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Synthetic Studies Towards
The Marine Toxin Portimine

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

Doctor of Philosophy

by

Harry Robert McRae Aitken

School of Chemical Sciences
University of Auckland
December 2016
To my parents; you make me so proud.
Abstract

This thesis describes synthetic endeavours towards portimine (1), a polycyclic marine toxin recently isolated from the dinoflagellate *Vulcanodinium rugosum* collected off the coast of Northland, New Zealand. Portimine (1) contains an unprecedented bridged spiroketal ring system and spirocyclic imine functionality. Whilst the spiroimine motif is commonly observed in a number of algae-derived toxins the 5,6-ring system is unique to portimine. Initial biological testing has indicated that it exhibits potent inhibition of leukaemia cells *in vitro* (P388 cells, EC$_{50}$ = 2.7 nM) despite demonstrating low *in vivo* toxicity, in stark contrast to other related natural products.

A convergent and flexible synthetic strategy for the preparation of portimine (1) was proposed, in which the molecular framework of 1 may be constructed by union of either polyketide fragment 238 or 239 with glyoxal 468 by C$_5$–C$_6$ aldol coupling. Subsequent Nozaki-Hiyama-Kishi mediated macrocyclisation to forge the C$_{14}$–C$_{15}$ bond would prepare the tricyclic core 481 or 482. Finally, spiroketalisation and stereoselective oxidation—to furnish the unusual $\alpha,\alpha'$-dihydroxyketone moiety—would complete the synthesis of portimine. It was unknown how the olefin geometry of 481 or 482 would affect stereochemistry of the $\alpha,\alpha'$-dihydroxyketone after oxidation so both vinyl halide isomers 238 and 239 were prepared for investigation.

Considerable synthetic effort was devoted to the development of a scalable, robust preparation of a series of viable polyketide coupling fragments such as 238 and 239 from common aldehyde
For application in the total synthesis. In turn, aldehyde 204 was prepared using a modified, stereocontrolled Leighton crotylation as the key step, allowing for efficient, enantioselective access to this key building block.

With the successful preparation of polyketide coupling fragments 238 and 239 established, attention then focused on examination of the proposed fragment coupling strategies. Notably, the unprecedented coupling of silyl enol ether 359 and model glyoxal electrophile 310 was shown to be a viable disconnection for the C5–C6 coupling of the polyketide and spirocyclic fragments of portimine. Preliminary model studies for the proposed C14–C15 Nozaki-Hiyama-Kishi macrocyclisation step resulted in the development of optimised conditions for the chromium(II)-mediated reaction of bromides 237, 238 and 239 with aldehyde 381.

Together with the successful preparation of polyketide fragments 238 and 239, the model fragment coupling strategies developed herein provide a strong basis from which a convergent total synthesis of portimine (1) may now be framed. Furthermore, these efforts may allow synthetic access to structural analogues of portimine (1) in order to probe its biological mode of action.
Acknowledgements

First, I would like to thank Margaret Brimble. I have relished the time I have spent in your research group and have received the best training in synthetic organic chemistry that I could have hoped for. I am in awe of your work ethic and dedication, and am truly grateful for your ongoing support.

Thank you Dan Furkert for all that help that you have given me during my PhD. Thanks for indulging some of my more outlandish ideas whilst keeping me sufficiently on track to eventually finish!

Many thanks to my lab mates, past and present, it has been a privilege to work alongside all of you. A number of especially amazing people have helped with my research, contributed suggestions for my thesis, or just been a wonderful friend over the last four years; thank you to James, Megan, Ben, George, Freda, Huimin, Xiaobo, Hans and Harry Shirley. Extra thanks to James for his sterling experimental proofreading as well!

I have also had the pleasure of learning from some really talented people. Jono, you have been a wonderful mentor throughout my postgraduate studies; I hold you in high regard. Paul, you handsome man: I have thoroughly enjoyed all our conversations from the wacky banter to the discussions about molecular modelling, you are a true friend. Darcy, you have always been on hand to help me ever since my first foray into research chemistry.

To Janice Choi and Tim Layt, I am incredibly grateful for your organisation behind the scenes, your hard work has not gone unnoticed. Thank you, also, to the wider SCS administrative and technical teams for ensuring that everything in the department keeps running smoothly.

Thank you to the University of Auckland for financial support in the form of a doctoral scholarship.

To my lovely partner Rachelle, dójeh! Thank you for sharing this journey with me. It hasn’t always been easy, but we got there together! Now we can relax and enjoy what the future brings.

To my family and friends, thank you for your support over the last four years, and for reminding me that there’s a world outside of chemistry. Susannah, you are the best sister a boy could hope for. Mum and Dad, you are both such amazing role models. Words cannot describe the gratitude I feel for the love and encouragement you have shown me over the years.
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Sections 2.2.4 to 2.2.6 and 2.5 of thesis. Working title of manuscript is: "Synthesis of the Portimine Polyketide via Asymmetric Crotylsilylation and Preliminary Fragment Coupling Studies", although it is yet to be submitted for publication.

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**Certification by Co-Authors**

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

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CHAPTER ONE

Introduction
1.1 Spiroimine Natural Products

1.1.1 Harmful Algal Blooms

Microalgae are a large and diverse group of predominantly aquatic organisms comprising eukaryotic photoautotrophic protists and prokaryotic cyanobacteria. These microbes are responsible for almost half of all photosynthetic activity and therefore play a critical role as primary producers in the global ecosystem. However, under certain conditions, microalgae are capable of rapid and uncontrolled proliferation, known as a harmful algal bloom. The first written reference to such a harmful algal bloom appears in the Old Testament: “... all the waters that were in the river were turned to blood. And the fish that was in the river died; and the river stank, and the Egyptians could not drink of the water of the river” (Exodus 7: 20–21). Nowadays, harmful algal blooms are ubiquitous and have been identified in every corner of the world. Although the cause of these blooms are complex, there is strong evidence to suggest that coastal water pollution and a systematic increase in seawater temperature—due to global warming—have led to an increase in frequency and severity of these outbreaks.

The blooms of certain species of algae from the dinoflagellate phylum—namely Vulcanodinium rugosum, Alexandrium sp., and Karenia selliformis—are of particular concern due to their production of toxic secondary metabolites. These toxins can bioaccumulate in the tissues and organs of filter-feeding shellfish such as mussels and oysters. Consequently, harmful algal blooms are now closely monitored due to their potential risk to human health, although they are still responsible for over 60,000 cases of toxicity annually with a mortality rate of 1.5%.

The toxins produced during dinoflagellate algal blooms are of interest to the synthetic community due to their exquisite molecular architecture and as potential lead compounds for the development of novel pharmaceuticals. Consequently, many organisations, such as the Cawthron Institute in New Zealand, are actively involved in the extraction and characterisation of complex toxins from marine microalgae. A growing class of these complex, dinoflagellate-produced toxins is the spirocyclic imine family of natural products. Since the discoveries of gymnodimine (2) and pinnatoxin A (3) in 1995, many spiroimine toxins have since been identified globally containing either a 6,6- or 7,6-spiroimine moiety. However, portimine (1) is the only marine toxin identified to date that possesses the 5,6-spiroimine motif (Figure 1.1).
Selected spiroimine-containing marine macrocyclic toxins.

1.1.2 Portimine

Portimine (1) is a complex polycyclic marine toxin, initially isolated from the marine microalgae *V. rugosum* collected off the coast of Northland, New Zealand in 2013 and very recently extracted from the same organism collected in the Gulf of Qatar. Portimine (1) contains a unique 5,6-spiroimine moiety and an unprecedented bridged ketal ring system (Figure 1.2).

Initial biological testing has shown that portimine is highly active against leukaemia cells *in vitro* (P388 cells, EC$_{50}$ = 2.7 nM). Importantly, portimine exhibits low toxicity *in vivo*, with delayed onset, in stark contrast to related spiroimine compounds. It has been suggested that the source of its anticancer activity is due to its action as an apoptosis inducer *via* caspase-3 activation, although the exact cellular target is yet to be elucidated. Sequential activation of caspases is necessary for programmed cell death (apoptosis). Interestingly, over-expression of the apoptosis inhibitor protein Bcl-2 prevented portimine-induced necrotic cell death providing further evidence for this mode of action. Apoptosis induction is a novel biological mechanism for spiroimine toxicity. Harnessing the unique toxicity profile of portimine may facilitate the development of novel pharmaceuticals.
1.1.3 The Pinnatoxin and Pteriatoxin Families

The pinnatoxin and pteriatoxin families comprise a major subcategory of spiroimine marine toxins. The structure of pinnatoxin A (3) was initially elucidated in 1995 by Uemura and co-workers, from samples extracted from the bivalve molluscs Pinna muricata, collected near Okinawa, Japan (Figure 1.3). Following identification of further members of the pinnatoxin family from various mollusc species, the microalgal producer of pinnatoxins has recently been identified as the dinoflagellate *V. rugosum*. An exhaustive phylogenetic analysis of microalgae collected throughout Japan, New Zealand and Australia has determined that *V. rugosum* is the sole species producing pinnatoxins E–G in these areas. Initial biological testing suggested that the pinnatoxin family were potent calcium channel activators. However, no significant calcium channel binding was observed during subsequent investigation of the mode of action of the pinnatoxins by Zakarian and co-workers. Rather, binding studies and molecular modelling have demonstrated high affinity of the pinnatoxins to multiple nicotinic acetylcholine receptors, in particular muscle-type receptor α1βγδ as well as the α7 and α4β2 neuronal receptors.

![Figure 1.3. The pinnatoxin and pteriatoxin family of marine toxins.](image-url)
Pteriatoxins A–C were isolated from the bivalve mollusc *Pteria penguin* near Okinawa in 2001. These alkaloids share a common macrocyclic core to the pinnatoxins, but differ in terms of their cysteine-derived sidechain (Figure 1.3, above). Mouse bioassays indicate that the pteriatoxins and pinnatoxins share a similar potency and toxicological profile.

Exposure of pinnatoxin A to acidic media and physiologically relevant aqueous conditions demonstrated high stability of the spiroimine moiety of these marine toxins, attributed to steric protection by the neighbouring quaternary centre and vicinal methyl groups. This stability has several implications for pinnatoxin bioavailability, as the spiroimine subunit has been shown to be the key pharmacophore. For instance, aminoketone 13—a derivative of pinnatoxin A that incorporates an open form of the imine ring—showed no binding activity with a variety of nicotinic acetylcholine receptor subtypes, in contrast to that observed for pinnatoxin A (3). Taking competitive binding experiments using the α7-5HT₃ subtype as an example, pinnatoxin A showed strong affinity to the receptor (Kᵢ = 0.35 nM) while aminoketone 13 showed no significant interaction (Kᵢ > 10 000 nM) (Scheme 1.1).

![Scheme 1.1. Pinnatoxin imine stability in physiologically relevant conditions.](image)
1.1.4 The Spirolide Family

Spirolides A–D were first identified by Wright and co-workers in 1995 during routine monitoring of shellfish extracts for marine toxins (Figure 1.4). Subsequent isolation of members of the spirolide family from dinoflagellates have suggested that these toxins are exclusively produced by organisms from the *Alexandrium* genus, a marine microalga with a global distribution.

The spirolides are fast-acting toxins which affect the central nervous system. Although the exact mode of action is not fully elucidated, the spirolides show potent inhibition of nicotinic acetylcholine receptors, in particular the $\alpha_7$ and $\alpha_4\beta_2$ subtypes, which ultimately causes a complex cascade of neurological symptoms. Alongside these inhibitory pathways, 13-desmethyl spirolide C (18) has been shown to weakly activate transmembrane calcium channels in mammalian systems, and irreversibly bind to muscarinic receptors.

In comparison to the cyclic imine spirolides, aminoketone spirolides E (21) and F (22) display significantly reduced toxicity in mouse bioassays, providing further evidence that the imine moiety is crucial for biological activity.
1.1.5 The Gymnodimine Family

The first spirocyclic imine toxin to be identified was gymnodimine A (2), simultaneously isolated in 1995 from blooms of the microalgae *K. selliformis* (formerly *Gymnodinium* cf. *mikimotoi*) and contaminated samples of the oyster *Tiostrea chilensis* collected at Foveaux Strait, New Zealand by Yasumoto and co-workers (Figure 1.5). The absolute stereochemistry was later confirmed by Blunt and Munro, who obtained an X-ray crystal structure of the reduced *p*-bromobenzoyl derivative 31. Congeners gymnodimine B (28) and gymnodimine C (29) were later isolated by Miles and co-workers from the dinoflagellate *K. selliformis*. More recently, 12-methyl gymnodimine (27) and gymnodimine D (30) have been independently identified from extracts of *A. osetenfeldii* blooms by the Wright and Miles groups, respectively.

![Chemical structures of gymnodimines](image)

**Figure 1.5.** The gymnodimine family of marine toxins.

Although less toxic than members of the spirolide family *in vivo*, gymnodimine A (2) is also a potent neurotoxin with sub-nanomolar affinities for various nicotinic acetylcholine receptors. An X-ray crystal structure of gymnodimine A (2) complexed to acetylcholine-binding complex revealed several binding interactions. In particular, the protonated cyclic imine moiety participated in a key hydrogen-bond with the tryptophan-147 residue of the protein binding pocket while the tetrahydrofuran and γ-butyrolactone rings anchor the toxin into the binding pocket.
1.1.6 Biosynthesis of Spiroimine Marine Toxins

The vast majority of dinoflagellate marine toxins are produced *via* a polyketide pathway.³⁷ In this pathway, polyketide chains are built up from acetate or propionate starter units followed by the successive addition of intact acetate units, although other simple metabolites may also be incorporated.³⁸ Extensive modification of the developing carbon chain through a variety of alkylation and carbon deletion processes, followed by oxidation and cyclisation then furnishes the natural product.³⁹ For fungal or bacterial polyketide biosynthesis these processes are typically consistent. However, for dinoflagellate-derived polyketides this is not the case, posing a significant challenge to unravelling their biosynthetic origins.³⁸

Despite the unpredictable nature of dinoflagellate biosynthesis,⁴⁰ the biosynthesis of 13-desmethyl spirolide C (18) has been proposed⁴⁰b and recently revised by the Wright group, using isotopic labelling of acetate and glycine precursors used to culture *A. ostenfeldii*.⁴¹ This work elucidated the origin of the majority of the carbon framework and confirmed that the spirocyclic imines are hybrid polyketide natural products, with a glycine starter unit (Figure 1.6).

![13-desmethyl spirolide C (18) labelling pattern as determined by Wright and co-workers.⁴¹](image)

Figure 1.6. 13-Desmethyl spirolide C (18) labelling pattern as determined by Wright and co-workers.⁴¹

Walter and co-workers have also examined the biosynthesis of 13-desmethyl spirolide C (18) and determined that an intramolecular Schiff base formation and [4+2] cycloaddition are the key transformations in the biosynthesis of the spiroimine moiety (Scheme 1.2).³³, ⁴⁰b
Wright and co-workers, among others, have postulated that the spirocyclic imine toxins share a common biogenetic origin on the basis of their clear structural similarities. Furthermore, the same group recently isolated both 12-methylgymnodimine (27) and 13-desmethylspirolide C (18) from the same organism—*A. peruvianum*—collected from the New River in North Carolina. This discovery represented the first time a member of the gymnodimine family was extracted from any organism other than the distantly related *K. selliformis*, suggesting possible lateral transmission of the relevant pathway genes and supporting a postulated common biogenetic origin.

Comparison of the putative linear polyketide chain of spirocyclic imine toxins indicates that the spirolide family may be regarded as a biogenetic hybrid of the gymnodimine and pinnatoxin natural products (Figure 1.7). In light of these similarities, Wright and co-workers have suggested that the spirolide biosynthesis pathway may be produced by a genetic recombination event.
Comparison of the putative linear precursors of gymnodimine A (2), 13-desmethyl spirolide C (18) and pinnatoxin A (3).
1.2 Synthesis of Spirocyclic Imine Natural Products

Spirocyclic imine marine toxins have received extensive attention from the synthetic community, due to their impressive biological activity and exquisite molecular architecture. Consequently, a number of elegant methods have been developed for the preparation of both the polyketide and spiroimine domains of these natural products. These efforts have recently been reviewed elsewhere.7, 11, 16a, 44 The aim of this section is to provide an overview of completed total syntheses of spirocyclic imine natural products, with a particular focus on key fragment disconnections and novel strategies for synthesis of the spiroimine moiety.

1.2.1 Synthesis of (−)-Pinnatoxin A and the Pteriatoxin Family (Kishi, 1998–2006)

In 1998, Kishi and co-workers reported a biomimetic45 total synthesis of the antipode of pinnatoxin A (3b), confirming the absolute stereochemistry of naturally produced pinnatoxin A. The synthetic strategy hinged on the successful execution of a late-stage intramolecular Diels-Alder macrocyclisation involving the elimination and direct cycloaddition of mesylate 38. Notably, extremely low concentration conditions (0.2 nM) were required to prevent dimerisation, with the reaction predominantly affording the desired exo-isomer of cyclohexene 39. In turn, mesylate 38 was prepared over 33 steps (longest linear sequence), using two Nozaki-Hiyama-Kishi reactions for the most advanced fragment couplings (Scheme 1.3).
Reagents and conditions: (a) 40, NiCl$_2$ (1 mol%), CrCl$_2$ (1 mol%), DMSO, 7.5 h, rt; (b) HF∙py, py/THF (1:4), 2 h, rt; (c) Dess-Martin periodinane, NaHCO$_3$, CH$_2$Cl$_2$, 1 h, rt; (d) 41, NiCl$_2$ (33 mol%), CrCl$_2$ (33 mol%), THF, 30 min, rt; (e) TFA/H$_2$O/CH$_2$Cl$_2$ (1:2:4), 1 h, rt; (f) MsCl, NEt$_3$, CH$_2$Cl$_2$, 6 h, −78 °C; (g) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$, 1 h, 0 °C; (h) DABCO, NEt$_3$, benzene, 1 h, rt.

Scheme 1.3. Synthesis of (−)-pinnatoxin A (3b) by Kishi and co-workers.\textsuperscript{45}

Using an analogous strategy, the Kishi group later reported total syntheses of pinnatoxins B (4) and C (5),\textsuperscript{46} alongside a unified total synthesis the pteriatoxin family.\textsuperscript{47} These efforts allowed unambiguous assignment of the previously unconfirmed relative and absolute stereochemistry of these natural products.
1.2.2 Formal Synthesis of (+)-Pinnatoxin A (Hirama, Inoue, 2004)

In 2004, Hirama, Inoue and co-workers reported a formal total synthesis of pinnatoxin A (3), intercepting an advanced imine precursor 50 that was converted to the natural product in two steps by the Kishi group. The formal synthesis hinged upon the preparation and union of bis-spiroketal domain 44 with fully functionalised cyclohexene ring 47. In turn, bis-spiroketal 44 was prepared by acid-catalysed cyclisation in high diastereoselectivity (~8:1) from open chain ketone 42. The remarkable degree of stereoselectivity observed was suggested to be due to an intramolecular hydrogen bond stabilising desired conformer 43 (Scheme 1.4). The synthesis of iodide fragment 48 employed a stereoselective, intramolecular nitrile alkylation to form cyclohexene ring 47, incorporating the challenging quaternary centre (Scheme 1.4).

![Chemical structures](image)

Reagents and conditions: (a) CSA, MeOH, 3 h, rt; (b) KHMDS, 2 h, 0 °C → rt.

Scheme 1.4. Synthesis of dithiane 44 and iodide 46 by Hirama, Inoue and co-workers.

The key fragment coupling steps were achieved by addition of dithiane 44 to iodide 48 followed by Grubbs II catalyst-mediated ring closing metathesis to generate macrocycle 49 (Scheme 1.5). Extensive functional group manipulation over a further 13 steps furnished aminoketone 50, which was readily converted to pinnatoxin A (3) following the two step protocol developed by the Kishi group.
Reagents and conditions: (a) t-BuLi, THF/HMPA (9:1), 5 h, −78 °C; (b) TBAF, THF, 2 h, 0 °C; (c) Grubbs II (10 mol%), CH₂Cl₂, 16 h, reflux.

Scheme 1.5. Hiram and Inoue formal synthesis of pinnatoxin A (3): fragment coupling and macrocyclisation.⁴⁸
1.2.3 Synthesis of (+)-Pinnatoxin A (Zakarian, 2011)

Zakarian and Stivala completed the total synthesis of pinnatoxin A (3) in 2008,49 and disclosed a second generation synthesis in 2011 based on a revised end-game sequence.19 The highlight of this synthesis was an elegant Ireland-Claisen rearrangement for the construction of the spiroimine subunit, based upon the stereoselective generation of the tetrasubstituted silyl ketene acetal 52 using chiral lithium amide 55 (Scheme 1.6).50 Fragment coupling was achieved by organolithium addition of iodide 56 to aldehyde 54, which was followed by ring-closing metathesis to forge the C_{26}–C_{27} alkene and furnish enone 57 (Scheme 1.6). Extensive functional group manipulation then afforded the natural product in a total of 44 steps (longest linear sequence).

Reagents and conditions: (a) 55, TMSCl, THF, 3 h, -78 °C → rt.

Scheme 1.6. Synthesis of pinnatoxin A (3) by Zakarian and Stivala.19,49
1.2.4 Synthesis of (+)-Pinnatoxin A (Nakamura, Hashimoto, 2008)

A fourth synthesis of pinnatoxin A (3) was reported by the group of Nakamura and Hashimoto in 2008, employing an elegant ruthenium-catalysed isomerisation to prepare the macrocyclic core.51 Another highlight of this work is the O-Michael addition terminated spiroketalisation of enone 58 to prepare the bis-spirocyclic ring system (Scheme 1.7).52 Elaboration of bis-spiroketal 59 to diene 60 was achieved in eight steps. Diene 60 then underwent Diels-Alder cycloaddition with exo-methylene lactone 62 in p-xylene at 160 °C, affording spirocyclic lactone 61, albeit with poor selectivity at the newly formed C-5 and C-30 stereocentres (endo:exo, 72:28; diastereofacial selectivity, 63:37).

Reagents and conditions: (a) LiOMe, THF/MeOH (10:1), 4 h, rt; (b) 4 Å molecular sieves, p-xylene, 12 h, 160 °C.

Scheme 1.7. Synthesis of spirocyclic lactone 61 by the group of Nakamura and Hashimoto.51-52

Following separation of the stereoisomers, requisite adduct 5R,30S-61 was isolated in modest yield and elaborated to enyne 63 over a further eight steps (Scheme 1.8). The key ruthenium-catalysed isomerisation proceeded with complete regioselectivity upon treatment of enyne 63 with pentamethylcyclopentadienyltris(acetonitrile)ruthenium(II) hexafluorophosphate in acetone, based on conditions developed by the Trost group for this transformation.53
Reagents and conditions: (a) [Cp₅Ru(MeCN)₃]PF₆ (10 mol%), acetone, 15 min, 50 °C.

Scheme 1.8. Macrocyclisation and final steps in the synthesis of pinnatoxin (3) by Hashimoto and co-workers.⁵¹-⁵²

1.2.5 Synthesis of (−)-Gymnodimine A (Romo, 2009)

Although several groups have disclosed a number of efficient synthetic studies for the synthesis of gymnomidine A (2),⁵⁴ to date only the Romo group has reported a complete total synthesis.⁵⁵ Their initial retrosynthetic strategy focused on the Barbier-type union of tetrahydrofuran fragment 65 with lactam 66, followed by Nozaki-Hiyama-Kishi macrocyclisation (Scheme 1.9).

Tetrahydrofuran 65 was prepared by 2,5-cis diastereoselective Hosomi-Sakurai allylation of the oxonium ion generated from acetal 68, while the synthesis of lactam 66 hinged upon an enantioselective catalytic Diels-Alder reaction. Copper(II)-bis(oxazoline) catalyst derived from ligand 72 mediated the cycloaddition of exo-methylene lactam 70 and diene 71 to afford cyclohexene 66 in 85% yield with excellent stereocontrol, thus establishing the challenging quaternary stereocentre at the core of the spirocyclic ring system (Scheme 1.10).
Reagents and conditions: (a) allyl-TMS, BF$_3$·OEt$_2$, toluene/CH$_2$Cl$_2$ (1:1), 6 h, $-78^\circ$C; (b) CuCl$_2$ (10 mol%), 72 (11 mol%), AgSbF$_6$ (7 mol%), CH$_2$Cl$_2$, 2 h, rt.

Scheme 1.10. Synthesis of tetrahydrofuran 65 and lactam 66 by Romo and co-workers.$^{55-56}$

Fragment coupling was initially achieved by lithium-halogen exchange of iodide 65 in the presence of lactam electrophile 66. However, attempted macrocyclisation of iodoalkene-aldehyde 72 only afforded deiodination products.$^{55}$ A revised coupling strategy, whereby Nozaki-Hiyama-Kishi coupling preceded a Barbier-type ring-closing reaction, afforded the macrocyclic core of gymnodimine (Scheme 1.11). Remarkably, this latter reaction depended on strict temperature optimisation, with addition of $t$-butyllithium at 23 $^\circ$C found to be crucial for reaction success. At $-78^\circ$C only trace cyclisation product 75 was observed upon work-up. Introduction of the $\gamma$-butyrolactone moiety and cyclisation to the imine moiety completed a convergent synthesis of gymnodimine A (2) (Scheme 1.11).

Reagents and conditions: (a) $t$-BuLi, Et$_2$O, 15 min, 23 $^\circ$C.

Scheme 1.11. Synthesis of gymnodimine A (2) by Romo and co-workers.$^{55-56}$
1.3 Synthetic Approaches to the Spiroimine Motif

As part of an on-going interest in spirocyclic natural products, a variety of strategies to prepare the spiroimine motif embedded within these compounds have been disclosed by the synthetic community. These efforts have recently been reviewed elsewhere.\(^7\), \(^11\), \(^{16a}\), \(^{44}\) Notable contributions to this literature are discussed here, with a focus on the synthesis of fragments with the requisite functionalisation and stereochemistry for application in a natural product synthesis.

1.3.1 Asymmetric Diels-Alder Cycloaddition of \textit{exo}-Methylene Lactams 79 and 82 (Murai, 2002)

The Murai group has disclosed several approaches for the asymmetric preparation of the 6,6- and 7,6-spiroimine subunit of the gymnodimine, spirolide and pinnatoxin families.\(^{54a}\), \(^{57}\) The highlight of this work was the development of an \textit{exo}-selective Diels-Alder cycloaddition of \textit{exo}-methylene lactam 76 and diene 78, performed in the presence of copper(II) triflate and bis(oxazoline) ligand 72 (Scheme 1.12). This transformation proceeded with remarkable stereocontrol, affording spirocyclic lactam 79 in 79% yield in 96% \textit{ee} and 99:1 \textit{exo}:\textit{endo} selectivity.\(^{57}\) However, when the same conditions were applied to the reaction of 6-membered \textit{exo}-methylene lactam 77 with diene 78 no desired product 80 was observed (Scheme 1.12).

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \text{ Cu(OTf)}_2 \ (20 \text{ mol%}), \text{ 72} \ (20 \text{ mol%}), \text{ AgSbF}_6 \ (40 \text{ mol%}), \text{ CH}_2\text{Cl}_2, \ 144 \text{ h}, \ 25 \ ^\circ\text{C}. \\
\text{Scheme 1.12.} & \quad \text{Synthesis of spirocyclic lactam 79 by Murai and co-workers.}^{57}
\end{align*}
\]

Given the poor reactivity observed between lactam 77 and diene 78 during the copper(II)-bis(oxazoline) complex-catalysed Diels-Alder cycloaddition, Murai and co-workers also investigated the use of copper(II)-bis(sulfinyl)imidoamide complex—derived from ligand 83—for this same reaction, employing conditions developed by the Ellman group for a similar transformation\(^58\) (Scheme 1.13).\(^{54a}\) These conditions furnished functionalised spirocyclic lactam 82 in excellent yield with good stereoselectivity. The high degree of \textit{exo}-selectivity observed in this cycloaddition was thought to be due to steric repulsion between the bis(sulfinyl)imidoamide ligand and the diene in the unfavourable \textit{endo} transition state.

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \text{ Cu(OTf)}_2 \ (20 \text{ mol%}), \text{ 72} \ (20 \text{ mol%}), \text{ AgSbF}_6 \ (40 \text{ mol%}), \text{ CH}_2\text{Cl}_2, \ 144 \text{ h}, \ 25 \ ^\circ\text{C}. \\
\text{Scheme 1.12.} & \quad \text{Synthesis of spirocyclic lactam 79 by Murai and co-workers.}^{57}
\end{align*}
\]
Reagents and conditions: (a) Cu(OTf)$_2$ (40 mol%), 83 (40 mol%), AgSbF$_6$ (80 mol%), CH$_2$Cl$_2$, 3 Å molecular sieves, 36 h, 25 °C.

Scheme 1.13. Synthesis of spirocyclic lactam 82 by Murai and co-workers.$^{54a}$
1.3.2 Desymmetrisation of Spiro Diester 87 (White, 2003 and 2007)

In 2003, White and co-workers reported their synthetic studies towards the spiroimine fragment of gymnodimine A (2) (Scheme 1.14). This work commenced from Diels-Alder cycloaddition of methylene 86—generated in situ from Meldrum’s acid derivative 85—and diene 84, which afforded a separable 1.2:1 mixture of spiro diesters 87a and 87b in 85% combined yield. As diester 87a incorporated the requisite S configuration at the C-2 stereocentre this compound was chosen for further elaboration. Accordingly, oxidative cleavage of the p-methoxybenzyl ether of diester 87a and cyclisation of the resultant alcohol generated lactone 88, breaking the symmetry of the quaternary centre. With the C-1 substituents thus differentiated, selective manipulation of the resultant carboxylic acid afforded nitrile 89 over six steps (Scheme 1.14). Although nitrile 89 was produced with total stereocontrol and contains the fully elaborated cyclohexene ring of gymnodimine, this synthesis was somewhat inefficient, due to the poor diastereoselectivity of the initial Diels-Alder cycloaddition, and the high step count required to manipulate lactone 88 to nitrile 89.

Reagents and conditions: (a) AcOH, EtOH, 48 h, rt; (b) DDQ, CH₂Cl₂ then TMSCH₂N₂, 16 h, rt.

1.3.3 Allylation/Isomerisation/[3+2]-Cycloaddition (Guillou, 2014)

Guillou, Chabaud and co-workers have reported several synthetic approaches to the 6,6-spiroimine moiety of the gymnodimine family of natural products.\textsuperscript{54c} Most recently, this group disclosed an asymmetric decarboxylative allylation for preparation of the challenging quaternary stereocentre.\textsuperscript{54d} They employed an asymmetric palladium complex derived from chiral phosphinoxazoline ligand 94, based on conditions developed by the Stoltz group for this transformation.\textsuperscript{60} Of most importance in this work was the allylation of ketone 90, which afforded alkene 91 in excellent yield and high enantioselectivity (Scheme 1.15). Subsequent olefin isomerisation and intramolecular [3+2]-azidoalkene cycloaddition-elimination afforded imine 93, although the latter step proceeded in poor yield (Scheme 1.15). Imine 93 incorporates the requisite functionality for further elaboration to a viable intermediate in the synthesis of the gymnodimine family.

\begin{center}
\begin{tikzpicture}
    % TikZ code for the scheme
    % (Example of a scheme diagram)
\end{tikzpicture}
\end{center}

*Reagents and conditions:* (a) Pd\textsubscript{2}(pmdb)\textsubscript{3} (4 mol\%), 94 (10 mol\%), Et\textsubscript{2}O, 16 h, 35 °C; (b) Pd(PhCN)\textsubscript{2}Cl\textsubscript{2} (10 mol\%), toluene, MW, 30 min, 60 °C; (c) toluene, MW, 1 h, 160 °C.

*Scheme 1.15.* Synthesis of imine 93 by Guillou, Chabaud and co-workers.\textsuperscript{54d}
1.3.4 *Exo*-Selective Diels-Alder Cycloaddition (Brimble, 2016)

As part of an ongoing research interest into the synthesis of spirocyclic imine natural products, our group has recently developed a novel *exo*-selective Diels-Alder reaction involving the cycloaddition of an *in situ* generated α,β-unsaturated *N*-acyl iminium ion dienophile with an appropriate dienophile. The reactive iminium ion species is typically prepared by treatment of carbamate 95 with an appropriate Lewis acid such as boron trifluoride (Scheme 1.16). When the reaction is quenched with triethylamine an iminium α-deprotonation furnishes enamine 98, which may provide a valuable synthetic handle for subsequent elaboration.

![Scheme 1.16](image)

**Scheme 1.16.** Novel Diels-Alder cycloaddition by Brimble and co-workers.

Although this work appears highly amenable to the synthesis of the 6,6-spiroimine motif found in the gymnodimine family, attempts to adapt the procedure for application in the preparation of the analogous 5,6-spiroimine moiety of portimine proved unsuccessful (Scheme 1.17). It is, at present, unclear what mechanisms have led to the discrepancy in reactivity of the five-membered cyclic dienophile 101 relative to the corresponding six-membered system.

![Scheme 1.17](image)

**Scheme 1.17.** Divergent reactivity observed during the preparation of 6,6- and 5,6-spiroimines by the Brimble group.

*Reagents and conditions:* (a) BF₃·OEt₂, CH₂Cl₂, 6 h, −78 °C.
1.4 Aims of the Present Research

Portimine (1) represents the most recent addition to the spirocyclic imine family of marine toxins. Initial biological testing has shown that it is highly active against leukaemia cells *in vitro* (P388 cells, EC$_{50}$ = 2.7 nM), yet exhibits low toxicity *in vivo*, in stark contrast to related spiroimine compounds. Synthetic access to both the natural product and derivatives thereof would allow further investigation of its cellular target and biological mode of action. The remarkable biological profile of portimine makes it an attractive synthetic target.

Synthesis of related spiroimine natural products has been an ongoing research interest within our group, however, the complex molecular architecture of portimine (1) provides a unique synthetic challenge. For instance, although the spiroimine subunit is a common motif found in a number of algae-derived marine toxins the 5,6-spiroimine has thus far only been identified in portimine. Furthermore, the unprecedented bridged spiroketal moiety, incorporating an \( \alpha,\alpha' \)-dihydroxyketone, provides an intriguing synthetic challenge and may require the development of novel synthetic methodology. Towards this aim, our retrosynthetic analysis of portimine (1) is presented in the following chapter, together with an extensive model study to enable a deeper understanding of these structural features of portimine (see section 2.1, page 29).

![Figure 1.8](image-url) The spirocyclic marine toxin portimine (1).
CHAPTER TWO

Results and Discussion
2.1  Retrosynthetic Analysis of Portimine

2.1.1  Overview

The primary aim of this project is to complete the total synthesis of portimine (1). However, alongside our efforts towards the natural product, we are also interested in preparing structural analogues to probe its biological profile. Accordingly, our proposed synthesis must be modular to allow flexible and specific incorporation of structural diversity. Thus, our retrosynthetic analysis hinges upon aldol-mediated C5–C6 union of polyketide fragment 106 or 107 with glyoxal 108 followed by Nozaki-Hiyama-Kishi C14–C15 macrocyclisation (Scheme 2.1) to afford tricyclic intermediate 104/105. Subsequent ketalisation would complete the polycyclic structural backbone of portimine. Finally, selective oxidation to the unusual α,α′-dihydroxyketone moiety would then complete the synthesis (Scheme 2.1).

![Scheme 2.1. Retrosynthetic analysis of portimine (1).](image)

2.1.2  Oxidation to the α,α′-Dihydroxyketone Moiety

There are very few direct strategies known in the literature for synthesis of α,α′-dihydroxyketones with the requisite relative stereochemistry of the C13–C15 triad of portimine. Previous syntheses of compounds containing this functionality have generally prepared this oxygenated moiety from a carbohydrate source. For instance, the Maier and Navickas synthesis of the proposed structure of queenslandon (116) began by manipulation of D-ribose (109) to protected triol 110.53 A late-stage selective deprotection-oxidation sequence unveiled the α,α′-dihydroxyketone. Subsequent global deprotection afforded the proposed structure of queenslandon 116 (Scheme 2.2).
Reagents and conditions: (a) LDA, THF/HMPA, 6 h, −80 °C, then H₂O₂, THF, 12 h, rt; (b) DDQ, CH₂Cl₂/H₂O (1:1), 2 h, rt; (c) Dess-Martin periodinane, CH₂Cl₂, 3 h, rt; (d) HCl, MeOH, rt; (e) BCl₃, CH₂Cl₂, −50 °C.

Scheme 2.2. Maier and Navickas’ synthesis of the proposed structure of queenslandon (116).⁶³

Employing a similar synthetic strategy, the synthesis of sporiolide A (122) by the Venkateswarlu group begins from D-mannitol derived aldehyde 118. Allylation, protecting group and oxidation level manipulation afforded aldehyde 119. Subsequent aldol addition and benzylation produced orthogonally protected triol 120, with selective methoxybenzyl ether cleavage and oxidation affording protected α,α′-dihydroxyketone 121. Ring-closing metathesis and hydrogenation furnished the natural product (Scheme 2.3).⁶⁴

Reagents and conditions: (a) LHMDS, THF, 6 h, −78 °C; (b) BzCl, pyridine, DMAP, 4 h, rt; (c) DDQ, CH₂Cl₂/H₂O (1:1), 2 h, rt; (d) Dess-Martin periodinane, CH₂Cl₂, 3 h, rt.

Scheme 2.3. Venkateswarlu and co-worker’s synthesis of sporiolide A (122).⁶⁴α
Although effective, these synthetic routes are somewhat inefficient, due to the high step count required to manipulate the starting carbohydrate into the requisite polyketide framework. For the synthesis of portimine, we envisioned a more direct synthesis of the \(\alpha,\alpha'\)-dihydroxyketone that eliminated the need for extensive protecting group and oxidation level manipulation. More specifically, we anticipated that the \(\alpha,\alpha'\)-dihydroxyketone of portimine could be produced by dihydroxylation of either allyl alcohol 104 or 105 followed by selective oxidation of the resultant triol (Scheme 2.4). In turn, allyl alcohols 104 and 105 are the product of glyoxal aldol coupling and Nozaki-Hiyama-Kishi macrocyclisation of \(E\)-106 and \(Z\)-107, respectively.

![Scheme 2.4. Complementary oxidation pathways to tricyclic intermediate 124.](image)

To produce the correct (13\(R\),15\(S\))-stereochemistry of portimine, dihydroxylation must proceed by either syn addition to the corresponding \(E\)-alkene (ie. 104) or anti to the \(Z\)-alkene 105 (Scheme 2.4). Both syn- and anti-addition pathways for dihydroxylation of allyl alcohols are known in the literature. For example, standard conditions such as Poli or Upjohn dihydroxylation, using catalytic osmium(IV) tetroxide and stoichiometric \(N\)-methylmorpholine \(N\)-oxide, generally favour anti-selectivity. However, the Donohoe group has found that high levels of
syn-selectivity are possible when similar conditions are employed in the presence of TMEDA, as it complexes to osmium(IV) tetraoxide producing a strong hydrogen bond acceptor that coordinates to the allylic alcohol directing dihydroxylation to the same face of the alkene. It is worth noting that although the products of these complimentary pathways differ in terms of their C-14 stereochemistry, this difference is rendered inconsequential following selective C-14 oxidation. Unfortunately, in either case, significant optimisation is often necessary to achieve high levels of diastereoselectivity. Furthermore, prior to this work, dihydroxylation of an allyl alcohol embedded into a large ring such as 104 or 105 has never been performed, and it was unclear how ring strain and conformation will impact the stereoselectivity of the proposed dihydroxylation. It was therefore deemed necessary to prepare both the E- and Z-vinyl halides 106 and 107, for extensive investigation of both possibilities for this step.

It was thought that the selective oxidation of either triol 104 or 105 could be achieved by employing a cationic neocuproine-palladium complex (129) developed by Waymouth and co-workers for the oxidation of glycerol to dihydroxyacetone. Since its discovery this catalyst has since been applied for the selective oxidation of a variety of tri- and polyol systems, including C-3 oxidation of glycosides by the Waymouth group and independently by de Vries, Minnaard, and co-workers (Scheme 2.5). However, utilisation of palladium complex 129 in the present work would represent a significant extension of this oxidation methodology. Prior to this work there are no reported examples of its application to macrocyclic or acyclic systems, or in complex natural product synthesis.

Reagents and conditions: (a) Benzoquinone or O2, 129, MeCN/(H2O), 1–20 h, rt–60 °C.

Scheme 2.5. Selective glycoside oxidation by the Waymouth group.
2.1.3 Retrosynthetic Analysis of Glyoxal 108

As discussed earlier (Section 1.3.4, page 24), previous work within our group has been directed to the development of an exo-selective Diels-Alder reaction involving an α,β-unsaturated N-acyl iminium ion generated in situ as the dienophile. Although this cycloaddition may be useful for preparation of the 6,6-spiroimine motif of gymnodimine, analogous efforts towards the 5,6-subunit of portimine have thus far proved unrewarding. Regardless, the cyclohexene ring of glyoxal 108 may still be synthesised via an alternative exo-selective Diels-Alder reaction. Catalytic Diels-Alder cycloadditions using α-methylene lactams and lactones are known to favour exo products. Thus, spirolactam 131 may be prepared via Diels-Alder reaction from a cyclic dienophile such as 132 and bromodiene 133. Suzuki cross-coupling of 131 with potassium vinyltrifluoroborate and subsequent methylolithium-mediated lactam opening provides ketone 130. Finally, α-oxidation of ketone 130 furnishes the key coupling fragment glyoxal 108 (Scheme 2.6).

![Scheme 2.6. Retrosynthetic analysis of glyoxal 108.](image)

2.1.4 Retrosynthetic Analysis of Polyketide Fragments 106 and 107

The primary initial focus of the present work was to develop scalable access to both the E- and Z-isomers of polyketide fragment, vinyl halides 106 and 107, respectively. Realisation of these compounds would permit exploration of the proposed glyoxal aldol and Nozaki-Hiyama-Kishi fragment couplings. Both of these polyketide fragments may be prepared from common intermediate aldehyde 134 (Scheme 2.7). As such, development of a scalable, stereoselective synthesis of aldehyde 134 was imperative. We chose to investigate preparation of 134 by asymmetric crotylation and oxidation of aldehyde 135 (Scheme 2.7).
2.2 Synthesis of Polyketide Fragments 106 and 107

The initial aim of the present work was to construct polyketide fragments 106 and 107, for investigation of the key glyoxal aldol and Nozaki-Hiyama-Kishi couplings. Successful coupling of both E- and Z-vinyl halides will enable further exploration of the stereocontrolled allyl alcohol oxidation to the challenging $\alpha,\alpha'$-dihydroxyketone moiety (see Scheme 2.4, page 31). We envisioned that both vinyl halide isomers 106 and 107 could be prepared from aldehyde 134. Thus, synthetic efforts first focused on developing a robust, scalable preparation of this common intermediate (Scheme 2.8). In turn, aldehyde 134 would be derived from asymmetric crotylation of aldehyde 135 followed by subsequent protection and alkene oxidation.

Scheme 2.8. Retrosynthetic analysis of portimine (1) and proposed synthesis of polyketide fragments 106 and 107 from aldehyde 135.
2.2.1 Crotylation of Aldehyde 135

**A. Attempted Racemic Crotylation of Aldehyde 135**

The proposed synthesis of aldehyde 134 was based on a stereoselective crotylation reaction as the key step (Scheme 2.9). Although there is a wealth of literature on the development of asymmetric crotylation methodology, most reported procedures suffer from one of several drawbacks, including the use of expensive, air-sensitive reagents, or non-commercially available catalytic systems. However, in 2009 Batey and co-workers disclosed a simple protocol for the allylation of aldehydes using potassium allyltrifluoroborate salts. The use of this methodology appealed as its successful application would allow immediate, large-scale access to building blocks such as alcohol 137 in order to rapidly investigate the subsequent downstream chemistry. Trifluoroborates are generally air- and moisture-stable and can be readily prepared on large scale.

![Scheme 2.9. Proposed crotylation of aldehyde 135.](image)

In the Batey crotylation procedure, either aldehydes or ketones are treated with allyltrifluoroborates in the presence of Lewis (eg. BF₃·OEt₂) or Brønsted acids (eg. montmorillonite clay), or under phase transfer catalysis (Scheme 2.10).

**Reagents and conditions:** (a) BF₃·OEt₂, CH₂Cl₂, 1 h, −78 °C; (b) Montmorillonite K10, CHCl₃/H₂O (15:1), 3–5 h, rt; (c) TBAI, CH₂Cl₂/H₂O (1:1), 10–24 h, rt.

![Scheme 2.10. Potassium trifluoroborate salts as allylation reagents.](image)

For our system, synthesis of the syn-crotyl alcohol was required. In the Batey crotylation, diastereoselectivity is determined by a Zimmerman-Traxler-like model. Thus, the reaction begins *via in situ* formation of an allylboron difluoride species (139) and proceeds through a six-membered, chair-like transition state with the carbonyl oxygen coordinated to boron and the allylic double bond attacking the electrophilic carbonyl carbon (Scheme 2.11). As the aldehyde...
substituent adopts the more favourable pseudoequatorial position, the product stereochemistry is directly determined by the stereochemistry of the double bond in the allyl boron species. For the synthesis of a syn crotyl alcohol, as required in the present work, the Z-crotyltrifluoroborate must be used.

Scheme 2.11. Batey allylation mechanism for the synthesis of syn crotyl alcohols.

To test this methodology on our substrate, the requisite potassium crotyltrifluoroborate salt 138 was first prepared by deprotonation of cis-butene with Schlosser’s base followed by addition of triisopropyl borate, then hydrolysis with aqueous potassium bifluoride (Scheme 2.12).\(^7\)\(^2\) Aldehyde 135 was prepared by acid-mediated ketalisation of commercially available ethyl levulinate (143), followed by DIBAL reduction (Scheme 2.12).\(^7\)\(^4\) Although the DIBAL reduction gave full and clean conversion to aldehyde 135, as evidenced by analysis of the crude \(^1\)H NMR spectrum, this substrate was both volatile and somewhat unstable. Thus, it was typically prepared as a solution in dichloromethane and used without purification or quantification. Disappointingly, in our hands, treatment of aldehyde 135 with trifluoroborate 138 and catalytic tetrabutylammonium iodide in dichloromethane/water (1:1) returned only unreacted starting material, despite high yields being reported for similar aliphatic aldehydes under these conditions (Scheme 2.12).\(^7\)\(^5\) Alternatively, the same reaction was performed using a montmorillonite K10 catalyst in aqueous chloroform (7% v/v), conditions identified by the Batey group as particularly effective for the allylation of less activated carbonyls.\(^7\)\(^0\) Unfortunately, use of these conditions in the present work also returned only starting aldehyde 135, even after prolonged reaction times (Scheme 2.12).
Reagents and conditions: (a) KOt-Bu, n-BuLi, THF, B(Ot-Pr)_3, 2 h, −78 °C; (b) KHF_2, H_2O/MeOH (9:1) 12 h, 0 °C; (c) ethylene glycol, TsOH·H_2O, benzene, 18 h, Dean-Stark reflux; (d) DIBAL (1 M in hexane), CH_2Cl_2, 2 h, −78 °C; (e) Montmorillonite K10, 138, CHCl_3/H_2O (15:1), 48 h, rt; (f) TBAI, 138, CH_2Cl_2, H_2O (1:1), 48 h, rt; (g) BF_3·OEt_2, 138, CH_2Cl_2, 26 h, −78 °C → rt.


Finally, no crotylation product was observed when reaction of aldehyde 135 with borate 138 was performed using catalytic boron trifluoride in dichloromethane at −78 °C. However, volatile ketone 145 was isolated as the sole product after the reaction mixture was allowed to warm to room temperature over 26 h (Scheme 2.12). Ketone 145, identified by comparison of its ¹H NMR spectrum to that reported in the literature, presumably arises by Lewis acid-catalysed rearrangement of aldehyde 135 to the sterically more favourable 145. As only degradation, or undesired rearrangements products were observed in these experiments, we postulated that the lack of desired reactivity was due to the presence of the acid-sensitive acetal functionality in aldehyde 135.
B. Attempted Racemic Crotylation of Model Aldehyde 146

To investigate whether the lack of desired reactivity was caused by the acetal moiety present in aldehyde 135 we began a brief crotylation study using aldehyde 146 (Figure 2.1). Aldehyde 146, incorporating an acid-stable methoxybenzyl ether, may be prepared as a model substrate from 1,4-butanediol by selective protection and oxidation.

![Figure 2.1. Aldehyde 135 and acid-stable model aldehyde 146.](image)

To prepare aldehyde 146, an excess of butanediol (1.5 equivalents) was first mono-protected by treatment with sodium hydride in tetrahydrofuran producing a white precipitate, followed by addition of tetrabutylammonium iodide and p-methoxybenzyl chloride as the limiting reagent. This reaction is highly selective for mono-protection and excellent yields can be reliably obtained without any observed over-protection to the dibenzyl ether. This selectivity is thought to be due to the fact that the monosodium salt derived from diol 147 is sparingly soluble in tetrahydrofuran but reacts rapidly with alkylating reagents such as p-methoxybenzyl chloride.76 The effect of this is that there are very few basic species in the reaction solution for deprotonation (and subsequent alkylation) of alcohol 148, which would lead to the dibenzyl ether. Subsequent Swern oxidation76 of alcohol 148 afforded requisite aldehyde 146 in 94% yield (Scheme 2.13).

![Scheme 2.13. Synthesis of aldehyde 146.](image)

Reagents and conditions: (a) NaH, TBAI, THF, 20 h, 0 °C → rt; (b) (COCl)$_2$, DMSO, NEt$_3$, CH$_2$Cl$_2$, 3 h, −78 °C.

Disappointingly, no reaction of aldehyde 146 was observed with crotyltrifluoroborate 138 under phase transfer conditions, or in the presence of either boron trifluoride or montmorillonite K10 (Scheme 2.14). In all cases, only starting material was observed followed by degradation at elevated temperatures. At this point it was decided to no longer focus on the Batey crotylation protocols, but rather find a suitable, asymmetric crotylation procedure to access aldehyde 134.
Reagents and conditions: (a) BF$_3$·OEt$_2$, 138, CH$_2$Cl$_2$, 12 h, –78 °C; (b) Montmorillonite K10, 138, CHCl$_3$/H$_2$O (15:1), 48 h, rt; (c) TBAI, 138, CH$_2$Cl$_2$, H$_2$O (1:1), 48 h, rt.

Scheme 2.14. Attempted crotylation of aldehyde 146 employing conditions developed by the Batey group.

2.2.2 Background and Overview of Asymmetric Crotylation Chemistry

First investigated in the late 1970s, the stereocontrolled addition of an allylic organometallic species to a carbonyl compound is one of the most widely studied and utilised transformations in organic synthesis. When the allylic organometallic reagent is substituted at the γ-position the reaction is known as a crotylation and produces two contiguous chiral centres in a stereocontrolled manner on an acyclic system (Scheme 2.15). In 1980, Yamamoto showed that Lewis-mediated reaction of crotyltin species with aldehydes give syn homoallylic alcohols regardless of the geometry of the double bond of the allylic tin.\textsuperscript{77} Contemporaneously, the Hoffmann group showed that (E)-crotylboronates produce syn-homoallylic alcohols while the corresponding (Z)-crotylboronates selectively give anti-addition.\textsuperscript{78} Since these seminal discoveries, it has been known that the stereochemical outcome of allylmetal addition to carbonyl compounds is dependent on the nature of the metal and reaction conditions.\textsuperscript{79} This dependence was formalised by Denmark, classifying allylations into three groups: Type 1, where the product syn/anti ratio reflects the Z/E ratio of the allyl moiety; Type 2, which are syn-selective regardless of allyl geometry and; Type 3, which are anti-selective regardless of allyl geometry.\textsuperscript{80} Type 1 allylations proceed via a rigid, chair-like transition state, with the bulkier carbonyl substituent occupying the pseudoequatorial position (Scheme 2.15). On the other hand, Type 2 allylations proceed through an open, acyclic transition state after Lewis acid carbonyl activation. Two possible transition states for allylmetal approach have been proposed, with the nucleophile approaching in either an antiperiplanar or synclinical fashion depending on the specific steric constraints of the reaction system (Scheme 2.15). Type 3 alkylation generally progresses through a similar cyclic transition state to Type 1 allylations, but involves a preequilibrium of the allylic organometallic species to the more stable E-alkene geometry (Scheme 2.15).
For the present work, a syn-selective transformation was required. Thus, a crotylation that proceeds through either a Type 1 or Type 2 mechanism is a viable approach for this disconnection. Although both reaction types have been studied in detail, Type 1 allylations have received by far the most attention, as they are generally more versatile and give higher chemoselectivity. Consequently, we chose to investigate these transformations in further detail. Asymmetric Type 1 allylation reactions can be divided further into two main groups: (i) those that induce enantioselectivity through the use of an asymmetric catalyst and, (ii) those that employ a chiral auxiliary directly bound to the metal.

A. Enantioselective Type 1 Crotylation by Ligand-Mediated Induction

Classically, asymmetric induction of Type 1 allylation has employed chiral ligands directly bonded to the metal atom. Throughout the 1980s a number of C2 symmetric chiral boron reagents have been used to effect this transformation, beginning with Brown’s pinane-derived allylboranes. Later contributions in this field came from Roush (tartarate boronates), Masamune (allylborolanes) and Corey [bis(sulfonamide) derivatives] (Figure 2.2). These compounds, in particular the pinane-derived boranes, are still the most widely used allylation reagents in natural product synthesis. However, they do suffer from several significant drawbacks. In particular, the chiral ligand employed is usually lost following oxidative workup and they show little reactivity with less electrophilic carbonyls such as ketones. To address these issues the Soderquist group has more recently developed a novel class of asymmetric borane...
reagents, derived from ring-expansion and resolution of the 9-borabicyclo[3.3.1]nonane scaffold (Figure 2.2).  

![Chemical structures](image)

**Figure 2.2.** Selected chiral boron reagents for asymmetric allylation.

In 1997 Kira and co-workers pioneered a conceptually distinct approach for aldehyde allylation, employing tartrate-derived silane 163 (Scheme 2.16). Although these investigations produced only moderate enantioselectivity (47–80% ee), excellent diastereoselectivity was observed, indicative of a Type 1 mechanism (Scheme 2.15, above). In this system, Kira postulated that tartrate ligand coordination to the silicon centre enhances its Lewis acidity facilitating coordination to the carbonyl compound. This carbonyl coordination then enhances the nucleophilicity of the γ-carbon of the allylsilane through σ-π conjugation.  

![Mechanism](image)

**Scheme 2.16.** Kira’s allylation using chiral silane 163.  

A significant improvement of this methodology was reported by Leighton and co-workers, who employed silane 165 as an asymmetric allylation reagent (Scheme 2.17). As well as reporting good enantioselectivity (78–96% ee) and substrate scope, these experiments demonstrated that conformational strain at the silicon centre is sufficient to promote reactivity through a phenomenon known as “strain-release Lewis acidity”. Mechanistic analysis by Houk and Leighton suggest that carbonyl coordination to the silicon centre produces a pentavalent, trigonal-bipyramidal intermediate. The silicon hypercoordination, and accompanying change to bond geometry, eases ring strain promoting reactivity of the cyclic allylsilane species.
Reagents and conditions: (a) Toluene, 2 h, −10 °C.

Scheme 2.17. Leighton’s allylation using chiral silane 165.88

This methodology was then refined in the development of crotylsilane 166, which conferred improved levels of stereocontrol (Figure 2.3).90 Activation of this reagent with catalytic scandium(III) triflate confers high reactivity, allowing allylation of both unactivated aldehydes and ketones.85 Scandium(III) triflate is thought to promote reactivity by coordinating to nitrogen and neutralising a deactivating electron donation from nitrogen to the silicon-chloride antibonding orbital. The most recent crotylation reagent developed by the Leighton group is silane 167.91 The added conformational constraints imposed by the fused aryl ring increase Lewis acidity of the silicon centre. Thus, allylsilane 167 facilitates efficient allylation of carbonyl compounds without requiring further Lewis acid activation (Figure 2.3).

Figure 2.3. Second and third generation allylation reagents developed by the Leighton group.85 90 91

B. Enantioselective Type 1 Crotylation by Catalytic Induction

The invention and development of catalytic, enantioselective reactivity has been one of the defining challenges of modern organic chemistry. However, the discovery of broadly applicable, catalytic allylation chemistry is a relatively recent phenomenon. The uptake of this methodology was initially limited by the observation that Lewis acid catalysis tends to promote open transition states, in preference to a Type 1 mechanism requisite for good stereocontrol. Thus, Lewis acid catalysis was deemed unfeasible for diastereoselective crotylation.92 In an elegant solution to this potential issue, the first catalytic crotylation methodology utilised chiral Lewis base activation of crotyltrichlorosilane (168).93 In this system, bimolecular Lewis base coordination of phosphoramidate 170 generates a reactive hypercoordinate silicon species, which can then further coordinate to a carbonyl, promoting a tight, cyclic transition state and conferring good enantio- and excellent diastereoselectivity (Scheme 2.18).94 Since the discovery of this reactivity mode,
a plethora of asymmetric Lewis bases have been employed for this transformation, including numerous phosphoramides, bisphosphoramides, phosphane oxides, sulfoxides, and N-oxides, often achieving excellent yields and good stereoselectivity.\textsuperscript{95}

Scheme 2.18. The first catalytic enantioselective Type 1 allylation (above) and representative chiral Lewis base catalysts.\textsuperscript{93}

Contemporaneous to the first asymmetric Lewis base-promoted crotylation reactions, Hall and co-workers reported a diastereoselective Lewis acid-catalysed addition of allylboronates to aldehydes.\textsuperscript{96} Subsequent kinetic studies suggested that the Lewis acid, scandium(III) triflate, was coordinating to one of the boronate oxygens, rather than the carbonyl oxygen.\textsuperscript{97} Following this discovery, and independent computational studies corroborating their proposed mechanism,\textsuperscript{23} a multitude of chiral Lewis and Brønsted acids have been developed to promote this reaction by selective coordination to the boronate oxygen (Scheme 2.19). These efforts, and other catalytic methods, for addition of allylic organometallic reagents to carbonyl compounds have been extensively reviewed elsewhere.\textsuperscript{92, 95, 98}

Scheme 2.19. Lewis acid-catalysed allylboration.
2.2.3 Brown Crotylation of Aldehyde 149

The asymmetric allylation reaction most frequently encountered in the literature is that reported by Brown and co-workers, employing \(B\)-allyldiisopinocampheylborane.\(^{81b}\) Therefore the search for an enantioselective preparation of alcohol 149 began with the Brown allylation as it is the most studied and best understood crotylation procedure.

As aldehyde 135 was difficult to handle due to its volatility and instability, aldehyde 146 was instead chosen for initial investigation. Following the Brown protocol, treatment of \(cis\)-butene with Schlosser’s base followed by \((+)-B\)-methoxydiisopinocampheylborane at \(-55\ \degree C\) generated the crotylation reagent \textit{in situ}.\(^{81b}\) Subsequent addition of boron trifluoride etherate and aldehyde 146 at \(-78\ \degree C\), followed by oxidative work-up afforded alcohol 149 in 63% yield, but with modest diastereoselectivity (11:1 \(dr\)) (Scheme 2.20).

\[
\begin{align*}
\text{OPMB} & \quad \text{OPMB} \\
146 & \quad 149 \\
\text{63\%} & \quad 11:1 \text{ \textit{dr}}
\end{align*}
\]

\textit{Reagents and conditions:} (a) \(cis\)-butene, KOt-Bu, \(\sigma\)-BuLi, THF, \((+)-(Ipc)\_2\text{BOMe then BF}_3\text{OEt}_2\), 146, then \(\text{H}_2\text{O}_2/\text{NaOH (1 M), CH}_2\text{Cl}_2, 1\ h, -55\ \degree C \rightarrow -78\ \degree C.}\]

\textbf{Scheme 2.20.} Crotylation of aldehyde 146 following the procedure described by Brown and co-workers.\(^{99}\)

Crucially, several complications were observed during the reaction, most notably: (i) \((+)-\text{methoxydiisopinocampheylborane is an expensive and highly moisture sensitive reagent, (ii) the requirement for a strict cryogenic temperature protocol made the reaction excessively labour intensive, and (iii) the isopinocampheol by-product co-eluted with alcohol 149, requiring successive chromatographic purifications. The combined effect of these issues suggested that scalability of the Brown crotylation would be problematic. Thus, we turned to the literature to find an alternative procedure that would enable reliable access to alcohol 149.
2.2.4 Application of the Leighton Crotylation

Shortly before this work commenced, Leighton and co-workers disclosed a highly stereoselective crotylation procedure using crotylsilane reagent 167, which can either be prepared from diamine 177 and a crotyltrichlorosilane 168 and used \textit{in situ}, or purified by filtration after precipitation of the DBU·HCl salt by-product (Scheme 2.21).\textsuperscript{91} The development of this procedure, and mechanistic considerations, have been discussed in an earlier section (see section 2.2.2, page 42).

Application of the Leighton crotylation to the synthesis of por timine appealed for several reasons, in particular: (i) the apparent procedural simplicity, and (ii) the diamine ligand can be readily recovered during workup by aqueous acid extraction (1 M HCl) and recrystallisation so this methodology has significant advantages over earlier crotylsilane procedures in terms of efficiency, sustainability and scalability.\textsuperscript{91} Although this methodology has since been employed by the Leighton and Taylor groups,\textsuperscript{100} we were also encouraged by the opportunity to be the first group to test this new procedure in a total synthesis setting.
A. Synthesis of Diamine Ligand 177 and (Z)-Crotylsilane 184

Preparation of the diamine ligand was relatively straightforward following literature conditions (Scheme 2.22).

Selective tert-butyloxycarbonyl (Boc) protection of (S,S)-diaminocyclohexane gave amine 179 in 67% yield on multigram scale (batches up to 15 g were produced). Ortho-formylation of tert-butylphenol (180) proved less reliable although moderate yields (~50%) could be obtained with prolonged reaction times using a large excess of paraformaldehyde at reflux. Imine condensation and lithium aluminium hydride reduction afforded ligand 177 in 88% yield over 2 steps.

Reagents and conditions: (a) Boc₂O, HCl, MeOH/H₂O (4:1), 16 h, 0 °C → rt; (b) (CH₂O)ₙ, MgCl₂, NEt₃, MeCN, 16 h, reflux; (c) EtOH, 5 h, reflux; (d) LiAlH₄, THF, 12 h, −10 °C → reflux.

Scheme 2.22. Synthesis of Leighton crotylation ligand 177.

Synthesis of the requisite Z-crotyltrichlorosilane 184 proved significantly more challenging than anticipated (Scheme 2.23). There are several procedures reported in the literature for the preparation of silane 184 based on the palladium-mediated hydrosilylation of dienes first reported by Hagihara. In the standard procedure butadiene and trichlorosilane are sequentially condensed into a pressure flask charged with tetrakis(triphenylphosphine)palladium(0) and the reaction is stirred neat at 120 °C. Alternatively, the procedure reported by Leighton and co-workers was performed in a tetrahydrofuran solution at room temperature with a significantly lower catalyst loading (1 mol % Pd(PPh₃)₄). In our hands, attempts to replicate the Leighton procedure were fruitless, with no product observed after 19 h by ¹H NMR analysis of a reaction aliquot (Scheme 2.23).

Reagents and conditions: (a) Pd(PPh₃)₄ (1 mol %), THF, 19 h, −78 °C → rt.

Scheme 2.23. Attempted synthesis of crotyltrichlorosilane 184.
However, the reaction of butadiene and trichlorosilane was also performed using a modification of the Tsuji procedure whereby the reagents are stirred neat at room temperature. Under these conditions a small amount of product was observed by $^1$H NMR aliquot analysis alongside significant loss of trichlorosilane.$^{105}$ Disappointingly, initial attempts to isolate this product proved unsuccessful as it rapidly polymerised upon exposure to air. Extensive experimentation revealed that the type of vessel used was crucial to reaction success. Best results were achieved when hydrosilylation was conducted in a round bottom Schlenk tube with a Teflon screw neck. Using this reaction vessel, total conversion of trichlorosilane to crotyl product 184 was achieved in 24 h at room temperature [5 mol % Pd(PPh$_3$)$_4$] or 100 h at a slightly reduced catalyst loading [2 mol % Pd(PPh$_3$)$_4$] (Scheme 2.24). Gratifyingly, careful air-free work up and vacuum distillation afforded crotyltrichlorosilane 184 in up to 79% yield on a reasonable scale (>10 g).

\[
\text{butadiene (183)} + \text{HSiCl}_3 \xrightarrow{(a)} \text{Cl}_3\text{Si} - \text{CCH} \quad (61-79\%) \\
\text{1.2 equivalents}
\]

Reagents and conditions: (a) Pd(PPh$_3$)$_4$ (2 mol %), 100 h, $-78 \, ^\circ\text{C} \rightarrow \text{rt.}$

B. Leighton Crotylation of Aldehyde 146

With reliable access to both ligand 177 and silane 184 established, the scene was set to investigate the Leighton crotylation protocol itself.

Aldehyde 146 was added dropwise to a solution of silane 185, prepared in situ from 184 and 177 in the presence of 1,8-diazabicycloundec-7-ene. Total conversion was observed within 2 h, and alcohol 149 could be obtained in near quantitative yield as a single diastereomer on a multigram scale (Scheme 2.25). Importantly, acid extraction (1 M HCl) and recrystallisation enabled excellent recovery of valuable chiral ligand 177 (88% recovery).

![Scheme 2.25. Leighton crotylation of aldehyde 146.](image)

Reagents and conditions: (a) 177, DBU, 184, CH2Cl2 then 146, 2 h, rt → 0 °C, then Et2O, TBAF (1 M in THF), then HCl (1 M), 5 min (88% of ligand 177 recovered after aqueous extraction).

The enantioselectivity of the crotylation of aldehyde 146 was determined to be 92% ee by NMR analysis of Mosher’s esters 186a and 186b. Esters 186a and 186b were derived from crotylation product alcohol 149 upon treatment with the appropriate Mosher’s acid in the presence of N,N’-dicyclohexylcarbodiimide and catalytic 4-dimethylaminopyridine (Scheme 2.26).

![Scheme 2.26. Synthesis of Mosher’s esters 186a and 186b.](image)

Reagents and conditions: (a) (R)- or (S)-MTPA, DCC, DMAP, CH2Cl2, 24 h, rt.

Typically, Mosher’s ester derivatives can be used to determine the enantiopurity of the parent alcohol by measuring the relative intensities of the resonances produced by each diastereomer in the $^{19}$F NMR spectrum. Unfortunately, in the present work these resonances overlapped preventing comparison of their integrals, with 186a producing a singlet at $\delta = 71.15$ ppm and...
186b producing a singlet at $\delta -71.12$ ppm (Figure 2.4). However, in the $^1$H NMR spectrum the $3-\text{CH}_3$ methyl protons were clearly resolved with 186a producing a doublet at $\delta 0.95$ ppm while 186b produced a doublet at $\delta 1.02$ ppm. Consequently, the relative intensities of these resonances were used to calculate the enantiomeric excess of alcohol 149, and hence the selectivity of the Leighton crotylation.

$^{19}$F NMR spectrum of 186a (on left) and 186b (on right)

$^1$H NMR spectrum of 186a (on left) and 186b (on right) for 3-CH$_3$

Figure 2.4. NMR spectra of Mosher’s esters 186a and 186b for analysis of enantiopurity of alcohol 149.
C. Leighton Crotylation of Aldehyde 135

With Leighton crotylation conditions established to reliably access alcohol 149 from aldehyde 146 attention turned to the application of the same transformation could be performed on aldehyde 135. As per earlier reactions using aldehyde 135, this compound was prepared as a solution in dichloromethane, following reduction of ester 144 and aqueous extraction of the resultant solution. When aldehyde 135 was added to a mixture of ligand 177, silane 184, and 1,8-diazabicyclo(5.4.0)undec-7-ene, clean conversion to alcohol 137 was observed when the reaction was monitored by thin layer chromatography (Scheme 2.27). However, acidic extraction for recovery of ligand 177 was found to cause concomitant hydrolysis of the acetal producing a mixture of non-isolable compounds.

\[ \text{Reagents and conditions:} \ (a) \text{DIBAL (1 M in hexane), CH}_2\text{Cl}_2, 2 \text{ h, } -78 \degree \text{C} \ (b) \text{DBU, THF, 2 h, rt } \rightarrow 0 \degree \text{C, then TBAF (1 M in THF), Et}_2\text{O (c) HCl (1 M), 5 min (94\% of ligand 177 recovered).} \]

Scheme 2.27. Leighton crotylation of aldehyde 135 with concomitant acetal hydrolysis.

The major species of the mixture generated upon acidic work-up of the Leighton crotylation was tentatively assigned as hydroxyketone 187 on the basis of mass spectral analysis ([M+Na] \( m/z = 179.1043 \), found 179.1041) and the observation of a distinctive singlet resonance in the crude \(^1\)H NMR spectrum at \( \delta = 2.18 \) ppm, corresponding to the methyl ketone of 187 (Figure 2.5). Unfortunately, repeated attempts to isolate this compound for complete characterisation proved unsuccessful, possibly due to equilibration between this species and hemiacetal 188.

\[ \text{Figure 2.5. Equilibration between hydroxyketone 187 and hemiacetal 188.} \]
The hydroxyketone 187 could not be carried forward in the synthesis without definitive structural elucidation. Conceivably, hydroxyketone 187 could be trapped as methyl acetal 189 upon acid-catalysed reaction with methanol, potentially producing a more stable intermediate for isolation, characterisation and homologation (Scheme 2.28). Methoxyacetal 189 can be considered a synthetic equivalent to acetal 137. Both compounds may be advanced to vinyl halide 191, the desired polyketide fragment of portimine (Scheme 2.28). Thus, both species are viable building blocks in the present synthesis, with use of methoxyacetal 189 potentially circumventing the problems caused by the acidic reaction work up used in the Leighton crotylation. Alternatively, methoxybenzyl ether 149, already prepared on good scale via Leighton crotylation, could be applied to the synthesis of vinyl halide 190 using an analogous homologation sequence. Subsequent deprotection-oxidation-alkylation would then produce the requisite methyl ketone functionality, although this was also considered too inefficient (Scheme 2.28).

Scheme 2.28. Alternative strategies to prepare polyketide fragment 191.

To find appropriate conditions for the preparation of acetal 189, hydroxyketone 187 was first treated with camphorsulfonic acid (CSA) in methanol, with the reaction monitored by TLC analysis (Table 2.1, entry 1). Pleasingly, the mixture readily converged to two non-polar spots on the TLC plate, presumed to be the two diastereomers derived from both epimers formed at the acetal stereocentre of acetal 192 (R = Me). Disappointingly, these compounds were found to be highly volatile and immediately decomposed upon concentration or attempted purification. To avoid these problems, a more hindered alternative alcohol was used. Unfortunately, attempted acetalisation using bulky commercially available alcohols (eg. t-BuOH, BnOH) proved fruitless, with no cyclisation observed despite screening several Bronsted and Lewis acids (Table 2.1, entries 3–6). However, a moderate yield of acetal 192 (R = C₆H₅OPMB) was obtained upon treatment of the mixture with four equivalents of 4-(4-methoxybenzyloxy)butan-1-ol in the
presence of CSA (Table 2.1, entry 7). Attempts to simultaneously reduce the excess of alcohol required and improve the yield by increasing the reaction temperature and concentration were unsuccessful, and this acetal protection strategy was ultimately deemed too inefficient for application in a total synthesis.

**Table 2.1. Attempted synthesis of acetal 192.**

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>CSA, rt, 5 h</td>
<td>Product unstable</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>CSA, rt, 14 h</td>
<td>product unstable</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOH</td>
<td>CSA, 50 °C, 48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOH</td>
<td>DOWEX 50W, 50 °C, 48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOH</td>
<td>InCl₃, 50 °C, 48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>BnOH</td>
<td>CSA, CH₂Cl₂, reflux, 14 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>CSA, rt, 15 h</td>
<td>36%</td>
</tr>
</tbody>
</table>

**D. Leighton Crotylation of Weinreb Amide-Aldehyde 193**

Attention turned to finding an alternative aldehyde containing acid-stable functionality equivalent to a masked methyl ketone, for use in the Leighton crotylation. One such species is Weinreb amide-aldehyde 193, as Weinreb amides can be readily converted to methyl ketones by addition of MeMgBr or MeLi (Scheme 2.29).

**Scheme 2.29. Proposed synthesis of polyketide fragment 191 starting from a Weinreb amide.**

Importantly, Weinreb amide containing alcohols such as 196 appear to be potentially valuable synthetic intermediates for a diverse range of polyketide natural products (Scheme 2.30).
Despite their potential, to the best of our knowledge there is only one known literature preparation of amide-alcohols such as 197. Performed by Taylor and co-workers,\textsuperscript{109} employing Soderquist’s 10-TMS-9-borabicyclo[3.3.2]decane, allylation of 198 afforded alcohol 199 in 66\% yield and 82\% de (Scheme 2.31).\textsuperscript{110} We were interested to investigate whether application of the Leighton protocol to Weinreb amide-aldehydes such as 196 could facilitate a more efficient enantioselective access to these densely functionalised alcohols.

\[ \begin{align*}
\text{Reagents and conditions: (a) allylMgBr, 200, BF}_3\cdot\text{OEt}_2, \text{ then 198, 4 h, } -78^\circ\text{C then H}_2\text{O}_2/\text{NaOH (1 M).}
\end{align*} \]

Scheme 2.31. Taylor’s allylation of Weinreb amide-aldehyde 198.\textsuperscript{109}

To employ this methodology in the present work Weinreb amide-aldehyde 193 was prepared in two steps from \( \gamma \)-butyrolactone (201) (Scheme 2.32). First, Lewis acid (Me\textsubscript{2}AlCl)-mediated ring opening of \( \gamma \)-butyrolactone afforded volatile alcohol 202 in modest yield, following literature precedent.\textsuperscript{111} Next, Parikh-Doering oxidation cleanly furnished aldehyde 193.\textsuperscript{112} For ease of handling, aldehyde 193 was used without purification as a solution in dichloromethane. Disappointingly, although subsequent Leighton crotylation gave total conversion to 194, unexpected partial cyclisation was observed upon workup (1 M HCl) to give a mixture of amide 194 (39\%) and lactone 203 (58\%) over two steps.
As efforts to employ the Leighton crotylation with ligand recovery met with failure, attention returned to the crotylation of aldehyde 135, with the intention of employing an acid-free work-up process. Alongside the acidic aqueous work-up for ligand extraction, a simplified alternative can be used whereby the reaction mixture is concentrated and directly purified by silica chromatography. Although this procedure is suitable for acid-sensitive substrates it is not possible to readily recover diamine 177. However, the excellent stereocontrol and yields obtained from the Leighton crotylation were deemed sufficient to offset the inefficiency caused by loss of ligand 177. Pleasingly, we found that by employing this alternative work-up procedure alcohol 137 could readily be prepared as a single diastereomer in excellent yield without any observed acetal cleavage. Interestingly, we found that flushing the silica used for chromatography with diethyl ether after complete elution of alcohol 137 returned small amounts of ligand 177. This result prompted further investigation into ligand recovery using chromatography, which culminated in the discovery that concentrating the reaction mixture and loading it directly onto a CombiFlash 200 automated column chromatography instrument gave excellent yields of crotyl alcohol 137 as a single diastereomer and with good ligand recovery (~75–89%) when performed on up to a 5 g scale (Scheme 2.33). Mosher’s ester analysis determined the enantiopurity of crotyl alcohol 137 as 94% ee, following a similar procedure to that described earlier (see Figure 2.4, page 48 and appendix, page 310 for further details).
Reagents and conditions: (a) DIBAL (1 M in hexane), CH₂Cl₂, 2 h, −78 °C; (b) 177, DBU, 184, THF, 2 h, 0 °C → rt, then TBAF (1 M in THF), Et₂O; (c) HCl, 5 min (1 M) (up to 89% of ligand recovered).

Scheme 2.33. Gram scale preparation of alcohol 137.

2.2.5 Elaboration to Aldehyde 204

With reliable, multigram access to alcohol 137 secured, synthesis of aldehyde 204 continued following a protection-oxidation sequence (Scheme 2.34). The protecting group for alcohol 137 must be orthogonal to the acetal motif, so the acetal can be selectively removed to afford a methyl ketone, prior to the key aldol fragment coupling. One such protecting group is the tert-butyldimethylsilyl group, one of the most widely used tools for the protection of hydroxyl groups in total synthesis.¹¹³

Scheme 2.34. Proposed elaboration of alcohol 137 to key intermediate aldehyde 204.

The chemistry of this protection-oxidation sequence was initially developed on alcohol 149 (Scheme 2.35). Although we were primarily interested in the synthesis of methyl ketones 205 and 206 (from 137) for investigation of the proposed glyoxal aldol fragment coupling, we recognised that substrates derived from alcohol 149 may also be applied to the synthesis of portimine in the event that an alternative coupling strategy was required. Furthermore, synthesis of alcohol 149 was more expedient than the preparation of 137, so 149 was a convenient model system for the more valuable alcohol 137.
Pressing forward, alcohol 149 was treated with a mixture of \textit{t}-butyldimethylsilyl chloride (TBSCl) and imidazole in dimethylformamide,\textsuperscript{114} however no reaction was observed after 100 h at 50 °C. Use of \textit{t}-butyldimethylsilyl triflate with 2,6-lutidine afforded silyl ether 207 in 97% yield after 5 min at 0 °C (Scheme 2.35).\textsuperscript{115} Hydroboration-oxidation of alkene 207 proceeded smoothly with two equivalents of 9-borabicyclo[3.3.1]nonane dimer in tetrahydrofuran for 5 h and, after oxidative work up, afforded alcohol 208 in 97% yield. Use of alternative hydroboration reagents (eg. BH₃·DMS or Ch₆BH) gave clean, but incomplete, conversion to 208 after work up. Subsequent Parikh-Doering oxidation cleanly afforded aldehyde 209 in 94% yield on a multigram scale (Scheme 2.35).

\[ \text{Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH₂Cl₂, 5 min, 0 °C; (b) 9-BBN dimer, THF, 5 h, rt, then NaOH (3 M), H₂O₂ (30% aq); (c) SO₃·py, DMSO, i-Pr₂NEt, CH₂Cl₂, 5 min, 0 °C.} \]

\textbf{Scheme 2.35. Synthesis of aldehyde 209.}

With the sequence to aldehyde 209 established, attention turned to the elaboration of alcohol 137, which contained the acetal precursor that would later reveal a methyl ketone for the key aldol fragment coupling. Accordingly, subjection of alcohol 137 to the aforementioned silylation conditions also proceeded smoothly, furnishing silyl ether 211 in 97% yield (Scheme 2.36). Alternatively, protection of 137 as the methoxybenzyl ether was found to be significantly more sluggish, with only moderate yields obtained even when a large excess of sodium hydride and PMBCl (3 equivalents each) were used (Scheme 2.36).

\[ \text{Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, 20 h, 0 °C → 40 °C; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 5 min, 0 °C.} \]

\textbf{Scheme 2.36. Alternative protection of alcohol 137.}

To ensure that acetal cleavage would be possible without concomitant desilylation a brief survey of acetal deprotection conditions was conducted (Table 2.2). Typically, acetal deprotection is performed in the presence of Brønsted acids, although a variety of conditions have been reported for this transformation.\textsuperscript{116} Although CSA and hydrochloric acid both caused concomitant
desilylation (Table 2.2, entries 1–3), use of either PdCl2(MeCN)2 in acetone (entry 4)117 or Amberlyst 15® acidic resin in acetone/dichloromethane (1:1) (entry 5) selectively effected acetal deprotection to ketone 212.

Table 2.2. Synthesis of ketone 212a

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>time</th>
<th>resultsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl (2 M) in acetone (40% v/v)</td>
<td>10 min</td>
<td>187/188 only</td>
</tr>
<tr>
<td>2</td>
<td>CSA (10 mol %) in acetone</td>
<td>14 h</td>
<td>211 and 212 (2.1:1)</td>
</tr>
<tr>
<td>3</td>
<td>CSA (10 mol %) in MeCN/MeOH/H2O (2:2:1)</td>
<td>24 h</td>
<td>211, 212, and 187/188 (3:2.3:1)</td>
</tr>
<tr>
<td>4</td>
<td>Amberlyst 15® in acetone/CH2Cl2 (1:1)</td>
<td>13 h</td>
<td>212 with trace 211</td>
</tr>
<tr>
<td>5</td>
<td>PdCl2(MeCN)2 (10 mol %) in acetone</td>
<td>24 h</td>
<td>212 only</td>
</tr>
</tbody>
</table>

*aAll reactions were performed at room temperature and gave total conversion to the mixtures identified above. bProduct ratios are assigned on the basis of crude 1H NMR analysis.

Amberlyst 15® was chosen as the reagent of choice based on its efficiency and ease of use; a gratifying yield of 90% was obtained using this procedure (Scheme 2.37).

Satisfied that the acetal moiety could be selectively manipulated when required, protected alcohol 211 was taken forward to aldehyde 204 by the established hydroboration-oxidation then Parikh-Doering oxidation sequence (Scheme 2.38). Overall, key intermediate 204 could be reliably prepared on multigram scale in 6 steps from commercially available starting materials in excellent yield and stereoselectivity.

Scheme 2.37. Selective deprotection of acetal 211.

Scheme 2.38. Oxidation of alkene 211.
With efficient access to key intermediate aldehyde 204 secured, attention turned to its elaboration to both vinyl halide isomers 214 and 215, for application in model glyoxal aldol and Nozaki-Hiyama-Kishi fragment couplings. As mentioned previously, preparation of both the E- and Z-isomers was essential as it was unknown how the olefin geometry would be used to introduce the correct stereochemistry of the α,α'-dihydroxyketone moiety after macrocyclisation and oxidation of the resultant allyl alcohol (see Scheme 2.4, page 31).

2.2.6 Synthesis of Vinyl Bromides 224 and 230

Synthesis of E-vinyl halide 214 and Z-vinyl halide 215 from aldehyde 204 were next investigated in turn (Scheme 2.39).

![Scheme 2.39. Proposed synthesis of vinyl halides 214 and 215.]

A. Synthesis of E-Vinyl Bromide 224

The most direct method for conversion of aldehyde 204 to the corresponding E-vinyl halide is by Takai olefination.\textsuperscript{118} Although disputed,\textsuperscript{119} the most widely accepted mechanism for this reaction proceeds via nucleophilic addition of a gem-dichromium species, generated in situ from chromium(II) chloride and iodoform, to a carbonyl compound.\textsuperscript{120} This nucleophilic addition is thought to occur through a pseudochair transition state in which the two chromium ions are linked by a halogen bridge with the large iodide and aldehyde substituents occupying the pseudoequatorial positions. Syn-elimination of the resultant intermediate 219 affords vinyl iodides with high levels of E-selectivity (Scheme 2.40).

![Scheme 2.40. Mechanism for the Takai olefination, adapted from Takai and co-workers.\textsuperscript{120a}]

\textsuperscript{120a}
We initially anticipated that use of the Takai olefination would allow facile, one-step synthesis of \( E \)-iodide 221 from aldehyde 204. To this end, aldehyde 204 was treated with chromium(II) chloride and iodoform in dimethylformamide and the reaction appeared to proceed smoothly to completion within 10 h, as visualised by TLC analysis (Scheme 2.41). However, attempts to purify and isolate the major reaction product, presumed to be vinyl iodide 221, by flash chromatography (either triethylamine buffered silica or neutral alumina) proved fruitless, primarily returning alkene 222 instead (Scheme 2.41).

![Chemical structure](image)

*Reagents and conditions:* (a) \( \text{CrCl}_2, \text{CHI}_3, \text{DMF}, 10 \text{ h}, 50 \text{ °C} \).

*Scheme 2.41. Attempted Takai olefination of aldehyde 204.*

As alkene 222 clearly formed after work-up (as determined by TLC analysis of the reaction mixture before and after attempted product isolation) it was reasoned that alkene 222 was the decomposition product of iodide 221, most likely caused by homolytic cleavage of the carbon-iodine bond. To circumvent this issue as it was anticipated that the corresponding bromide 224 would be significantly more stable due to the higher carbon-bromine bond dissociation enthalpy.\(^{121}\) Thus, attention turned to the synthesis of vinyl bromide 224.

The Takai olefination using bromoform is known to be low yielding and problematic.\(^{118}\) However, the Hodgson group reported that diiodomethyl(tributyl)stannane (225) is a competent coupling partner for the synthesis of \( E \)-vinyl stannanes, which are precursors to \( E \)-vinyl bromides using tin-halogen exchange.\(^{122}\) Thus, following the strategy of Patterson and co-workers, we proposed that preparation of bromide 225 could be achieved in two steps using the Hodgson variant of the Takai olefination, followed by tin-bromine exchange (Scheme 2.42).\(^{123}\) Surprisingly, when aldehyde 204 was subjected to these conditions only trace olefination product 223 was observed with the reaction affording small quantities of vinyl bromide 224 (\( E \) to \( Z = 5:1 \)) after treatment of the crude mixture with \( N \)-bromosuccinimide, alongside almost total recovery of aldehyde 204.
Although the olefination step of this procedure was low yielding we were pleased to find that the small amounts of bromide 224 obtained were bench-top stable and showed no decomposition after prolonged storage (~2 months at room temperature), in stark contrast to the corresponding iodide 221. Furthermore, this experiment also demonstrated that tin-bromine exchange was facile for stannane 223, and thus it was a viable intermediate for the preparation of bromide 224. Disappointingly, however, attempts to access this stannane through other methods proved unreliable. For instance, radical hydrostannylation-bromination (AIBN, Bu₃SnH then NBS)¹²⁴ of alkyne 226, prepared by Seyferth-Gilbert homologation of aldehyde 204 in 93% yield,¹²⁵ afforded vinyl bromide 224 in variable yield (20-75%) (Scheme 2.43). Unfortunately, these reactions also proceeded with poor stereoselectivity (E to Z = 3.5:1), suggesting bromide 224 was not sufficiently hindered for substrate-derived stereocontrol under equilibrating reaction conditions.

Hydrozirconation of alkynes proceeds via syn-addition of Schwartz reagent, selectively giving E-alkene products upon treatment with an appropriate electrophile.¹²⁶ Consequently, it was anticipated that use of this procedure would circumvent the stereoselectivity issues encountered using radical-mediated olefination procedures. As Schwartz reagent is both light and moisture sensitive,¹²⁷ these reactions were performed under argon in a covered flask protected from light.
Disappointingly, despite these precautions, repeated attempts to effect hydrozirconation of alkyne 226 in dichloromethane or tetrahydrofuran gave inconsistent results, often leading to complex mixtures or degradation products upon addition of N-bromosuccinimide (Scheme 2.44).

![Scheme 2.44. Attempted hydrozirconation of alkyne 226.](Image)

Product mixtures from these experiments were analysed by comparison of their crude $^1$H NMR spectra. Surprisingly, these spectra often showed little similarity, even when experiments were run in identical conditions. Intriguingly, the most striking commonality of these mixtures was a clear decrease in the relative integral of the signal for the protons that corresponded to the acetal group. Thus, it was proposed that acetal cleavage was playing a key role in initiating decomposition. To test this hypothesis, alkyne 228—lacking the sensitive acetal moiety—was subjected to the same hydrozirconation conditions used above. Pleasingly, this reaction gave clean conversion to vinyl bromide 229, providing further evidence that acetal deprotection was intrinsically involved in the decomposition of alkyne 226 (Scheme 2.45).

![Scheme 2.45. Successful hydrozirconation of alkyne 228.](Image)

As acid catalysis is by far the most common and facile method for acetal cleavage, we postulated that the degradation observed might be caused by residual acid, perhaps present in the reaction mixture as hydrogen bromide impurity in the commercial N-bromosuccinimide used. Thus, hydrozirconation of alkyne 226 was repeated using freshly recrystallised N-bromosuccinimide that had been dried in vacuo for 18 h prior to reaction setup. Unfortunately, these efforts came to no avail, returning a similar mixture of undesired side products alongside significant acetal cleavage. Varying the source of Schwartz reagent also failed to improve reaction performance. Further experimentation involved addition of excess organic base to the reaction mixture in order
to remove trace acid from the solution. To our delight, when hydrozirconation was repeated in the presence of five equivalents of triethylamine the reaction proceeded smoothly and reliably with no decomposition observed, affording bromide 224 in 90% yield (Scheme 2.46).

\[
\begin{align*}
\text{Scheme 2.46. Hydrozirconation of alkyne 226 in the presence of triethylamine.}
\end{align*}
\]

Although this discovery supports the hypothesis that earlier hydrozirconation attempts were diverted by the presence of trace acid, other decomposition pathways cannot be definitively discounted. It is also unclear how acid impurities may have been introduced to the reaction. To the best of our knowledge, however, this is the first time that a hydrozirconation reaction has been facilitated by an additive such as triethylamine.

**B. Synthesis of Z-Vinyl Bromide 230**

Although there are a multitude of procedures for Z-selective homologation of an aldehyde to a haloalkene,\(^{128}\) synthesis of vinyl bromide 230 proved somewhat challenging. Of the available options, Wittig olefination of aldehyde 204 was first chosen for application in the present work as the requisite phosphonium salt (231) can be readily prepared following the procedure of Erikson and Wolinsky.\(^{129}\) Unfortunately, treatment of aldehyde 204 with the ylid formed from 231 deprotonated with KHMDS at \(-40^\circ C\) afforded bromide 230 in moderate yield, but with poor stereoselectivity (2.7:1, Z to E) (Scheme 2.47). Attempts to improve the stereoselectivity by lowering reaction temperature proved unsuccessful, while switching the base to NHMDS\(^{130}\) resulted in poor conversion and the formation of significant amounts of alkene 221, even when a large excess of phosphonium salt was used.

\[
\begin{align*}
\text{Scheme 2.47. Wittig olefination of aldehyde 204.}
\end{align*}
\]
In order to avoid the stereoselectivity issues encountered during Wittig olefination of aldehyde 204 an alternative sequence was envisioned whereby cis-selective reduction of alkynyl bromide 232 would exclusively give the corresponding Z-olefin. To this end, silver nitrate-mediated bromination of alkyne 226, produced by Seyferth-Gilbert homologation of aldehyde 227, smoothly afforded bromide 232 in near quantitative yield (Scheme 2.48).

![Scheme 2.48. Attempted cis-reduction of bromoalkyne 232.](image)

Initial efforts to effect cis-reduction of alkyne 232 employed diimide generated by in situ elimination from o-nitrobenzenesulfonylhydrazide (NBSH), a procedure first reported by Hunig and co-workers in 1965.\textsuperscript{131} Thus, following the conditions of Jacobsen and co-workers,\textsuperscript{132} NBSH (1.05 equivalents) was added to a solution of alkyne 232 and triethylamine in i-propanol/tetrahydrofuran (1:1) at room temperature, although this procedure returned only starting material (Table 2.3, entry 1). Attempts to induce reactivity by employing excess NBSH (3.0 equivalents), gave an unquantified, inseparable mixture of starting material 232, product 230, and the corresponding alkane 233 produced by over-reduction (entry 2). On the other hand, performing the reaction in refluxing water/tetrahydrofuran (1:1) with sodium acetate primarily returned starting material alongside trace reduction products (entry 3).\textsuperscript{133}

![Table 2.3. Attempted cis-reduction of alkyne 232](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBSH (1.05 eq.), NEt₃, i-PrOH/THF (1:1), 48 h, rt</td>
<td>recovered 232</td>
</tr>
<tr>
<td>2</td>
<td>NBSH (3 eq.), NEt₃, i-PrOH/THF (1:1), 16 h, rt</td>
<td>inseparable 232, 230, 233</td>
</tr>
<tr>
<td>3</td>
<td>NBSH (1.1 eq.), NaOAc, H₂O/THF (1:1), 6 h, reflux</td>
<td>recovered 232 and trace 230, 233</td>
</tr>
<tr>
<td>4</td>
<td>Ch₂BH (2 eq.), Et₂O/pentane (1:1), then AcOH, 4 h, rt</td>
<td>recovered 232 from a complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>9-BBN (2 eq.), THF, then AcOH, 4 h, rt</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>
In 1989, Brown and co-workers published an efficient, general protocol for a formal two-step \textit{cis}-reduction of haloalkynes by hydroboration followed by protonolysis with acetic acid.\textsuperscript{134} Since its disclosure, this procedure has been widely used by the synthetic community in the total synthesis of a variety of natural products,\textsuperscript{135} suggesting this methodology would be amenable to the present work.

Accordingly, a suspension of dicyclohexylborane in pentane was generated \textit{in situ} by addition of two equivalents of cyclohexene to borane-dimethylsulfide complex. Upon dropwise addition of alkyne \textbf{232}, the mixture became homogenous, indicating completion of the initial hydroboration. However, to our dismay, addition of acetic acid caused partial decomposition of the reaction mixture leading to isolation of a complex mixture of starting material and uncharacterised by-products (Table 2.3, entry 4, above). Similar results were obtained when the reaction was repeated with 9-BBN dimer in tetrahydrofuran (entry 5, above).

A brief survey of the literature for a stereoselective synthesis of \textit{Z}-vinyl halides uncovered the palladium-catalysed hydrogenolysis of \textit{gem}-dibromides with tributyltin hydride, first reported by Uenishi and co-workers in 1996.\textsuperscript{136} As oxidative addition of palladium(0) is particularly facile at the less hindered \textit{trans} position excellent stereoselectivity can be achieved in this reaction under incredibly mild conditions (neutral pH, ambient temperatures). To apply this reaction to our synthesis of vinyl bromide \textbf{230}, aldehyde \textbf{204} was first converted to requisite dibromide \textbf{234} in 97\% yield by a modified-Wittig olefination using a combination of triphenylphosphine and carbon tetrabromide.\textsuperscript{137} Subjection of geminal dibromide \textbf{234} to the hydrogenolysis conditions furnished vinyl bromide \textbf{230} in 99\% yield as a single stereoisomer (Scheme 2.49). These same conditions also proved reliable for aldehyde \textbf{209}, affording vinyl bromide \textbf{236} over two steps, albeit in a slightly lower yield (Scheme 2.49).
Reagents and conditions: (a) PPh₃, CBr₄, NEt₃, CH₂Cl₂, 1 h, −78 °C → 0 °C; (b) Pd(OAc)₂, PPh₃, Bu₃SnH, CH₂Cl₂, 4 h, rt.

Scheme 2.49. Synthesis of vinyl bromides 230 and 236.

C. Acetal Deprotection of Vinyl Bromides 224 and 230 and Bromoalkyne 232

Next, acetal cleavage to liberate the methyl ketone was required prior to glyoxal aldol fragment couplings. Accordingly, both compounds 224 and 230 were treated with Amberlyst 15® acidic resin in dichloromethane/acetone (1:1), conditions previously developed for the selective deprotection of acetal 211 (Scheme 2.37, page 57). Pleasingly, these conditions smoothly afforded ketones 238 and 239 in excellent yield, without concomitant desilylation (Scheme 2.50). Bromoalkyne 232, prepared during the synthesis of vinyl bromide 230, was also identified as a potentially valuable intermediate for fragment coupling studies. Accordingly, it was also deprotected in an excellent 92% yield to afford bromoalkyne 237.

Reagents and conditions: (a) Amberlyst 15®, acetone/CH₂Cl₂ (1:1), 15 h–20 h, rt.

Scheme 2.50. Synthesis of methyl ketones 237, 238, and 239.

2.2.7 Summary of Polyketide Fragment Synthesis

Starting from commercially available ethyl levulinate (143), vinyl bromides 238 and 239 were prepared in 9 steps each, with excellent yield and stereocontrol in both cases. Alkynyl bromide 237, another potentially valuable intermediate, was also prepared using analogous chemistry.
(Scheme 2.51). All three of these glyoxal aldol coupling precursors were prepared from common aldehyde 204.

The synthesis of aldehyde 204 relied on a modified Leighton crotylation as the key step, providing excellent yields and stereoselectivity. Purification by automated chromatography allowed for the effective recovery of ligand 177. Subsequent protection as a tert-butylidemethylsilyl ether and oxidation furnished aldehyde 204. Vinyl ketone 224 was prepared following the procedure of Unieshi and co-workers for the selective synthesis of E-vinyl bromide and subsequent acetal cleavage. Alternatively, aldehyde 204 was transformed into alkyne 226 upon treatment with the Ohira-Bestmann reagent (227) and potassium carbonate in methanol. Hydrozirconation and subsequent acetal cleavage deprotection gave 238, while silver-mediated bromination and deprotection of the same alkyne intermediate 226 gave bromoalkyne 237.

Reagents and conditions: (a) ethylene glycol, TsOH-H2O, benzene, 18 h, Dean-Stark reflux; (b) DIBAL (1 M in hexane), CH2Cl2, 2 h, −78 °C; (c) 177, DBU, 184, THF, 2 h, 0 °C → rt then TBAF (1 M in THF), Et2O; (d) TBSOTf, 2,6-lutidine, CH2Cl2, 5 min, 0 °C; (e) 9-BBN dimer, THF, 3.5 h, rt, then NaOH (3 M), H2O2 (30% aq.); (f) SO3·py, DMSO, i-Pr2NEt, CH2Cl2, 5 min, 0 °C; (g) K2CO3, 227, MeOH, 1 h, rt; (h) AgNO3, NBS, acetone, 2 h, rt; (i) Amberlyst 15®, acetone/CH2Cl2 (1:1), 15 h−20 h, rt; (j) PPh3, CBr4, NEt3, CH2Cl2, 1 h, −78 °C → 0 °C; (k) Pd(OAc)2, PPh3, Bu3SnH, CH2Cl2, 4 h, rt; (l) Cp2ZrHCl, NBs, NEt3, CH2Cl2, 3 h, rt.

Scheme 2.51. Summary of the synthesis polyketide fragments 237, 238, and 239.
Alongside the preparation of ketones 237, 238, and 239, \( p \)-methoxybenzyl ethers 229 and 236 were synthesised using an analogous sequence of reactions (Scheme 2.52). Synthesis of 229 and 236 allow access to a diverse range of alternative coupling strategies, should the proposed glyoxal aldol coupling prove unsatisfactory.

Reagents and conditions: (a) 177, DBU, 184, THF, 2 h, 0 °C → rt then TBAF (1 M in THF), Et₂O; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 5 min, 0 °C; (c) 9-BBN dimer, THF, 5 h, rt, then NaOH (3 M), H₂O₂ (30% aq.); (d) SO₃·py, DMSO, \( t \)-Pr₂NEt, CH₂Cl₂, 5 min, 0 °C; (e) K₂CO₃, 227, MeOH, 1 h, rt; (f) PPh₃, CBr₄, NEt₃, CH₂Cl₂, 1 h, -78 °C → 0 °C; (g) Pd(OAc)₂, PPh₃, Bu₃SnH, CH₂Cl₂, 4 h, rt; (h) Cp₂ZrHCl, NBS, CH₂Cl₂, 3 h, rt.

Scheme 2.52. Synthesis of methoxybenzyl ethers 229 and 236.
2.3 The Glyoxal Aldol Fragment Coupling

With access to methyl ketones 237, 238 and 239 secured, attention turned to investigation of the key fragment coupling, an unprecedented glyoxal Mukaiyama aldol reaction (Scheme 2.53).

Scheme 2.53. Proposed C5–C6 fragment coupling in the synthesis of portimine.

2.3.1 Background to the Use of Glyoxals in Natural Product Synthesis

Glyoxals are 1,2-dicarbonyl compounds possessing adjacent aldehyde and ketone functionality. Typically, the aldehyde group reacts rapidly with various nucleophiles, activated by the electron-withdrawing α-ketone. When the nucleophile is water the glyoxal is converted to its hydrate form, which is often highly unstable.\(^{138}\) Due to their high reactivity but potential instability, there are few instances of the use of glyoxal-containing substrates in natural product synthesis. Of the examples are available, the compounds involved are often simple aromatic derivatives and the dicarbonyl moiety is only ever produced transiently and converted immediately to the desired functionality, often without purification or isolation. Moreover, these dicarbonyl compounds are almost exclusively employed in simple condensation reactions to form heterocycles. Representative examples of the use of glyoxals include the Mahboobi synthesis of botryllazine B (246),\(^{139}\) the Jiang synthesis of slagenin B (250),\(^{140}\) and the Bharate and Vishwakarma synthesis of fascaplysin (254) (Scheme 2.54).\(^{141}\)
Reagents and conditions: (a) NaOH, air, MeOH then HCl, 12 h, rt; (b) HF (40% aq. v/v), MeOH, 30 h, rt; (c) AcOH, Pd/C (10 mol%), 3 h, reflux.

Scheme 2.54. Selected examples of glyoxal heterocyclisation in natural product synthesis.

A conceptually different application of glyoxal compounds is to exploit the high aldehyde electrophilicity in carbon-carbon bond forming reactions. To the best of our knowledge, there is only one reported example of a glyoxal-containing species being used in a natural product synthesis in this way. In the Krische synthesis of bryostatin 7 (259) a rhodium-catalysed reductive coupling of alkyne 256 and glyoxal 255 provides rapid and direct access to key fragment 257 with good yield and stereoselectivity (Scheme 2.55).
Reagents and conditions: (a) Rh(cod)₂OTf (5 mol%), (R)-Tol-BINAP (5 mol%), Ph₃CCOOH (1.5 mol%), H₂ (1 atm), DCE, 3 h, 65 °C; (b) Ac₂O, NEt₃, DMAP, CH₂Cl₂, 2 h, 25 °C; (c) HF·py, THF, 3 h, 25 °C; (d) Dess-Martin periodinane, CH₂Cl₂, 2 h, 25 °C.

Scheme 2.55. Synthesis of bryostatin 7 (259) by Krishe, Lu, and Woo.142a

2.3.2 Proposed Model System for the Glyoxal Aldol

The Krische bryostatin 7 synthesis demonstrated the clear utility of glyoxal intermediates for carbon-carbon bond forming processes in natural product synthesis, and encouraged us to further explore this methodology in the present work. Thus, we proposed a Mukaiyama aldol reaction for the key C₅–C₆ fragment coupling of portimine, employing a similar β-quaternary glyoxal electrophile to that used in the Krische synthesis (Scheme 2.56). Although such a reaction has never been rigorously tested in a natural product synthesis context, this reaction has been reported in several methodology studies.143

As mentioned, however, the application of glyoxal intermediates in natural product synthesis is incredibly limited. Therefore, to investigate the viability of this proposed fragment coupling we proposed a preliminary model coupling. Glyoxals 261 and 262 were chosen as model substrates primarily due to the fact that it shares several key structural features with the proposed fragment coupling partner 108. In particular, both compounds incorporate a γ-quaternary centre and protected alcohol which may be used as a synthetic handle for subsequent macrocyclisation (Scheme 2.56). Although glyoxal 262 (n = 2) bears more structural similarity to the coupling fragment required for the synthesis of portimine, glyoxal 261 (n = 1) was initially chosen for investigation due to its anticipated ease of synthesis.
2.3.3 Synthesis of a Simple Glyoxal Model System

Having adopted a glyoxal aldol fragment coupling strategy, it was first necessary to synthesise a model glyoxal system for investigation of this key reaction. As mentioned, model glyoxal 261 was initially chosen as a model substrate based on its anticipated ease of synthesis. Preparation of similar glyoxal-containing compounds, benzyl ether 267 and acetate ester 268, have independently been reported by the groups of Krische and Day, respectively. Both groups utilised a selenium dioxide oxidation of the corresponding methyl ketone to install the 1,2-dicarbonyl functionality (Scheme 2.57).144

Scheme 2.57. Proposed model system 261 and similar compounds found in the literature.142b, 144

A. Attempted Synthesis of Glyoxal 261 by α-Keto Oxidation

Given the precedent provided by the Krische and Day groups, it was envisioned that synthesis of model glyoxal 261 could be achieved in three steps from 3-methyl-2-butanone (269),142b using
an aldol reaction with formaldehyde, followed by protection and selenium dioxide-catalysed α-keto oxidation (Scheme 2.58).

\[
\begin{align*}
\text{269} & \rightarrow \text{270} \rightarrow \text{271} \rightarrow \text{261}
\end{align*}
\]

**Scheme 2.58.** Proposed synthesis of glyoxal 261 following the precedent of Krische and Day.\textsuperscript{142b}

An acid-catalysed aldol reaction of butanone 269 with formaldehyde afforded the thermodynamically favoured product 270 in 89% yield (Scheme 2.59). Subsequent protection of alcohol 270 as the p-methoxybenzyl ether proved surprisingly challenging. Attempts to prepare p-methoxybenzyl ether 271 under strongly basic conditions (PMBCl/TBAI/NaH) failed to generate any desired product 271. Instead the reaction afforded a complex mixture, thought to be due to a competing α-keto deprotonation pathway that led to a mixture of undesired aldol-type products. Milder conditions, for instance, heating alcohol 270 with p-methoxybenzyl chloride in neat diisopropylethylamine at reflux returned only clean starting material.\textsuperscript{145} On the other hand, treatment of alcohol 270 with freshly prepared p-methoxybenzyl-2,2,2-trichloroacetimidate (272) and catalytic CSA furnished ketone 271 in a modest 26% yield after 40 h (Scheme 2.59).\textsuperscript{146} A brief survey of stronger Brønsted or Lewis acids (TfOH, BF₃·OEt₂) led to rapid degradation of the starting material. As the reagents required for the preparation of 271 were inexpensive and easily obtained it was decided that sufficient material could be produced from the acetimidate/CSA procedure. Thus, synthetic efforts turned to the oxidation of ketone 271 to glyoxal 261.

\[
\begin{align*}
\text{269} & \rightarrow \text{270} \rightarrow \text{271} \rightarrow \text{261}
\end{align*}
\]

**Scheme 2.59.** Attempted synthesis of glyoxal 261 by oxidation of ketone 271.

Following the oxidation procedure of Krische and Cho, ketone 271 was treated with a stoichiometric quantity of selenium dioxide in refluxing dioxane/water (1:1) for 20 h (Table 2.4, entry 1).\textsuperscript{144} Pleasingly, inspection of the \( ^1\)H NMR spectrum of the crude reaction mixture suggested good conversion to the desired product 261, as indicated by a distinctive glyoxal proton resonance at \( \delta \) 9.22 ppm. In the crude \( ^{13}\)C NMR spectrum resonances at \( \delta \) 202.9 and
δ 188.6 ppm were observed, also indicative of a 1,2-dicarbonyl functionality. Notably, the ketone resonance for compound 271 at δ 212.9 ppm was absent from this spectrum, suggesting total consumption of the starting material. However, attempts to purify glyoxal 261 by chromatographic separation or Kugelrohr distillation, following literature methods, proved fruitless.

Disappointingly, further attempts to reproduce the oxidation of ketone 271 under the same conditions gave inconsistent results. In most instances, only trace quantities of glyoxal 261 were observed within complex product mixtures. Although messy, the crude 1H NMR spectrum often showed a new set of aldehyde and aromatic peaks, suggesting possible oxidative cleavage of the electron-rich benzyl ether. In order to suppress this undesired reactivity, ketone 271 was subjected to triethylamine-buffered selenium dioxide in tetrahydrofuran at reflux, a mild alternative for this transformation reported by Kozlowski and co-workers.147 Unfortunately, these conditions primarily returned starting material 271 alongside trace quantities of degradation products (entry 2).

Table 2.4. Attempted selenium dioxide-mediated α-oxidation

<table>
<thead>
<tr>
<th>entry</th>
<th>P</th>
<th>conditions</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMB</td>
<td>SeO₂, reflux dioxane/H₂O (1:1)</td>
<td>irreproducible 261</td>
</tr>
<tr>
<td>2</td>
<td>PMB</td>
<td>SeO₂, NEt₃, H₂O THF, reflux</td>
<td>returned 271</td>
</tr>
<tr>
<td>3</td>
<td>Ac</td>
<td>SeO₂, AcOH, reflux</td>
<td>trace 261, complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>Ac</td>
<td>SeO₂, AcOH, 80 °C</td>
<td>266 with trace 268</td>
</tr>
<tr>
<td>5</td>
<td>Ac</td>
<td>SeO₂, reflux dioxane/H₂O (1:1)</td>
<td>trace 268, complex mixture</td>
</tr>
</tbody>
</table>

In light of these results it appeared that replacing the p-methoxybenzyl ether with an alternative protecting group that was not oxidation labile would enable preparation of a suitable model glyoxal. As synthesis of the analogous acetate ester 268 has been reported in the literature by the Day group,144 this compound was chosen next for investigation. Following their procedure, ketone 266 was prepared in quantitative yield by one-pot aldol-esterification with formaldehyde and acetic acid (Scheme 2.60).
Disappointingly, attempts to reproduce the oxidation of ketone 266 performed by Day and co-workers (SeO\textsubscript{2} in refluxing acetic acid) afforded only trace quantities of the desired product 268 in our hands, alongside significant degradation (Table 2.4, entry 3, above). Repeating the reaction under modified conditions (\textit{i.e.} at a reduced temperature [80 °C] for a prolonged reaction time, or with excess selenium dioxide) failed to improve conversion of ketone 266 to glyoxal 268 (entry 4, above). Likewise, when ketone 266 was treated with selenium dioxide in dioxane/water (1:1) no glyoxal product was formed (entry 5, above). It is unclear what caused the underlying discrepancy observed for this oxidation between the Day group and the same reaction in our hands. However, subsequent analysis of the literature revealed that these oxidations are often highly dependent on the quality and source of selenium dioxide. In our case, an older bottle (purchased ~5 years prior to use) of commercially available selenium dioxide was used for all experiments.

\textbf{B. Attempted Synthesis of Glyoxal 261 by Kornblum Oxidation}

Following the unsuccessful attempts to prepare glyoxal 261 by selenium dioxide-mediated oxidation of the corresponding methyl ketone 271 we consulted the literature for an alternative procedure for the synthesis of this compound. Of the available strategies for the preparation of 1,2-dicarbonyl compounds, the Kornblum α-bromoketone oxidation\textsuperscript{149} seemed particularly suitable for glyoxal 261, as it had been successfully used by the Krische group during model studies for the synthesis of bryostatin 7 to prepare a similar α-quaternary glyoxal (Scheme 2.61).\textsuperscript{142a}
In this modification of the Kornblum oxidation, the reaction proceeds via nucleophilic substitution of dimethyl sulfoxide onto in situ-generated nitrate 276. Deprotonation by sodium acetate produces ylide 278, which then undergoes proton transfer through a five-membered transition state to produce glyoxal 279 (Scheme 2.62).150

Scheme 2.62. General mechanism for the Kornblum oxidation.149-150

To apply this methodology to the present work, bromide 280 was first prepared by treatment of 271 with bromine in methanol at −20 °C (Scheme 2.63). This compound was then subjected to Krische’s modified Kornblum oxidation conditions.142a Accordingly, bromide 280 was stirred with three equivalents of silver nitrate in a flask protected from light for 48 h, at which point TLC analysis indicated complete consumption of the starting material and formation of a white precipitate, presumed to be silver bromide. Unfortunately, after subsequent addition of a large excess dimethylsulfoxide and sodium acetate no further reaction was observed, even after prolonged reaction times (48 h).

Reagents and conditions: (a) Br2, MeOH, 2 h, −20 °C; (b) AgNO3, MeCN, 48 h, rt, then DMSO, NaOAc, 2 h, rt.

Scheme 2.63. Attempted synthesis of glyoxal 261 by Kornblum oxidation.

C. Attempted Synthesis of Glyoxal 285 by Enone Ozonolysis

Given the unsuccessful Kornblum reaction described above, enone ozonolysis was next examined as it has been used for the reliable preparation of a variety of 1,2-dicarbonyls.151 For instance, Cook and co-workers employed this strategy in the preparation of a variety of polyquinane derivatives using glyoxal 282 as a key intermediate (Scheme 2.64).151c
Reagents and conditions: (a) O₃, THF, −78 °C, then H₂, Pd/C, rt.

Scheme 2.64. Ozonolysis of enone 282 by Cook and co-workers.¹⁵¹c

It was anticipated that a similar enone ozonolysis reaction to that reported by the Cook group could be applied in the present work. Furthermore, we expected that an appropriate enone precursor for this transformation could be prepared by aldol condensation of the corresponding methyl ketone 283 and benzaldehyde. The tert-butylsilyl protected ketone 283 was chosen for investigation of this two-step procedure due to its perceived stability to the basic and oxidative conditions required for the aldol and ozonolysis reactions, respectively (Scheme 2.65).

Scheme 2.65. Proposed synthesis of glyoxal 285 by enone ozonolysis.

Accordingly, enone 284 was uneventfully prepared in three steps from ketone 270 in moderate yield. Unfortunately, attempted ozonolysis (O₃ then DMS or PPh₃) returned only a complex mixture which degraded upon attempted chromatographic separation (triethylamine buffered silica or neutral alumina) and purification of the major product spots (Scheme 2.66).

Reagents and conditions: (a) TBSCI, imidazole, DMF, 18 h, rt; (b) LHMDS, benzaldehyde, THF, 2 h, −78 °C; (c) MsCl, DBU, CH₂Cl₂, 3 h, reflux; (d) O₃, THF, 1 h, −78 °C, then PPh₃ or DMS.

Scheme 2.66. Attempted synthesis of glyoxal 285 by enone ozonolysis.
D. Attempted Synthesis of Glyoxal 285 by α-Hydroxyketone Oxidation

Oxidation of an α-hydroxyketone functionality by treatment with hypervalent iodine species 2-iodoxybenzoic acid (IBX) has also been used for the preparation of glyoxal compounds. To apply this methodology to the synthesis of glyoxal 285, it was envisioned that the corresponding hydroxyketone 286 precursor would first be prepared by Rubottom oxidation of ketone 283 (Scheme 2.67).


Mechanistically, Rubottom oxidation proceeds via epoxidation and acid-catalysed ring opening to produce intermediate oxonium ion 289, which undergoes facile silyl migration. The resultant α-silyloxyketone 291 is then readily hydrolysed to generate the hydroxyketone (Scheme 2.68).

Scheme 2.68. Proposed mechanism for the Rubottom oxidation.

In the present work, silyl ether derivative 293 was first prepared by treatment of ketone 283 with lithium bis(trimethylsilyl)amide followed by trimethylsilyl chloride. Following aqueous work-up the crude mixture was subjected to m-chloroperbenzoic acid in dichloromethane. Subsequent aqueous extraction of excess perbenzoic acid and rearrangement-desilylation with methanolic citric acid generated hydroxyketone in acceptable yield (Scheme 2.69).

Reagents and conditions: (a) LHMDS, TMSCl, THF, 2 h, −78 °C; (b) m-CPBA, CH₂Cl₂, 3 h, 0 °C; (c) citric acid, MeOH, 15 min, rt.285

Scheme 2.69. Synthesis of hydroxyketone 286 and attempted oxidation to glyoxal 285.
Unfortunately, attempted IBX oxidation in either dimethylsulfoxide\textsuperscript{154} or refluxing ethyl acetate\textsuperscript{155} proved unsuccessful, leading to immediate degradation of hydroxyketone 286 without any observed formation of glyoxal 285 (Table 2.5, entries 1 and 2). Alternatively, subjection of hydroxyketone 286 to Parikh-Doering oxidation conditions—which had been widely used for the mild preparation of aldehydes in the course of this work—produced a complex mixture (entry 3). Analysis of the crude $^1$H NMR spectrum showed the presence of a new resonance at $\delta$ 9.25 ppm, potentially indicative of glyoxal formation. Disappointingly, attempts to isolate the compound corresponding to this resonance proved unsuccessful, suggesting that if a glyoxal was indeed furnished under these conditions then it was insufficiently stable for standard purification techniques.

\textbf{Table 2.5.} Attempted synthesis of glyoxal 285 by oxidation of hydroxyketone 286

\begin{tabular}{|l|l|l|}
\hline
entry & Conditions & comments \\
\hline
1 & IBX, EtOAc, reflux, 16 h & degradation \\
2 & IBX, DMSO, rt, 16 h & degradation \\
3 & $\text{SO}_3\cdot$py, DMSO, $i$-Pr$_2$NEt, CH$_2$Cl$_2$, 0 $^\circ$C, 10 min & complex mixture \\
\hline
\end{tabular}
E. Synthesis of Glyoxal 297 by Diazoketone Oxidation

At this point, all attempts to prepare and isolate various glyoxal products by a number of different α-ketone oxidation strategies had thus far proved unsuccessful, with most oxidative conditions leading to rapid degradation, or a complex mixture of by-products. Furthermore, when crude NMR analysis suggested formation of the desired glyoxal product, this species rapidly degraded during attempted purification by flash chromatography or Kugelrohr distillation. In 1962, Ihmels and co-workers first reported the synthesis of glyoxal compounds from the corresponding diazoketone (Scheme 2.70).156 This transformation has since been used for the preparation of a number of sensitive dicarbonyl substrates.140,157 Of particular importance to the present work, acetone and nitrogen gas are the only by-products generated during this reaction, so clean glyoxal can typically be obtained upon concentration of the reaction mixture and used without further purification.

Scheme 2.70. Diazoketone oxidation with dimethyldioxirane by Ihmels and co-workers.156

In an attempt to circumvent the purification and degradation problems encountered during earlier attempted oxidations it was envisioned that glyoxal 297 might instead be prepared by treatment of diazoketone 296 with dimethyldioxirane. To apply this reaction to the present work, diazoketone 296 may be prepared from known carboxylic acid 295 (Scheme 2.71).

Scheme 2.71. Proposed synthesis of glyoxal 297 from known carboxylic acid 295.

To this end, diazoketone 296 was first prepared over four steps from neopentyl glycol (298). Initially mono-protection of neopentyl glycol with benzoyl chloride as the limiting reagent afforded alcohol 299 in 79% yield (Scheme 2.72). Parikh-Doering oxidation, followed by Pinnick oxidation of the resultant aldehyde 300 then furnished carboxylic acid 295 as white crystals. Pleasingly, a modest yield of diazoketone 296 could then be obtained via the corresponding acid chloride, prepared by treatment with oxalyl chloride and catalytic
dimethylformamide in dichloromethane. Alternatively, when thionyl chloride in dichloromethane was employed to generate the acid chloride this too gave low yields and returned significant starting material (Scheme 2.72).

Reagents and conditions: (a) BzCl, DMAP, CH₂Cl₂, 16 h, 0 °C; (b) SO₃∙py, DMSO, i-Pr₂NEt, CH₂Cl₂, 10 min, 0 °C; (c) NaClO₂, NaH₂PO₄, 2-methyl butene, THF/H₂O/t-BuOH (4:4:1), 15 h, 0 °C; (d) (COCl)₂, DMF, CH₂Cl₂, 3 h, rt; (e) TMSCHN₂ (2 M in hexane), MeCN, 16 h, rt.

Scheme 2.72. Synthesis of diazoketone 296.

The significant quantities of starting material returned during the transformation of carboxylic acid 295 to diazoketone 296 suggested that the conversion of carboxylic acid 295 to the corresponding acid chloride was incomplete, potentially due to steric hindrance from the α-quaternary centre. In 1999, the Nicolaou group reported a one-pot protocol for the synthesis of hindered diazoketones via diazomethane addition to a highly reactive in situ generated acyl mesylate intermediate,¹⁵⁹ a procedure that appeared appropriate for the synthesis of diazoketone 296 (Scheme 2.73).

Reagents and conditions: (a) MsCl, NEt₃, CH₂N₂, CH₂Cl₂, 40 min, 0 °C.

Scheme 2.73. Synthesis of hindered diazoketone 302 by Nicolaou and co-workers.¹⁵⁹

As diazomethane is a highly toxic and extremely sensitive explosive gas, we were interested in developing a modification of these conditions, employing TMS-diazomethane as a safer alternative. Unfortunately, when carboxylic acid 295 was treated with a large excess of mesyl chloride, triethylamine and TMS-diazomethane only started material was recovered after aqueous work-up. TLC analysis of the reaction mixture was unreliable so it is, as yet, unclear whether formation of the postulated intermediate acyl mesylate occurred, or if reactivity was limited by the poor nucleophilicity of TMS-diazomethane.
Regardless of the poor yield obtained during the synthesis of diazoketone 296, we decided that synthetic efforts were best spent on investigation of the transformation of this compound to glyoxal 297 and pressed forward to examine this reaction. When dimethyldioxirane—prepared as a dilute solution in acetone (69 mM) following the procedure of Taber and co-workers—was added to neat diazoketone 296 immediate gas evolution was observed, as expected for successful nitrogen-oxygen exchange. After the reaction mixture was concentrated under a stream of nitrogen, 1H NMR analysis showed clean conversion of diazoketone 296 to a mixture of glyoxal 297 and an unidentified side product (Scheme 2.74). Unfortunately, attempts to separate or purify these compounds in order to elucidate the structure of the by-product were met with frustration, although glyoxal formation was confirmed by 13C NMR, IR and mass spectral analysis (see experimental section for further details). Disappointingly, glyoxal 297 was found to degrade within minutes when stored in chloroform or as a neat oil, prohibiting its use in model aldol reactions.

\[
\begin{align*}
\text{N}_{2}\text{O} & \rightarrow \text{O} \\
296 & \text{O} \rightarrow \text{OBz} \\
297 & \text{O} \rightarrow \text{OBz}
\end{align*}
\]

Reaction conditions: (a) Dimethyldioxirane (69 mM in acetone), 2 min, rt.

Scheme 2.74. Synthesis of glyoxal 297.

F. Synthesis of Glyoxal 310 by Diazoketone Oxidation

Encouraged by the above transient formation of glyoxal 297 we set about the synthesis of glyoxal 306 using an analogous diazoketone oxidation strategy. We anticipated that glyoxal 306 may potentially have increased stability relative to glyoxal 297, as the increased carbon chain length between glyoxal and protected alcohol moieties could permit more conformational flexibility, and therefore reduce potential destabilising dipole interactions within these highly oxygenated compounds. Importantly, glyoxal 306 is also a closer structural analogue of the proposed coupling fragment 108 for the natural product synthesis (see Scheme 2.56, page 71). We envisioned that the carboxylic acid precursor for 306 might be accessed by ring opening of \( \gamma \)-butyrolactone 303 in the presence of benzyl bromide, following a procedure previously employed by our group for the synthesis of model spirocyclic systems (Scheme 2.75).\(^{161}\)

\[
\begin{align*}
\text{O} & \rightarrow \text{OBn} \\
\text{O} & \rightarrow \text{OBz} \\
\text{HO} & \rightarrow \text{OBn} \\
\text{N}_{2}\text{O} & \rightarrow \text{OBn} \\
\text{O} & \rightarrow \text{OBn}
\end{align*}
\]

Scheme 2.75. Proposed synthesis of glyoxal 306.
Dimethylation of γ-butyrolactone (201) proceeded readily to give lactone 303, which was used without purification. Subsequent potassium hydroxide-mediated ring opening under Dean-Stark reflux in the presence of excess benzyl bromide afforded ester 307. Saponification with aqueous potassium hydroxide furnished carboxylic acid 304 in a modest 34% yield over three steps. However, attempts to prepare diazoketone 305 by treatment of carboxylic acid 304 with oxalyl chloride and catalytic dimethylformamide, followed by TMS-diazoketone, led to degradation products (Scheme 2.76). This result was somewhat surprising, given the earlier successful conversion of benzoate ester-containing carboxylic acid 295 to diazoketone 296 under the same conditions.

![Scheme 2.76. Attempted synthesis of diazoketone 305.](image)

Reagents and conditions: (a) MeI, NaH (60% w/w in mineral oil), THF, 3 h, reflux; (b) KOH, BnBr, toluene, 13 h, Dean-Stark reflux; (c) KOH, MeOH/H₂O (2:1), 16 h, reflux; (d) (COCl)₂, DMF, CH₂Cl₂, 3 h, rt; (e) TMSCHN₂ (2 M in hexane), MeCN, 16 h, rt.

Given the discrepancy in reactivity between carboxylic acids 295 and 304, we hypothesised that the benzyl ether of 304 was facilitating degradation. To test this hypothesis, benzyl ether 304 was subjected to ruthenium(VIII) catalysed oxidation, affording benzoate ester 308 in 89% yield (Scheme 2.77). Pleasingly, treatment of ester 308 with oxalyl chloride and catalytic dimethylformamide afforded diazoketone 309 in 47% yield, alongside returned starting material. Further experimentation led to the discovery that gradual addition of excess oxalyl chloride (4 equivalents) and dimethylformamide (3 equivalents) concurrently over 3 h gave full conversion of carboxylic acid 308 to the corresponding acid chloride, alongside significant quantities of a yellow precipitate presumed to be the Vilsmeier reagent.¹⁶² Complete removal of this solid could be achieved by dilution of the reaction mixture with pentane and filtration through a plug of silica. After concentration of the filtrate under a stream of nitrogen gas, the resultant oil was stirred with TMS-diazomethane in acetonitrile furnishing diazoketone 309 in a gratifying 91% yield (Scheme 2.77). To our delight, addition of a solution of dimethyldioxirane (69 mM in acetone) to diazoketone 309 gave instantaneous conversion to glyoxal 310, as evidenced by TLC analysis and nitrogen gas generation (Scheme 2.77). The structure of glyoxal...
310 was confirmed on the basis of mass spectral analysis ([M+Na] m/z = 271.0941, found 271.0935) and full NMR characterisation.

Reagents and conditions: (a) NaIO₄, RuCl₃·xH₂O, EtOAc/H₂O (2:1), 3 h, rt; (b) (COCl)₂, DMF, CH₂Cl₂, 2 h, rt; (c) TMSCHN₂ (2 M in hexane), MeCN, 16 h, rt; (d) dimethyldioxirane (69 mM in acetone), 2 min, rt.

Scheme 2.77. Synthesis of glyoxal 310.

Unfortunately, glyoxal 310 was highly unstable, degrading within minutes when stored neat at room temperature. However, this compound could be readily converted into the corresponding hydrate 311, upon dissolution in a mixture of deuterated acetone/water (1:1) (Scheme 2.78). Disappointingly, although hydrate 311 was found to be relatively stable in solution (t₁/₂ = ~24 h), it also degraded immediately upon attempted isolation.

Reagents and conditions: (a) H₂O, 2 min, rt.

Scheme 2.78. Synthesis of hydrate 311 from glyoxal 310.

Despite the instability of glyoxal 310 and hydrate 311, these compounds still appeared to be viable coupling partners in model Mukaiyama aldol reactions, provided they were used immediately upon generation. As such, attention turned to investigation of this key Mukaiyama aldol step.
2.3.4 Mukaiyama Aldol Using a Glyoxal Electrophile

There are a limited number of examples of Mukaiyama aldol reactions employing glyoxal compounds as electrophiles, almost all of which employ simple, achiral transition metal Lewis acid catalysts. However, in the present work it was anticipated that there would be little substrate-derived stereoinduction and a chiral catalytic system would be required to achieve high levels of stereocontrol. Thus, the challenge posed by this transformation was two-fold: (i) to identify a suitable catalytic system for the reaction of silyl enol ether 315 and glyoxal 310 using Lewis acids described in the literature for glyoxal aldol reactions and, (ii) to modify the catalytic system to facilitate an enantioselective transformation.

Scheme 2.79. Proposed Mukaiyama aldol fragment coupling for the synthesis of portimine (above) and model coupling of silane 315 with glyoxal 310 (below).

A. Initial Investigations

With synthetic access to unstable glyoxal 310 secured, attention turned to its application in model aldol coupling studies. Initial efforts aimed at identifying appropriate Mukaiyama aldol coupling conditions, employing acetophenone-derived silyl enol ether 318 as a model for the polyketide fragment (Scheme 2.80). Silyl enol ether 318 was chosen for these early experiments for several reasons; in particular: (i) there is more precedent for the use of aryl silanes such as 318 in glyoxal aldol couplings than there is for aliphatic silanes such as 312, 313, or 314; (ii) acetophenone may be removed in vacuo from product mixtures enabling straightforward NMR analysis without laborious purification and; (iii) silyl enol ether 318 is readily accessible from commercially
available acetophenone whereas polyketide silanes 312, 313, and 314 must be prepared over a ten step sequence.

Scheme 2.80. Initial model system for optimisation of the Mukaiyama glyoxal fragment coupling.

Initial reaction conditions for the union of silyl enol ether 318 with glyoxal 310 were based on literature precedent for aldol couplings that employed a glyoxal electrophile. Silyl enol ether 318 was prepared by treatment of acetophenone with the trimethylsilyl triflate in the presence of triethylamine, followed by mild acidic aqueous extraction (0.5 M citric acid). The crude 1H NMR spectrum indicated complete and clean conversion in all cases, and silyl enol ether 318 was thus used without further purification (Table 2.6).

Following the procedure developed by the Mukaiyama group, freshly prepared glyoxal 310 was added dropwise to a solution of silyl enol ether 318 premixed with titanium tetrachloride, although this led immediately to rapid degradation (Table 2.6, entry 1).\textsuperscript{164} Likewise, when the bulkier tert-butyldimethylsilyl enol ether 320 was employed as the nucleophile similar degradation was also observed. When dichlorotitanium diisopropoxide, a weak Lewis acid, was employed for the reaction of silyl enol ether 318 with glyoxal 310, formation of a complex mixture was observed after 6 h (Table 2.6, entry 3). Likewise, no desired product 319 was obtained from the complex mixture formed during the reaction of glyoxal 310 with silyl enol ether 318 in the presence of catalytic scandium triflate (Table 2.6, entry 4).\textsuperscript{165}

Ytterbium(III) triflate has been shown to effect Hosumi-Sakurai allylation of phenylglyoxal in aqueous media.\textsuperscript{163} We were thus intrigued to see whether this catalytic system would also prove suitable for an analogous Mukaiyama aldol reaction. Thus, glyoxal 310 and silyl enol ether 318 were treated with ytterbium(III) triflate in aqueous tetrahydrofuran, although these conditions only resulted in the transient formation of glyoxal hydrate 311 followed by degradation of both starting materials (Table 2.6, entry 4). Boron trifluoride-mediated Mukaiyama aldol reactions have been successfully employed by our group in natural product synthesis\textsuperscript{166} and this Lewis acid has been shown to catalyse allylation of glyoxals.\textsuperscript{167} However, in our hands the attempted
boron trifluoride-catalysed reaction of glyoxal 310 and silane 318 resulted in a complex mixture, without formation of the desired hydroxydione 319 (Table 2.6, entry 7).

**Table 2.6.** Model fragment coupling of glyoxal 310 and acetophenone derived silanes 318, 320, and 321

<table>
<thead>
<tr>
<th>entry</th>
<th>R₃SiOTf</th>
<th>Lewis acid</th>
<th>conditions</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf</td>
<td>TiCl₄</td>
<td>CH₂Cl₂, 2 h, −78 °C</td>
<td>trace 322</td>
</tr>
<tr>
<td>2</td>
<td>TBSOTf</td>
<td>TiCl₄</td>
<td>CH₂Cl₂, 2 h, −78 °C</td>
<td>trace 322</td>
</tr>
<tr>
<td>3</td>
<td>TMSOTf</td>
<td>Ti(Oi-Pr)₂Cl₂</td>
<td>toluene, 6 h, −78 °C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>TMSOTf</td>
<td>Sc(OTf)₃</td>
<td>THF, 12 h, −78 °C → rt</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>TMSOTf</td>
<td>Yb(OTf)₃</td>
<td>MeCN, 12 h, 0 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>6</td>
<td>TMSOTf</td>
<td>Yb(OTf)₃</td>
<td>THF/H₂O (4:1), 12 h, rt</td>
<td>degradation</td>
</tr>
<tr>
<td>7</td>
<td>TMSOTf</td>
<td>BF₃</td>
<td>CH₂Cl₂, 2 h, −78 °C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>TMSOTf</td>
<td>Cu(OTf)₂</td>
<td>CH₂Cl₂, 12 h, −78 °C → rt</td>
<td>degradation</td>
</tr>
<tr>
<td>9</td>
<td>TMSOTf</td>
<td>Cu(OTf)₂/(+)-72</td>
<td>CH₂Cl₂, 24 h, −20 °C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>10</td>
<td>TBSOTf</td>
<td>Cu(OTf)₂/(+)-72</td>
<td>CH₂Cl₂, 24 h, −20 °C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>11</td>
<td>TIPSOTf</td>
<td>In(OTf)₃/(+)-328</td>
<td>CH₂Cl₂, 12 h, −20 °C</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

*Reactions were performed on diazoketone 309 (25 mg) with acetophenone (2 eq.). Neither glyoxal 310 or intermediate silane were purified before use.

Inspired by the growing body of literature on enantioselective Mukaiyama aldol reactions between glyoxylates and silyl enol ethers, we decided to investigate whether these same conditions could be applied to the union of glyoxals and silyl enol ethers. For instance, the Evans group has employed C₂-symmetric copper(II) complexes as chiral Lewis acids for the addition of ketene silyl thioacetals to glyoxylate and pyruvate esters. In this system, bidentate glyoxylate substrate-catalyst coordination is postulated to generate a square planar complex, activating the glyoxylate to nucleophilic addition (Scheme 2.81). Unfortunately, when this methodology was applied to the coupling of glyoxal 310 and either silyl enol ether 318 or 320...
in the present work, only degradation of glyoxal 310 was observed in the mixture of reaction products (Table 2.6, entries 9 and 10).

Scheme 2.81. Proposed mechanism for the Cu(II)-box catalysed Mukaiyama aldol.\textsuperscript{168a-c}

More recently, the Loh group reported the indium(III)-pybox complex-catalysed Mukaiyama aldol reaction of glyoxylates and enolsilanes derived from aryl ketones (Scheme 2.82).\textsuperscript{78c, 102} Notably, this catalytic system was found to be uniquely efficient for catalysing reactions involving acetophenone-derived silane nucleophiles. Glyoxylate chelation to indium(III) is thought to generate a facially discriminated complex, conferring an impressive degree of stereoselectivity during the nucleophilic addition of silyl enol ether 327 ($ee = 90$–$98\%$). However, when glyoxal 310 and triisopropylsilyl enol ether 321 were treated with a mixture of pybox ligand 329 and indium(III) triflate in acetonitrile, no hydroxydione 319 was observed by NMR analysis of the complex mixture obtained upon aqueous work-up of the reaction mixture (Table 2.6, entry 11, above).

Reagents and conditions: (a) InBr$_3$ (5 mol%), AgSbF$_6$ (5 mol%) (+)-329 (6 mol%), 4 Å molecular sieves, MeCN, 19 h–70 h, $–20$ °C.

Scheme 2.82. Enantioselective glyoxylate Mukaiyama aldol by Loh and co-workers.\textsuperscript{143c}

The lack of reactivity between silane 321 and glyoxal 319 in the present work contrasts with the excellent yields obtained by Loh and co-workers using the same silane 319 with glyoxylate electrophiles (compare Table 2.6, entry 11 with Scheme 2.82, both above). Intrigued by this
discrepancy, we hypothesised that these differing reactivity rates may be due to the relative ability of glyoxal and glyoxylate substrates to undergo bidentate coordination to a metal catalyst. Although glyoxylate bidentate coordination is well documented, there are very few examples of glyoxal compounds coordinating in the same way. This difference may be partially explained by inspection of the glyoxal bond geometry. For example, gas-phase electron diffraction experiments have revealed that the carbonyl groups of phenyl glyoxal (330) are non-planar with a torsional angle O=C—C=O of 130°, likely due to unfavourable dipole-dipole interactions. Importantly, no evidence for the presence of a second conformer was found in the experiments, suggesting the cis-conformation of glyoxal compounds (required for bidentate coordination) is highly unfavourable (Scheme 2.83).

Scheme 2.83. Torsional angle and favoured conformation of phenyl glyoxal.

B. Oxazaborolidine-Aluminium Bromide Catalysed Aldol Reactions

In 2006, the Corey group reported the use of chiral oxazaborolidine-aluminum bromide complex 332 for enantioselective Diels-Alder reactions of enone dienophiles. Previous work within our group utilised this catalyst for the cycloaddition of silyloxydiene 102 with enone 333 (Scheme 2.84).

Scheme 2.84. Diels-Alder reaction of enone 333 and silyloxydiene 102 using Corey’s oxazaborolidine-aluminum bromide complex 332.
Although the reaction proceeded smoothly at −78 °C, almost total desilylation of diene 102 was observed when the mixture was allowed to warm to −30 °C. Based on this observation, it was postulated that in the appropriate reaction conditions the oxazaborolidine-aluminum bromide complex 332 may facilitate Mukaiyama aldol reaction for application in the present work (Scheme 2.85).

Scheme 2.85. Proposed oxazaborolidine-aluminum bromide complex 332 catalysed Mukaiyama aldol reaction.

To explore this hypothesis, freshly prepared glyoxal 310 and two equivalents of silyl enol ether 320 were added to premixed (S)-oxazaborolidine 331 and aluminium bromide at −60 °C. To our delight, the reaction afforded hydroxydione 319, albeit in low yield alongside significant desilylation (Table 2.7, entry 1). Encouraged by this result we conducted a brief substrate scope study to probe the potential of this novel catalytic system for the Mukaiyama aldol reaction. Moderate yields could be achieved from Mukaiyama aldol reactions using simple aldehyde 146 with either aryl silane 320 or aliphatic silane 339 as the limiting reagent (Table 2.7, entries 2 and 3). It is worth noting that in both cases the reaction proceeded cleanly, with desilylated ketones 317 and 212 isolated as the major side products from each reaction. Interestingly, attempts to suppress this undesired desilylation by performing the reaction at −90 °C with the less labile triisopropylsilyl enol ether 340 proved unsuccessful (Table 2.7, entry 4). Likewise, dropwise addition of silane 339 over 20 min had little effect on product yield (Table 2.7, entry 5).
Table 2.7. Optimisation of the Mukaiyama aldol reaction catalysed by oxazaborolidine-aluminium tribromide complex 332

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>silane</th>
<th>aldehyde</th>
<th>conditions</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^de$</td>
<td><img src="ketone1.png" alt="Image" /></td>
<td><img src="silane1.png" alt="Image" /></td>
<td><img src="aldehyde1.png" alt="Image" /></td>
<td>A: TBSOTf B: 2 eq 310</td>
<td><img src="product1.png" alt="Image" /></td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td><img src="ketone2.png" alt="Image" /></td>
<td><img src="silane1.png" alt="Image" /></td>
<td><img src="aldehyde2.png" alt="Image" /></td>
<td>A: TBSOTf</td>
<td><img src="product2.png" alt="Image" /></td>
<td>52 (341) 27 (317)</td>
</tr>
<tr>
<td>3</td>
<td><img src="ketone3.png" alt="Image" /></td>
<td><img src="silane3.png" alt="Image" /></td>
<td><img src="aldehyde3.png" alt="Image" /></td>
<td>A: TBSOTf</td>
<td><img src="product3.png" alt="Image" /></td>
<td>35 (342) 41 (212)</td>
</tr>
<tr>
<td>4</td>
<td><img src="ketone4.png" alt="Image" /></td>
<td><img src="silane4.png" alt="Image" /></td>
<td><img src="aldehyde4.png" alt="Image" /></td>
<td>A: TIPSOTf B: $-90, ^\circ C$</td>
<td><img src="product4.png" alt="Image" /></td>
<td>24 (342) 48 (212)</td>
</tr>
<tr>
<td>5</td>
<td><img src="ketone5.png" alt="Image" /></td>
<td><img src="silane3.png" alt="Image" /></td>
<td><img src="aldehyde4.png" alt="Image" /></td>
<td>A: TBSOTf B: $-70, ^\circ C$, dropwise addition of silane</td>
<td><img src="product5.png" alt="Image" /></td>
<td>16 (342) 66 (212)</td>
</tr>
</tbody>
</table>

$^a$Reactions were performed on ketone 317 or 212 (25 mg) with aldehyde 146/glyoxal 310 (1.6 eq.) unless otherwise noted. Intermediate silanes were not purified before use. $^b$Neither the absolute configuration of the newly formed alcohol stereocenter or the stereoselectivity were conclusively determined for these experiments. $^c$Yield reported over two steps from ketone 212 unless otherwise noted. $^d$Yield based on diazoketone 309 (25 mg) over two steps. $^e$Glyoxal 310 was prepared from diazoketone 309 and used without purification.

Careful examination of the literature revealed that Rhu and co-workers performed a similar Mukaiyama aldol. In this work, silyl ketene acetal 344 was reacted with a wide variety of aldehydes upon treatment with cationic oxazaborolidinium catalyst 346 (Scheme 2.86). Notably, Rhu found that triphenylphosphine oxide was an essential additive to achieve high enantioselectivities ($ee = 74–93\%$ with $PPh_3O$ [50 mol\%] vs. $ee = 20\%$ without).
Triphenylphosphine oxide is thought to coordinate to cationic silicon species generated during the reaction, preventing them from promoting a racemic reaction pathway.\textsuperscript{171}

\[
\text{RCHO} + \text{MeO} \text{SiMe}_3 \xrightarrow{(a) \text{ 70-96\%}} \text{RCH(O)O} \text{Me} \\
\text{Reagents and conditions: (a) 346 (20 mol\%), PPh}_3\text{O (50 mol\%), toluene, 15–48 h, −40 °C, then TBAF (1 M in THF).}
\]

Scheme 2.86. Enantioselective Mukaiyama aldol by Rhu and co-workers.\textsuperscript{171}

Given the beneficial effect of triphenylphosphine oxide observed by the Rhu group in a similar Mukaiyama aldol reaction, we repeated the oxazaborolidine-aluminum bromide complex 332 catalysed reaction of silane 339 and aldehyde 146 in the presence of this additive. However, in this instance only a trace quantity of product 342 was obtained, alongside significant desilylation (Scheme 2.87). There are a variety of plausible explanations for the differing impact of triphenylphosphine oxide between the Mukaiyama aldol reactions performed by the Rhu group and the present work. For instance, as oxazaborolidine-aluminum bromide complexes are known to be more active Lewis acid complexes than the oxazaborolidinium triflate used by Rhu,\textsuperscript{170} it may be that triphenylphosphine oxide is able to irreversibly coordinate to the former—inhibiting the catalytic cycle—but not the latter. However, these and other mechanistic considerations were not probed in further detail.

\[
\text{Reagents and conditions: (a) TBSOTf, NEt}_3, \text{CH}_2\text{Cl}_2, 1 \text{ h, −10 °C; (b) 146, 332 (20 mol\%), PPh}_3\text{O (50 mol\%), toluene, 2 h, −60 °C.}
\]

Scheme 2.87. Oxazaborolidine-aluminium bromide complex-catalysed Mukaiyama aldol reaction in the presence of triphenylphosphine oxide.

Further optimisation of the oxazaborolidine-aluminum bromide complex-catalysed Mukaiyama aldol reaction using aldehyde 146 was not pursued, as our primary aim was to effect an aldol reaction between glyoxal 310 and an aliphatic methyl ketone (eg. 212), in order to model the key
fragment coupling of portimine. Thus, focus instead turned to this transformation. However, to
our disappointment, when silane 339 and excess glyoxal 310 were treated with oxazaborolidine-
aluminum bromide complex 332 in toluene at −60 °C, no product was observed (Scheme 2.88).

Reagents and conditions: (a) TBSOTf, NEt3, CH2Cl2, 1 h, −10 °C; (b) DMDO (69 mM in acetone), 2 min, rt; (c) 332 (20 mol%), toluene, 2 h, −60 °C.

Scheme 2.88. Attempted Mukaiyama aldol reaction between silyl enol ether 339 and glyoxal 310.

As repeated attempts to effect the coupling of glyoxal 310 with silyl ether 339 proved fruitless,
it became clear that the oxazaborolidine-aluminum bromide complex 332 catalysed Mukaiyama
aldol reaction was not suitable for application in the present work. Thus, the scope and
optimisation of this catalytic system was put to one side, and attention returned to finding
appropriate glyoxal aldol coupling conditions.

2.3.5 Asymmetric Glyoxal Aldol Using a \( N,N' \)-Dioxide-Nickel(II) Catalyst

Recently, the Feng group has developed a novel asymmetric \( N,N' \)-dioxide-nickel(II) complex to
catalyse the Mukaiyama aldol reaction of aryl glyoxal electrophiles. This system is the only
chiral catalyst that has been shown to be effective for this transformation. Although good yields
and high enantioselectivities were achieved by the Feng group the substrate scope was limited
to the coupling of acetophenone-derived silanes with aryl glyoxal compounds. However, in the
present work, the desired coupling required the use of two aliphatic derivatives, namely silane
352 and glyoxal 310, potentially representing a significant extension of the Feng group’s work
(Scheme 2.89). Undeterred by the limited substrate scope reported by Feng and co-workers for
the \( N,N' \)-dioxide-nickel(II) complex catalysed Mukaiyama aldol reaction we were eager to
investigate the suitability of this transformation for the present work.
Reagents and conditions: (a) 351 (12 mol%), Ni(BF₄)₂·6H₂O (10 mol%), CH₂Cl₂, 20–28 h, 30 °C.

Scheme 2.89. Enantioselective Mukaiyama aldol by the Feng group (above) and proposed reaction of silyl enol ether 352 and glyoxal 310 (below).
A. Synthesis of N,N'-Dioxide Ligand 351

The requisite N,N'-dioxide ligand 351 was prepared uneventfully over four steps. Following literature procedures, Boc-L-proline (353) was first treated with iso-butyl chloroformate and 2,6-diethylaniline to afford amide 354. Trifluoroacetic acid-catalysed deprotection and alkylation of the resultant amine with half an equivalent of 1,3-dibromopropane furnished diamine 356 in excellent yield over three steps. m-Chloroperbenzoic acid-mediated oxidation of diamine 356 produced ligand 351 in 97% yield (Scheme 2.90).^{172-173}

![Scheme 2.90. Synthesis of N,N-dioxide ligand 351 following the Feng group’s procedure.^{172-173}]

Reagents and conditions: (a) i-butyl chloroformate, NEt₃, 2,6-diethylaniline, CH₂Cl₂, 20 h, rt; (b) TFA/CH₂Cl₂ (1:1), 1 h, rt; (c) 1,3-dibromopropane, K₂CO₃, MeCN, 15 h, reflux; (d) m-CPBA, CH₂Cl₂, 2 h, rt.

B. Discovery of a Novel Ene-Type Reaction Between Silane 359 and Glyoxal 310

With ligand 351 prepared, the stage was set for investigation of the Mukaiyama aldol coupling. Following the procedure of Feng and co-workers, silyl enol ether 352 and glyoxal 310 were simultaneously added to nickel(II) tetrafluoroborate complexed with ligand 351 in dichloromethane. To our delight, small quantities of hydroxydione 347 were obtained from the reaction mixture in good stereoselectivity (13:1 dr) (Scheme 2.91).
Reaction conditions: (a) TMSOTf, NEt₃, CH₂Cl₂, 1 h, −10 °C; (b) DMDO (69 mM in acetone), 2 min, rt; (c) 351 (10 mol%), Ni(BF₄)·6H₂O (10 mol%), CH₂Cl₂, 8 h, 25 °C.

Scheme 2.91. Mukaiyama aldol reaction of silane 352 and glyoxal 310 using Feng’s catalyst.¹⁴³c

Stereoselectivity was determined by comparison of the relative integral of the newly formed epimeric hydroxyl proton. By analogy with the transition state proposed by the Feng group for this transformation, whereby the silyl enol ether undergoes nucleophilic addition to a facially discriminated, activated glyoxal complex,¹⁴³c the newly generated C-5 stereogenic centre was assigned as the desired S configuration (Scheme 2.92).

Scheme 2.92. Favourable transition state for the glyoxal Mukaiyama aldol, proposed by the Feng group.¹⁴³c

It appeared that reaction performance was primarily limited by a competing desilylation of enol ether 352. Thus, initial optimisation attempts focused on the use of the more hindered t-butyldimethylsilane 339. Interestingly, the major product from the reaction of silane 339 and glyoxal 310 was silyl enol ether 357, isolated as a 14:1 diastereomeric mixture in 29% yield.
Silyl enol ether is postulated to form via an *ene*-type mechanism (Scheme 2.93), a well-documented reaction pathway for *N,N*-dioxide-metal catalysis. \(^{174}\)

**Scheme 2.93. Proposed formation of silyl enol ether 357 via an ene-type mechanism.**

Although the relative stereochemistry of silyl enol ether 357 was not conclusively demonstrated, we reasoned that if both the *N,N*-dioxide-nickel(II) complex-catalysed *ene* and aldol reactions proceed by nucleophilic attack to an activated glyoxal species—following the transition state proposed by Feng—then the facial discrimination governing product stereoselectivity should be the same in both instances. Therefore, both silane 357 and dione 347 should have the desired *S* configuration at the newly formed stereogenic centre.

Standing silane 357 in deuterated chloroform overnight resulted in clean cleavage of the silyl ether, affording hydroxydione 347 (Scheme 2.94). Presumably, this desilylation is catalysed by residual acid formed from the degradation of wet chloroform. Importantly, the NMR spectral data obtained from hydroxydione 347 produced in this way was identical to the spectra obtained from the aldol formed from the addition of trimethylsilyl enol ether 352 with glyoxal 310, providing further evidence that the *N,N*-dioxide-nickel(II) complex catalysed *ene* and aldol reactions proceed with the same facial selectivity.

**Scheme 2.94. Hydrolysis of silane 357 during NMR characterisation.**

As silyl enol ether 357 could be readily hydrolysed to produce the desired hydroxydione functionality (Scheme 2.94, above), we realised that either the *ene* reaction of a hindered silyl enol ether or an aldol coupling of a trimethylsilyl enol ether would be suitable for the key fragment coupling of portimine. Furthermore, increasing the steric bulk of the silyl enol ether
from TMS-derivative \textbf{352} to TBS-derivative \textbf{339} gave slightly improved reaction yield and stereoselectivity (21\%, 13:1 \textit{dr} vs. 29\%, 14:1 \textit{dr}), albeit by changing the reaction from an aldol coupling to an \textit{ene}-type mechanism. This improvement in yield was primarily attributed to a significant decrease in the rate of competing silyl ether hydrolysis. Further optimisation efforts therefore involved the preparation and use of the more hindered triisopropylsilyl enol ether derivative \textbf{340}. Unfortunately, when triisopropylsilyl enol ether \textbf{340} was reacted with glyoxal \textbf{310} in the presence of $N,N'$-dioxide \textbf{351} and nickel(II) tetrafluoroborate and the resultant silyl ether product hydrolysed in wet chloroform, only 23\% of hydroxydione \textbf{347} was produced (Table 2.8, entry 2). However, in this case, TLC analysis of the \textit{ene} reaction mixture showed negligible competing desilylation prior to work-up, in contrast to the reactions of silanes \textbf{352} and \textbf{339}. Rather, it appeared that when triisopropylsilyl enol ether \textbf{340} was employed in this reaction the sole factor limiting the yield of the desired product was the stability of glyoxal \textbf{310} to the reaction conditions.
Table 2.8. Optimisation of $N,N'$-dioxide-nickel(II) complex-catalysed $\textit{ene}$-type reaction$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>silane</th>
<th>time</th>
<th>product</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>212</td>
<td>339</td>
<td>24 h</td>
<td>347</td>
<td>29 (347, 14:1 dr) 17 (212)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>212</td>
<td>340</td>
<td>40 h</td>
<td>347</td>
<td>19 (347, 14:1 dr) 44 (212)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>358</td>
<td>359</td>
<td>24 h</td>
<td>360</td>
<td>16 (360, &gt;19:1 dr) 48 (358)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4$^c$</td>
<td>358</td>
<td>359</td>
<td>24 h</td>
<td>360</td>
<td>32 (360, &gt;19:1 dr) 55 (358)</td>
</tr>
</tbody>
</table>

$^a$Reactions were performed on ketone 212 or 358 (25 mg) with glyoxal 310 (1.3 eq.) unless otherwise noted. Neither silane 339, 340 or 359 were purified before use. $^b$Yield reported over three steps from starting ketone. $^c$Glyoxal 310 (3 eq.) was added in three portions over 3 h.

Further optimisation was conducted employing the tert-butyldimethylsilyl enol ether derived from ketone 358 with glyoxal 310. Ketone 358 possesses terminal alkyne functionality that may be readily elaborated to a vinyl or alkynyl bromide for synthesis of model macrocyclic substrates. Ketone 358 was prepared by treatment of acetal 226 with acidic Amberlyst 15 resin (Scheme 2.95), following a procedure previously employed in the present work (see Scheme 2.37, page 57).
Initial attempts to effect the ene-type reaction of silyl enol ether 359 with glyoxal 310 afforded moderate conversion to the resultant silane, alongside rapid degradation of glyoxal 310 (Table 2.8, entry 3, above). Further optimisation of this reaction employed a larger excess of glyoxal 310 (3 equivalents, added in three portions over a period of 3 h) and afforded an improved yield of intermediate silane, which was immediately converted to hydroxydione 360 (Table 2.8, entry 4). In this reaction, only minimal concomitant desilylation of enol ether 359 was observed prior to work-up, suggesting improved yields could be achieved using an even larger excess of unstable glyoxal 310. Although this may have been a viable strategy for the Mukaiyama aldol reaction of glyoxal 310 and ketone 358, we were mindful that this system was a model for the coupling of ketone 241 or 242 with glyoxal 108, a significantly more complex and valuable substrate (see Scheme 2.56, page 71). As such, further optimisation of the N,N'-dioxide-nickel(II) complex-catalysed Mukaiyama aldol reaction was not pursued and instead our attention turned to an alternative coupling strategy that did not require the use of unstable glyoxal intermediates.
2.3.6 Glyoxal Aldol Summary

A. Synthesis of Model Glyoxals 297 and 310

Preparation of model glyoxals 297 and 310 were achieved in six and eight steps, from γ-butyrolactone (201) and neopentyl glycol (298), respectively (Scheme 2.96). These compounds were both found to be highly unstable, degrading within minutes at room temperature preventing purification and full characterisation in the case of glyoxal 297.

\[
\begin{align*}
\text{HO-} & \text{H} & \text{O} & \text{3 steps} & \text{HO-} & \text{O} & \text{Bz} & \text{(a), (b)} & \text{34\% (2 steps)} & \text{HO-} & \text{O} & \text{Bz} & \text{(c)} & \text{HO-} & \text{O} & \text{Bz} \\
298 & & & & 295 & & & 296 & & 297
\end{align*}
\]

Reagents and conditions: (a) (COCl)₂, DMF, CH₂Cl₂, 2–5 h, rt; (b) TMSCHN₂ (2 M in hexane), MeCN, 13–16 h, rt; (c) DMDO (69 mM in acetone), 2 min, rt.

Scheme 2.96. Synthesis of model glyoxals 297 and 310.

B. Application of Corey’s Oxazaborolidine-Aluminium Bromide Complex 332

Extensive investigation of Mukaiyama aldol reaction of acetophenone-derived silyl enol ether 320 with glyoxal 310 uncovered a novel catalytic system for this transformation, namely use of Corey’s oxazaborolidine-aluminium bromide complex 332 (Scheme 2.97). A brief substrate scope study indicated that this catalytic system may be broadly applicable and merits further optimisation and examination of its stereoselectivity. However, attempts to effect Mukaiyama aldol of silyl enol ether 339 and glyoxal 310 in the presence of oxazaborolidine-aluminium bromide complex 332 proved unsuccessful and further development of this catalytic system was not pursued.
Reagents and conditions: (a) TBSOTf, NEt₃, CH₂Cl₂, 1 h, −10 °C; (b) 332 (20 mol%), toluene, 2 h, −60 °C; (c) DMDO (69 mM in acetone), 2 min, rt.

Scheme 2.97. Oxazaborolidine-aluminium bromide complex-catalysed Mukaiyama aldol reaction.

C. Application of Feng’s N,N’-Dioxide-Nickel(II) Complex

Treatment of silyl enol ether 358 and glyoxal 310 with Feng’s N,N’-dioxide-nickel(II) complex in dichloromethane afforded silane 362 via an ene-type reaction mechanism. Silane 362 could be smoothly converted to the corresponding hydroxydione 360 when subjected to trace hydrochloric acid in chloroform in 32% over three steps (Scheme 2.98). However, as a relatively large excess of unstable glyoxal 310 was required to achieve this yield, we were concerned that similar problems would be encountered during the synthesis and Mukaiyama aldol of more elaborate glyoxal 108, rendering this route unfeasible for the proposed portimine fragment coupling.
Reagents and conditions: (a) TMSOTf, NEt$_3$, CH$_2$Cl$_2$, 1 h, −10 °C; (b) DMDO (69 mM in acetone), 2 min, rt; (c) 351 (10 mol%), Ni(BF$_4$)$_2$$\cdot$6H$_2$O (10 mol%), CH$_2$Cl$_2$, 8 h, 25 °C; (d) trace HCl in CHCl$_3$, 10 h, rt.

Scheme 2.98. Mukaiyama aldol coupling of silane 359 with model glyoxal 310 using Feng’s catalyst.$^{143c}$
2.4 Model Enone Aldol Fragment Coupling

Given the difficulties encountered during the preparation and aldol reaction of glyoxal 310, an alternative coupling strategy was sought in order to circumvent the use of this unstable functionality. Conceivably, directed aldol reaction of methyl ketone 235, 236, or 237 with enal 363, followed by a protection and directed dihydroxylation/oxidative cleavage sequence, may be used to produce the requisite hydroxydione substitution pattern of portimine (Scheme 2.99). To investigate the feasibility of this approach, we first chose to examine the synthesis of model allyl alcohol 371 using an aldol reaction of ketone 212 with enal 370 (Scheme 2.99).

Scheme 2.99. Proposed synthesis of an hydroxydione intermediate *en route* to the total synthesis of portimine (1) (above) and model enal aldol reaction (below).
2.4.1 Preliminary Considerations

Although the aldol reaction is one of the most thoroughly studied and widely utilised transformations in organic synthesis, there are relatively few examples in the literature employing \textit{exo}-methylene enal acceptors (eg. model 370) for this reaction, in part because 1,2-addition of an enolate to this substrate is complicated by a potential competing 1,4-conjugate addition resulting in undesired regioisomers (Scheme 2.100).

\begin{center}
\textbf{Scheme 2.100.} Aldol reaction mechanism with potential competing 1,4-conjugate addition.
\end{center}

There have been very few systematic studies into the requirements that discriminate between the 1,2- and 1,4-addition pathway for enolates with α,β-unsaturated carbonyls. In one of the few studies available, Schultz and Yee reported in 1976 that the regioselectivity of the addition of lithium ester enolates to 2-cyclohexen-1-one was highly dependent reaction conditions. Lower temperatures and shorter reaction times favoured 1,2-addition, presumed to be the kinetically more favourable reaction product. However, under equilibrating conditions, this 1,2-addition was found to be reversible, facilitating formation of the thermodynamic 1,4-addition adduct.

The requirement for kinetic reaction conditions imposes several restrictions on the methodology available for the union of ketone 212 with enal 370. Of the available literature methods for the aldol reaction of enal acceptors, boron-derived enolates are by far the most widely represented class of nucleophiles. For instance, the Paterson group has reported the aldol condensation of ketone 373 with enal 372 (Scheme 2.101). Following this precedent Kozmin and co-workers performed a similar reaction to prepare allylic alcohol 377 en route to their total synthesis of leucascandrolide A.
Reagents and conditions: (a) Chx$_2$BCl, NEt$_3$, Et$_2$O, 16 h, 0 °C → −78 °C.

Scheme 2.101. Boron-mediated aldol reactions by the Paterson and Kozmin groups.$^{178a, 179}$

Importantly, boron-mediated aldol reactions are amenable to asymmetric induction by judicious ligand selection on the boron metal centre. Perhaps the most frequently employed ligand-mediated asymmetric aldol is the work of the Paterson group, whereby facial selectivity is derived from isopinocampheol ligands.$^{179}$ As boron-mediated aldol reactions have been shown to give excellent 1,2-regioselectivity with enone electrophiles, and may be readily modified for asymmetric induction, the use of this methodology was attractive for application to the aldol reaction of methyl ketone 212 with enal 370.

2.4.2 Synthesis of Model Enal 370

Prior to investigation of model aldol coupling of methyl ketone 212 with enal 370, synthesis of enal 370 was completed in four steps from 3,3-dimethylglutaric anhydride (378) (Scheme 2.102). Initially, lithium aluminium hydride-mediated reduction afforded diol 379 in 88% yield. Mono-protection of diol 379 then generated benzoate ester 380, albeit with moderate yield and chemoselectivity.$^{180}$ To our delight, subsequent Parikh-Doering oxidation and installation of the exo-methylene moiety following the procedure developed by the Pihko group$^{181}$ cleanly afforded novel enal 370 in 90% yield over both steps without requiring purification beyond a simple aqueous extraction (0.5 M citric acid) after each step (Scheme 2.102). The structure of enal 370 was confirmed by mass spectral analysis ([M+Na] $m/z =$ 269.1148, found 269.1151), alongside observed resonances in the $^1$H NMR spectrum at $\delta$ 9.53 ppm and $\delta$ 6.35 and 5.99 ppm characteristic of the aldehyde and exo-methylene functionality, respectively.
Reagents and conditions: (a) LiAlH₄, THF, 15 h, 0 °C → rt; (b) BzCl, NaH (60% in mineral oil), THF, 20 h, 0 °C → rt; (c) SO₃·py, DMSO, NEt(i-Pr)₂, CH₂Cl₂, 5 min, 0 °C; (d) pyrrolidine (10 mol%), propionic acid (11 mol%), CH₂O (37% w/w in H₂O), 14 h, rt.

Scheme 2.102. Synthesis of enal 370.

2.4.3 Boron-Mediated Aldol Reactions With Model Enal 370

With enal 370 reliably prepared, investigations into the model fragment couplings were initially undertaken using the boron enolate derivative of methyl ketone 212, which had been readily prepared earlier (see Scheme 2.37, page 57).

![Scheme 2.103. Proposed model aldol reaction of methyl ketone 212 and enal 370.](image)

To this end, ketone 212 was added to a mixture of dicyclohexylboron chloride (1.5 equivalents) and triethylamine (1.7 equivalents) in ether at 0 °C. After cooling the resultant slurry to −78 °C, enal 370 was added dropwise and the reaction was allowed to warm to room temperature over 16 h. Following oxidative work-up with hydrogen peroxide (30% w/w) and sodium hydroxide (1 M), aldol product 371 was cleanly afforded as a 1:1 mixture of diastereomers in 47% yield, together with a substantial amount of recovered starting materials 212 and 370 (Table 2.9, entry 1). Disappointingly, attempts to improve the reaction conversion using a larger excess of reagents were ineffective and the reaction reached a plateau at 55% yield (entry 2). Likewise, attempts to improve aldol efficiency by employing the boron enolate derived from ketone 212 with either dibutylboron triflate or 9-methoxy-9-borabicyclo[3.3.1]nonane also proved fruitless (entries 3–5).182
Table 2.9. Optimisation of the boron-mediated aldol reaction of ketone 212 with enal 370

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chx₂BCl (1.5 eq.), NEt₃ (1.7 eq.) Et₂O, then 370 (1.7 eq.)</td>
<td>47 (371), 2 (382), 42 (212)</td>
</tr>
<tr>
<td>2</td>
<td>Chx₂BCl (2.5 eq.), NEt₃ (2.8 eq.) Et₂O, then 370 (3.0 eq.)</td>
<td>55 (371), 36 (212)</td>
</tr>
<tr>
<td>3</td>
<td>Bu₂BOTf (1.8 eq.), i-Pr₂NEt (2.0 eq.) CH₂Cl₂, then 370 (2.0 eq.)</td>
<td>39 (371), 4 (382), 28 (212)</td>
</tr>
<tr>
<td>4</td>
<td>Bu₂BOTf (1.8 eq.), i-Pr₂NEt (2.0 eq.) Et₂O, then 370 (2.0 eq.)</td>
<td>trace (371)</td>
</tr>
<tr>
<td>5</td>
<td>9-BBNOMe (1.8 eq.), i-Pr₂NEt (2.0 eq.) Et₂O, then 370 (2.0 eq.)</td>
<td>recovered 212 only</td>
</tr>
</tbody>
</table>

aIsolated yield as a 1:1 diastereomeric mixture.

Despite the modest yields obtained in these experiments, all the boron-enolate aldol reactions attempted proceeded cleanly, with small quantities of aldehyde 382 the only by-product observed from any of these reaction mixtures (Table 2.9, entries 1 and 3). Although aldehyde 382 was isolated in insufficient quantity and purity from these product mixtures for characterisation its structure was unambiguously determined after it was prepared by an alternative method, namely Mukaiyama-Michael addition reaction of ketone 212 with enal 339 (Scheme 2.104).183

Reagents and conditions: (a) TBSOTf, NEt₃, CH₂Cl₂, 1 h, –10 °C; (b) 370, BF₃·OEt₂, CH₂Cl₂, 14 h, –78 °C → rt.

Scheme 2.104. Mukaiyama-Michael reaction of silane 339 and enal 370.

To enable direct comparison with the optimised glyoxal aldol reaction of methyl ketone 358, this compound was also subjected to the boron-mediated aldol conditions with glyoxal 370, cleanly furnishing hydroxyketone 383 in 41% yield (Scheme 2.105).
Recognising that the boron-mediated aldol reaction of ketone \(358\) and enal \(370\) gave exceedingly clean conversion to hydroxyketone \(383\) and therefore excellent yields based on returned starting material, further optimisation of this reaction was put to one side in order to focus attention on the investigation of the proposed Nozaki-Hiyama-Kishi macrocyclisation reaction.

### 2.4.4 Model Enal Aldol Summary and Future Work

Model enal \(370\) was prepared uneventfully over four steps from commercially available 3,3-dimethyl glutaric anhydride \(378\). To our delight, boron-mediated aldol reaction with model ketone \(212\) cleanly afforded allyl alcohol \(371\), albeit in moderate yield (Scheme 2.106). These results suggest that use of an enal aldol fragment coupling may be feasible for the synthesis of portimine.
2.5 Model Studies for the Nozaki-Hiyama-Kishi Reaction

Concurrent to our aldol fragment coupling studies, we were also interested in examining the Nozaki-Hiyama-Kishi reaction for the preparation of the 14-membered ring of intermediate 387, 388 or 389. In our synthetic plan, this reaction would be performed as an intramolecular macrocyclisation of bromide-aldehyde 384, 385, or 386 (Scheme 2.107). However, for our initial model study the intermolecular coupling of alkynyl bromide 237 and vinyl bromides 238 and 239 with aldehyde 381 were investigated. Although these reactions are intermolecular, it was anticipated that this system would provide a reasonable model for either macrocyclisation or fragment union. For instance, in a pioneering and exhaustive study of ring-closing reactions, Illuminati and Mandolini have shown that reaction rates for intramolecular large ring formation are often comparable to their intermolecular counterparts, despite a significant entropic cost in the transition state.184

Scheme 2.107. Proposed Nozaki-Hiyama-Kishi macrocyclisation for the synthesis of portimine (above) and initial model system with aldehyde 381 (below).
2.5.1 Background to the Nozaki-Hiyama-Kishi Reaction

The chromium(II) chloride-mediated coupling of allyl halides and aldehydes was first reported by Nozaki and Hiyama in 1977, with the substrate scope later extended to vinyl and aryl halides. During studies on the synthesis of palytoxin, Kishi and co-workers found that reaction success was heavily dependent on the chromium(II) chloride source. Rationalising that this reproducibility problem was likely due to an unknown contaminant, Kishi surveyed the effect of transition metals on this reaction and determined that addition of either catalytic nickel(II) chloride or palladium(II) acetate was effective for facilitating reliable couplings. In the same year, Nozaki reported that batches of chromium(II) chloride used in their original vinyl halide/aldehyde couplings contained trace nickel(II) chloride. Based on these findings both the Kishi and Nozaki groups proposed that the reaction proceeds through a catalytic cycle, whereby nickel(II) is first reduced to nickel(0) which undergoes oxidative addition to the carbon-halide bond (Scheme 2.108). Transmetallation produces a chromium(III) intermediate, regenerating nickel(II). Nucleophilic addition of the organochromium species to an aldehyde gives the desired coupling product, with the reaction driven to completion by formation of the thermodynamically stable chromium-oxygen bond.

A. Overview of the Enantioselective Nozaki-Hiyama-Kishi Reaction

The requirement for at least two equivalents of toxic and expensive chromium(II) salts has historically limited the application of the traditional Nozaki-Hiyama-Kishi reaction in industry and for other large scale applications, although examples are known. To address this issue, there has been significant interest in the development of a modified, catalytic in chromium Nozaki-Hiyama-Kishi protocol. Conceptually, a coupling that is catalytic in chromium requires
the addition of two stoichiometric species: (i) an oxophilic reagent to displace the chromium(III) alkoxide and (ii) a sacrificial reductant to then regenerate chromium(II) from chromium(III). An initial approach towards this goal was developed by the Furstner group, utilising trimethylsilyl chloride and manganese—for transmetallation and chromium(III) reduction, respectively—in order to complete the catalytic cycle and furnish silylated allylic alcohol products (Scheme 2.109). Further investigation from the Kishi group revealed that zirconocene dichloride was also an effective chromium dissociating agent and may be employed in place of trimethylsilyl chloride. Electrochemical reduction of chromium(III), instead of chemical reduction with manganese, has also been employed as a viable strategy to complete the chromium catalytic cycle.

Importantly, the development of a Nozaki-Hiyama-Kishi coupling that is catalytic in chromium has paved the way for an enantioselective variant. Consequently, significant effort in the synthetic community has focussed on preparation of appropriate chiral ligands for coordination to the organochromium species, in order to direct aldehyde facial selectivity during the key carbon-carbon bond forming step (Scheme 2.109, above). Recently, these efforts have been extensively reviewed elsewhere, although selected examples are highlighted below (Figure 2.6).
B. The Nozaki-Hiyama-Kishi Reaction in Natural Product Synthesis

The high chemoselectivity for aldehydes renders the Nozaki-Hiyama-Kishi reaction uniquely compatible with a wide range of functional groups. Consequently, it has been employed in the total synthesis of a plethora of complex natural products. Perhaps the most prominent example of this is the first generation synthesis of halichondrin B (397) by Kishi and co-workers, wherein the reaction is strategically employed in five carbon-carbon bond forming steps. These disconnections are shown below (Figure 2.7).\textsuperscript{187b, 195}

Of more relevance to the present work are instances where the Nozaki-Hiyama-Kishi reaction is used to complete a macrocyclic carbon framework. Selected examples of this application of the Nozaki-Hiyama-Kishi reaction are outlined below, with a particular focus on the preparation of 14-membered ring systems (Scheme 2.110). For instance, Still and Mobilio reported a highly diastereoselective cyclisation as the penultimate step in the synthesis of asperdiol (399).\textsuperscript{196} More recently, an intramolecular Nozaki-Hiyama-Kishi was employed by Feick and co-workers as the key step in the synthesis of (3S)-3-dihydroronarbonolide (401)—permitting a formal synthesis of the polyketide natural product narbonolide\textsuperscript{197}—while the Banwell group used a similar approach \textit{en route} to cochliomycin B (403).\textsuperscript{198} In light of these results, and others,\textsuperscript{199} we envisioned a similar strategy for preparation of an advanced tricyclic intermediate in our retrosynthetic analysis of portimine (see Scheme 2.1, page 29).
Reagents and conditions: (a) CrCl₂, THF, 6 h, rt; (b) NH₃, Na, EtOH/THF (3:2), −10 °C; (c) CrCl₂, NiCl₂, DMSO, 48 h, rt; (d) Dess-Martin periodinane, CH₂Cl₂, 12 h, rt; (e) CrCl₂, NiCl₂, DMF, 30 h, rt; (f) TBAF (1 M in THF), THF, 24 h, reflux.

Scheme 2.110. Selected examples of Nozaki-Hiyama-Kishi macycyclisation.¹⁹⁶-¹⁹⁸
2.5.2 Initial Optimisation of the Nozaki-Hiyama-Kishi Coupling

Initial optimisation of the Nozaki-Hiyama-Kishi reaction was conducted using aldehyde 381 and bromoalkyne 232 (Scheme 2.111), as a reliable synthetic route to both of these substrates had already been established. Aldehyde 381 was prepared in three steps from 3,3-dimethylglutaric anhydride (Scheme 2.102, page 106) while bromoalkyne 232 was prepared over nine steps from ethyl levulinate (see Scheme 2.48, page 63).

![Scheme 2.111. Model system for initial optimisation of the Nozaki-Hiyama-Kishi reaction conditions.](image)

Given that the Nozaki-Hiyama-Kishi reaction requires handling the expensive and air-sensitive reagent chromium(II) chloride, early attempts to effect the union of bromoalkyne 232 with aldehyde 381 focused on procedurally simple alternatives for this coupling reaction. For instance, when aldehyde 381 was subjected to reaction with the lithium acetylide prepared from bromoalkyne 232 and t-butyllithium only a trace amount of product 404 was detected by $^1$H NMR analysis of the complex product mixture (Table 2.10, entry 1). This result is thought to be due to the nucleophilicity of the organolithium intermediate, and competing nucleophilic addition to the benzoyl protecting group cannot be ruled out. On the other hand, attempts to prepare the Grignard derivative of bromoalkyne 232 proved unsuccessful, returning clean starting material without evidence of magnesium insertion (entry 2). These results indicated that the relatively benign chromium(II)/nickel(II) conditions of the Nozaki-Hiyama-Kishi reaction would be essential to effect successful coupling of bromoalkyne 232 with aldehyde 381.

The complications encountered during the lithiation of bromoalkyne 232 necessitated the use of mild Nozaki-Hiyama-Kishi chromium(II)-mediated coupling conditions, which are generally highly efficient and chemoselective for aldehyde addition. However, chromium(II) chloride undergoes rapid air oxidation, especially in the presence of moisture. Consequently, all reactions were carried out using freshly distilled and degassed solvent in flame-dried glassware. The chromium(II) and nickel(II) salts used were weighed in an inert atmosphere and reactions were performed under argon. Disappointingly, despite these precautions, initial coupling attempts returned only alkyne 226 alongside clean recovery of aldehyde 381 (entry 3). Analysis
of the reaction mixture by TLC visualisation indicated that dehalogenation occurred prior to the aqueous work-up and therefore dehalogenation must occur during the reaction by proton-metal exchange, either immediately after nickel insertion or following chromium(III) transmetallation. We anticipated that trace water contaminant in the solvent was the most likely proton source and that addition of an appropriate, activated drying agent to the reaction mixture might suppress this undesired reactivity.

Unfortunately, addition of either 4 Å molecular sieves or potassium carbonate to the reaction proved deleterious to coupling success with the former leading to a mixture of unidentified side products and the latter causing total decomposition of both reagents (entries 4 and 5). Use of less polar solvents resulted in no reactivity, even at elevated temperatures, likely due to the limited solubility of the chromium salts in dimethoxyethane or acetonitrile (entries 7 and 8).

<table>
<thead>
<tr>
<th>entry</th>
<th>metal</th>
<th>additive</th>
<th>solvent</th>
<th>product (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>t-BuLi</td>
<td>-</td>
<td>Et₂O</td>
<td>226 (4), 404 (trace)</td>
</tr>
<tr>
<td>2d</td>
<td>Mg</td>
<td>-</td>
<td>Et₂O</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>CrCl₂, NiCl₂</td>
<td>-</td>
<td>DMF/THF (3:1)</td>
<td>226 (64)</td>
</tr>
<tr>
<td>4</td>
<td>CrCl₂, NiCl₂</td>
<td>4 Å mol sieves</td>
<td>DMF/THF (3:1)</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>CrCl₂, NiCl₂</td>
<td>K₂CO₃</td>
<td>DMF/THF (3:1)</td>
<td>complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>CrCl₂, NiCl₂</td>
<td>DBU</td>
<td>DMF/THF (3:1)</td>
<td>226 (78)</td>
</tr>
<tr>
<td>7</td>
<td>CrCl₂, NiCl₂</td>
<td>-</td>
<td>DME</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>CrCl₂, NiCl₂</td>
<td>-</td>
<td>MeCN</td>
<td>226 (trace), 232 (89)</td>
</tr>
<tr>
<td>9</td>
<td>CrCl₂, NiCl₂</td>
<td>-</td>
<td>NMP</td>
<td>404 (12), 232 (22), 226 (54)</td>
</tr>
<tr>
<td>10e</td>
<td>CrCl₂, NiCl₂</td>
<td>-</td>
<td>NMP</td>
<td>404 (69)</td>
</tr>
</tbody>
</table>

*All reactions were performed using bromoalkyne 232 (20 mg) with aldehyde 381 (2 eq.) at 40 °C for 24 h unless otherwise specified. bIsolated yield as a 1:1 diastereomeric mixture. c−78 °C. dRoom temperature. eReaction performed on aldehyde 381 (10 mg) with bromoalkyne 232 (1.5 eq.) at 50 °C.

Pleasingly, successful coupling of bromoalkyne 232 with aldehyde 381 was finally accomplished by performing the reaction in N-methylpyrrolidone, although significant debromination of alkyne 226 was observed as the major side product (entry 9). Extensive experimentation found that good yields of alkynol 404 could be achieved when coupling partner stoichiometry was
reversed, such that aldehyde 381 was used as the limiting reagent with excess bromoalkyne 232. Furthermore, improved yields were achieved at slightly higher temperature (50 °C) and concentration (0.3 M). When all of these changes were implemented, the coupling afforded alkynol 404 in 69% yield as a ~1:1 mixture of diastereomers (entry 10). Importantly, the only major by-product, dehalogenated alkyne 226, could be readily recycled to the starting bromide by treatment with catalytic AgNO₃ and NBS (see Scheme 2.48, page 63).

2.5.3 Nozaki-Hiyama-Kishi Coupling of Bromides 390–392 and 404–406

Following identification of optimised Nozaki-Hiyama-Kishi reaction conditions using bromoalkyne 232, these same conditions were applied to the union of the related E- and Z-vinyl bromides 224 and 230 with aldehyde 381. Initial attempts to effect these couplings, however, resulted in moderate yields (33–47%) due to poor mass recovery, despite clean conversion of aldehyde 381 to the corresponding allyl alcohol, as determined by TLC visualisation and ¹H NMR analysis of the crude reaction (Scheme 2.112).

![Scheme 2.112. Nozaki-Hiyama-Kishi coupling of bromides 224 and 230 with model aldehyde 381.](image)

Reagents and conditions: (a) CrCl₂, NiCl₂, NMP, 16 h, 50 °C.

Poor mass recovery is a well-documented complication of chromium-mediated coupling reactions under standard work-up conditions (ie. aqueous ammonium chloride quench and ethyl acetate extraction). To circumvent this issue, the Kishi group developed an alternative work-up procedure, whereby aqueous ammonium chloride is replaced with a dilute solution of hydrochloric acid and potassium serinate, which chelates strongly to chromium salts leading to a simple extractive separation.²⁰⁰

Employing a similar principle to the Kishi work-up procedure, we found that quenching the reaction with a 1:1 mixture of aqueous citric acid (0.5 M) and saturated aqueous ammonium chloride and extracting with diethyl ether was also effective for good mass recovery. When the Nozaki-Hiyama-Kishi coupling of E- and Z-vinyl bromides 224 and 230 with aldehyde 381 were
repeated using this modified work-up allyl alcohols 405 and 406 were furnished in 84% and 72% yields, respectively (Table 2.11, entries 2 and 3).

Good yields were also obtained for compounds 237–239, with a slight increase in coupling efficiency observed for the vinyl bromides over alkynyl bromide 237 (entries 4–6). All products obtained were furnished without any substrate-derived stereocontrol, as a 1:1 mixture of diastereomers. Crucially, the unprotected ketone of compounds 237–239 did not interfere with the desired coupling.

Table 2.11. Optimised Nozaki-Hiyama-Kishi coupling of aldehyde 381 with bromides 237–239

<table>
<thead>
<tr>
<th>entry</th>
<th>bromide</th>
<th>geometry</th>
<th>X</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>232</td>
<td>alkynyl</td>
<td>-OCH₂CH₂O-</td>
<td>404</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>224</td>
<td>E-vinyl</td>
<td>-OCH₂CH₂O-</td>
<td>405</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>230</td>
<td>Z-vinyl</td>
<td>-OCH₂CH₂O-</td>
<td>406</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>237</td>
<td>alkynyl</td>
<td>O</td>
<td>390</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>238</td>
<td>E-vinyl</td>
<td>O</td>
<td>391</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>239</td>
<td>Z-vinyl</td>
<td>O</td>
<td>392</td>
<td>81</td>
</tr>
</tbody>
</table>

*aAll reactions were performed using aldehyde 381 (10 mg) with an excess of the appropriate bromide (1.6 eq.) in NMP in the presence of CrCl₂ (3 eq.) and NiCl₂ (10 mol%) at 40 °C for 15 h. *Isolated yield as a 1:1 diastereomeric mixture.
2.5.4 Attempted Catalytic, Asymmetric Nozaki-Hiyama-Kishi Coupling

Due to the inherent lack of stereocontrol and large excess of chromium salts required for the above coupling of bromides 237–239 with aldehyde 381 a catalytic, enantioselective alternative was desired. As mentioned earlier, identification of appropriate asymmetric ligands for a stereocontrolled variant of the Nozaki-Hiyama-Kishi reaction is a very active research area. Perhaps most prominently, the Kishi group has invested significant effort in the development of a series of sulfonamide ligands for this transformation. 194a, 201 Recently, they have applied this methodology to selective haloacetylene-aldehyde coupling for an expedient synthesis of the halichondrin family of natural products (Scheme 2.113). 202 Importantly, total diastereo- and chemoselectivity was observed in these experiments, even when the coupling was applied to highly functionalised intermediates. Encouraged by these results, we thus began preparation of requisite ligand \((R)-395\) for exploration of this powerful fragment coupling.

Reagents and conditions: (a) \(\text{CrCl}_2\) (20 mol%), \((S)-395\) (22 mol%), proton sponge (22 mol%), LiCl, Mn, TESCl, EtCN, 7 h, rt; (b) TFA/H₂O/CH₂Cl₂ (4:1:10), 1 h, rt.

Scheme 2.113. Stereocontrolled NHK reaction by the Kishi group using sulfonamide ligand \((S)-395\).

A. Synthesis of Sulfonamide Ligand \((R)-395\)

Following the sequence reported by Kishi and co-workers, sulfonamide ligand \((R)-395\) was prepared over four steps from \(o\)-anisidine \((410)\) (Scheme 2.114). 201a, 202 Initially, protection of \(o\)-anisidine using di-tert-butyl dicarbonate in tetrahydrofuran afforded carbamate \(411\) in quantitative yield. Treatment of this compound with excess \(t\)-butyllithium at \(-78^\circ\text{C}\), followed by careful addition of phenoxy cyanide, furnished nitrile \(412\) in modest yield. Subjection of this nitrile to a one-pot zinc chloride-mediated condensation and deprotection sequence with D-valinol generated amine \(413\) in 86% yield. Finally, this condensation product was reacted with methanesulfonyl chloride in the presence of catalytic \(N,N\)-dimethylaminopyridine and triethylamine to produce ligand \((R)-395\) for investigation of the asymmetric Nozaki-Hiyama-Kishi reaction.
Conditions and reagents: (a) Boc₂O, THF, 18 h, rt; (b) t-BuLi (1.6 M in pentane), PhOCN, Et₂O, 16 h, −78 °C → rt; (c) D-valinol, ZnCl₂ (20 mol%), PhCl, 14 h, reflux; (d) MsCl, NEt₃, DMAP, CH₂Cl₂, 15 h, rt.

Scheme 2.114. Synthesis of sulfonamide ligand 395 following the procedures of Kishi and co-workers.²⁰¹a,²⁰²

B. Attempted Asymmetric Nozaki-Hiyama-Kishi Reaction of Alkyne 232 and Aldehyde 381

With sulfonamide ligand (R)-295 in hand we were eager to examine the asymmetric, catalytic Nozaki-Hiyama-Kishi reaction of alkynyl bromide 232 with aldehyde 381. Interestingly, when this coupling was first reported, Kishi and co-workers found that added nickel catalyst was not essential for reaction success, although they postulated that trace nickel or another unknown metal contaminant may still be involved in activation of the bromoacetylene.²⁰² Following these conditions, a catalytic amount of ligand (R)-395 and chromium(II) chloride was treated with 1,8-diazabicyclo(5.4.0)undec-7-ene to generate the active catalyst complex. Zirconocene dichloride, manganese, and lithium chloride were then added to the resultant solution, followed by bromoalkyne 232 and aldehyde 381 in freshly distilled propionitrile. Disappointingly, no conversion to desired alkynol 404a was observed with the mixture instead returning clean starting materials bromoalkyne 232 and aldehyde 381 (Scheme 2.115).

Reagents and conditions: (a) CrCl₂ (20 mol%), 395 (22 mol%), proton sponge (22 mol%), LiCl, Mn, Cp₂ZrCl₂, EtCN, 48 h, 50 °C.


The recovery of bromoalkyne 232 in this reaction suggested that addition of a nickel catalyst would be essential to promote the reaction via an initial bromoalkyne insertion. Importantly, this finding provided further evidence that the coupling of bromide 232 and aldehyde 381 performed by Kishi and co-workers was indeed catalysed by trace metal impurities (Scheme 2.115, above).
Thus, the reaction was repeated in the presence of either nickel(II)-neocuproine complex 414\textsuperscript{203} or dichloro(1,3-bis(diphenylphosphino)propane)nickel (415),\textsuperscript{204} both of which have been shown to effectively facilitate asymmetric Nozaki-Hiyama-Kishi couplings in conjunction with sulfonamide ligand 395. Unfortunately, in both instances, only debrominated alkyne 226 was returned from the reaction mixture (Scheme 2.116).

\begin{center}
\includegraphics[width=\textwidth]{image}
\end{center}

\textit{Reagents and conditions:} (a) CrCl\textsubscript{2} (20 mol\%), 395 (22 mol\%), proton sponge (22 mol\%), 414 (5 mol\%), LiCl, Mn, Cp\textsubscript{2}ZrCl\textsubscript{2}, EtCN, 24 h, 50 °C; (b) CrCl\textsubscript{2} (20 mol\%), 395 (22 mol\%), proton sponge (22 mol\%), 415 (5 mol\%), LiCl, Mn, Cp\textsubscript{2}ZrCl\textsubscript{2}, EtCN, 24 h, 50 °C.

\textbf{Scheme 2.116.} Attempted stereocontrolled Nozaki-Hiyama-Kishi using sulfonamide ligand 395 with either nickel(II) complex 414 or 415.

At this point, attempts to perform an asymmetric Nozaki-Hiyama-Kishi coupling of bromoalkyne 232 and aldehyde 381 were discontinued. It is worth noting that for intermediates 384–386, the proposed macrocyclisation precursors for the synthesis of portimine, incorporates an \(\alpha\)-stereocentre relative to the aldehyde moiety, and significant steric constraint on the developing ring system, both of which may influence diastereoselectivity of this reaction (Scheme 2.117). As such, extensive investigation of the stereocontrolled Nozaki-Hiyama-Kishi reaction was considered unnecessary at this time.

\begin{center}
\includegraphics[width=\textwidth]{image}
\end{center}

\textbf{Scheme 2.117.} Proposed macrocyclisation of aldehyde 384, 385, or 386 for the synthesis of portimine.
2.5.5 Summary

Optimised Nozaki-Hiyama-Kishi fragment coupling conditions were identified using bromoalkyne 232 and model aldehyde 381. Pleasingly, these conditions were found to be suitable for the coupling of vinyl bromides 238 and 239, both of which smoothly reacted with aldehyde 381, affording allyl alcohols 391 and 392, respectively (Scheme 2.118). Crucially, the unprotected ketone of these compounds did not interfere with the desired coupling. Thus, these investigations provide a strong basis for the proposed macrocyclisation of aldehyde 381 (Scheme 2.117, above).

Reagents and conditions: (a) CrCl₂ NiCl₂, NMP, 16 h, 50 °C.

2.6 Towards Model Ketal 419

In addition to our efforts towards the polyketide fragment of portimine (1), we were also interested in learning more about the unique structural features of this natural product through preparation of simple model systems. One such system is ketal 419. We envisioned that ketal 419 could be prepared by Nozaki-Hiyama-Kishi coupling of aldehyde 204 with vinyl iodide 416, followed by cyclisation and ozonolysis (Scheme 2.119). A scalable, stereocontrolled route to aldehyde 204 had already been established in the present work (see Scheme 2.38, page 57).

![Scheme 2.119. Proposed synthesis of ketal model 419.](image)

2.6.1 Synthesis of Allyl Alcohol 423

Having adopted a Nozaki-Hiyama-Kishi coupling strategy for the preparation of ketal 419, it was first necessary to synthesise vinyl iodide coupling partner 422. To this end, alcohol 421 was first prepared as a single regioisomer via addition of in situ generated hydrogen iodide, following a procedure developed by Ishii and co-workers for the synthesis of internal vinyl iodides from propargyl alcohol (420).205 Subsequent protection of alcohol 421 as a triisopropylsilyl ether afforded coupling partner 422 in 52% yield over two steps (Scheme 2.120).

![Scheme 2.120. Synthesis of iodide coupling partner 422.](image)

Reagents and conditions: (a) TMSCl, NaI, H2O, MeCN, 17 h, 0 °C → rt; (b) TIPSCI, NEt3, DMAP, CH2Cl2, 5 h, rt.
With aldehyde 204 (see Scheme 2.38, page 57) and vinyl iodide 422 in hand, attention turned to the Nozaki-Hiyama-Kishi reaction. After extensive investigation, it was discovered that the order of addition of the reagents was critical for successful coupling. In order to effect the cross-coupling of iodide 422 and aldehyde 204 it was thus essential to first weigh the chromium(II) chloride and nickel(II) chloride salts in a glovebox under inert conditions, prior to addition of a solution of both reactants 204 and 422 in dimethylformamide/tetrahydrofuran (3:1). Gratifyingly, careful reaction setup afforded allyl alcohol 423 in 78% yield, albeit without significant diastereoselectivity (~1.2:1 dr) (Scheme 2.121). As the diastereomeric mixture was inseparable, allyl alcohols 423a and 423b were used as a mixture in the subsequent cyclisation experiments.

Reagents and conditions: (a) CrCl₂, NiCl₂, DMF/THF (3:1), 14 h, 50 °C.

Scheme 2.121. Nozaki-Hiyama-Kishi coupling of aldehyde 204 with vinyl iodide 422.

2.6.2 Initial Cyclisation Considerations

Conceptually, conversion of allyl alcohol 423 to bicyclic ketal 418 could be accomplished via a one-pot deprotection/cyclisation cascade, as both silyl ether and acetal protecting groups could be readily cleaved under acidic conditions. However, it is also possible that the C-8 alcohol may undergo a competing cyclisation pathway to afford undesired ketal 425 (Scheme 2.122).

Scheme 2.122. Divergent ketalisation of triol 424.
At this stage, it was unclear whether the C-8 or C-10 cyclisation pathway would predominate for the ketalisation of either model alcohol 423 or for advanced intermediates *en route* to the total synthesis of portimine. There are several examples of ketalisation to the undesired [4.2.1]-ring system known in the literature, although the dihydroxyketones used in these reactions are generally incorporated into more complex polycyclic structures—with extensive conformational strain—unlike the present work. An example of this is the penultimate step in the commercial synthesis of the anti-cancer drug eribulin (trade name Halaven®) (Scheme 2.123).206

![Scheme 2.123. Ketalisation in the commercial synthesis of eribulin (Halaven®).206](image)

To the best of our knowledge there are no prior examples of ketalisation to the desired [6.2.1]-ketal system reported in the literature. However, Mikami and co-workers reported the preparation of [5.2.1]-ketal 430 by acid-catalysed cyclisation of allyl alcohol 429, a very similar approach to our proposed synthesis of ketal 418 (Scheme 2.124).207

![Scheme 2.124. Mikami and co-workers’ synthesis of ketal 430.207](image)

Interestingly, the Mikami group found that treatment of ketal 430 with mesoporous acids such as Amberlyst 15® or montmorillonite K10 gave *ene*-type rearrangement to aldehyde 433 (Scheme 2.125).207 Use of these conditions also directly produced aldehyde 433 from either hemiacetal 428 or 429, albeit in slightly reduced yields.
Given the structural similarity of ketal 430 to our proposed model system 418 it was imperative to first determine whether a similar undesired ene rearrangement to that observed by Mikami would occur in the present work. To this end, a 1.2:1 diastereomeric mixture of allyl alcohols 423a and 423b was stirred in the presence of catalytic Amberlyst 15®. Surprisingly however, these conditions resulted in divergent reactivity of the two diastereomers, producing a separable mixture of ketone 434 and ketal 435 in 97% combined yield (Scheme 2.126). Although no ene-type rearrangement was observed, this experiment clearly indicated that the C-8 alcohol was capable of facile cyclisation. Consequently, masking this functionality with a protecting group would be necessary prior to further ketalisation studies (see section 2.6.4, page 131).

The absolute stereochemistry of ketal 435 could be unambiguously assigned on the basis of nOe cross-correlation data (see appendix, page 310 for spectrum). Pleasingly, analysis of the NOESY spectrum showed a clear H-3↔H-5 correlation, indicative of cis-substitution of the central seven-membered ketal (Figure 2.8). The stereochemistry of the newly formed C-1 chiral centre was determined on the basis of an observed H-8↔H-3′ correlation. As the C-3′ methylene is positioned below the seven-membered ring, C-8 must also be located below the plane of the ketal. Since the absolute stereochemistry of both the C-4 and C-5 carbons are derived from an enantioselective Leighton crotylation and known to exist in the 4S,5S configuration, the absolute configuration of ketal 435 can be assigned as 1S,3S,5S,6S.
2.6.3 Mechanistic Considerations for the Desilylation of Alcohol 434a

The exclusive formation of ketal 435 is particularly remarkable, as the apparent diastereoselectivity of this reaction is almost without precedent (Scheme 2.127). Clearly, the relative stereochemistry of the C-8 alcohol has a dramatic impact on the rate of desilylation, although exactly how this plays out mechanistically is currently uncertain. However, there are several plausible explanations for this selectivity, which are discussed in turn.

**Reagents and conditions:** (a) Amberlyst 15®, CH₂Cl₂/acetone (1:1), 20 min, rt.

**Scheme 2.127.** Treatment of allyl alcohol 423 with Amberlyst 15®.

### A. Through-Bond Orbital Interactions

An extensive literature search uncovered only a single prior example of a diastereoselective desilylation reaction. In 1995 de Groot, Wijnberg and co-workers reported kinetic studies on the TBAF-mediated silyl cleavage of compounds 436–438. These compounds exhibited distinct differences in desilylation rates, in the order 436 > 437 > 438 (Table 2.12).
Table 2.12. Kinetic analysis of desilylation by de Groot and Wijnberg$^{208}$

<table>
<thead>
<tr>
<th>entry$^a$</th>
<th>substrate</th>
<th>structure</th>
<th>pseudo-first order rate constant$^b$</th>
<th>correlation coefficient$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>436</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>15.4</td>
<td>0.999</td>
</tr>
<tr>
<td>2</td>
<td>437</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>4.3</td>
<td>0.996</td>
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<tr>
<td>3</td>
<td>438</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>1.3</td>
<td>0.996</td>
</tr>
</tbody>
</table>

$^a$All reactions were performed in triplicate with TBAF (10 eq.) in MeCN at 25 °C. $^{b}k_{obs} \times 10^{-3}$ min$^{-1}$. $^{c}$Correlation coefficient of calculated rate constant.

De Groot and Wijnberg proposed that the observed rate of desilylation was directly related to stabilisation of the alkoxide leaving group (rather than steric effects), due to subtle differences in through-bond orbital interactions of the conformationally rigid species.$^{208}$ In the present work, concomitant desilylation and ketalisation was performed under acidic conditions on an unconstrained system. It is therefore highly unlikely that these through-bond orbital interactions play any role in the selective desilylation of ketone 434.

### B. Pentacoordinate Silicon Substitution

It appears more plausible that the C-8 alcohol plays an active role in the desilylation reaction, perhaps through an intramolecular coordination process that enhances the rate of silicon substitution. For instance, the C-8 oxygen could coordinate to the silicon atom, producing a pentacoordinate silicon centre that is activated to substitution from an external nucleophile (Scheme 2.128). Crucially, this requires cyclisation of alcohol 434a to seven-membered ring intermediate 439a. If desilylation does indeed proceed through a cyclic intermediate such as 439a—but desilylation of alcohol 434b is not observed—then it is anticipated that the formation of cyclic intermediate 439b would be strongly disfavoured, perhaps due to increased transannular strain.
Scheme 2.128. Proposed mechanism for the diastereoselective desilylation and ketalisation of alcohol 434a.

The hypothesised cyclisation of alcohol 434a to siliconate 439a prior to desilylation relies on several key assumptions. Most importantly, cyclisation must either be under thermodynamic control, or the transition state energies required for cyclisation of alcohols 434a and 434b must reflect a similar energetic trend to the energies of the intermediates formed, 439a and 439b respectively. Crucially, there is good reason to believe these conditions are met. Most likely, the cyclisation of alcohols 434a and 434b to dioxysiliconates 439a and 439b is an endothermic process, due to the formation of a zwitterionic siliconate species. If this is the case, it would be expected that the relative transition state energies of cyclisation would be reflected in the energies of postulated intermediates 439a and 439b, according to Hammond’s postulate. If the selective desilylation of alcohol 434a does indeed involve the formation of a pentacoordinate silicon species, then the energy difference between posited cyclic intermediates 439a and 439b ought to correlate to the experimentally observed difference in desilylation rates between alcohol epimers 434a and 434b, providing the aforementioned assumptions hold true.

The mechanism proposed above rests on another key assumption: that the rate of desilylation must be significantly greater for pentacoordinate silicon species such as 439a than for tetracoordinate silicon species 434a or 434b. To address this assumption, a brief discussion of nucleophilic silicon substitution is presented in the following section, with a particular focus on the reaction rate for penta- and tetracoordinate species.
C. Experimental and Theoretical Precedent for Pentacoordinate Silicon Substitution

Experimental studies of nucleophilic silicon substitution have demonstrated dramatically increased reactivity for pentacoordinate species over the corresponding tetracoordinate silicon compounds. For instance, Bassindale and Borbaruah prepared $N,N$-bisdimethylsilylmethyl acetamide 441 to probe the effects of co-ordination on silicon reactivity (Figure 2.9). In this system, there are two silicon centres that differ solely by coordination level, allowing for direct measurement of competitive kinetic substitution. It was found that silicon-bromine and silicon-chlorine bonds were both activated towards substitution by coordination of an oxygen nucleophile, whereas the silicon-fluoride bond was deactivated.

![Figure 2.9. Bassindale and Borbaruah's $N,N$-bisdimethylsilylmethyl acetamide (441).](image)

In a seminal study, Corriu and co-workers found that the relative reactivity of pentacoordinate $\text{PhMeSiF}_3^-$ and tetracoordinate $\text{PhMeSiF}_2$ to $t$-BuMgBr was $>$1000:1. Of particular relevance to the present work, $\text{Ph}_3\text{Si}(\text{OMe})_2^-$ was also found to undergo hydrolysis significantly faster than $\text{Ph}_3\text{Si}(\text{OMe})$ under either acidic, basic or neutral conditions. Mechanistic experiments conducted by the same authors in wet tetrahydrofuran suggested that hydrolytic substitution occurs via an addition-elimination pathway involving a pentacoordinate anionic silicon species.

Theoretical studies pioneered by Holmes have shown a lengthening of bonds in pentacoordinate silicon species relative to the corresponding tetracoordinate compounds. Counterintuitively, these calculations also suggested that at higher coordination levels the silicon atom is more electropositive, even when the coordinated ligands are formally anionic. The combined effect of a weakened and more polarised silicon-oxygen bond is an accelerated rate of nucleophilic substitution. A more recent study by González has also demonstrated that the mechanism of $\text{Si(OMe)}_4$ hydrolysis proceeds via precomplexation of an external ligand (i.e. $\text{OH}^-$ or $\text{NH}_3$), followed by nucleophilic substitution. Acid-catalysed nucleophilic substitution at pentacoordinate silicon is also known.

In light of these findings, it is not unreasonable to postulate the formation of a pentacoordinate silicon species as an intermediate in the desilylation and cyclisation of ketone 434a (Scheme 2.129).
**Scheme 2.129.** Proposed mechanism for the diastereoselective desilylation and ketalisation of alcohol 434a.

### D. Alternative Mechanisms

Although there is good reason to believe that a pentacoordinate silicate intermediate such as 439a is involved in the desilylation of alcohol 434a, alternative intermediates cannot be explicitly discounted. For instance, it may be possible that intramolecular hydrogen bonding from the C-8 alcohol to the C-5 oxygen stabilises the developing negative charge in the desilylation transition state (Scheme 2.130).

**Scheme 2.130.** Possible mechanism for the desilylation of alcohol 434a by H-bond activation.

In this scenario, hydrogen bonding activates the C-5 oxygen, facilitating cleavage of the silicon-oxygen bond. This type of hydrogen bond-oxygen activation is a well-documented phenomena,
and is especially prevalent in biological systems. Recently, Song and co-workers have harnessed this reactivity in the development of an asymmetric polyether-potassium complex for desilylative kinetic resolution of protected secondary alcohols (Figure 2.10). In this system, hydrogen bonding simultaneously activates the silyl ether oxygen and directs coordination of the substrate to form a highly ordered, rigid transition state. A second hydrogen bond dampens the strong Lewis basicity of the fluoride anion, suppressing undesired reactivity. Conceptually, a similar process might be occurring in the selective desilylation of acetal 423, whereby an intramolecular hydrogen bond to the silicon-oxygen bond promotes desilylation.

Figure 2.10. Bifunctional, asymmetric hydrogen bond activated desilylation by Song and co-workers.

However, in the present work the desilylation reaction was performed in acidic media, presumably in the presence of liberated ethylene glycol. In these conditions it is unclear why intramolecular hydrogen bonding through a seven-membered ring would significantly increase reaction rate, relative to other possible processes such as intermolecular proton donation. On these grounds, we consider this possibility highly unlikely, although it cannot be definitively discounted.

2.6.4 Attempted Cyclisation of Protected Allyl Alcohols 445 and 454

The exact origin of diastereoselectivity observed during cyclisation to ketal 435 remains unclear at present. Importantly, this experiment also demonstrated that undesired cyclisation of the C-8 alcohol of 423 was particularly facile (see Scheme 2.122, page 123). Thus, hydroxyl protection of allyl alcohol 423 was necessary to prevent this competing ketalisation pathway (Scheme 2.131).

Scheme 2.131. Proposed synthesis of ketal 444 by protection and cyclisation of alcohol 423.
A. Attempted Ketalisation of Acetate Ester 445

Initially, alcohol 423 was protected as the corresponding acetate ester 445, anticipating that the acetate moiety would be stable to the acidic conditions required for cyclisation and saponification could then be readily achieved by treatment with mild base when required. Accordingly, ester 445 was prepared quantitatively by treatment of alcohol 423 with acetic anhydride in the presence of 4-dimethylaminopyridine and triethylamine (Scheme 2.132).

![Scheme 2.132. Preparation of acetate 445.](image)

Reagents and conditions: (a) Ac₂O, NEt₃, DMAP, CH₂Cl₂, 18 h, 50 °C.

As Mikami and co-workers had shown that use of strong Brønsted acids could lead to ene-type rearrangement products on a related system (see Scheme 2.125, page 125)²⁰⁷ we envisioned a two-step cyclisation pathway for the preparation of protected dihydroxyketone 445. In this strategy the silyl ethers were to be first removed under buffered conditions (ie. by treatment with fluoride anion), followed by mild acid catalysis to effect ketalisation and furnish the desired acetal 449. Disappointingly, however, treatment of silyl diether 445 with buffered hydrogen fluoride sources favoured either acetal hydrolysis (Table 2.13, entry 1) or resulted in decomposition (entry 2). Of the fluoride sources trialled, only acetic acid-buffered tetrabutyl ammonium fluoride was observed to cause any desilylation, and in this case only cleavage of the primary triisopropylsilyl ether was observed, requiring prolonged reaction times (entry 3).

![Table 2.13. Attempted synthesis of diol 448](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Conditions</th>
<th>time</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HF·py in CH₂Cl₂ (10% v/v)</td>
<td>18 h</td>
<td>446ᵃ</td>
</tr>
<tr>
<td>2</td>
<td>3HF·NEt₃ in CH₂Cl₂ (10% v/v)</td>
<td>24 h</td>
<td>degradation</td>
</tr>
<tr>
<td>3</td>
<td>TBAF·3AcOH (3 eq.) in CH₂Cl₂</td>
<td>72 h</td>
<td>447ᵇ</td>
</tr>
</tbody>
</table>

ᵃ100% conversion by crude ¹H NMR analysis.ᵇ50% conversion by crude ¹H NMR analysis.
Discouraged by these results, our attention returned to a one-pot global deprotection/cyclisation cascade. As the acetal is the more labile protecting group, initial attempts at ketalisation of acetate 445 were based on methods known to be effective for cleavage of the hindered silyl ethers. Accordingly, acetate 445 was stirred in a mixture of tetrahydrofuran/acetic acid/water (4:2:1). Unfortunately, this only liberated ketone 446, without affecting either of the silyl ether groups (Table 2.14, entry 1). Likewise, the use of catalytic camphorsulfonic acid resulted in initial formation of ketone 446 (as visualised by TLC analysis) and subsequent degradation (entry 2). Stronger acids gave immediate decomposition of the reaction mixture (entries 3 and 4).

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>time</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF/AcOH/H₂O (4:2:1)</td>
<td>20 h</td>
<td>446</td>
</tr>
<tr>
<td>2</td>
<td>CSA (10 mol%) in acetone</td>
<td>10 h</td>
<td>degradation</td>
</tr>
<tr>
<td>3</td>
<td>HF (48% aq.) in MeCN (0.5% v/v)</td>
<td>5 min</td>
<td>degradation</td>
</tr>
<tr>
<td>4</td>
<td>HCl (1 M) in acetone (20% v/v)</td>
<td>6 h</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

*100% conversion by crude ¹H NMR analysis.

Several decomposition pathways are possible for allylic acetates. A comprehensive literature search uncovered a potential complication associated with 1,3-protected diols such as cyclisation precursor 445. In 2000, Fleming and Barden reported the formation of silyl orthoesters 451 and 452 during the attempted protection of alcohol 450 (Scheme 2.133). Although no orthoesters were observed in our reactions, their formation as intermediates in degradation pathways cannot be ruled out in the cyclisations attempted above.

**Scheme 2.133.** Attempted protection of alcohol 450 by Fleming and Barden.²²⁰
Alternatively, the C-8 acetate may have facilitated a variety of side reactions, by activating the allyl alcohol toward either $\text{SN}_2'$ substitution or elimination. For these reasons, we hypothesised that use of a less electron-withdrawing protecting group might help suppress this undesired reactivity. Suitable acid-stable protecting groups are generally limited to benzyl, allyl and $p$-methoxybenzyl ethers.

**B. Attempted Ketalisation of Allyl Ether 454**

Given the problems encountered during attempted cyclisation of acetate-protected alcohol 445, the allyl protecting group was next chosen for incorporation into cyclisation precursor 454, as it has a comparable steric bulk to the acetate group. Furthermore, it was envisioned that the allyl protecting group could be readily removed by oxidative cleavage following cyclisation. It was hoped that this reaction could be performed in a one-pot procedure with concurrent alkene oxidation$^{221}$ to afford hydroxyketone 419 (Scheme 2.134). Thus, alcohol 423 was treated with sodium hydride in the presence of allylbromide and tetrabutylammonium iodide to generate allyl ether 454 in 85% yield.

![Scheme 2.134](image)

*Reagents and conditions:* (a) NaH (60% in mineral oil), allylbromide, TBAI, DMF, 18 h, 50 °C; (b) H⁺; (c) OsO₄, NaIO₄, dioxane/H₂O (3:1).

With allyl ether 454 in hand, attention turned towards its conversion to ketal 419. Disappointingly, repeated attempts effect this cyclisation proved unsuccessful. Instead, treatment of allyl ether 454 with either formic acid or Amberlyst 15® resin afforded ketone 456 (Table 2.15, entries 1 and 2). On the other hand, when acetal 454 was subjected to a solution of aqueous hydrochloric acid gave excellent conversion to a mixture of dihydroxyketone 457 and hemiacetal 458, existing as an equilibrium with one another (entry 3).
Structural assignment of the mixture of hydroxyketone 457 and hemiacetal 458 was non-trivial, with analysis of the NMR spectrum further complicated by the fact that ketone 457 exists as a ~1:1 mixture of diastereomers, which in combination with the newly formed C-2\textsubscript{b} stereocenter in hemiacetal 458 results in four possible diastereomers (Figure 2.11). However, high resolution electron-spray ionisation mass spectrometry of the mixture produced a molecular ion peak at 293.1724, corresponding to a molecular formula of C\textsubscript{15}H\textsubscript{26}O\textsubscript{4} (C\textsubscript{15}H\textsubscript{26}O\textsubscript{4} + Na has an m/z of 293.1724), as expected for both ketone 457 and hemiacetal 458, but not ketal 455.

Analysis of the $^1$H NMR spectrum of the mixture of hemiacetal 458 and hydroxyketone 457 indicated that both silyl groups present in compound 454 had been removed. The C-8 allyl ether remained intact, as evidenced by COSY correlations from H-1’ and H-3’ to the distinctive H-2’ resonance at $\delta$ 5.93–5.81 ppm. For both compounds, the H-8\textsubscript{a} and H-8\textsubscript{b} proton resonances were observed overlapping with H-1’\textsubscript{a}/\textsubscript{b} at $\delta$ 3.89–4.05 ppm. These signals were assigned on the basis of observed edited HSQC correlations to $^{13}$C NMR resonances at $\delta$ 80.5 ppm and $\delta$ 80.0 ppm, respectively. Tentative assignment of the $^1$H NMR spectrum from H-8 to H-3 of both compounds could be accomplished by careful analysis of the COSY and edited HSQC spectra. Based on earlier syntheses of similar methyl ketone and monomethyl lactol compounds (see Scheme 2.27,
(page 50), it was anticipated that H-1\textsubscript{a} and H-1\textsubscript{b} would give rise to distinct signals at $\delta \sim 2.15$ ppm and $\delta \sim 1.50$ ppm, respectively. Accordingly, a clear singlet was observed at $\delta 2.16$ ppm and assigned as H-1\textsubscript{a}, together with a multiplet at $\delta 1.51–1.48$ ppm corresponding to the four possible environments of H-1\textsubscript{b} in the four diastereomers of hemiacetal 458. The combined integral of these signals corresponded to three protons. The relative integrals of these sets of resonances was used to calculate the ratio between the open-chain species 457 and hemiacetal 458 (~2:1).

Neither mass spectrometry nor NMR analysis indicated formation of desired ketal 455 during structural analysis of the mixture of hydroxyketone 457 and hemiacetal 458. However, this does not preclude ketalisation, however disfavoured (Scheme 2.135). If this cyclisation can occur, it may be possible produce ketal 455 as the sole product in anhydrous conditions. Removal of water from the reaction medium would break down the equilibrium between hemiacetal 458 and intermediate oxonium ion 460, thus trapping the mixture solely as ketal product 455 upon cyclisation of the C-10 alcohol (Scheme 2.135).

![Scheme 2.135. Proposed mechanism for the interconversion of ketone 457 and hemiacetal 458 and proposed synthesis of acetal 455 under anhydrous acid catalysis.](image)

In order to test this hypothesis, we treated the mixture of dihydroxyketone 457 and hemiacetal 458 with mild acid in the presence of various drying agents. Reactions were conducted in anhydrous dichloromethane. To our disappointment, no cyclisation to ketal 455 was observed, with all reactions returning clean starting material (Table 2.16, entries 1–5). Exposure of ketone 457/hemiacetal 458 to triflimide under anhydrous conditions led to rapid decomposition (entry 6).
Realising that an extensive screen of acidic conditions for the synthesis of ketal 455 was unlikely to overcome the apparent thermodynamic preference for the ketone 457/hemiacetal 458 mixture, no further experimentation was conducted. The difficulties encountered in these studies clearly show that synthesis of the [6.2.1]-ring system of portimine is not facile. However, the increased structural rigidity of portimine may lead to an increased conformational ring strain that aids cyclisation. These results therefore suggest that for the natural product synthesis, ketalisation may be most readily achieved using late stage intermediates such as tricycle 461 (Scheme 2.136).

Scheme 2.136. Proposed late-stage ketalisation to generate the structural framework of portimine.

### 2.6.5 Summary

Allyl alcohol 423 was successfully synthesised as a 1.2:1 mixture of diastereomers by Nozaki-Hiyama-Kishi reaction of aldehyde 204 and vinyl iodide 422. Surprisingly, treatment of alcohol
423 with Amberlyst® 15 resin gave divergent reactivity of the C-8 epimers, affording ketal 435 and ketone 434 in a combined yield of 97% (Scheme 2.137).

Reagents and conditions: (a) Amberlyst 15®, CH₂Cl₂/acetone (1:1), 20 min, rt. (b) CrCl₂, NiCl₂, DMF/THF (3:1), 14 h, 50 °C.

Scheme 2.137. Synthesis of ketal 435.

Subsequent protection of alcohol 423, as either the acetate ester (445) or allyl ether (454), proceeded in high yield but cyclisation of either of these species under various conditions was unsuccessful. Disappointingly, model ketalisation reactions of dihydroxyketone 457 using anhydrous, acidic conditions met with failure, primarily returning unreacted starting material (Scheme 2.138). These results suggest that for the synthesis of the natural product, ketalisation must be performed at a late stage, on an advanced macrocyclic intermediate in which increased conformational ring strain can be used to facilitate spirocyclisation.

Scheme 2.138. Attempted synthesis of model ketal 419.
2.7 Overall Summary and Conclusions

In summary, an expedient synthetic approach to several viable polyketide fragments of portimine has been developed, alongside extensive examination of the proposed fragment coupling strategies. In particular aldol reactions between ketone 358 and either a glyoxal or enal electrophile were investigated, and shown to be a viable transformation for the union of the polyketide and spirocyclic fragments of portimine. Furthermore, the Nozaki-Hiyama-Kishi reaction was successfully employed in a model coupling system during studies on the subsequent macrocyclisation step.

The synthesis of vinyl bromides 238 and 239, and alkynyl bromide 237, were completed in nine steps each from commercially available ethyl levulinate. The key transformation in this sequence was a Leighton crotylation of aldehyde 135. In order to make this transformation amenable to the use of acid sensitive substrates such as aldehyde 135, a modified work-up and ligand recovery procedure was developed. Protection and oxidation of crotyl alcohol 137 allowed for an efficient, scalable, stereocontrolled synthesis of the common intermediate aldehyde 204, from which the polyketide fragment couplings were prepared (Scheme 2.139).
Reagents and conditions: (a) ethylene glycol, TsOH ∙ H₂O, benzene, 18 h, Dean-Stark reflux; (b) DIBAL (1 M in hexane), CH₂Cl₂, 2 h, −78 °C; (c) 1, DBU, THF, 2 h, 0 °C → rt then TBAF (1 M in THF), Et₂O (d) TBSOTf, 2,6-lutidine, CH₂Cl₂, 5 min, 0 °C; (e) 9-BBN dimer, THF, 3.5 h, rt, then NaOH (3 M), H₂O₂ (30% aq.); (f) SO₃py, DMSO, t-Pr₂NEt, CH₂Cl₂, 5 min, 0 °C; (g) K₂CO₃, THF, 1 h, rt; (h) AgNO₃, NBS, acetone, 2 h, rt; (i) Amberlyst 15®, acetone/CH₂Cl₂ (1:1), 15 h-20 h, rt; (j) PPh₃, CBr₄, NEt₃, CH₂Cl₂, 1 h, −78 °C → 0 °C; (k) Pd(OAc)₂, PPh₃, Bu₃SnH, CH₂Cl₂, 4 h, rt; (l) Cp₂ZrCl₂, NBS, NEt₃, CH₂Cl₂, 3 h, rt.

Scheme 2.139. Summary of the synthesis polyketide fragments 237, 238, and 239.

With reliable access to polyketide fragments 237, 238, and 239 established, we pressed forward with investigation of the key aldol fragment coupling. Recently, Feng and co-workers have developed a novel method for the asymmetric Mukaiyama aldol reaction of glyoxal electrophiles, utilising an N,N′-dioxide-nickel(II) complex. Employing this method, the reaction of silyl enol ether 359 with glyoxal 310 proceeded cleanly, albeit through an unexpected ene-type mechanism. Hydrolysis of the resultant silane generated the requisite hydroxydione moiety, furnishing alcohol 356 in moderate yield but with excellent stereocontrol over three steps. The main limitation in this reaction sequence was the generation and application of unstable glyoxal intermediate 310. To circumvent the use of this compound, an alternative route using a boron-mediated aldol reaction was briefly investigated, and found to proceed cleanly with methyl ketone 358 and model enal 370 (Scheme 2.140). It is anticipated that ozonolysis of the resultant allyl alcohol moiety would generate the requisite hydroxyketone of portimine (1).
**Reagents and conditions:** (a) TMSOTf, NEt₃, CH₂Cl₂, 1 h, −10 °C; (b) Ni(BF₄)₂·6H₂O (10 mol%), 351, CH₂Cl₂, 8 h, 25 °C; (c) trace HCl in CHCl₃, 10 h, rt; (d) Chx₂BCl, NEt₃, 370, Et₂O, 16 h, −78 °C → rt.

**Scheme 2.140.** Proposed aldol fragment coupling in the synthesis of portimine (above) and model aldol couplings of methyl ketone 358 with either glyoxal 310 or enal 370 (below).

Preliminary investigation of the proposed Nozaki-Hiyama-Kishi macrocyclisation focused on the union of protected bromoalkyne 232 with model aldehyde 381. Optimised conditions were identified, with the use of N-methylpyrrolidone as solvent found to be crucial to coupling success. Pleasingly, these conditions were found to be amenable to the coupling of bromides 237–239, without any observed interference from the ketone moiety (Scheme 2.141).
Reagents and conditions: (a) CrCl₂ NiCl₂, NMP, 16 h, 50 °C.


Finally, acid-catalysed cyclisation of a mixture of hydroxyketone 457 and hemiacetal 458 was also studied in an attempt to determine appropriate conditions for the key ketalisation step in the synthesis of portimine. However, this reaction proved unsuccessful using a range of Brønsted acids. The inability to effect ketalisation of open chain 457 suggests that the structural rigidity provided by the spirocyclic imine may be essential to effect cyclisation in the ultimate synthesis of the natural product (Scheme 2.142).

Scheme 2.142. Attempted synthesis of ketal 455 by acid-catalysed cyclisation.

The synthetic studies reported herein describe a thorough examination of the polyketide fragment of portimine (1), including potential fragment coupling strategies, and provide a strong basis from which a convergent total synthesis of portimine (1) may now be framed. Furthermore, these efforts may also allow synthetic access to structural analogues in order to facilitate a detailed exploration of the biological mode of action and cellular targets of portimine.
2.8 Future Work

The synthetic studies reported herein have uncovered several novel reactivity pathways, and provide a solid foundation for future efforts towards the total synthesis of the marine toxin portimine (1). However, this endeavour still poses several major synthetic challenges.

2.8.1 Synthesis of the Spirocyclic Fragment 468 or 470

Synthetic studies reported in this thesis have focused on efforts towards the polyketide fragment of portimine (1) and investigations into model fragment couplings. At present, however, work towards the spirocyclic fragment 466 is ongoing within our laboratory. A proposed synthesis of this key intermediate involves an exo-selective Diels-Alder reaction between exo-methylene lactam 463 and bromodiene 464 (Scheme 2.143). If successful, an enantioselective variant of this transformation could potentially be developed employing a chiral catalyst such as Evan’s copper(II)-bis(oxazoline) complex or Corey’s oxazaborolidine-aluminum bromide complex, both of which have successfully been employed in similar cycloadditions. Palladium-mediated cross-coupling of bromide 465 may be employed to install the diene functionality.

![Scheme 2.143. Proposed synthesis of spirocyclic lactam 466.](image)

Elaboration of spirocyclic lactam 466 to glyoxal coupling fragment 468 may be achieved following an analogous route to that used for the synthesis of glyoxal model 310 (see Scheme 2.77, page 83). Alternatively, if spirocyclic glyoxal 468 was found to be too unstable for use in the total synthesis of portimine then lactam 466 may also be converted to enal 470 following a sequence of reduction and homologation, then exo-methylene installation to the resultant aldehyde 469 (Scheme 2.144). Either glyoxal 468 or enal 470 may be employed as electrophiles in an aldol fragment coupling, similar to the model reactions performed in the present work.
2.8.2 Preparation of the $\alpha,\alpha'$-Dihydroxyketone Moiety

Initially, we proposed that stereoselective synthesis of the challenging $\alpha,\alpha'$-dihydroxyketone moiety could be achieved by hydroxyl-directed dihydroxylation of either an $E$- or $Z$-allyl alcohol, followed by selective oxidation of the resultant triol (Scheme 2.145). However, preparation of this unusual functionality is yet to be fully investigated in the present work. In particular, it is unclear how the allyl alcohol olefin geometry will relate to the diol stereochemistry after oxidation.

Another potential issue encountered in this oxidation procedure is the proposed use of Waymouth’s palladium complex 129 for the chemoselective oxidation of triol 472. Application of this complex for the oxidation of an acyclic or macrocyclic system would potentially represent a significant extension in the substrate scope of this transformation.
A. Model Systems 474 and 475

Z- and E- allyl alcohols 391a and 392a—prepared during initial studies on the Nozaki-Hiyama-Kishi fragment coupling—may potentially be elaborated to simple 14-membered macrocycles 474 and 475, respectively, by functional group manipulation and ring-closing enolate alkylation. These compounds may be applied to a detailed investigation of the proposed oxidation to the \( \alpha,\alpha' \)-dihydroxyketone moiety, in order to develop optimised reaction conditions and determine how olefin geometry, ring strain and conformation will impact the stereoselectivity of the proposed dihydroxylation (Scheme 2.146).

Scheme 2.146. Proposed model systems for investigation of the stereocontrolled oxidation of macrocyclic allyl alcohols 474 and 475.

B. Application to the Total Synthesis of Portimine

Following identification of the olefin isomer most appropriate for the stereocontrolled allyl alcohol oxidation to generate the requisite \( \alpha,\alpha' \)-dihydroxyketone functionality, this methodology must then be applied \textit{en route} to the total synthesis of portimine. It is anticipated that the fragment coupling strategies investigated in the present work will be amenable for the preparation of the appropriate allyl alcohol precursor 477 or 478. Thus, with a reliable synthesis of either spirocyclic fragment 468 or 470 in hand, and allyl alcohol oxidation conditions established during the synthesis of model macrocyclic system 476 the preparation and oxidation of macrocycle 477 or 478 must be undertaken (Scheme 2.147). Aside from the key coupling reactions, it is anticipated that the major synthetic problem posed by this strategy would be the chemoselective allyl alcohol dihydroxylation in the presence of the diene moiety. However, selective oxidations directed by hydroxyl-metal coordination are well known.\textsuperscript{65a, 66, 224}
2.8.3 Total Synthesis of the Marine Toxin Portimine

Once reliable access to \(\alpha,\alpha'-\text{dihydroxyketone} 480\) is achieved, imine condensation and ketalisation would complete the synthesis of portimine (Scheme 2.148). The selective cyclisation to ketal 480 may pose a significant synthetic challenge, in light of the findings reported herein. However, it is anticipated that the structural rigidity provided by the spiroimine subunit may facilitate this reaction.

Scheme 2.148. Proposed late-stage cyclisations in the preparation of the marine toxin portimine (1).
CHAPTER THREE

Experimental
**Experimental Section**

**General Procedures.** Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen using standard techniques. Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl. CH₂Cl₂ was freshly distilled from calcium hydride. All other reagents were used as received unless otherwise noted. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as the visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Silica gel (60, 230–400 mesh) was used for flash column chromatography. NMR spectra were recorded at room temperature in CDCl₃ solution on either a spectrometer operating at 500 MHz for ¹H nuclei and 125 MHz for ¹³C nuclei or a spectrometer operating at 400 MHz for ¹H nuclei and 100 MHz for ¹³C nuclei. Chemical shifts are reported in parts per million on the δ scale, and coupling constants, J, are in hertz. 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” (multiplet). Where distinct from those due to the major diastereomer, resonances due to minor diastereomers are denoted by an asterisk. ¹H and ¹³C NMR resonances were assigned using a combination of DEPT 135, COSY, HSQC, HMBC, and NOESY spectra. Infrared (IR) spectra were recorded using a thin film on a composite of zinc selenide and diamond crystal on an FT-IR system transform spectrometer. Melting points are uncorrected. High resolution mass spectrometry (HRMS) was performed using a spectrometer operating at a nominal accelerating voltage of 70 eV or a TOF-Q mass spectrometer. All values reported at 3sf except when V < 10mL, n < 1 mmol, m <100 mg, then reported at 2sf.
Potassium (Z)-but-2-en-1-yltrifluoroborate 138

\[
\begin{array}{c}
\text{BF}_3\text{K} \\
\text{3} \\
\text{4} \\
\text{1}
\end{array}
\]

To a solution of \textit{cis}-butene (6.0 mL, 69.0 mmol) in tetrahydrofuran (40 mL) at −78 °C was added potassium \textit{tert}-butoxide (6.85 g, 61.0 mmol) followed by \textit{n}-butyllithium (38 mL, 1.6 M in hexane, 61.0 mmol) dropwise over 20 min. The reaction mixture was then warmed to −25 °C for 45 min then recooled to −78 °C and triisopropylborate (15.9 mL, 69.0 mmol) was added dropwise over 10 min and stirred for a further 45 min. The reaction mixture was then rapidly poured into aqueous hydrochloric acid (1 M, 100 mL) saturated with sodium chloride and the aqueous layer extracted with ethyl acetate (3 × 80 mL). The combined organic layers were concentrated \textit{in vacuo} and dissolved in methanol (7 mL) and added to a stirred solution of potassium bifluoride (16.7 g, 214 mmol) in water (60 mL). After 30 min the reaction mixture was removed from stirring and cooled to 0 °C for 12 h. The resultant white precipitate was collected \textit{via} vacuum filtration. Purification by recrystallisation from acetonitrile afforded the title product 138 (5.18 g, 52%) as a colourless white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 5.57–5.49 (m, 1H, H-3), 5.14–5.07 (m, 1H, H-2), 1.53 (dtd, $J = 6.6, 0.8, 0.8$ Hz, 3H, H-4), 0.95 (bs, 2H, H-1). The data obtained were in agreement with that reported in the literature.$^{72}$
To a solution of hydrochloric acid (7.3 mL, 12 M, 87.6 mmol) in methanol (30 mL) at 0 °C was added (1S,2S)-cyclohexane-1,2-diamine (10.0 g, 87.6 mmol) and the solution warmed to room temperature over 20 min. Water (10 mL) was added to the reaction mixture followed by a solution of di-tert-butyl dicarbonate (20.0 g, 92.0 mmol) in methanol (10 mL) after 15 min. The reaction mixture was stirred for 16 h then concentrated in vacuo and dissolved in dichloromethane (60 mL). The mixture was quenched with aqueous sodium hydroxide (40 mL) and extracted with dichloromethane (3 × 60 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by gradient flash chromatography using hexanes/ethyl acetate (3:1) then ethyl acetate/methanol (3:1) as eluent afforded the title product 179 (12.7 g, 67%) as a white solid.

**mp:** 113–115 °C; [α]D 20: 30 (c 3.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ: 4.44 (s, 1H), 3.23–3.00 (m, 1H), 2.31 (td, J = 10.3, 4.0 Hz, 1H), 2.06–1.88 (m, 2H), 1.78–1.63 (m, 2H), 1.44 (s, 9H), 1.39–1.04 (m, 6H). The data obtained were in agreement with that reported in the literature.91
To a suspension of paraformaldehyde (8.83 g, 294 mmol) in acetonitrile (100 mL) was added magnesium chloride (8.61 g, 90.4 mmol), tert-butylphenol (7.0 mL, 45.2 mmol), and triethylamine (22.0 mL, 158 mmol) and the suspension heated to reflux for 16 h. The reaction mixture was then cooled to room temperature, quenched with aqueous hydrochloric acid (80 mL, 2 M) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by distillation (140 °C, 50 mbar) afforded the title compound 181 (3.70 g, 46%) as a pale yellow oil. 

**1H NMR** (400 MHz, CDCl₃) δ: 11.78 (s, 1H), 9.88 (s, 1H), 7.53 (dd, $J = 7.6$, 1.7 Hz, 1H), 7.40 (dd, $J = 7.7$, 1.7 Hz, 1H), 6.95 (dd, $J = 7.7$, 7.6 Hz, 1H), 1.42 (s, 9H). The data obtained were in agreement with that reported in the literature.⁹¹
**tert-Butyl ((1S,2S)-2-(((E)-3-(tert-butyl)-2-hydroxybenzylidene)amino)cyclohexyl)carbamate**

To a solution of aldehyde 181 (7.51 g, 42.1 mmol) in ethanol (250 mL) was added amine 179 (9.03 g, 42.1 mmol) and the solution heated to reflux for 5 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo*. The resultant crude residue was used without further purification for the next step. An analytic sample of the *title compound* 182 was purified as long yellow needles by recrystallisation from ethanol.

**mp**: 152–154 °C, lit. 153–155 °C\(^9\); **\([\alpha]\)\(^D\)**: 110 (c 1.2, CHCl\(_3\)); **\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\): 13.71 (s, 1H), 8.32 (s, 1H), 7.32 (dd, \(J = 7.7\), 1.7 Hz, 1H), 7.08 (dd, \(J = 7.6\), 1.7 Hz, 1H), 6.79 (dd, \(J = 7.7\), 7.6 Hz, 1H), 4.34 (s, 1H), 3.63–3.40 (m, 1H), 3.01 (s, 1H), 2.12–2.05 (m, 1H), 1.92–1.85 (m, 1H), 1.82–1.65 (m, 3H), 1.42 (s, 9H), 1.41–1.32 (m, 3H), 1.31 (s, 9H). The data obtained were in agreement with that reported in the literature.\(^9\)
To a suspension of lithium aluminium hydride (4.79 g, 126 mmol) in tetrahydrofuran (250 mL) at −10 °C was cannulated a solution of crude imine 182 (~42.1 mmol) in tetrahydrofuran (100 mL) over 10 min. The suspension was warmed to room temperature, stirred for 30 min, and then heated to reflux. After 12 h the mixture was cooled to −10 °C and carefully quenched with aqueous sodium hydroxide (4.8 mL, 3 M) followed by water (4.8 mL), diluted with diethyl ether (300 mL), and stirred for 15 min before magnesium sulfate (6 g) was added. After a further 30 min of vigorous stirring the mixture was filtered and concentrated in vacuo. The residue was washed with hexanes to afford the title compound 177 (10.8 g, 88% over 2 steps) as a white solid. mp: 112–114 °C, lit. 114–116 °C; \([\alpha]_D^{20}\): 106 (c 1.3, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ: 7.17 (dd, J = 7.8, 1.7 Hz, 1H, H-3), 6.89 (m, 1H, H-5), 6.70 (t, J = 7.6 Hz, 1H, H-5′), 3.93 (ABq, Δδ_{AB} = 0.18, J_{AB} = 13.5 Hz, 2H, H-7), 2.39 (s, 3H, NHCH₃), 2.21–2.11 (m, 4H, H-1′, H-2′, 1 × H-3′, 1 × H-6′) 1.78–1.70 (m, 2H, 1 × H-3′, 1 × H-6′), 1.42 (s, 9H, C(CH₃)₃), 1.29–1.15 (m, 3H, H-5′, 1 × H-4′), 1.15–1.03 (m, 1H, 1 × H-4′). The data obtained were in agreement with that reported in the literature.
To a slurry of trichlorosilane (12.0 mL, 119 mmol) and tetrakis(triphenylphosphine) palladium(0) (2.74 g, 2.37 mmol) in a Schlenk tube at −78 °C under argon was cannulated butadiene (12.4 mL, 142 mmol) condensed at -78 °C in a graduated cylinder. The slurry was allowed to slowly warm to room temperature over 5 days, diluted with diethyl ether (100 mL), filtered through cotton wool, and concentrated under reduced pressure. Purification by distillation (138 °C, 150 mbar) afforded the title compound 184 (13.7 g, 61%) as a colourless oil.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\): 5.75–5.69 (m, 1H, H-2), 5.48–5.37 (m, 1H, H-3), 2.39–2.33 (m, 2H, H-1), 1.70–1.65 (m, 3H, H-4). The data obtained were in agreement with that reported in the literature.\(^{225}\)
To a suspension of sodium hydride (60% in mineral oil, 5.63 g, 141 mmol) in tetrahydrofuran (80 mL) at 0 °C was added 1,4-butandiol (19.2 g, 213 mmol) in tetrahydrofuran (25 mL) dropwise. After 30 min tetrabutylammonium iodide (4.70 g, 12.8 mmol) was added, followed by p-methoxybenzyl chloride (17.3 mL, 128 mmol) dropwise, and the mixture allowed to warm slowly to room temperature over 20 h. The reaction was quenched with saturated ammonium chloride (80 mL), extracted with ethyl acetate (2 × 100 mL) and the combined organic layers were dried over sodium sulfate and concentrated1808018 in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (1:1) as eluent afforded the title product 148 (27.1 g, quantitative) as a colourless oil.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\): 7.28–7.23 (m, 2H, Ar-H), 6.90–6.85 (m, 2H, Ar-H), 4.45 (s, 2H, O\(\text{C}_6\text{H}_4\text{OCH}_3\)), 3.80 (s, 3H, O\(\text{C}_6\text{H}_4\text{OCH}_3\)), 3.63 (t, \(J = 5.4\) Hz, 2H, H-1), 3.49 (t, \(J = 5.8\) Hz, 2H, H-4), 2.30 (s, 1H, 1-OH) 1.75–1.61 (m, 4H, H-2, H-3). The data obtained were in agreement with that reported in the literature.226
To a solution of oxalyl chloride (3.7 mL, 42.8 mmol) in dichloromethane (60 mL) at −78 °C was added dimethyl sulfoxide (6.1 mL, 85.6 mmol) dropwise. After 20 min a solution of alcohol 148 (6.00 g, 28.5 mmol) in dichloromethane (15 mL) was added dropwise and the solution stirred for 2 h. Triethylamine (20.0 mL, 143 mmol) was then added dropwise and the reaction mixture allowed to warm slowly to room temperature. After 20 min the mixture was quenched with brine (20 mL), extracted with dichloromethane (2 × 60 mL) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (3:1) as eluent afforded the title product 146 (5.58 g, 94%) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 9.77 (td, $J = 1.6$, 0.6 Hz, 1H, H-1), 7.25–7.22 (m, 2H, Ar-H), 6.89–6.86 (m, 2H, Ar-H), 4.41 (s, 2H, OCH$_2$C$_6$H$_4$OCH$_3$), 3.80 (d, $J = 0.6$ Hz, 3H, OCH$_2$C$_6$H$_4$OCH$_3$), 3.47 (t, $J = 6.3$ Hz, 2H, H-4), 2.53 (td, $J = 6.9$, 1.2 Hz, 2H, H-2), 1.92 (tt, $J = 6.9$, 6.5 Hz, 2H, H-3). The data obtained were in agreement with that reported in the literature.$^{227}$
**Method A:**

To a solution of cis-butene (1.6 mL, 15.6 mmol) in tetrahydrofuran (20 mL) at −78 °C was added potassium tert-butoxide (1.41 g, 12.6 mmol) followed by n-butyllithium (12.6 mL, 1 M in cyclohexane, 12.6 mmol) dropwise over 5 min. The reaction mixture was then warmed to −55 °C for 45 min then recooled to −78 °C and a solution of (+)-B-methoxydiisopinocampheylborane (4.180 g, 13.2 mmol) in tetrahydrofuran (20 mL) was added dropwise. After 30 min boron trifluoride etherate (1.9 mL, 15.6 mmol) was added dropwise, followed by a solution of aldehyde 146 (2.50 g, 12.0 mmol) in tetrahydrofuran (30 mL), dropwise over 10 min. After a further 3 h, sodium hydroxide (5.8 mL, 3 M) and aqueous hydrogen peroxide (30% w/w, 2.3 mL) were added dropwise concurrently. After 16 h the reaction was diluted with water (40 mL) and extracted with diethyl ether (3 × 80 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (4:1 then again with 9:1→2:1) as eluent afforded the title product 149 (2.01 g, 63%, 18:1 mixture of diastereomers) as a colourless oil.

**Method B:**

To a solution of ligand 177 (6.75 g, 23.2 mmol) and 1,8-diazabicycloundec-7-ene (10.4 mL, 69.3 mmol) in dichloromethane (50 mL) at 0 °C was added Z-but-2-en-1-yltrichlorosilane (184) (4.0 mL, 25.3 mmol) dropwise and the mixture allowed to warm to room temperature. After 1 h the solution was cooled to 0 °C and aldehyde 146 (4.40 g, 21.1 mmol) was added dropwise. After 2 h the reaction was concentrated in vacuo and suspended in diethyl ether (80 mL) and vigorously stirred for 20 min then filtered to remove the resultant precipitate. To the filtrate was added tetrabutylammonium fluoride (23.2 mL, 1 M, 23.2 mmol). After 30 min the mixture was diluted with hydrochloric acid (1 M, 116 mL) and extracted with ether (3 × 100 mL). The aqueous layer was set aside and the combined organic layers were washed with saturated sodium bicarbonate (250 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (3:1) as eluent afforded the title product 149 (5.11 g, 91%) in 92% ee as a yellow oil. Ligand 177 (6.20 g, 92%) was recovered as beige needles from the aqueous layer following the procedure of Leighton and co-workers.αD20: −20.1 (c
1.9, CHCl₃); \textbf{IR spectrum} (film), cm⁻¹: 3441, 2934, 2865, 1613, 1512, 1245, 1034, 819;

\textbf{¹H NMR} (400 MHz, CDCl₃) δ: 7.27–7.24 (m, 2H, Ar-H), 6.89–6.86 (m, 2H, Ar-H), 5.79 (ddd, \(J = 17.1, 10.5, 7.5\) Hz, 1H, H-6), 5.09–5.03 (m, 2H, H-7), 4.45 (s, 2H, OCH₂C₆H₄OCH₃), 3.80 (s, 3H, OCH₂C₆H₄OCH₃), 3.49–3.44 (m, 3H, H-4, H-1), 2.30–2.22 (m, 2H, H-5, 4-OH), 1.80–1.62 (m, 3H, 1 × H-3, H-2), 1.45–1.36 (m, 1H, 1 × H-3), 1.03 (d, \(J = 6.8\) Hz, 3H, 3-CH₃);

\textbf{¹³C NMR} (100 MHz, CDCl₃) δ: 159.3 (Ar-C), 141.3 (C-6), 130.5 (Ar-C), 129.5 (2 × Ar-CH), 115.1 (C-7), 113.9 (2 × Ar-CH), 74.7 (C-4), 72.8 (OCH₂C₆H₄OCH₃), 70.3 (C-1), 55.4 (OCH₂C₆H₄OCH₃), 43.8 (C-5), 31.6 (C-3), 26.7 (C-2), 14.8 (5-CH₃); \textbf{HRMS} [ESI, (M+Na)⁺] \(m/z\): calculated for (C₁₆H₂₄NaO₃) 287.1618, found: 287.1615.
To a solution of alcohol 149 (10 mg, 0.038 mmol) in dichloromethane (0.5 mL) was added a solution of (R)-(+)\(\alpha\)-methoxy\(\alpha\)-trifluoromethylphenylacetic acid (13 mg, 0.058 mmol) in dichloromethane (0.5 mL), followed by \(N,N'\)-dicyclohexylcarbodiimide (20 mg, 0.095 mmol) and 4-dimethylaminopyridine (0.92 mg, 0.0076 mmol). The reaction mixture was stirred for 16 h then filtered from a plug of Celite and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (3:1) as eluent afforded the title product 186a (18.4 mg, quant.) in 92% de as a colourless oil.

**IR spectrum** (film), cm\(^{-1}\): 2952, 2853, 1742, 1513, 1246, 1167, 1017, 718; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.57–7.53 (m, 2H, Ar-H), 7.41–7.34 (m, 3H, Ar-H), 7.27–7.21 (m, 2H, Ar-H), 6.90–6.85 (m, 2H, Ar-H), 5.64 (ddd, \(J = 17.4, 10.5, 7.2\) Hz, 1H, H-2), 5.10–5.04 (m, 1H, H-4), 5.01–4.93 (m, 2H, H-1), 4.41 (s, 2H, 1-OCH\(_2\)C\(_6\)H\(_4\)OC\(_3\)H\(_3\)), 3.81 (s, 3H, 1-OCH\(_2\)C\(_6\)H\(_4\)OC\(_3\)H\(_3\)), 3.55–3.52 (m, 3H, 2\(^{\prime}\)-C\(_3\)H\(_3\)), 3.47–3.36 (m, 2H, H-7), 2.53–2.42 (m, 1H, H-3), 1.81–1.52 (m, 4H, H-5, H-6), 0.95 (d, \(J = 6.9\) Hz, 3H, 3-CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 166.4 (C-1\(^{\prime}\)), 159.3 (Ar-C), 139.1 (C-2), 132.4 (Ar-C), 130.7 (Ar-C), 129.7 (Ar-CH), 129.4 (2 \(\times\) Ar-CH), 128.5 (2 \(\times\) Ar-CH), 127.6 (2 \(\times\) Ar-CH), 125.0 (2\(^{\prime}\)-CF\(_3\)), 122.1 (C-2\(^{\prime}\)), 115.8 (C-1), 113.9 (2 \(\times\) Ar-CH), 80.1 (C-4), 72.6 (7-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 69.4 (C-7), 55.6 (2\(^{\prime}\)-OCH\(_3\)), 55.4 (7-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 40.7 (C-3), 28.0 (C-5), 25.7 (C-6), 14.8 (3-CH\(_3\)); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\): -71.15 (2\(^{\prime}\)-CF\(_3\)); HRMS [ESI, (M+Na)]\(^+\) \(m/z\): calculated for (C\(_{26}\)H\(_{31}\)F\(_3\)NaO\(_5\)) 503.2016, found: 503.2013.
(3S,4S)-7-(4-Methoxybenzyl(oxy)-3-methylhept-1-en-4-yl (S)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 186b

To a solution of alcohol 149 (10 mg, 0.038 mmol) in dichloromethane (0.5 mL) was added a solution of (S)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (13 mg, 0.058 mmol) in dichloromethane (0.5 mL), followed by \( \text{N,N’-dicyclohexylcarbodiimide (20 mg, 0.095 mmol) and 4-dimethylaminopyridine (0.92 mg, 0.0076 mmol). The reaction mixture was stirred for 16 h then filtered through a plug of Celite and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (3:1) as eluent afforded the title product 186b (17.8 mg, 98%) in 92% de as a colourless oil.}

**IR spectrum** (film), cm\(^{-1}\): 2952, 2853, 1742, 1513, 1247, 1168, 1018, 718; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 7.57–7.53 (m, 2H, Ar-H), 7.44–7.34 (m, 3H, Ar-H), 7.25–7.20 (m, 2H, Ar-H), 6.90–6.84 (m, 2H, Ar-H), 5.75 (ddd, \( J = 17.1, 10.5, 6.8 \text{ Hz} \), 1H, H-2), 5.11–5.02 (m, 3H, H-1, H-4), 4.37 (s, 2H, 1-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 3.81 (s, 3H, 1-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 3.54–3.52 (m, 3H, 2′-OCH\(_3\)), 3.42–3.30 (m, 2H, H-7), 2.58–2.48 (m, 1H, H-3), 1.76–1.40 (m, 4H, H-5, H-6), 1.02 (d, \( J = 7.0 \text{ Hz} \), 3H, 3-CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 166.5 (C-1′), 159.3 (Ar-C), 139.3 (C-8), 132.4 (Ar-C), 130.7 (Ar-C), 129.7 (Ar-C), 129.3 (2 × Ar-C), 128.5 (2 × Ar-C), 127.7 (2 × Ar-C), 125.0 (2′-CF\(_3\)), 122.1 (C-2′), 115.9 (C-1′), 113.9 (2 × Ar-C), 80.2 (C-4), 72.6 (7-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 69.4 (C-7), 55.6 (2′-OCH\(_3\)), 55.4 (7-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 40.7 (C-3), 27.7 (C-5), 25.4 (C-6), 14.9 (3-CH\(_3\)); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \): –71.12 (2′-CF\(_3\)); HRMS [ESI, (M+Na\(^+\))] \( m/z \): calculated for (C\(_{26}\)H\(_{31}\)F\(_3\)NaO\(_5\)) 503.2016, found: 503.2013.
To a solution of alcohol \(149\) (4.56 g, 17.2 mmol) and 2,6-lutidine (6.0 mL, 51.6 mmol) in dichloromethane (10 mL) at 0 °C was added tert-butyldimethylsilyl trifluoromethanesulfonate (4.8 mL, 20.7 mmol) dropwise. After 30 min the reaction was quenched with saturated ammonium chloride (20 mL), extracted with dichloromethane (2 × 20 mL) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (50:1) as eluent afforded the title product \(207\) (6.31 g, 97%) as a colourless oil.

\([\alpha]_D^{20}: -12.8\) (c 1.2, CHCl₃); \textbf{IR spectrum} (film), cm\(^{-1}\): 2955, 2856, 1513, 1246, 1090, 1037, 832, 772; \textbf{\(^1\)H NMR} (400 MHz, CDCl₃) \(\delta\): 7.27–7.24 (m, 2H, Ar-H), 6.89–6.86 (m, 2H, Ar-H), 5.89–5.80 (m, 1H, H-6), 5.02–4.99 (m, 1H, 7 × H-1), 4.89–4.96 (m, 1H, 1 × H-7), 4.42 (s, 2H, OCH₂C₆H₄OCH₃), 3.80 (s, 3H, OCH₂C₆H₄OCH₃), 3.56–3.52 (m, 1H, H-4), 3.46–3.37 (m, 2H, H-1), 2.34–2.26 (m, 2H, H-5), 1.74–1.37 (m, 4H, H-2, H-3), 0.96 (d, \(J = 6.9\) Hz, 3H, 5-C₃H₃) 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃); \textbf{\(^{13}\)C NMR} (100 MHz, CDCl₃) \(\delta\): 159.2 (Ar-C), 141.5 (C-6), 131.0 (Ar-C), 129.3 (2 × Ar-CH), 114.0 (C-7), 113.9 (2 × Ar-CH), 75.9 (C-1), 72.6 (OCH₂C₆H₄OCH₃), 70.5 (C-4), 55.4 (OCH₂C₆H₄OCH₃), 42.9 (C-5), 30.3 (C-3), 26.1 (Si(CH₃)₂C(CH₃)₃), 25.7 (C-2), 18.3 (Si(CH₃)₂C(CH₃)₃), 15.2 (3-C₃H₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃); \textbf{HRMS} [ESI, (M+Na)⁺] \(m/z\): calculated for (C₂₂H₃₈NaO₃Si) 401.2482, found: 401.2488.
To a solution of alkene 207 (2.10 g, 5.55 mmol) in tetrahydrofuran (40 mL) was added 9-borabicyclo[3.3.1]nonane dimer (2.71 g, 11.1 mmol) with vigorous stirring. After 5 h sodium hydroxide (37 mL, 3 M) and aqueous hydrogen peroxide (30% w/w, 11.4 mL) were added dropwise concurrently. After 16 h the reaction was diluted with water (40 mL) and extracted with diethyl ether (3 × 80 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (4:1) as eluent afforded the title product 208 (2.13 g, 97%) as a colourless oil.

\[ \alpha \] _D^20: −3.5 (c 1.3, CHCl₃); **IR spectrum** (film), cm⁻¹: 3426, 2954, 2856, 1613, 1513, 1246, 1036, 832, 772; **¹H NMR** (400 MHz, CDCl₃) δ: 7.27–7.24 (m, 2H, Ar-H), 6.89–6.86 (m, 2H, Ar-H), 4.43 (s, 2H, OCH₂C₆H₄OCH₃), 3.80 (s, 3H, OCH₂C₆H₄OCH₃), 3.69–3.55 (m, 3H, H-1, H-4), 3.48–3.38 (m, 2H, H-7), 2.45 (s, 1H, 1-OH), 1.81–1.65 (m, 3H, H-3, 1 × H-5, 1 × H-6), 1.56–1.46 (m, 3H, H-2, 1 × H-6), 1.42–1.34 (m, 1H, 1 × H-5), 0.90 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.87 (d, J = 6.8 Hz, 3H, 3-CH₃), 0.06 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃), 0.06 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 159.3 (Ar-C), 130.9 (Ar-C), 129.4 (2 × Ar-CH), 113.9 (2 × Ar-CH), 76.7 (C-4), 72.7 (OCH₂C₆H₄OCH₃), 70.3 (C-7), 62.1 (C-1), 55.4 (OCH₂C₆H₄OCH₃), 37.1 (C-3), 35.6 (C-5), 28.9 (C-2), 26.8 (C-6), 26.1 (Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 16.9 (3-CH₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃), −4.3 (1 × Si(CH₃)₂C(CH₃)₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₂₂H₄₀NaO₄Si) 419.2588, found: 419.2582.
To a solution of alcohol 208 (2.65 g, 6.68 mmol), dimethyl sulfoxide (4.7 mL, 66.8 mmol), and diisopropylethylamine (5.83 mL, 33.4 mmol) in dichloromethane (50 mL) at 0 °C was added sulfur trioxide-pyridine complex (3.19 g, 20.0 mmol) in one portion. After 10 min the reaction was quenched with saturated ammonium chloride (40 mL) and washed with brine (40 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (6:1) as eluent afforded the title product 209 (2.49 g, 94%) as a colourless oil.

$[\alpha]_{D20}^20$: 0.0 (c 2.2, CHCl$_3$); IR spectrum (film), cm$^{-1}$: 2955, 2857, 1724, 1513, 1247, 1035, 833, 773; $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.75 (t, $J$ = 2.0 Hz, H-1), 7.27–7.23 (m, 2H, Ar-H), 6.89–6.86 (m, 2H, Ar-H), 4.43 (s, 2H, OCH$_2$C$_6$H$_4$OCH$_3$), 3.80 (s, 3H, OCH$_2$C$_6$H$_4$OCH$_3$), 3.60–3.56 (m, 1H, H-4), 3.48–3.39 (m, 2H, H-7), 2.64–2.55 (m, 1H, 1 × H-2), 2.29–2.16 (m, 2H, 1 × H-2, H-3), 1.74–1.64 (m, 1H, 1 × H-6), 1.58–1.47 (m, 2H, 1 × H-5, 1 × H-6), 1.40–1.30 (m, 1H, 1 × H-5), 0.91–0.86 (m, 12H, 3 × CH$_3$, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.04 (s, 3H, 1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.03 (s, 3H, 1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 202.9 (C-1), 159.3 (Ar-C), 130.8 (Ar-C), 129.4 (2 × Ar-CH), 113.9 (2 × Ar-CH), 75.2 (C-4), 72.7 (OCH$_2$C$_6$H$_4$OCH$_3$), 70.2 (C-7), 55.4 (OCH$_2$C$_6$H$_4$OCH$_3$), 46.9 (C-2), 33.5 (C-3), 29.4 (C-5), 26.5 (C-6), 26.0 (3 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 18.2 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 15.3 (3-CH$_3$), −4.2 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), −4.2 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); HRMS [ESI, (M+H)$^+$] m/z: calculated for (C$_{22}$H$_{39}$O$_4$Si) 395.2612, found: 395.2591.
To a suspension of potassium carbonate (398 mg, 2.88 mmol) in methanol (4 mL) was added dimethyl (1-diazo-2-oxopropyl)phosphonate (0.67 mL, 2.88 mmol). After 20 min a solution of 209 (555 mg, 1.41 mmol) in methanol (2 mL) was added. The reaction was stirred for 40 min diluted with water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (19:1) as eluent afforded the title product 228 (425 mg, 77%) as a colourless oil.

$[\alpha]_D^{20}$: $-5.2$ (c 1.2, CHCl$_3$); IR spectrum (film), cm$^{-1}$: 2955, 2856, 1613, 1513, 1247, 1089, 1034, 832, 772; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.28–7.23 (m, 2H, Ar-H), 6.90–6.85 (m, 2H, Ar-H), 4.43 (s, 2H, 1-OCH$_2$C$_6$H$_4$OCH$_3$), 3.81 (s, 3H, 1-OCH$_2$C$_6$H$_4$OCH$_3$), 3.71 (td, $J = 6.1$, 3.3 Hz, 1H, H-4), 3.43 (t, $J = 6.4$ Hz, 2H, H-1), 2.28 (ddd, $J = 16.6$, 6.3, 2.7 Hz, 1H, 1 × H-6), 2.03 (ddd, $J = 16.6$, 7.9, 2.7 Hz, 1H, 1 × H-6), 1.93 (t, $J = 2.6$ Hz, 1H, H-8), 1.84–1.72 (m, 1H, H-5), 1.68–1.39 (m, 4H, H-2, H-3), 0.93 (d, $J = 6.8$ Hz, 3H, 5-CH$_3$), 0.88 (s, 9H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.05 (s, 3H, 1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.05 (s, 3H, 1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 159.3 (Ar-C), 130.9 (Ar-C), 129.4 (2 × Ar-CH), 113.9 (2 × Ar-CH), 84.3 (C-7), 74.0 (C-1), 72.6 (OCH$_2$C$_6$H$_4$OCH$_3$), 70.2 (C-4), 69.0 (C-8), 55.4 (OCH$_2$C$_6$H$_4$OCH$_3$), 37.6 (C-5), 30.4 (C-3), 26.2 (C-2), 26.1 (3 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 22.3 (C-6), 18.3 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 13.9 (5-CH$_3$), -4.1 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), -4.4 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); HRMS [ESI, (M+H)$^+$] m/z: calculated for (C$_{23}$H$_{39}$O$_3$Si) 391.2663, found: 391.2650.
To a solution of alkyne 228 (100 mg, 0.256 mmol) in dichloromethane (2 mL) under argon was added zirconocene hydrochloride (86 mg, 0.333 mmol) followed by a further portion of zirconocene hydrochloride (20 mg, 0.078 mmol) after 1 h. The reaction was stirred for 30 min and N-bromosuccinimide (73 mg, 0.410 mmol) was added in one portion. After 2 h the mixture was diluted with saturated aqueous sodium bicarbonate (3 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were washed with brine (6 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (9:1 + 0.25% triethylamine) as eluent afforded the title product 229 (118 mg, 97%) as a colourless oil alongside trace alkene 483.

$[\alpha]_D^{20} : -2.6$ (c 1.3, CHCl₃); IR spectrum (film), cm⁻¹: 2927, 2854, 1614, 1512, 1247, 1091, 1038, 834, 772; $^1$H NMR (400 MHz, CDCl₃) δ: 7.27–7.24 (m, 2H, Ar-H), 6.90–6.86 (m, 2H, Ar-H), 6.13 (ddd, $J = 13.5$, 8.1, 7.0 Hz, H-7), 5.99 (d, $J = 13.5$ Hz, H-8), 4.43 (s, 2H, OCH₂C₆H₄OCH₃), 3.81 (s, 3H, OCH₂C₆H₄OCH₃), 3.56–3.53 (td, m, 1H, H-4), 3.42 (td, $J = 6.3$, 2.0 Hz, 2H, H-1), 2.27–2.20 (m, 1H, 1 × H-6), 1.84–1.76 (m, 1H, 1 × H-6), 1.69–1.34 (m, 5H, H-2, H-3, H-5), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.83 (d, $J = 7.2$ Hz, 3H, 5-CH₃), 0.03 (s, 6H, 2 × Si(CH₃)₂C(CH₃)₃), 0.02 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); $^{13}$C NMR (100 MHz, CDCl₃) δ: 159.3 (Ar-C), 137.6 (C-7), 130.9 (Ar-C), 129.4 (2 × Ar-CH), 113.9 (2 × Ar-CH), 104.7 (C-8), 75.3 (C-1), 72.6 (OCH₂C₆H₄OCH₃), 70.3 (C-4), 55.4 (OCH₂C₆H₄OCH₃), 38.0 (C-5), 35.9 (C-6), 29.8 (C-3), 26.4 (C-2), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 14.4 (5-CH₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.3 (1 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)+] $m/z$: calculated for (C₂₃H₃₉BrNaO₅Si) 493.1744, found: 493.1733.
(4S,5S)-4-(tert-Butyldimethylsilyl)oxy-1-(4-methoxybenzyl)oxy-5-methyloct-7-ene

$\alpha_D^{20}$: $-0.6$ (c 1.0, CHCl$_3$); IR spectrum (film), cm$^{-1}$: 2928, 2854, 1731, 1513, 1246, 1038, 909, 833, 772; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.28–7.25 (m, 2H, Ar-H), 6.90–6.86 (m, 2H, Ar-H), 5.81–5.71 (m, 1H, H-7), 5.02–4.95 (m, 2H, H-8), 4.43 (s, 2H, OCH$_2$C$_6$H$_4$OCH$_3$), 3.81 (s, 3H, OCH$_2$C$_6$H$_4$OCH$_3$), 3.56 (ddd, $J = 4.9, 3.5, 3.5$ Hz, 1H, H-4), 3.42 (td, $J = 6.5, 2.4$ Hz, 2H, H-1), 2.29–2.23 (m, 1H, 1 × H-6), 1.83–1.76 (ddd, $J = 14.1, 8.9, 8.4$ Hz, 1H, 1 × H-6), 1.71–1.36 (m, 5H, H-2, H-3, H-5), 0.89 (s, 9H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.82 (d, $J = 6.8$ Hz, 3H, 3-CCH$_3$), 0.03 (s, 3H, 2 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 159.2 (Ar-C), 138.4 (C-7), 130.9 (Ar-C), 129.4 (2 × Ar-CH), 115.5 (C-8), 113.7 (2 × Ar-CH), 75.5 (C-1), 72.6 (OCH$_2$C$_6$H$_4$OCH$_3$), 70.4 (C-4), 55.4 (OCH$_2$C$_6$H$_4$OCH$_3$), 38.1 (C-5), 36.9 (C-6), 29.9 (C-3), 26.4 (C-2), 26.1 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 18.3 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 14.3 (5-CH$_3$), $-4.1$ (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), $-4.3$ (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); HRMS [ESI, (M+Na)$^+$] m/z: calculated for (C$_{23}$H$_{40}$NaO$_3$Si) 415.2639, found: 415.2652.
To a solution of alkyne 228 (40 mg, 0.102 mmol) in acetone (2 mL) was added silver nitrate (2 mg, 0.010 mmol) followed by $N$-bromosuccinimide (22 mg, 0.123 mmol). After 2 h the reaction was diluted with hexanes/ethyl acetate (9:1), filtered through silica and concentrated \textit{in vacuo} to afford the \textit{title product} 484 (48 mg, quant.) as a colourless oil.

$[\alpha]_{D}^{20}$: 4.8 (c 1.0, CHCl$_3$); \textbf{IR spectrum} (film), cm$^{-1}$: 2929, 2856, 1613, 1512, 1462, 1246, 1035, 833, 772; \textbf{$^1$H NMR} (400 MHz, CDCl$_3$) $\delta$: 7.28–7.24 (m, 2H, Ar-H), 6.89–6.86 (m, 2H, Ar-H), 4.43 (s, 2H, OCH$_2$C$_6$H$_4$OCH$_3$), 3.80 (s, 3H, OCH$_2$C$_6$H$_4$OCH$_3$), 3.68 (td, $J$ = 6.3, 3.2 Hz, 1H, H-4), 3.43 (td, $J$ = 6.3, 0.9 Hz, 2H, H-1), 2.29 (dd, $J$ = 16.6, 6.4 Hz, 1H, 1 × H-6), 2.05 (dd, $J$ = 16.6, 8.0 Hz, 1H, 1 × H-6), 1.82–1.73 (m, 1H, H-5), 1.67–1.38 (m, 4H, H-2, H-3), 0.91 (d, $J$ = 6.8 Hz, 3H, 5-CH$_3$), 0.88 (s, 9H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.04 (s, 3H, 1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.04 (s, 3H, 1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); \textbf{$^{13}$C NMR} (100 MHz, CDCl$_3$) $\delta$: 159.2 (Ar-C), 130.8 (Ar-C), 129.4 (2 × Ar-CH), 113.9 (2 × Ar-CH), 80.0 (C-7), 73.9 (C-1), 72.6 (1 OCH$_2$C$_6$H$_4$OCH$_3$), 70.1 (C-4), 55.4 (OCH$_2$C$_6$H$_4$OCH$_3$), 38.2 (C-8), 37.4 (C-5), 30.4 (C-3), 26.1 (C-2), 26.0 (3 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 23.5 (C-6), 18.2 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 13.9 (5-CH$_3$), −4.1 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), −4.5 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); \textbf{HRMS} [ESI, (M+Na)$^+$] m/z: calculated for (C$_{23}$H$_{37}$BrNaO$_3$Si) 491.1588, found: 491.1591.
(4S,5S)-8,8-Dibromo-4-(tert-butyldimethylsilyl)oxy-1-(4-methoxybenzyl)oxy-5-methyloct-7-ene

To a solution of triphenylphosphine (199 mg, 0.759 mmol) in dichloromethane (2 mL) at −78 °C was added carbon tetrabromide (168 mg, 0.506 mmol) and the mixture warmed to 0 °C. After 15 min a solution of aldehyde 209 (100 mg, 0.253 mmol) and triethylamine (88 μL, 0.633 mmol) in dichloromethane (1 mL) was added. After 1 h the reaction was diluted with petroleum ether (5 mL), filtered through silica and concentrated in vacuo. The resultant oil was used without further purification.
To a solution of palladium(II) acetate (5.1 mg, 0.023 mmol) and triphenylphosphine (30 mg, 0.114 mmol) in dichloromethane (0.5 mL) was added a solution of crude geminal dibromide 235 (~0.253 mmol) in dichloromethane (1 mL) followed by tributyl tin hydride (0.18 mL, 0.681 mmol). After 4 h the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography using petroleum ether/diethyl ether (29:1) as eluent afforded the title product 236 (92 mg, 77% over 2 steps) as a colourless oil.

\([\alpha]_D^{20}\): 0.3 (c 1.0, CHCl₃); IR spectrum (film), cm\(^{-1}\): 2954, 2855, 1613, 1513, 1247, 1090, 1036, 834, 772, 669; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\): 7.29–7.23 (m, 2H, Ar-H), 6.91–6.85 (m, 2H, Ar-H), 6.20–6.15 (m, 1H, H-7), 6.12–6.05 (m, 1H, H-8), 4.43 (s, 2H, OCH₂C₆H₄OCH₃), 3.81 (s, 3H, OCH₂C₆H₄OCH₃), 3.59–3.53 (m, 1H, H-4), 3.49–3.38 (m, 2H, H-1), 2.31–2.22 (m, 1H, 1 × H-6), 2.15–2.04 (m, 1H, 1 × H-6), 1.76–1.33 (m, 5H, H-2, H-3, H-5), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.85 (d, \(J = 6.8\) Hz, 3H, 5-CH₃), 0.04 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃), 0.04 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\): 159.3 (Ar-C), 134.4 (C-7), 130.9 (Ar-C), 129.4 (2 × Ar-CH), 113.9 (2 × Ar-CH), 111.1 (C-8), 75.6 (C-1), 72.6 (OCH₂C₆H₄OCH₃), 70.4 (C-4), 55.4 (OCH₂C₆H₄OCH₃), 37.8 (C-5), 32.9 (C-6), 30.0 (C-3), 26.3 (C-2), 26.1 (Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 14.5 (5-CH₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.3 (1 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)⁺] m/z: calculated for (C₂₃H₃₉BrNaO₃Si) 493.1744, found: 493.1733.
4-hydroxy-N-methoxy-N-methylbutanamide 202

To a solution of N,O-dimethylhydroxylamine hydrochloride (1.76 g, 18.0 mmol) in dichloromethane (100 mL) was added a solution of dimethylaluminium chloride (20 mL, 0.9 M in heptane, 18.0 mmol) at 0 °C. After 1 h γ-butyrolactone (1.3 ml, 16.4 mmol) was added dropwise over 15 min and the mixture was allowed to warm up to room temperature over 30 min. The reaction mixture was then quenched with saturated sodium bicarbonate (50 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (3:1) as eluent afforded the title product 144 (896 mg, 37%) as a colourless oil.

1H NMR (400 MHz, CDCl₃): δ 3.72–3.67 (m, 5H, H-4, 1-N(CH₃)OC₃H₃) 3.20 (s, 3H, 1-N(C₃H₃)OCH₃), 2.63–2.58 (m, 3H, H-2, 4-OH), 1.95–1.86 (m, 2H, H-3). The data obtained were in agreement with that reported in the literature.¹¹¹
**N-Methoxy-N-methyl-4-oxobutanamide 193**

![Chemical Structure](image1)

To a solution of 4-hydroxy-N-methoxy-N-methylbutanamide (202) (100 mg, 0.679 mmol), dimethyl sulfoxide (0.48 mL, 6.79 mmol), and diisopropylethylamine (0.59 mL, 3.40 mmol) in dichloromethane (4 mL) at 0 °C was added sulfur trioxide-pyridine complex (0.324 mg, 2.04 mmol) in one portion. After 10 min the reaction was quenched with aqueous citric acid (0.5 M, 4 mL) and washed with brine (4 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. The resultant crude oil was used without further purification for the next step.

**[(4S,5S)-4-Hydroxy-N-methoxy-N,5-dimethylhept-6-enamide 194 and](4S,5S)-4-Hydroxy-N-methoxy-N,5-dimethylhept-6-enamide 194**

![Chemical Structure](image2)

**[(S)-5-((S)-but-3-en-2-yl)dihydrofuran-2(3H)-one 203](S)-5-((S)-but-3-en-2-yl)dihydrofuran-2(3H)-one 203**

To a solution of ligand 177 (218 mg, 0.750 mmol) and 1,8-diazabicycloundec-7-ene (0.34 mL, 2.25 mmol) in dichloromethane (2 mL) at 0 °C was added Z-but-2-en-1-yltrichlorosilane (184) (0.13 mL, 0.815 mmol) dropwise and the mixture allowed to warm to room temperature. After 1 h the solution was cooled to 0 °C and a solution of crude aldehyde 193 (~0.679 mmol) in dichloromethane (0.5 mL) was added dropwise. After 2 h the reaction was concentrated in vacuo and suspended in diethyl ether (4 mL) and vigorously stirred for 20 min then filtered to remove the resultant precipitate. To the filtrate was added tetrabutylammonium fluoride (0.75 mL, 1 M, 0.750 mmol). After 30 min the mixture was diluted with hydrochloric acid (1 M, 3.75 mL) and extracted with ether (3 × 5 mL). The combined organic layers were washed with saturated sodium bicarbonate (10 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (3:1) as eluent afforded the *title products* 194 (39 mg, 39%) as a colourless oil and 203 (56 mg, 59%) as a colourless oil over two steps.
(4S,5S)-4-Hydroxy-N-methoxy-N,5-dimethylhept-6-enamide 194

\[ \alpha \]D\text{20} = -10.3 (c 2.0, CHCl\text{3}); IR spectrum (film), cm\text{−1}: 3434, 2965, 1640, 1419, 1388, 1181, 1055, 998; \text{1H NMR} (400 MHz, CDCl\text{3}) \delta: 5.78 (ddd, \( J = 17.6, 10.3, 7.5 \text{ Hz} \), 1H, H-6), 5.09–5.02 (m, 2H, H-7), 3.68 (s, 3H, 1-N(CH\text{3})OCH\text{3}), 3.49–3.44 (m, 1H, H-4), 3.18 (s, 3H, 1-N(CH\text{3})OCH\text{3}), 2.66–2.54 (m, 3H, H-2, 4-OH), 2.32–2.23 (m, 1H, H-5), 1.87 (dddd, \( J = 14.3, 7.1, 7.1, 2.8 \text{ Hz} \), 1H, 1 × H-3), 1.67 (dddd, \( J = 14.3, 9.7, 7.0, 7.0 \text{ Hz} \), 1H, 1 × H-3), 1.05 (dt, \( J = 6.7 \text{ Hz} \), 3H, 5-CH\text{3}); \text{13C NMR} (100 MHz, CDCl\text{3}) \delta: 141.0 (C-6), 115.3 (C-7), 74.9 (C-4), 61.4 (1-N(CH\text{3})OCH\text{3}), 44.3 (1-N(CH\text{3})OCH\text{3}), 32.4 (C-2), 29.0 (C-5), 28.7 (C-3), 15.1 (5-CH\text{3}). Quaternary C-1 was not observed; HRMS [ESI, (M+Na)+] \text{m/z}: calculated for (C\text{10}H\text{19}NNaO\text{3}) 224.1257, found: 224.1264.

(S)-5-((S)-But-3-en-2-yl)dihydrofuran-2(3H)-one 203

\[ \alpha \]D\text{20} = -10.0, (c 1.0, CHCl\text{3}); IR spectrum (film), cm\text{−1}: 2979, 1768, 1459, 1175, 1018, 911; \text{1H NMR} (400 MHz, CDCl\text{3}) \delta: 5.70 (ddd, \( J = 17.6, 10.3, 7.4 \text{ Hz} \), 1H, H-6), 5.18–5.12 (m, 2H, H-7), 4.31 (ddd, \( J = 7.3, 7.3, 7.3 \text{ Hz} \), 1H, H-4), 2.51 (dd, \( J = 9.5, 7.1 \text{ Hz} \), 2H, H-2), 2.44 (dq, \( J = 7.3, 7.0 \text{ Hz} \), 1H, H-5), 2.21 (dddd, \( J = 13.3, 7.1, 7.0, 7.0 \text{ Hz} \), 1H, 1 × H-3), 2.00–1.90 (m, 1H, 1 × H-3), 1.13 (d, \( J = 6.6 \text{ Hz} \), 3H, 5-CH\text{3}); \text{13C NMR} (100 MHz, CDCl\text{3}) \delta: 177.3 (C-1), 137.7 (C-6), 117.1 (C-7), 83.8 (C-4), 42.7 (C-2), 28.9 (C-5), 25.4 (C-3), 16.0 (5-CH\text{3}); HRMS [ESI, (M+Na)+] \text{m/z}: calculated for (C\text{8}H\text{12}NaO\text{2}) 163.0730, found: 163.0724.
To a solution of ethylene glycol (5.8 mL, 104 mmol) and p-toluene sulfonic acid monohydrate (230 mg, 1.20 mmol) in benzene (80 mL) was added ethyl levulinate (9.9 mL, 69.0 mmol) and the resultant solution was heated to reflux under Dean-Stark conditions for 18 h. The reaction mixture was then cooled to room temperature, quenched with saturated sodium bicarbonate (60 mL) and washed with water (60 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (3:1) as eluent afforded the title product 144 (12.6 g, 97%) as a colourless oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta: 4.13 (q, J = 7.2 \text{ Hz}, 3H, OCH}_2\text{CH}_3), 3.98–3.90 (m, 4H, OCH}_2\text{CH}_2\text{O}), 2.39 (t, J = 7.7 \text{ Hz}, 2H, H-2), 2.02 (t, J = 7.7 \text{ Hz}, 2H, H-3), 1.32 (s, 3H, H-5), 1.25 (t, J = 7.2 \text{ Hz}, 2H, OCH}_2\text{CH}_3). \] The data obtained were in agreement with that reported in the literature.\(^{228}\)
4,4-Ethylenebisoxypentanal 135

To a solution of ester 144 (828 mg, 4.40 mmol) in dichloromethane (10 mL) at −78 °C was added diisobutyl aluminium hydride (5.72 mL, 1 M in cyclohexane, 5.72 mmol) dropwise and the resultant solution stirred for 2 h. The reaction mixture was then quenched with methanol (2.8 mL) and warmed to room temperature. Saturated Rochelle’s salt (5 mL) and water (5 mL) were added and the mixture was vigorously stirred for a further 3 h. The biphasic mixture was then extracted with dichloromethane (10 mL), washed with saturated Rochelle’s salt (10 mL), dried over sodium sulfate and concentrated under reduced pressure. The resultant crude oil was used without further purification for the next step. An analytic sample of the title compound was purified by flash chromatography using pentane/diethyl ether (3:1) as eluent.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ: 9.71 (t, $J = 2.0$ Hz, 1H, H-1), 3.97–3.87 (m, 4H, OCH$_2$CH$_2$O), 2.39 (td, $J = 7.0$, 2.0 Hz, 2H, H-2), 2.07 (t, $J = 7.1$ Hz, 2H, H-3), 1.33 (s, 3H, H-5). The data obtained were in agreement with that reported in the literature.$^{228}$
To a solution of ligand 177 (159 mg, 0.549 mmol) and 1,8-diazaacycloundec-7-ene (0.25 mL, 1.65 mmol) in dichloromethane (2 mL) at 0 °C was added Z-but-2-en-1-yltrichlorosilane (184) (0.95 mL, 0.599 mmol) dropwise and the mixture allowed to warm to room temperature. After 1 h the solution was cooled to 0 °C and aldehyde 146 (72 mg, 0.499 mmol) was added dropwise. After 2 h the reaction was concentrated in vacuo and suspended in diethyl ether (5 mL) and vigorously stirred for 20 min then filtered to remove the resultant precipitate. To the filtrate was added tetrabutylammonium fluoride (0.55 mL, 1 M, 549 mmol). After 30 min the mixture was diluted with hydrochloric acid (1 M, 5 mL) and extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and concentrated under reduced pressure.

The result oil was dissolved in dichloromethane (1 mL). To this solution was added alcohol 145 (0.3 mL), followed by camphorsulfonic acid (12 mg, 0.050 mmol). After 16 h, the reaction was quenched with saturated sodium bicarbonate (3 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (9:1) as eluent afforded the title product 485 (30 mg, 34%, 2:1 mixture of diastereomers) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 2939, 1613, 1513, 1302, 1248, 1068, 1034, 912, 820; ¹H NMR (400 MHz, CDCl₃) δ: 7.27–7.24 (m, 2H, Ar-H), 6.89–6.85 (m, 2H, Ar-H), 5.81–5.64 (m, 1H, H-2”), 5.11–4.97 (m, 2H, 1 × H-1”), 4.45 (s, OCH₂C₆H₄OCH₃*), 4.43 (s, 2H, OCH₂C₆H₄OCH₃), 3.88–3.74 (m, 1H, H-5), 3.80 (s, 3H, OCH₂C₆H₄OCH₃), 3.63 (t, J = 5.4 Hz, 2H, H-1*”) 3.56–3.36 (m, 4H, H-1’, H-4’), 2.69–2.52 (m, 1H, H-3”*), 2.35–1.53 (m, 8H, H-3, H-4, H-2’, H-3’), 1.42 (s, 3H, 2-CH₃*), 1.11 (d, J = 6.8 Hz, 3H, H-4”*), 1.02 (d, J = 6.9 Hz, 3H, H-4”); ¹³C NMR (100 MHz, CDCl₃) δ: 159.4 (Ar-C*), 159.2 (Ar-C), 140.6 (C-2”*), 140.4 (Ar-CH), 130.9 (Ar-CH), 130.4 (Ar-C), 129.5 (2 × Ar-CH*), 129.3 (2 × Ar-CH), 115.7 (C-1”*), 114.8 (C-1”), 114.0 (2 × Ar-CH*), 113.9 (2 × Ar-CH), 107.5 (C-2), 107.3 (C-2”), 84.5 (C-5*), 82.2 (C-5), 74.5 (OCH₂C₆H₄OCH₃*), 72.9 (OCH₂C₆H₄OCH₃), 72.7
(OCH₂C₆H₄OCH₃*), 70.2 (C-4'), 70.1 (C-4*''), 62.8, 60.7 (C-1*''), 60.6 (C-1*'), 55.4 (OCH₂C₆H₄OCH₃), 44.8 (C-3''*), 44.2 (C-3''*''), 42.3 (C-3'''), 40.7 (C-4*'), 39.1 (C-4*), 38.1 (C-4), 30.4 (C-3'), 30.2 (C-3*''), 29.4 (C-3'**), 27.9 (C-2'', 27.5 (C-2*'), 27.1 (C-2*''), 27.1 (C-3*'), 26.9 (C-3*'), 26.8 (C-3), 22.9 (2-CH₃*), 22.3 2-CH₃, 17.4 (C-4'''), 16.1 (C-4''), 14.9 (C-4''*) ; HRMS [ESI, (M+Na)⁺] m/z: calculated for (C₂₁H₃₂NaO₄) 371.2193, found: 371.2190.
(3S,4S)-7,7-Ethylenebisoxy-3-methyloct-1-en-4-ol 137

To a solution of ligand 177 (1.40 g, 4.84 mmol) and 1,8-diazabicycloundec-7-ene (2.2 mL, 14.5 mmol) in dichloromethane (8 mL) at 0 °C was added Z-but-2-en-1-yltrichlorsilane (184) (1.0 mL, 5.28 mmol) dropwise and the mixture was allowed to warm to room temperature. After 1 h the solution was cooled to 0 °C and a solution of crude aldehyde 135 (~4.40 mmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred at 0 °C for a further 2 h then concentrated in vacuo. The residue was suspended in diethyl ether (15 mL) and vigorously stirred for 20 min then filtered to remove the resultant precipitate. To the stirred filtrate was added tetrabutylammonium fluoride (4.8 mL, 1 M in tetrahydrofuran, 4.84 mmol) and after 30 min the mixture was concentrated in vacuo. Purification by CombiFlash® automated chromatography using pentane/diethyl ether (8:1 → 1:3) as eluent afforded the title product 137 (722 mg, 82% over 2 steps) in 94% ee as a colourless oil and recovered ligand 177 as beige needles (1.25 g, 89%).

\[ \alpha \]_D^20: −33.9 (c 1.2, CHCl_3); IR spectrum (film), cm\(^{-1}\): 3429, 2962, 1377, 1220, 1051, 911; \(^1\)H NMR (400 MHz, CDCl_3) \( \delta \): 5.78 (ddd, \( J = 17.4, 10.3, 7.4 \) Hz, 1H, H-2), 5.12–5.03 (m, 2H, H-1), 3.98–3.91 (m, 4H, OCH_2CH_2O), 3.50–3.45 (m, 1H, H-4), 2.67 (ddq, \( J = 10.3, 6.7, 6.6 \) Hz, 1H, H-3), 1.91–1.39 (m, 4H, H-5, H-6), 1.32 (s, 3H, H-8), 1.04 (d, \( J = 6.8 \) Hz, 3H, 3-CH_3); \(^13\)C NMR (100 MHz, CDCl_3) \( \delta \): 141.2 (C-2), 115.3 (C-1), 110.2 (d, \( J = 11.7 \) Hz, C-7), 75.0 (C-4), 64.8 (OCH_2CH_2O), 64.7 (OCH_2CH_2O), 43.9 (C-3), 35.8 (C-6), 28.6 (C-5), 23.9 (C-8), 14.7 (3-CH_3); HRMS [ESI, (M+Na)+] m/z: calculated for (C_{11}H_{20}NaO_3) 223.1305, found: 223.1299.
(3S,4S)-7,7-Ethylenebisoxy-3-methyloct-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 486a

To a solution of alcohol 137 (15 mg, 0.075 mmol) in dichloromethane (0.5 mL) was added a solution of (S)-(−)‐α-methoxy‐α-trifluoromethylphenylacetic acid (26 mg, 0.112 mmol) in dichloromethane (0.5 mL), followed by N,N'-dicyclohexylcarbodiimide (39 mg, 0.187 mmol) and 4-dimethylaminopyridine (1.8 mg, 0.015 mmol). The reaction mixture was stirred for 16 h then filtered through a plug of Celite and concentrated *in vacuo*. Purification by flash chromatography using petroleum ether/ethyl acetate (3:1) as eluent afforded the title product 486a (31.3 mg, quant.) in 94% de as a colourless oil.

**IR spectrum** (film), cm⁻¹: 2980, 1743, 1258, 1169, 1017, 720; **¹H NMR** (400 MHz, CDCl₃) δ: 7.58–7.53 (m, 2H, Ar-H), 7.43–7.36 (m, 3H, Ar-H), 5.81–5.71 (m, 1H, H-2), 5.10–4.98 (m, 3H, H-4, H-1), 3.95–3.78 (m, 4H, OCH₂CH₂O), 3.56–3.53 (m, 3H, 2'-OCH₃), 2.58–2.47 (m, 1H, H-3), 1.76–1.61 (m, 2H, H-6), 1.57–1.44 (m, 2H, H-5), 1.22 (s, 3H, H-8), 1.03 (d, J = 6.8 Hz, 3H, 3-C₃H₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 166.5 (C-1'), 139.2 (C-2), 132.4 (Ar-C), 129.7 (Ar-CH), 128.5 (2 × Ar-CH), 127.7 (2 × Ar-CH), 125.0 (2'-CF₃), 122.1 (C-2'), 116.0 (C-1), 109.6 (C-7), 80.3 (C-4), 64.7 (OCH₂CH₂O), 64.7 (OCH₂CH₂O), 55.6 (2'-OCH₃), 40.7 (C-3), 34.4 (C-5), 25.5 (C-6), 23.9 (C-8), 15.0 (3-CH₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₂₁H₂₇F₃NaO₅) 439.1703, found: 439.1709.
To a solution of alcohol 137 (15 mg, 0.075 mmol) in dichloromethane (0.5 mL) was added a solution of \((R)-(+)-\alpha\)-methoxy-\(\alpha\)-trifluoromethylphenylacetic acid (26 mg, 0.112 mmol) in dichloromethane (0.5 mL), followed by \(N,N\)'-dicyclohexylcarbodiimide (39 mg, 0.187 mmol) and 4-dimethylaminopyridine (1.8 mg, 0.015 mmol). The reaction mixture was stirred for 16 h then filtered from a plug of Celite and concentrated \textit{in vacuo}. Purification by flash chromatography using petroleum ether/ethyl acetate (3:1) as eluent afforded the \textit{title product} 486b (29.9 mg, 96%) in 93% de as a colourless oil.

\textbf{IR spectrum} (film), cm\(^{-1}\): 2980, 2883, 1743, 1254, 1167, 1017, 719; \textbf{\(1\)H NMR} (400 MHz, CDCl\(_3\)) \(\delta\): 7.58–7.53 (m, 2H, Ar-H), 7.43–7.37 (m, 3H, Ar-H), 5.70–5.59 (m, 1H, H-2), 5.11–5.04 (m, 1H, H-4), 5.03–4.95 (m, 2H, H-1), 3.97–3.83 (m, 4H, O\(\text{CH}_2\text{CH}_2\text{O}\), 3.56–3.54 (m, 3H, 2′-O\(\text{CH}_3\)), 2.52–2.42 (m, 1H, H-3), 1.80–1.59 (m, 4H, H-5, H-6), 1.27 (s, 3H, H-8), 0.96 (d, \(J = 6.8\) Hz, 3H, 3-\(\text{CH}_3\)); \textbf{\(13\)C NMR} (100 MHz, CDCl\(_3\)) \(\delta\): 166.4 (C-1′), 139.1 (C-2), 132.5 (Ar-C), 129.7 (Ar-CH), 128.5 (2 × Ar-CH), 127.6 (2 × Ar-CH), 125.0 (2′-CF\(_3\)), 122.1 (C-2′), 115.9 (C-1), 109.6 (C-7), 80.2 (C-4), 64.8 (O\(\text{CH}_2\text{CH}_2\text{O}\), 64.8 (O\(\text{CH}_2\text{CH}_2\text{O}\), 55.6 (2′-O\(\text{CH}_3\)), 40.8 (C-3), 34.6 (C-5), 25.8 (C-6), 24.0 (C-8), 15.0 (3-\(\text{CH}_3\)); \textbf{HRMS} [ESI, (M+Na)\(^+\)] \(m/z\): calculated for (C\(_{21}\)H\(_{27}\)F\(_3\)NaO\(_5\)) 439.1703, found: 439.1703.
To a solution of alcohol 137 (50 mg, 0.245 mmol) in dimethylformamide (1 mL) at 0 °C was added sodium hydride (60% in mineral oil, 30 mg, 0.749 mmol) and the mixture allowed to warm to room temperature. After 30 min tetrabutylammonium iodide (30 mg, 0.075 mmol) was added, followed by p-methoxybenzyl chloride (0.10 mL, 0.749 mmol) dropwise. After 22 h the reaction was quenched with saturated ammonium chloride (5 mL) and extracted with dichloromethane (3 × 6 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (9:1) as eluent afforded the title product 210 (44 mg, 55%) as a colourless oil.

\[ \alpha \text{D}_{20} \]: $-18.6 \ (c \ 1.2, \ CHCl_3); \text{IR spectrum (film)}, \ cm^{-1}: \ 2958, 2874, 1612, 1512, 1245, 1034, 819; \text{H NMR (400 MHz, CDCl}_3) \ \delta: \ 7.29–7.25 (m, 2H, Ar-H), 6.89–6.85 (m, 2H, Ar-H) 5.78 (ddd, \ J = 17.4, 10.2, 7.2 Hz, 1H, H-2), 5.07–5.00 (m, 2H, H-1), 4.46 (ABq, \ \Delta \delta_{AB} = 0.02, \ J_{AB} = 12.0 \ Hz, 2H, OCH_2C_6H_4OCH_3), 3.96–3.88 (m, 4H, OCH_2CH_2O), 3.80 (s, 3H, OCH_2C_6H_4OCH_3), 3.27–3.23 (m, 1H, H-4), 2.50–2.40 (m, 1H, H-3), 1.86–1.79 (m, 1H, 1 × H-6), 1.67–1.52 (m, 3H, H-5, 1 × H-6), 1.30 (s, 3H, H-8), 1.05 (d, \ J = 6.8 \ Hz, 3H, 3-CH_3); \text{C NMR (100 MHz, CDCl}_3) \ \delta: \ 159.2 (Ar-C), 141.1 (C-2), 131.2 (Ar-C), 129.6 (2 × Ar-CH), 114.5 (C-1), 113.9 (2 × Ar-CH), 110.3 (C-7), 82.6 (C-4), 71.4 (OCH_2C_6H_4OCH_3), 64.7 (OCH_2CH_2O), 64.7 (OCH_2CH_2O), 55.4 (OCH_2C_6H_4OCH_3), 41.0 (C-3), 34.7 (C-5), 25.6 (C-6), 23.9 (C-8), 16.0 (3-CH_3); \text{HRMS [ESI, (M+K)] m/z: calculated for (C}_{19}H_{28}KO_4) 359.1619, found: 359.1617.
To a solution of alcohol 137 (2.00 g, 9.99 mmol) and 2,6-lutidine (3.5 mL, 30.0 mmol) in dichloromethane (5 mL) at 0 °C was added tert-butyldimethylsilyl trifluoromethanesulfonate (3.4 mL, 15.0 mmol) dropwise. After 30 min the reaction was quenched with saturated ammonium chloride (10 mL), extracted with dichloromethane (2 × 10 mL) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (19:1) as eluent afforded the title product 211 (3.06 g, 97%) as a colourless oil.

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[a]_D^{20} : -17.3 \ (c \ 1.3, \ CHCl_3); \ IR \ spectrum \ (film), \ cm^{-1} : 2959, 1473, 1376, 1255, 1071, 835; \\
^1H \ NMR \ (400 MHz, CDCl_3) \ \delta : 5.83 \ (ddd, J = 17.3, 10.5, 7.1 Hz, 1H, H-2), 5.03–4.97 \ (m, 2H, H-1), 3.96–3.88 \ (m, 4H, OCH_2CH_2O), 3.53 \ (dt, J = 5.4, 5.4 Hz, 1H, H-4), 2.33–2.24 \ (m, 1H, H-3), 1.77–1.69 \ (m, 1H, 1 × H-6), 1.64–1.46 \ (m, 3H, H-5, 1 × H-6), 1.30 \ (s, 3H, H-8), 0.98 \ (d, J = 6.9 Hz, 3H, 3-CH_3), 0.89 \ (s, 9H, Si(CH_3)_2C(CH_3)_3), 0.05 \ (s, 3H, 1 × Si(CH_3)_2C(CH_3)_3), 0.04 \ (s, 3H, 1 × Si(CH_3)_2C(CH_3)_3); ^13C \ NMR \ (100 MHz, CDCl_3) \ \delta : 141.4 \ (C-2), 114.1 \ (C-1) 110.4 \ (C-7), 75.9 \ (C-4), 64.7 \ (OCH_2CH_2O), 43.0 \ (C-3), 34.4 \ (C-6), 28.4 \ (C-5), 26.0 \ (3 × Si(CH_3)_2C(CH_3)_3), 23.9 \ (C-8), 18.3 \ (Si(CH_3)_2C(CH_3)_3), 15.5 \ (3-CH_3), -4.2 \ (1 × Si(CH_3)_2C(CH_3)_3), -4.3 \ (1 × Si(CH_3)_2C(CH_3)_3); \ HRMS \ [ESI, \ (M+Na)^+] \ m/z: \ calculated \ for \ (C_{17}H_{34}NaO_3Si) \ 337.2169, \ found: \ 337.2165.
(5S,6S)-5-(tert-Butyldimethylsilyl)oxy-6-methyloct-7-en-2-one 212

To a solution of acetal 211 (150 mg, 0.477 mmol) in acetone/dichloromethane (1:1, 4 mL) was added Amberlyst® 15 (40 mg). After 9 h the reaction was diluted with hexanes/ethyl acetate (9:1), filtered through Celite® and concentrated in vacuo to afford the title product 212 (116 mg, 90%) as a colourless oil.

\[\alpha\]D20: −18.5 (c 0.27, CHCl3); IR spectrum (film), cm⁻¹: 2957, 2858, 1719, 1361, 1253, 1077, 833, 773; ¹H NMR (400 MHz, CDCl₃) δ: 5.87–5.78 (m, 1H, H-7), 5.04–5.02 (m, 1H, 1 × H-8), 5.00–4.98 (m, 1H, 1 × H-8), 3.58–3.52 (m, 1H, H-5), 2.55–2.40 (m, 2H, H-3), 2.33–2.24 (m, 1H, H-6), 2.13 (s, 3H, H-1), 1.78–1.57 (m, 2H, H-4), 0.99 (d, J = 6.8 Hz, 3H, 6-CH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.05 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃), 0.04 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ: 209.2 (C-2), 140.7 (C-7), 114.4 (C-8), 75.0 (C-5), 43.0 (C-6), 39.3 (C-3), 30.1 (C-1), 27.4 (C-4), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 15.7 (6-CH₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃), −4.3 (1 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)⁺] m/z: calculated for (C₁₅H₃₀NaO₂Si) 293.1907, found: 293.1904.
(3S,4S)-7,7-Ethylenedioxy-4-(tert-butyldimethylsilyl)oxy-3-methyloctan-1-ol 213

To a solution of alkene 211 (3.00 g, 9.54 mmol) in tetrahydrofuran (60 mL) was added 9-borabicyclo[3.3.1]nonane dimer (2.91 g, 11.9 mmol) with vigorous stirring. After 3.5 h a solution of aqueous sodium hydroxide (64 mL, 3 M) and aqueous hydrogen peroxide (30% w/w, 25 mL) were added dropwise concurrently. After 16 h the reaction was diluted with water (80 mL) and extracted with diethyl ether (3 × 120 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (3:1) as eluent afforded the title product 213 (2.92 g, 92%) as a colourless oil.

\[ \alpha \] D\text{20}: −8.9 (c 1.0, CHCl\text{3}); \text{IR spectrum (film), cm}^{-1}: 3412, 2929, 2857, 1251, 1043, 832, 772; \text{\textsuperscript{1}H NMR (400 MHz, CDCl\text{3})} \delta: 3.97–3.89 (m, 4H, OCH\text{2}CH\text{2}O), 3.75–3.53 (m, 3H, H-4, H-1), 2.25 (br s, 1H, 1-OH), 1.81–1.71 (m, 3H, H-3, H-6), 1.59–1.49 (m, 3H, H-5, 1 × H-2), 1.42–1.33 (m, 1H, 1 × H-2), 1.31 (s, 3H, H-8), 0.90 (s, 9H, Si(CH\text{3})\text{2}C(CH\text{3})\text{3}), 0.88 (d, J = 6.8 Hz, 3H, 3-CH\text{3}), 0.07 (s, 3H, 1 × Si(CH\text{3})\text{2}C(CH\text{3})\text{3}), 0.07 (s, 3H, 1 × Si(CH\text{3})\text{2}C(CH\text{3})\text{3}); \text{\textsuperscript{13}C NMR (100 MHz, CDCl\text{3})} \delta: 110.3 (C-7), 76.7 (C-4), 64.8 (OCH\text{2}CH\text{2}O), 62.0 (C-1), 36.7 (C-3), 36.0 (C-6), 35.6 (C-2), 26.9 (C-5), 26.1 (3 × Si(CH\text{3})\text{2}C(CH\text{3})\text{3}), 23.9 (C-8), 18.3 (Si(CH\text{3})\text{2}C(CH\text{3})\text{3}), 16.7 (3-CH\text{3}), −4.1 (1 × Si(CH\text{3})\text{2}C(CH\text{3})\text{3}), −4.2 (1 × Si(CH\text{3})\text{2}C(CH\text{3})\text{3}); \text{HRMS [ESI, (M+Na\text{+})] m/z: calculated for (C_{17}H_{36}NaO_4Si) 355.2275, found: 355.2274.}
(3S,4S)-7,7-Ethylenebis(oxy)-4-(tert-butyldimethylsilyl)oxy-3-methyloctanal 204

To a solution of alcohol 213 (600 mg, 1.80 mmol), dimethyl sulfoxide (1.3 mL, 5.41 mmol) and diisopropylethylamine (1.6 mL, 9.02 mmol) in dichloromethane (15 mL) at 0 °C was added sulfur trioxide-pyridine complex (862 mg, 5.41 mmol) in one portion. After 10 min the reaction was diluted with dichloromethane (5 mL), quenched with saturated ammonium chloride (15 mL) and washed with brine (15 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (5:1) as eluent afforded the title product 204 (560 mg, 94%) as a colourless oil.

$[\alpha]_D^{20}$: 3.4 (c 1.0, CHCl$_3$); IR spectrum (film), cm$^{-1}$: 2958, 1726, 1378, 1253, 1044, 835; $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.75 (dd, $J = 2.2, 1.5$ Hz, 1H, H-1), 3.96–3.88 (m, 4H, OCH$_2$CH$_2$O), 3.59–3.55 (m, 1H, H-4), 2.65–2.56 (m, 1H, 1 × H-2), 2.21–2.17 (m, 2H, 1 × H-2, and H-3), 1.80–1.70 (m, 1H, 1 × H-6), 1.58–1.36 (m, 3H, H-5, 1 × H-6), 1.30 (s, 3H, H-8), 0.90 (d, $J = 6.6$ Hz, 3H, 3-CH$_3$), 0.88 (s, 9H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.05 (s, 3H, 1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.03 (s, 3H, 1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 202.8 (C-1), 110.1 (C-7), 75.4 (C-4), 64.8 (OCH$_2$CH$_3$O), 64.8 (OCH$_2$CH$_2$O), 46.9 (C-2), 35.7 (C-6), 33.4 (C-3), 27.2 (C-5), 26.0 (3 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 24.0 (C-8), 18.2 (Si(CH$_3$)$_2$C(CH$_3$)$_3$) 15.3 (3-CH$_3$), −4.2 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), −4.2 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); HRMS [ESI, (M+Na)$^+$] $m/z$: calculated for (C$_{17}$H$_{34}$NaO$_4$Si) 353.2119, found: 353.2112.
To a solution of aldehyde 204 (248 mg, 0.750 mmol) in methanol (5 mL) was added potassium carbonate (187 mg, 1.35 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (0.23 mL, 1.50 mmol). The reaction was stirred for 20 h then diluted with water (15 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (19:1) as eluent afforded the title product 226 (229 mg, 93%) as a colourless oil.

\[ \alpha \] D': 8.5 (c 1.0, CHCl₃); IR spectrum (film), cm⁻¹: 2956, 2857, 1472, 1377, 1252, 1068, 1038, 834, 773; \(^1\)H NMR (400 MHz, CDCl₃) δ: 3.96–3.88 (m, 4H, OCH₂CH₂O), 3.70–3.66 (m, 1H, H-5), 2.27 (dd, \( J = 16.6, 6.2, 2.7 \) Hz, 1H, 1 × H-7), 2.03 (ddd, \( J = 16.7, 8.0, 2.7 \) Hz, 1H, 1 × H-7), 1.93 (dd, \( J = 2.6 \) Hz, 2.6 Hz, 1H, H-9), 1.82–1.72 (m, 1H, H-6), 1.71–1.60 (m, 1H, 1 × H-3), 1.59–1.46 (m, 3H, 1 × H-3, H-4), 1.30 (s, 3H, H-1), 0.94 (d, \( J = 6.8 \) Hz, 6-CH₃), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.05 (s, 6H, Si(CH₃)₂C(CH₃)₃); \(^{13}\)C NMR (100 MHz, CDCl₃) δ: 110.2 (C-2), 84.1 (C-2), 74.2 (C-5), 69.0 (C-9), 64.8 (OCH₂CH₂O), 37.6 (C-6), 35.3 (C-3), 28.3 (C-4), 26.0 (3 × Si(CH₃)₂C(CH₃)₃), 24.0 (C-1), 22.3 (C-7), 18.3 (Si(CH₃)₂C(CH₃)₃), 14.0 (6-CH₃), −4.0 (1 × Si(CH₃)₂C(CH₃)₃), −4.4 (1 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na⁺)] m/z: calculated for (C₁₈H₃₄NaO₃Si) 349.2169, found: 349.2162.
To a solution of alkyne 226 (20 mg, 0.61 mmol) in dichloromethane (1 mL) under argon was added triethylamine (17 μL, 0.12 mmol) followed by zirconocene hydrochloride (24 mg, 0.092 mmol). The reaction was stirred for 30 min and N-bromosuccinimide (20 mg, 0.11 mmol) was added in one portion. After 2 h the mixture was diluted with saturated aqueous sodium bicarbonate (2 mL) and extracted with dichloromethane (3 × 2 mL). The combined organic layers were washed with brine (4 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (19:1 + 0.25% triethylamine) as eluent afforded the title product 224 (22 mg, 90%) as a colourless oil.

\[ \alpha \] D20: −2.2 (c 1.2, CHCl3); IR spectrum (film), cm\(^{-1}\): 2956, 2857, 1377, 1251, 1068, 1042, 940, 833, 772; \(^1\)H NMR (400 MHz, CDCl3) δ: 6.14 (ddd, \( J = 13.5, 8.3, 6.9 \) Hz, 1H, H-1), 6.02–5.97 (m, 1H, H-2), 3.98–3.87 (m, 4H, OCH₂CH₂O), 3.56–3.50 (m, 1H, H-5), 2.29–2.20 (m, 1H, 1 × H-3), 1.86–1.40 (m, 6H, 1 × H-3, H-4, H-6, H-7), 1.31 (s, 3H, H-9), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.84 (d, \( J = 6.9 \) Hz, 3H, 4-CH₃), 0.05 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃), 0.03 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); \(^{13}\)C NMR (100 MHz, CDCl₃) δ: 137.6 (C-2), 110.2 (C-8), 104.7 (C-1), 75.5 (C-5), 64.8 (OCH₂CH₂O), 38.1 (C-4), 35.9 (C-7), 35.6 (C-3), 27.6 (C-6), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 23.9 (C-9), 18.3 (Si(CH₃)₂C(CH₃)₃) 14.5 (4-CH₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.3 (1 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)\(^+\)] m/z: calculated for (C₁₈H₃₅BrNaO₃Si) 429.1431, found: 429.1441.
To a solution of alkyne 226 (200 mg, 0.613 mmol) in acetone (4 mL) was added silver nitrate (10 mg, 0.061 mmol) followed by N-bromosuccinimide (125 mg, 0.705 mmol). After 2 h the reaction was diluted with hexanes/ethyl acetate (9:1), filtered through silica and concentrated in vacuo to afford the title product 232 (241 mg, 97%) as a colourless oil.

\([\alpha]_D^{20}\): 7.4 (c 1.2, CHCl₃); IR spectrum (film), cm⁻¹: 2930, 2857, 1463, 1378, 1252, 1080, 1041, 836, 774; ¹H NMR (400 MHz, CDCl₃) δ: 3.97–3.89 (m, 4H, OCH₂CH₂O), 3.66 (td, \(J = 6.0, 3.5\) Hz, 1H, H-5), 2.29 (dd, \(J = 16.6, 6.3\) Hz, 1H, 1 × H-3), 2.06 (dd, \(J = 16.6, 7.9\) Hz, 1H, 1 × H-3), 1.81–1.72 (m, 1H, H-4), 1.71–1.46 (m, 4H, H-6, H-7), 1.31 (s, 3H, H-9), 0.92 (d, \(J = 7.1\) Hz, 3H, 4-CH₃), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.06 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃), 0.05 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ: 110.1 (C-8), 79.9 (C-2), 74.2 (C-5), 64.8 (OCH₂CH₂O), 38.2 (C-1), 37.5 (C-4), 35.3 (C-7), 28.3 (C-6), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 24.0 (C-9), 23.6 (C-3), 18.3 (Si(CH₃)₂C(CH₃)₃), 14.0 (4-CH₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.5 (1 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)⁺] \(m/z\): calculated for \((C_{18}H_{33}BrNaO₃Si)\) 427.1280, found: 427.1276.
To a solution of triphenylphosphine (631 mg, 2.41 mmol) in dichloromethane (4 mL) at −78 °C was added carbon tetrabromide (532 mg, 1.60 mmol) and the mixture warmed to 0 °C. After 15 min a solution of aldehyde 204 (265 mg, 0.802 mmol) and triethylamine (0.28 mL, 2.01 mmol) in dichloromethane (2 mL) was added. After 1 h the reaction was diluted with petroleum ether (10 mL), filtered through Celite® and concentrated in vacuo. Purification by flash chromatography using petroleum ether/diethyl ether (19:1) as eluent afforded the title product 234 (378 mg, 97%) as a colourless oil.

\([\alpha]_D^{20}: -5.5 \text{ (c 1.0, CHCl}_3); \text{IR spectrum (film), cm}^{-1}: 2956, 2930, 1252, 1068, 832, 772; \]

\(\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3) \delta: 6.39 \text{ (dd, } J = 7.9, 6.6 \text{ Hz, 1H, H-2), 3.96–3.87 (m, 4H, OCH}_2CH}_2O), 3.54–3.51 (m, 1H, H-5), 2.23–2.16 (m, 1H, 1 \times H-3), 2.00–2.92 (m, 1H, 1 \times H-3), 1.75–1.64 (m, 2H, H-4, 1 \times H-6), 1.58–1.36 (m, 3H, 1 \times H-6, H-7), 1.30 (s, 3H, H-9), 0.88 (s, 9H, Si(CH}_3)_2C(CH}_3)_3), 0.86 (d, } J = 6.8 \text{ Hz, 3H, 4-CH}_3), 0.04 (s, 3H, 1 \times Si(CH}_3)_2C(CH}_3)_3), 0.03 (s, 3H, 1 \times Si(CH}_3)_2C(CH}_3)_3); \]

\(\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3) \delta: 138.3 \text{ (C-2), 110.1 \text{ (C-8), 89.0 \text{ (C-1), 75.6 \text{ (C-5), 64.8 \text{ (OCH}_2CH}_2O), 37.7 \text{ (C-4), 36.2 \text{ (C-3), 35.5 \text{ (C-7), 27.7 \text{ (C-6), 26.1 \text{ (3 \times Si(CH}_3)}_2C(CH}_3)_3), 23.9 \text{ (C-9), 18.2 \text{ (Si(CH}_3)_2C(CH}_3)_3), 14.6 \text{ (4-CH}_3), -4.1 \text{ (1 \times Si(CH}_3)_2C(CH}_3)_3), -4.3 \text{ (1 \times Si(CH}_3)_2C(CH}_3)_3); HRMS \text{ [ESI, } (M+Na)^+] m/z: calculated for (C}_18H}_34Br}_2NaO}_3Si \text{ 507.0536, found: 507.0539.} \)
To a solution of palladium(II) acetate (2.3 mg, 0.0097 mmol) and triphenylphosphine (14 mg, 0.052 mmol) in dichloromethane (0.2 mL) was added a solution of geminal dibromide (47 mg, 0.097 mmol) in dichloromethane (0.3 mL) followed by tributyltin hydride (75 μL, 0.31 mmol). After 4 h the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography using petroleum ether/diethyl ether (29:1) as eluent afforded the title product (40 mg, 99%) as a colourless oil.

\[ \alpha \]_D^20: −0.7 (c 1.1, CHCl₃); IR spectrum (film), cm⁻¹: 2956, 2930, 1252, 1070, 1040, 833, 772, 671; ¹H NMR (400 MHz, CDCl₃) δ: 6.18 (ddd, J = 7.0, 1.4, 1.4 Hz, 1H, H-1), 6.12–6.07 (m, 1H, H-2), 3.98–3.89 (m, 4H, OCH₂CH₂O), 3.57–3.53 (m, 1H, H-5), 2.28 (ddddd, J = 14.5, 6.2, 4.7, 1.6 Hz, 1H, 1 × H-3), 2.10 (ddddd, J = 14.5, 9.4, 7.8, 1.4 Hz, 1H, 1 × H-3), 1.76–1.48 (m, 5H, H-4, H-6, H-7), 1.32 (s, 3H, H-9), 0.90 (s, 9H, Si(CH₃)₃C(CH₃)₃), 0.87 (d, J = 6.9 Hz, 3H, 4-CH₃), 0.06 (s, 3H, 1 × Si(CH₃)₃C(CH₃)₃), 0.05 (s, 3H, 1 × Si(CH₃)₃C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ: 134.3 (C-2), 110.3 (C-8), 108.4 (C-1), 75.8 (C-5), 64.8 (OCH₂CH₂O), 37.8 (C-4), 35.4 (C-7), 32.9 (C-3), 27.9 (C-6), 26.1 (3 × Si(CH₃)₃C(CH₃)₃), 24.0 (C-9), 18.3 (Si(CH₃)₃C(CH₃)₃), 14.6 (4-CH₃), −4.1 (1 × Si(CH₃)₃C(CH₃)₃), −4.3 (1 × Si(CH₃)₃C(CH₃)₃); HRMS [ESI, (M+Na)⁺] m/z: calculated for (C₁₈H₃₅BrNaO₃Si) 429.1431, found: 429.1430.
(5S,6S)-9-Bromo-5-(tert-butyldimethylsilyl)oxy-6-methylnon-8-yn-2-one 237

To a solution of alkyne 226 (80 mg, 0.245 mmol) in acetone (2 mL) was added silver nitrate (4 mg, 0.025 mmol) followed by N-bromosuccinimide (48 mg, 0.270 mmol). After 2 h the reaction was diluted with hexanes/ethyl acetate (9:1), filtered through silica and concentrated in vacuo. The resultant oil was dissolved in acetone/dichloromethane (1:1, 2 mL) and Amberlyst® 15 (10 mg) was added. After 20 h the reaction was diluted with petroleum ether/ethyl acetate (15:1), filtered through Celite and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (19:1) as eluent afforded the title product 237 (82 mg, 92%) as a colourless oil.

\[ \alpha \text{D}^2_0: 2.0 (c 1.2, \text{CHCl}_3); \text{IR spectrum (film), cm}^{-1}: 2956, 2857, 1718, 1360, 1252, 1025, 834, 774; ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta: 3.65 (ddd, J = 6.6, 5.6, 3.9 Hz, 1H, H-5), 2.51–2.35 (m, 2H, H-3), 2.30 (dd, J = 16.7, 6.2 Hz, 1H, 1 × H-7), 2.14 (s, 3H, H-1), 2.05 (dd, J = 16.8, 8.4 Hz, 1H, 1 × H-7), 1.79–1.58 (m, 3H, H-4, H-6), 0.93 (d, J = 6.8 Hz, 3H, 6-CH3), 0.88 (s, 9H, Si(CH3)2C(CH3)3), 0.05 (s, 6H, Si(CH3)2C(CH3)3); ^13\text{C NMR (100 MHz, CDCl}_3\text{)} \delta: 208.5 (C-2), 79.7 (C-8), 73.5 (C-5), 40.0 (C-3), 38.4 (C-9), 37.8 (C-6), 30.1 (C-1), 27.3 (C-4), 26.0 (3 × Si(CH3)2C(CH3)3), 23.1 (C-7), 18.2 (Si(CH3)2C(CH3)3), 14.3 (6-CH3), −4.2 (1 × Si(CH3)2C(CH3)3), −4.4 (1 × Si(CH3)2C(CH3)3); HRMS [ESI, (M+Na)\textsuperscript{+}] m/z: calculated for (C16H25BrNaO2Si) 383.1012, found: 383.1006.
(5S,6S,E)-9-Bromo-5-(tert-butyldimethylsilyl)oxy-6-methylnon-8-en-2-one 238

To a solution of acetal 224 (40 mg, 0.098 mmol) in acetone/dichloromethane (1:1, 1 mL) was added Amberlyst® 15 (5 mg). After 15 h the reaction was diluted with petroleum ether/ethyl acetate (15:1), filtered through Celite® and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (19:1) as eluent afforded the title product 238 (32 mg, 90%) as a colourless oil.

\([\alpha]_D^{20} : -10.1 \) (c 1.1, CHCl₃); IR spectrum (film), cm⁻¹: 2956, 2857, 1718, 1360, 1252, 1079, 940, 834, 774; \(^1\)H NMR (400 MHz, CDCl₃) δ: 6.18–6.07 (m, 1H, H-9), 6.03–5.96 (m, 1H, H-8), 3.54 (dt, \(J = 8.1, 4.0 \) Hz, 1H, H-5), 2.57–2.32 (m, 2H, H-3), 2.31–2.21 (m, 1H, 1 × H-7), 2.13 (s, 3H, H-1), 1.85–1.49 (m, 4H, 1 × H-7, H-4, H-6), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.85 (d, \(J = 6.8 \) Hz, 3H, 6-C₃H₃), 0.04 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃), 0.03 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); \(^13\)C NMR (100 MHz, CDCl₃) δ: 208.8 (C-2), 137.4 (C-8), 104.9 (C-9), 74.8 (C-5), 40.2 (C-3), 38.4 (C-1), 35.3 (C-7), 30.1 (C-6), 26.4 (C-4), 26.0 (3 × Si(CH₃)₂C(CH₃)₃), 18.2 (Si(CH₃)₂C(CH₃)₃), 14.8 (6-C₃H₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)⁺] m/z: calculated for (C₁₆H₃₁BrNaO₂Si) 385.1169, found: 385.1166.
(5S,6S,Z)-9-Bromo-5-(tert-butyldimethylsilyl)oxy-6-methylnon-8-en-2-one 239

To a solution of acetal 230 (93 mg, 0.228 mmol) in acetone/dichloromethane (1:1, 2 mL) was added Amberlyst® 15 (10 mg). After 20 h the reaction was diluted with petroleum ether/ethyl acetate (15:1), filtered through Celite® and concentrated in vacuo to afford the title product 239 (79 mg, 95%) as a colourless oil.

[a]D20: −9.9 (c 1.1, CHCl3); IR spectrum (film), cm⁻¹: 2957, 2857, 1718, 1361, 1079, 836, 774, 675; ¹H NMR (400 MHz, CDCl3) δ: 6.19 (ddd, J = 7.0, 1.5, 1.5 Hz, 1H, H-9), 6.11–6.06 (m, 1H, H-8), 3.58–3.53 (m, 1H, H-5), 2.53 (dd, J = 17.4, 9.4, 5.8 Hz, 1H, 1 × H-3), 2.42 (dd, J = 17.3, 9.3, 6.1 Hz, 1H, 1 × H-3), 2.30 (dd, J = 14.4, 6.2, 4.5, 1.7 Hz, 1H, 1 × H-7), 2.15 (s, 3H, H-1), 2.08 (dd, J = 14.5, 9.6, 7.9, 1.4 Hz, 1H, 1 × H-7), 1.79–1.60 (m, 3H, H-4, H-6), 0.90 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.88 (d, J = 7.1 Hz, 3H, 6-CH₃), 0.05 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃), 0.05 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); ¹³C NMR (100 MHz, CDCl3) δ: 208.9 (C-2), 134.1 (C-8), 108.6 (C-9), 75.0 (C-5), 40.1 (C-3), 38.2 (C-6), 32.3 (C-7), 30.1 (C-1), 26.8 (C-4), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃) 14.9 (6-CH₃), −4.2 (2 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)⁺] m/z: calculated for (C₁₆H₃₁BrNaO₂Si) 385.1169, found: 385.1154.
**4-Hydroxy-3,3-dimethylbutan-2-one 270**

![Chemical structure]

To a solution of 3-methylbutan-2-one (3.0 mL, 28.0 mmol) in trifluoroacetic acid (6.2 mL, 83.9 mmol) was added paraformaldehyde (1.01 g, 33.6 mmol) and the mixture heated to reflux for 20 h. The reaction was then cooled to room temperature and a solution of saturated sodium bicarbonate (80 mL) was carefully added with vigorous stirring. After 10 h the aqueous mixture was extracted with dichloromethane (3 × 60 mL) and the combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the *title product 270* (2.89 g, 89%) as a colourless oil.

$^1$H NMR (400 MHz, CDCl₃) δ: 3.56 (s, 2H, H-4), 2.51 (s, 1H, OH), 2.16 (s, 3H, H-1), 1.16 (s, 6H, 2 × 3-CH₃). The data obtained were in agreement with that reported in the literature.
To a suspension of sodium hydride (40% in mineral oil, 175 mg, 4.35 mmol) in diethyl ether (20 mL) at 0 °C was added \( p \)-methoxybenzyl alcohol (5.4 mL, 43.5 mmol). After 30 min trichloroacetonitrile (5.0 mL, 4.99 mmol) was added dropwise and the reaction stirred for 2 h. The mixture was then concentrated in vacuo, suspended in pentane (50 mL) and methanol (0.3 mL) and stirred for a further 30 min. The resultant suspension was filtered through Celite, concentrated in vacuo, and dissolved in dichloromethane (100 mL). To this solution was added alcohol \( 270 \) (3.37 g, 29.0 mmol) and camphorsulfonic acid (670 mg, 2.90 mmol). After 40 h the mixture was filtered through Celite and concentrated in vacuo. The crude oil was purified twice by flash chromatography using petroleum ether/ethyl acetate (8:1) as eluent to afford the title product \( 271 \) (1.80 g, 26%) as a colourless oil.

**IR spectrum** (film), cm\(^{-1}\): 2969, 1706, 1512, 1245, 1087, 1033, 818; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 7.23–7.19 (m, 2H, Ar-H), 6.88–6.84 (m, 2H, Ar-H), 4.42 (s, 2H, 4-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 3.78 (s, 3H, 4-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 3.40 (s, 2H, H-4), 2.12 (s, 3H, H-1), 1.12 (s, 6H, 2 × 3-CH\(_3\)); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 212.9 (C-2), 159.3 (Ar-C), 130.4 (Ar-C), 129.2 (2 × Ar-CH), 113.9 (2 × Ar-CH), 76.9 (C-4), 73.1 (4-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 55.4 (4-OCH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 48.8 (C-3), 25.9 (C-1), 22.1 (2 × 3-CH\(_3\)); HRMS [ESI, (M+Na)\(^+\)] \( m/z \): calculated for (C\(_{14}\)H\(_{20}\)NaO\(_3\)) 259.1305, found: 259.1310.
2,2-Dimethyl-3-oxobutyl acetate 266

To a solution of 3-methylbutan-2-one (2.0 mL, 18.6 mmol) in acetic acid (6 mL) was added p-toluenesulfonic acid monohydrate (35 mg, 0.186 mmol) and paraformaldehyde (728 mg, 24.2 mmol) and the mixture heated to reflux. After 7 h the reaction was diluted with diethyl ether (50 mL), quenched with saturated aqueous sodium bicarbonate (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the title product 266 (2.95 g, quant.) as a colourless oil.

$^1$H NMR (400 MHz, CDCl₃) δ: 4.10 (s, 2H, H-1), 2.15 (s, 3H, OCOC₃H₃), 2.02 (s, 3H, H-4), 1.15 (s, 6H, 2 × 2-CH₃). The data obtained were in agreement with that reported in the literature.$^{230}$
To a solution of ketone 271 (400 mg, 3.44 mmol) in methanol (2 mL) at −20°C was added bromine (0.19 mL, 3.61 mmol) dropwise. After 20 min the reaction was quenched with saturated aqueous sodium bicarbonate (3 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo to afford the title product 280 (670 mg, quantitative) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 2936, 2837, 1722, 1612, 1512, 1245, 1088, 1034, 820; **¹H NMR** (400 MHz, CDCl₃) δ: 7.23–7.19 (m, 2H, Ar-H), 6.88–6.84 (m, 2H, Ar-H), 4.42 (s, 2H, 4-OCH₂C₆H₄OCH₃), 4.21 (s, 2H, H-1), 3.81 (s, 3H, 4-OCH₂C₆H₄OC₂H₃), 3.40 (s, 2H, H-4), 3.40 (s, 2H, H-4), 1.12 (s, 6H, 2 × 3-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 204.9 (C-2), 159.4 (Ar-C), 130.6 (Ar-C), 129.4 (2 × Ar-CH), 114.0 (2 × Ar-CH), 76.9 (C-4), 73.3 (4-OCH₂C₆H₄OCH₃), 55.4 (4-OCH₂C₆H₄OCH₃), 48.8 (C-3), 34.1 (C-1), 22.5 (2 × 3-CH₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₁₄H₂₀BrNaO₃) 337.0410, found: 337.0411.
4-(tert-Butyldimethylsilyloxy)-3,3-dimethylbutan-2-one 283

To a solution of alcohol 270 (600 mg, 5.17 mmol) in dimethylformamide (2.5 mL) was added imidazole (530 mg, 7.76 mmol), and tert-butyldimethylsilyl chloride (935 mg, 6.20 mmol). After 18 h the reaction was quenched with aqueous citric acid (0.5 M, 10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/diethyl ether (15:1) as eluent afforded the title product 283 (723 mg, 61%) as a colourless oil.

$\text{^1H NMR (400 MHz, CDCl}_3\text{)} \delta$: 3.57 (s, 2H, H-4), 2.15 (s, 3H, H-1), 1.09 (s, 6H, 2 × 3-CH$_3$), 0.86 (s, 9H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.02 (s, 6H, 2 × Si(CH$_3$)$_2$C(CH$_3$)$_3$). The data obtained were in agreement with that reported in the literature.$^{229}$
To a solution of ketone 283 (100 mg, 0.434 mmol) in diethyl ether (3 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (0.6 M in tetrahydrofuran, 0.87 mL, 0.521 mmol). After 20 min benzaldehyde (57 μL, 0.564 mmol) was added dropwise. The mixture was stirred for a further 2 h then warmed to room temperature, quenched with saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (15:1) as eluent afforded the title product 487 (89 mg, 61%) as a colourless oil.

**IR spectrum** (film), cm\(^{-1}\): 3458, 2963, 2875, 1717, 1602, 1371, 1267, 1113, 1026, 708;

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\): 7.38–7.25 (m, 5H, Ar-H), 5.12 (ddd, \(J = 7.8, 4.5, 3.1\) Hz, H-1), 3.67 (d, \(J = 2.7\) Hz, 1-OH), 2.97–2.84 (m, 2H, H-2), 1.12 (s, 6H, 2 × 4-CH\(_3\)), 0.84 (s, 9H, Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.04 (s, 3H, 1 × Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.04 (s, 3H, 1 × Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\));

**\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)) \(\delta\): 216.1 (C-3), 143.3 (Ar-C), 128.5 (2 × Ar-CH), 127.5 (Ar-CH), 125.8 (2 × Ar-CH), 70.3 (C-1), 70.1 (C-5), 49.9 (C-4), 47.3 (C-2), 25.9 (3 × Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 21.3 (1 × 4-CH\(_3\)), 21.3 (1 × 4-CH\(_3\)), 18.3 (Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), −5.5 (2 × Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\));

**HRMS** [ESI, (M+Na\(^+\))] \(m/z\): calculated for (C\(_{19}\)H\(_{32}\)NaO\(_3\)Si) 359.2013, found: 359.2028.
To a solution of alcohol 487 (20 mg, 0.059 mmol) in dichloromethane (0.5 mL) at 0 °C was added 1,8-diazabicycloundec-7-ene (27 μL, 0.18 mmol) and methanesulfonyl chloride (6 μL, 0.071 mmol) and the mixture heated to reflux. After 3 h the reaction was cooled to room temperature, quenched with saturated ammonium chloride (2 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (19:1) as eluent afforded the title product 284 (18 mg, 96%) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 2956, 2857, 1683, 1608, 1251, 1099, 1065, 834, 774; **¹H NMR** (400 MHz, CDCl₃) δ: 7.62 (d, J = 15.7 Hz, 1H, H-1), 7.58–7.54 (m, 2H, Ar-H), 7.41–7.34 (m, 3H, Ar-H), 7.15 (d, J = 15.6 Hz, 1H, H-2), 3.67 (s, 2H, H-5), 1.19 (s, 6H, 2 × 4-CH₃), 0.86 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.02 (s, 6H, 2 × Si(CH₃)₂C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 203.5 (C-3), 142.3 (C-1), 135.2 (Ar-C), 130.2 (Ar-CH), 128.9 (2 × Ar-CH), 128.4 (2 × Ar-CH), 122.0 (C-2), 69.9 (C-5), 48.9 (C-4), 25.9 (3 × Si(CH₃)₂C(CH₃)₃), 21.6 (2 × 4-CH₃), 18.3 (Si(CH₃)₂C(CH₃)₃), −5.5 (2 × Si(CH₃)₂C(CH₃)₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₁₉H₃₀NaO₂Si) 341.1907, found: 341.1906.
To a solution of ketone 283 (100 mg, 0.434 mmol) in tetrahydrofuran (1.5 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (0.6 M in tetrahydrofuran, 0.80 mL, 0.477 mmol) followed by trimethylsilyl chloride (0.10 mL, 0.781 mmol) after a further 20 min. The mixture was stirred for 2 h then warmed to room temperature, quenched with saturated aqueous sodium bicarbonate (3 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. The resultant oil was dissolved in dichloromethane (3 mL), cooled to 0 °C and m-chloroperbenzoic acid (77% w/w, 117 mg, 0.521 mmol) was added portionwise. After 3 h, the mixture was diluted with aqueous sodium bicarbonate/sodium thiosulfate (both 5% w/w, 5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. The resultant oil was stirred in methanol (2 mL) and citric acid (17 mg, 0.087 mmol) was added. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/diethyl ether (19:1) as eluent afforded the title product 286 (75 mg, 70%) as a colourless oil.

IR spectrum (film), cm⁻¹: 3486, 2956, 2858, 1706, 1473, 1254, 1095, 1038, 835, 775, 669; ¹H NMR (400 MHz, CDCl₃) δ: 4.37, (s, 2H, H-1), 3.53 (s, 2H, H-4), 3.22 (s, 1H, 1-OH), 1.12 (s, 6H, 2 × 3-CH₃), 0.84 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.00 (s, 6H, 2 × Si(CH₃)₂C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ: 214.6 (C-2), 70.2 (C-1), 66.1 (C-4), 47.8 (C-3), 25.9 (3 × Si(CH₃)₂C(CH₃)₃), 21.2 (2 × 3-CH₃), 18.3 (Si(CH₃)₂C(CH₃)₃), −5.6 (2 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)⁺] m/z: calculated for (C₁₂H₂₆NaO₃Si) 269.1543, found: 269.1540.
3-Benzoyloxy-2,2-dimethylpropanol 299

To a solution of neopentyl glycol (2.69 g, 25.8 mmol) at 0 °C in dichloromethane (50 mL) was added dimethylaminopyridine (157 mg, 1.29 mmol), pyridine (1.0 mL, 12.9 mmol), then benzoyl chloride (1.5 mL, 12.9 mmol) dropwise. The mixture was stirred for 16 h then diluted with aqueous citric acid (0.5 M, 40 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine (120 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (2:1) as eluent afforded the title product 299 (2.13 g, 79%) as a colourless oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta: 8.07–8.03 (m, 2H, Ar-H), 7.60–7.55 (m, 1H, Ar-H), 7.48–7.43 (m, 2H, Ar-H), 4.19 (s, 2H, H-1), 3.39 (s, 2H, H-3), 2.25 (s, 1H, 1-OH), 1.02 (s, 6H, 2×2-CH}_3\text{).} \]

The data obtained were in agreement with that reported in the literature.\textsuperscript{231}

3-Benzoyloxy-2,2-dimethylpropanal 300

To a solution of alcohol 299 (1.00 g, 4.80 mmol), dimethyl sulfoxide (3.4 mL, 48.0 mmol), and diisopropylethylamine (4.2 mL, 24.0 mmol) in dichloromethane (40 mL) at 0 °C was added sulfur trioxide-pyridine complex (2.29 g, 14.4 mmol) in one portion. After 10 min the reaction was quenched with saturated ammonium chloride (30 mL) and the organic layer was washed with brine (30 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (3:1) as eluent afforded the title product 300 (935 mg, 94%) as a yellow oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta: 9.64 (s, 1H, H-1), 8.01–7.97 (m, 2H, Ar-H), 7.60–7.53 (m, 1H, Ar-H), 7.46–7.40 (m, 2H, Ar-H), 4.37 (s, 2H, H-3), 1.21 (s, 6H, 2×2-CH}_3\text{).} \]

The data obtained were in agreement with that reported in the literature.\textsuperscript{232}
3-Benzoyloxy-2,2-dimethylpropanoic acid 295

To a solution of aldehyde 300 (915 mg, 4.44 mmol) in tetrahydrofuran/water/tert-butanol (4:4:1, 6 mL) at 0 °C was added 2-methyl butene (0.50 mL) and monosodium phosphate (3.73 g, 31.0 mmol), followed by sodium chlorite (1.61 g, 17.8 mmol) portionwise. After 15 h the reaction diluted with water (15 mL) then acidified to pH = 3 using polyphosphoric acid and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (3:1) as eluent afforded the title product 295 (904 mg, 92%) as a white solid.

\[ \text{\textbf{1H NMR}} \quad (400 \text{ MHz, CDCl}_3) \delta: 8.04–8.01 \ (\text{m, 2H, Ar-H}), 7.58–7.52 \ (\text{m, 1H, Ar-H}), 7.45–7.39 \ (\text{m, 2H, Ar-H}), 4.37 \ (\text{s, 2H, H-3}), 1.36 \ (\text{s, 6H, 2 × 2-CH}_3) \]. The data obtained were in agreement with that reported in the literature.\textsuperscript{233}
To a solution of carboxylic acid 295 (200 mg, 0.892 mmol) in dichloromethane 2 mL was added oxalyl chloride (0.12 mL, 1.43 mmol) and dimethylformamide (1 drop). The mixture was then stirred for 3 h then concentrated under a stream of nitrogen and dried in vacuo. The crude oil was dissolved in acetonitrile (4 mL) and trimethylsilyldiazomethane (2 M in hexane, 0.84 mL, 1.78 mmol) was added. After 16 h the mixture was concentrated under a stream of nitrogen. Purification by flash chromatography using petroleum ether/ethyl acetate (5:1) as eluent afforded the title product 296 (75 mg, 34%) as a yellow oil.

**IR spectrum** (film), cm⁻¹: 2973, 2101, 1717, 1625, 1350, 1267, 1110, 708; **¹H NMR** (400 MHz, CDCl₃) δ: 8.04–7.99 (m, 2H, Ar-H), 7.60–7.54 (m, 1H, Ar-H), 7.48–7.41 (m, 2H, Ar-H), 5.52 (s, 1H, H-1), 4.33 (s, 2H, H-4), 1.27 (s, 6H, 2 × 3-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 197.9 (C-2), 166.3 (4-OCOC₆H₅), 133.3 (Ar-CH), 130.0 (Ar-C), 127.9 (2 × Ar-CH), 128.6 (2 × Ar-CH), 70.4 (C-4), 53.2 (C-1), 46.3 (C-3), 22.6 (2 × 3-CH₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₁₃H₁₄N₂NaO₃) 269.0902, found: 269.0898.
3,3-Dimethyldihydrofuran-2(3H)-one 303

To a suspension of sodium hydride (60% in mineral oil, 5.58 g, 139 mmol) in tetrahydrofuran (40 mL) heated at reflux was added a solution of methyl iodide (9.0 mL, 145 mmol) and γ-butyrolactone (4.4 mL, 58.1 mmol) in tetrahydrofuran (10 mL) over 15 min. After 3 h the mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (40 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and filtered through a plug of silica, washing with diethyl ether (50 mL). The solution was then concentrated in vacuo and the resultant crude oil was used without further purification for the next step.
To a solution of crude lactone 303 (6.3 g) in toluene (180 mL) was added crushed potassium hydroxide (11.4 g, 203 mmol) followed by benzyl bromide (27.6 mL, 232 mmol). The mixture was heated under Dean-Stark for 13 h, cooled to room temperature and concentrated in vacuo. The resultant residue was suspended in methanol/water (2:1, 200 mL) and potassium hydroxide (6.51 g, 116 mmol) was added and the mixture heated to reflux. After 16 h the reaction was cooled and extracted with diethyl ether (100 mL). The aqueous phase was then acidified with hydrochloric acid (pH = 3) and further extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (9:1→5:1) as eluent afforded the title product 304 (4.42 g, 34% over 2 steps) as a white solid.

**mp:** 45–48 °C; **IR spectrum** (film), cm⁻¹: 2973, 1698, 1474, 1454, 1365, 1102, 735, 697; **¹H NMR** (400 MHz, CDCl₃) δ: 7.35–7.23 (m, 5H, Ar-H), 4.48 (s, 2H, 4-OCH₂C₆H₅), 3.55 (t, J = 6.7 Hz, 2H, H-4), 1.92 (t, J = 6.7 Hz, 2H, H-3), 1.23 (s, 6H, 2 × 2-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 183.2 (C-1), 138.4 (Ar-C), 128.5 (2 × Ar-CH), 127.7 (2 × Ar-CH), 127.5 (Ar-CH), 73.2 (4-OCH₂C₆H₅), 67.2 (C-4), 40.8 (C-2), 39.6 (C-3), 25.5 (2 × 2-CH₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₁₃H₁₈NaO₃) 245.1148, found: 245.1142.
4-Benzoyloxy-2,2-dimethylbutanoic acid 308

To a solution of carboxylic acid 304 (1.50 g, 6.75 mmol) in ethyl acetate (150 mL) was added an aqueous solution of sodium periodate (11% w/w, 75 mL, 36.9 mmol) and ruthenium(III) chloride hydrate (140 mg, 0.270 mmol). The mixture was vigorously stirred for 3 h, diluted with aqueous citric acid (0.5 M, 60 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (4:1) as eluent afforded the title product 308 (1.40 g, 88%) as a white solid.

mp: 50–53 °C; IR spectrum (film), cm⁻¹: 2975, 1717, 1698, 1271, 1113, 710; ¹H NMR (400 MHz, CDCl₃) δ: 8.04–7.98 (m, 2H, Ar-H), 7.58–7.50 (m, 1H, Ar-H), 7.46–7.38 (m, 2H, Ar-H), 4.40 (t, J = 6.7 Hz, 2H, H-4), 2.07 (t, J = 6.7 Hz, 2H, H-3), 1.30 (s, 6H, 2 × 2-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ: 183.2 (C-1), 166.6 (4-OCOC₆H₅), 133.1 (Ar-CH), 130.3 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 61.9 (C-4), 40.8 (C-2), 38.6 (C-3), 25.4 (2 × 2-CH₃); HRMS [ESI, (M+Na)+] m/z: calculated for (C₁₃H₁₆NaO₄) 259.0941, found: 259.0940.
To a solution of carboxylic acid 308 (213 mg, 0.902 mmol) in dichloromethane (4 mL) was added oxalyl chloride (0.60 mL, 6.93 mmol) and dimethylformamide (0.21 mL, 2.71 mmol) concurrently over 2 h. The mixture was then diluted with pentane (4 mL), filtered through a plug of silica washing with dichloromethane/pentane (3:1, 10 mL), and concentrated under a stream of nitrogen and dried in vacuo. The crude oil was then dissolved in acetonitrile (7 mL) and trimethylsilyldiazomethane (2 M in hexane, 0.92 mL, 1.80 mmol) was added. After 1 h the mixture was concentrated under a stream of nitrogen. Purification by flash chromatography using petroleum ether/diethyl ether (3:1) as eluent afforded the title product 309 (213 mg, 91%) as a yellow oil.

**IR spectrum** (film), cm⁻¹: 3093, 2968, 2999, 1713, 1624, 1347, 1270, 1111, 710; **¹H NMR** (400 MHz, CDCl₃) δ: 8.02–7.94 (m, 2H, Ar-H), 7.59–7.51 (m, 1H, Ar-H), 7.47–7.39 (m, 2H, Ar-H), 5.43 (s, 1H, H-5), 4.36 (t, J = 6.9 Hz, 2H, H-1), 2.03 (t, J = 6.8 Hz, 2H, H-2), 1.22 (2 × 2-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 199.8 (C-4), 166.7 (1-OCOC₆H₅), 133.1 (Ar-CH), 130.3 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 61.9 (C-1), 52.7 (C-5), 44.6 (C-3), 38.9 (C-2), 25.4 (2 × 3-CH₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₁₄H₁₆N₂O₃) 283.1053, found: 283.1051.
3,3-Dimethyl-4,5-dioxopentyl benzoate 310

![Chemical Structure of 3,3-Dimethyl-4,5-dioxopentyl benzoate 310](chemistry.png)

To stirred diazoketone 310 (104 mg, 0.400 mmol) was rapidly added dimethyldioxirane (69 mM in acetone, 6.7 mL, 0.466 mmol). The mixture was vigorously stirred for 2 min, and concentrated under a stream of nitrogen. The resultant crude oil was used without further purification.

**IR spectrum** (film), cm\(^{-1}\): 2972, 1716, 1452, 1316, 1274, 1113, 1026, 712; **\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\): 9.20 (s, 1H, H-5), 7.91–7.86 (m, 2H, Ar-H), 7.59–7.52 (m, 1H, Ar-H), 7.47–7.40 (m, 2H, Ar-H), 4.36 (t, \(J = 6.1 \text{ Hz}\), 2H, H-1), 2.31 (t, \(J = 6.1 \text{ Hz}\), 2H, H-2), 1.35 (2 \(\times\) 3-CH\(_3\)); **\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)) \(\delta\): 202.3 (C-4), 188.7 (C-5), 166.4 (1-OCOC\(_6\)H\(_5\)), 133.3 (Ar-CH), 129.7 (Ar-C), 129.6 (2 \(\times\) Ar-CH), 128.6 (2 \(\times\) Ar-CH), 61.5 (C-1), 44.3 (C-3), 37.8 (C-2), 24.0 (2 \(\times\) 3-CH\(_3\)); **HRMS** [ESI, (M+Na)\(^+\)] \(m/z\): calculated for (C\(_{14}\)H\(_{16}\)NaO\(_4\)) 271.0941, found: 271.0935.
To a solution of acetophenone (23 mg, 0.192 mmol) in dichloromethane (0.5 mL) at −10 °C was added diisopropylethylamine (0.10 mL, 0.576 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (52 μL, 0.230 mmol). After 1 h the reaction was quenched with saturated sodium bicarbonate (2 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting oil was dissolved in petroleum ether (10 mL), filtered through a plug of Celite and concentrated in vacuo to give crude silyl enol ether 320.

To diazoketone 309 (25 mg, 0.096 mmol) was added a solution of dimethyldioxirane (69 mM in acetone, 1.5 mL, 0.106 mmol) and the mixture concentrated under a stream of nitrogen then in vacuo to give crude glyoxal 310.

To a solution of (S)-(+) - o-tolyl-CBS-oxazaborolidine (0.5 M in toluene, 48 μL, 0.024 mmol) in dichloromethane (0.1 mL) under argon at −60 °C was added aluminium bromide (1 M in dibromomethane, 24 μL, 0.024 mmol) dropwise and the mixture stirred vigorously for 30 min. A solution of the aforementioned glyoxal 310 and silyl enol ether 320 in dichloromethane (0.5 mL) was added and the mixture stirred for 20 min then quenched with triethylamine (50 μL) and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (4:1) as eluent afforded the title product 319 (8.9 mg, 25%) as a colourless oil.

\[ \alpha \] D 20: 0.4 (c 0.23, CHCl 3); IR spectrum (film), cm −1: 3471, 2971, 1714, 1683, 1114, 713, 689; 1H NMR (400 MHz, CDCl 3) \( \delta \): 8.03–7.98 (m, 2H, Ar-H), 7.91–7.86 (m, 2H, Ar-H), 7.48–7.39 (m, 4H, Ar-H), 5.07 (td, \( J = 7.0, 4.2 \) Hz, 2H, H-5), 4.43–4.31 (m, 2H, H-1), 3.66 (d, \( J = 7.0 \) Hz, 5-OH), 3.35–3.22 (m, 2H, H-6), 2.13 (ddd, \( J = 14.1, 7.1, 7.0 \) Hz, 1H, 1 × H-6), 1.38 (s, 3H, 1 × 3-CH 3); 13C NMR (100 MHz, CDCl 3) \( \delta \): 214.4 (C-4), 198.9 (C-7), 166.7
(1-OCOC₆H₅), 136.7 (Ar-C), 133.8 (Ar-CH), 133.1 (Ar-CH), 130.3 (Ar-C), 129.8 (2 × Ar-CH), 128.8 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 70.7 (C-5), 62.0 (C-1), 46.0 (C-3), 42.1 (C-6), 38.3 (C-2), 25.6 (1 × 3-CH₃), 24.5 (1 × 3-CH₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₂₂H₂₄NaO₅) 391.1516, found: 391.1511.
To a solution of diisopropylamine (46 μL, 0.325 mmol) in tetrahydrofuran (1 mL) at −78 °C was added n-butyllithium (2 M in cyclohexane, 0.15 mL, 0.300 mmol) and the mixture warmed to −10 °C for 5 min. At −78 °C, acetophenone (30 mg, 0.250 mmol) was added dropwise. After 30 min tert-butyldimethylsilyl trifluoromethanesulfonate (75 μL, 0.325 mmol) was added and the mixture stirred for 1 h then quenched with saturated sodium bicarbonate (2 mL) and extracted with diethyl ether (2 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure then dissolved in petroleum ether (10 mL), filtered through a plug of Celite and concentrated in vacuo to give crude silyl enol ether 320.

To a solution of (S)-(+)–o-tolyl-CBS-oxazaborolidine (0.5 M in toluene, 0.10 mL, 0.050 mmol) in dichloromethane (0.2 mL) under argon at −40 °C was added aluminium bromide (1 M in dibromomethane, 50 μL, 0.050 mmol) dropwise and the mixture stirred vigorously for 30 min. A solution of the aforementioned silyl enol ether and aldehyde 146 (78 mg, 0.375 mmol) in dichloromethane (0.8 mL) was added and the mixture stirred for 20 min then quenched with triethylamine (50 μL) and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (3:1) as eluent afforded the title product 341 (42.5 mg, 52%) as a colourless oil.

[a]D<sup>20</sup>: −4.5 (c 1.0, CHCl₃); IR spectrum (film), cm⁻¹: 3436, 2934, 2857, 1679, 1513, 1247, 1095, 1034, 755, 691; \(^1\)H NMR (400 MHz, CDCl₃) δ: 7.97–7.93 (m, 2H, Ar-H), 7.61–7.55 (m, 1H, Ar-H), 7.50–7.44 (m, 2H, Ar-H), 7.28–7.23 (m, 2H, Ar-H), 6.90–6.84 (m, 2H, Ar-H), 5.07 (td, J = 7.0, 4.2 Hz, 2H, H-3), 4.45 (s, 2H, OCH₂C₆H₄OCH₃), 4.28–4.19 (m, 1H, H-3), 3.79 (s, 3H, OCH₂C₆H₄OCH₃), 3.55–3.47 (m, 3H, H-6, 3-OH), 3.18–3.03 (m, 2H, H-2), 1.96–1.59 (m, 4H, H-4, H-5); \(^1\)C NMR (100 MHz, CDCl₃) δ: 200.9 (C-1), 159.3 (Ar-C), 137.0 (Ar-C), 133.6 (Ar-CH), 130.6 (Ar-C), 129.5 (2 × Ar-CH), 128.8 (2 × Ar-CH), 128.2 (2 × Ar-CH), 113.9 (2 × Ar-CH), 72.8 (OCH₂C₆H₄OCH₃), 70.1 (C-6), 67.8 (C-3), 55.4 (OCH₂C₆H₄OCH₃), 45.3 (C-2), 33.8 (C-4), 26.1 (C-5); HRMS [ESI, (M+Na)⁺] m/z: calculated for (C₂₀H₂₄NaO₄) 351.1567, found: 351.1575.
To a solution of ketone 212 (26 mg, 0.096 mmol) in dichloromethane (0.5 mL) at −10 °C was added diisopropylethylamine (51 μL, 0.29 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (27 μL, 0.12 mmol). After 1 h the reaction was quenched with saturated sodium bicarbonate (2 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The resultant oil was dissolved in petroleum ether (10 mL), filtered through a plug of Celite and concentrated in vacuo to give crude silyl enol ether 339.

To a solution of (S)-(+)-o-tolyl-CBS-oxazaborolidine (0.5 M in toluene, 43 μL, 0.021 mmol) in dichloromethane (0.1 mL) under argon at −78 °C was added aluminium bromide (1 M in dibromomethane, 21 μL, 0.021 mmol) dropwise and the mixture stirred vigorously for 30 min. A solution of the aforementioned silyl enol ether and aldehyde 146 (78 mg, 0.375 mmol) in dichloromethane (0.8 mL) was added and the mixture stirred for 5 min then quenched with triethylamine (50 μL) and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (9:1 → 3:1) as eluent afforded the title product 342 (13 mg, 35%) as a colourless oil, alongside recovered ketone 212 (12 mg, 41%).

[α]D20: −16.9 (c 0.26, CHCl3); IR spectrum (film), cm⁻¹: 3441, 2954, 2856, 1709, 1513, 1247, 1090, 1035, 834, 774; ¹H NMR (400 MHz, CDCl₃) δ: 7.27–7.22 (m, 2H, Ar-H), 6.89–6.85 (m, 2H, Ar-H), 5.90–5.76 (m, 1H, H-11), 5.07–4.97 (m, 2H, H-12), 4.43 (s, 2H, 1-OCH₂C₆H₄OCH₃), 4.03 (bs, 1H, H-4), 3.80 (s, 3H, 1-OCH₂C₆H₄OC₃H₃), 3.64–3.53 (m, 1H, H-9), 3.50–3.45 (m, 2H, H-1), 3.31 (bs, 1H, 4-Oh), 2.56–2.16 (m, 5H, H-5, H-7, H-10), 1.80–1.44 (m, 6H, H-2, H-3, H-8), 0.98 (d, J = 6.8 Hz, 3H, 10-CH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.10–0.02 (m, 6H, Si(CH₃)₂C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ: 212.1 (C-6), 159.4 (Ar-C), 140.6 (C-11), 130.6 (C-Ar), 129.5 (2 × Ar-CH), 114.7 (C-12), 114.0 (2 × Ar-CH), 75.0 (C-9), 72.8
(1-OCH₂C₆H₄OCH₃), 70.1 (C-1), 67.6 (C-4), 55.4 (1-OCH₂C₆H₄OCH₃), 49.3 (C-5), 43.1 (C-10), 39.3 (C-2), 39.2 (C-7), 33.8 (C-3), 27.2 (C-8), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 15.7 (10-CH₃), −4.2 (2 × Si(CH₃)₂C(CH₃)₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₂₇H₄₆NaO₅Si) 501.3007, found: 501.3012.
To a solution of ketone 212 (60 mg, 0.222 mmol) in dichloromethane (1 mL) at −10 °C was added diisopropylethylamine (0.12 mL, 0.666 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (64 μL, 0.278 mmol). After 1 h the reaction was quenched with saturated sodium bicarbonate (2 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure then dissolved in petroleum ether (10 mL), filtered through a plug of cotton wool and concentrated in vacuo to give crude silyl enol ether 339.

To diazoketone 309 (104 mg, 0.400 mmol) was added a solution of dimethyldioxirane (70 mM in acetone, 6.7 mL, 0.466 mmol) and the mixture concentrated under a stream of nitrogen then in vacuo to give crude glyoxal 310.

To a solution of diamine-\(N\)-dioxide ligand 351 (12 mg, 0.022 mmol) in dichloromethane (1 mL) at 30 °C was added nickel tetrafluoroborate hexahydrate (7.6 mg, 0.022 mmol) and the mixture stirred vigorously for 30 min then concentrated in vacuo. A solution of the aforementioned glyoxal 310 and silyl enol ether 339 in dichloromethane (2 mL) was added and the mixture warmed to 30 °C. After 18 h the reaction was quenched with aqueous citric acid (0.5 M, 3 mL) and stirred for 30 min then extracted with dichloromethane (3 × 3 mL). The combined organic layers were washed with brine (6 mL), dried over sodium sulfate and concentrated under reduced pressure. The resultant oil was stood in chloroform for 14 h then concentrated in vacuo. Purification by flash using petroleum ether/ethyl acetate (15:1) as eluent afforded the title product 347 (33 mg, 29%, 14:1 mixture of diastereomers) as a colourless oil, alongside returned starting ketone 212 (10 mg, 17%).
**IR spectrum** (film), cm\(^{-1}\): 3356, 2960, 2889, 1706, 1367, 1277, 1068, 925, 716; **\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\): 8.01–7.97 (m, 2H, Ar-H), 7.58–7.52 (m, 1H, Ar-H), 7.46–7.40 (m, 2H, Ar-H), 5.86–5.76 (m, 1H, H-12), 5.04–4.97 (m, 2H, H-13), 4.86 (dd, \(J = 6.7, 4.6\) Hz, 2H, H-5), 4.38–4.26 (m, 2H, H-1), 3.57–3.51 (m, 2H, H-10, 5-OH), 2.76–2.64 (m, 2H, H-6), 2.60–2.41 (m, 2H, H-8), 2.33–2.22 (m, 1H, H-11), 2.22–2.05 (m, 2H, H-2), 1.78–1.55 (m, 2H, H-9), 1.32 (s, 3H, 1 \(\times\) 3-CH\(_3\)), 1.32 (s, 3H, 1 \(\times\) 3-CH\(_3\)), 0.98 (d, \(J = 7.0\) Hz, 3H, 11-CH\(_3\)), 0.88 (s, 9H, Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.04 (s, 3H, Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.03 (s, 3H, Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)); **\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)) \(\delta\): 214.4 (C-4), 209.9 (C-7), 166.7 (OCOC\(_6\)H\(_5\)), 140.6 (C-12), 133.1 (Ar-CH), 130.3 (Ar-C), 129.7 (2 \(\times\) Ar-CH), 128.5 (2 \(\times\) Ar-CH), 114.6 (C-13), 74.9 (C-10), 70.6 (C-5), 61.9 (C-1), 45.9 (C-6), 45.8 (C-3), 43.0 (C-8), 39.5 (C-11), 27.0 (C-9), 26.1 (3 \(\times\) Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 25.4 (1 \(\times\) 3-CH\(_3\)), 24.6 (1 \(\times\) 3-CH\(_3\)), 21.9 (C-2), 18.3 (Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 15.7 (11-CH\(_3\)), -4.2 (2 \(\times\) Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)); **HRMS** [ESI, (M+H\(^+\))]: \(m/z\): calculated for (C\(_{29}\)H\(_{46}\)NaO\(_6\)Si) 541.2956, found: 541.2956.
To a solution of acetal 226 (175 mg, 0.536 mmol) in acetone/dichloromethane (1:1, 4 mL) was added Amberlyst® 15 (20 mg). After 18 h the reaction was diluted with petroleum ether/ethyl acetate (15:1), filtered through Celite® and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (19:1) as eluent afforded the title product 358 (114 mg, 75%) as a colourless oil.

$[\alpha]_D^{20}$: 1.0 (c 1.0, CHCl$_3$); IR spectrum (film), cm$^{-1}$: 2931, 2857, 1718, 1361, 1253, 1080, 1027, 834, 774; $^1$H NMR (400 MHz, CDCl$_3$) δ: 3.69 (ddd, $J = 5.2, 5.2, 4.7$ Hz, 1H, H-5), 2.52–2.36 (m, 2H, H-3), 2.29 (ddd, $J = 16.7, 5.9, 2.8$ Hz, 1H, 1 × H-7), 2.14 (s, 3H, H-1), 2.03 (ddd, $J = 16.7, 8.2, 2.5$ Hz, 1H, 1 × H-7), 1.93 (dd, $J = 2.9, 2.5$ Hz, 1H, H-9), 1.80–1.58 (m, 1H, H-6), 1.71–1.60 (m, 1H, 1 × H-3), 1.59–1.46 (m, 3H, H-4, H-6), 0.96 (d, $J = 6.9$ Hz, 3H, 6-CH$_3$), 0.89 (s, 9H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.06 (s, 6H, Si(CH$_3$)$_2$C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 208.6 (C-2), 83.9 (C-8), 73.5 (C-5), 69.2 (C-9), 40.0 (C-3), 37.9 (C-6), 30.1 (C-1), 27.3 (C-4), 26.0 (3 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), 21.9 (C-7), 18.3 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 14.3 (6-CH$_3$), −4.2 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), −4.4 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); HRMS [ESI, (M+Na)$^+$] m/z: calculated for (C$_{16}$H$_{30}$NaO$_2$Si) 305.1907, found: 305.1896.
(5S,10S,11S)-10-(tert-Butyldimethylsilyl)oxy-5-hydroxy-3,3,11-trimethyl-4,7-dioxotetradec-13-yn-1-yl benzoate 360

To a solution of ketone 358 (40 mg, 0.142 mmol) in dichloromethane (1 mL) at −10 °C was added triethylamine (97 μL, 0.71 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (65 μL, 0.28 mmol). After 1 h the reaction was quenched with saturated sodium bicarbonate (2 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure then dissolved in petroleum ether (10 mL), filtered through a plug of cotton wool and concentrated in vacuo to give crude silyl enol ether 359.

To a solution of diamine-N-dioxide (8.7 mg, 0.015 mmol) in dichloromethane (1 mL) at 30 °C was added nickel tetrafluoroborate hexahydrate (4.8 mg, 0.014 mmol) and the mixture stirred vigorously for 30 min then concentrated and dried in vacuo for 5 h. A solution of crude glyoxal 310 (~0.142 mmol) and silyl enol ether in dichloromethane (1 mL) was added and the mixture warmed to 30 °C. After 2 h, a solution of glyoxal 310 (~0.142 mmol) in dichloromethane (0.5 mL) was added dropwise followed by another solution of glyoxal 310 (~0.142 mmol) in dichloromethane (0.5 mL) after a further 2 h. The reaction was then stirred for 18 h and quenched with aqueous citric acid (0.5 M, 3 mL) and stirred for 30 min then extracted with dichloromethane (3 × 3 mL). The combined organic layers were washed with brine (6 mL), dried over sodium sulfate and concentrated under reduced pressure. The resultant oil was stood in chloroform for 14 h then concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (15:1) as eluent afforded the title product 360 (24 mg, 32%) as a colourless oil, alongside returned starting ketone 358 (22 mg, 55%).
$[\alpha]_D^{20}$: 2.2 (c 2.4, CHCl$_3$); **IR spectrum** (film), cm$^{-1}$: 3480, 2958, 2857, 1716, 1275, 1113, 1027, 837, 776, 713; **$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$: 8.01–7.97 (m, 2H, Ar-H), 7.59–7.53 (m, 1H, Ar-H), 7.46–7.40 (m, 2H, Ar-H), 4.90–4.83 (m, 1H, H-5), 4.39–4.27 (m, 2H, H-1), 3.71–3.67 (m, 1H, H-10), 3.60–3.56 (m, 1H, 5-OH), 2.65–2.57 (m, 2H, H-6), 2.58–2.36 (m, 2H, H-8), 2.28 (ddd, $J$ = 16.6, 5.8, 2.6 Hz, 1H, 1 × H-12), 2.23–1.98 (m, 3H, H-2, 1 × H-12), 1.95 (dd, $J$ = 3.0, 2.6 Hz, 1H, H-14), 1.80–1.62 (m, 3H, H-9, H-11), 1.33 (s, 3H, 1 × 3-CH$_3$), 1.33 (s, 3H, 1 × 3-CH$_3$), 0.96 (d, $J$ = 6.9 Hz, 3H, 11-CH$_3$), 0.88 (s, 9H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.06 (s, 6H, Si(CH$_3$)$_2$C(CH$_3$)$_3$); **$^{13}$C NMR** (100 MHz, CDCl$_3$) $\delta$: 214.4 (C-4), 209.4 (C-7), 166.7 (1-OCOC$_6$H$_5$), 133.2 (Ar-CH), 130.3 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 83.9 (C-13), 73.4 (C-10), 70.6 (C-5), 69.2 (C-14), 61.9 (C-1), 46.0 (C-6), 45.8 (C-3), 40.2 (C-8), 38.3 (C-2), 37.9 (C-11), 26.9 (C-9), 26.0 (3 Si(CH$_3$)$_2$C(CH$_3$)$_3$), 25.4 (1 × 3-CH$_3$), 24.6 (1 × 3-CH$_3$), 21.9 (C-12), 18.2 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 14.4 (11-CH$_3$), −4.1 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), −4.4 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$); **HRMS** [ESI, (M+H)$^+$]: $m/z$: calculated for (C$_{30}$H$_{46}$NaO$_6$Si) 553.2956, found: 553.2957.
To a suspension of sodium hydride (60% in mineral oil, 1.14 g, 28.7 mmol) in tetrahydrofuran (60 mL) at 0 °C was added 3,3-dimethylpentane-1,5-diol (379) (3.80 g, 28.7 mmol) dropwise. After 30 min benzoyl chloride (2.8 mL, 23.9 mmol) was added dropwise and the mixture allowed to warm slowly to room temperature over 20 h. The reaction was quenched with aqueous citric acid (0.5 M, 50 mL), extracted with ethyl acetate (2 × 70 mL) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (1:1) as eluent afforded the title product 380 (2.67 g, 47%) as a colourless oil.

**1H NMR** (400 MHz, CDCl₃) δ: 8.05–8.01 (m, 2H, Ar-H), 7.58–7.52 (m, 1H, Ar-H), 7.46–7.41 (m, 2H, Ar-H), 4.40 (t, \( J = 7.3 \) Hz, 2H, H-1), 3.76 (t, \( J = 7.6 \) Hz, 2H, H-5), 1.75 (t, \( J = 7.3 \) Hz, 2H, H-2), 1.65–1.59 (m, 3H, H-4, 1-OH), 1.02 (s, 6H, 2 × 3-CH₃); **13C NMR** (100 MHz, CDCl₃) δ: 166.9 (1-OCOC₆H₅), 133.0 (Ar-CH), 130.6 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 62.4 (C-1), 59.8 (C-5), 44.8 (C-2), 40.4 (C-4), 31.9 (C-3), 27.9 (2 × 3-CH₃); **HRMS** [ESI, (M+H)⁺]: \( m/z \): calculated for (C₁₄H₂₁O₃) 237.1485, found: 237.1487.
3,3-Dimethyl-5-oxopentyl benzoate 381

To a solution of alcohol 380 (200 mg, 0.846 mmol), dimethyl sulfoxide (0.60 mL, 8.46 mmol), and diisopropylethylamine (0.74 mL, 4.23 mmol) in dichloromethane (7 mL) at 0 °C was added sulfur trioxide-pyridine complex (0.404 mg, 2.54 mmol) in one portion. After 10 min the reaction was quenched with aqueous citric acid (0.5 M, 5 mL) and washed with brine (5 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. The resultant crude oil was used without further purification for the next step. An analytic sample of the title compound was purified by flash chromatography using petroleum ether/ethyl acetate (4:1) as eluent.

**IR spectrum** (film), cm⁻¹: 2962, 1714, 1316, 1271, 1112, 709; **¹H NMR** (400 MHz, CDCl₃) δ: 9.88 (t, J = 2.9 Hz, 1H, H-5), 8.04–8.00 (m, 2H, Ar-H), 7.59–7.53 (m, 1H, Ar-H), 7.47–7.41 (m, 2H, Ar-H), 4.42 (t, J = 7.0 Hz, 2H, H-1), 2.39 (d, J = 2.9 Hz, 2H, H-4), 1.88 (t, J = 7.0 Hz, 2H, H-2), 1.17 (s, 6H, 2 × 3-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 202.8 (C-5), 166.7 (1-OOC₆H₅), 133.1, (Ar-CH), 130.3 (Ar-C), 129.7 (2 × C, Ar-CH), 128.5 (2 × Ar-CH), 61.9 (C-1), 55.1 (C-4), 40.5 (C-2), 32.9 (C-3), 27.9 (2 × 3-CH₃); **HRMS** [ESI, (M+H)⁺]: m/z: calculated for (C₁₄H₁₈NaO₃) 257.1148, found: 257.1146.
3,3-Dimeth-2-methylene-5-oxopentyl benzoate 370

To a solution of crude aldehyde 381 (~0.846 mmol), pyrrolidine (7 μL, 0.085 mmol), and propionic acid (7 μL, 0.093 mmol) in isopropanol (1 mL) was added aqueous formaldehyde (37% w/w, 69 μL, 0.930 mmol). After 14 h the reaction was diluted with diethyl ether (10 mL), quenched with aqueous citric acid (0.5 M, 6 mL) and washed with saturated sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo to afford the title compound 370 (187 mg, 90% over 2 steps) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 2935, 1717, 1696, 1452, 1273, 1114, 954, 712; **¹H NMR** (400 MHz, CDCl₃) δ: 9.53 (s, 1H, H-1), 8.00–7.96 (m, 2H, Ar-H), 7.57–7.51 (m, 1H, Ar-H), 7.45–7.39 (m, 2H, Ar-H), 6.35 (s, 1H, 1 × 4-C₆H₂), 5.99 (s, 1H, 1 × 4-C₆H₂), 4.20 (t, J = 6.9 Hz, 2H, H-2), 2.20 (t, J = 6.9 Hz, 2H, H-2), 1.27 (s, 6H, 2 × 3-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 194.9 (C-5), 166.7 (1-OCOC₆H₅), 155.9 (C-4), 135.7 (4-C₆H₂), 133.0, (Ar-CH), 130.4 (Ar-C), 129.6 (2 × Ar-CH), 128.5 (2 × Ar-CH), 62.4 (C-1), 37.8 (C-2), 36.2 (C-3), 27.4 (2 × 3-CH₃); **HRMS** [ESI, (M+Na)⁺]: m/z: calculated for (C₁₅H₁₈NaO₃) 269.1148, found: 269.1151.
(10S,11S)-10-(tert-Butyldimethylsilyloxy)-5-hydroxy-3,3,11-trimethyl-4-methylene-7-oxotridec-12-en-1-yl benzoate 371

To a solution of chlorodicyclohexylborane (1 M in hexane, 0.22 mL, 0.220 mmol) in diethyl ether (1.5 mL) at 0 °C was added triethylamine (35 μL, 0.252 mmol) dropwise. After 5 min a solution of ketone 212 (40 mg, 0.148 mmol) in diethyl ether (1 mL) was added dropwise and the mixture stirred for 15 min. After cooling to −78 °C, a solution of aldehyde 370 (62 mg, 0.252 mmol) in diethyl ether (0.5 mL) was added dropwise and the slurry was allowed to warm slowly to room temperature over 15 h. The reaction was quenched with aqueous hydrogen peroxide (30% w/w, 0.3 mL) and diluted with ethyl acetate (3 mL) and saturated sodium bicarbonate (3 mL). After vigorous stirring for 2 h the biphasic mixture was extracted with ethyl acetate (2 × 5 mL) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/diethyl ether (19:1 → 4:1) as eluent afforded the title product 371 (36 mg, 47%, 1:1 mixture of diastereomers) as a colourless oil, alongside recovered ketone 212 (17 mg, 42%).

IR spectrum (film), cm⁻¹: 3497, 2928, 2859, 1719, 1412, 1301, 1274, 1112, 712

¹H NMR (400 MHz, CDCl₃) δ: 8.03–7.99 (m, 2H, Ar-H), 7.57–7.51 (m, 1H, Ar-H), 7.45–7.39 (m, 2H, Ar-H), 5.87–5.77 (m, 1H, H-12), 5.33 (s, 1H, 1 × 4-CH₂), 5.13 (s, 1H, 1 × 4-CH₂), 5.03–4.98 (m, 2H, H-13), 4.74–4.69 (m, 1H, H-5), 4.43–4.20 (m, 2H, H-1), 3.65–3.50 (m, 1H, H-10), 3.11 (bs, 1H, 5-OH), 2.80–2.71 (m, 1H, 1 × H-6), 2.63–2.43 (m, 3H, H-8, 1 × H-6), 2.33–2.23 (m, 1H, H-11), 2.05–1.53 (m, 4H, H-2, H-9), 1.19 (s, 3H, 1 × 3-CH₃), 1.12 (s, 3H, 1 × 3-CH₃), 0.98 (d, J = 6.9 Hz, 3H, 11-CH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃*), 0.05 (s, 6H, Si(CH₃)₂C(CH₃)₃), 0.04 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*), 0.03 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*);

¹³C NMR (100 MHz, CDCl₃) δ: 211.6 (C-7), 166.9 (OCOC₂H₅), 157.1 (C-4), 140.7 (C-12), 140.6 (C-12*), 133.0 (Ar-CH), 130.5 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 114.6 (C-13), 114.5 (C-13*), 111.7 (4-CH₂), 75.0 (C-5), 74.9 (C-5*), 65.5 (C-10), 65.5 (C-10*), 62.7 (C-1), 50.8 (C-6), 43.0 (C-11), 39.3 (C-8), 39.2 (C-8*), 38.9 (C-2), 38.0 (C-2*), 35.7 (C-3), 27.8 (1 × 3-CH₃, 1 × 3-CH₃*), 27.2 (C-9), 27.1 (C-9*), 26.9 (1 × 3-CH₃), 26.9 (1 × 3-CH₃*), 26.0 (3 × Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 15.7 (11-CH₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃);

HRMS [ESI, (M+Na)⁺]: m/z: calculated for (C₃₀H₄₈NaO₅Si) 539.3163, found: 539.3175.
To a solution of ketone 212 (40 mg, 0.148 mmol) and diisopropylethylamine (77 μL, 0.444 mmol) in dichloromethane (1 mL) at −10 °C was added tert-butyldimethylsilyl trifluoromethanesulfonate (44 μL, 0.192 mmol). The mixture was stirred for 2 h then quenched with saturated sodium bicarbonate (2 mL) and extracted with diethyl ether (2 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure then dissolved in petroleum ether (10 mL), filtered through a plug of Celite and concentrated in vacuo to give crude silyl enol ether 339.

To a solution of aldehyde 370 (51 mg, 0.207 mmol) in dichloromethane (1 mL) at −78 °C was added boron trifluoride etherate (24 μL, 0.192 mmol) dropwise and the mixture stirred vigorously for 30 min. A solution of the aforementioned silyl enol ether 339 in dichloromethane (1 mL) was added and the mixture allowed to warm to room temperature over 13 h then quenched with saturated sodium bicarbonate (2 mL) and extracted with dichloromethane (2 × 3 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/diethyl ether (19:1 → 4:1) as eluent afforded the title product 382 (23.7 mg, 31%, 1:1 mixture of diastereomers) as a colourless oil.

IR spectrum (film), cm⁻¹: 2959, 2889, 1716, 1111, 1070, 834, 774, 710; ¹H NMR (400 MHz, CDCl₃) δ: 9.75 (d, J = 4.4 Hz, 1H), 8.03–7.99 (m, 2H, Ar-H), 7.58–7.52 (m, 1H, Ar-H), 7.46–7.40 (m, 2H, Ar-H), 5.86–5.75 (m, 1H, H-12), 5.03–4.97 (m, 2H, H-13), 4.41 (t, J = 7.2 Hz, 2H, H-1), 3.53 (dt, J = 5.5, 5.5 Hz, 1H, H-10), 2.49–2.21 (m, 5H, H-4, H-6, H-8), 2.16–2.07 (m, 1H, H-11), 1.97–1.53 (m, 6H, H-2, H-5, H-9), 1.12 (s, 3H, 1 × 3-CH₃), 1.11 (s, 3H, 1 × 3-CH₃), 0.97 (d, J = 6.9 Hz, 3H, 11-CH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.04 (s, 6H, Si(CH₃)₂C(CH₃)₃), 0.03 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*, 0.03 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*); ¹³C NMR (100 MHz, CDCl₃) δ: 210.1 (C-7), 205.6 (4-CO), 166.7 (OCOC₆H₅), 140.7 (C-12), 133.1 (Ar-CH), 130.3 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 114.5 (C-13), 75.0 (C-10), 61.5 (C-1), 60.2 (C-4), 60.2 (C-4*), 43.0 (C-11), 40.6
(C-6), 38.9 (C-8), 38.5 (C-2), 35.5 (C-3), 27.4 (C-5), 26.0 (3 × Si(CH₃)₂C(CH₃)₃), 25.7 (1 × 3-CH₃), 25.3 (1 × 3-CH₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 18.1 (C-9), 15.7 (11-CH₃), −4.2 (2 × Si(CH₃)₂C(CH₃)₃); **HRMS** [ESI, (M+Na)⁺]: m/z: calculated for (C₃₀H₄₈NaO₅Si) 539.3163, found: 539.3179.
To a solution of chlorodicyclohexylborane (1 M in hexane, 0.25 mL, 0.248 mmol) in diethyl ether (1 mL) at 0 °C was added triethylamine (38 μL 0.273 mmol) dropwise. After 5 min a solution of ketone 358 (35 mg, 0.124 mmol) in diethyl ether (1 mL) was added dropwise and the mixture stirred for 30 min. After cooling to −78 °C, a solution of aldehyde 370 (76 mg, 0.310 mmol) in diethyl ether (0.5 mL) was added dropwise and the slurry was allowed to warm slowly to room temperature over 13 h. The reaction was quenched with aqueous hydrogen peroxide (30% w/w, 1 mL) and diluted with ethyl acetate (4 mL) and saturated sodium bicarbonate (4 mL). After vigorous stirring for 1 h the biphasic mixture was extracted with ethyl acetate (2 × 8 mL) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/diethyl ether (19:1 → 4:1) as eluent afforded the title product 383 (27 mg, 41%, 1:1 mixture of diastereomers) as a colourless oil, alongside recovered ketone 358 (18 mg, 53%).

**IR spectrum** (film), cm⁻¹: 3498, 2957, 2857, 1714, 1315, 1247, 1112, 1027, 836, 775, 712; **¹H NMR** (400 MHz, CDCl₃) δ: 8.03–7.98 (m, 2H, Ar-H), 7.55 (dd, J = 7.4, 7.4 Hz, 1H, Ar-H), 7.42 (t, J = 7.7 Hz, 2H, Ar-H), 5.33 (s, 1H, 1 × 4-CH₂), 5.14 (s, 1H, 1 × 4-CH₂), 4.74 (bs, 1H, H-5), 4.72 (bs, 1H, H-5*), 4.36–4.19 (m, 2H, H-1), 3.73–3.67 (m, 1H, H-10), 3.07 (d, J = 3.4, 3.4 Hz, 1H, H-14), 3.07 (d, J = 3.3 Hz, 1H, 5-OH), 2.78 (dd, J = 17.1, 9.9 Hz, 1H, 1 × H-6), 2.62–2.39 (m, 3H, H-8, 1 × H-6), 2.29 (ddd, J = 16.8, 5.8, 2.4 Hz, 1H, 1 × H-12), 2.07–1.65 (m, 6H, H-2, H-9, H-11, 1 × H-12), 1.19 (s, 3H, 1 × 3-CH₃), 1.13 (s, 3H, 1 × 3-CH₃), 0.96 (d, J = 6.9 Hz, 3H, 11-CH₃), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃*), 0.06 (s, 6H, Si(CH₃)₂C(CH₃)₃), 0.06 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*), 0.05 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*); **¹³C NMR** (100 MHz, CDCl₃) δ: 211.0 (C-7), 166.9 (OCOC₆H₅), 157.1 (C-4), 133.1 (Ar-CH), 130.4 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 111.7 (4-CH₂), 83.9 (C-13), 73.5 (C-5), 73.4 (C-5*), 69.2 (C-14), 69.2 (C-14*), 65.5 (C-10), 62.7 (C-1), 50.9 (C-6), 40.0 (C-8), 39.8 (C-8*), 38.9 (C-2), 38.0 (C-11*), 37.8 (C-11), 35.7 (C-3), 27.8 (2 × 3-CH₃), 27.0 (C-9), 27.0 (C-9*), 26.9 (1 × 3-CH₃*), 26.9 (1 × 3-CH₃*), 26.0 (3 × Si(CH₃)₂C(CH₃)₃), 21.9
(C-12), 18.2 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 14.3 (11-CH$_3$), 14.3 (11-CH$_3$*), −4.1 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), −4.2 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$), −4.4 (2 × Si(CH$_3$)$_2$C(CH$_3$)$_3$*); HRMS [ESI, (M+Na)$^+$]: m/z: calculated for (C$_{31}$H$_{48}$NaO$_5$Si) 574.3066, found: 551.3154.
To a mixture of chromium(II) chloride (13 mg, 0.10 mmol) and nickel(II) chloride (0.4 mg, 0.0034 mmol) under argon was added a solution of alkynyl bromide 232 (19 mg, 0.047 mmol) and aldehyde 381 (8.0 mg, 0.034 mmol) in N-methylpyrrolidone (0.3 mL), washing with further N-methylpyrrolidone (0.1 mL). The mixture was heated to 40 °C for 15 h, diluted with diethyl ether (5 mL), quenched with aqueous ammonium chloride (2 M, 5 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (5:1) as eluent afforded the title product 404 (13 mg, 69%, 1:1 mixture of diastereomers) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 3480, 3480, 2959, 1717, 1316, 1273, 1114, 1027, 711; **¹H NMR** (400 MHz, CDCl₃) δ: 8.06–8.01 (m, 2H, Ar-H), 7.57–7.52 (m, 1H, Ar-H), 7.46–7.40 (m, 2H, Ar-H), 4.53–4.47 (m, 1H, H-5), 4.46–4.36 (m, 2H, H-1), 3.97–3.88 (m, 4H, OCH₂CH₂O), 3.66–3.61 (m, 1H, H-10), 2.26 (ddd, J = 16.8, 6.3, 2.0 Hz, 1H, 1 × H-8), 2.06 (ddd, J = 16.7, 7.9 Hz, 2.0 Hz, 1H, 1 × H-8), 1.88–1.49 (m, 9H, H-2, H-4, H-9, H-11, H-12), 1.31 (s, 3H, H-14), 1.07 (s, 6H, 2 × 3-CH₃), 0.92 (d, J = 6.8 Hz, 3H, 9-CH₃), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.05 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃), 0.04 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 168.8 (1-OCOC₆H₅), 133.0 (Ar-CH), 130.6 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 110.2 (C-13), 85.1 (C-6), 83.4 (C-7), 74.5 (C-10), 64.8 (OCH₂CH₂O), 62.4 (C-1), 60.1 (C-5), 50.3 (C-4), 50.2 (C-4*), 40.4 (C-2), 37.6 (C-9), 35.2 (C-12), 32.3 (C-3), 28.2 (C-11), 28.1 (1 × 3-CH₃), 28.0 (1 × 3-CH₃), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 24.0 (C-14), 22.6 (C-8), 18.3 (Si(CH₃)₂C(CH₃)₃), 14.4 (9-CH₃), 14.4 (9-CH₃*), −4.0 (1 × Si(CH₃)₂C(CH₃)₃), −4.4 (1 × Si(CH₃)₂C(CH₃)₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₃₂H₅₂NaO₆Si) 583.3425, found: 583.3414.
(9S,10S,E)-10-(tert-Butyldimethylsilyl)oxy-13,13-ethylenedioxy-5-hydroxy-3,3,9-trimethyl-tetradec-6-en-1-yl benzoate

To a mixture of chromium(II) chloride (16 mg, 0.128 mmol) and nickel(II) chloride (0.6 mg, 0.0043 mmol) under argon was added a solution of vinyl bromide (28 mg, 0.068 mmol) and aldehyde (10 mg, 0.043 mmol) in N-methylpyrrolidone (0.2 mL), washing with further N-methylpyrrolidone (0.1 mL). The mixture was heated to 40 °C for 15 h, diluted with diethyl ether (5 mL), quenched with aqueous citric acid (2 M, 5 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (5:1) as eluent afforded the title product (20 mg, 84%, 1:1 mixture of diastereomers) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 3489, 2956, 1719, 1274, 1069, 835, 773, 712; **¹H NMR** (400 MHz, CDCl₃) δ: 8.05–8.01 (m, 2H, Ar-H), 7.57–7.52 (m, 1H, Ar-H), 7.45–7.40 (m, 2H, Ar-H), 5.64–5.55 (m, 1H, H-6), 5.54–5.36 (m, 1H, H-7), 4.45–4.35 (m, 2H, H-1), 4.28–4.25 (m, 1H, H-5), 3.97–3.87 (m, 4H, OCH₂CH₂O), 3.55–3.49 (m, 1H, H-10), 2.21 (ddd, J = 13.7, 5.5, 5.3 Hz, 1H, 1 × H-8), 1.89–1.74 (m, 3H, H-2, 1 × H-8), 1.74–1.66 (m, 1H, 1 × H-12), 1.74–1.66 (m, 6H, H-4, H-9, H-11 1 × H-12), 1.45–1.37 (m, 1H, 5-OH), 1.31 (s, 3H, H-14), 1.06 (s, 3H, 1 × 3-CH₃), 1.05 (s, 3H, 1 × 3-CH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.82 (d, J = 6.8 Hz, 3H, 9-CH₃), 0.81 (d, J = 6.8 Hz, 9-CH₃*), 0.04 (s, 6H, 2 × Si(CH₃)₂C(CH₃)₃), 0.03 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*), 0.02 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*);

**¹³C NMR** (100 MHz, CDCl₃) δ: 166.9 (1-OOCR₃H₃), 135.9 (C-6), 135.9 (C-6*), 132.9 (Ar-CH), 130.6 (Ar-C), 130.6 (C-7), 130.3 (C-7*), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 110.3 (C-13), 110.3 (C-13*), 75.8 (C-10), 70.7 (C-5), 70.6 (C-5*), 64.7 (OCH₂CH₂O), 62.6 (C-1), 49.2 (C-4), 49.2 (C-4*), 40.6 (C-2), 38.4 (C-9), 38.3 (C-9*), 35.5 (C-8), 35.4 (C-12), 35.2 (C-8*), 32.3 (C-3), 28.3 (1 × 3-CH₃), 28.3 (1 × 3-CH₃*), 28.2 (1 × 3-CH₃), 27.8 (C-11), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 24.0 (C-14), 18.3 (Si(CH₃)₂C(CH₃)₃), 14.8 (9-CH₃), 14.6 (9-CH₃*), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃); **HRMS [ESI, (M+Na)⁺] m/z**: calculated for (C₃₂H₅₄NaO₆Si) 585.3582, found: 585.3569.
(9S,10S,Z)-10-(tert-Butyldimethylsilyl)oxy-13,13-ethylenebisoxy-5-hydroxy-3,3,9-trimethyl-tetradec-6-en-1-yl benzoate

To a mixture of chromium(II) chloride (16 mg, 0.128 mmol) and nickel(II) chloride (0.6 mg, 0.0043 mmol) under argon was added a solution of vinyl bromide 230 (28 mg, 0.068 mmol) and aldehyde 381 (10 mg, 0.043 mmol) in N-methylpyrrolidone (0.2 mL), washing with further N-methylpyrrolidone (0.1 mL). The mixture was heated to 40 °C for 15 h, diluted with diethyl ether (5 mL), quenched with aqueous citric acid (2 M, 5 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (5:1) as eluent afforded the title product 406 (17 mg, 72%, 1:1 mixture of diastereomers) as a colourless oil.

IR spectrum (film), cm⁻¹: 3497, 2958, 2857, 1718, 1316, 1273, 1070, 834, 710; ¹H NMR (400 MHz, CDCl₃) δ: 8.05–8.01 (m, 2H, Ar-H), 7.57–7.51 (m, 1H, Ar-H), 7.45–7.40 (m, 2H, Ar-H), 5.52–5.34 (m, 2H, H-6, H-7), 4.67–4.59 (m, 1H, H-5), 4.46–4.34 (m, 2H, H-1), 3.97–3.87 (m, 4H, OCH₂CH₂O), 3.59–3.52 (m, 1H, H-10), 2.30–1.38 (m, 12H, H-2, H-4, H-8, H-9, H-11, H-12, 5-OH), 1.30 (s, 3H, H-14), 1.07 (s, 3H, 1 × 3-CH₃), 1.05 (s, 3H, 1 × 3-CH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.88 (s, Si(CH₃)₂C(CH₃)₃*), 0.86 (d, J = 7.0 Hz, 3H, 9-CH₃), 0.84 (d, J = 7.0 Hz, 9-CH₃*), 0.04 (s, 6H, 2 × Si(CH₃)₂C(CH₃)₃), 0.04 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*), 0.03 (s, 3H, 1 × Si(CH₃)₂C(CH₃)₃*); ¹³C NMR (100 MHz, CDCl₃) δ: 166.9 (1-OOC₆H₅), 134.9 (C-6), 134.9 (C-6*), 132.9 (Ar-CH), 130.7 (C-7), 130.4 (C-7*), 130.0 (Ar-C), 129.7 (2 × Ar-CH), 128.4 (2 × Ar-CH), 110.2 (C-13), 76.0 (C-10), 75.9 (C-10*), 65.1 (C-5), 65.0 (C-5*), 64.8 (OCH₂CH₂O), 62.6 (C-1), 49.4 (C-4), 49.3 (C-4*), 40.8 (C-2), 38.8 (C-9), 38.2 (C-9*), 35.4 (C-12), 32.4 (C-3), 32.4 (C-3*), 30.7 (C-8), 28.3 (1 × 3-CH₃), 28.1 (1 × 3-CH₃), 28.0 (C-11), 27.8 (C-11*), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 24.0 (C-14), 18.3 (Si(CH₃)₂C(CH₃)₃), 15.0 (9-CH₃), 14.4 (9-CH₃*), −4.0 (1 × Si(CH₃)₂C(CH₃)₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃*), −4.2 (1 × Si(CH₃)₂C(CH₃)₃), −4.3 (1 × Si(CH₃)₂C(CH₃)₃*); HRMS [ESI, (M+Na)+] m/z: calculated for (C₃₂H₅₄NaO₆Si) 585.3582, found: 585.3579.
(5S,6S)-5-(tert-Butyldimethylsilyl)oxy-10-hydroxy-3,3,6-trimethyl-2-oxotetradec-8-yn-14-yl benzoate 390

To a mixture of chromium(II) chloride (16 mg, 0.128 mmol) and nickel(II) chloride (0.6 mg, 0.0043 mmol) under argon was added a solution of alkynyl bromide 237 (25 mg, 0.068 mmol) and aldehyde 381 (10 mg, 0.043 mmol) in N-methylpyrrolidone (0.2 mL), washing with further N-methylpyrrolidone (0.1 mL). The mixture was heated to 40 °C for 15 h, diluted with diethyl ether (5 mL), quenched with aqueous citric acid (2 M, 5 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (5:1) as eluent afforded the title product 390 (16 mg, 72%, 1:1 mixture of diastereomers) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 3490, 2957, 2857, 1717, 1361, 1274, 1113, 1026, 835, 775, 712; 

**¹H NMR** (400 MHz, CDCl₃) δ: 8.06–8.01 (m, 2H, Ar-H), 7.58–7.51 (m, 1H, Ar-H), 7.46–7.40 (m, 2H, Ar-H), 4.53–4.47 (m, 1H, H-10), 4.46–4.35 (m, 2H, H-14), 3.69–3.63 (m, 1H, H-5), 2.52–2.36 (m, 2H, H-3), 2.27 (ddd, J = 16.7, 6.1, 2.0 Hz, 1H, 1 × H-7), 2.14 (s, 3H, H-1), 2.05 (ddd, J = 16.7, 8.0 Hz, 2.0 Hz, 1H, 1 × H-7), 1.91 (s, 1H, 10-OH), 1.87–1.63 (m, 7H, H-4, H-6, H-11, H-13), 1.07 (s, 6H, 2 × 12-CH₃), 0.93 (d, J = 6.8 Hz, 3H, 6-CH₃), 0.88 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.05 (s, 6H, 2 × Si(CH₃)₂C(CH₃)₃); 

**¹³C NMR** (100 MHz, CDCl₃) δ: 209.0 (C-2), 166.9 (OCOC₆H₅), 133.0 (Ar-CH), 130.6 (Ar-C), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 84.8 (C-9), 83.6 (C-8), 72.6 (C-5), 62.5 (C-14), 60.1 (C-10), 50.2 (C-11), 50.2 (C-11*), 40.4 (C-3), 40.0 (C-13), 37.8 (C-6), 32.3 (C-12), 30.1 (C-1), 28.1 (1 × 12-CH₃), 28.0 (1 × 12-CH₃), 27.5 (C-4), 26.0 (3 × Si(CH₃)₂C(CH₃)₃), 22.2 (C-7), 18.3 (Si(CH₃)₂C(CH₃)₃), 14.5 (6-CH₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.3 (1 × Si(CH₃)₂C(CH₃)₃); 

**HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₃₀H₄₈NaO₅Si) 539.3163, found: 539.3166.
To a mixture of chromium(II) chloride (16 mg, 0.128 mmol) and nickel(II) chloride (0.6 mg, 0.0043 mmol) under argon was added a solution of vinyl bromide 238 (25 mg, 0.068 mmol) and aldehyde 381 (10 mg, 0.043 mmol) in N-methylpyrrolidone (0.2 mL), washing with further N-methylpyrrolidone (0.1 mL). The mixture was heated to 40 °C for 15 h, diluted with diethyl ether (5 mL), quenched with aqueous citric acid (2 M, 5 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (5:1) as eluent afforded the title product 391 (19 mg, 85%, 1:1 mixture of diastereomers) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 3492, 2957, 1718, 1276, 1114, 836, 775, 713; **¹H NMR** (400 MHz, CDCl₃) δ: 8.05–8.01 (m, 2H, Ar-H), 7.57–7.52 (m, 1H, Ar-H), 7.45–7.40 (m, 2H, Ar-H), 5.63–5.47 (m, 2H, H-8, H-9), 4.45–4.35 (m, 2H, H-14), 4.27 (brs, 1H, H-10), 3.53 (dt, J = 7.7, 4.0 Hz, 1H, H-5), 2.53–2.36 (m, 2H, H-3), 2.28–2.20 (m, 1H, 1 × H-7), 2.14 (s, 3H, H-1), 1.89–1.36 (m, 9H, H-4, H-6, 1 × H-7, H-11, H-13, 10-OH), 1.06 (s, 3H, 1 × 12-CH₃), 1.05 (s, 3H, 1 × 12-CH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.83 (d, J = 6.7 Hz, 3H, 6-CH₃), 0.82 (d, J = 6.5 Hz, 3H, 6-CH₃*), 0.04 (s, 6H, 2 × Si(CH₃)₂C(CH₃)₃), 0.03 (s, 1 × Si(CH₃)₂C(CH₃)₃*), 0.03 (s, 1 × Si(CH₃)₂C(CH₃)₃*); **¹³C NMR** (100 MHz, CDCl₃) δ: 209.1 (C-2), 209.0 (C-2*), 166.9 (14-OCOC₆H₅), 136.1 (C-9), 136.1 (C-9*), 133.0 (Ar-CH), 130.7 (Ar-C), 130.3 (C-8), 130.0 (C-8*), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 75.0 (C-5), 70.6 (C-10), 70.5 (C-10*), 62.6 (C-14), 49.3 (C-11), 49.2 (C-11*), 40.8 (C-13*), 40.6 (C-13), 40.3 (C-3), 40.2 (C-3*), 38.7 (C-6), 38.6 (C-6*), 34.7 (C-7), 34.6 (C-7*), 32.4 (C-12), 30.1 (C-1), 28.3 (1 × 12-CH₃), 28.3 (1 × 12-CH₃*), 28.2 (1 × 3-CH₃), 26.8 (C-4), 26.8 (C-4*), 26.1 (3 × Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 15.0 (6-CH₃), 14.9 (6-CH₃*), −4.2 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃); **HRMS** [ESI, (M+Na)⁺] m/z: calculated for (C₃₀H₅₀NaO₅Si) 541.3320, found: 541.3319.
(5S,6S,Z)-5-(tert-Butyldimethylsilyl)oxy-10-hydroxy-3,3,6-trimethyl-2-oxotetradec-8-en-14-yl benzoate 392

To a mixture of chromium(II) chloride (16 mg, 0.128 mmol) and nickel(II) chloride (0.6 mg, 0.0043 mmol) under argon was added a solution of vinyl bromide 239 (25 mg, 0.068 mmol) and aldehyde 381 (10 mg, 0.043 mmol) in N-methylpyrrolidone (0.2 mL), washing with further N-methylpyrrolidone (0.1 mL). The mixture was heated to 40 °C for 15 h, diluted with diethyl ether (5 mL), quenched with aqueous citric acid (2 M, 5 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (5:1) as eluent afforded the title product 392 (18 mg, 81%, 1:1 mixture of diastereomers) as a colourless oil.

IR spectrum (film), cm⁻¹: 3493, 2957, 1718, 1276, 1114, 1071, 836, 775, 713; ¹H NMR (400 MHz, CDCl₃) δ: 8.05–8.01 (m, 2H, Ar-H), 7.57–7.52 (m, 1H, Ar-H), 7.45–7.40 (m, 2H, Ar-H), 5.53–5.46 (m, 1H, H-9), 5.42–5.32 (m, 1H, H-8), 4.67–4.59 (m, 1H, H-10), 4.46–4.35 (m, 2H, H-14), 3.60–3.53 (m, 1H, H-5), 2.55–2.37 (m, 2H, H-3), 2.27 (dd, J = 16.7, 6.1, 2.0 Hz, 1H, 1 × H-7), 2.33–1.59 (m, 7H, H-4, H-6, 1 × H-7, 1 × H-11, H-13), 2.13 (s, 3H, H-1), 2.13 (s, 3H, H-1*), 1.45–1.36 (m, 1H, 1 × H-11), 1.07 (s, 3H, 1 × 12-CH₃), 1.05 (s, 3H, 1 × 12-CH₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.89 (s, 9H, Si(CH₃)₂C(CH₃)₃*), 0.87 (d, J = 6.9 Hz, 3H, 6-CH₃), 0.85 (d, J = 6.9 Hz, 3H, 6-CH₃*), 0.04 (s, 6H, 2 × Si(CH₃)₂C(CH₃)₃, 1 × Si(CH₃)₂C(CH₃)₃*), 0.03 (s, 1 × Si(CH₃)₂C(CH₃)₃*); ¹³C NMR (100 MHz, CDCl₃) δ: 209.0 (C-2), 208.9 (C-2*), 166.9 (14-OCOC₆H₄), 135.1 (C-9), 134.8 (C-9*), 132.9 (Ar-CH), 130.7 (Ar-C), 130.2 (C-8), 129.8 (C-8*), 129.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 75.2 (C-5), 75.1 (C-5*), 65.1 (C-10), 65.0 (C-10*), 62.6 (C-14), 49.4 (C-11), 49.3 (C-11*), 40.8 (C-3*), 40.3 (C-13), 40.1 (C-13*), 39.1 (C-3), 38.6 (C-6), 32.4 (C-12), 32.4 (C-12*), 30.2 (C-1), 30.1 (C-7), 28.3 (1 × 12-CH₃), 28.1 (1 × 12-CH₃), 28.1 (1 × 12-CH₃*), 27.0 (C-4), 26.8 (C-4*), 26.0 (3 × Si(CH₃)₂C(CH₃)₃), 18.3 (Si(CH₃)₂C(CH₃)₃), 15.2 (6-CH₃), 14.8 (6-CH₃*), −4.2 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃); HRMS [ESI, (M+Na)+] m/z: calculated for (C₃₀H₅₀NaO₅Si) 541.3320, found: 541.3324.
To a suspension of sodium iodide (1.86 g, 12.4 mmol) in acetonitrile (20 mL) at 0 °C was added trimethylsilyl chloride (1.6 mL, 12.4 mmol) and the solution stirred for 5 min. Water (0.11 mL, 6.18 mmol) was added followed by propargyl alcohol (420) (0.40 mL, 6.87 mmol) after a further 10 min, and the mixture was allowed to slowly warm to room temperature. After 16 h the mixture was quenched with aqueous sodium thiosulfate/sodium bicarbonate (1:1, both 5% w/w, 20 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulfate and concentrated under reduced pressure. The resultant oil was stirred in dichloromethane (25 mL) and cooled to 0 °C. To this solution was added triethylamine (3.8 mL, 27.5 mmol), dimethylaminopyridine (84 mg, 0.687 mmol) and triisopropylsilyl chloride (2.7 mL, 12.4 mmol) and the mixture was allowed to slowly warm to room temperature. After 10 h the reaction was quenched with saturated ammonium chloride (20 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (100:1 + 0.25% triethylamine) as eluent afforded the title product 422 (1.22 g, 52%) as a colourless oil.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta: 6.51–6.50 \text{ (m, 1H, 1 × H-3), 5.83 \text{ (dt, } J = 1.7 \text{ Hz, 1.7 Hz, 1H, } 1 \times \text{ H-3), 4.26 \text{ (t, } J = 2.0 \text{ Hz, 2H, H-1), 1.16–1.10 \text{ (m, 3H, Si(CH(CH}_3)_2)_3\), 1.09–1.06 \text{ (m, 18H, Si(CH(CH}_3)_2)_3\).}\]

The data obtained were in agreement with that reported in the literature. 228
(5S,6S)-9,9-Ethyleneoxy-5-methyl-2-methylene-6-(tert-butyldimethylsilyl)oxy-1-(triisopropylsilyl)oxydecan-3-ol 423

To a solution of chromium(II) chloride (180 mg, 1.47 mmol) and nickel(II) chloride (4.33 mg, 0.033 mmol) in dimethylformamide (0.5 mL) under argon at 0 °C was added a solution of vinyl iodide 422 (317 mg, 0.932 mmol) and aldehyde 204 (220 mg, 0.666 mmol) in dimethylformamide (1 mL), washing with tetrahydrofuran (0.5 mL). The mixture was allowed to warm to room temperature over 18 h, diluted with diethyl ether (10 mL), quenched with saturated ammonium chloride (8 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and concentrated in vacuo. The resultant crude oil was used without further purification for the next step. Purification by flash chromatography using petroleum ether/ethyl acetate (8:1) as eluent afforded the title product 423 (284 mg, 78%, 1.2:1 diastereomeric mixture) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 3485, 2945, 2866, 1463, 1252, 1064, 835, 774; **¹H NMR** (400 MHz, CDCl₃) δ: 5.13–5.06 (m, 2H, 2-CH₂), 4.44–4.37 (m, 1H, H-6), 4.31–4.21 (m, 2H, H-1), 3.97–3.88 (m, 4H, OCH₂CH₂O), 3.60–3.54 (m, 1H, H-3), 1.90–1.38 (m, 7H, H-4, H-5, H-7, H-8), 1.31 (s, 3H, H-10), 1.31 (s, H-10*), 1.18–0.90 (m, 21H, Si(CH₃)₂C(CH₃)₃), 0.92–0.87 (m, 12H, Si(CH₃)₂C(CH₃)₃, 5-CH₃), 0.07–0.01 (m, 6H, Si(CH₃)₂C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 151.0 (C-2*), 149.4 (C-2), 111.5 (2-CH₂*), 110.2 (2-CH₂), 110.1 (C-9), 77.0 (C-6*), 75.7 (C-6), 73.3 (C-3), 72.0 (C-3*), 65.0 (C-1), 64.7 (OCH₂CH₂O), 39.8 (C-4), 38.6 (C-4), 35.8 (C-8), 35.4 (C-5*), 34.9 (C-5), 27.9 (C-7), 27.6 (C-7*), 27.2, 26.1 (Si(CH₃)₂C(CH₃)₃), 26.0 (Si(CH₃)₂C(CH₃)₃*), 23.9 (C-10), 18.3 (Si(CH(CH₃)₂)₃*), 18.1 (Si(CH(CH₃)₂)₃), 15.4 (5-CH₃), 15.0 (5-CH₃*), 12.0 (Si(CH(CH₃)₂)₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃); **HRMS** [ESI, (M+Na)+]: m/z: calculated for (C₂₉H₆₀NaO₅Si₂) 567.3871, found: 567.3850.
To a solution of acetal 423 (20 mg, 0.037 mmol) in acetone/dichloromethane (1:1, 0.5 mL) was added Amberlyst® 15 (5 mg). After 1 h the reaction was diluted with petroleum ether/ethyl acetate (15:1), filtered through Celite and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (19:1→4:1) as eluent afforded the title products ketone 434 (9.0 mg, 53%, 3.5:1 mixture of diastereomers) acetal 435 (6.0 mg, 44%) and as a colourless oil.

(5S,6S)-5-(tert-Butyldimethylsilyl)oxy-8-hydroxy-6-methyl-9-methylene-10-(triisopropylsilyl)oxydecan-2-one 434

**IR spectrum** (film), cm⁻¹: 3469, 2929, 2865, 1717, 1463, 1252, 1052, 835, 774; **¹H NMR** (400 MHz, CDCl₃) δ: 5.13–5.04 (m, 2H, 9-CH₂), 4.45–4.21 (m, 3H, H-8, H-10), 3.57 (ddd, J = 7.7, 4.9, 3.1 Hz, 1H, H-5), 2.96 (s, 8-OH*), 2.75 (s, 8-OH), 2.57–2.34 (m, 2H, H-3), 2.13 (s, 3H, H-1), 1.84–1.61 (m, 4H, H-4, H-6, 1 × H-7), 1.51–1.34 (m, 1H, 1 × H-7), 1.18–1.04 (m, 21H, Si(CH₃)₂C(CH₃)₃), 0.93–0.87 (m, 12H, Si(CH₃)₂C(CH₃)₃, 5-CH₃), 0.07 (s, 1 × Si(CH₃)₂C(CH₃)₃*), 0.06 (s, 1 × Si(CH₃)₂C(CH₃)₃*), 0.04 (s, 1 × Si(CH₃)₂C(CH₃)₃), 0.02 (s, 1 × Si(CH₃)₂C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 149.4 (C-9), 111.6 (9-CH₂), 74.9 (C-5), 73.4 (C-8), 65.1 (C-10), 40.4 (C-3), 38.1 (C-7), 35.2 (C-6), 30.1 (C-1), 27.1 (C-4), 26.1 (Si(CH₃)₂C(CH₃)₃), 18.4 (Si(CH(CH₃)₂)₃), 15.8 (6-CH₃), 12.0 (Si(CH(CH₃)₂)₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃). Quaternary C-2 carbon not observed; **HRMS** [ESI, (M+Na)⁺]: m/z: calculated for (C₂₇H₅₆NaO₄Si₂) 523.3609, found: 523.3594.
(1S,3S,5S,6S)-1,5-Dimethyl-3-(1-(triisopropylsilyl)oxyprop-2-en-2-yl)-2,9-dioxabicyclo[4.2.1]nonane 435

$[\alpha]_D^{20}$: $-12.0$ (c 0.20, CHCl$_3$); **IR spectrum** (film), cm$^{-1}$: 2942, 2866, 1463, 1378, 1055, 1013; **$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$: 5.19–5.18 (m, 1H, 1 × H-3'), 5.08–5.07 (m, 1H, 1 × H-3'), 4.39 (d, $J = 10.3$ Hz, 1H, H-3), 4.31 (ddd, $J = 7.4$, 4.6, 4.6 Hz, 1H, H-6), 4.30–4.20 (m, 2H, H-1'), 2.14–2.05 (m, 1H, H-5), 2.00 (ddd, $J = 11.4$, 6.2, 3.0 Hz, 1H, 1 × H-8), 1.86–1.67 (m, 4H, 1 × H-4, H-7, 1 × H-8), 1.48–1.40 (m, 4H, 1 × H-4, 1-CH$_3$), 1.17–1.04 (m, 21H, Si(CH$_3$)$_2$)$_3$), 0.82 (d, $J = 7.0$ Hz, 3H, 5-CH$_3$); **$^{13}$C NMR** (100 MHz, CDCl$_3$) $\delta$: 150.3 (C-2'), 108.6 (C-3'), 106.5 (C-1), 84.1 (C-6), 69.5 (C-3), 64.4 (C-1'), 39.7 (C-8), 38.7 (C-4), 35.7 (C-5), 23.1 (1-CH$_3$), 22.5 (C-7), 18.2 (6 × Si(CH$_3$)$_2$)$_3$, 16.3 (5-CH$_3$), 12.2 (3 × Si(CH$_3$)$_2$)$_3$; **HRMS** [ESI, (M+Na)$^+$]: $m/z$: calculated for (C$_{21}$H$_{40}$NaO$_3$Si) 391.2639, found: 391.2625.
(5S,6S)-9,9-Ethylenbisoxaoxy-5-methyl-2-methylene-6-(tert-butyltrimethylsilyl)oxy-1-(triisopropylsilyl)oxydecane-3-yl acetate 445

To a solution of crude allyl alcohol 423 (~0.398 mmol) in dichloromethane (4 mL) at 0 °C was added triethylamine (0.17 mL, 1.19 mmol), dimethylaminopyridine (9.7 mg, 0.080 mmol) and acetic anhydride (75 μL, 0.796 mmol) and the mixture was allowed to slowly warm to room temperature. After 1 h the reaction was quenched with aqueous citric acid (0.5 M, 5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (15:1) as eluent afforded the title product 445 (109 mg, 47% over 2 steps, 1.2:1 diastereomeric mixture) as a colourless oil.

IR spectrum (film), cm⁻¹: 2944, 2866, 1740, 1463, 1371, 1234, 1042, 833, 773; ¹H NMR (400 MHz, CDCl₃) δ: 5.33–5.20 (m, 2H, H-3, 1 × 2-C₆H₄), 5.13–5.07 (m, 1H, 1 × 2-C₆H₄), 4.29–4.19 (m, 2H, H-1), 3.95–3.86 (m, 4H, OCH₂CH₂O), 3.52–3.48 (m, 1H, H-6), 2.01 (s, 3-OCOCH₃*), 2.00 (s, 3H, 3-OCOCH₃), 1.94–1.32 (m, 7H, H-4, H-5, H-7, H-8), 1.29 (s, H-10*), 1.28 (s, 3H, H-10), 1.15–1.01 (m, 21H, Si(CH₃)₂C(CH₃)₃, 5-CH₃), 0.04–0.01 (m, 6H, Si(CH₃)₂C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ: 170.4 (3-OCOCH₃*), 170.2 (3-OCOCH₃), 148.3 (C-2*), 147.0 (C-2), 111.3 (C-9), 110.3 (2-CH₂*), 110.2 (C-9*), 110.1 (2-CH₂), 76.2 (C-6*), 75.4 (C-6), 74.3 (C-3), 72.6 (C-3*), 64.7 (OCH₂CH₂O), 63.5 (C-1*), 62.8 (C-1), 36.5 (C-8), 36.0 (C-4), 35.8 (C-4*), 35.6 (C-8), 35.0 (C-5*), 34.7 (C-5), 27.8 (C-7), 27.3 (C-7*), 26.1 (Si(CH₃)₂C(CH₃)₃), 26.0 (Si(CH₃)₂C(CH₃)₃*), 23.9 (C-10), 21.3 (3-OCOCH₃), 21.2 (3-OCOCH₃*), 18.2 (Si(CH(CH₃)₂)₃*), 18.1 (Si(CH(CH₃)₂)₃), 17.8 (Si(CH(CH₃)₂)₃*), 14.8 (5-CH₃), 14.3 (5-CH₃*), 12.1 (Si(CH(CH₃)₂)₃), 12.1 (Si(CH(CH₃)₂)₃*), −4.1 (1 × Si(CH₃)₂C(CH₃)₃*), −4.2 (1 × Si(CH₃)₂C(CH₃)₃), −4.2 (1 × Si(CH₃)₂C(CH₃)₃*), −4.3 (1 × Si(CH₃)₂C(CH₃)₃) HRMS [ESI, (M+Na)⁺]: m/z: calculated for (C₃₁H₆₂NaO₆Si₂) 609.3977, found: 609.3958.
(5S,6S)-3-Allyloxy-9,9-ethylenebisoxy-5-methyl-6-(tert-butyldimethylsilyl)oxy-2-((triisopropylsilyloxy)methyl)decan-1-ene

To a solution of allyl alcohol (152 mg, 0.279 mmol) in dimethylformamide (1 mL) at 0 °C was added sodium hydride (17 mg, 0.419 mmol, 60% in mineral oil) and the mixture was allowed to slowly warm to room temperature. After 30 min tetrabutylammonium iodide (10 mg, 0.028 mmol) and allylbromide (72 μL, 0.83 mmol) were added sequentially and the mixture warmed to 50 °C for 18 h. The reaction was then cooled to room temperature and quenched with saturated aqueous ammonium chloride (3 mL) and extracted with diethyl ether (3 × 4 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (19:1) as eluent afforded the title product (139 mg, 85%, 1.2:1 diastereomeric mixture) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 2930, 2866, 1463, 1377, 1251, 1067, 834, 773; **¹H NMR** (400 MHz, CDCl₃) δ: 5.93–5.81 (m, 1H, OCH₂C₃H₂), 5.37–5.02 (m, 4H, OCH₂CH₂, 2C₃H₂), 4.27–4.19 (m, 2H, H-1), 4.01–3.84 (m, 6H, H-3, 1 × OCH₂CH₂CH₂, OCH₂CH₂O), 3.78–3.71 (m, 1H, 1 × OCH₂CH₂CH₂), 3.54–3.49 (m, 1H, H-6), 1.85–1.41 (m, 7H, H-4, H-5, H-7, H-8), 1.30 (s, H-10*), 1.30 (s, 3H, H-10), 1.28–1.17 (m, 1 × H-4*), 1.17–1.04 (m, 21H, Si(CH₃)₂C(CH₃)₃), 0.89–0.82 (m, 12H, Si(CH₃)₂C(CH₃)₃), 0.04–0.02 (m, 6H, Si(CH₃)₂C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ: 148.9 (C-2*), 147.9 (C-2), 135.4 (OCH₂CH₂CH₂*), 135.2 (OCH₂CH₂CH₂), 116.9 (OCH₂CH₂CH₂), 116.5 (OCH₂CH₂CH₂*), 111.5 (2CH₂), 110.5 (2CH₂*), 110.3 (C-9*), 110.2 (C-9), 80.7 (C-3), 78.8 (C-3*), 76.3 (C-6*), 75.6 (C-6), 69.3 (OCH₂CH₂CH₂*), 69.2 (OCH₂CH₂CH₂), 64.8 (OCH₂CH₂O), 62.4 (C-1*), 61.8 (C-1), 38.5 (C-4*), 37.2 (C-4), 35.6 (C-8), 35.5 (C-8*), 35.2 (C-5), 33.9 (C-5*), 28.4 (C-7*), 28.1 (C-7), 26.1 (Si(CH₃)₂C(CH₃)₃), 24.0 (C-10), 23.9 (C-10*), 18.3 (Si(CH(CH₃)₂)₃), 18.3 (Si(CH(CH₃)₂)₃), 18.2 (Si(CH(CH₃)₂)₃), 15.0 (5CH₃), 13.6 (5CH₃*), 12.2 (Si(CH(CH₃)₂)₃), 12.2 (Si(CH(CH₃)₂)₃*), −4.0 (Si(CH₃)₂C(CH₃)₃), −4.1 (1 × Si(CH₃)₂C(CH₃)₃*), −4.2 (1 × Si(CH₃)₂C(CH₃)₃*), −4.3 (1 × Si(CH₃)₂C(CH₃)₃); **HRMS** [ESI, (M+Na)⁺]: m/z: calculated for (C₃₁H₆₂NaO₆Si₂) 609.3977, found: 609.3958.
To a solution of acetal 454 (20 mg, 0.034 mmol) in acetone/dichloromethane (1:1, 0.6 mL) was added Amberlyst® 15 (5 mg). After 2 h the reaction was diluted with hexanes/ethyl acetate (9:1), filtered through Celite® and concentrated in vacuo to afford the title product 456 (17 mg, 92%, 2:1 mixture of diastereomers) as a colourless oil.

**IR spectrum** (film), cm$^{-1}$: 2929, 2865, 1720, 1463, 1252, 1067, 834, 773; **$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$: 5.93–5.81 (m, 1H, OCH$_2$C$_2$H$_2$), 5.37–5.02 (m, 4H, OCH$_2$CHCH$_2$, 9-CH$_2$), 4.27–4.19 (m, 2H, H-10), 4.01–3.70 (m, 3H, H-8, OCH$_2$CHCH$_2$), 3.57–3.50 (m, 1H, H-5), 2.53–2.34 (m, 2H, H-3), 2.13 (s, H-1*), 2.12 (s, 3H, H-1), 1.84–1.59 (m, 5H, H-4, H-6, H-7), 1.46–1.38 (m, H-7*, H-6*), 1.17–1.04 (m, 21H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 6-CH$_3$), 0.05–0.02 (m, 21H, Si(CH$_3$)$_2$C(CH$_3$)$_3$); **$^{13}$C NMR** (100 MHz, CDCl$_3$) $\delta$: 208.8 (C-2), 147.9 (C-9), 135.2 (OCH$_2$CHCH$_2$), 116.9 (OCH$_2$CHCH$_2$), 116.5 (OCH$_2$CHCH$_2$*), 111.5 (2-CH$_2$), 110.6 (2-CH$_2$*), 80.7 (C-3), 78.9 (C-3*), 75.3 (C-6*), 74.6 (C-6), 69.3 (OCH$_2$CHCH$_2$*), 69.2 (OCH$_2$CHCH$_2$), 62.5 (C-1*), 61.9 (C-1), 40.3 (C-3), 36.7 (C-7), 35.4 (C-6), 34.0 (C-6*), 30.0 (C-1), 27.4 (C-4*), 27.2 (C-4), 26.1 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 24.0 (C-10), 18.2 (Si(CH(CH$_3$)$_2$)$_3$), 18.3 (Si(CH(CH$_3$)$_2$)$_3$), 17.9 (Si(CH(CH$_3$)$_2$)$_3$), 15.7 (6-CH$_3$), 12.4 (Si(CH(CH$_3$)$_2$)$_3$), 12.2 (Si(CH(CH$_3$)$_2$)$_3$), -4.0 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), -4.1 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$*), -4.2 (1 × Si(CH$_3$)$_2$C(CH$_3$)$_3$*); **HRMS** [ESI, (M+Na)$^+$]: $m/z$: calculated for (C$_{31}$H$_{62}$NaO$_6$Si$_2$) 609.3977, found: 609.3958.
To a solution of acetal 454 (37 mg, 0.063 mmol) in acetone (2 mL) was added aqueous hydrochloric acid (2 M, 0.5 mL). After 15 h the reaction was quenched with saturated aqueous sodium bicarbonate (3 mL) and extracted with ethyl acetate (3 × 5 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent afforded a 3:1 equilibrium mixture of title compounds 457 and 458 (14 mg, 84%) as a colourless oil.

**IR spectrum** (film), cm⁻¹: 3446, 2982, 1714, 1648, 1378, 1206, 1120, 1070, 914. **¹H NMR** (400 MHz, CDCl₃) δ: 5.92–5.81 (m, 1H, OCH₂CH₂), 5.28–5.07 (m, 4H, OCH₂CHCH₂, 9–CH₂), 4.24–4.08 (m, 2H, H-10), 4.05–3.89 (m, 2H, H-8, 1 × OCH₂CHCH₂), 3.85–3.75 (m, 1H, 1 × OCH₂CHCH₂), 3.52–3.48 (m, 1H, H-5), 2.71–2.51 (m, H-3), 2.16 (s, H-1), 2.12–1.37 (m, H-1b, H-3b, H-4, H-6, H-7), 0.92–0.89 (m, 3H, 6–CH₃). **¹³C NMR** (100 MHz, CDCl₃) δ: 210.0, 209.9, 148.0, 147.2, 146.7, 134.5, 134.4, 117.6, 117.5, 117.2, 115.4, 114.5, 113.2, 80.6, 80.1, 74.4, 74.0, 69.6, 69.4, 69.4, 62.9, 62.8, 41.2, 41.0, 38.5, 37.7, 35.7, 30.2, 27.8, 27.7, 14.5, 14.0; **HRMS** [ESI, (M+Na)⁺]: m/z: calculated for (C₁₅H₂₆NaO₄) 293.1723, found: 293.1724.
Appendix
NMR Spectra of Novel Compounds

(4S,5S)-1-(4-Methoxybenzyl)oxy-5-methylhept-6-en-4-ol 149
(3S,4S)-7-(4-Methoxybenzyloxy)-3-methylhept-1-en-4-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 186a
(3S,4S)-7-(4-Methoxybenzyloxy)-3-methylhept-1-en-4-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 186a cont.
(3S,4S)-7-(4-Methoxybenzyloxy)-3-methylhept-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 186b
(3S,4S)-7-(4-Methoxybenzyloxy)-3-methylhept-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 186b cont.
(4S,5S)-4-(tert-Butyldimethylsilyl)oxy-1-(4-methoxybenzyl)oxy-5-methylhept-6-ene 207
(3S,4S)-4-(tert-Butyldimethylsilyl)oxy-7-(4-methoxybenzyl)oxy-3-methylheptan-1-ol 208
(3S,4S)-4-(tert-Butyldimethylsilyl)oxy-7-(4-methoxybenzyl)oxy-3-methylheptanal 209
(4S,5S,E)-8-Bromo-4-(tert-butyldimethylsilyloxy)-1-(4-methoxybenzyl)oxy-5-methyloct-7-ene
(4S,5S)-4-(tert-Butyldimethylsilyloxy)-1-(4-methoxybenzyl)oxy-5-methyloct-7-ene
(4S,5S)-8-Bromo-4-(tert-butyldimethylsilyl)oxy-1-(4-methoxybenzyl)oxy-5-methyloct-7-yne
(4S,5S)-8,8-Dibromo-4-(tert-butyldimethylsilyl)oxy-1-(4-methoxybenzyl)oxy-5-methyloct-7-ene
(4S,5S,Z)-8-Bromo-4-(tert-butylidimethylsilyl)oxy-1-(4-methoxybenzyl)oxy-5-methyloct-7-ene
(4S,5S)-4-Hydroxy-N-methoxy-N,5-dimethylhept-6-enamide 194
(S)-5-((S)-But-3-en-2-yl)dihydrofuran-2(3H)-one 203
(3S,4S)-7,7-Ethylenebisoxy-3-methyloct-1-en-4-ol 137
(3S,4S)-7,7-Ethylenebisoxy-3-methylene-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 486a
(3S,4S)-7,7-Ethylenebiosoxy-3-methylox-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 486a cont.
(3S,4S)-7,7-Ethylenebisoxy-3-methyloct-1-en-4-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 486b
(3S,4S)-7,7-Ethylenbis(oxy)-3-methyloct-1-en-4-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 486b cont.
(3S,4S)-7,7-Ethylenebisoxy-4-(4-methoxybenzyl)oxy-3-methyloct-1-ene 210

OPMB
(3S,4S)- 4-(tert-Butyldimethylsilyl)oxy-7,7-ethylenebisoxy-3-methyloct-1-ene 211
(5S,6S)-5-(tert-Butyldimethylsilyl)oxy-6-methyloct-7-en-2-one 212
(3S,4S)-7,7-Ethylenebisoxy-4-(tert-butyldimethylsilyl)oxy-3-methyloctanal 204
(4S,5S,E)-1-Bromo-8,8-ethylenebisoxy-5-(tert-butyldimethylsilyl)oxy-4-methylnon-1-ene
(4S,5S)-1-Bromo-8,8-ethylenebiosoxy-5-(tert-butyldimethylsilyl)oxy-4-methylnon-1-yne
(4S,5S)-1,1-Dibromo-8,8-ethylenebisoxy-5-(tert-butyldimethylsilyl)oxy-4-methylnon-1-ene
(4S,5S,Z)-1-Bromo-8,8-ethylenebisoxy-5-(tert-butyldimethylsilyl)oxy-4-methylnon-1-ene 230
(5S,6S)-9-Bromo-5-(tert-butyldimethylsilyloxy)-6-methylnon-8-yn-2-one
(5S,6S,E)-9-Bromo-5-(tert-butyldimethylsilyl)oxy-6-methylnon-8-en-2-one 238
(5S,6S,Z)-9-Bromo-5-(tert-butyldimethylsilyl)oxy-6-methylnon-8-en-2-one
4-(4-Methoxybenzyloxy)-3,3-dimethylbutan-2-one 271
1-Bromo-4-((4-methoxybenzyl)oxy)-3,3-dimethylbutan-2-one 280
5-(tert-Butyldimethylsilyl)oxy-1-hydroxy-4,4-dimethyl-1-phenylpentan-3-one
(E)-5-(tert-Butyldimethylsilyl)oxy-4,4-dimethyl-1-phenylpent-1-en-3-one 284
4-tert-Butyldimethylsilyloxy-1-hydroxy-3,3-dimethylbutan-2-one
4-Benzoyloxy-1-diazo-3,3-dimethyl-butan-2-one

\[ \text{N}_2 = \text{O} \]

\[ \text{OBz} \]

\[ 296 \]
4-Benzyloxy-2,2-dimethylbutanoic acid 304
4-Benzoyloxy-2,2-dimethylbutanoic acid 308
5-Diazo-3,3-dimethyl-4-oxopentyl benzoate 309
3,3-Dimethyl-4,5-dioxopentyl benzoate 310
5-Hydroxy-3,3-dimethyl-4,7-dioxo-7-phenylheptyl benzoate 319
3-Hydroxy-6-(4-methoxybenzyl)oxy-1-phenylhexan-1-one
(9S,10S)-9-(tert-Butyldimethylsilyl)oxy-4-hydroxy-1-(4-methoxybenzyl)oxy-10-methyldodec-11-en-6-one
(5S,10S,11S)-10-(tert-Butyldimethylsilyl)oxy-5-hydroxy-3,3,11-trimethyl-4,7-dioxotridec-12-en-1-yl benzoate 347
(5S,6S)-5-(tert-Butyldimethylsilyl)oxy-6-methyl-1-non-8-yn-2-one
(5S,10S,11S)-10-(tert-Butyldimethylsilyl)oxy-5-hydroxy-3,3,11-trimethyl-4,7-dioxotetradec-13-yn-1-yl benzoate 360
5-Hydroxy-3,3-dimethylpentyl benzoate 380
3,3-Dimethyl-5-oxopentyl benzoate 381
3,3-Dimethy-2-methylene-5-oxopentyl benzoate 370
(10S,11S)-10-(tert-Butyldimethylsilyloxy)-5-hydroxy-3,3,11-trimethyl-4-methylene-7-oxotridec-12-en-1-yl benzoate 371
(10S,11S)-10-(tert-Butyldimethylsilyl)oxy-4-formyl-3,3,11-trimethyl-7-oxotridec-12-en-1-yl benzoate 382
(10S,11S)-10-(tert-Butyldimethylsilyl)oxy-5-hydroxy-3,3,11-trimethyl-4-methylene-7-oxotetradec-13-yn-1-yl benzoate 383
(9S,10S)-10-(tert-Butyldimethylsilyl)oxy-13,13-ethylenedioxy-5-hydroxy-3,3,9-trimethyl-tetradec-6-yn-1-yl benzoate 404
(9S,10S,E)-10-(tert-Butyldimethylsilyl)oxy-13,13-ethylenebisoxy-5-hydroxy-3,3,9-trimethyl-tetradec-6-en-1-yl benzoate
(9S,10S,Z)-10-(tert-Butyldimethylsilyl)oxy-13,13-ethylenebisoxy-5-hydroxy-3,3,9-trimethyltetradec-6-en-1-yl benzoate
(5S,6S)-5-(tert-Butyldimethylsilyl)oxy-10-hydroxy-3,3,6-trimethyl-2-oxotetradec-8-yn-14-yl benzoate 390
(5S,6S,E)-5-(tert-Butyldimethylsilyl)oxy-10-hydroxy-3,3,6-trimethyl-2-oxotetradec-8-en-14-yl benzoate 391
(5S,6S,Z)-5-(tert-Butyldimethylsilyl)oxy-10-hydroxy-3,3,6-trimethyl-2-oxotetradec-8-en-14-yl benzoate 392
(5S,6S)-9,9-Ethyleneoxy-5-methyl-2-methylene-6-(tert-butyldimethylsilyl)oxy-1-(triisopropylsilyl)oxydecan-3-ol 423
(5S,6S)-5-(tert-Butyldimethylsilyl)oxy-8-hydroxy-6-methyl-9-methylene-10-(triisopropylsilyl)oxydecan-2-one 434
(1S,3S,5S,6S)-1,5-Dimethyl-3-(1-(triisopropylsilyl)oxyprop-2-en-2-yl)-2,9-dioxabicyclo[4.2.1]nonane 435
(1S,3S,5S,6S)-1,5-Dimethyl-3-(1-(triisopropylsilyl)oxyprop-2-en-2-yl)-2,9-dioxabicyclo[4.2.1]nonane 435 cont.
(5S,6S)-9,9-Ethylenebisoxy-5-methyl-2-methylene-6-(tert-butyldimethylsilyl)oxy-1-(triisopropylsilyl)oxydecane-3-yl acetate
(5S,6S)-3-Allyloxy-9,9-ethylenebisoxy-5-methyl-6-(tert-butyldimethylsilyl)oxy-2-((triisopropylsilyloxy)methyl)decan-1-ene 454
(5S,6S)-8-Alyloxy-6-methyl-9-methylene-5-(tert-butyldimethylsilyl)oxy-10-(triisopropylsilyl)oxydecan-2-one
Ketone 457 and hemiacetal 458
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