \\
\end{align*} \]
2-Iodo-1,3-bis(ethoxymethoxy)benzene (209)

\( ^1H \) NMR (400 MHz, CDCl\(_3\)):

\( ^13C \) NMR (100 MHz, CDCl\(_3\)):
(S)-3-(2,6-Bis(ethoxymethoxy)phenyl)-N-((1R,2R)-1-hydroxy-1-phenylpropan-2-yl)-N,2-dimethylpropanamide (214)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{OH} & \quad \text{N} \\
& \quad \text{EOMO} \\
& \quad \text{OEM} \\
& \quad \text{N,2-dimethylpropanamide (214)}
\end{align*}
\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)):

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):
(S)-4-(2,6-Bis(ethoxymethoxy)phenyl)-3-methylbutan-2-one (207)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
Appendix

(S)-3-(Ethoxymethoxy)butanal (233)

\[
\begin{align*}
\text{EOMO} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[\text{H NMR (400 MHz, CDCl}_3)\):

\[\begin{array}{cccccccccc}
\end{array}\]

\[\text{13C NMR (100 MHz, CDCl}_3)\):

\[\begin{array}{cccccccccccccccccccccc}
15.1 & 20.7 & 50.9 & 63.5 & 68.6 & 76.8 & 77.2 & 77.5 & 93.7 & 201.3
\end{array}\]
NMR Spectra of Novel Compounds

(2S,7S)-1-(2,6-Bis(ethoxymethoxy)phenyl)-5-((tert-butyldimethylsilyl)oxy)-7-(ethoxymethoxy)-2-methyloctan-3-one (236)

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3) : \]

\[ \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3) : \]
(2S,7S)-7-((Benzyloxy)methoxy)-1-(2,6-bis(ethoxymethoxy)phenyl)-5-hydroxy-2-methyloctan-3-one (237)

$^1$H NMR (400 MHz, CDCl$_3$):

$^13$C NMR (100 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds

(2S,7S)-1-(2,6-Bis(ethoxymethoxy)phenyl)-7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methyloctan-3-one (238)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(2S,5R,7S)-1-(2,6-Bis(ethoxymethoxy)phenyl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyloctan-3-one (247)

\[ \text{PMBO} \quad \text{OH} \quad \text{O} \quad \text{OEOM} \]
\[ \text{EOM} \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)):

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):
(4R,6S)-2-((S)-1-(2,6-Bis(ethoxymethoxy)phenyl)propan-2-yl)-2-methoxy-6-methyltetrahydro-2H-pyran-4-ol (248)

\[\begin{array}{c}
\text{EOM} \\
\text{H} \\
\text{OEM} \\
\text{HO} \\
\text{OMe}
\end{array}\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)):

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):
(((4R,6S)-2-((S)-1-(2,6-Bis(ethoxymethoxy)phenyl)propan-2-yl)-2-methoxy-6-methyltetrahydro-2H-pyran-4-yl)oxy)triisopropylsilane (250)

\[ \begin{align*}
&
\end{align*} \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)):

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):
(Benzyloxy)methyl 3,5-bis((benzyloxy)methoxy)-4-bromobenzoate (265)

\[
\text{\textbf{NMR Spectra of Novel Compounds}}
\]

1H NMR (400 MHz, CDCl$_3$):

\[
\begin{align*}
7.5 & \quad 7.0 & \quad 6.5 & \quad 6.0 & \quad 5.5 & \quad 5.0 & \quad 4.5 & \quad 4.0 & \quad 3.5 & \quad 3.0 & \quad 2.5 & \quad 2.0 & \quad 1.5 & \quad 1.0 & \quad 0.5 & \quad \text{ppm} \\
4.73 & \quad 4.79 & \quad 5.41 & \quad 5.57 & \quad 7.25 & \quad 7.28 & \quad 7.29 & \quad 7.30 & \quad 7.30 & \quad 7.31 & \quad 7.33 & \quad 7.33 & \quad 7.33 & \quad 7.35 & \quad 1.13 & \quad 2.08 & \quad 2.16 & \quad 1.13 & \quad 7.89 & \quad 1.00 & \quad 170 & \quad 160 & \quad 150 & \quad 140 & \quad 130 & \quad 120 & \quad 110 & \quad 100 & \quad 90 & \quad 80 & \quad 70 & \quad 60 & \quad 50 & \quad 40 & \quad 30 & \quad 20 & \quad 10 & \quad \text{ppm}
\end{align*}
\]

13C NMR (100 MHz, CDCl$_3$):

\[
\begin{align*}
140.2 & \quad 135.0 & \quad 70.6 & \quad 72.2 & \quad 76.8 & \quad 77.2 & \quad 77.5 & \quad 89.4 & \quad 93.0 & \quad 110.2 & \quad 110.5 & \quad 128.0 & \quad 128.1 & \quad 128.2 & \quad 128.6 & \quad 130.2 & \quad 136.9 & \quad 137.0 & \quad 155.0 & \quad 165.3
\end{align*}
\]
(3,5-Bis((benzyloxy)methoxy)-4-bromophenyl)methanol (266)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
3,5-Bis((benzyloxy)methoxy)-4-bromobenzaldehyde (262)

$^1$H NMR (400 MHz, CDCl$_3$):

$^1$C NMR (100 MHz, CDCl$_3$):
3,5-Bis((benzyloxy)methoxy)-4-bromo-1-(E)-prop-1-en-1-ylbenzene (261)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(S)-3-(2,6-Bis((benzyloxy)methoxy)-4-((E)-prop-1-en-1-yl)phenyl)-N-(1R,2R)-1-hydroxy-1-phenylpropan-2-yl)-N,2-dimethylpropanamide (273)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(S,E)-4-(2,6-Bis((benzyloxy)methoxy)-4-(prop-1-en-1-yl)phenyl)-3-methylbutan-2-one (260)

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{):} \\
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR (100 MHz, CDCl}_3\text{):} \\
\end{align*}
\]
(2S,5R,7S)-1-(2,6-Bis((benzyloxy)methoxy)-4-((E)-prop-1-en-1-yl)phenyl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyldecan-3-one (259)

^1^H NMR (400 MHz, CDCl₃):

\[ \text{Chemical Shifts} \]

\[ \text{Resonance Peaks} \]

^1^C NMR (100 MHz, CDCl₃):

\[ \text{Chemical Shifts} \]

\[ \text{Resonance Peaks} \]
(2S,5R,7S)-1-(2,6-Bis((benzyloxy)methoxy)-4-((1S,2S)-1,2-dihydroxypropyl)phenyl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyloctan-3-one (281)

\[
\begin{align*}
\text{PMBO} & \quad \text{OH} & \quad \text{O} & \quad \text{OBOM} \\
\text{BOMO} & \quad \text{OH} & & \\
\end{align*}
\]

\( ^1\text{H NMR (400 MHz, CDCl}_3\): \)

\( ^1\text{C NMR (100 MHz, CDCl}_3\): \)
NMR Spectra of Novel Compounds

\((2R,3S,4'R,6'S)-7-((1S,2S)-1,2-Dihydroxypropyl)-3,6'-\text{dimethyl}-3',4',5',6'-\text{tetrahydrospiro[chroman-2,2'-pyran]-4',5-diol (282)}\)

\(^1\text{H NMR (400 MHz, (CD}_3\text{)}_2\text{CO):}\)

\(^{13}\text{C NMR (100 MHz, (CD}_3\text{)}_2\text{CO):}\)
(S)-4-(2,6-Bis((benzyloxy)methoxy)-4-((15,25)-1,2-dihydroxypropyl)phenyl)-3-methylbutan-2-one (302)

\[ \text{\H NMR (400 MHz, CDCl}_3\text{):} \]

\[ \text{\C NMR (100 MHz, CDCl}_3\text{):} \]
(S)-4-(2,6-Bis((benzyloxy)methoxy)-4-((1S,2S)-1,2-dihydroxypropyl)-3-iodophenyl)-3-methylbutan-2-one (301)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(S)-5,7-Bis((benzyloxy)methoxy)-3-((S)-1-hydroxyethyl)-6-((S)-2-methyl-3-oxobutyl)isobenzofuran-1(3H)-one (300)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(S)-5,7-Bis((benzylxy)methoxy)-3-((S)-1-((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxyethyl)-6-((S)-2-methyl-3-oxobutyl)isobenzofuran-1(3H)-one (378)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds

(S)-5,7-Bis((benzyloxy)methoxy)-6-((2S,5R,7S)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyl-3-oxooctyl)-3-((S)-1-hydroxyethyl)isobenzofuran-1(3H)-one (299)

\[
\begin{align*}
\text{PMBO} & \quad \text{BOMO} \\
\text{HO} & \quad \text{BOMO}
\end{align*}
\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)):

\(^1\)C NMR (100 MHz, CDCl\(_3\)):
Virgatolide B (2)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds
Cyclohexyl 3-diazo-2-oxopropanoate (311)

\[
\text{\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}}:
\]

\[
\text{\textbf{\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3})}}:
\]
NMR Spectra of Novel Compounds

(±)-(1R*,3R*)-3-Phenyl-1-vinylcyclohexanol ((±)-320)

1H NMR (400 MHz, CDCl3):

13C NMR (100 MHz, CDCl3):
(±)-(1S*,3R*)-3-phenyl-1-vinylcyclohexanol ((±)-319)

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{):} \\
\text{13C NMR (100 MHz, CDCl}_3\text{):}
\end{align*}
\]
(E)-Ethyl 3-((1S*,3R*)-1-hydroxy-3-phenylcyclohexyl)acrylate ((±)-318)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(±)-(5R*,7R*)-7-Phenyl-1-oxaspiro[4.5]decan-2-one ((±)-317)

$^{1}$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds

(±)-(3R*,5R*)-5-phenyl-1-oxaspiro[2.5]octane ((±)-333) and
(±)-(3S*,5R*)-5-phenyl-1-oxaspiro[2.5]octane ((±)-331)

\[ \text{1H NMR (400 MHz, CDCl}_3\text{):} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{):} \]
(±)-(1R*,3R*)-3-Phenyl-1-(prop-2-yn-1-yl)cyclohexanol ((±)-334)

^1^H NMR (300 MHz, CDCl$_3$):

^1^C NMR (75 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds

(±)-(1S*,3R*)-3-Phenyl-1-(prop-2-yn-1-yl)cyclohexanol ((±)-330)

\[ \text{HO} \]
\[ \text{Ph} \]

\(^1\)H NMR (300 MHz, CDCl\(_3\)):

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)):
Appendix

(±)-(1R*,3R*)-1-(3-Bromoprop-2-yn-1-yl)-3-phenylcyclohexanol ((±)-339)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):

283
(±)-(5S*,7R*)-7-Phenyl-1-oxaspiro[4.5]decan-2-one ((±)-340)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(S)-N-Methoxy-3-((4-methoxybenzyl)oxy)-N-methylbutanamide (348)

\[
\begin{align*}
\text{PMBO} & \quad \text{O} \\
\quad & \quad \text{NOMe}
\end{align*}
\]

\(^1\text{H NMR (300 MHz, CDCl}_3\):}

\[^{13}\text{C NMR (75 MHz, CDCl}_3\):}
NMR Spectra of Novel Compounds

(S)-4-((4-Methoxybenzyl)oxy)pentan-2-one (346)

$^1$H NMR (300 MHz, CDCl$_3$):

$^1$C NMR (75 MHz, CDCl$_3$):

$^{13}$C NMR (75 MHz, CDCl$_3$):
(S)-Triisopropyl((4-((4-methoxybenzyl)oxy)pent-1-en-2-yl)oxy)silane (350)

$^{1}$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(2R,6S,Z)-Ethyl 2-hydroxy-6-((4-methoxybenzyl)oxy)-4-((triisopropylsilyl)oxy)hept-4-enoate (351)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(2R,6S,Z)-Ethyl 6-((4-methoxybenzyl)oxy)-2-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)-4-((triisopropylsilyl)oxy)hept-4-enoate (354)

$^{1}$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(2R,6S)-Ethyl 2-hydroxy-6-((4-methoxybenzyl)oxy)-4-oxoheptanoate (352)

\[
\begin{align*}
\text{PMBO} & \quad \text{O} & \quad \text{OH} & \quad \text{OEt} \\
\end{align*}
\]

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
(2R,6S)-Ethyl 2,6-dihydroxy-4-oxoheptanoate (356)

\[
\text{HO} \quad \text{O} \quad \text{O} \quad \text{OH} \quad \text{OEt}
\]

\(^1\)H NMR (400 MHz, CDCl₃):

\(^{13}\)C NMR (100 MHz, CDCl₃):
(4R,8S)-Ethyl 2,2,8-trimethyl-6-oxo-1,3,2-dioxasilocane-4-carboxylate (357)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
NMR Spectra of Novel Compounds

\[(2R,6S)\text{-Ethyl 2,6-bis((4-methoxybenzyl)oxy)-4-oxoheptanoate (358)}\]

\[\text{PMBO} \quad \text{O} \quad \text{OPMB} \quad \text{OEt}\]

\[\text{H NMR (400 MHz, CDCl}_3\):}\]

\[\text{C NMR (100 MHz, CDCl}_3\):}\]
(2R,6S)-Ethyl 6-((4-methoxybenzyl)oxy)-4-oxo-2-((triisopropylsilyl)oxy)heptanoate (359)

$\text{PMBO} \quad O \quad \text{OTIPS}$

$\text{OEt}$

$^1$H NMR (400 MHz, CDCl$_3$):

$^1$C NMR (100 MHz, CDCl$_3$):
(2R,6S)-Ethyl 6-((4-methoxybenzyl)oxy)-4-oxo-2-((triethylsilyl)oxy)heptanoate (360)

$^1$H NMR (400 MHz, CDCl$_3$):

$^{13}$C NMR (100 MHz, CDCl$_3$):
References
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