Synthetic approaches to medicinally relevant *Euphorbia* diterpenes

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Doctor of Philosophy

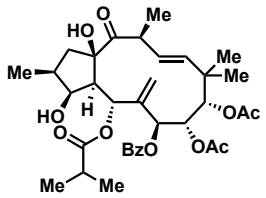
Abstract

This thesis is divided into six chapters. Chapter 1 provides an overview of the role of natural product synthesis in the 21st century, and provides a scientific and historical context for the research undertaken in this thesis, including prior work undertaken in the Jonathan W. Burton group towards the total synthesis of target compounds euphodendroidin D **1.17** and pepluanin A **1.18**.

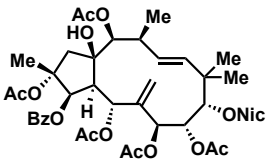
Chapter 2 provides a description our work on the synthesis of racemic cyclopentane **1.102** *via* a palladium-catalysed cyclisation, and the derivatisation thereof to racemic lactone **2.50**. Chapter 3 covers our unsuccessful efforts to develop an enantioselective synthesis of **1.102**, and our successful asymmetric synthesis of **2.50** *via* an alternative route. It also covers our extensive investigations into the allylic oxidation of **2.50**.

Chapter 4 details our attempts to conduct a series of further redox manipulations, ultimately resulting in the scalable and high-yielding synthesis of **4.38**, a densely functionalised intermediate, and the furthest point reached in our attempt to synthesise euphodendroidin D **1.17**. Chapter 5 describes our asymmetric synthesis of **5.24**, an advanced sulfone intermediate which was also necessary for our planned convergent synthesis of euphodendroidin D **1.17**.

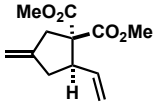
Finally, chapter 6 summarises our achievements and suggests a prospective improvement to the synthetic plan should the project be continued.



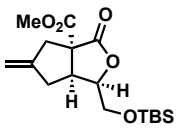
1.17
euphodendroidin D



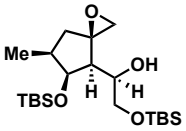
1.18
pepluanin A



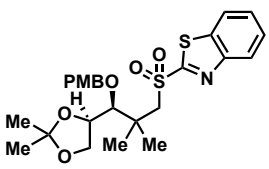
1.102



2.50



4.38



5.24

Declaration

The work described herein is entirely the work of the author, except where specifically indicated, and does not include any collaborative research.

This thesis has not been previously submitted for a degree, diploma, or any other qualification at the University of Oxford or elsewhere.

Jack Sutro

April 2022

Acknowledgements

Firstly, I would like to thank Professor Jon Burton for being a simply unbelievably brilliant supervisor. The extraordinary amounts of intelligence, kindness, and enthusiasm with which he has supported me and my project have suffused my entire DPhil experience with a roseate hue, and he will forever stand as a paragon of mentorship in my mind. I will dearly miss frequent exposure to his wonderful sense of humour, his encyclopaedic knowledge of the chemical literature, and his sagacious cooking tips.

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willingness to meditate upon chemistry problems, both in my company and by himself in the Stygian depths of night. I am also grateful to Nicoleta Lazar for the zen calmness she exudes, and for her extraordinary ability to bring positivity and sunshine into any room or conversation she finds herself in. I'd like to thank Sam Chan for inspiring me to never relent or compromise in pursuit of a deeper and richer understanding of chemistry; the complexity of the subject has seemed fearful at times, but he and his work are an indelible testament to what can be achieved through intellectual rigour. In that vein, I'd like to thank Sean Guggiari for teaching me to always strive for higher degrees of precision and meticulousness in experimental chemistry, and I would like to apologise to him for the trauma of having to share a fumehood with me when I was still in the larval stage of my DPhil. Of the colleagues whose company I've only spent a year or less in, I would like to single out Maryn Brown especially for being such a great Part II student. Thank you for helping me to learn about being a supervisor; I hope you enjoyed working with me as much as I enjoyed working with you. I'd also like to thank Diana ~~Berichi~~ Berheci for her tremendous positivity and kindness, and for her company on 'our' side of the lab. President Scott Hextall has been an invaluable proof-reader during the last few months; I am also grateful to Kilian Garrec, Joe Mason, Manjeet Kumar, Penny Streatfeild, Steve Park, Claire Mainwaring, Denis Hartmann, and Maxime Bonsir, each of whom was a warmly cherished colleague in their time. I would like to thank Erin Shepherd, whom I sadly never met, but whose thesis has been an indispensible *vade mecum* during my project.

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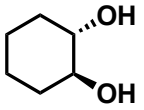
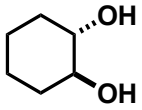
A note on convention

Throughout this text, wedged bonds are used to denote absolute and relative configuration in enantioenriched compounds, whereas straight bonds are used to denote relative stereochemistry in racemic compounds.



enantioenriched



racemic

Abbreviations

ABC	ATP-binding cassette
ABNO	9-azabicyclononane *N*-oxyl
Ac	acetyl
aq.	aqueous
Ar	aryl
ATP	adenosine triphosphate
BBN	9-borabicyclononane
Bn	benzyl
b.p.	boiling point
BQ	benzoquinone
brsm	based on recovered starting material
BSA	bistrimethylsilylacetamide
Bu	butyl (*n* unless otherwise specified)
Bz	benzoyl
cat.	catalyst
CFL	compact fluorescent lamp
conc.	concentrated
COSY	correlation spectroscopy
Cy	cyclohexyl
d	day(s)
dba	dibenzylideneacetone
DCE	dichloroethane
DET	diethyl tartrate
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutyl aluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
E	generic ester group
e.e.	enantiomeric excess
eq.	equivalent(s)
e.r.	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
h	hour(s)
HFIP	hexafluoroisopropanol
HG-II	Hoveyda-Grubbs catalyst (2nd gen.)
HMBC	heteronuclear multiple bond coherence
HMDS	hexamethyldisilazide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
i	iso
IR	infrared

J	coupling constant
LA	generic Lewis acid
lit.	literature
LRMS	low-resolution mass spectrometry
M	molar
MDR	multidrug resistance
Me	methyl
Mes	mesityl
min	minute(s)
mol	mole(s)
MOM	methyloxymethylene
m.p.	melting point
MS	molecular sieves
Ms	methanesulfonyl
MTPA	α-methoxy-α-trifluoromethyl-phenylacetate
m/z	mass/charge ratio
Nic	nicotinoyl
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
Phox	phosphinooxazoline
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl (n unless otherwise specified)
R	generic group
R.f.	retention factor
rt	room temperature
RCM	ring-closing metathesis
s	second(s)
SAR	structure-activity relationship
sat.	saturated
TBA	tetrabutyl ammonium
TBHP	*tert*-butyl hydroxperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	tetramethylpiperidine *N*-oxyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TPP	tetraphenylporphyrin
TS	transition state
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	generic leaving group or anion

Contents

Chapter 1: Introduction

1.1 Chapter introduction

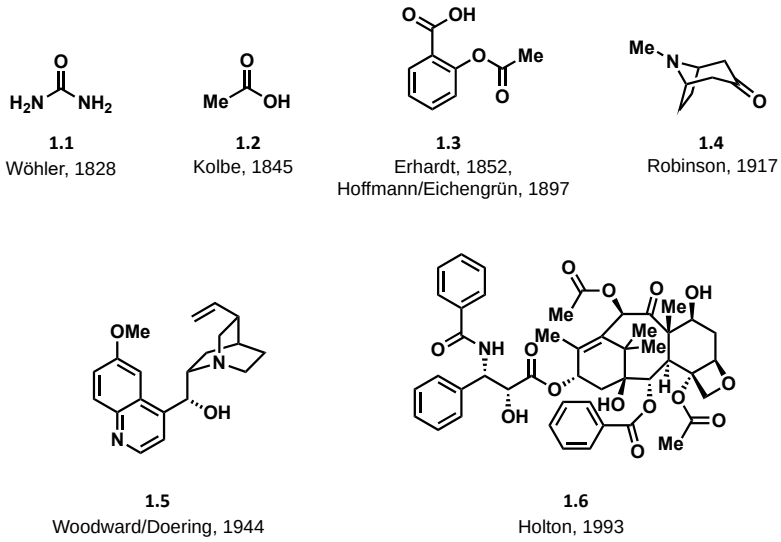
Natural product total synthesis is a field of research which has deservedly elicited an impressive volume of enthusiasm and energy from the organic chemistry community over the last century.[1] As such, modern endeavours within this domain are the products of a rich heritage, and their methods and goals have grown complex and abstruse. In light of this, this chapter will offer an overview of the scientific and historical context and core concepts relevant to the project at hand.

1.2 Natural product total synthesis in the 21st century

The chemistry of natural products, by definition, underpins all life and provides the material framework within which the biological and social sciences take place. Natural products comprise the physical constitution of organisms in the form of structural lipids, proteins, and sugars; they are incarnations of our innermost personal lives as nucleic acids, hormones, and neurotransmitters; and they are a medium through which living things interact with each other and the environment, as poisons, pheromones, and nutrient transporters. Historically, the study of natural products has been driven both by scientific curiosity and by the pharmacological benefit of unpicking life's chemical fabric. The term 'total synthesis' is usually constrained to the construction of 'small' molecules, rather than biopolymers such as proteins and nucleic acids, and although this limitation is not definitional, it is a convention that we will adopt henceforth.

The earliest instances of natural product total synthesis are considered to be Wöhler's synthesis of urea **1.1** from ammonium cyanate in 1828 and Kolbe's synthesis of acetic acid **1.2** from carbon disulfide in 1845.[2, 3] These achievements dispelled the theory of vitalism and established organic chemistry as a field which was accessible through the principles and techniques previously employed

for the study of inorganic and physical chemistry.[4] Amongst many other worthy historical milestones are the syntheses of aspirin **1.3** (Gerhardt, 1852, or Hoffmann/Eichengrün, 1897),[5] tropinone **1.4** (Robinson, 1917),[6] quinine **1.5** (Woodward/Doering, 1944),[7] and taxol **1.6** (Holton, 1993);[8, 9] these landmarks punctuate the evolution of the field and showcase the degrees of capability and ambition which have accumulated within it (Scheme 1.1).



Scheme 1.1: Evolution of the targets accessed by natural product total synthesis over the last two centuries.

The benefits conferred by this discipline bear enumeration; in addition to utility within the study of natural products themselves, there are compelling pharmacological and pedagogical arguments for the pursuit of natural product total synthesis.

It is straightforward to affirm that total synthesis has a gainful impact on the scientific understanding of the origin and function of natural products. Historically, the deliberate construction of a natural product presented a convincing means of proving a structural proposal prior to the advent of modern analytical techniques; although the introduction of high-resolution NMR experiments has largely obviated this, a recent review by Kim and co-workers highlights the ongoing role of synthesis as a tool for the structural confirmation of complex small molecules where other means have proven fallible.[10] In this vein, the developing field has produced instances of 'anticipation through synthesis', where the attempted creation of one target instead gives rise to another which is then subsequently discovered

to be itself a natural product; a recent article by Hetzler, Trauner, and Lawrence covers this phenomenon.[11] Moreover, the synthesis of natural products through certain 'biomimetic' routes enables the exploration of biosynthetic pathways *in vitro*. A compelling recent example of such an exploration was undertaken contemporaneously with the work in this thesis in the same laboratory, wherein a plausible biosynthesis of *Laurencia* natural products *via* complex oxonium ions was demonstrated.[12] Beyond these structural and biosynthetic concerns, total synthesis constitutes a means of producing a significant quantity of natural products for investigations into their function in a biological context; moreover, the ability to selectively modify compounds at sites of interest offers an otherwise inaccessible parameter space for experimental design within such research.

The prospect of a deeper understanding of natural product function within nature hints at the chief societal benefit of total synthesis. The human use of natural products and their derivatives as therapeutics bestrides history as both the primitive pharmacy evidenced in paleolithic graves[13] and, and as the cutting edge of clinical technology in the form of complex natural products such as taxol **1.6** (above) and radiolabelled compounds for medical imaging.[14] The proportion of approved drugs which natural products and their descendants comprise has been assiduously catalogued by Newman and Cragg in a series of reviews published regularly since 1997, and remains high and more-or-less constant in spite of the rise of combinatorial and fragment-based approaches to drug discovery.[15-20] In short, due to their innate biocompatibility and their sculpture by evolutionary pressure within the context of biochemistry, natural product structures and close analogues thereof constitute some of the most reliable candidates for the selective inhibition of medicinally relevant targets; total synthesis is an indispensable means of generating quantities of material for this research, and the only means in the case of structurally modified variants of natural products. This motive underlies the work presented in this thesis.

Although the arguments delineated above are frequently cited and present a strong justification for natural product total synthesis from a community-wide perspective, there are more proximate causes for undertaking total synthesis projects which deserve mention. The intricate structures and

transformations found within a retrosynthetically planned route to a target offer an opportunity to test modern synthetic methodologies in a complex context. The difficulty of total synthesis provides a testing ground for novel chemical transformations, as well as an inspiration for their design. This aspect of total synthesis has a more human reflection: the pursuit of a natural product target acts as a whetstone for chemists as well as chemistry. The range of challenges presented by a typical project within this field are often cited as requiring a broad range of laboratory procedures and techniques to answer, resulting in students with an equal breadth of training.[21]

The project described herein is driven by a range of these motives. The target compounds are members of a structurally diverse and medicinally relevant class of natural products, the synthesis of which remains elusive; our attempt to access them draws on modern synthetic techniques, bringing them to bear on a complex and challenging system.

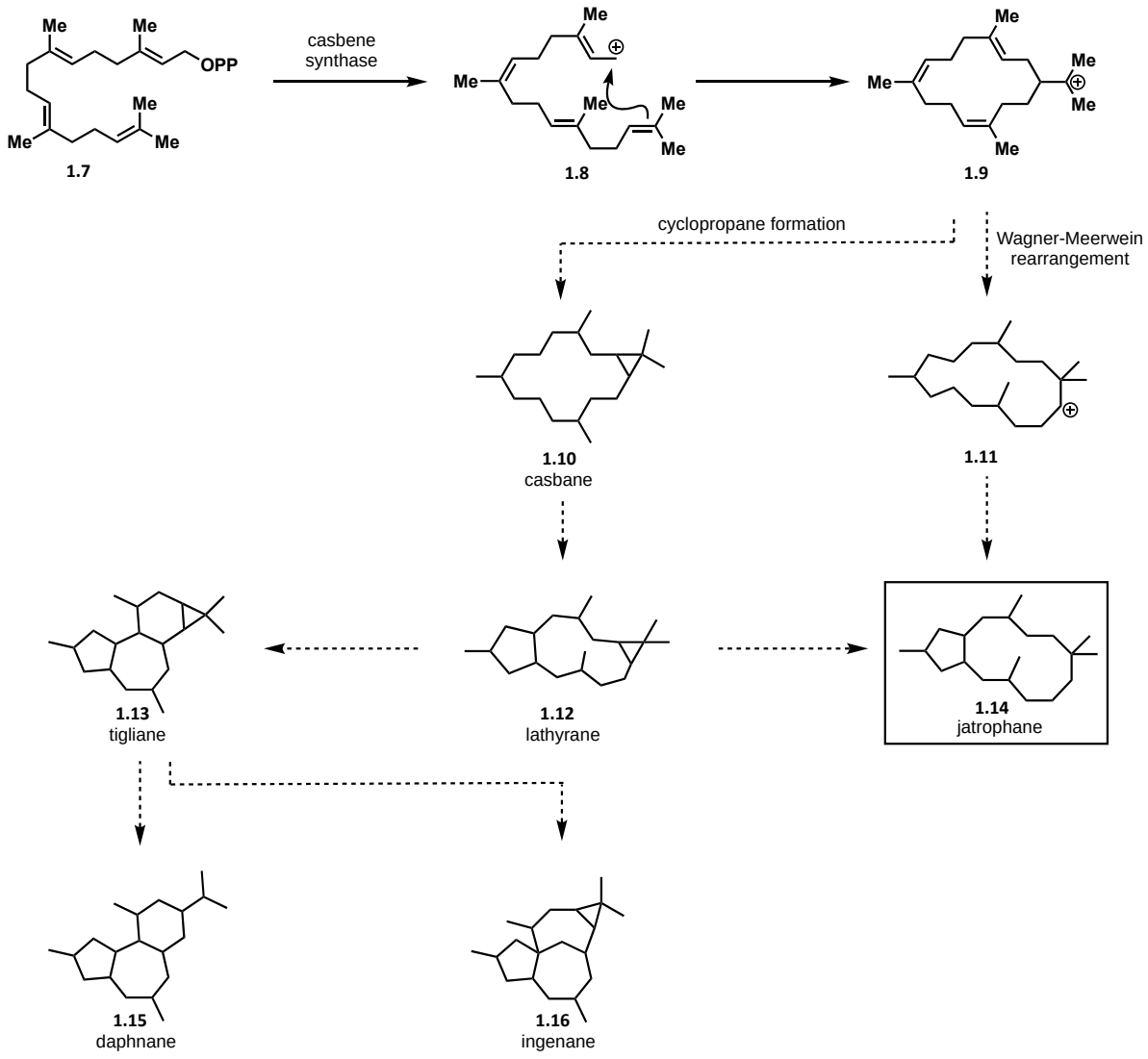
1.3 The jatrophane diterpenes

1.3.1 Euphorbia diterpenes

Euphorbia is a genus of flowering plants contained within the Euphorbiaceae, or spurge family. With over 2,100 classified members found across the globe, it is among the largest, most diverse, and most widespread of flowering plant genera; members are characterised by the milky white irritant latex which they secrete when cut. The name of the genus pays homage to Euphorbos, an ancient Greek physician, who is believed to have employed latex from *Euphorbia resinifera* as a laxative;[22] this salutary employment in the clinics of antiquity is indicative of the rich pharmaceutical potential of the genus, which modern medicinal chemistry continues to validate. Indeed, studies on the phytochemistry of the members of the *Euphorbia* genus have disclosed a range of diterpenoid structures, known collectively as the '*Euphorbia* diterpenes', which exhibit a rich array of biological activities.[23] The target natural compounds of this synthesis project are members of the jatrophane class within the *Euphorbia* diterpenes.

1.3.2 Biosynthesis of the jatrophanes and related diterpenes

The jatrophanes are presently believed to be biosynthetic derivatives of the cembrene cation **1.9**, along with a number of other diterpene classes. A complete understanding of this pathway remains elusive; a straightforward proposal from Adolf and Hecker is given below (Scheme 1.2).[24] Geranylgeranyl pyrophosphate **1.7** undergoes a Prins-type cyclisation to give **1.9** in the presence of the Casbene synthase enzyme; a Wagner-Meerwein rearrangement then yields **1.11**. A series of functionalisations and a five-membered ring formation then give rise to the characteristic bicyclo-[10.3.0]-pentadecane scaffold **1.14** of the jatrophanes.

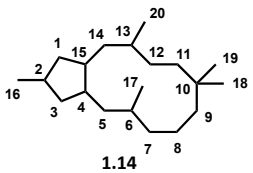


Scheme 1.2: Proposed biosynthetic pathway for the jatrophane class and closely related classes of diterpene.

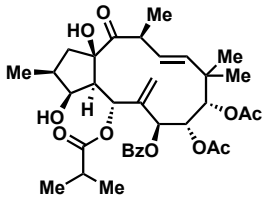
Many other carbon skeletons characteristic of other categories of *Euphorbia* diterpenes can be accessed through such a cation cyclisation pathway from the cembrene cation **1.0**;[25] notably, several of these skeletons (lathyrane **1.12**, tigliane **1.13**, ingenane **1.16**) contain a cyclopropane ring, and are believed to be biosynthetically derived from casbane **1.10**, itself a derivative of **1.9**. There has long been speculation that the jatrophanes are the products of a cyclopropane opening of either the casbanes or lathyranes, in contrast to the Wagner-Meerwein pathway shown explicitly below. A suite of enzymatic oxidations of the scaffold **1.14** and subsequent functionalisations are believed to give rise to the members of the jatrophane class of natural products, which are individually characterised by various oxygenation, unsaturation, and esterification states around the bicyclic carbon skeleton. It is worth noting that, although elegant, the transformations in this biosynthetic proposal do not lend themselves readily to a biomimetic strategy for total synthesis. Indeed, the cationic macrocyclisations and site-selective oxidations involved typify the kinds of enzyme-mediated transformations which generally remain beyond the reach of synthetic chemistry; this foreclosure of biosynthetic inspiration is a significant part of the difficulty in complex terpene total synthesis.

1.3.3 Medicinal relevance of the jatrophane class

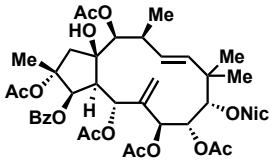
As stated above, the *Euphorbia* terpenes in general are a trove of pharmacological potential, and the jatrophanes are no exception. Recent reviews by Kemboi and co-workers[26] and Khan and co-workers[25] disclose the huge range of inhibitory and cytotoxic activities of the *Euphorbia* diterpenes.



1.14
jatrophane skeleton



1.17
euphodendroidin D



1.18
pepluanin A

Scheme 1.3: Numbered jatrophane skeleton **1.14**, and the structures of **1.17** and **1.18**, the target compounds of this project.

The putative target compounds of this project, euphodendroidin D **1.17** and pepluanin A **1.18** (Scheme 1.3), were first isolated and characterised by Corea *et al.* from *Euphorbia dendroides* in 2003 and *Euphorbia peplus* in 2004, respectively.[27, 28] They showed that **1.17** and **1.18** exhibited potent inhibition of P-glycoprotein efflux of daunomycin in human leukemic cells, with **1.18** proving approximately twice as effective as cyclosporin A, the then and current clinical gold standard. Moreover, in 2009, the Corea group reviewed the P-glycoprotein inhibition data of a series of *Euphorbia* diterpenes and began to infer a structure-activity relationship (SAR) profile for this inhibitory activity.[29] The SAR they obtained is complex; within the jatrophanes, they showed that having a ketone at C14 and free alcohols on C3 and C15 led to a positive impact on P-glycoprotein inhibition, whilst C2 oxygenation, acetoxylation at C14, and nicotinoyloxylation at C5 and C9 generally led to a reduction in activity. The complexity of this SAR is somewhat illuminated by two factors. The first, observed by Appendino and co-workers[30] and Jakupovic and co-workers,[31] is that the ^{1}H NMR coupling constant and NOESY data of the jatrophanes is indicative of two distinct conformations of the 12-membered ring. This phenomenon arises because the *exo*-methylene group (C17) is oriented perpendicular to the mean plane of this ring, and can thus either point 'up' or 'down' with respect to it. One of these conformers is favoured in any given natural product, and the steric interactions between the ester groups around the ring are believed to drive this preference; in other words, each substituent can exert a dramatic effect on the overall topology of the molecule. Thus, varying the substituent pattern would lead to a more significant impact on inhibitory activity than might otherwise be expected. The second SAR-relevant observation was published by Ferreira in 2011,[32] in a study which consisted of a computational analysis of a database of compounds known to cause multidrug resistance (MDR) reversal. They concluded that both hydrophobicity and hydrogen bond acceptor sites were positive attributes for MDR reversal; their model pharmacophore consists of a single hydrogen bond acceptor and three hydrophobic binding sites. The complexity of this picture correlates well with that found in the empirical studies on the *Euphorbia* diterpenes mentioned previously. It is additionally noteworthy that pepluanin A **1.18** outperforms the clinical gold standard despite the fact

that it features C2 oxygenation and C9 nicotinoyloxylation, which are structural motifs associated with a decrease in inhibitory activity.

The biological activity against P-glycoprotein exhibited by **1.17** and **1.18** would be of clinical significance if it could be leveraged in a therapeutic manner. As efflux pumps within the ATP binding cassette (ABC) superfamily, P-glycoproteins straddle the cell membrane and mediate the active transport of exogenous compounds from the intracellular environment to the extracellular.[33] This usually benign activity becomes problematic in cancer cases when cancerous cell lines develop which overexpress P-glycoprotein; this results in an increased resistance to chemotherapy, through the increase in P-glycoprotein-mediated efflux of chemotherapeutic compounds. This is believed to lead to the phenomenon of MDR in such cancer cases. As such, an effective and selective P-glycoprotein inhibitor would be a strong candidate for co-administration with chemotherapy in cases where MDR develops.

1.4 Prior art in the area of jatrophane total synthesis

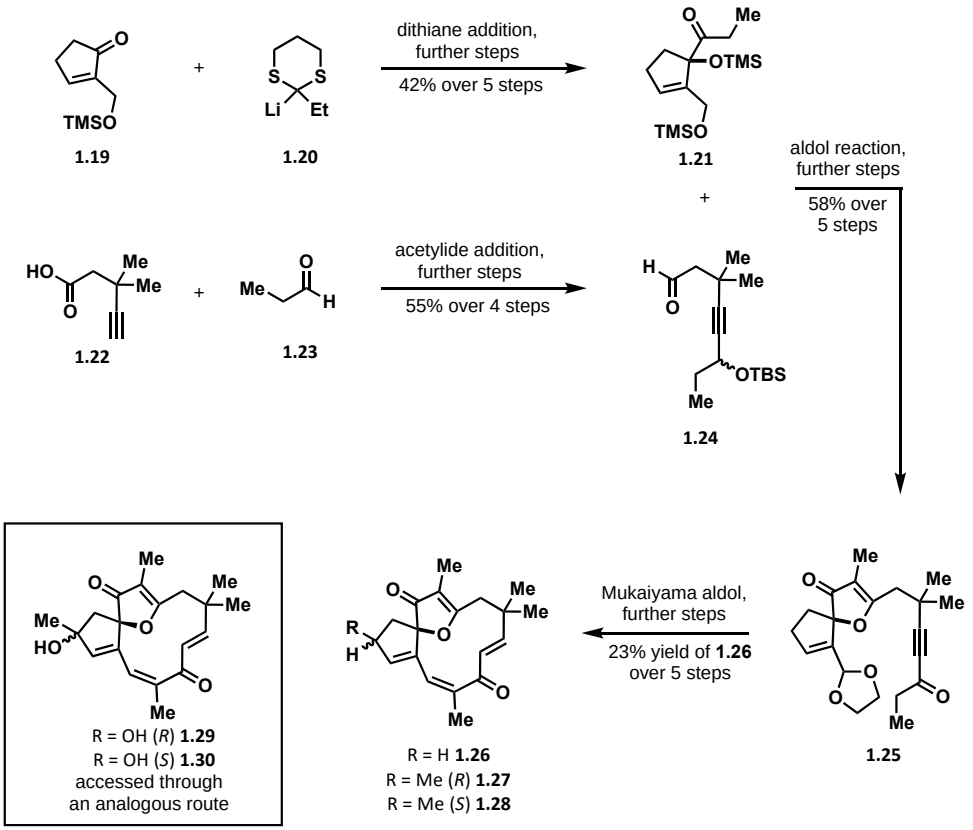
1.4.1 A survey of completed and attempted total syntheses of the jatrophane diterpenes

The jatrophane natural products present several challenges from a synthetic perspective. The *trans*-fusion of the 5- and 12- membered rings is a nearly universal structural feature (the first apparent exception to this was recently uncovered by Xiang and colleagues);[34] along with the *trans*- olefin in the medium-sized ring, this presumably limits the number of feasible conformations of these molecules, and imposes a severe entropic barrier to macrocyclisation. Beyond this general difficulty, in the case of heavily oxygenated jatrophanes the large number of stereogenic centres poses a challenge for stereoselective synthesis; this arrangement of these centres is such that they must generally be set individually or in pairs (e.g. by stereoselective epoxidation). The obstacle presented by the large number of oxygenated sites is frequently compounded by the esterification of these groups with a variety of acyl substituents; in compounds such as such as **1.17** and **1.18**, this imposes daunting constraints on any prospective protecting group strategy.

In light of these complexities, we offer a brief survey of some prior strategies published in the literature for accessing the jatrophanes, both successful and unsuccessful. These investigations were comprehensively reviewed by Rinner in 2015,[22] and as such we will offer an overview on the main approaches taken and advances made in this field rather than a full enumeration of the state of the art.

1.4.2 Synthetic approaches to the jatrophones

The first foray into the synthesis of jatrophane-like compounds was that of Smith and co-workers in their 1981 syntheses of racemic normethyljatrophone **1.26**, racemic jatrophone **1.27**, and racemic epi-jatrophone **1.28**,[35] and their subsequent 1989 syntheses of hydroxyjatrophones A **1.29** and B **1.30** through an analogous route.[36] The first of these is shown below for simplicity (Scheme 1.4). The tertiary oxygenated stereocentre at C15 was generated through the addition of lithiated 1,3-dithiane



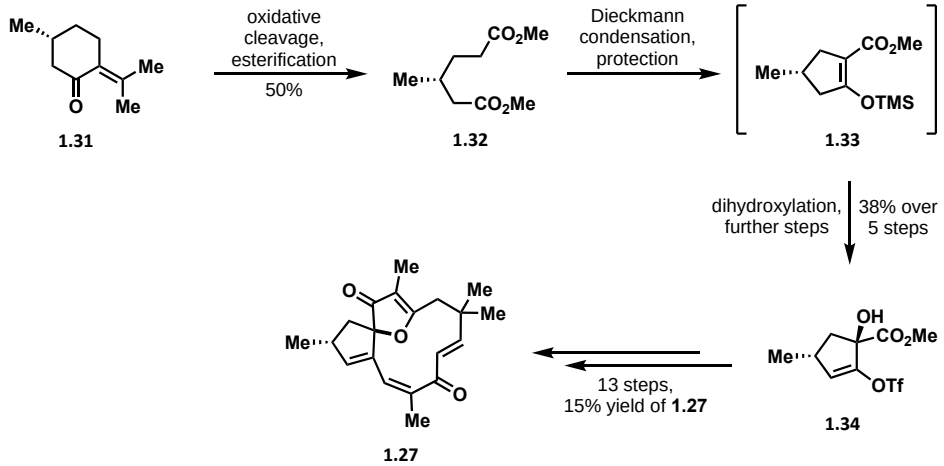
Scheme 1.4: Overview of Smith's synthetic approach to norjatrophone **1.26**, jatrophone **1.27** and *epi*-jatrophone **1.28**, and hydroxyjatrophones A **1.29** and B **1.30**.

1.20 into cyclopentenone **1.19** to give **1.21**; this was then coupled with an aldehyde **1.24**, derived from the acetylide addition of **1.22** into aldehyde **1.23**, to ultimately give **1.25**.

A Mukaiyama aldol reaction was used to close the medium ring, and subsequent transformations resulted in the formation of **1.26** in a yield of 6% over 15 steps. The authors note at the end of the publication that they completed the syntheses of natural products **1.27** and **1.28** between manuscript submission and publication. Hydroxyjatrophones **1.29** and **1.30** were subsequently synthesised enantioselectively (using a chiral resolution) using a similar route in 1989.

Syntheses of racemic **1.27** and racemic **1.28** were subsequently published by Stille (posthumously) and Hegedus in 1990.[37] Their approach was similar to that employed by Smith, using a 1,3-dithiane addition to construct the C15 tertiary alcohol; the principal difference in their route was the use of a carbonylative Stille coupling to close the macrocycle.

In 1992, an asymmetric synthesis of jatrophone **1.27** was published by Han and Wiemer (Scheme 1.5).[38] Again closing the macrocycle with a Stille coupling, the main novelty of their route was to synthesise functionalised cyclopentene **1.34**, containing the C15 tertiary alcohol, from the chiral pool starting material (+)-pulegone **1.31**. Oxidative cleavage and esterification gave **1.32**, the Dieckmann condensation of which formed the cyclopentane ring to give enoate **1.33**. A diastereoselective osmium-catalysed dihydroxylation, followed by enol triflation, gave functionalised cyclopentane **1.34**, which was subsequently converted to the natural product **1.27** in a short synthesis with a high yield.

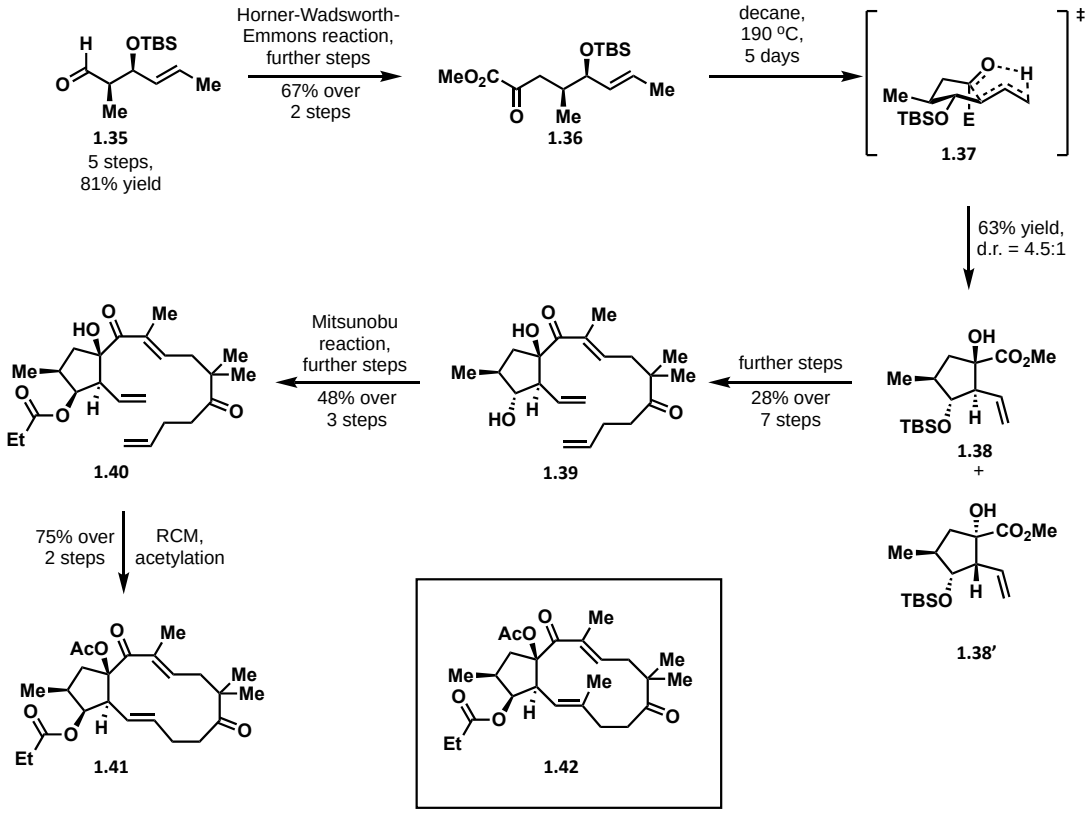


Scheme 1.5: Overview of Han and Wiemer's synthetic approach to jatrophone **1.27**.

This is an impressive set of total syntheses which elicit a high yield over a comparatively low step count. The construction of the C15 tertiary alcohol *via* the addition of a 1,3-dithiane into a cyclopentanone is certainly a disconnection suggested by the structures of the natural products, and Smith and Stille and co-workers use it to good effect; the diastereoselective dihydroxylation used by Wiemer is a creative and very successful alternative. In light of comments made in Section 1.4.1, there are two noteworthy features rendering jatrophones somewhat more approachable than their jatrophane cousins from a synthetic perspective. Firstly, the comparative lack of oxygenated and esterified sites allows for a straightforward protecting group strategy. Secondly, the level of unsaturated around the skeleton, most notably between C3 and C4, and the presence of the spirocycle significantly alleviate the entropic penalties associated with macrocyclisation.

1.4.3 Successful synthetic approaches to the jatrophanes

In 2004, Hiersemann *et al.* reported a highly innovative asymmetric synthesis of the cyclopentane core of the jatrophanes (Scheme 1.6).[39] Having accessed chiral aldehyde **1.35** in five steps through a sequence involving an Evans aldol reaction, they derivatised it to α-ketoester **1.36**; this was subsequently heated in decane for five days, resulting in the formation of cyclopentanol **1.38** *via* an intramolecular carbonyl-ene reaction postulated to proceed through transition state **1.37**. Although the conditions used are harsh, the assembly of such a highly-substituted cyclopentane from a linear precursor is an impressive achievement. In 2009, the Hiersemann group employed this chiral fragment in a synthesis of the unnatural 15-acetyl-3-propionyl-17-norcharaciol **1.41**, a close analogue of the natural jatrophane 15-acetyl-3-propionyl-17-characiol **1.42**.[40] Derivatisation of **1.38** to **1.39** was followed by the inversion of the C3 stereocentre through a Mitsunobu esterification; a ring-closing olefin metathesis (RCM) and acetylation then gave **1.41** in an overall yield of 4% over 20 steps. When transferred to the 'true' system in an effort to reach **1.42**, the introduction of the extra methyl group at C6 caused the RCM to fail; however the Hiersemann group persevered, and in 2009 they reported the synthesis of **1.42** through a similar route employing an RCM to close the macrocycle at the enone.[41]



Scheme 1.6: Overview of Hiersemann's synthetic approach to **1.41** and **1.42**.

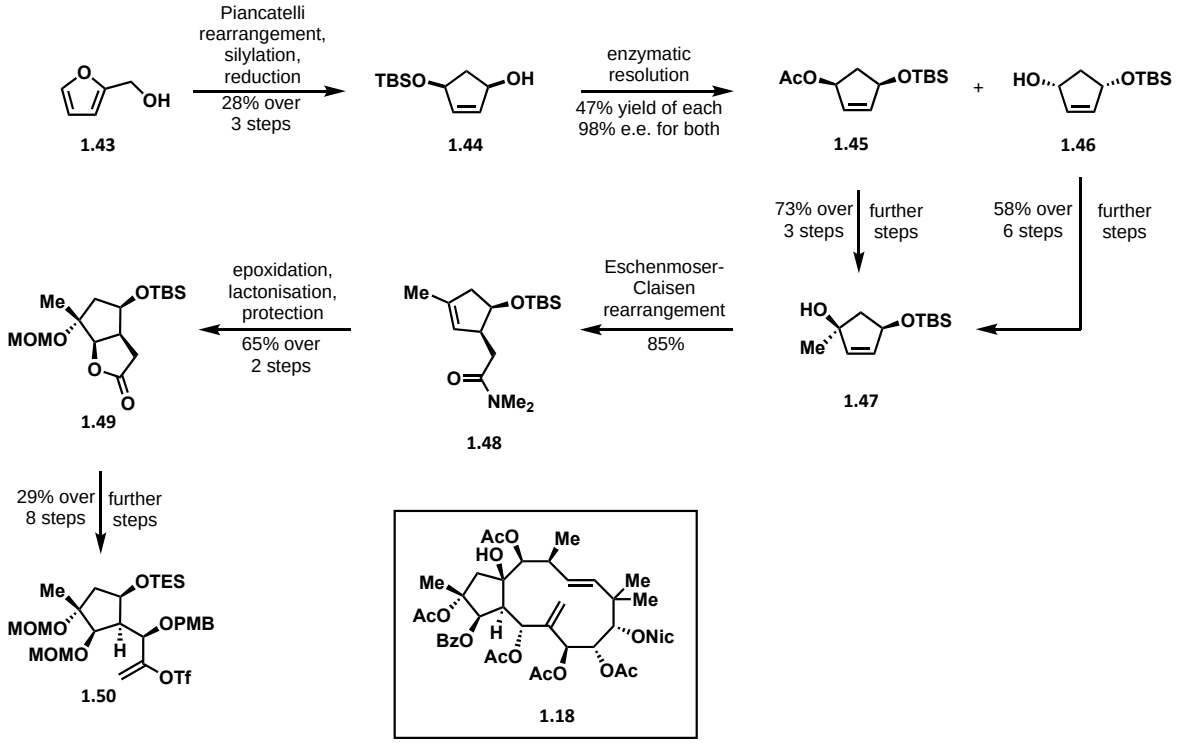
To date, the synthesis of 15-acetyl-3-propionyl-17-characiol **1.42** by the Hiersemann group remains the only successful synthesis of a jatrophane natural product other than the tricyclic jatrophones.

1.4.4 Reported partial synthetic approaches to the jatrophanes

Aside from the successful instances of jatrophone and jatrophane synthesis delineated above, there have been occasional partial syntheses reported in the literature. These usually focus on the cyclopentane core as a target, and frequently disclose that an ensuing effort to form the 12-membered ring was unsuccessful.

In publications in 2004 and 2005, Mulzer and co-workers disclosed the asymmetric synthesis of the highly functionalised core of pepluanin A **1.18** (Scheme 1.7).[42, 43] Starting with furfuryl alcohol **1.43**, a cheap feedstock chemical, they accessed cyclopentenol **1.44** *via* a Piancatelli rearrangement followed

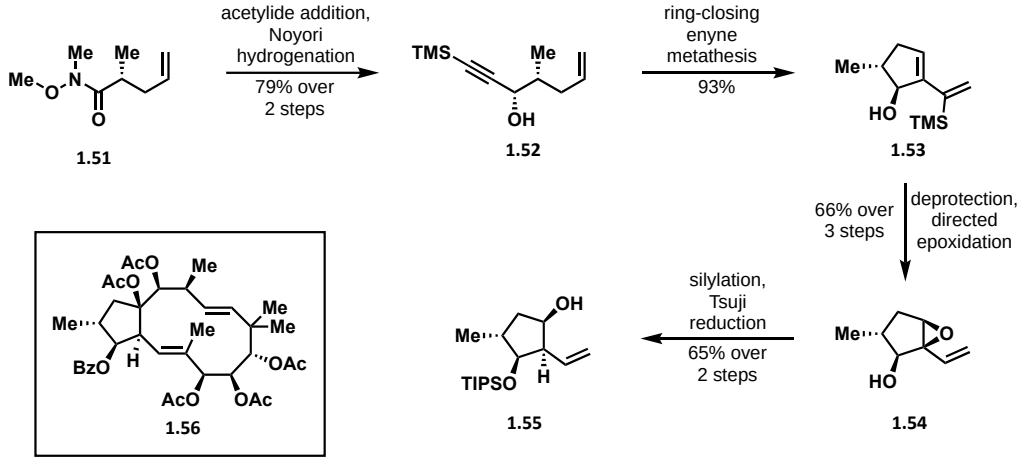
by a silylation and reduction. This was followed by an enzymatic resolution using pancreatin in a procedure from Curran *et al.* to give **1.45** and **1.46**;[44] differential protecting group manipulation, oxidation, then organometallic addition allowed access to **1.47** from both enantiomeric series. A highly diastereoselective Eschenmoser-Claisen rearrangement then gave amide **1.48**; alkene epoxidation and lactonisation then gave cyclopentane-fused lactone **1.49**, which was subsequently derivatised to **1.50** giving a total yield of 3% over 15 steps.



Scheme 1.7: Mulzer's synthetic approach to the core **1.50** of pepluanin A **1.18**.

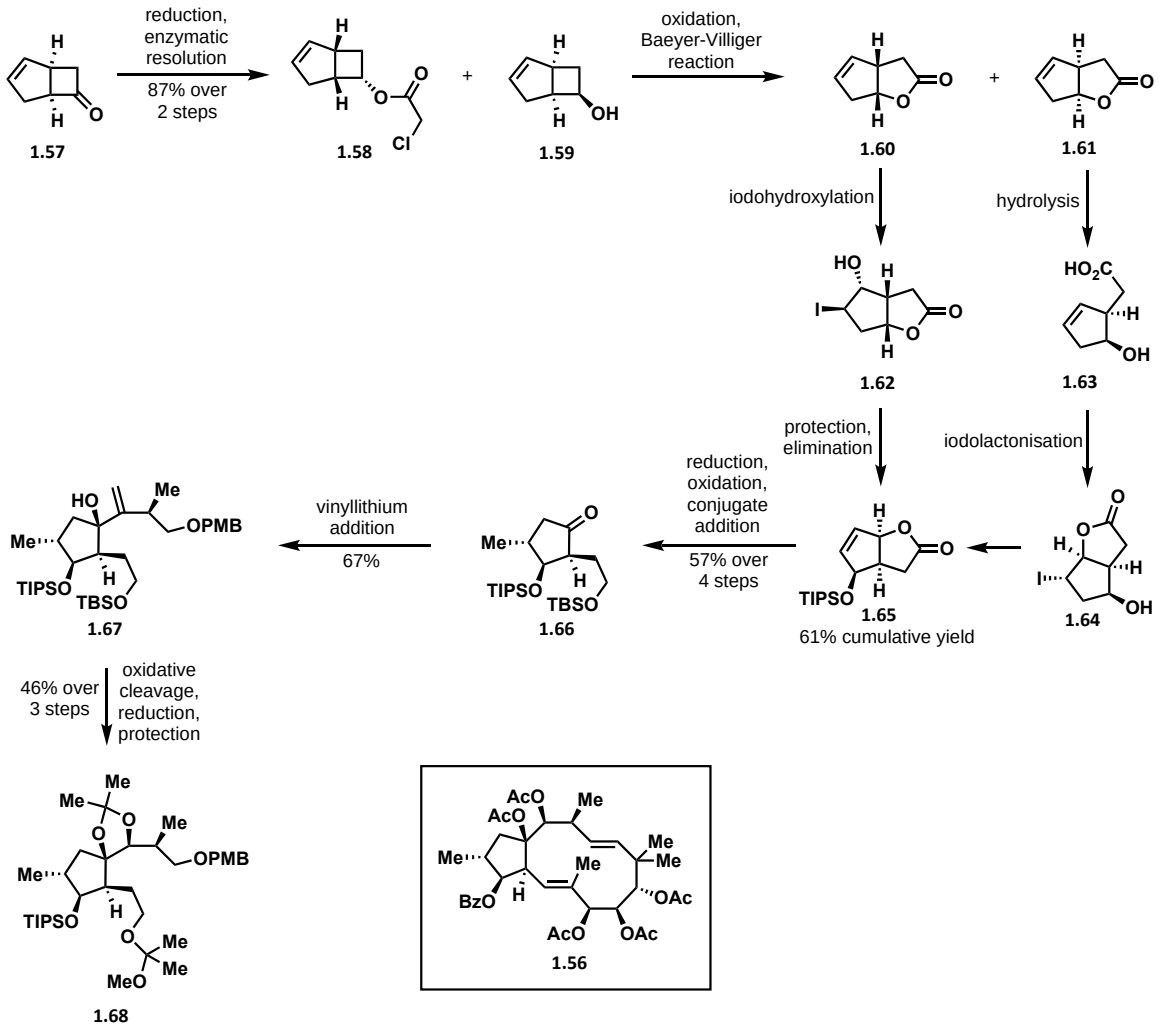
The Rinner group has undertaken several creative syntheses of jatrophane fragments; following an initial publication in the area in 2009,[45] they completed a concise route to the cyclopentane core **1.55** of the natural product PI-3 **1.56** in 2013 (Scheme 1.8).[46] Weinreb amide **1.51** was prepared enantioselectively through an asymmetric alkylation using a Myers' pseudoephedrine auxiliary, and subsequently derivatised to chiral alcohol **1.52** *via* the addition of an acetylide nucleophile followed by a catalyst-controlled asymmetric hydrogenation of the resulting ketone. A ring-closing enyne metathesis then gave diene **1.53**, which was converted to epoxide **1.54** *via* a substrate-controlled diastereoselective epoxidation. An ensuing catalyst-controlled diastereoselective Tsuji reduction then

gave **1.55**. This sequence resulted in an impressive 22% yield of fragment **1.55** over nine steps; however the need for three distinct enantioselective methodologies to establish four contiguous stereocentres might be regarded as an unfortunate weakness of this strategy.



Scheme 1.8: Rinner's first synthetic approach to the core **1.55** of PI-3 **1.56**.

In 2014, the Rinner group published an updated synthesis of the cyclopentane core of PI-3 **1.56** which featured a highly elegant approach to set the desired stereochemistry (Scheme 1.9).[47] Starting from the readily available racemic bicyclic ketone **1.57**, a diastereoselective hydride reduction followed by an enzymatic resolution gave ester **1.58** and alcohol **1.59**, allowing for the easy separation of enantiomers. A subsequent re-oxidation to the ketone, followed by a Baeyer-Villiger reaction gave cyclopentane-fused lactones **1.60** and **1.61** in each enantiomeric series. In one series, iodination of **1.60** under basic aqueous conditions gave **1.62**, which was then silylated and eliminated to give alkene **1.65**; in the other, **1.61** was hydrolysed to **1.63**, which subsequently underwent iodolactonisation to give **1.64**. After silylation of the alcohol, elimination of the iodide gave **1.65** in a beautiful example of strategically designed enantioconvergence. A series of transformations resulted in cyclopentanone **1.66**, which accepted a vinyllithium species to give **1.67**; cleavage of the *exo*-alkene followed by reduction and protection then gave advanced intermediate **1.68**.



Scheme 1.9: Rinner's synthetic approach to the core **1.68** of **1.56**.

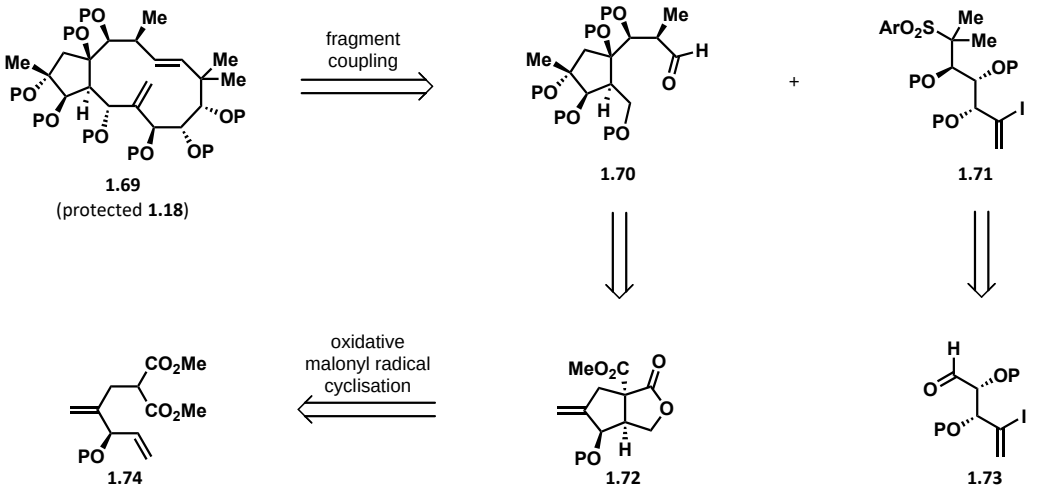
This selection of syntheses of jatrophane fragments is not comprehensive; several other syntheses of cyclopentane cores of jatrophanes or simplified jatrophanes have been published by the groups of Uemura, Mohan, and Rinner.[48-53] The syntheses shown above showcase the various innovative approaches chemists have adopted in attempting to access this challenging class of natural product, and provide a global research context for the work presented in this thesis.

1.5 Research context of the project with the Jonathan Burton group

1.5.1 Summary of the DPhil of Dr Erin Shepherd

The generation of malonyl radicals and their synthetic utility, especially as participants in cyclisation processes, have long been areas of active research within the Burton group; this interest has led to the successful total synthesis of a range of natural products containing five-membered rings.[54-57] The stereochemically intricate cyclopentane ring of the jatrophanes presented an enticing challenge for this powerful methodology, which was taken up by Dr Erin Shepherd during her tenure as a DPhil student within the group.[58]

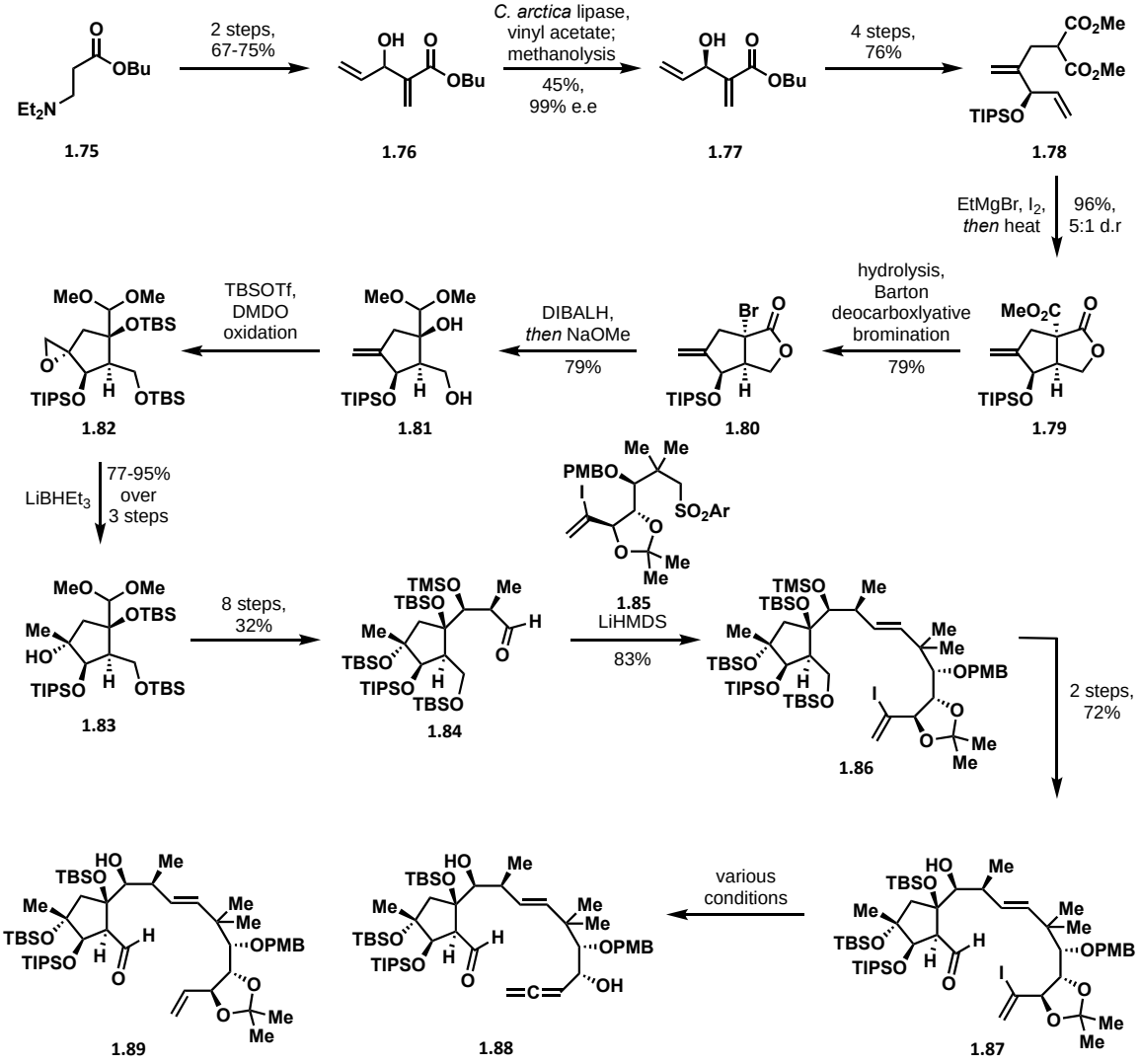
The retrosynthetic plan developed for Dr Shepherd's project is outlined below (Scheme 1.10). Taking protected pepluanin A **1.69** as a putative target, the major simplifying disconnection is to cleave the bicyclo-[10.3.0]-pentadecane into a cyclopentanoid 'western' fragment **1.70** and an open-chain 'eastern' fragment **1.71**. **1.70** was to be generated from the cyclopentane-fused lactone **1.72**, itself generated from the tandem malonyl radical cyclisation-lactonisation of chiral fragment **1.74**, whilst the eastern fragment was to be accessed from a chiral pool-derived starting material **1.73**.



Scheme 1.10: Retrosynthesis of protected pepluanin A **1.69** during the DPhil project of Erin Shepherd.

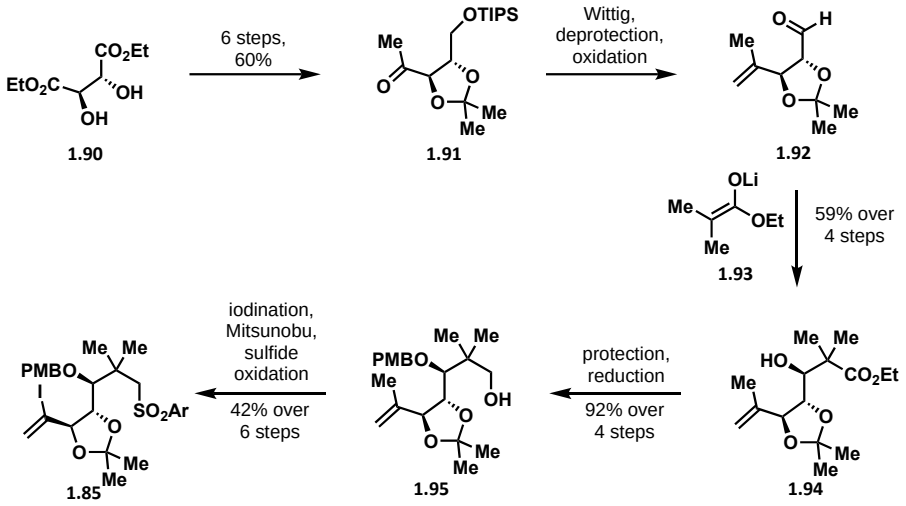
Realised through the transformations delineated below in Scheme 1.11, this approach was largely successful.[59] Optical purity was introduced through the enzymatic resolution of racemic alcohol **1.76**; this stereochemical information was then propagated in an iodocarbocyclisation step (which was

found to be more efficient than an analogous malonyl radical cyclisation) to give lactone **1.79** selectively. Hydrolysis, followed by a decarboxylative bromination[60] gave **1.80**, setting the stage for an elegant reduction which resulted in acetal **1.81**. Subsequent DMDO oxidation of the exocyclic alkene and hydride reduction of the resulting epoxide **1.82** gave alcohol **1.83**; acetal deprotection and a Masamune-Abiko aldol reaction[61] ultimately allowed access to **1.84**. Olefinative coupling with **1.85** (see Scheme 1.12) gave **1.86**, which was derivatised to **1.87**. Attempts to carry out a macrocyclisation using a Nozaki-Hiyama-Kishi reaction[62] failed, giving either no reactivity, protodehalogenation product **1.89**, or the elimination product **1.88**.



Scheme 1.11: Dr Erin Shepherd's work towards the synthesis of protected pepluanin A **1.69**.

The eastern fragment **1.85** was synthesised from chiral pool starting material diethyl L-tartrate **1.90** as shown below (Scheme 1.12). A sequence of six steps elaborated **1.90** to ketone **1.91**, which was then protected using a Wittig reaction and transformed into aldehyde **1.92**. A Felkin-Nguyen[63] controlled enolate addition of **1.93** to give **1.94** installed the dimethylated quaternary carbon atom, and protection and ester reduction then gave alcohol **1.95**. A Mitsunobu reaction[64] with an aryl thiol and a subsequent sulfide oxidation converted the primary alcohol into a sulfone, whilst ozonolysis followed by Barton iodination[65] converted the isopropenyl group into a vinyl iodide to give **1.85**.

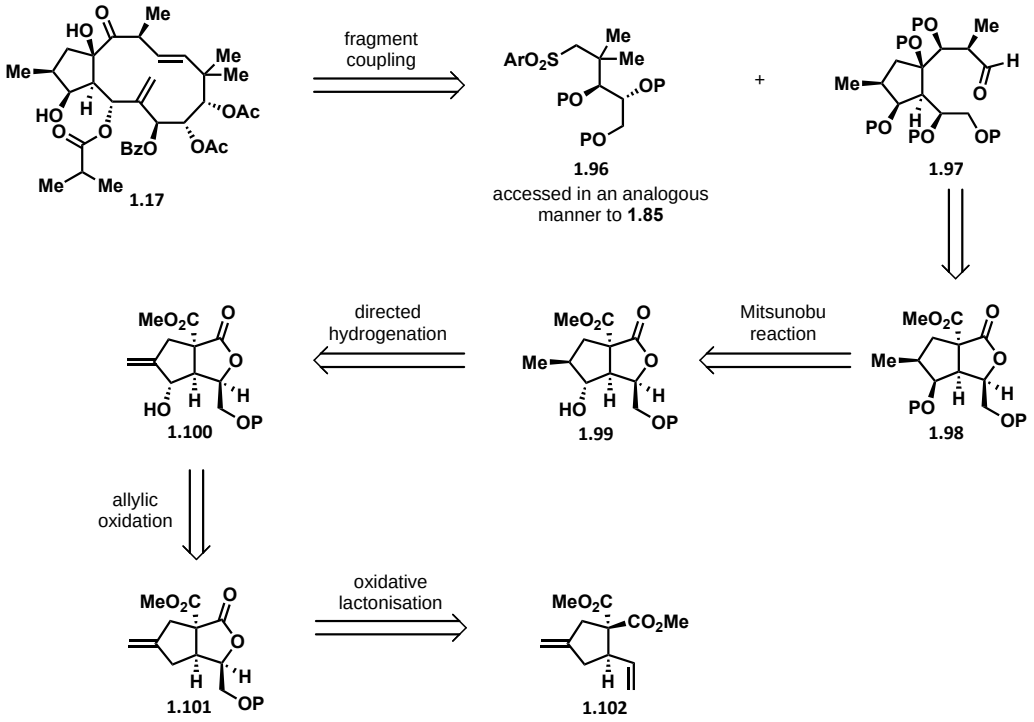


Scheme 1.12: Dr Erin Shepherd's synthesis of eastern fragment **1.85**.

Although the Nozaki-Hiyama-Kishi macrocyclisation reaction proved unsuccessful, this route presented a successful strategy for accessing the cyclopentane core of the jatrophanes. The primary drawback of this approach was the low yield of the enzymatic resolution step, which made it difficult to generate a large amount of material. As such, a new route was planned.

1.5.2 Retrosynthesis used in this project

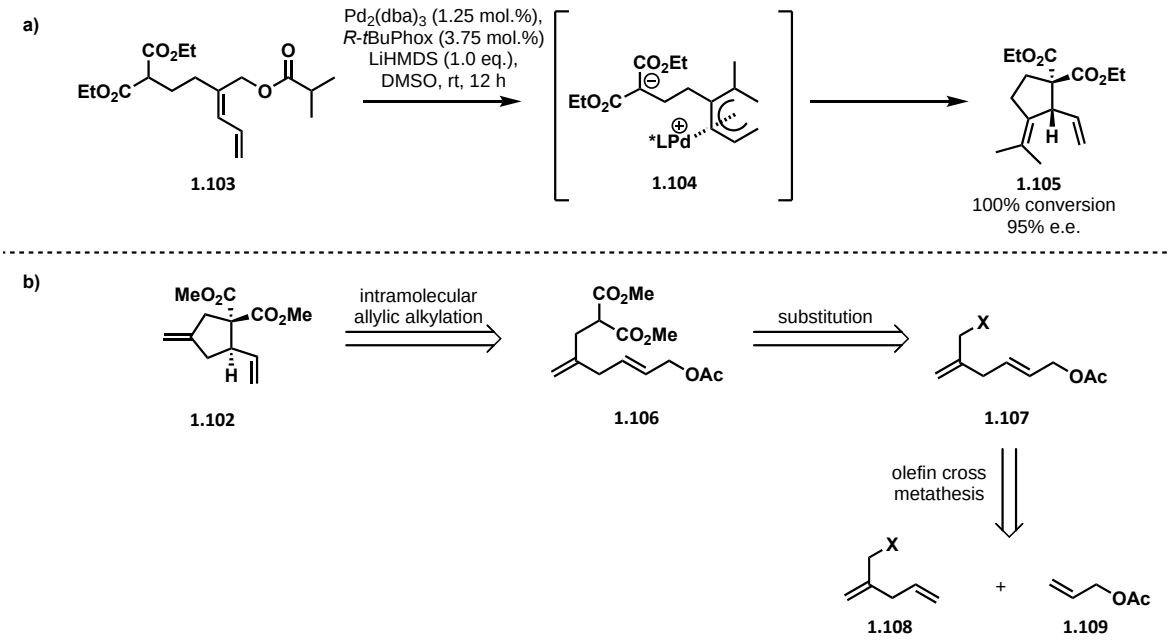
The second generation route aimed for euphodendroidin D **1.17**, as it presented a slightly more manageable target from a protecting group strategy perspective. This route was the focus of the postdoctoral research of Dr Bruno Sousa (Scheme 1.13) and this thesis, the same retrosynthetic approach was adopted as above, with one significant alteration. Given the lack of success experienced in the attempted Nozaki-Hiyama-Kishi cyclisation of **1.87** above, the positions of the aldehyde and vinyl iodide were reversed to give **1.96** and **1.97** as coupling partners. Although this modification simplifies the construction of the eastern fragment **1.96** (discussed in Chapter 5), it places a greater burden of complexity on the synthesis of western fragment **1.97**, which is now equipped with an extra stereocentre. This fragment is reduced back to cyclopentane-fused lactone **1.98** *via* an analogous set of transformations as used by Dr Shepherd. The two strategies diverge in a backwards sense here; in the second generation, the C1 stereocentre is achieved through the inversion of alcohol **1.99** using a Mitsunobu reaction; the *exo*-alcohol is used to direct a hydrogenation reaction to the *exo*- face of the oxabicyclo-[3.3.0]-octane scaffold using Crabtree's methodology,[66] retrosynthetically yielding allylic



Scheme 1.13: Second generation Burton group route towards the jatrophanes, with euphodendroidin D **1.17** as a target.

alcohol **1.100**. This will be the product of an allylic oxidation reaction on **1.101**; the cyclopentane-fused lactone will be accessed *via* the stereoselective oxidative functionalisation of diene **1.102**.

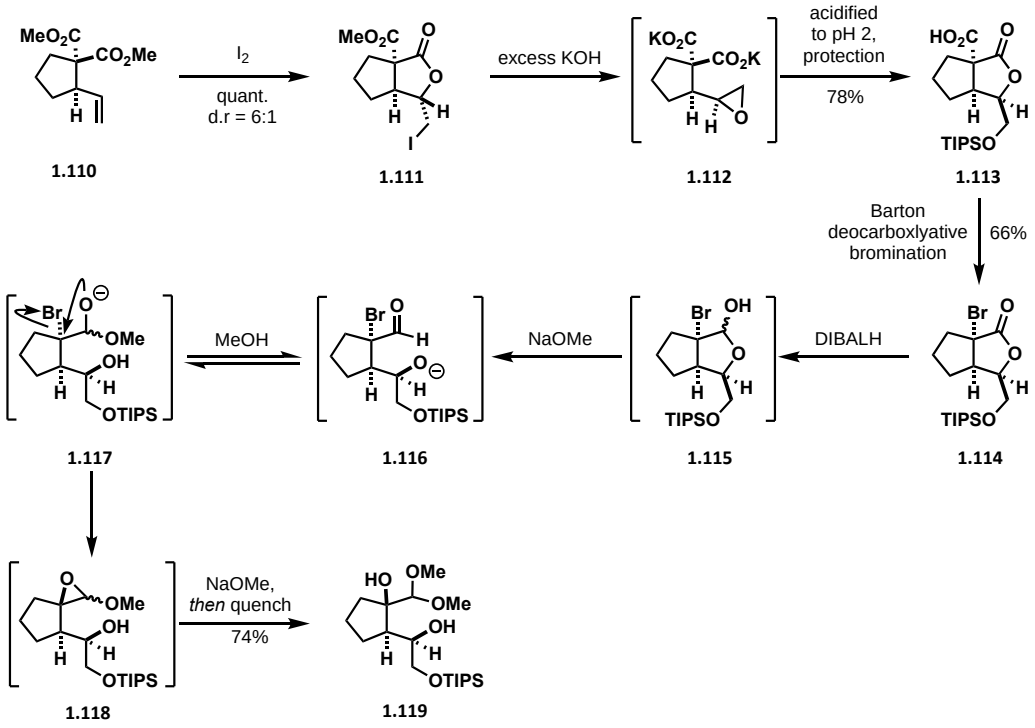
Taking inspiration from the work of Ready *et al*.[67] on the synthesis of nigellamine A2, the five-membered ring was to be accessed through the enantioselective transition-metal catalysed allylic substitution reaction of **1.106** (Scheme 1.14). The malonate group will be installed *via* a nucleophilic substitution of **1.107**, and a cross-metathesis of the internal alkene gives **1.108** and **1.109** in a retrosynthetic sense.



Scheme 1.14: a) Ready's asymmetric cyclopentane synthesis. **b)** Applicability of Ready's chemistry to the synthesis of **1.102** and continued retrosynthesis.

1.5.3 Model system research by Dr Bruno Sousa

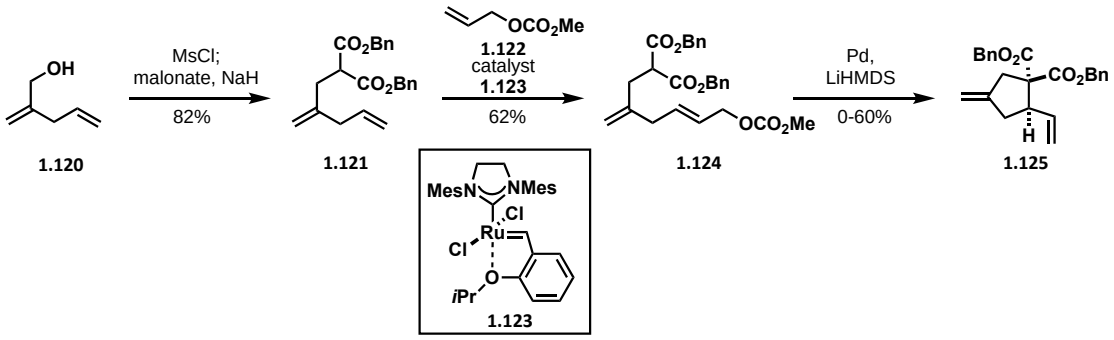
During his postdoctoral tenure in the Burton group, the jatrophane total synthesis project was continued by Dr Bruno Sousa.[68] He began by synthesising the model substrate **1.110** (Scheme 1.15). On this system, he developed an elegant sequence to obtain the desired *endo*- stereochemistry required in the oxymethyl substituent in **1.101**. An iodolactonisation gave predominantly the *exo*-iodomethyl species **1.111**; basic hydrolysis followed by acidification gave acid **1.113** *via* dicarboxylate **1.112**, where an S_N2-type opening of the epoxide in aqueous acid led to a net inversion of the stereochemistry at the lactone γ-carbon. Subsequent protection and brominative decarboxylation allowed Dr Sousa to test the reduction of the α-bromolactone **1.114**. This reaction is believed to proceed *via* the formation of lactol **1.115** through the initial reduction; quenching with sodium methoxide initially leads to aldehyde **1.116**, which reacts with a further equivalent of methanol to give acetalate **1.117**. A 3-*exo*-tet cyclisation then gives oxirane acetal **1.118**, which can be opened by a further equivalent of methoxide to give **1.119** after work-up. The inversion of the α-carbon, installation of the hydroxyl group, and delivery of a protected aldehyde are all synthetic



Scheme 1.15: Work undertaken by Dr Bruno Sousa on the synthesis of simplified jatrophane core **1.119**.

advantages to this highly efficient transformation. The relative configuration of **1.119** was confirmed through single-crystal X-ray analysis.

In addition to the work on this model system, Dr Sousa and a subsequent student, Niamh Jimenez, began work on the 'true' system for the route outlined above.[69] Their work is shown below (Scheme 1.16). Alcohol **1.120** was converted to substituted malonate **1.121** *via* mesylation and substitution; an olefin cross metathesis with allyl methyl carbonate **1.122** then gave cyclisation precursor **1.124**. Various conditions for the intramolecular transition metal-catalysed allylic alkylation were then explored, with yields of **1.125** as high as 60% obtained.



Scheme 1.16: Work undertaken by Dr Bruno Sousa and Niamh Jimenez towards the synthesis of a jatrophane core.

1.6 Objectives of the project

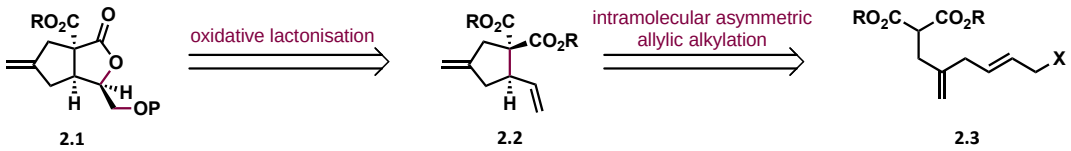
Given the context provided above, the objectives of the project described in this thesis at the outset were as follows:

1. To consolidate the results in Scheme 1.16 to deliver a high-yielding and scalable route to cyclopentanes **1.102** or **1.125**, and to render the transition metal-catalysed intramolecular allylic alkylation enantioselective through the use of a chiral ligand.
2. To apply the chemistry established by Dr Sousa and shown in Scheme 1.15 to the synthesis of lactone **1.97**.
3. To continue with the synthesis of the jatrophane diterpenes developed by Dr Shepherd and shown in Scheme 1.11 and Scheme 1.12.

Chapter 2: Synthesis of racemic lactone 2.50

2.1 Chapter introduction

The development of a robust and scalable synthetic route to key lactone intermediate **2.1** was the initial focus of the project. As detailed in Section 1.5.2, our strategy involved performing a stereoselective oxidative lactonisation sequence on vinylcyclopentane **2.2**; this decision was based upon the inviting possibility of an enantioselective synthesis of **2.2** through the use of a transition metal-catalysed asymmetric intramolecular allylic alkylation. As such, the project required the synthesis of acyclic skipped diene **2.3** as a starting point (Scheme 2.1). This chapter will cover our attempts to synthesise **2.1** through this approach in the racemic sense.



2.1 **2.2** **2.3**

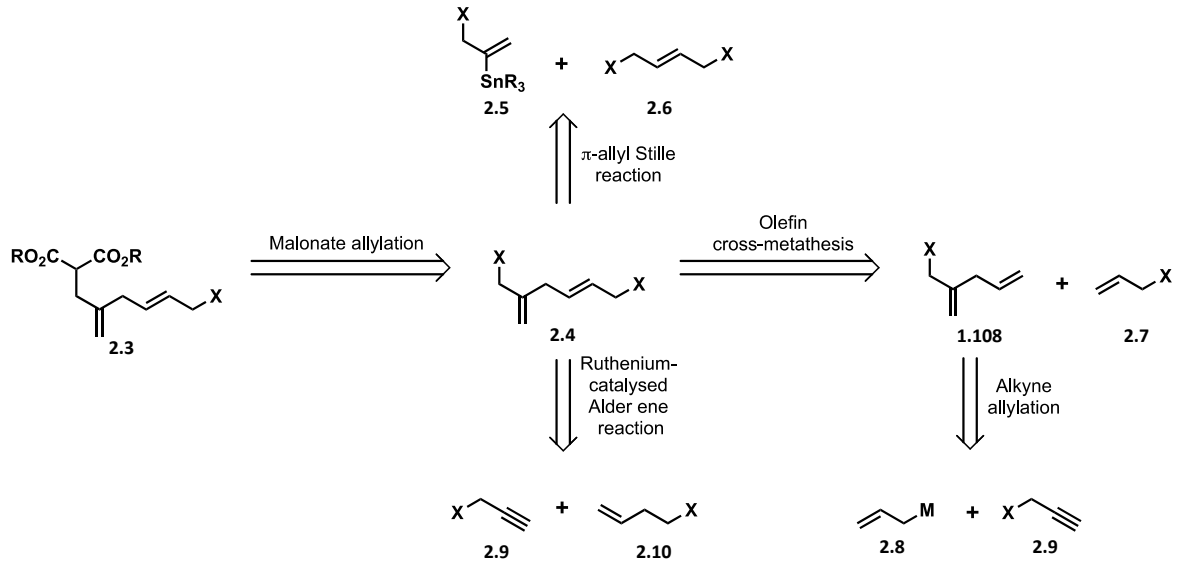
Scheme 2.1: General Strategy for accessing **2.1** from **2.3** *via* **2.2**.

2.2 Synthesis of racemic compound 1.125

2.2.1 Skipped diene synthesis

Skipped dienes, or 1,4-dienes, are less commonly discussed in synthetic chemistry relative to their conjugated counterparts; in 2021 they were the topic of two review articles, one of which describes the prior literature coverage of skipped dienes as 'scant'.[70, 71] The motif occurs in several natural product classes, with examples found amongst alkaloids, terpenes, polyketides, and fatty acids; as such, the synthetic chemistry community has developed several robust techniques for their synthesis, which are covered in the reviews cited above. Our target was relatively uncomplicated; the only stereochemical element found in **2.3** is double bond geometry, which would be ablated upon

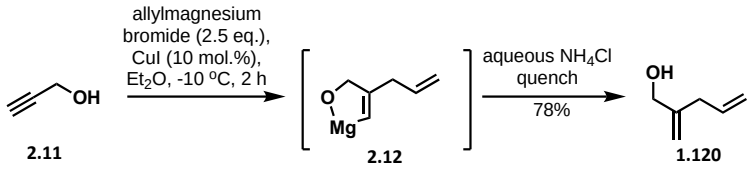
formation of a transition metal π-allyl complex. As such, only a few of the simpler strategies for skipped diene synthesis were considered; these are summarised in Scheme 2.2.



Scheme 2.2: Prospective synthetic approaches to skipped diene **2.3**.

Given the alternatives, the use of toxic organotin reagents required by the π-allyl Stille reaction[72] was unappealing as a starting point for our synthesis. Of the remaining choices, both of which required the use of similarly expensive ruthenium catalysts, alkyne allylation followed by olefin cross-metathesis seemed a more robust and well-precedented approach than the ruthenium-catalysed Alder-ene reaction,[73] and thus was the strategy we pursued.

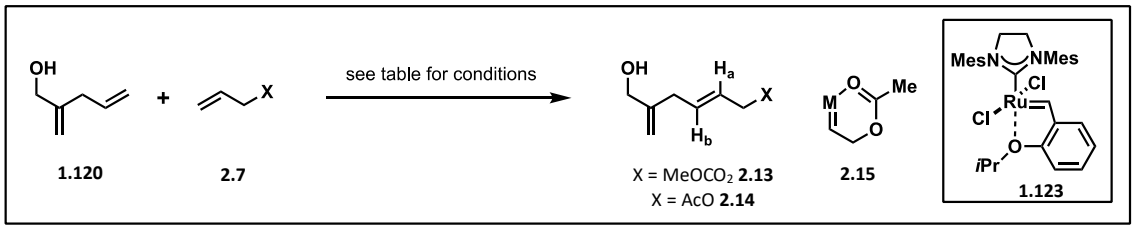
Following the precedent of Duboudin and Josseaume,[74] propargyl alcohol **2.11** was treated with allylmagnesium bromide in the presence of copper(I) iodide followed by aqueous work-up to give **1.120** (Scheme 2.3). This procedure proved to be reliably high-yielding at all scales on which it was conducted. The crude organic extract obtained from this reaction could be concentrated to an approximately 75% (by weight) solution of **1.120** in diethyl ether and used directly in the subsequent reaction; however, prolonged storage of this solution in the freezer resulted in the development of a yellow colouration, acrid odour, and a range peaks in the ^{1}H NMR spectrum attributed to decomposition products. As such, on large scale it was more convenient to distil the product.



Scheme 2.3: Preparation of **1.120** *via* alkyne organocupration following the precedent of Duboudin and Josseaume.

Our next task was to convert the terminal alkene into an allylic electrophile such that we could generate a transition metal π-allyl complex in the planned intramolecular asymmetric allylic alkylation. Olefin cross-metathesis conditions[75] for the coupling of **1.120** with allyl methyl carbonate **1.122** had been previously found to be unsuccessful by Niamh Jimenez during her time in the Burton group;[69] as such, we chose to employ the alternative, commercially available coupling partner allyl acetate **1.109**. The results of this investigation are summarised in Table 2.1. A large excess (10.0 equivalents) of metathesis partner was maintained, as the reaction we sought to achieve is a Type I/Type I cross-metathesis as defined by Grubbs and co-workers,[76] and thus yields a statistical mixture of products; under the conditions trialled, no homodimerisation of **1.120** was observed. It was found that allyl acetate **1.109** was a more tractable cross-metathesis partner than allyl methyl carbonate **1.122** at reduced (1.5 mol.%) catalyst loadings, giving good yields of **2.14** (entries 1 and 2). We considered whether the formation of a chelate **2.15** might impede the rate of catalyst turnover relative to the rate of catalyst decomposition, and result in lower yields. Iodide-containing and oxophilic additives were screened as additives to explore whether additional stabilisation of the catalyst or disruption of a ruthenium chelate would increase the yield based upon the results of Lipshutz[77] and Davis[78] respectively, but with no success (entries 3 and 4). Additionally, it was found that running the reaction at room temperature rather than reflux resulted in optimal yields (entry 5). Finally, it was discovered that running the reaction on scale and under nitrogen flow applied through a Schlenk manifold resulted in a marginal improvement in yield (entry 6).

Based on the observation that the product and the products of subsequent reaction would exhibit fluorescence under UV irradiation when this reaction was conducted on a large (30 mmol or greater)



Entry	X =	Catalyst loading (mol.%)	Additive	Temperature (°C)	Yield of product (%)
1[a]	$MeOCO_2$	15	-	40	-
2	AcO	1.5	-	40	53%
3	AcO	1.5	LiI	40	26%
4	AcO	1.5	$MgCl_2$	40	27%
5	AcO	1.5	-	20	72%
6[b]	AcO	1.5	-	20	77%

Table 2.1: Conditions screened for olefin cross-metathesis reaction. Reactions conditions were: 1.0 eq. **1.120**, 10.0 eq. coupling partner, Hoveyda-Grubbs II catalyst **1.123**, 0.1 M in **1.120** in dichloromethane under nitrogen, run until conversion stopped as assessed by TLC. [a] Result obtained by Niamh Jimenez. [b] Yield obtained at 40 mmol scale, reaction run under house nitrogen supplied through a Schlenk manifold rather than a balloon.

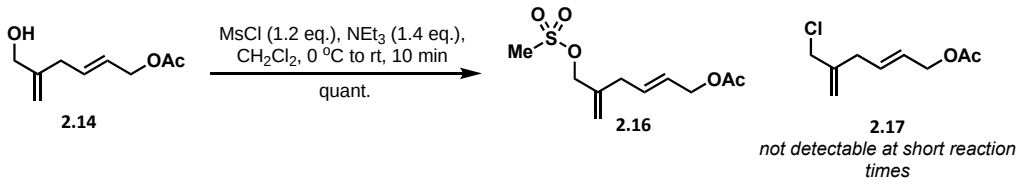
scale, we speculated that residual ruthenium contaminants in the product could persist even after dimethyl sulfoxide quenching followed by column chromatography; this contamination exerted a significant and deleterious effect on a later reaction (see Section 2.3.2). Several methods for the removal of residual ruthenium exist in the literature; in our case, the most practical was to apply the protocol developed by Kim.[79] As such, the product was treated with 20 mass equivalents of activated charcoal which resulted in the disappearance of UV activity after subsequent filtration through Celite™. Across all of the conditions shown above, the *E*/*Z* selectivity of this reaction was approximately 10:1, with the *E* isomer **(*E*)-2.14** as the major product. This assignment was made based on the coupling constants between protons H_a and H_b (J_{ab} = 15.3 Hz).

We had thus constructed the skipped diene unit of our cyclisation precursor **2.3** in a high-yielding and scalable two-step sequence using alkyne organocupration followed by cross-metathesis.

2.2.2 Malonate installation

Our next task was to install the malonate ester unit of **2.3** required to act as an internal nucleophile during the planned transition metal-catalysed intramolecular allylic alkylation. As such, we needed to activate the alcohol as a leaving group, and then perform an allylic S_N2 reaction.

We elected to convert **2.14** into a methanesulfonate (mesylate) ester **2.16** for practicality reasons: sulfonylation is an operationally straightforward and usually high-yielding procedure which yields by-products which are removable through a simple aqueous work-up. We opted to make the mesylate ester over the toluenesulfonate (tosylate) ester on the basis that the use of mesyl chloride generally results in significantly more rapid sulfonylation reaction than tosyl chloride, due to the accessibility of the sulfene pathway.[80] This rate difference has a bearing on the reaction outcome, as stereoelectronically activated alcohols such as allylic or benzylic substrates are known to form the corresponding chlorides under prolonged reaction times; this arises from nucleophilic attack by the chloride anion onto the initially generated allylic or benzylic sulfonate.[81] Indeed, when the sulfonylation reaction was run for longer than 15 minutes, a low polarity product (r.f = 0.70 in 20% ethyl acetate in pentane, not isolated, presumed to be **2.17**) could be seen to develop by TLC; quenching of the reaction after 10 minutes led to the quantitative formation of analytically pure **2.16** (Scheme 2.4).

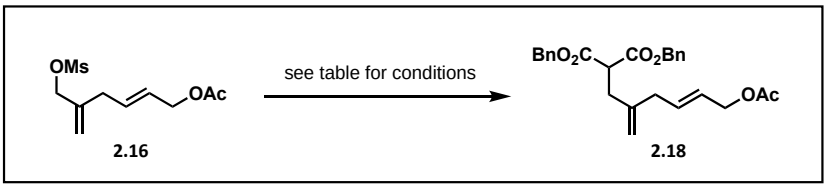


Scheme 2.4: Preparation of **2.16** *via* the mesylation of **2.14**.

Given that the next two steps in our route both featured a deprotonated malonate ester acting as a nucleophile, we aimed to develop a 'one-pot' reaction where a single set of reaction conditions would achieve two transformations. A deprotonated malonate ester would initially act as a nucleophile in an S_N2-type allylic substitution reaction, followed by a second deprotonation and subsequent cyclisation onto an electrophilic transition metal π-allyl complex. We thus sought to find S_N2 conditions which

would likely be compatible with a subsequent organometallic step. We chose a regime which would use a weak base as we felt that a mild set of reaction conditions was more likely to result in a successful cascade.

Based on the work of Itoh and co-workers,[82, 83] we explored phase-transfer conditions using dibenzyl malonate as the nucleophile. The results of this investigation are summarised in Table 2.2. Toluene proved an incompetent solvent for the reaction (entry 1); however, the tetrahydrofuran-potassium phosphate system immediately gave an excellent yield of **2.18** (entry 2). We validated the role of the tetrabutylammonium cation in tetrabutylammonium iodide (TBAI) as a phase-transfer catalyst for this reaction by showing that substituting it with potassium iodide led to a reduction in rate; however, even the inclusion of potassium iodide gave a significantly enhanced rate relative to a control, implicating the iodide anion as an additional catalyst for this reaction, presumably by performing an *in situ* Finkelstein reaction (entries 3 and 4).



2.16 **2.18**

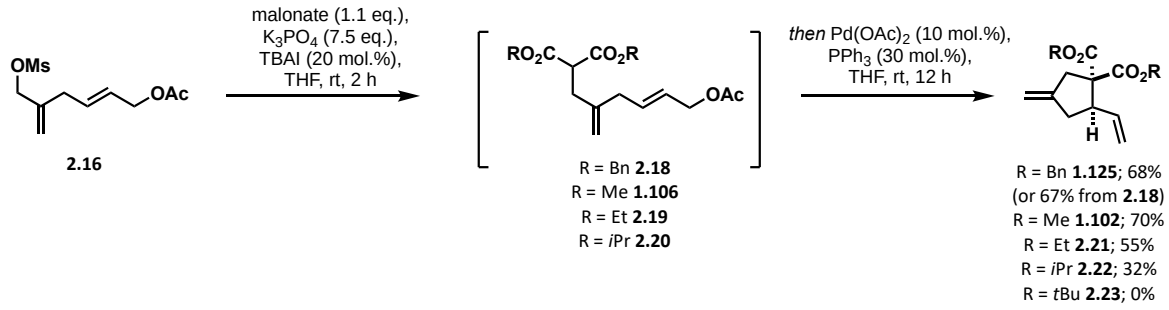
Entry	Solvent	Base	Additive	Ratio of 2.16:2.18 after two hours	Yield of product (%)
1[a]	PhMe	NaOAc, Cs_2CO_3, K_3PO_4	TBAI	-	trace[b] using K_3PO_4
2	THF	K_3PO_4	TBAI	Only **2.18** observed	67% (isolated)
3[c]	THF	K_3PO_4	KI	1:2	-
4[c]	THF	K_3PO_4	none	5:2	-

Table 2.2: Conditions screened for S_N2 reaction. Reactions conditions were: 1.0 eq. **2.16**, 1.1 eq. dibenzyl malonate, 10.0 eq. base, additive (20 mol.%), 0.5 M in **2.16**, room temperature. [a] Reactions were heated to reflux for 12 h. [b] **2.18** detected in the crude reaction mixture by LRMS. [c] Ratios determined by ^{1}H NMR spectroscopic analysis of the reaction mixture, products not isolated. No other products were observed.

2.2.3 Transition metal-catalysed intramolecular allylic alkylation

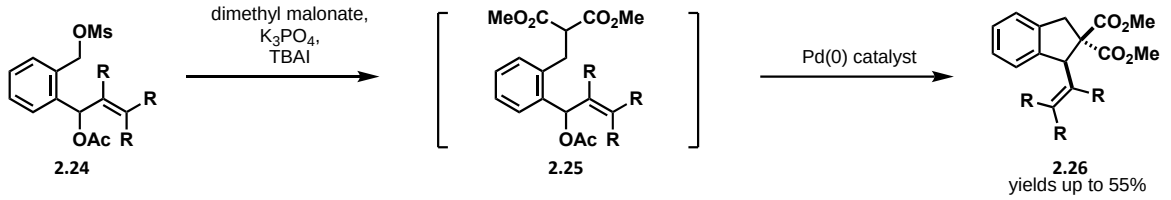
Having found conditions to form **2.18**, we sought to conduct the transition metal-catalysed intramolecular allylic alkylation to give **1.125**. Such allylic alkylation reactions are frequently found in the synthetic chemistry literature;[84] as discussed in the Section 1.5.2, we were confident that it would prove a relatively straightforward transformation to implement in our system. Indeed, under the same conditions that we had developed for the S_N2 reaction, the palladium(II) acetate-triphenylphosphine system accomplished this transformation in a good yield; we then confirmed that the entire sequence could be conducted in the same pot by simply adding the palladium catalyst as a solution in tetrahydrofuran after the consumption of **2.16** was observed by TLC, to ultimately give **1.125** in good yields. This reaction proved robust up to the 20 mmol scale, at which point slightly longer reaction times were required to achieve full conversion; this scale-dependence of the reaction rate might be attributed to the biphasic nature of the system.

Pleased with this result, we briefly investigated whether this process would work well with other malonate esters. It was found that the highest yield was obtained using dimethyl malonate, giving **1.102**; diethyl malonate and diisopropyl malonate gave **2.21** and **2.22** respectively in reduced yields, whilst the reaction with di-*tert*-butyl malonate failed to form any **2.23**. This reactivity trend is in accordance with what might be predicted based on steric considerations, as the formation of the cyclopentane product would lead to an increased degree of strain. These results are summarised in Scheme 2.5.



Scheme 2.5: Preparation of cyclopentanes *via* the transition metal-catalysed annulation of **2.18** and relatives.

The generality of this one-pot synthetic approach to five-membered rings was further explored by Maryn Brown, who applied it to the synthesis of indane diesters such as **2.26** from **2.24** *via* **2.25** during her Part II project in the Burton group (Scheme 2.6).[85]

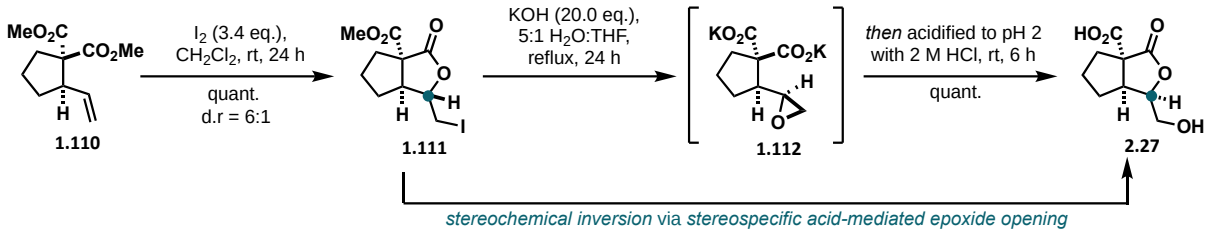


Scheme 2.6: Extension of the one-pot five-membered ring synthesis to indanes by Maryn Brown.

2.3 Synthesis of lactone 2.50

2.3.1 Strategy for the construction of 2.49

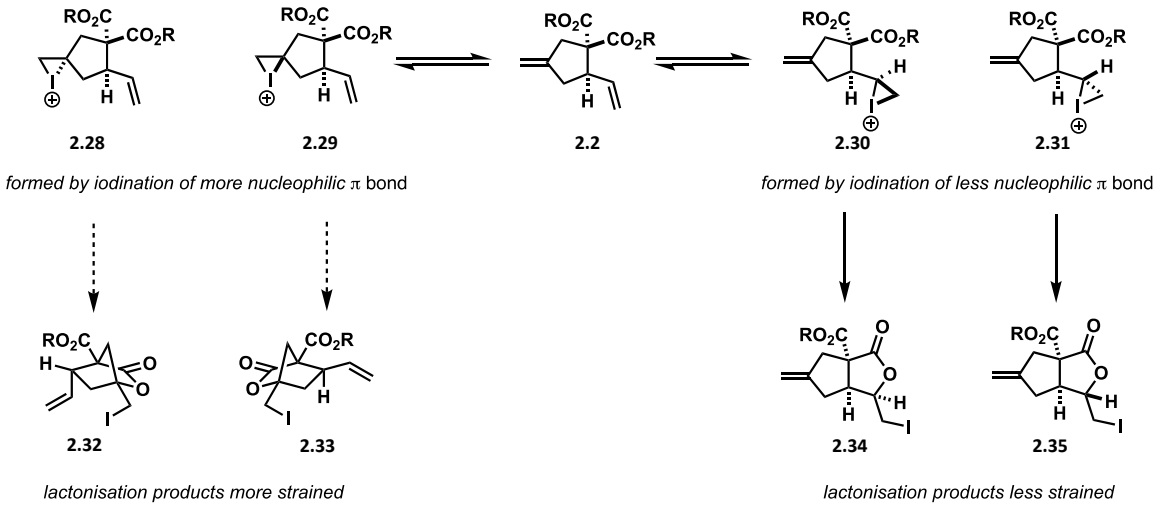
Having achieved the syntheses of cyclopentanes **1.125** and relatives, we elected to validate our route to lactone **2.1** on the racemic system. Accessing **2.1** from **1.125** entails a formal oxidation of the exocyclic vinyl group of the latter and presents two major challenges from a strategic perspective. Firstly, there is an issue of site-selectivity in functionalising a monosubstituted alkene in the presence of a presumably more reactive 1,1-disubstituted alkene. Secondly, there is an issue of diastereoselectivity, as the required lactone stereochemistry for the natural product would have the substituent occupying the more sterically congested *endo*- face of the oxabicyclo-[3.3.0]-octane ring system. In his work on the model system for this project, Dr Bruno Sousa had employed an iodolactonisation to selectively acquire the 'undesired' stereochemistry for the project (forming **1.111** from **1.110**), followed by a stereospecific hydrolysis-lactonisation sequence *via* an epoxide intermediate **1.112** to obtain the desired product **2.27** (Scheme 2.7). This sequence served as our starting point for reaching **2.1**.



Scheme 2.7: Dr Bruno Sousa's approach to **2.27** in his work on the model substrate.

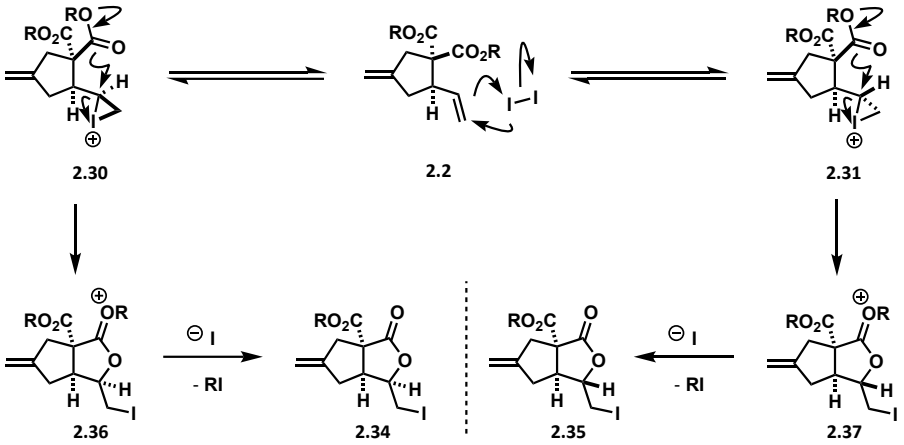
2.3.2 Selectivity considerations for iodolactonisation

Although this model substrate lacks the 1,1-disubstituted alkene which raises the question of site-selectivity for the real system, we reasoned that the likely mechanism for this reaction involved the initial reversible formation of iodonium ions **2.28-2.31**, followed by nucleophilic attack from the proximal *cis*- ester to give **2.32-2.35** (Scheme 2.8). Within this model, the functionalisation of the alkene occurs due to its proximity in space to the nucleophilic ester and the geometric ease of lactonisation rather than its intrinsic electronically reactivity. As such, we deemed it plausible that the increase of strain in transforming iodonium ions **2.28**-**2.29** into **2.32-2.33** would be sufficient to address the site-selectivity issue. Thus, we chose to subject **1.125** to molecular iodine in the presence of a non-nucleophilic buffer; the iodide anion generated *in situ* would serve as a nucleophile to quench the oxocarbenium ion intermediates **2.36**-**2.37** (Scheme 2.9).



Scheme 2.8: Reversibility of halonium ion formation addresses potential site-selectivity issues.

Within this mechanistic paradigm, the new stereocentre is formed during the initial iodination of the reacting alkene to form **2.30-2.31**. Given the reversibility of this step, the diastereoselectivity would be a function of both the forward and reverse rates of iodonium ion formation and the rate of lactonisation for each of the diastereomeric series (i.e. a Curtin-Hammett scenario). As the initial iodonium formation is likely to be facially unselective, the diastereoselectivity would likely predominantly be controlled by the kinetics of the lactonisation step to give **2.36** and **2.37**.

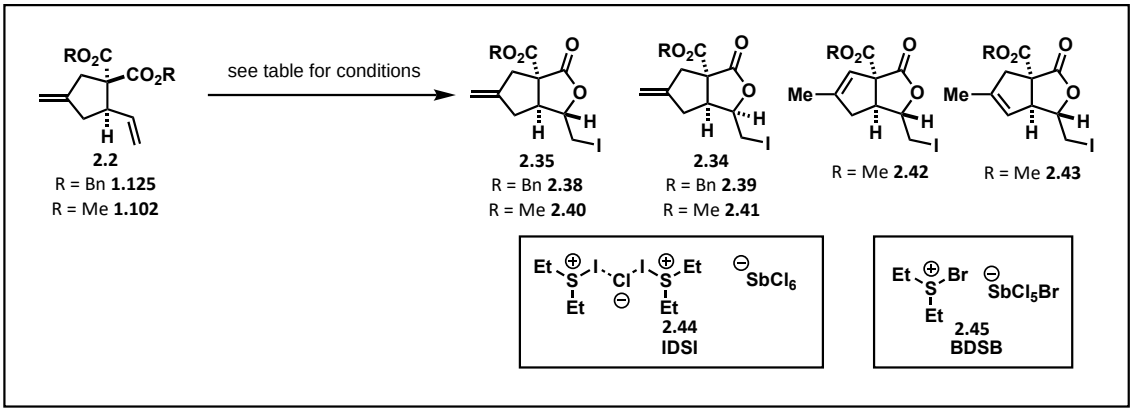


Scheme 2.9: Putative mechanism for iodolactonisation of **2.2** to form **2.34** and **2.35**.

2.3.3 Conditions for iodolactonisation

A summary of the results of our efforts to optimise this transformation are given in Table 2.3. Disappointingly, the dibenzyl substrate **1.125** gave the lactones **2.38** and **2.39** in a poor diastereomeric ratio (entry 1), surprisingly with the *endo*-iodomethyl isomer **2.39** dominating. This result was consistent across all solvents tried (with the exception of acetone, in which the reaction failed; entries 2-6); this is perhaps unsurprising, given that the diastereoselectivity is likely controlled by a step which transitions between two intermediates with the same charge, as discussed in Section 2.3.2. The low diastereoselectivity can be attributed to rapid kinetic trapping of the nucleophilic benzyl ester by either of the iodonium ions; the slight predominance of **2.39** has not been explored. Considering the 6:1 diastereomeric ratio obtained for the (dimethyl) model system **1.111**, and reasoning that the use of a system with a less nucleophilic ester might lead to greater discrimination between the two

diastereomeric products, **1.102** was trialled. The dimethyl substrate required longer reaction times and gave significantly improved diastereomeric ratio; however the use of this system introduced double bond migration of the exocyclic alkene as an unforeseen problem, giving rise to **2.42** and **2.43** in varying degrees (entry 7). **2.42** tended to predominate over **2.40** and **2.43** in these mixtures, and on several occasions was the only isolable product; this would be expected on a thermodynamic basis, as **2.42** features the more substituted alkene in the position in which the eclipsing interactions of the adjacent quaternary carbon atom are minimised. Iodine is a known reagent for inducing double bond migration; however such transformations usually require harsher conditions than those found here (e.g. in benzene at reflux).[86, 87] This unwanted reactivity presented a challenging problem to solve, as the system exhibited a strong degree of irreproducibility on a batch-to-batch basis. At length, it was discovered that the two variables which controlled the degree of isomerisation were dilution and trace ruthenium residues from the previous cross-metathesis reaction (see Section 2.2.1). Conducting the reaction at a 0.025 molar concentration with respect to starting material and the use of appropriately purified starting material led to the disappearance of **2.42** and **2.43** as side products (entry 8). Although both the presence of a small amount of solid iodine and the presence of trace quantities of a transition metal are not unreasonable as factors which might cause double bond migration under these conditions, the exact mechanistic nature of this side reaction and the reasons why it occurs with the dimethyl system **1.102** and not the dibenzyl system **1.125** remain unclear. Other halolactonisation reagents were also trialled: bromodiethylsulfonium bromopentachloroantimonate (BDSB) **2.45**[88] (entry 9) and molecular bromine (entry 10) gave complex mixtures of products, and iododiethylsulfonium iodopentachloroantimonate (IDSI) **2.44**[88] (entry 11) gave yields comparable to molecular iodine. Thus, with the issues above solved, iodolactonisation proved to be a synthetically tractable approach to generating **2.40** from **1.102**.



Entry	Substrate	Oxidant (equivalents)	Solvent	Result[a]
1	**1.125**	I_2 (2.0)	CH_2Cl_2	80% yield **2.39** + **2.38**, 3:2 d.r
2	**1.125**	I_2 (2.0)	3:1 CH_2Cl_2:H_2O	63% yield **2.39** + **2.38**, 3:2 d.r
3	**1.125**	I_2 (2.0)	3:1 $CHCl_3$:H_2O	59% yield **2.39** + **2.38**, 3:2 d.r
4	**1.125**	I_2 (2.0)	Et_2O	47% yield **2.39** + **2.38**, 3:2 d.r
5	**1.125**	I_2 (2.0)	acetone	trace conversion
6	**1.125**	I_2 (2.0)	THF	40% yield **2.39** + **2.38**, 6:5 d.r
7	**1.102**	I_2 (2.0)	CH_2Cl_2	25-68% yield **2.40**, 6:1 d.r, variable formation of **2.42** and **2.43**
8[b]	**1.102**	I_2 (4.0)	CH_2Cl_2	77% yield **2.40**, 6:1 d.r
9	**1.102**	**2.45**	CH_2Cl_2	complex mixture of products[c]
10	**1.102**	Br_2 (2.0)	CH_2Cl_2	complex mixture of products[c]
11	**1.102**	**2.44**	CH_2Cl_2	72% yield **2.40**, 6:1 d.r

Table 2.3: Conditions screened for iodolactonisation reaction. Reactions conditions were: 1.0 eq. alkene, oxidant, 0.1 M in alkene, room temperature. [a] Sets of diastereomers were chromatographically inseparable; product ratios determined by ^{1}H NMR spectroscopy. [b] Reaction run at 0.025 M in substrate. Substrate batch had been treated with activated charcoal as described by Kim.[77] [c] Many species visible by TLC, many olefinic species visible in the ^{1}H NMR spectrum of the crude reaction mixture.

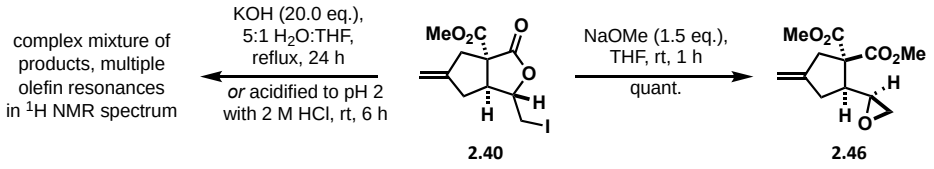
The exclusive generation of *cis*-fused lactone products was assumed based upon the extensive precedent in the chemical literature on bicyclo-[3.3.0]-octane ring systems,[89] as well as precedent within the Jonathan Burton group. Aside from this, the relative configuration of the lactones **2.38**, **2.39**, and **2.40** were assigned based on the ^{1}H NMR resonances of the epimeric lactone proton; **2.41** was never isolated. Previous projects in the Jonathan Burton group dealing with substituted cyclopentane-fused lactones of this kind have shown that this diagnostic resonance reliably occurs approximately 0.4-0.6 ppm lower in the H-*endo* epimer (e.g **2.38**) than in the H-*exo* epimer (**2.39**).[55] This is a result which is in keeping across all relevant compounds synthesised in this project. Moreover, a ^{1}H NMR NOESY experiment performed on the double-bond isomerisation product **2.42**, shown to be the product of resubjecting **2.40** to iodine, gives further evidence to this assignment (Scheme 2.10). A reciprocal NOE correlation with the bridgehead proton enabled the assignment of the *exo*- disposed methylene proton. The *endo*- disposed methylene proton exhibited a reciprocal NOE correlation with the lactone alkyl proton, indicating that this proton was also on the *endo*- face of the bicycle. A reciprocal NOE correlation between the bridgehead proton and the protons of the iodomethyl group cemented this assignment. This assignment is in keeping with all other observations and theory covered in this thesis.

Scheme 2.10: Selected ^{1}H NOESY correlations used in the stereochemical assignment of **2.42**.

2.3.4 Epoxide formation *via* basic solvolysis

As discussed in Section 2.3.1 and shown in Scheme 2.7, the sequential treatment of model substrate **1.111** with aqueous sodium hydroxide at reflux and aqueous hydrochloric acid had given **2.27** in quantitative yields, presumably *via* epoxide **1.112**. We now subjected **2.40** to these conditions in the hope of achieving the analogous transformation. Disappointingly, this sequence led to a complex mixture of products, with multiple resonances visible in the olefin region of the ^{1}H NMR spectrum. Subsequent experiments showed that both the basic and the acidic steps of this protocol led to this undesirable outcome; given the proclivity for isomerisation exhibited by the exocyclic alkene under various conditions trialled for iodolactonisation (Section 2.3.3), this is perhaps an unsurprising result. Thus we endeavoured to develop a strategy which would use more mild conditions to achieve the same result.

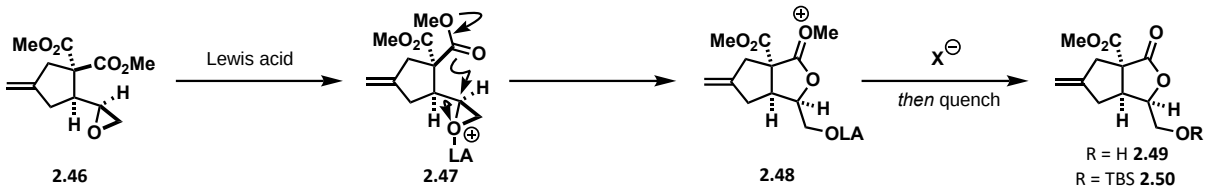
We reasoned that the need for aggressive conditions required for the base-mediated step arises from the need to generate a proximal dianion under the reaction conditions; as such, the cleavage of the lactone to generate a non-acidic functional group, would be achievable with mild reagents. Thus **2.40** was treated with sodium methoxide in tetrahydrofuran; pleasingly, this led to the quantitative formation of epoxide **2.46** in one hour, with no double bond migration observed (Scheme 2.11).



Scheme 2.11: Epoxide formation from lactone **2.40** under mild conditions

It was now necessary to open the newly-formed epoxide **2.46** with the *cis*- methyl ester. This is a transformation analogous to that seen in the iodolactonisation discussed in Section 2.3.3, and requires a reagent system that meets two criteria: there must be a Lewis acidic component to effect the initial cyclisation, as epoxides are significantly less electrophilic than iodonium ions (**2.46** was found to be

stable at room temperature), and there must be a nucleophilic component present to quench the oxocarbenium ion intermediate **2.48** *via* dealkylation (Scheme 2.12).



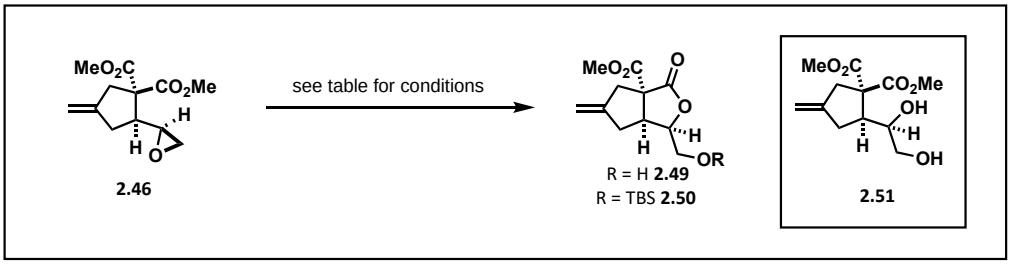
Scheme 2.12: Mechanistic considerations for the intramolecular opening of epoxide **2.46**

Initially we planned to open the epoxide using a silyl triflate as a Lewis acid with a sterically hindered base to buffer the reaction and quench **2.48**; this would deliver the protected product **2.50**, thereby avoiding an additional protection step. This strategy proved somewhat effective, but suffered from reproducibility issues (Table 2.4, entry 1). Equimolar quantities of silyl triflate and 2,6-lutidine would accomplish the desired transformation in yields as high as 82%; however, due to the lability of silyl triflates to hydrolysis, this was only practical when using a reasonably fresh bottle of the reagent. An excess of 2,6-lutidine over silyl triflate shut down reactivity; this effect might be attributed to a catalytic role served by a trace amount of triflic acid. An excess of silyl triflate over 2,6-lutidine led to extensive decomposition to a complex mixture of products, with multiple resonances visible in the olefin region of the ^{1}H NMR spectrum. As such, we sought a more practical protocol which would accomplish the desired lactonisation and protection steps in a sequential manner.

Epoxide **2.46** was thus exposed to various Lewis and Brønsted acids. Most of the reagents screened proved ineffective, leading either to no consumption of **2.46** or decomposition (entries 2-7). Tin(IV) chloride in dichloromethane succeeded in achieving the desired transformation in a good yield (entry 8);[90] however, when the reaction was performed on a larger scale (greater than 10 mmol), purification of the product was complicated by the large quantity of tin(IV) oxide generated in the aqueous work-up. As such, a more practical alternative was sought. It was found that iron(III) chloride could effect the transformation in a superior yield to that offered by tin(IV) chloride (entry 9); moreover, the iron(III) oxide precipitated from the reaction following a basic quench proved a far more tractable by-

product to remove than tin(IV) oxide. We reasoned that the role of the iron(III) unit in this process is essentially catalytic, whereas a full equivalent of the chloride anion is required (to demethylate the intermediate **2.48**). In line with this reasoning, we found that lowering the loading of iron(III) chloride to 0.35 equivalents led to full conversion, whereas a loading of 0.3 equivalents or less led to incomplete conversion (entry 10). This was a further advantage over the tin(IV)-mediated protocol, which required two stoichiometric equivalents of metal chloride for the reaction to reach full conversion. To the best of our knowledge, our use of iron(III) chloride for this transformation is unprecedented in the literature.

It should be noted that, in cases where the metal chloride was partially hydrated due to the use of old reagent, some amount of hydrolysis product **2.51** could be detected by TLC and LRMS (ESI^+ peak at 281.1 = $[M+Na]^+$) analysis of the crude reaction product. Although this side-product cyclised to the desired **2.49** on silica, it was found that column chromatography could be avoided by simply treating the crude product of the reaction with 10 mol.% *para*-toluenesulfonic acid in methanol. Moreover, when using the iron(III) chloride protocol, it was found that the addition of 0.1 solvent volumes of methanol directly to the completed reaction would achieve the same outcome, presumably by liberating a small amount of hydrochloric acid *via* methanolysis of the residual iron(III) chloride.



Entry	Reagents (equivalents)	Solvent	Result
1	TBSOTf (2.0), 2,6-lutidine (2.0)	CH_2Cl_2	Variable yield of **2.50**
2	AcOH (solvent)	-	No reaction
3	TsOH (0.1 eq.)	THF	No reaction
4	BF_3 (2.0)	CH_2Cl_2	Decomposition
5	BF_3 (2.0), NaI (2.0)	CH_2Cl_2	Decomposition
6	$Sc(OTf)_3$ (2.0)	CH_2Cl_2	No reaction
7	$MgBr_2{\bullet}Et_2O$ (2.0)	Et_2O	No reaction
8	$SnCl_4$ (2.0)	CH_2Cl_2	66% yield of **2.49**[a]
9[b]	$FeCl_3$ (2.0)	THF	72% yield of **2.49**
10[b]	$FeCl_3$ (0.35)	THF	72% yield of **2.49**

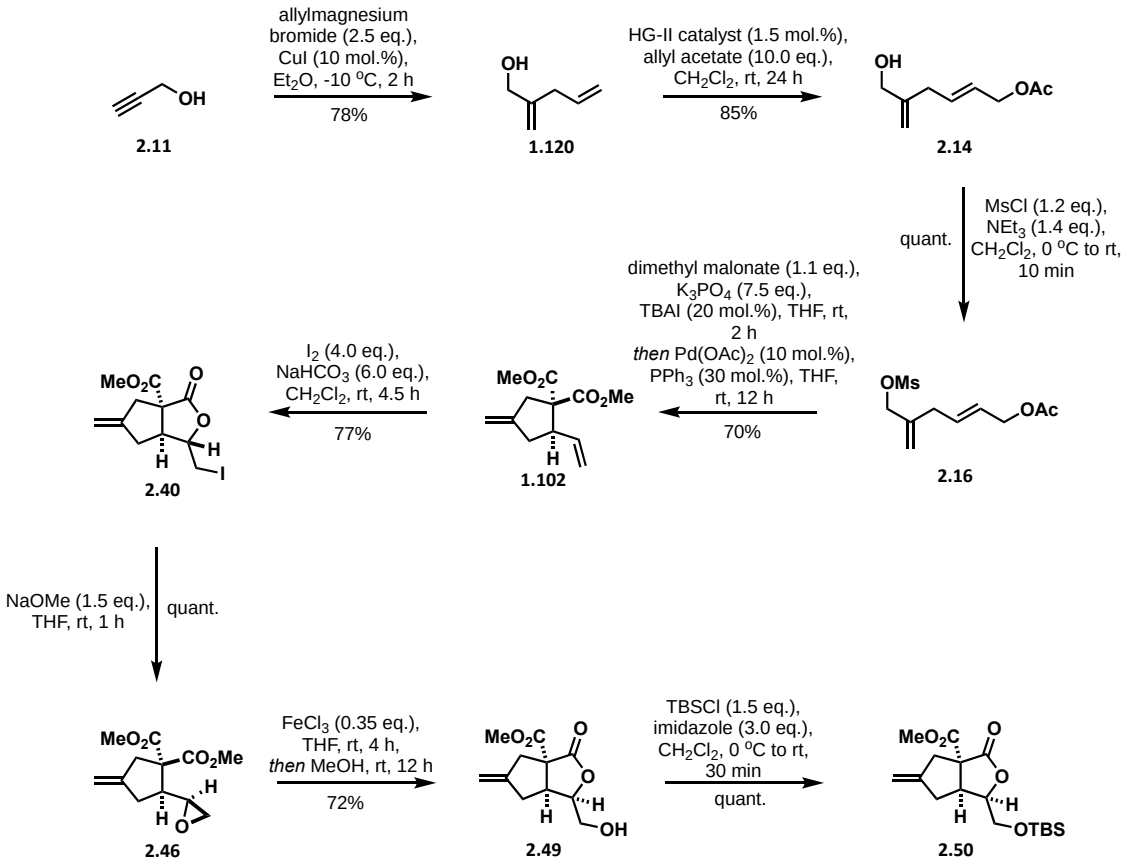
Table 2.4: Conditions screened for epoxide opening reaction. Reactions conditions were: 1.0 eq. epoxide, reagents, 0.1 M in alkene, room temperature. [a] Crude product stirred with TsOH in methanol (10 mol.%). [b] Methanol (0.1 volume equivalents with respect to solvent) added after full starting material consumption.

Lactone **2.49** was subsequently silylated under standard conditions to give **2.50**. A ^{1}H NMR NOESY experiment performed on this lactone enabled the confident assignment of the relative configuration. As before (Section 2.3.3), a reciprocal NOE correlation with the bridgehead proton enabled the assignment of the *exo*- disposed methylene proton as shown (Scheme 2.13). An additional reciprocal NOE correlation between the bridgehead proton and the lactone alkyl proton indicated the inversion of configuration at this site during the epoxide-formation epoxide-opening sequence described above; this assignment was further evidenced by a reciprocal NOE correlation between the *endo*- disposed methylene proton and the protons of the silyloxymethyl group as shown.

Scheme 2.13: Selected ^{1}H NOESY correlations used in the stereochemical assignment of **2.50**

2.4 Chapter Summary

We had completed our planned synthesis of racemic **2.50** in eight steps with a total yield of 26% (Scheme 2.14). This was achieved using a series of transition metal-catalysed transformations to form key carbon-carbon bonds, and the necessary relative configuration was accessed using a diastereoselective iodolactonisation followed by an innovative 3-*exo*-tet/epoxide opening sequence.

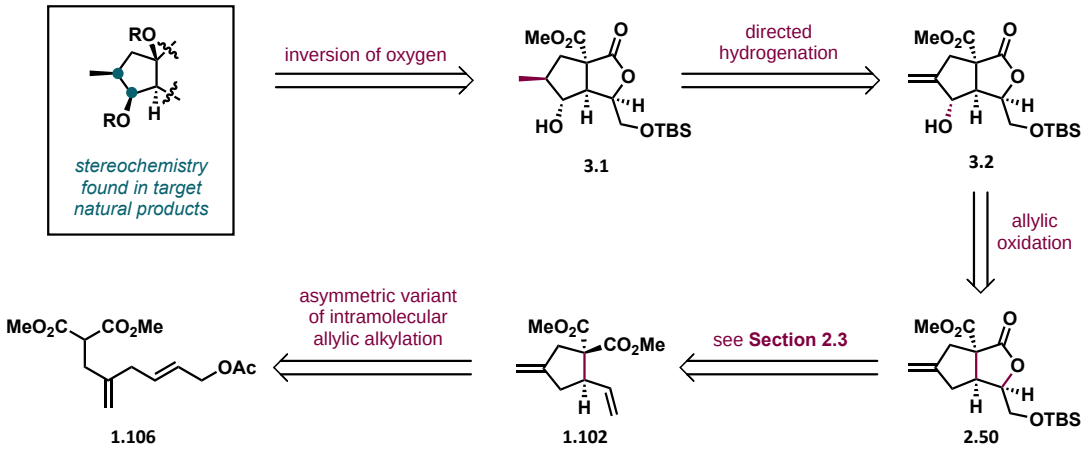


Scheme 2.14: Racemic synthesis of **2.50** in eight steps in a total yield of 26%.

Chapter 3: Asymmetric lactone synthesis and allylic oxidation

3.1 Chapter introduction

Having established a synthetic route to racemic lactone **2.50**, we were faced with two tasks: to develop our racemic route into an asymmetric one, and to conduct a sequence of redox manipulations on **2.50** to install the substituents and stereochemistry required by the natural product targets **1.17** and **1.18**. We intended to accomplish the former task through the use of a chiral palladium complex in our previously developed intramolecular allylic alkylation to form **1.125** (see Section 2.2.3). Our strategy for the latter task was to use a regio- and stereoselective allylic C-H oxidation to install an oxygen atom to give alcohol **3.2**, which would subsequently be used to direct a hydrogenation reaction onto the desired face of the exocyclic methylene group to attain **3.1** (Scheme 3.1). Following these transformations, we would be able to complete our synthesis of the targeted cyclopentane core of the jatrophane natural products. This chapter will cover our efforts towards these ends.

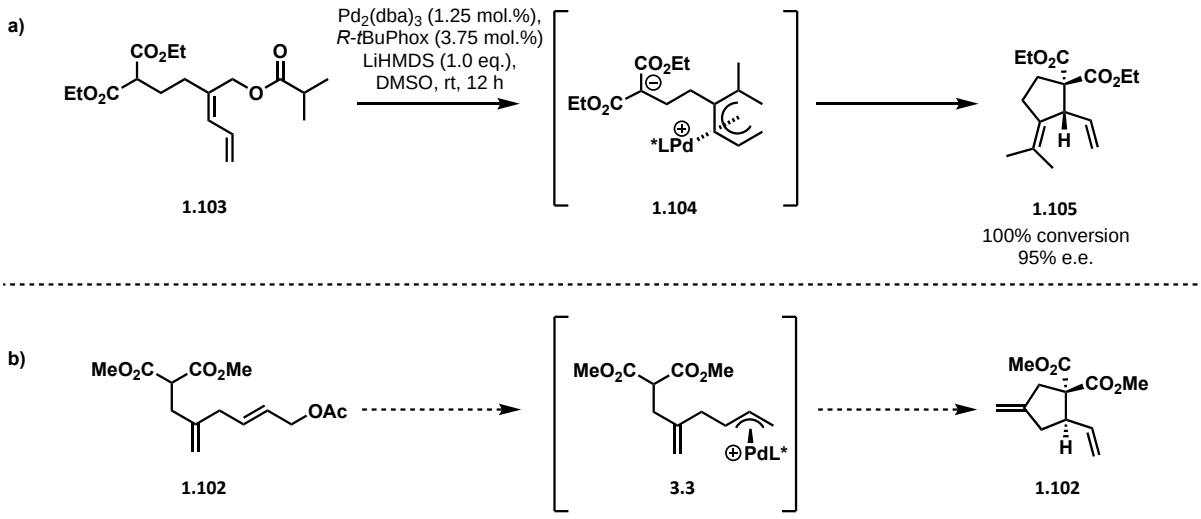


Scheme 3.1: Strategy for accessing the absolute and relative stereochemistry of the jatrophanes *via* asymmetric intramolecular allylic alkylation, allylic oxidation, and directed hydrogenation.

3.2 Asymmetric synthesis of 2.50

3.2.1 Asymmetric intramolecular allylic alkylation

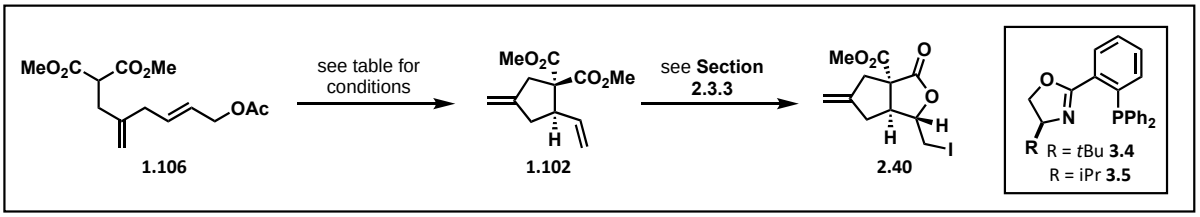
As discussed in Section 1.5.2, we intended to use an asymmetric intramolecular allylic alkylation as the tool with which to forge the transannular bond in **1.17** and **1.18**, and as the enantioinductive step in our synthesis. This choice was based on Ready and co-workers' use of such a reaction to construct an analogous system in their synthesis of nigellamine A2 (Scheme 3.2).[67]



Scheme 3.2: a) Ready and co-workers' asymmetric intramolecular allylic alkylation to make cyclopentane **1.105**. **b)** Our intended asymmetric intramolecular allylic alkylation to make cyclopentane **1.102**.

As such, malonate derivative **1.102** was subjected to conditions which might be expected to engender such a cyclisation, employing ligands from the Phox class used in Ready's system as well as many intermolecular examples in the literature.[91, 92] The results of this effort are summarised in Table 3.1. To our surprise, neither Ready's conditions nor a modified version of our original conditions resulted in any conversion whatsoever (entries 1 and 2). Our first exploration of the reaction parameters was to vary the palladium source, which proved somewhat instructive. Although $Pd(dba)_2$, $Pd_2(dba)_3$ (entries 3 and 4), and palladium(II) acetate all yielded no workable results, the combination of allylpalladium chloride dimer and ligand **3.4** elicited the desired reactivity and gave good conversion after 24 hours. This marked difference in catalytic capability can be attributed to ligand inhibition in

the instances where dibenzylidene acetone was present in the precatalyst,[93, 94] but has no obvious explanation in the case of palladium(II) acetate, which performed adequately in the racemic variant. Given the comparative apolarity of **1.102** and the absence of a strong UV chromophore, we elected to derivatise the product obtained from the asymmetric reaction to iodolactone **2.40** *via* the protocol described in Section 2.3.3 in order to facilitate HPLC analysis. Disappointingly, the enantiomeric ratio was found to be 5:3, corresponding to an enantiomeric excess of 25%. The use of the *tert*-butyl-substituted ligand, or Ready's solvent/base combination, failed to ameliorate this (entries 5 and 6).

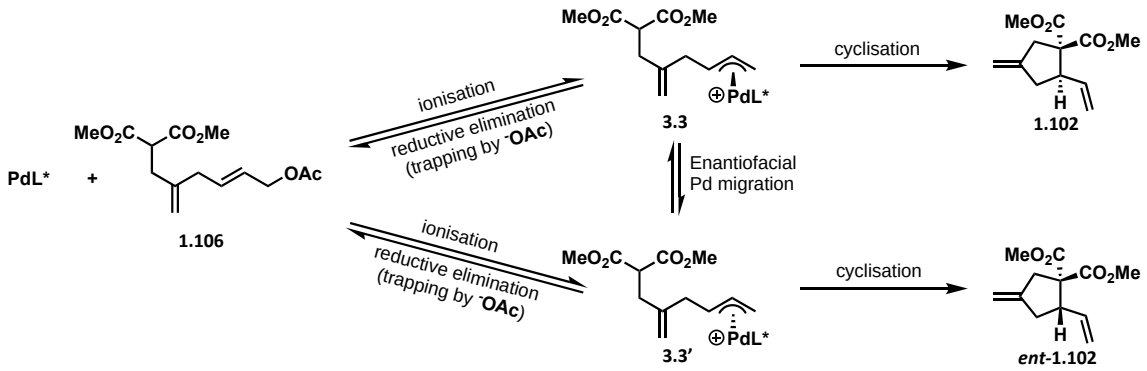


Entry	Ligand	Pd source	Base (equivalents)	Solvent	Result
1	***(R)*-3.4**	Pd_2dba_3	LiHMDS (1.0)	DMSO	No product observed
2	***(R)*-3.4**	$Pd(OAc)_2$	K_3PO_4 (7.5)	THF	Trace product observed
3	***(R)*-3.4**	Pd_2dba_3	K_3PO_4 (7.5)	THF	No product observed
4	***(R)*-3.4**	$Pd(dba)_2$	K_3PO_4 (7.5)	THF	No product observed
5	***(R)*-3.4**	$[(allyl)PdCl]_2$	K_3PO_4 (7.5)	THF	87% yield of **1.102**, e.r. = 8:9
6	***(S)*-3.5**	$[(allyl)PdCl]_2$	LiHMDS (1.0)	DMSO	62% yield of **1.102**, e.r. = 5:3

Table 3.1: Conditions screened for asymmetric intramolecular allylic alkylation. Reactions conditions were: 1.0 eq. **1.106**, Pd source (1.5 eq. Pd), ligand (2.3 eq.), base, rt, 24 h.

Given the time constraints faced at this stage of the project, the decision was taken to pursue an alternative strategy for enantioinduction. Before moving on to a discussion of that phase of the project, it is worthwhile to comment briefly upon the discrepancy between our experience and that of the Ready group.

An irreversible reaction performed under putatively asymmetric conditions which evinces little or no enantioselectivity has insufficient kinetic discrimination between the pathways leading to each of the enantiomers of the product. A simplified mechanism for the transformation, using our system as an example and with a focus on stereochemical aspects, is given below (Scheme 3.3).[84]



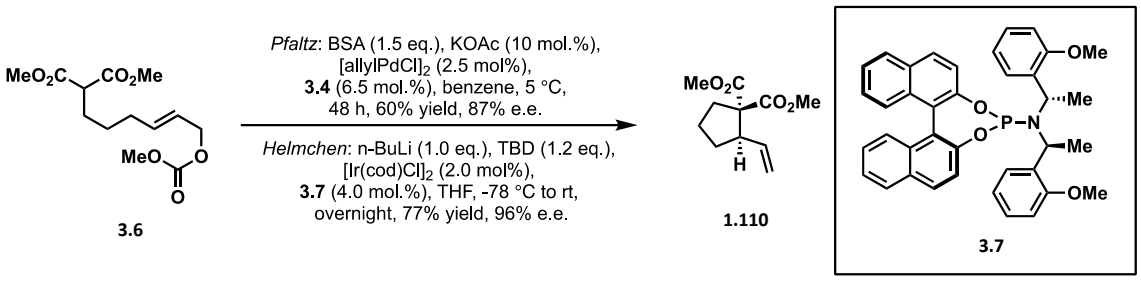
Scheme 3.3: Simplified mechanism for palladium-catalysed intramolecular allylic alkylation. Adapted from that presented by Trost and co-workers.[82]

There are three general cases where high selectivity for **1.102** would be found: i) equilibration between **3.3** and **3.3'** is slow relative to cyclisation, and **3.3** is formed preferentially in the initial ionisation step by enantiofacial discrimination of the catalyst; ii) equilibration between **3.3** and **3.3'** is rapid relative to cyclisation, and the rate of cyclisation is significantly higher in the top (as shown) series than in the bottom series; iii) equilibration between **3.3** and **3.3'** is rapid relative to cyclisation, and **3.3** predominates within that equilibrium such that **1.102** forms predominantly even if cyclisation rates are comparable in either series. Scenarios ii) and iii), or a combination thereof, would instantiate Curtin-Hammett-type kinetics.

The lack of enantioselectivity indicates that none of these scenarios are in operation in our system. An instructive case in the literature was published by Pfaltz and Koch in 1996;[91] when trying to accomplish a highly analogous transformation, they found that the choices of leaving group, base, and solvent all had significant implications for the reaction outcome, and from their observations they concluded that a low rate of cyclisation was the important factor to achieve (Scheme 3.4).

The implication of cyclisation rate as the key factor leading to the degree of enantioselectivity in such reactions indicates that these systems are governed the Curtin-Hammett principle, as terminal π-allyl complexes are known to equilibrate.[84] As the cyclisation in Ready's system interrupts the conjugation between two alkene units, which would impact the energetic favourability of such a process, this seems a cogent explanation of their results: cyclisation is slow relative to the equilibration between the two diastereomeric π-allyl complexes. Whether the major factor is the predominance of one π-allyl complex in that equilibrium, or the difference in cyclisation barrier height for the two diastereomeric π-allyl complexes is difficult to say in the absence of computational results. The ease of cyclisation in our system under the conditions trialled is a likely cause of poor enantioselectivity.

Pfaltz and Koch achieved a higher degree of enantioselectivity by using the methyl carbonate leaving group (the analogous acetate was unreactive in their protocol), bis-trimethylsilylacetamide (BSA) as a base with catalytic potassium acetate, and benzene as a solvent. This system led to moderate yields and reasonable enantioselectivity after 48 hours, and could prospectively be applied to our reaction. Alternatively, Helmchen and co-workers have shown that the use of iridium complexes featuring chiral phosphoramidite ligands such as **3.7** in tandem with n-butyllithium as a base represents a robust avenue for accessing the same substrate.[95]



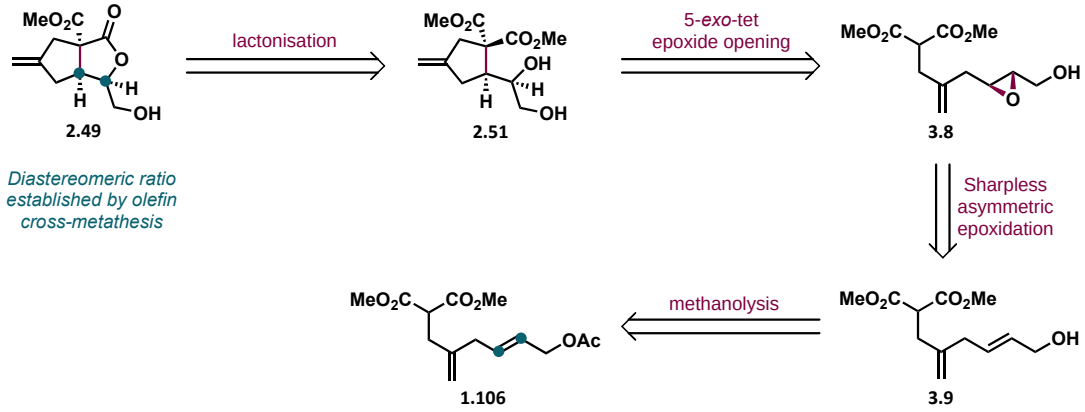
Scheme 3.4: Results from Pfaltz and Helmchen which are applicable to future work on the asymmetric intramolecular allylic alkylation reaction.

Either of these avenues could be pursued in a future effort to realise the asymmetric intramolecular allylic alkylation approach to **1.102**; in our project, the need for such an effort was obviated by the development of an alternative asymmetric approach to **2.50**.

3.2.2 Strategy for lactone synthesis *via* epoxide-opening

Given the time constraints faced during the phase of the project detailed above in Section 3.2.1, we concurrently explored alternative disconnections which might allow for an asymmetric synthesis of **2.50**. The strategy of generating **2.49** *via* the intramolecular opening of an epoxide with a malonate anion was one which presented several conspicuous virtues (Scheme 3.5).

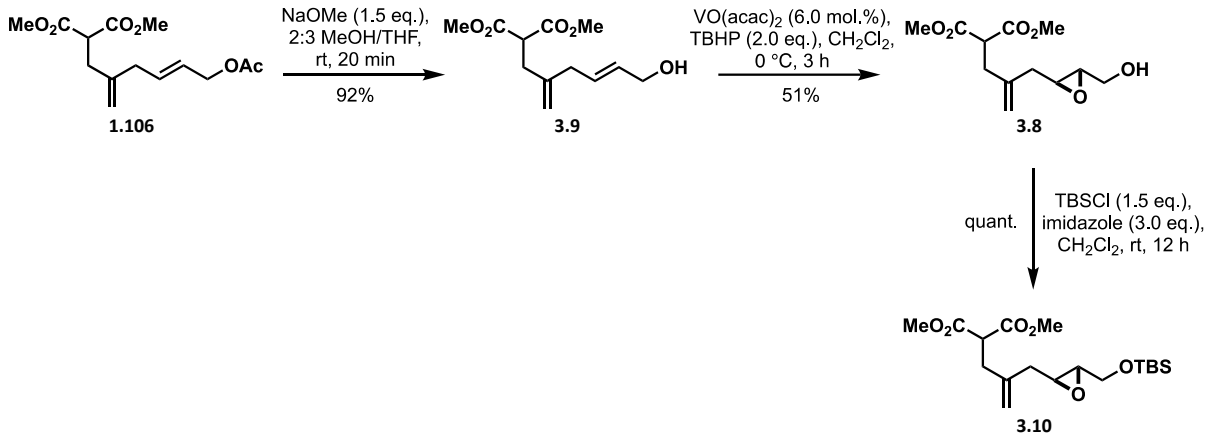
Firstly, the key 5-*exo*-tet cyclisation from **3.8** to **2.51** is kinetically favoured under Baldwin's rules,[96] and could conceivably take place in the presence of a Lewis acidic metal ion which would effect the subsequent cyclisation to **2.49**. Secondly, the starting material for this transformation **3.8** bears an epoxide adjacent to a terminal (protected) alcohol as its only stereogenic element; such a retron is highly suggestive of a Sharpless epoxidation,[97] a reaction which is well-known for its robustness, scope, and cost-effectiveness. Thirdly, the desired relative stereochemistry in the product would originate from the thermodynamically preferable *trans*- geometry of the 1,2-disubstituted alkene in the intermediate **3.9**. Finally, as **3.9** can be related to the previously obtained **1.106** by an ester cleavage, an exploration of this approach would interface well with our existing route. Given these virtues, we chose to investigate the feasibility of this pathway.



Scheme 3.5: Overview of epoxide-opening-based enantioselective route from **1.106** to **2.49**.

3.2.3 Implementation of lactone synthesis *via* epoxide-opening

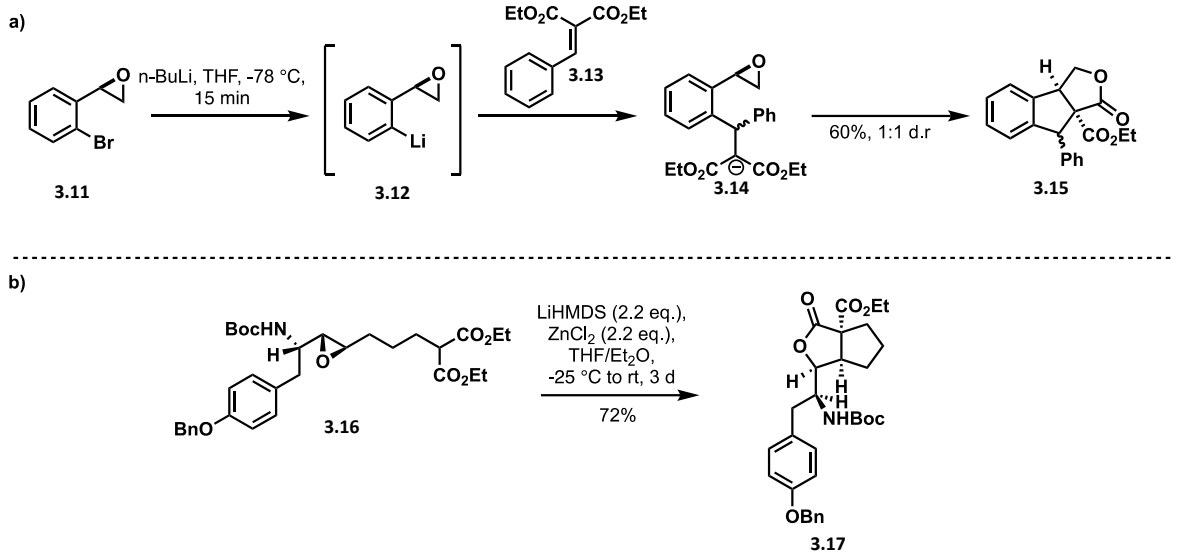
We chose to validate the epoxide-opening strategy in a racemic sequence before investigating the asymmetric variant (Scheme 3.6). The acetyl group in **1.106** was rapidly cleaved in the presence of a slight excess of sodium methoxide in a mixture of methanol and tetrahydrofuran to yield allylic alcohol **3.9** in high yield. The use of vanadyl acetylacetonate enabled the selective *tert*-butylhydroperoxide (TBHP)-mediated epoxidation of the 1,2-disubstituted alkene in the presence of the 1,1-disubstituted alkene, cleanly supplying racemic **3.8** in a moderate yield. This was then silylated to give TBS ether **3.10** (Scheme 3.6).



Scheme 3.6: Racemic transformation of **1.106** into **3.10**.

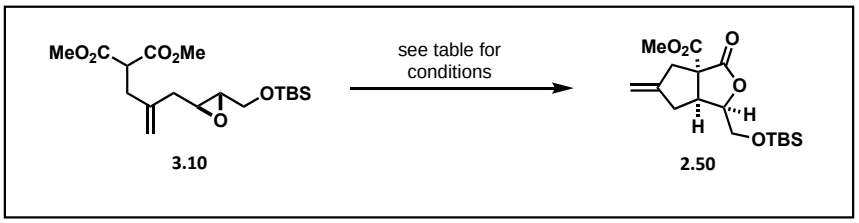
The intramolecular tandem epoxide-opening-lactonisation sequence for forming carbocycle-fused lactones proposed above has scant literature precedent; this is curious, given that both malonates and epoxides are workhorse functional groups in carbon-carbon bond formation. An elegant example of such a sequence being used in a cascade process was published by Florio and co-workers in 2008;[98] given that their system featured a more reactive styrene oxide electrophile **3.14**, we chose to instead apply the conditions used by Thompson and co-workers in their synthesis of an isostere of the HIV protease inhibitor cleavage site.[99] They demonstrated that the use of lithium hexamethyldisilazide (LiHMDS) and zinc(II) chloride gave high yields of the desired product after three days at room temperature (Scheme 3.7). We were pleased when the use of such conditions on **3.10** led to

approximately 50% conversion to the desired product **2.50**, and subsequently discovered that running the reaction under reflux led to quantitative conversion in two hours (Table 3.2).



Scheme 3.7: Literature precedent for epoxide-opening-lactonisation sequence. **a)** Cascade developed by Florio and co-workers; **b)** reaction developed by Thompson and co-workers en route to a HIV protease cleavage site isostere.

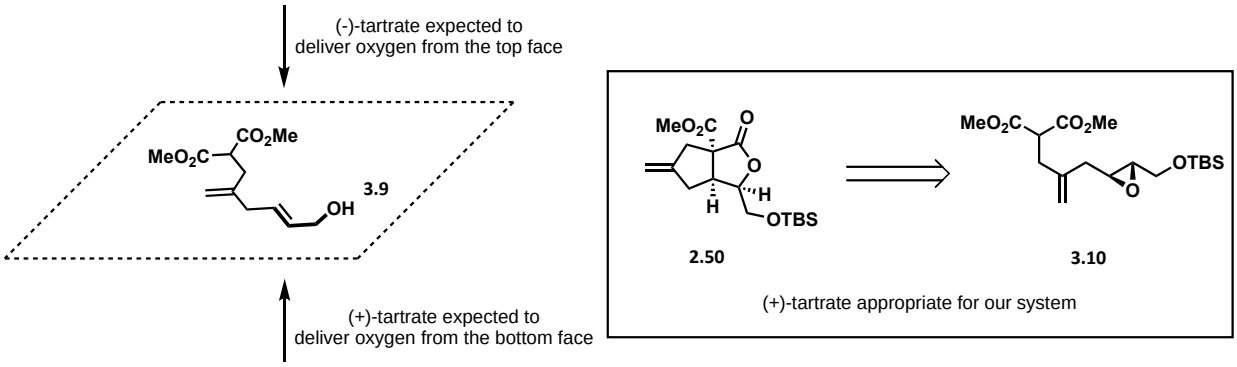
The product thus obtained was found to be a single diastereomer, and was identical to that obtained previously from the iodolactonisation sequence (see Section 2.2.1).



Entry	Temperature	Duration	Result
1	20 °C	3 days	50% conversion, no other products observed
2	70 °C	2 hours	Quantitative yield of **2.50**

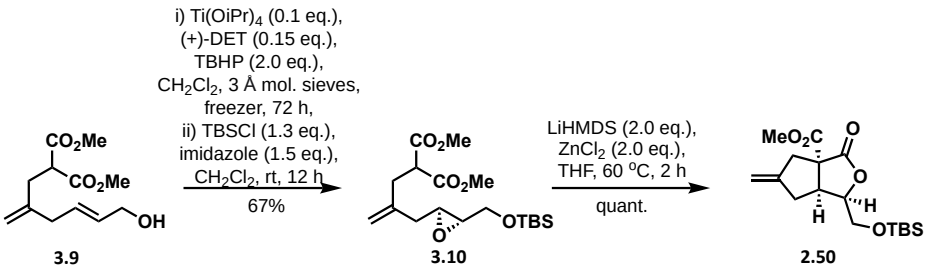
Table 3.2: Conditions screened for epoxide-opening. Reactions conditions were: 1.0 eq. **3.10**, LiHMDS (2.0 eq.), $ZnCl_2$ (2.0 eq.), THF, temperature, duration.

Having established the validity of the epoxide-opening approach to **2.50** in a racemic context, we sought to convert these results into a successful asymmetric route. As discussed above, the Sharpless epoxidation was the tool we chose for this task; the simplified model for predicting the enantioinduction of this reaction is given below (Scheme 3.8) in the context of our **3.9** as a substrate.



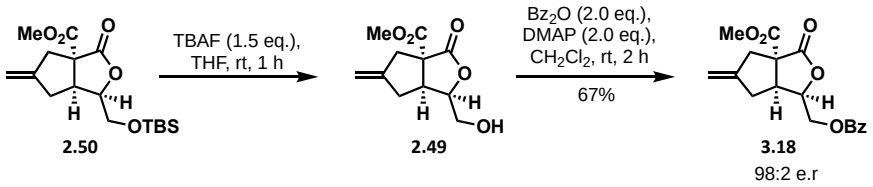
Scheme 3.8: Stereochemical considerations for Sharpless asymmetric epoxidation as applied to **3.9**.

The conditions used in the Sharpless epoxidation resulted in the full consumption of **3.9** after 72 hours at -24 °C; however the (+)-diethyl tartrate used in the reaction proved to be chromatographically inseparable from the product. Sharpless addressed this by including an alkaline hydrolysis step in the work-up protocol; the presence of the dimethylmalonate unit in **3.9** obviously rendered such a procedure inappropriate. We elected to simply remove inorganic and otherwise aqueous-soluble impurities *via* filtration and aqueous work-up to give a crude organic product, which was treated with an excess of silyl chloride and imidazole in order to silylate **3.8** to give **3.10**. Material thus obtained was found to be readily purified by column chromatography, disclosing a high yield; subsequently it was converted to **2.50** (Scheme 3.9).



Scheme 3.9: Successful implementation of Sharpless epoxidation on **3.9** to give **3.10** and **2.50**.

In order to supply the structure with a strong chromophore and increase its polarity to facilitate HPLC analysis, we chose to replace the silyl ether with a benzoate. As such, in both the racemic and enantioenriched series, **2.50** was converted into **2.49** *via* treatment with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran. **2.49** was then treated with benzoic anhydride and 4-dimethylaminopyridine (DMAP) in dichloromethane to give **3.18** in high yields (Scheme 3.10). Chiral HPLC analysis of this ester revealed an enantiomeric ratio of 98:2, corresponding to an enantiomeric excess of 96%; we deemed this satisfactory. The absolute configuration of the material thus obtained was determined to be that desired for the project and depicted here *via* a Mosher's ester analysis at a subsequent stage of the project (Section 3.4).[100]



Scheme 3.10: Verification of enantioselectivity *via* derivatisation to benzoate ester **3.18**.

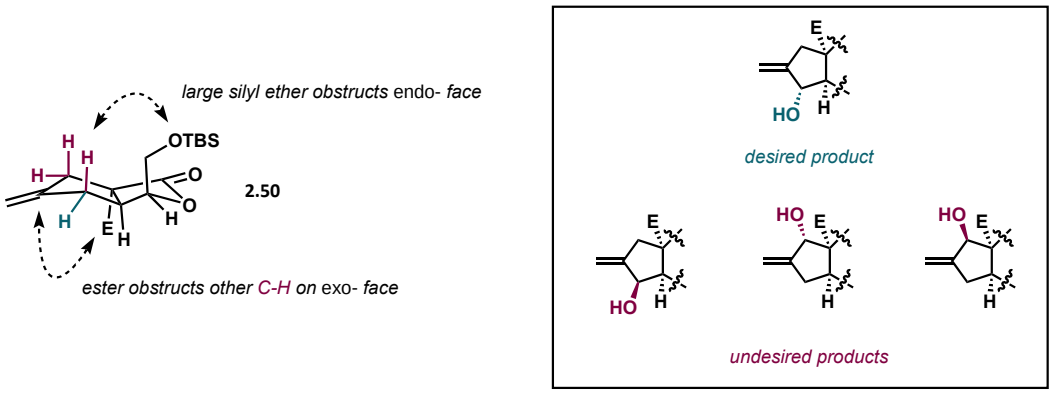
In addition to providing a high degree of enantioinduction, the adoption of this route increases the cumulative yield for the sequence from **2.14** to **2.50** from 39% to 61%.

3.3 Allylic oxidation of compound 2.50

3.3.1 Requirements for the allylic oxidation of compound 2.50

As delineated in Section 3.1, our strategy for the installation of the required methyl and hydroxyl groups found in the natural product was to perform a site- and stereoselective allylic oxidation, which would install the hydroxyl group on the *exo*- face of the oxabicyclo-[3.3.0]-octane. This would then enable the direction of a subsequent hydrogenation reaction onto the *exo*- face, which would establish the methyl substituent with *endo*- stereochemistry.

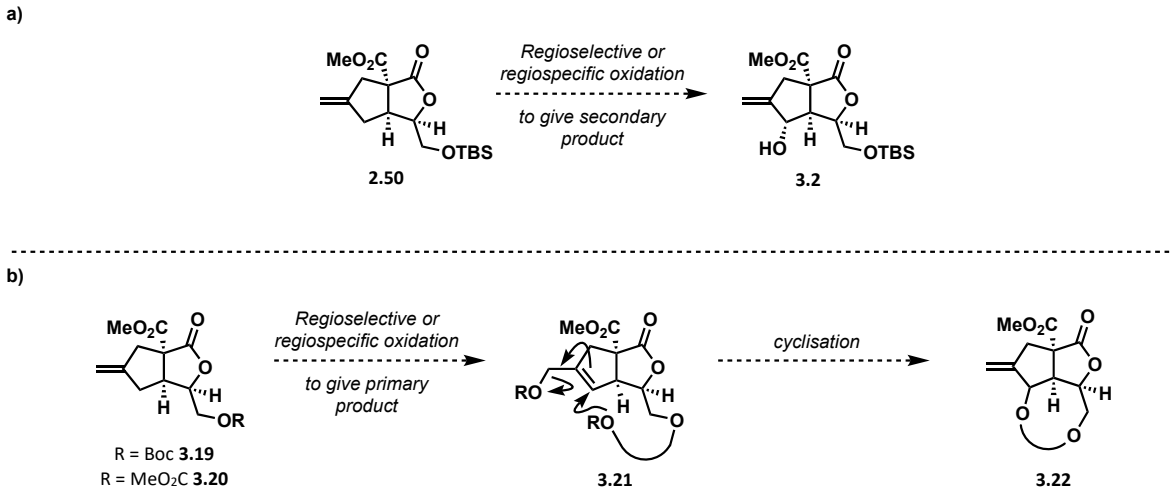
The prospect of such an allylic oxidation posed several challenges. Firstly, there was the question of site-selectivity: there are two allylic methylene sites, only one of which we wished to oxidise. Secondly, there was the issue of stereoselectivity, as we desired the *exo*- alcohol only. Finally, there was the issue of regioselectivity: many allylic oxidation methodologies proceed *via* allylic radicals or transition metal π-allyl complexes, and such reaction pathways might be expected to yield the (presumably) more thermodynamically stable primary allylic alcohol in precedence over the desired secondary allylic alcohol. We felt that **2.50** presented the best opportunity to address these issues through the inherent bias of the substrate; the quaternary carbon and methyl ester would sterically shield the methylene group we wished to remain intact, and the 'bowl' of the oxabicyclo-[3.3.0]-octane and the large silyl ether substituent on the *endo*- face would direct reactivity to the *exo*- face. These considerations are summarised in Scheme 3.11.



Scheme 3.11: Selectivity considerations for the allylic oxidation of **2.50**. **E** denotes the methyl ester substituent.

3.3.2 Strategies for the allylic oxidation of compound 2.50

Broadly, we investigated two strategies to install the hydroxyl group at the desired site. The first was our initial idea: to directly access the required alcohol through a regioselective or regiospecific transformation such as a Kharasch-Sosnovsky reaction[101] or Guillemonat oxidation (i.e. selenium dioxide-mediated allylic oxidation).[102] This clearly represented the most straightforward approach in a strategic sense, but we anticipated that executing such a reaction cleanly might be challenging. The second approach occurred to us on account of a later result in the project (see Section 4.2.2): to access the *undesired* primary alcohol selectively, which would likely prove more facile, and then perform an allylic transposition to give the desired secondary alcohol. These two alternatives were investigated concurrently and are delineated in Scheme 3.12.

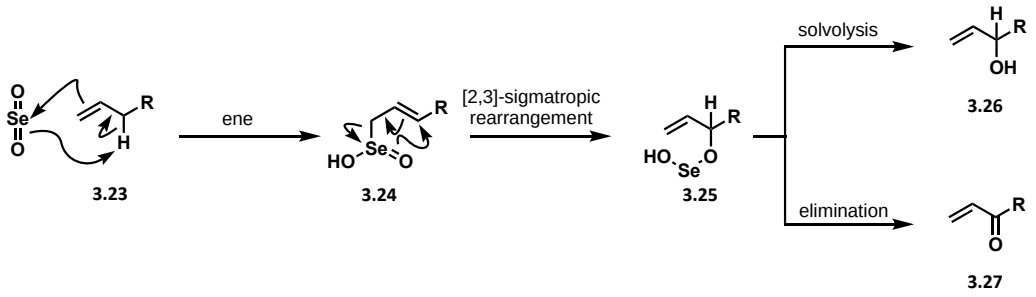


Scheme 3.12: Strategies for the installation of the secondary hydroxyl group. **a)** Direct installation of secondary alcohol; **b)** installation of primary alcohol followed by formal S_N2' cyclisation**.**

3.3.3 Allylic oxidation of compound 2.50 at the secondary site with selenium dioxide

The Guillemonat reaction is perhaps the most well-known protocol for the oxidation of allylic positions in organic chemistry. Along with the Riley oxidation,[103] it has cemented the place of selenium dioxide in the reagent toolkit of synthetic laboratories. First disclosed in 1939, in addition to being a very early example of what would nowadays be termed 'C-H activation', the reaction possesses the unusual regiochemical property of retaining the position of the double bond found in the starting material,

even when that position is thermodynamically unfavourable with respect to an alternative. This arises as a consequence of the mechanism of the reaction, which was first proposed by Sharpless and Lauer in 1972,[102] was subsequently reinforced by Sharpless, Arigoni, and co-workers in 1973,[104] and is shown below in Scheme 3.13. An initial ene reaction between selenium dioxide and the alkene (represented as simplified structure **3.23**) gives an allylseleninic acid **3.24**; this then undergoes a [2,3]-sigmatropic rearrangement to give a selenium(II) ester **3.25**. This ester can then undergo either solvolysis to give the allylic alcohol product **3.26**, or an elimination analogous to the Kornblum-Delamare rearrangement to give the unsaturated carbonyl product **3.27**.

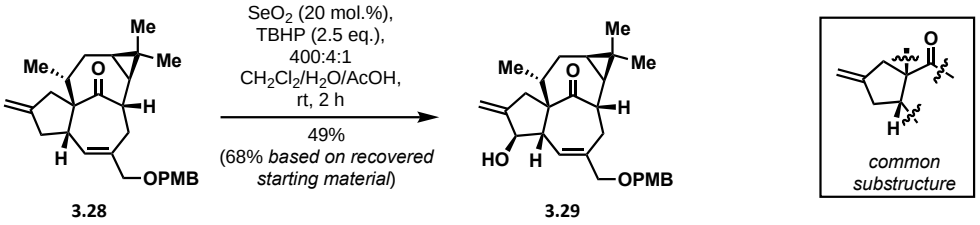


Scheme 3.13: Mechanism of selenium dioxide-mediated allylic oxidation, as proposed by Sharpless and Lauer.

In 1979, Stephenson and Speth performed a combined isotopic/stereochemical labelling study which demonstrated that the 'ene model' depicted above fails to account for the entirety of the stereochemical outcome, and suggested that pathways involving ionic intermediates might also be accessible.[105] In 2000, Singleton and Hang performed a kinetic isotope study supported by calculations and concluded that, although there is evidence for alternative pathways as proposed by Stephenson and Speth, the mechanism proposed by Sharpless and Lauer described above "would appear to be the major mechanistic pathway operative in these reactions".[106]

Selenium dioxide is a comparatively toxic reagent,[107] and the mechanism above yields selenium(II) and selenium(0) by-products which, in addition to also being toxic, can be chemically promiscuous and challenging to remove from crude reaction products. As such, a common implementation of the Guillemonat oxidation is the Sharpless modification,[108] which uses *tert*-butylhydroperoxide (TBHP) as a stoichiometric oxidant. This addresses both issues: toxicity is of less concern due to the

substoichiometric loading of selenium dioxide, and the low oxidation state selenium species are re-oxidised to selenium dioxide at the end of the reaction. Assessing the literature, we chose the conditions for this reaction used by the Wood group in their synthesis of ingenol[109] as a starting point for our investigation, due to the similarities between their system and ours (Scheme 3.14).

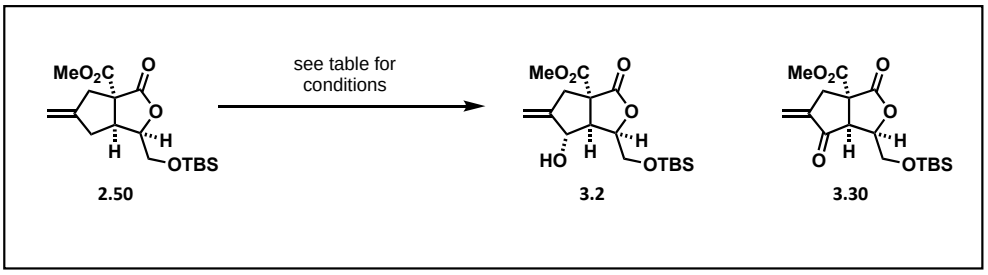


3.28 3.29

Scheme 3.14: Selenium dioxide oxidation carried out by the Wood group *en route* to ingenol.

Our investigations into selenium dioxide as a reagent to effect the allylic oxidation of **2.50** are summarised in Table 3.3. We were pleased to discover that, on smaller scales (below 0.5 mmol), we obtained **3.2** in a moderate yield using Wood's conditions. Similar to them, we found that the best results were obtained when the reaction was stopped prematurely; presumably significant product degradation occurs on a timescale similar to that required for the full conversion of starting material **2.50**. Unfortunately, these results could not be replicated on larger scales (greater than 0.5 mmol), where yields were found to drop to around 25%. We explored several of the reaction parameters in order to attempt to ameliorate this. Conducting the reaction at 0 °C, in an attempt to inhibit degradation processes, elicited no reactivity. Running the reaction under anhydrous conditions at reflux resulted in the formation of **3.30**; this was found to be unstable on silica, was identified by the presence of resonances in the ^{1}H NMR spectrum at 6.1 and 5.4 ppm. Drawing on our prior experience with the iodolactonisation reaction (Section 2.3.3), we reasoned that inhomogeneity might be responsible for the scalability issue; thus we sought to find a solvent system which would lead to the dissolution of all components. After several experiments, it was found that the inclusion of methanol into Wood's solvent system gave a homogeneous solution. Conducting the reaction in this mixture of solvents required refluxing temperatures and gave a 48% yield of **3.2**, which was, pleasingly,

reproducible on scale. Wet 1,4-dioxane, hexafluoroisopropanol (HFIP) and *tert*-butanol all achieved full dissolution of the reaction components and also required high temperatures; however, none elicited an improvement in outcome over the modified Wood conditions. Running the reaction in isopropanol gave curious results; 24 hours were needed to achieve full conversion (as opposed to 2.5 hours in *tert*-butanol), the ^{1}H NMR spectrum of the reaction was significantly cleaner, but the yield obtained was an unimpressive 25%.



Entry	Solvent	Temperature (°C)	Reaction time (hours)	Result
1[a]	400:4:1 CH_2Cl_2/H_2O/AcOH	20	4.5	62% yield of **3.2** (*75% brsm*)
2[b]	400:4:1 CH_2Cl_2/H_2O/AcOH	20	4.5	25% yield of **3.2** (*50% brsm*)
3	400:4:1 CH_2Cl_2/H_2O/AcOH	0	-	No significant reactivity
4	400:40:4:1 CH_2Cl_2/MeOH/H_2O/AcOH	40	6	48% yield of **3.2**
5	CH_2Cl_2	40	2	High crude yields of **3.30**[c]
6	1,4-dioxane	100	2	22% yield of **3.2**, **3.30** also formed[d]
7	HFIP	60	2	8% yield of **3.2**, **3.30** also formed[d]
8	*t*-BuOH	82	2	14% yield of **3.2**, **3.30** also formed[d]
9	iPrOH	82	24	25% yield of **3.2**

Table 3.3: Conditions screened for allylic oxidation. Reactions conditions were: 1.0 eq. **2.50**, selenium dioxide (20 mol.%), *tert*-butylhydroperoxide (2.5 eq.), solvent, temperature, duration rapidly stirred. [a]Wood's conditions, below 0.5 mmol scale. [b]Wood's conditions, above 0.5 mmol scale. [c]Compound unstable, decomposes on silica, detected in the ^{1}H NMR spectrum of the crude product as the major component. [d] detected in the ^{1}H NMR spectrum of the crude product.

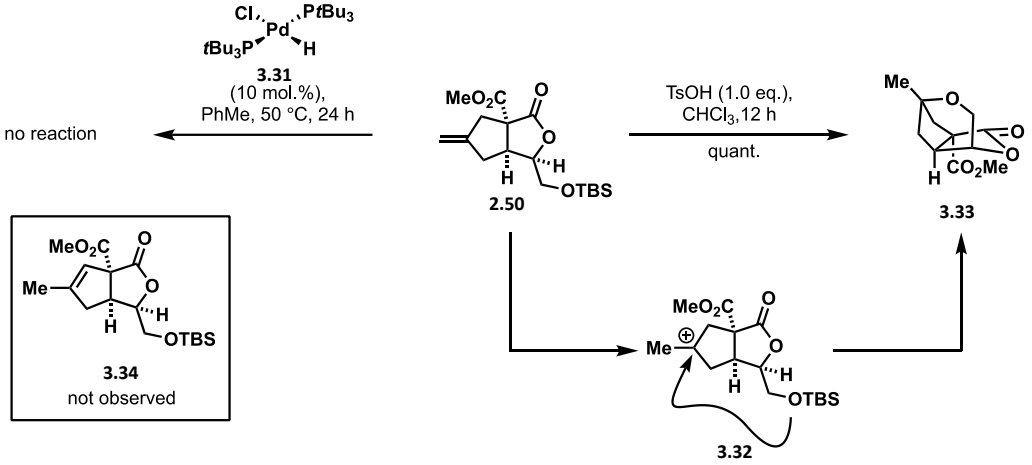
The relative configuration of **3.2** was confirmed by a ^{1}H NOESY experiment, the results of which are indicated below in Scheme 3.15. The bridgehead proton showed reciprocal NOE correlations to both the lactone alkyl proton and the hydroxylic proton, suggesting that the hydroxyl group occupied the *exo*- face of the oxabicyclo-[3.3.0]-octane skeleton. This assignment was corroborated by reciprocal NOE correlations between the alkyl proton of the secondary alcohol and the protons on the silyloxymethyl group on the *endo*- face of the molecule.

Scheme 3.15: Selected NOESY correlations of compound **3.2**.

3.3.4 Allylic oxidation of compound 2.50 at the secondary site – other approaches

In addition to the straightforward selenium dioxide-mediated approach outlined above, several other avenues were investigated.

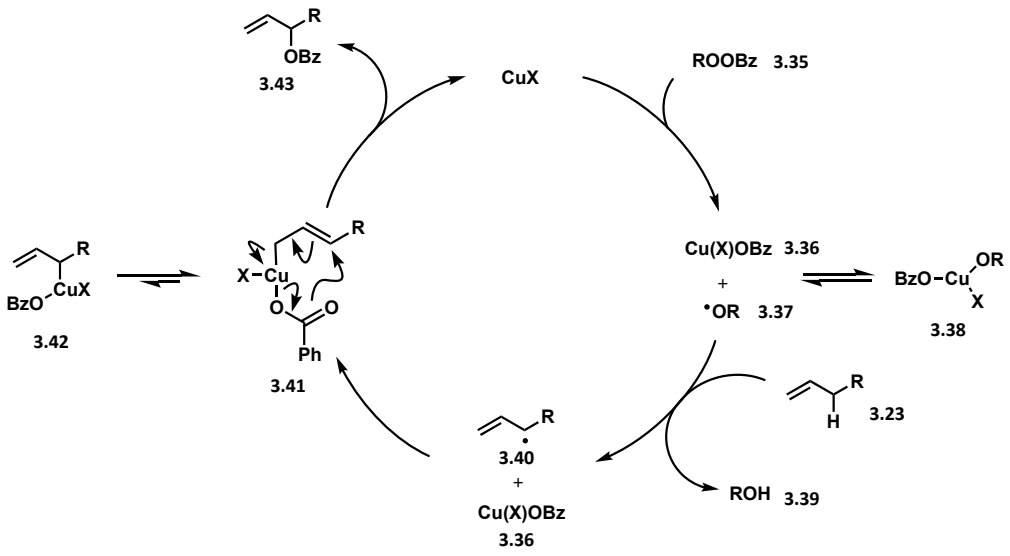
The possibility of conducting a double bond migration to yield an alternative starting material **3.34** was briefly considered (Scheme 3.16). Both acid- and transition metal hydride-catalysed isomerisation were trialled; *para*-toluenesulfonic acid gave quantitative conversion to the tricyclic structure **3.33**, presumably *via* protonation of the alkene to give cation **3.32** followed be desilylative cycloetherification. Skrydstrup's hydride **3.31**[110] elicited no conversion of **2.50** after 24 hours.



Scheme 3.16: Unsuccessful attempts to isomerise **2.50** to give **3.34**.

The Kharasch-Sosnovsky reaction was first disclosed in 1958, five months after the death of Professor Morris Kharasch.[101] In the original publication, Kharasch and Sosnovsky relate their discovery that *tert*-butyl perbenzoate in the presence of a transition metal salt is capable of converting alkenes into the corresponding allylic benzoates; today, the reaction tends to specifically refer to such transformations as performed by copper salts. The reaction has been the subject of a reasonable volume of contemporary research, most of which has focused on the prospect of rendering the transformation enantioselective through the use of chiral ligands;[111, 112] it has also enjoyed occasional use in the context of total synthesis, such as in Corey and Lee's synthesis of pentacyclic triterpenes.[113] The salient property of the Kharasch-Sosnovsky reaction in the context of the project at hand is that the product distribution generally favours the more substituted benzoate products (i.e. the secondary

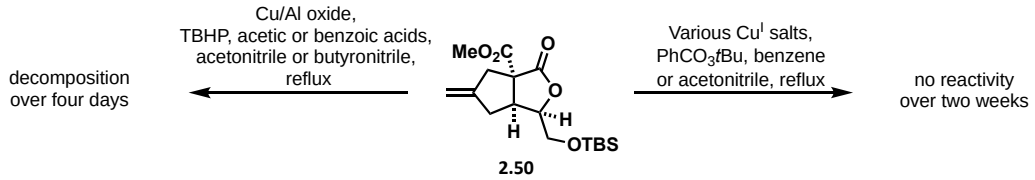
product in the context of our system). This arises as a result of the mechanism, shown below (Scheme 3.17); the generic alkene substrate **2.23** is once again invoked. The copper(I) ion is oxidised by the perester **3.35**, resulting in an alkoxy copper(III) carboxylate **3.38**; this then undergoes homolysis to generate the corresponding copper(II) carboxylate **3.36** and alkoxy radical **3.37**. Hydrogen atom abstraction of **3.23** by **3.37** ensues to yield the stabilised and ambident allylic radical **3.40**, which recombines with the copper(II) species **3.36** to give an allylic copper(III) carboxylate **3.41-3.42**. This species is postulated to exist in an equilibrium between the two allylic transposition isomers, with the less sterically congested isomer dominating. Reductive elimination then occurs through a cyclic seven-membered transition state to install the ester at the more sterically congested site of the allylic fragment, yielding **3.43**, and regenerating the catalytic copper(I) species.[114]



Scheme 3.17: Mechanism of the Kharasch-Sosnovsky reaction

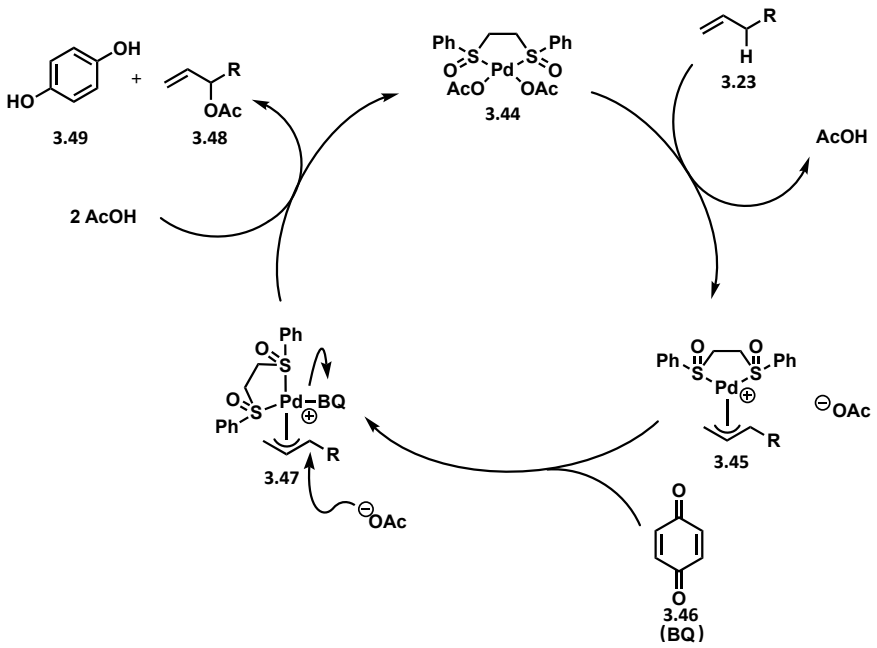
The exposure of **2.50** to a variety of copper salts in the presence of *tert*-butyl perbenzoate failed to elicit any reactivity whatsoever over two-week reaction times at reflux (Scheme 3.18). We attribute this lack of reactivity to the steric hindrance of the substrate. As an alternative, the methodology published by Guerra and co-workers for allylic oxidation using a copper-aluminium mixed oxide was investigated.[115] The mixed oxide catalyst was prepared according to their procedure, and **2.50** was

subjected to their conditions; this led only to the slow decomposition of material, with no identifiable products detected in the reaction mixture at any stage.



Scheme 3.18: Unsuccessful attempts to perform copper-catalysed allylic oxidation on **2.50**

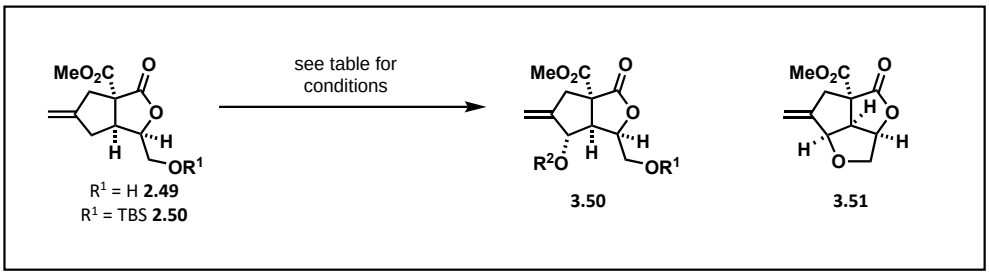
The other major class of transition metal-catalysed reaction investigated for the oxidation of **2.50** was that of palladium-catalysed allylic C-H activations. This area has seen consistent activity in the literature over the past two decades; an early development of this particular aspect of palladium(II) reactivity into a synthetically useful methodology was carried out by White and co-workers,[116] building on the work of Åkermark.[117] Their observation that reactions undertaken in dimethyl sulfoxide were selective for branched allylic ester products led to the design of a palladium bis-sulfoxide complex **3.44** which integrated this unusual regioselectivity into the reaction when it was performed in other solvents. One particularly impressive implementation of this methodology by the White group has been in an oxidative macrolactonisation reaction.[118] The mechanism of this transformation features oxidative addition of palladium(II) into the allylic C-H bond to yield a π-allyl complex **3.45**; benzoquinone **3.46** then participates in an oxidatively-induced reductive elimination *via* complex **3.47** to immediately regenerate the palladium(II) species **3.44**, hydroquinone **3.49**, and the product **3.48** (Scheme 3.19).



Scheme 3.19: Mechanism of the White oxidation.

Lactone **2.50** did not succumb to any of the conditions attempted during the investigation of the intermolecular variant of this reaction. Various solvents and nucleophiles were trialled, including the accelerated variant employing silver(I) carbonate and 4-nitrobenzoic acid recently published by Mashima and co-workers.[119] Given that we knew **2.50** was able to form a palladium π-allyl complex through C-H activation due to a concurrent investigation (Section 3.3.5), we deemed that the steric congestion of the *endo*- face of the oxabicyclo-[3.3.0]-octane might be preventing an outer-sphere reductive elimination process. As such, **2.49** was trialled; although none of the desired product resulted, a 23% yield of cyclic ether **3.51** was obtained after two days.

This hopeful but unactionable result inspired us to attempt an intramolecular variant of the reaction (Table 3.4). As such, **3.53** was prepared by performing consecutive Dess-Martin[120] and Pinnick[121] oxidation protocols on **2.49** (Scheme 3.20). The carboxylic acid thus obtained was subjected to White's conditions for oxidative lactonisation. After four days' reaction time, the starting material had undergone approximately 40% conversion to a new, less polar product which was highly unstable on silica.

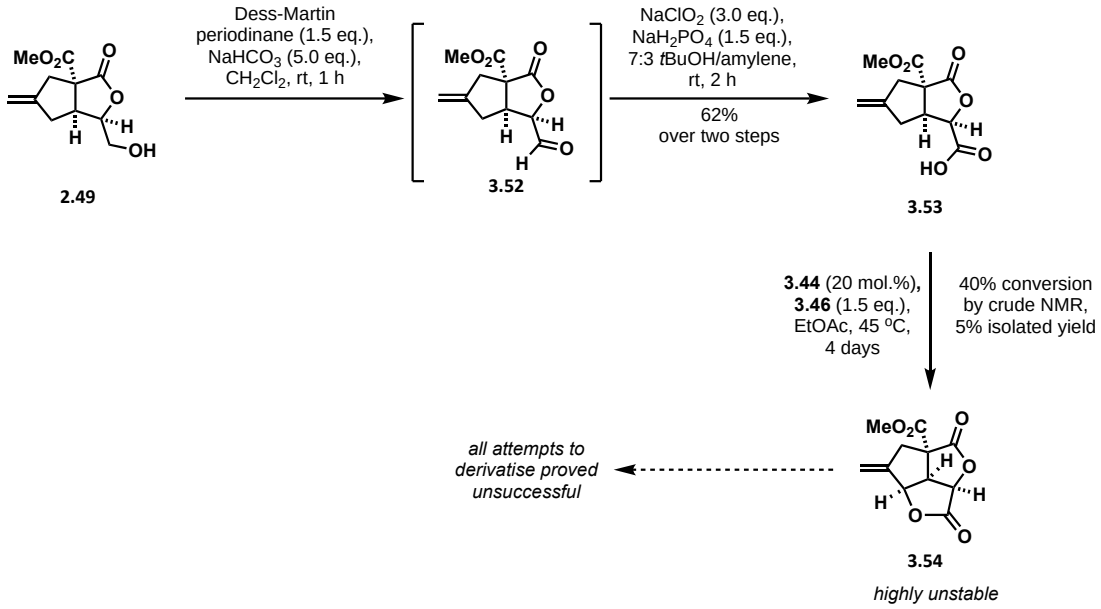


Entry	Substrate	Pronucleophile	Solvent	Result
1	**2.50**	AcOH	EtOAc	No reaction
2	**2.50**	AcOH	1,4-dioxane	No reaction
3[a]	**2.50**	4-nitrobenzoic acid	1,4-dioxane	No reaction
4	**2.50**	AcOH	1,4-dioxane	No reaction
5[a]	**2.50**	4-nitrobenzoic acid	1,4-dioxane	No reaction
6	**2.49**	AcOH	1,4-dioxane	23% conversion to **3.51**[b]

Table 3.4: Conditions screened for White oxidation. Reactions conditions were: 1.0 eq. substrate, White catalyst **3.44** (20 mol.%), pronucleophile (4.0 eq.), benzoquinone **3.46** (1.5 eq.), solvent, reflux, 7 days. [a]Reaction also included silver(I) carbonate (20 mol.%); conditions adapted from Mashima *et al.*.[117] [b]Remainder of the material was unconverted substrate.

Rapid flash column chromatography enabled the purification of the crude material from the residual benzoquinone and dihydroquinone by-product **3.49** to provide **3.54** in an isolated yield of 5%. This was a pleasing result, however the instability of this new bis-lactone presented a serious challenge to any attempts to capitalise upon it. Yields could not be improved by any variation in solvent, or by the inclusion of chromium(III) additives as prescribed by White;[122] it was clear that the instability of the product to be the most fundamental obstacle. We attempted to assess this instability in an effort to elucidate any native reactivity which might be leveraged to synthetic ends: exposure of **3.54** to basic conditions (potassium carbonate or triethylamine in methanol) elicited prompt decomposition to no isolable products; exposure to neutral methanol gave no reaction. The introduction of a small amount of activated silica gel to a solution of **3.54** in deuterated chloroform simply led to the diminishment of

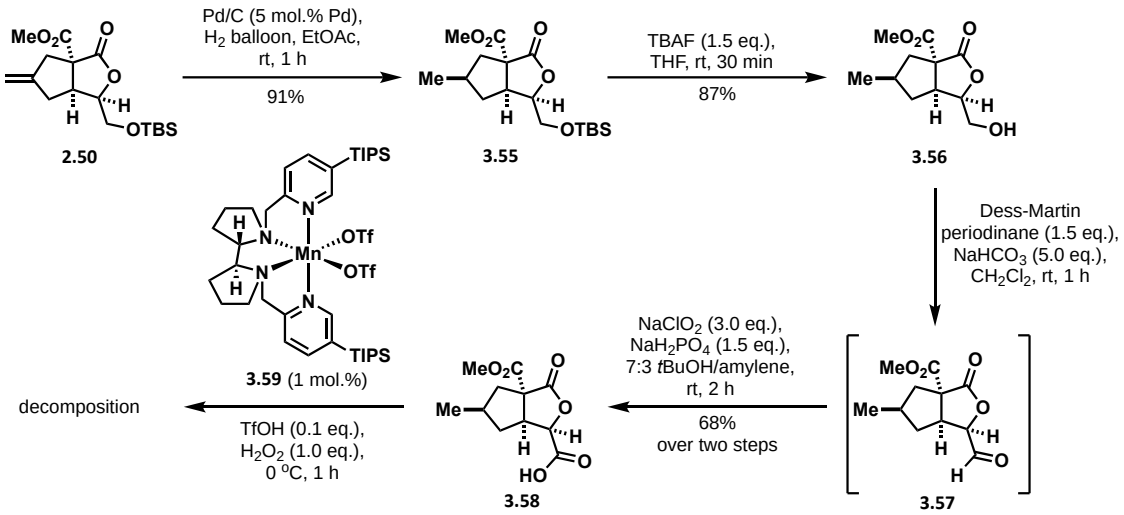
the resonances corresponding to **3.54** in the ^{1}H NMR spectrum with no other resonances appearing. Derivatisation of the crude reaction material proved equally unsuccessful in all cases. Given the extended reaction time and surplus of material required to obtain even an analytical quantity of **3.54**, the frustration of any attempt to derivatise it, and the time constraints of the project, this line of synthetic investigation was discontinued. It should be noted that Stahl's aerobic palladium-catalysed allylic oxidation protocol, which will be discussed in due course in Section 3.3.5, showed no facility for the conversion of **3.53** into **3.54**. These results are summarised in Scheme 3.20.



Scheme 3.20: Sequential Dess-Martin and Pinnick oxidations of **2.50** to **3.53** *via* **3.52** and White oxidative lactonisation to **3.54**.

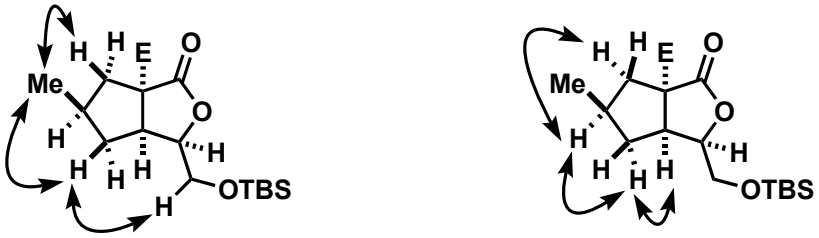
The notion of introducing the C3 oxygen atom with an oxidative C-H lactonisation led us to consider whether the saturated analogue **3.58** would prove a viable substrate for an aliphatic variant of this transformation. Such a scheme would rely on a diastereoselective hydrogenation in order to access the appropriate configuration at the C2 methyl-bearing stereocentre, rather than a later alcohol-controlled hydrogenation as laid out in Scheme 3.1. Gratifyingly, hydrogenation of **2.50** using palladium-on-carbon gave the desired isomer **3.55** exclusively (Scheme 3.21); presumably this arises from the kinetically-controlled delivery of hydrogen to the *exo*- face of the oxabicyclo-[3.3.0]-octane ring system. A subsequent deprotection with TBAF gave alcohol **3.56** in high yield; this alcohol was subjected to the same oxidation sequence shown in Scheme 3.20 to give carboxylic acid **3.58** *via*

aldehyde **3.57**. This acid was then subjected to the protocol published by Costas *et al*. using the manganese catalyst **3.59**;[123] this choice of methodology was made due to reagent availability. This led to the decomposition of the starting material **3.58**, with no products obtained. Due to time constraints, this approach was abandoned; it could be further investigated in the future using White's variant of this transformation.[124]



Scheme 3.21: Derivatisation of **2.50** to **3.58**, and failed aliphatic C-H lactonisation thereof.

Scheme 3.22 shows the selected correlations observed in the ^{1}H NMR NOESY spectrum of **3.55** which justified the assignment of the relative configuration. Reciprocal NOE correlations with the bridgehead proton enabled the assignment of the *exo*- disposed methylene proton vicinal to it. This proton additionally showed a reciprocal NOE correlation with the newly-formed methine proton, suggesting that it too occupied the *exo*- face of the molecule. On the *endo*- face, the protons of the silyloxymethyl group showed reciprocal NOE correlations with the *endo*- methylene proton vicinal to the bridgehead, which in turn showed a reciprocal NOE correlation with the protons of the newly-formed methyl group, corroborating the stereochemical assignment shown.



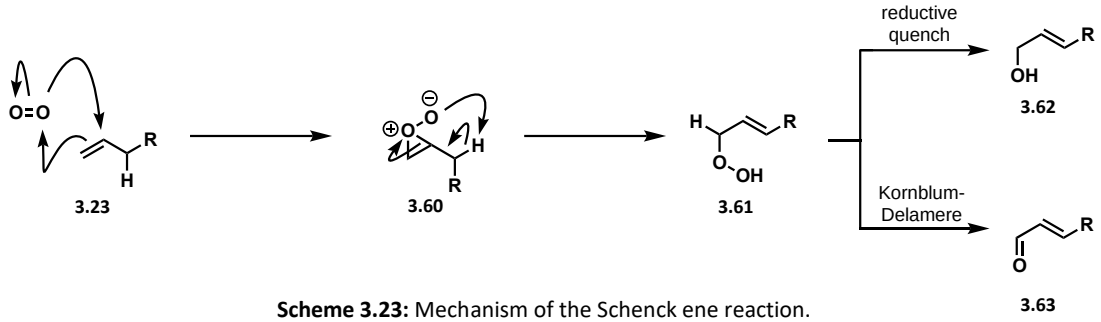
Scheme 3.22: Selected NOESY correlations of compound **3.55**. E = CO_2Me.

3.3.5 Allylic oxidation of compound 2.50 at the primary site

As discussed above in Section 3.3.2 and depicted in Scheme 3.12, the second strategy for the installation of the allylic oxygen atom we investigated was the initial oxidation to form a primary (activated) allylic alcohol, followed by a formal S_N2' cyclisation from a nearby oxygen atom to give a tricycle. This approach was inspired by the formation of **3.51** by desilylative cycloetherification during an attempted Mitsunobu reaction (see Section 4.2.2) and during an attempted White oxidation (see Section 3.3.4), and the formation of **3.33** by desilylative cycloetherification during an attempted acid-catalysed double bond migration (see Section 3.3.4). We deemed that the installation of an oxygen atom at the primary position would be more straightforward on steric and stereoelectronic grounds, and that an allyl cation equivalent derived thence might be a competent electrophile to engage in a cyclisation with some internal nucleophile; the *endo*- disposed oxymethyl substituent provided a useful handle for the installation of such a nucleophile.

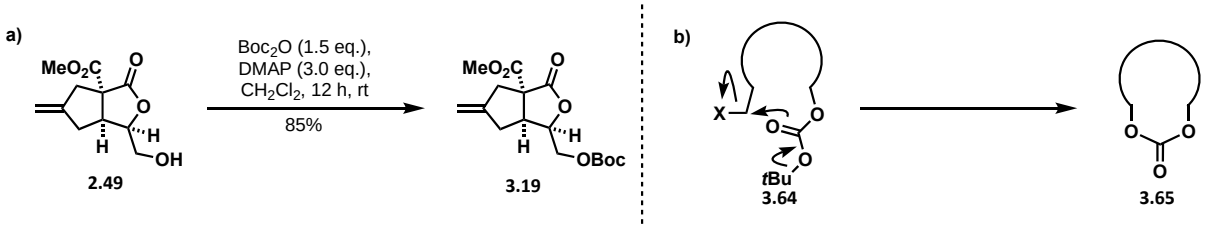
The Schenck ene reaction[125] presents a useful regiospecific complement to the Guillemonat oxidation; whereas the latter allylic oxidation retains the position of the double bond found in the starting material, the former results in exclusive transposition. The mechanism is generally accepted to proceed *via* a perepoxide intermediate **3.60**; this can then rearrange to give an allyl peroxide **3.61** (Scheme 3.23).[126] This can then be converted into either the corresponding allylic alcohol **3.62** *via* the introduction of a reductant such as a phosphine, or the unsaturated carbonyl compound **3.63** *via* a Kornblum-Delamare rearrangement. As a highly economical 'green' transformation, the Schenck ene reaction has enjoyed sustained coverage in the literature;[127] its stereochemical aspects have been

recently reviewed by von Wangelin and co-workers,[126] and a recent example in the synthetic literature can be found in the asymmetric synthesis of Taxol by the Li group.[128]



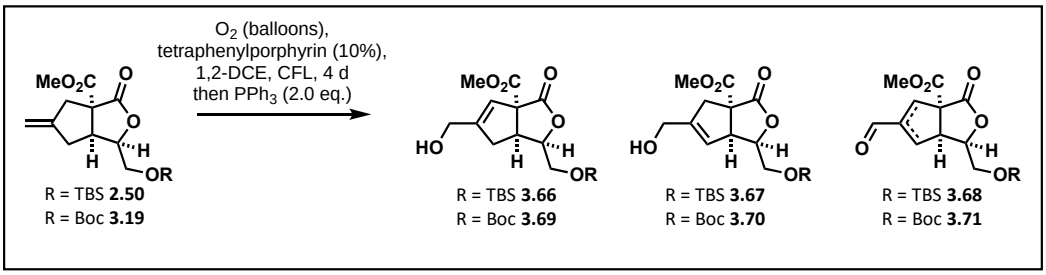
Scheme 3.23: Mechanism of the Schenck ene reaction.

Exposure of **2.50** to an atmosphere of oxygen in the presence of CFL irradiation and a 10% loading of tetraphenylporphyrin (TPP) over four days, followed by the introduction of superstoichiometric triphenylphosphine, led to approximately 60% conversion of starting material to a 4:1 ratio of desired regioisomer **3.67** and undesired regioisomer **3.66**. Resonances in the aldehyde region of the ^{1}H NMR spectrum of the crude material were also observed, indicating the presence of Kornblum-Delamere products **3.68**; however aldehydes were not recovered after column chromatography (Table 3.5). Satisfied that this result represented a promising overture for our investigation into primary-selective oxidations, **3.19** was prepared in good yield *via* the treatment of **2.49** with di-*tert*-butyl dicarbonate in the presence of DMAP (Scheme 3.24). Curiously, **3.19** proved an inferior substrate for the Schenck ene reaction, within the context of our project; the conditions which had led to moderate success with **2.50** gave a more complex result with the new substrate. The ^{1}H NMR spectrum of the crude material indicated less conversion of starting material, a poorer regiomeric ratio of approximately 2:1 between products **3.70** and **3.69**, and a more significant degree of degradation to aldehyde side-products **3.71**. Desired alcohol **3.70** was the only compound which was successfully isolated from this mixture, in a



Scheme 3.24: a) Carboxylation of **2.49** to yield **3.19**. **b**) Intended use of *tert*-butyl carbonate in cyclisation.

yield of 19%. This disparity in efficacy between the reaction conducted on the silyl ether **2.50** and the *tert*-butyl carbonate **3.19** may have arisen as a result of a genuine difference in reactivity, or it may simply be a reflection of the difficulty of conducting a biphasic photochemical reaction reproducibly on the test scale (10 μmol) (Table 3.5).

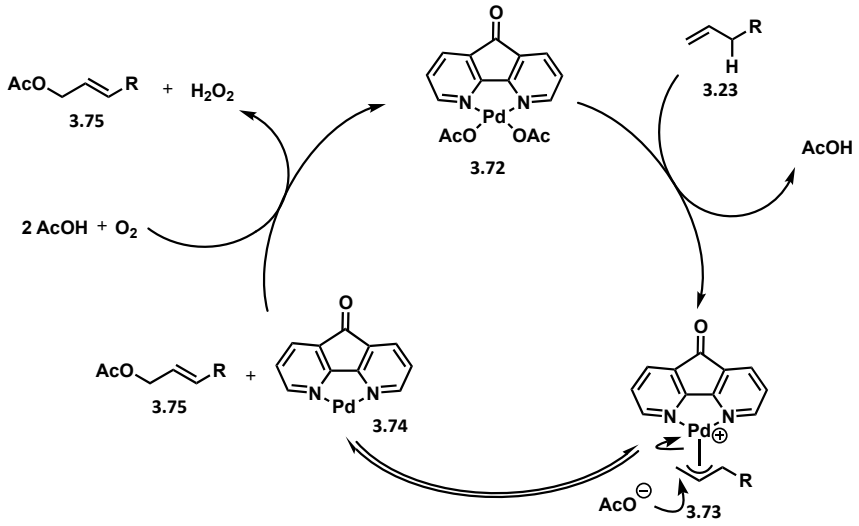


Entry	Substrate	Result
1	**2.50**	Approximately 60% conversion of substrate, yielding a 4:1 ratio of **3.67**:**3.66**; Small proportion of aldehyde species **3.68** also detected.
2	**3.19**	Approximately 40% conversion of substrate, yielding a 2:1 ratio of **3.70**:**3.69**; Large proportion of aldehyde species **3.71** also detected.

Table 3.5: Attempted Schenck ene reactions. Outcomes determined by ^{1}H NMR spectroscopic analysis of the crude reaction material.

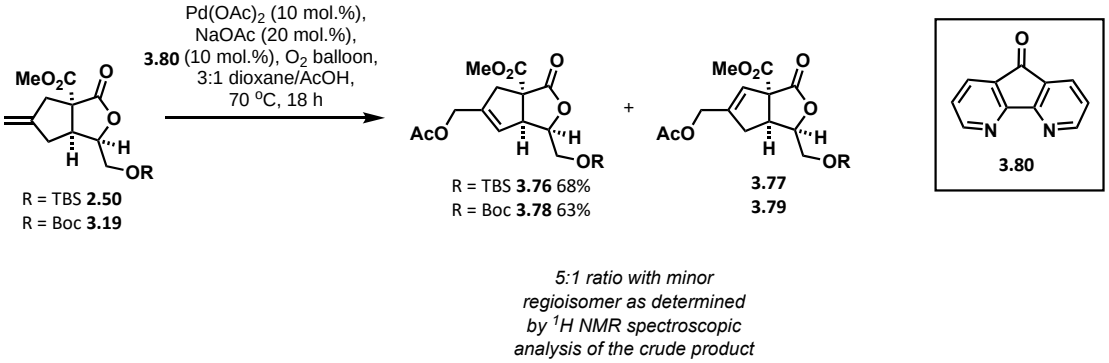
Alongside the Schenck ene reaction, Stahl's protocol for the palladium-catalysed allylic oxidation of alkenes was also investigated as a method for installing an oxygen atom at the primary position.[129] First disclosed in 2010, this reaction is a 'greener' realisation of palladium-catalysed allylic oxidation; the innovation of the Stahl group was to develop a complex **3.72** which enables aerobic catalytic turnover, escaping a previously benzoquinone-dominated paradigm. The mechanism for this process, shown below in Scheme 3.25, is analogous to that previously depicted in the context of White's chemistry; one distinction is that, where White's reaction is believed to proceed *via* oxidatively-induced reductive elimination, Stahl's relies on an equilibrium between the palladium π-allyl complex **3.73** and product **3.75**/palladium(0) from which the palladium(0) complex **3.74** is trapped by

molecular oxygen to regenerate the palladium(II) catalyst **3.72**. As the regioselectivity offered by the White oxidation and the aerobic turnover offered by the Stahl oxidation each arise as a consequence of ligand design, these two virtues cannot presently be united in a single reaction.



Scheme 3.25: Mechanism of Stahl's aerobic acetoxylation.

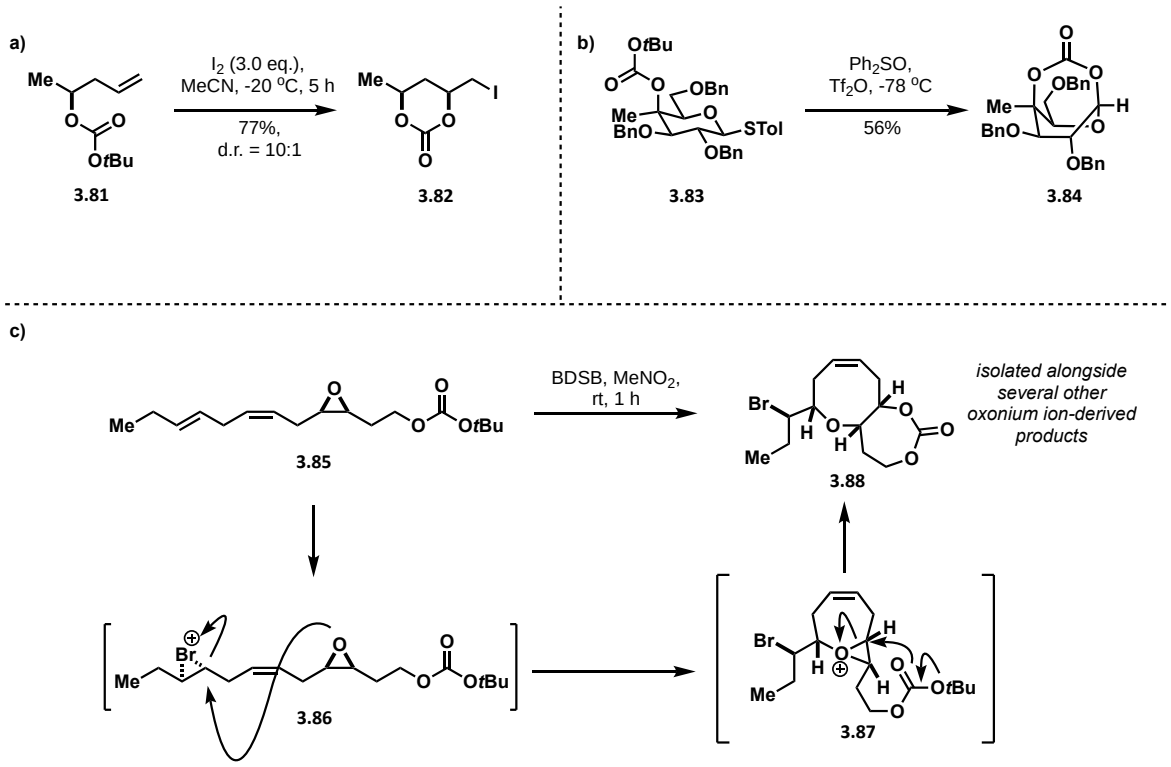
As such, **2.50** and **3.19** were subjected to Stahl's conditions. Gratifyingly, this led to full and comparatively clean conversion to products **3.76** and **3.78** respectively after 18 hour reaction times, in synthetically useful yields with neither of the undesired regioisomers **3.77** and **3.79** isolated, though they were visible in the crude ^{1}H NMR spectrum (Scheme 3.26). The implication of this is that the initial formation of the palladium π-allyl complex occurs under steric control.



Scheme 3.26: Oxidation of **2.50** and relatives *via* Stahl's aerobic acetoxylation reaction.

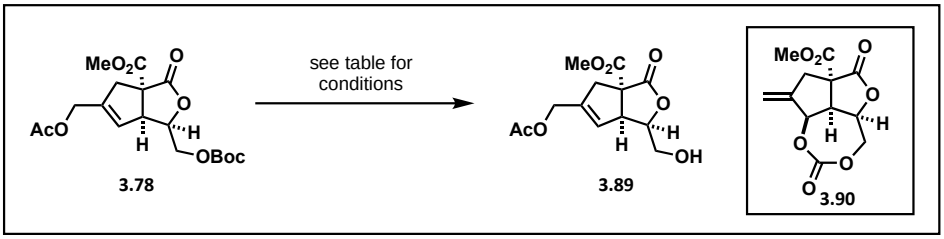
3.3.6 Attempted formal S_N2' cyclisation

We were now in a position to investigate the possibility of conducting an intramolecular formal S_N2' reaction. We had chosen **3.19** as a starting material for this sequence in order to attempt to use the *tert*-butyl carbonate group as the nucleophile for this reaction, taking as a blueprint the Bartlett iodocarbonate cyclisation.[130] In addition to the initial work by Bartlett and co-workers, there are several examples of carbonate cyclisations which yield seven-membered rings in the literature; all are distinguished by the use of reactive electrophiles. Examples include the work of Crich and co-workers on the characterisation of dioxocarbenium ions,[131] and the work of Braddock and Bonney on the assembly of *Laurencia* natural products *via* halonium opening (Scheme 3.27).[132]



Scheme 3.27: a) Bartlett and co-workers' iodocarbonate cyclisation (1982); **b**) seven-membered cyclic carbonate formation from Crich and co-workers' study on glycosyl and oxocarbenium ions (2021); **c**) seven-membered cyclic carbonate formation from Braddock and Bonney's study on the biosynthesis of *Laurencia* natural products (2012).

We recognised that the acetate group of **3.78** supplied by the Stahl acetoxylation reaction might prove to be an inadequate leaving group for the purpose we intended; nonetheless, we subjected **3.78** to a range of conditions. The results of this investigation are summarised in Table 3.6. Simply heating **3.78** in toluene resulted only in slow cleavage of the *tert*-butyl carbonate group, which proceeded to approximately 20% conversion to **3.89** over 24 hours (entry 1). Following the precedent of Cossy and co-workers,[133] **3.78** was treated with both indium(III) chloride and iron(III) chloride in acetonitrile (entries 2 and 3); this too resulted in slow formation of **3.89**, with approximately 60% conversion over 24 hours in both cases. The use of boron trifluoride in dichloromethane at 0 °C, led to immediate full conversion of **3.78**, giving **3.89** in a yield of 79% (entry 4).

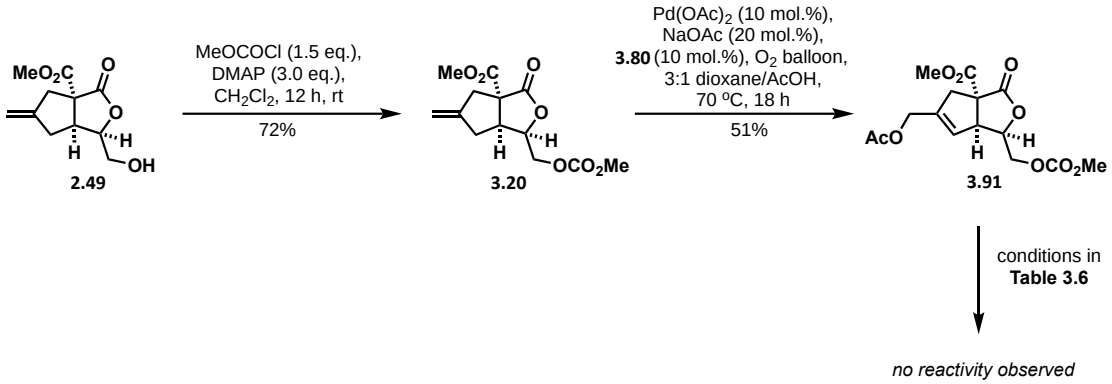


Entry	Solvent	Temperature (°C)	Additive (mol.%)	Result
1	PhMe	110	-	4:1 ratio of **3.78** to **3.89** after 24 hours.
2[a]	MeCN	20	$InCl_3$ (20)	2:3 ratio of **3.78** to **3.89** after 24 hours.
3[a]	MeCN	20	$FeCl_3$ (20)	2:3 ratio of **3.78** to **3.89** after 24 hours.
4	CH_2Cl_2	0	BF_3 (100)	100% conversion of **3.78** immediately, 79% yield of **3.89**

Table 3.6: Attempted thermal and acid-mediated carbonate cyclisations of **3.78**. [a]Conditions established by Cossey and co-workers.[131]

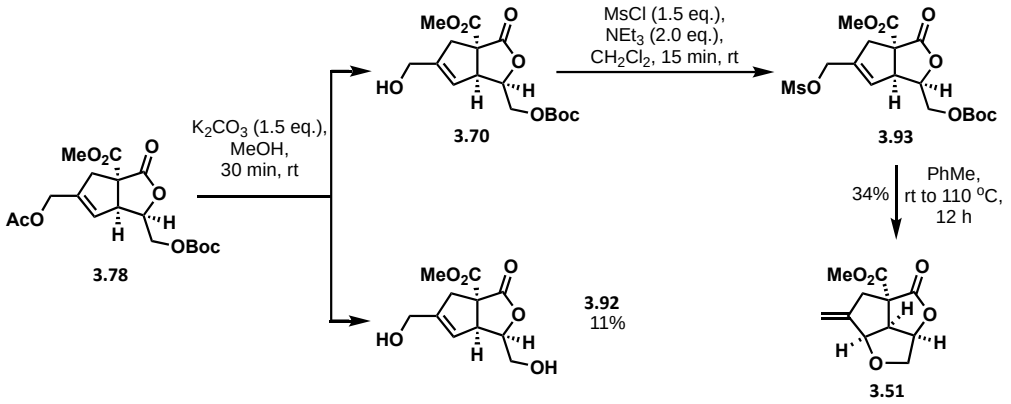
Evidently *tert*-butyl carbonate cleavage was a more kinetically accessible process than the cyclisation under both thermal and acidic conditions. Two prospective solutions to this problem presented themselves: we could modify the carbonate to reduce its lability, or we could alter the leaving group to improve electrophilicity. These possibilities were explored in parallel.

Methyl carbonate **3.20** was prepared *via* the treatment of **2.49** with methyl chloroformate in the presence of DMAP, and then subjected to the Stahl acetoxylation to provide **3.91** in a good yield (Scheme 3.28). Exposure of this carbonate to the same series of conditions as those used on **3.78** led to no conversion of the starting material, indicating that the lability of the *tert*-butyl carbonate was not the only factor contributing to the lack of desired reactivity.



Scheme 3.28: Synthesis of **3.91** *via* Stahl acetoxylation and attempted carbonate cyclisation thereof.

As such, **3.78** was treated with potassium carbonate in methanol in order to provide alcohol **3.70**; diol **3.92** was also obtained as a minor product from this reaction, indicating that the steric bulk of the *tert*-butyl group did not completely preclude carbonate deprotection. Alcohol **3.70** was then converted into mesylate **3.93** (not isolated), and this compound was gradually heated in toluene to 110 °C. The starting material was fully consumed as observed by TLC analysis after 24 hours, with **3.51** isolated as the only product in a yield of 34%; this is indicative of a tandem *tert*-butyl carbonate cleavage -cyclisation process. The liberation of methanesulfonic acid as a by-product of this transformation presumably accelerates the carbonate cleavage step *via* acid catalysis, resulting in an autocatalytic effect. This might account for the accelerated rate of thermal carbonate cleavage with respect to that observed in the heating of **3.78** (Table 3.6, entry 1). The same reaction run in the presence of 50 mol.% TBAI led exclusively to decomposition. These results are summarised in Scheme 3.29.

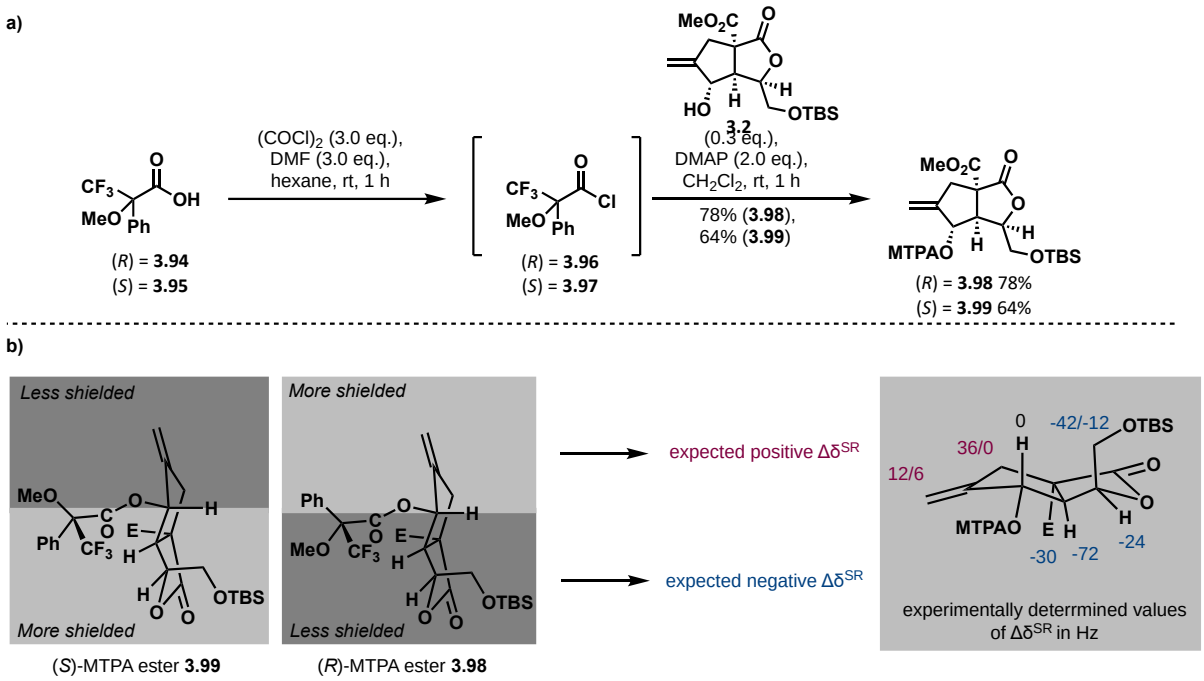


Scheme 3.29: Exploration of carbonate cyclisation with a more activated electrophile **3.93**.

Given the discouraging results and the time constraints of the project, this approach was discontinued, and the result obtained from the selenium dioxide-mediated allylic hydroxylation (Section 3.3.3) was deemed the appropriate allylic oxidation choice for our route.

3.4 Determination of absolute configuration *via* Mosher ester analysis

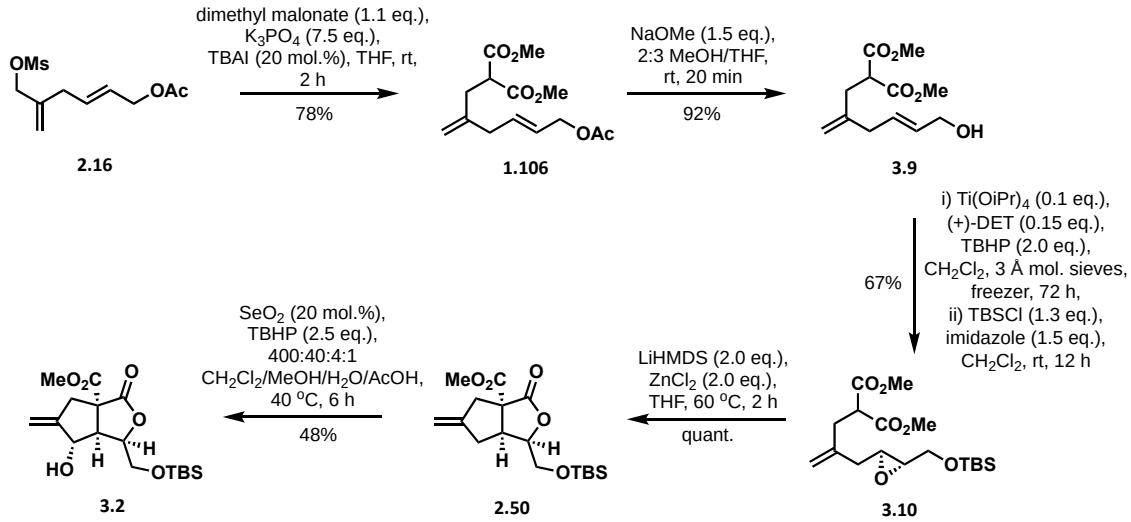
Although several of the compounds prepared during this project were solids, we were unsuccessful in our attempts to crystallise them for X-ray diffraction analysis due to their low polarity. As such, we required an alternative confirmation of the absolute configuration attained in the Sharpless epoxidation (Section 3.2.3) and propagated throughout the synthesis. The introduction of a sterically accessible secondary alcohol in the synthesis of **3.2** enabled the use of Kakisawa's modification of Mosher's method for this purpose.[100, 134] According to the method prescribed by Ward and Rhee,[135] (*R*)- and (*S*)-methoxytrifluoromethylphenylacetic acid (MPTA) **3.94** and **3.95** were converted into the corresponding acid chlorides **3.96** and **3.97**, and subsequently reacted with enantioenriched alcohol **3.2** in separate experiments in the presence of DMAP. This gave rise to (*R*)- and (*S*)-MTPA esters **3.98** and **3.99**, the NMR shifts of which were examined. In addition to this data confirming that **3.2** was essentially enantiopure, the use of Hoye's formulation[136] of Kakisawa's method clearly demonstrated that the absolute configuration found in **3.2** is that predicted by the mnemonic for the Sharpless epoxidation given in Section 3.2.3, and required for the project (Scheme 3.30).



Scheme 3.30: a) Preparation of **3.2** MTPA esters **3.98** and **3.99**. **b)** Mosher ester analysis of **3.2**. E=CO_2Me.

3.5 Chapter summary

In summary, we have successfully developed a high-yielding, scalable, and highly enantioselective route to key lactone **2.50** utilising a Sharpless epoxidation as the enantioinductive transformation; we then explored a range of allylic oxidation conditions within two strategic paradigms, eventually determining that the Guillemonat oxidation was the most synthetically viable (Scheme 3.31).

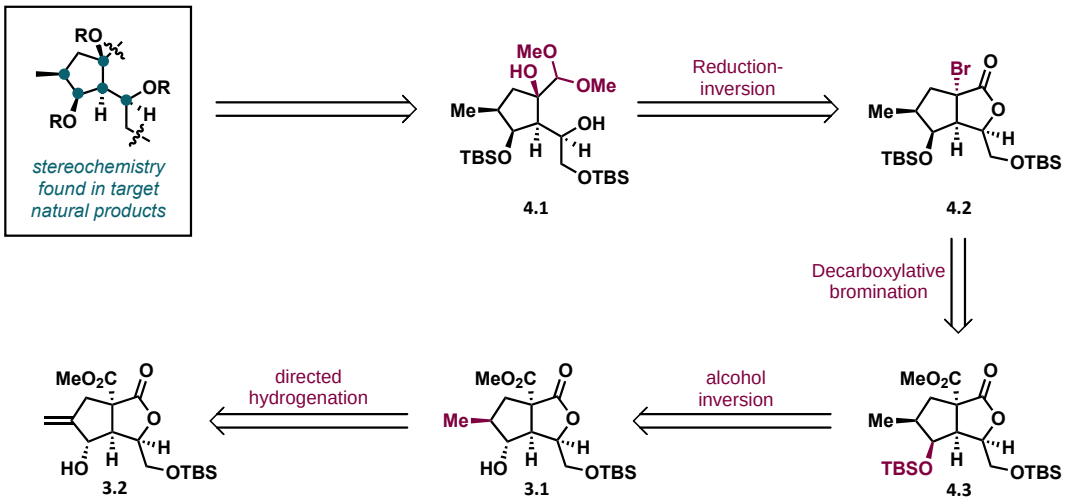


Scheme 3.31: Route to **3.2** developed in this chapter.

Chapter 4: Synthesis of the cyclopentane core 4.38

4.1 Chapter introduction

Having developed an enantioselective synthesis of lactone **2.50** and established suitable conditions for the allylic oxidation to give **3.2**, the stage was set for the next important transformation in our planned route (Section 1.5.2), the hydrogenation of the 1,1-disubstituted alkene to deliver a methyl group. Stereochemistry was the principal concern in planning this reaction: the putative target natural product **1.17** is furnished with the *S* configuration at the methyl-bearing carbon atom C2. Our initial strategy was to use the recently installed hydroxyl group to direct hydrogen delivery during this process, and to subsequently invert the stereochemistry of this hydroxyl group through the use of a Mitsunobu reaction.[64] Following this, we planned to convert the lactone fragment of **4.3** into an α-bromolactone **4.2**, and perform the reduction methodology outlined in Scheme 1.15 to provide the α-hydroxyacetal **4.1** (Scheme 4.1). This would constitute a synthesis of the core of euphodendroidin D **1.17**, and subsequent work would focus on preparing this fragment for coupling with the eastern fragment. This chapter will cover our investigations into this sequence.

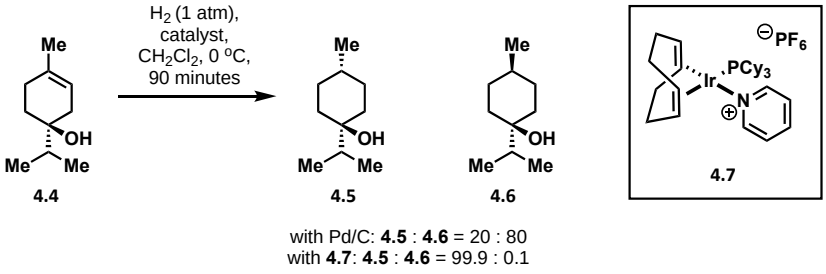


Scheme 4.1: Strategy for accessing the absolute and relative configuration of the jatrophanes *via* directed hydrogenation, alcohol inversion, decarboxylative bromination, and reduction-inversion.

4.2 Diastereoselective hydrogenation and alcohol inversion

4.2.1 Hydroxyl-directed hydrogenation using Crabtree's catalyst 4.7

The cationic iridium complex **4.7** was first synthesised by Robert Crabtree and George Morris in 1977,[137] and was subsequently found to be a highly active catalyst for the hydrogenation of alkenes.[138] In 1983, Crabtree and Davis disclosed that the hydrogenation of terpinen-4-ol using **4.4** exhibits a remarkably high diastereoselectivity, a phenomenon which they attribute to coordination of the Lewis basic hydroxyl group prior to hydrogen delivery (Scheme 4.2).[66] The selectivity observed was complementary to that afforded by a heterogeneous palladium-on-carbon catalyst, where the product distribution was ascribed to steric control of hydrogen delivery. Since these findings, 'Crabtree's catalyst' **4.7** has become a mainstay of stereoselective synthesis, and its reactivity a classic example of substrate-controlled stereoselectivity in catalysis.

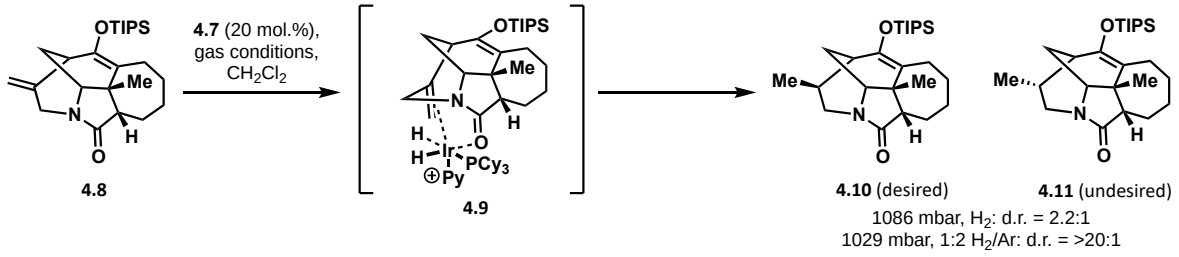


Scheme 4.2: Results from Crabtree and Davis regarding the directing effect observed in the hydrogenation of terpinene-4-ol **4.4** by Crabtree's catalyst **4.7**.

Racemic lactone **3.2** was exposed to a standard balloon-contained hydrogen atmosphere in the presence of 20 mol.% of **4.7** in dichloromethane (Table 4.1, entry 1). This led to rapid consumption of the starting material, with full conversion achieved in 30 minutes. NMR spectroscopic analysis of the crude reaction product revealed two compounds in a ratio of 2:1; a difficult chromatographic separation followed by the acquisition of NOESY ^{1}H NMR spectra allowed characterisation of these compounds as stereoisomers **4.12** and **3.1** (see Scheme 4.4 below for this analysis), with the desired isomer **3.1** formed as the major product. Although this was a promising result, the conversion of a

third of the substrate material to a difficult-to-separate and irrecoverable by-product led us to deem that it required optimisation before it could be considered synthetically useful. Alternatively, we performed the hydrogenation using palladium-on-carbon in ethyl acetate, which resulted in a diastereomeric ratio of 3:1 with **4.12** formed as the major product (entry 2). This indicated that **4.12** was likely the preferred product on either a steric or thermodynamic basis. This inauspicious result led us to investigate avenues through which the diastereoselectivity of the Crabtree's catalyst-mediated hydrogenation of **3.2** might be improved in favour of the desired product **3.1**.

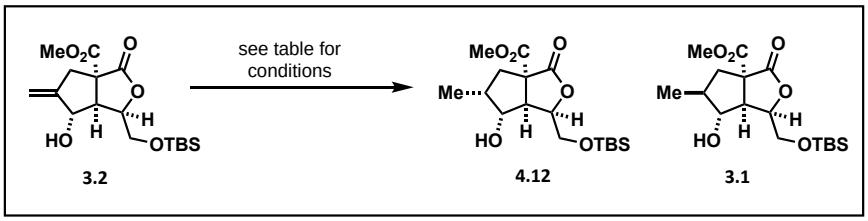
Fortunately, we were aware of Dixon's 2017 synthesis of himalensine A;[139] amidst a generally impressive series of results, their observations regarding the effect of partial hydrogen pressure on the stereochemical outcome of a Crabtree's catalyst-mediated hydrogenation of **4.8** stand out. They had observed a significant spike in selectivity for the directed product **4.10** over the 'steric' product **4.11** upon a reduction in partial hydrogen pressure, an effect which they attribute to a coordinative saturation of the iridium species at high hydrogen concentration precluding chelation by the Lewis basic amide (Scheme 4.3).



Scheme 4.3: Results from Dixon *et al.* regarding the effect of hydrogen partial pressure on the diastereoselectivity of the hydrogenation of **4.8** by Crabtree's catalyst **4.7**.

In line with this, we varied the partial hydrogen pressure by using single-skinned balloons and doping the gas mixture with nitrogen. A 1:1 gaseous mixture of nitrogen/hydrogen in a single-skinned balloon gave a 5:2 ratio of **3.1** to **4.12** (entry 3); a 3:1 mixture gave a ratio of approximately 10:1 (entry 4).

We considered this result to be useful to the project, in addition to a corroboration of the finding of Dixon and co-workers and a further indication that partial pressure effects can play a decisive role in the stereochemical outcome of substrate-directed Crabtree's catalyst-mediated hydrogenation. This utility comes with a caveat, however, in the context of our project: the scalability of this process was never explored and could potentially prove problematic. In particular, it should be noted that Crabtree's catalyst is known to have a comparatively short lifetime under typical reaction conditions;[138, 140] as such, one might expect that this catalyst is ill-suited to a large-scale heterogeneous reaction under a low hydrogen pressure, where gas-solution mass transfer effects impose a limit on productive turnover. Additionally, the administration of a stoichiometric volume of hydrogen at low partial pressure might require specialised laboratory equipment on a large scale.



Entry	Catalyst (mol.%)	Solvent	H_2/N_2 volume ratio	Result
1	**4.7** (20)	CH_2Cl_2	Pure H_2	**4.12**/**3.1** = 1 : 2
2	Pd/C (10)	EtOAc	Pure H_2	**4.12**/**3.1** = 3 : 1
3[a]	**4.7** (20)	CH_2Cl_2	1:1	**4.12**/**3.1** = 2 : 5
4[a]	**4.7** (20)	CH_2Cl_2	1:3	**4.12**/**3.1** = 1 : 10

Table 4.1: Results of the hydrogenation of **3.2** under different catalytic conditions and hydrogen partial pressures. Reactions conditions were: **3.2** (1.0 eq.), catalyst, solvent, gas balloon, 20 °C. Product ratio was determined by inspection of the ^{1}H NMR spectrum of the crude reaction material. [a]Gas balloon was single-skinned.

The relative configurations of **4.12** and **3.1** were confirmed by ^{1}H NMR NOESY experiments. The key correlations used for each stereochemical assignment are shown below in Scheme 4.4. In compound **4.12**, a reciprocal NOE correlation between the bridgehead proton and the protons of the methyl

group implied the *exo*- disposition of the methyl group. This was corroborated by a reciprocal NOE correlation between the methyl group and the proton of the hydroxyl group. On the *endo*- face, the protons of the silyloxymethyl group and the alkyl proton of the secondary alcohol showed reciprocal NOE correlations to the alkyl proton of the methyl-bearing methine group, further corroborating this assignment. In compound **3.1**, the bridgehead proton showed a reciprocal NOE correlation with the alkyl proton of the methyl-bearing methine group, implying an *exo*- disposition. Both the protons of the silyloxy group and the secondary alcohol alkyl proton showed reciprocal NOE correlations with the protons of the methyl group, implying that the methyl group was *endo*-, in keeping with the assignment of **4.12**.

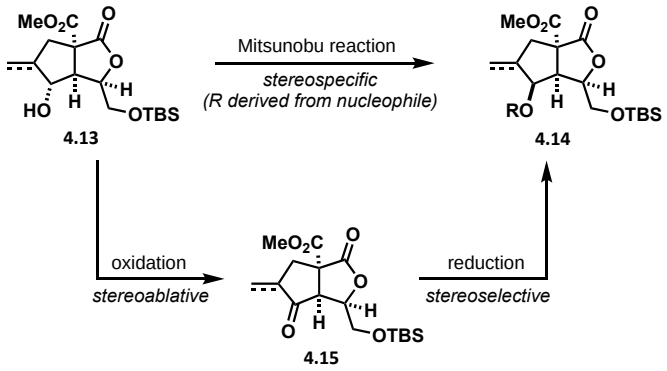
a)

b)

Scheme 4.4: Selected NOESY correlations used in the stereochemical assignments of compounds **4.12** and **3.1**. **a)** Correlations for **4.12**. **b)** Correlations for **3.1**. E = CO_2Me.

4.2.2 Mitsunobu reaction

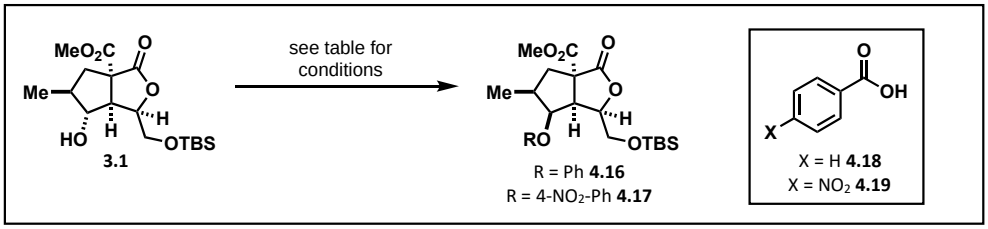
Having set the configuration of the methyl-bearing carbon atom, we now sought to invert the configuration of the hydroxyl-bearing carbon atom. The most prevalent strategies for alcohol inversion in the literature are stereospecific inversion *via* activation of the hydroxyl and subsequent S_N2 reaction, and oxidation to the ketone followed by stereoselective reduction. Of these methods, the former has certain advantages in the general case: it constitutes a more efficient transfer of stereochemical information, and is typically achieved using the Mitsunobu reaction,[64] a reliable protocol which allows for one-pot activation and substitution and tolerates a range of useful nucleophiles. The latter strategy of oxidation-reduction constitutes the destruction and re-establishment of stereochemical information and relies on substrate control for diastereoselectivity, which is disadvantageous in the general case; however, it is ideally suited for systems where one face of the ketone intermediate is significantly more hindered than the other, which are precisely the systems where one would expect the Mitsunobu reaction to be challenging due to unfavourable steric interactions in either the activation or S_N2 steps. As such, there is a strong degree of complementarity between these two strategies, which are shown in Scheme 4.5.



Scheme 4.5: Different strategies for alcohol inversion.

We began by investigating the Mitsunobu reaction in the context of our system. The results of this experimentation are summarised in Table 4.2. Initial attempts in refluxing tetrahydrofuran using benzoic or nitrobenzoic acid as a nucleophile with DIAD and triphenylphosphine led to no conversion

of the starting material (entry 1, entry 2). Moving into refluxing toluene enabled the slow conversion of material into a new compound which was isolated in a yield of 52% after 24 hours reaction time, and subsequently found to be the desired benzoate ester **4.16** (entry 3). An increase in the concentration of the other reagents and extension of the reaction time to 48 hours led to full conversion of the starting material and a 78% yield of **4.16** (entry 4).

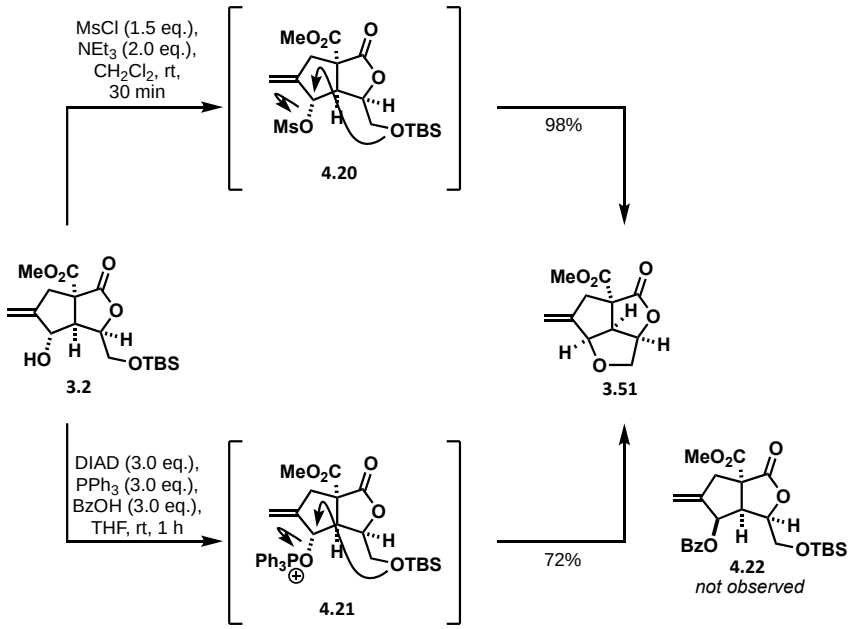


Entry	Nucleophile	Solvent	Temperature (°C)	Result
1	**4.18**	THF	70	No reactivity
2	**4.19**	THF	70	No reactivity
3	**4.18**	PhMe	110	52% yield of **4.16** after 24 hours
4[a]	**4.18**	PhMe	110	78% yield of **4.16** after 48 hours

Table 4.2: Results of the investigation into the Mitsunobu reaction of **3.1**. Reaction conditions were: **4.16** (1.0 eq.), triphenylphosphine (3.0 eq.), DIAD (3.0 eq.), nucleophile (3.0 eq.), temperature. [a] 5.0 equivalents of all reagents used.

Although this was a successful result, the harsh conditions, extended reaction time, and large excess of challenging-to-separate reagents required for this transformation encouraged us to consider alternatives. We reasoned that allylic alcohol **3.2** was a prospectively interesting substrate for the Mitsunobu protocol as the unsaturation should accelerate the desired S_N2 reaction. This would give an inverted allylic ester **4.22**, which would allow us to investigate hydrogenation using steric control rather than direction by the hydroxyl group.

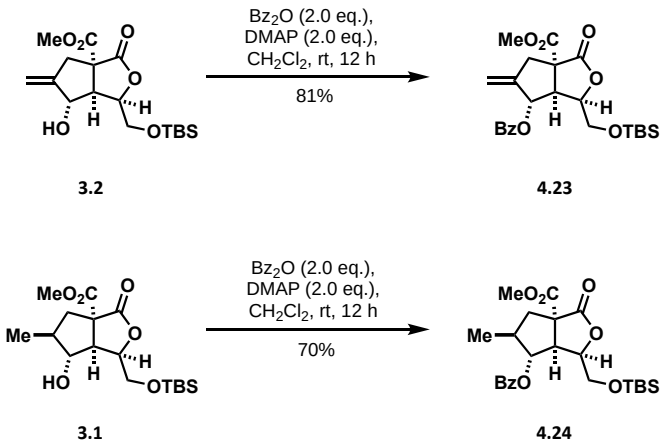
Exposure of **3.2** to Mitsunobu conditions led to the full consumption of starting material at room temperature in one hour, a result which was surprising given the inertia of **3.1**. Although the product was chromatographically inseparable from the triphenylphosphine oxide formed during the reaction, analysis of the ^{1}H NMR spectrum of the product showed the loss of the silyl group and the retention of the double bond. We tentatively assigned the structure of this product as desilylative cycloetherification product **3.51**. (This compound has already been mentioned in Section 3.3.4; this is a reflection of the topical, rather than chronological, arrangement of this thesis. This result was the initial seed of the S_N2'-based strategy investigated in that chapter). In order to confirm this assignment, we resolved to prepare an authentic sample of **3.51** *via* mesylation of **3.2** to give mesylate **4.20**, followed by fluoride deprotection of the silyl group to engender a cyclisation. Indeed, such was the facility of this cyclisation that no deprotection step was required, with **3.51** being formed in a nearly quantitative yield from the mesylation reaction (Scheme 4.6). Although this result is undesirable from a synthetic perspective, it further corroborates the assignment of the relative configuration of **3.2**. The absence of such a cyclisation in the Mitsunobu reaction of **3.1** bears brief comment: presumably, the electrophilicity of the allylic oxophosphonium **4.21** is increased to such an extent compared with the saturated system that the weakly nucleophilic silyl ether can engage it in



Scheme 4.6: Facile desilylative cycloetherification of **3.2** under Mitsunobu or mesylation conditions to give **3.51**.

the unsaturated system. The reduced steric accessibility of the C-O antibonding orbital in **3.1** may also be a contributing factor, as may the ground state conformational change induced by the *endo*-disposed methyl group. However, the former would also exert a comparatively inhibitory effect on the (successful) intermolecular S_N2 step of the Mitsunobu reaction of **3.1**, and the latter might be expected to be overcome by the high reaction temperature and extended duration of that Mitsunobu reaction.

It should be noted that esters **4.23** and **4.24** were prepared *via* standard DMAP-catalysed esterification of **3.2** and **3.1** during the above investigation into the Mitsunobu reaction; this was to lend confidence to the stereochemical assignment of the products by enabling us to distinguish true Mitsunobu products from direct starting material acylation products (**Scheme 4.7**).[141]

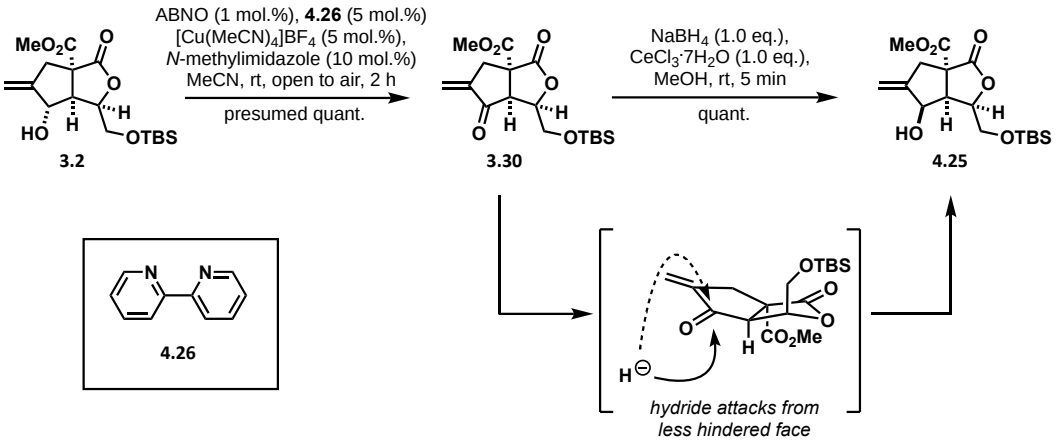


Scheme 4.7: Preparation of **4.23** and **4.24** by acylation to add weight to the stereochemical assignment of **4.16**.

4.2.3 Oxidation followed by hydride reduction

The drawbacks of the Mitsunobu reaction when performed on the saturated substrate **3.1** and failure when performed on the allylic substrate **3.2** prompted us to explore the feasibility of the oxidation-reduction strategy for alcohol inversion discussed at the beginning of Section 4.2.2. Oxidation of alcohol **3.2** to **3.30** was attempted using the ABNO variant of Stahl's copper-catalysed aerobic oxidation protocol;[142-144] after one hour at room temperature, the reaction was a blue-green colour,

indicative of persistent copper(II) species and the completion of the reaction. Although the simple bipyridyl ligand **4.26** could be used, no reaction was observed when TEMPO was used in place of ABNO. Enone **3.30** was the only compound visible in the ^{1}H NMR spectrum of the crude reaction mixture; as observed previously (Section 3.3.3), this compound was unstable under chromatographic conditions. As such, the crude material was subject to Luche's conditions for the reduction of unsaturated ketones;[145, 146] this resulted in the extremely rapid formation of **4.25** as the only product. The exclusive addition of hydride to the *exo*- face of enone **3.30** further evidences the crowded steric environment inside the 'bowl' of the oxabicyclo-[3.3.0]-octane (Scheme 4.8).



Scheme 4.8: Stahl oxidation and Luche reduction of **3.2** to give **4.25** *via* **3.30** (not isolated).

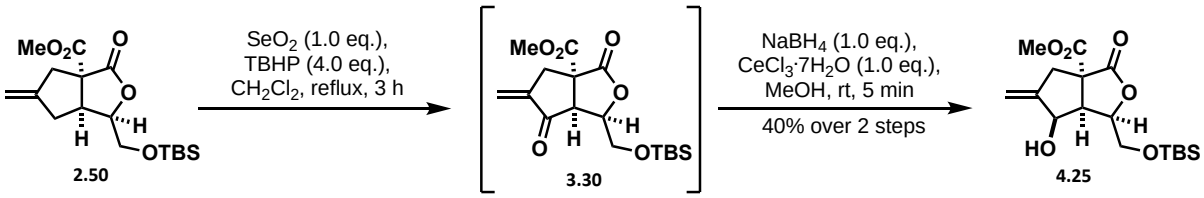
The stereochemistry of **4.25** was ascertained through a ^{1}H NOESY experiment (Scheme 4.9). Reciprocal NOE correlations between the bridgehead proton and the alkyl proton of a secondary alcohol indicated that hydride delivery had occurred on the *exo*- face. Reciprocal NOE correlations between the hydroxyl proton and the protons of the silyloxymethyl group corroborated this assignment.

Additionally, all other data indicated that **4.25** was a diastereomer of **3.1**. Comparative analysis between the NOESY spectra of **3.1** and **4.25** further cemented our stereochemical assignments of both, and these assignments are in keeping with mechanistic rationale (Scheme 4.9, Scheme 3.15).

Scheme 4.9: Selected NOESY correlations used in the stereochemical assignments of compounds **4.25**. E = CO_2Me.

It was now necessary to investigate whether hydrogenation of **4.25** would allow us to access the appropriate configuration at the methyl-bearing carbon atom through steric control. As such **4.25**, synthesised as delineated above, was subjected to standard hydrogenation conditions using palladium-on-carbon; this resulted in conversion to a promising 10:1 ratio of two products, as determined by ^{1}H NMR spectroscopic analysis of the crude reaction material. Only the major product, **4.26**, was isolated from column chromatography, and it was to our considerable chagrin that a NOE analysis indicated that this was the undesired hydrogenation epimer (see Scheme 4.11 below).

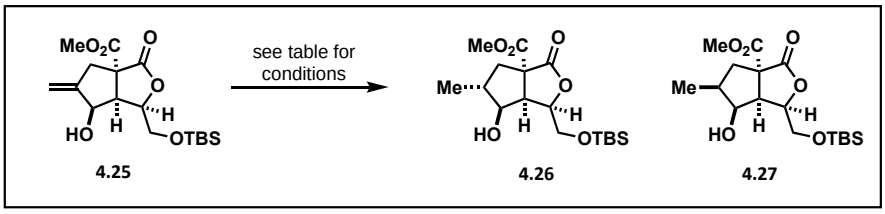
Whilst awaiting the NOE data for **4.26**, we attempted to repeat this result on a larger scale. Performing the Guillemonat oxidation on **2.50** at reflux in anhydrous dichloromethane gave enone **3.30** directly; a Luche reduction then gave **4.25** in a yield of 40%. Given the quantitative yield of **4.25** obtained by Stahl oxidation of **3.2** followed by Luche reduction, this implies that the true practical yield of the selenium dioxide-mediated step is 40%.



Scheme 4.10: Sequence for the synthesis of **4.25** from **2.50** *via* allylic oxidation to compound **3.30** followed by reduction.

When this batch of **4.25** was hydrogenated using the same conditions as before, a 3:2 ratio of diastereomers was obtained, a strikingly different outcome to that observed previously. Undesired product **4.26** remained the major product, whilst the minor product was found to be the desired stereoisomer **4.27** (Table 4.3, entry 1). This apparent irreproducibility of outcome in the hydrogenation of **4.25** demanded an explanation. A repeat experiment conducted on material which had been purified by two rounds of column chromatography confirmed the discrepancy and gave a product ratio of 3:2. Given that the chemical history of the starting material batch was the most obvious difference between the two results, a series of spiking experiments was performed. It was

found that the inclusion of approximately 0.1 mol.% of Cu(bipy)BF_4 (0.01 equivalents with respect to palladium) led to the high selectivity outcome (entry 2). Increasing this loading any further led to complete inhibition of hydrogenation, with no appreciable conversion observed after twelve hours (entry 3). Although **4.26** was not the stereoisomer we desired to access in the context of a total synthesis of natural product **1.17**, the ability to access this stereoisomer is relevant to any structure-activity relationship studies of **1.17** or other jatrophane natural products which might be carried out in the future. Moreover, this result highlights that dramatic changes in selectivity can be elicited by catalyst poisoning. The application of these poisoned hydrogenation conditions to other hydrogenation reactions undertaken in this project led to no significant changes in selectivity, indicating a strong degree of system-dependence in this chemistry. We attribute this phenomenon to catalyst poisoning.[147]



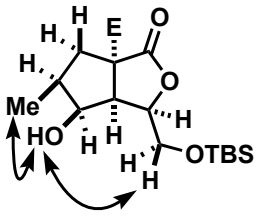
Entry	Additive (mol.%)	Result
1	None	3:2 ratio **4.27** to **4.26**, 92% combined
2	Cu(bipy)BF_4 (0.1)	10:1 ratio **4.27** to **4.26**, 87% combined
3	Cu(bipy)BF_4 (2.0)	No reactivity

Table 4.3: Results of the investigation into the hydrogenation of **4.25**. Reactions conditions were: **4.25** (1.0 eq.), palladium on carbon (10 mol.%), additive, hydrogen balloon, ethyl acetate, room temperature.

The relative configurations of **4.26** and **4.27** were determined by ^{1}H NOESY experiments. For **4.26,** a reciprocal NOE correlation between the alkyl proton of the secondary alcohol and the protons of the methyl group indicated the *exo*- disposition of the methyl group. This assignment was corroborated by a reciprocal NOE correlation between the alkyl proton of the methine group and the hydroxyl proton of the secondary alcohol on the *endo*- face of the oxabicyclo-[3.3.0]-octane system. The assignment of compound **4.27** was less facile due to overlapping peaks in the ^{1}H NMR spectrum; however a reciprocal NOE correlation between the hydroxyl proton and the protons of the methyl group was indicative. This assignment was corroborated by comparing the ^{1}H NOESY spectra of the two diastereomers.

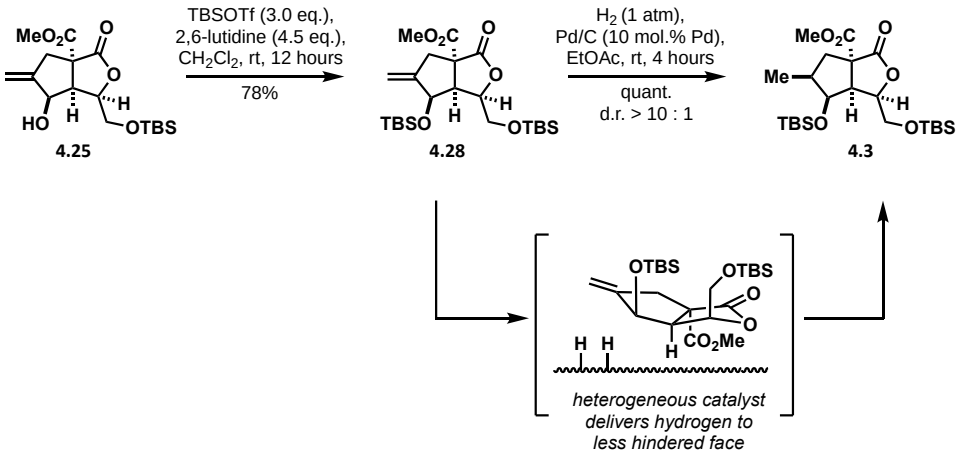
a)

b)



Scheme 4.11: Selected NOESY correlations used in the stereochemical assignments of compounds **4.26** and **4.27**. **a)** Correlations for **4.26**. **b)** Correlations for **4.27**. E = CO_2Me.

At this stage, having found methods for accessing all three undesired stereoisomers at the methyl- and oxygen-bearing carbon atoms in the cyclopentane ring in greater than 5:1 selectivity, we determined to access the desired **4.3**. To achieve this, we opted to overwhelm any native selectivity in the system with a large steric blocking group. **4.25** was silylated using *tert*-butyldimethylsilyl triflate (TBSOTf) in the presence of 2,6-lutidine to give **4.28** in a yield of 78% after twelve hours. The use of the analogous silyl chloride (TBSCl) failed to elicit any conversion of the starting material, as did the use of triisopropylsilyl triflate (TIPSOTf); these failures presumably stem from the need to introduce the large silyl group onto the already sterically congested *endo*- face of the oxabicyclo-[3.3.0]-octane. The silyl ether **4.28** thus obtained was then hydrogenated using palladium-on-carbon as a heterogeneous catalyst. Pleasingly, this delivered **4.3** as the sole product in a quantitative yield after four hours, affirming the validity of the sterically controlled approach (Scheme 4.12). It should be mentioned that this hydrogenation reaction was somewhat capricious; reproducible successful results were obtained when the substrate solution was sparged first with nitrogen and then with hydrogen, before being added to a flask under nitrogen containing the catalyst. Rapid stirring and a fresh, triple-skinned hydrogen balloon also led to a faster reaction.



Scheme 4.12: Silylation and hydrogenation of **4.25** *via* **4.28** to give **4.3** as the major product.

The relative configuration of **4.3** was confirmed by a ^{1}H NOESY experiment (Scheme 4.13). A reciprocal NOE correlation between the alkyl methine proton and the alkyl proton of the secondary silyl ether

indicated that hydrogenation had been successfully directed to the *exo*- face. This assignment was corroborated by a reciprocal NOE correlation between the protons of the methyl group and those of the alkyl protons of the silane, and are in keeping with other stereochemical assignments made throughout this project.

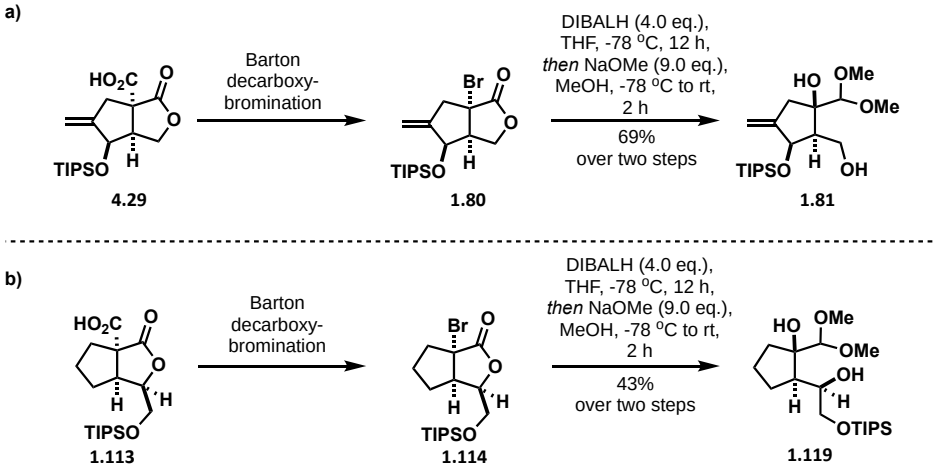
Scheme 4.13: Selected NOESY correlations used in the stereochemical assignment of compound **4.3**. E = CO_2Me.

4.3 Bromination and reduction

4.3.1 Prior art and use of 2.50 as model substrate

Having set the stereochemistry at the methyl- and oxygen-bearing carbon atoms, the next task was to convert the lactone structure into α-hydroxyacetal **4.1**. As discussed in Section 1.5.2 and Scheme 4.1, we had chosen to achieve this *via* the DIBALH-mediated reduction of α-bromolactone **4.2**, which would be accessed *via* the decarboxylative bromination of **4.3**. Given that **2.50** was furnished with the same relevant functionality as **4.3**, it was chosen as a model substrate for this sequence.

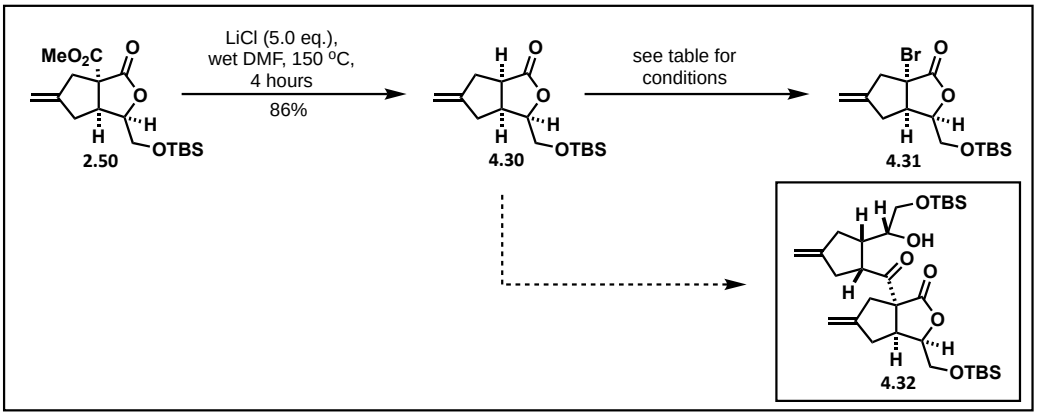
During his work on the more simplified model system, Dr Bruno Sousa had accessed the α-bromolactone **1.114** from the carboxylic acid **1.113** through the use of a Barton radical decarboxylation in the presence of bromotrichloromethane.[60] This was for two reasons. Firstly, it was the sequence performed by Dr Erin Shepherd during her attempted synthesis of pepluanin A **1.18**, where an attempted Krapcho decarboxylation-anionic bromination sequence had failed;[58, 148] secondly, the epoxide formation/opening conditions used on the model system had given the carboxylic acid directly (see Section 2.3.1; Scheme 4.14).



Scheme 4.14: Decarboxylative halogenation and reduction sequences performed by **a)** Dr Erin Shepherd on **4.29** and **b)** Dr Bruno Sousa on **1.113**.

As lactone **2.50** is endowed with a methyl ester rather than a carboxylic acid, and given our prior difficulties with basic hydrolysis in this system (Section 2.3.4), it was convenient to briefly explore the Krapcho decarboxylation-anionic bromination sequence on our model system. As such, **2.50** was treated with lithium chloride in wet dimethylformamide at reflux; after four hours, this resulted in an

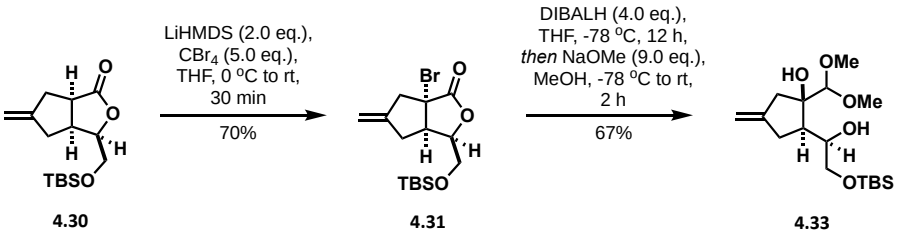
86% yield of lactone **4.30**. Anionic bromination proved slightly more challenging. Attempts to deprotonate the starting material with lithium hexamethyldisilazide (LiHMDS) followed by the addition of carbon tetrabromide resulted in no isolable compounds; the ESI^+ mass spectrum of the crude material contained a peak corresponding to the mass of Claisen self-condensation product **4.32** (*m/z* = 587.3 = $[M+Na]^+$, not isolated). Similar results were obtained using inverse addition; this indicated that the undesired Claisen condensation was outcompeting deprotonation. As such, LiHMDS was added to a mixture of starting material **4.30** and 20 equivalents of carbon tetrabromide in order to statistically outcompete the Claisen process. Gratifyingly, this led to a 68% yield of α-bromolactone **4.31**. The stoichiometry of carbon tetrabromide could be lowered to five equivalents without impairing this outcome; these results are summarised in Table 4.4.



Entry	Method	Equivalents of CBr_4	Result
1	LiHMDS added to substrate	3.0	No products isolated, **4.32** observed by MS
2	Substrate added to LiHMDS	3.0	No products isolated, **4.32** observed by MS
3	LiHMDS added to substrate and CBr_4	20.0	68% yield of **4.31**
4	LiHMDS added to substrate and CBr_4	5.0	70% yield of **4.31**

Table 4.4: Results of the investigation into the anionic bromination of **4.30**. Reactions conditions were: **4.30** (1.0 eq.), carbon tetrabromide, LiHMDS (2.0 eq.), tetrahydrofuran, 0 °C to rt, 30 minutes.

Having accessed α-bromolactone **4.31**, we now needed to trial the DIBALH-mediated reduction. Exposure of **4.31** to four equivalents of DIBALH at -78 °C for twelve hours, followed by the introduction of sodium methoxide in methanol, led to the formation of **4.33** in a yield of 67%. This compound was found to be stable on the timescale of column chromatography and characterisation. This result is summarised in Scheme 4.15.



4.30 **4.31** **4.33**

Scheme 4.15: Bromination and reduction of compound **4.30** to give acetal **4.33**.

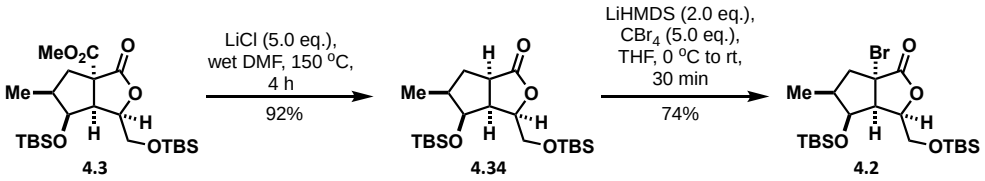
The relative configuration of **4.33** was assigned with comparison to the results of Dr Sousa and Dr Shepherd (Section 1.4, 1.5), and is the only diastereomer which can be obtained from the above conditions which is in keeping with the mechanistic rationale. A ^{1}H NOESY experiment was run to cement this assignment, however due to overlapping peaks in the ^{1}H NMR spectrum, all correlations which would either clearly prove or disprove this assignment were ambiguous.

4.3.2 Extension of the reduction sequence to lactone 4.3

Having devised appropriate conditions for, and accomplished, the desired decarboxylation-bromination-reduction sequence on the model system **2.50**, we now sought to apply this methodology to the more advanced **4.3**. This 'real' substrate retains the salient functionality from the model substrate and much of the peripheral substitution; the main chemical difference is the increase in steric crowding in the 'bowl' of the oxabicyclo-[3.3.0]-octane system on account of the methyl and silyloxy groups.

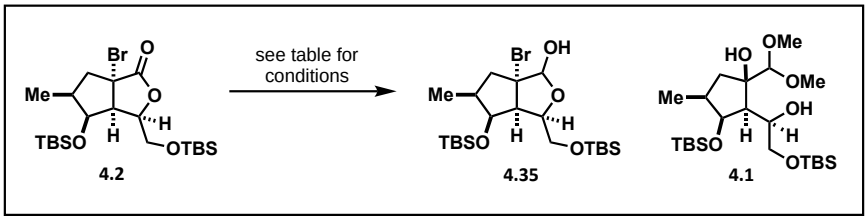
Subjection of **4.3** to the same Krapcho decarboxylation conditions outlined previously resulted in the complete consumption of starting material and the formation of **4.34** in an isolated yield of 92%. The

anionic bromination conditions delineated in Table 4.3 led to the formation of **4.2** in a yield of 74%, vindicating the use of the model system for the investigation of this sequence. This set of results is summarised in Scheme 4.16.



Scheme 4.16: Krapcho decarboxylation and anionic bromination of **4.3** to give **4.2**.

The reduction of the α-bromolactone **4.2** proved to be less comparable to the reduction of the model system α-bromolactone **4.31**; the summary of our investigation to that end is contained within Table 4.5. Following an initial failure to replicate the reactivity of the model system, we chose to focus on the initial reduction step to the lactol **4.35**, before subsequently converting this to the desired acetal **4.1**. Difficulties associated with maintaining test-scale reactions at -78 °C overnight engendered a degree of irreproducibility in the initial results; at length it was determined that performing the reaction in tetrahydrofuran at -78 °C elicited no conversion of the starting material even after 36 hours. This deserves brief commentary in light of Dr Erin Shepherd's and our finding that **1.80** and **4.31** respectively succumbed to these conditions; evidently the hydride reduction of the lactone to an aluminium-bound acetal can tolerate the steric demand of either of the *endo*- disposed silyloxy groups, but not both, at -78 °C (entry 1). Running the reaction at 0 °C in tetrahydrofuran resulted in the slow consumption of starting material through to lactol **4.35**, however the TLC profile and ^{1}H NMR spectrum of the reaction material at full starting material conversion (six hours) exhibited a rich array of products which could not be identified on the test scale (entry 2). We ascribed this undesirable outcome to the rate of product degradation being competitive with that of starting material consumption. As such, we examined whether the use of a non-coordinating solvent might accelerate the reduction step; indeed, performing the reaction in toluene resulted in a 58% yield of lactol **4.35** after 20 minutes at 0 °C, followed by rapid column chromatography (entry 3).



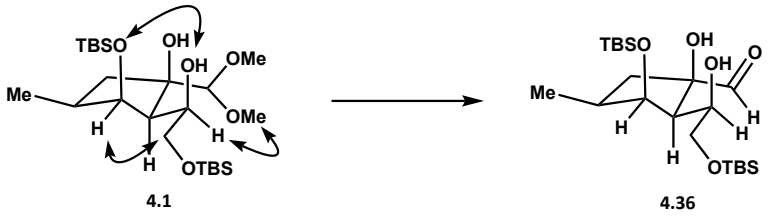
Entry	Solvent	Temperature (°C)	Result
1	THF	-78	No consumption of **4.2**
2	THF	0	Slow consumption of **4.2**, wide range of products after six hours
3	PhMe	0	58% yield of **4.35** after 20 minutes

Table 4.5: Results of the investigation into the reduction of **4.2**. Reactions conditions were: **4.2** (1.0 eq.), DIBALH (4.0 eq.), solvent, temperature.

With lactol **4.35** in hand, it was treated with sodium methoxide in methanol and tetrahydrofuran with the intention of reaching acetal **4.1**. This led to the formation of an inseparable mixture of compounds, characterised as the desired acetal **4.1** and the aldehyde **4.36** (Scheme 4.17) with full conservation of mass. Presuming that **4.36** arose from the partial hydrolysis of **4.1** during work-up or in the NMR sample on the small scale of this reaction (0.002 mmol), we attempted to repeat this transformation on a larger scale to access **4.1** cleanly. Performing the reduction on **4.2** on a larger scale (0.020 mmol) and subsequently treating the crude material, rather than purified lactol **4.35**, with sodium methoxide gave two interesting results: firstly, **4.1** and **4.36** were both obtained, again in a ratio of 5:2**;** secondly, there was a significant proportion of epoxide **4.38** isolated.

The retention of the ratio of **4.1** to **4.36** implies that the partial hydrolysis of **4.1** was not an artefact of performing the reaction on a small scale, and is in fact a reliable result of performing the aqueous work-up. The reason for the increased tendency of this acetal to hydrolyse as compared with the model substrate **4.33** or acetal **1.81** made by Dr Erin Shepherd is unclear. One possibility is that a general increase in steric compression around the cyclopentane ring in **4.1** as compared with these

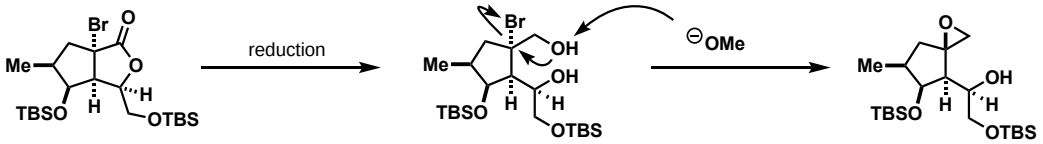
less hindered species leads to a greater propensity for the acetal to ionise to release this compression (Scheme 4.17).



4.1 4.36

Scheme 4.17: Steric interactions around the cyclopentane ring of **4.1** possibly driving acetal hydrolysis.

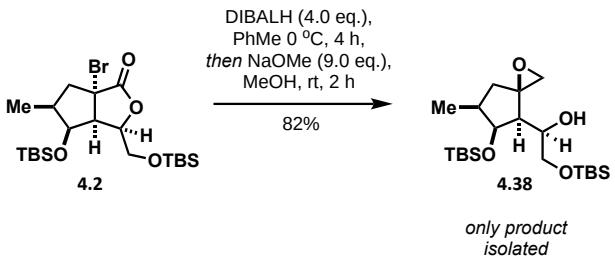
The formation of the epoxide **4.38** presumably arises *via* the production of diol **4.37** from the reduction of the lactol **4.35**, followed by a 3-*exo*-trig cyclisation upon exposure to base (Scheme 4.18). Presumably diol **4.37** could be isolated from the reduction reaction using appropriate chromatographic conditions, and this result explains the loss of mass balance previously observed (Table 4.4).



4.2 4.37 4.38

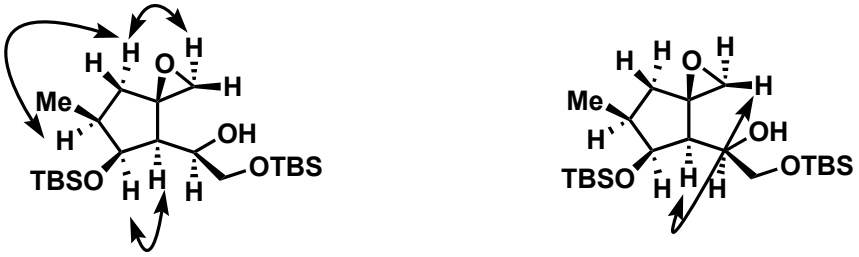
Scheme 4.18: Presumed pathway for the formation of epoxide **4.38** *via* diol **4.37** (not isolated).

As the acetal **4.1** could not be accessed cleanly, we reasoned that epoxide **4.38** presented a more synthetically useful intermediate for our synthesis. As such, we repeated the sequence described in this section with a four-hour reaction time for the DIBALH reduction followed by brief exposure to sodium methoxide; this ultimately led to the isolation of epoxide **4.38** in a yield of 82% from **4.2** (Scheme 4.19).



Scheme 4.19: One-pot reaction to yield epoxide **4.38** directly from lactone **4.2**.

The stereochemistry of epoxide **4.38** was confirmed by ^{1}H NMR NOESY experiments, the key correlations of which are shown below (Scheme 4.20). Reciprocal NOE correlations between the epoxide protons and alkyl protons on the lower face (as shown) of the cyclopentane ring indicated the assignment shown, which is in keeping with all other results obtained and mechanistic rationale.

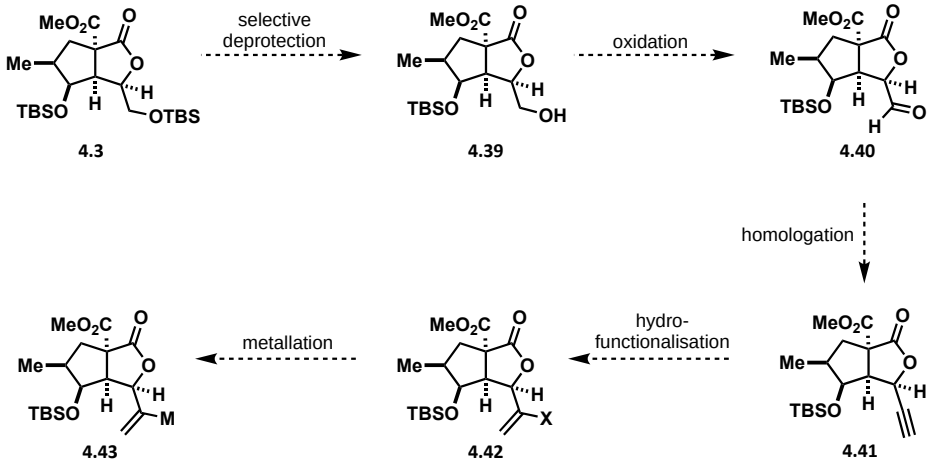


Scheme 4.20: Selected NOESY correlations used in the stereochemical assignments of compound **4.38**.

4.4 Attempts to install an α-vinyl pronucleophile

4.4.1 Strategy for the installation of a vinyl pronucleophile

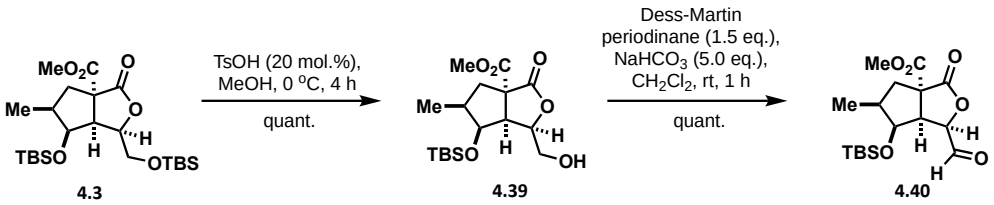
Having installed the five major stereocentres of the natural product core, the next challenge was to install a vinyl pronucleophile at the site occupied by the silyloxy group of lactone **4.3**. We chose **4.3** as the putative model substrate for this transformation due to its ease of accessibility and stability. Our plan for this sequence was to carry out a site-selective cleavage of the primary silyl ether to reach **4.39**, followed by an oxidation to an aldehyde **4.40**, and homologation to alkyne **4.41**. This terminal alkyne would then serve as the basis for derivatisation to the vinyl pronucleophile **4.42** (Scheme 4.21).



Scheme 4.21: Prospective transformation of silyl ether **4.3** into vinylmetallic reagent **4.43**.

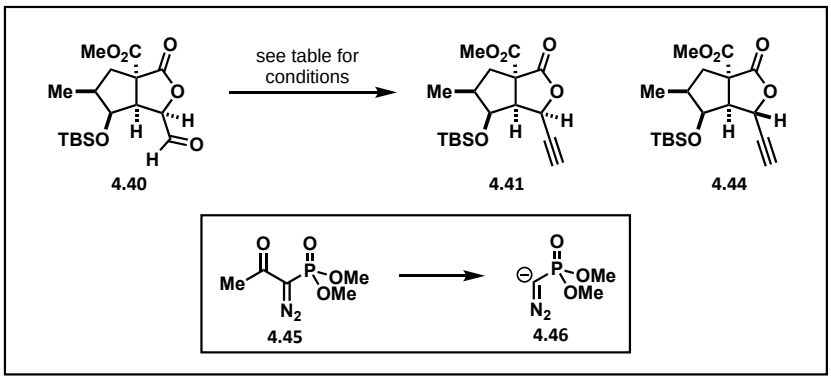
4.4.2 Synthesis of alkyne 4.41

The selective deprotection of **4.3** at the primary silyl ether was achieved by subjecting the starting material to catalytic *para*-toluenesulfonic acid in methanol at 0 °C. This proceeded quantitatively to give **4.39**, with no deprotection of the secondary silyl ether observed. Primary alcohol **4.39** was then treated with Dess-Martin periodinane buffered with sodium bicarbonate, which resulted in the formation of aldehyde **4.40** in a quantitative yield as a single diastereomer, which was confirmed by inference from subsequent data (Scheme 4.23) to be the desired (non-epimerised) one. These results are summarised in Scheme 4.22.



Scheme 4.22: Successful selective deprotection and oxidation of **4.3** to give **4.40**.

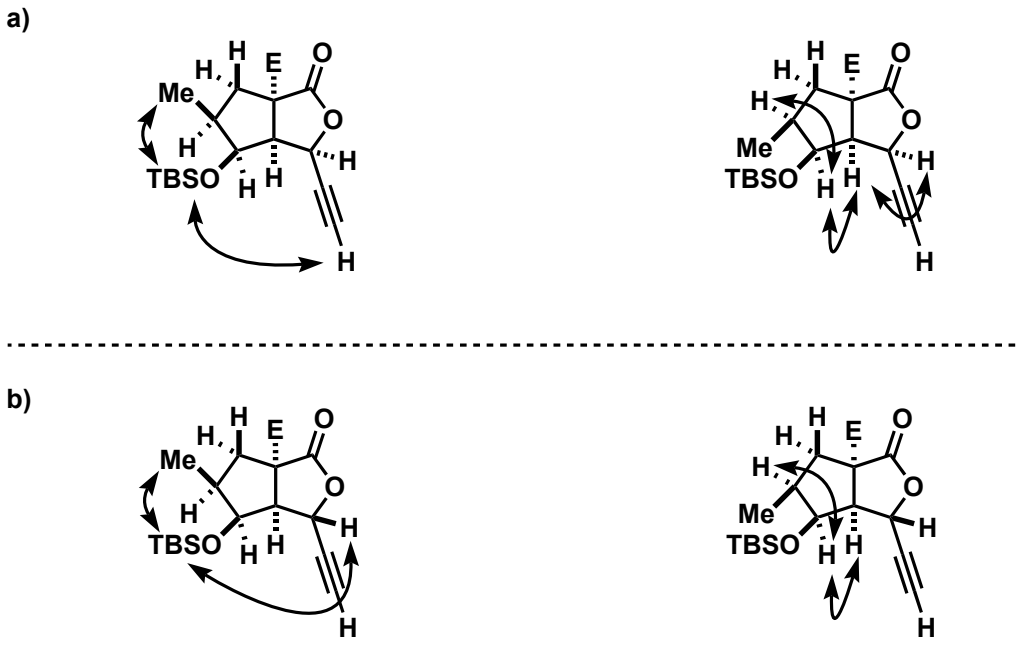
Having successfully reached aldehyde **4.40**, the next task was to perform a homologation to convert the aldehyde into an alkyne. There are several methods for achieving this within the synthetic canon; whilst the Ramirez-Corey-Fuchs sequence[149, 150] of reactions is a common approach, we chose to employ the Ohira-Bestmann reagent **4.45**[151, 152] on account of the milder reaction conditions. Aldehyde **4.40** and potassium carbonate were stirred in methanol at room temperature, and **4.45** was added (Table 4.6, entry 1). This led to rapid conversion of the starting material over the course of approximately ten minutes; however, inspection of the ^{1}H NMR spectrum of the crude reaction product revealed the presence of two alkyne species, assigned as diastereomers **4.41** and **4.44**, in a ratio of 3:2. It seemed evident that basic epimerisation of the starting material by potassium carbonate was the cause of this. Performing the same reaction at 0 °C had no effect on the outcome (entry 2). Given the rapidity of the homologation reaction, we reasoned that the order of reagent addition might exert a significant effect. Indeed, adding potassium carbonate to a stirred solution of **4.40** and **4.45** resulted in the formation of the products in a significantly more favourable ratio of 5:1 (entry 3); evidently the brief period in the first case when **4.40** and potassium carbonate were allowed to stir prior to **4.45** addition was sufficient for a significant degree of epimerisation to occur. Another prospective solution to this problem would be to pre-form the anionic Seyferth-Gillbert reagent **4.46** *in situ* by treatment of **4.45** with one equivalent of sodium methoxide prior to the addition of substrate.



Entry	Method	Temperature (°C)	Result
1	**4.45** added to a solution of **4.40** and K_2CO_3	20	3:2 ratio of **4.41**:**4.44**, 66% combined yield
2	**4.45** added to a solution of **4.40** and K_2CO_3	0	3:2 ratio of **4.41**:**4.44**, 64% combined yield
3	K_2CO_3 added to a solution of **4.40** and **4.45**	20	5:1 ratio of **4.41**:**4.44**, 71% combined yield

Table 4.6: Results of the investigation into the homologation of **4.40**. Reactions conditions were: **4.40** (1.0 eq.), **4.45** (2.0 eq.), potassium carbonate (3.0 eq.), methanol, temperature, 30 minutes.

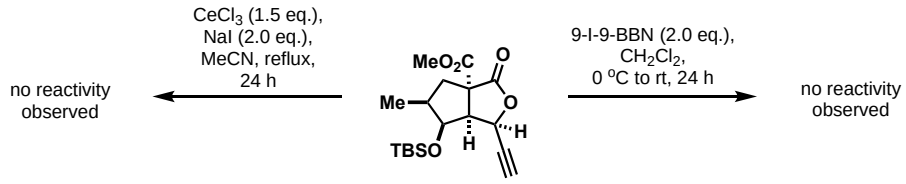
The stereochemistry of **4.41** and **4.44** was assigned by a ^{1}H NOESY experiment conducted on the mixture of the two (Scheme 4.23). For **4.41**, reciprocal NOE correlations between the terminal proton of the alkyne and the protons of the silane indicated that the transformations shown above had occurred without epimerisation of the α-proton of the aldehyde. This was corroborated by reciprocal NOE correlations between the lactone alkyl proton and the bridgehead proton on the *endo*- face. For **4.44**, reciprocal NOE correlations between the lactone alkyl proton and the protons of the silane were indicative of the assignment shown, which is in keeping with the assignment of **4.41**.



Scheme 4.23: Selected NOESY correlations used in the stereochemical assignments of compounds **a**) **4.41** and **b**) **4.44**.

Having successfully accessed terminal alkyne **4.41** in good yield, we now faced the challenge of converting it into a vinyl pronucleophile for use in a later macrocyclisation. As the Nozaki-Hiyama-Kishi reaction was the intended methodology for macrocyclisation (see Section 1.5.2), we focused on the installation of either an iodide or a tosylate at the internal position of the alkyne.

In general, most simple methods for the synthesis of α-vinyl iodides rely on the use of hydroiodic acid or a surrogate thereof. Given the acid-sensitive protecting groups found throughout our planned synthesis, we deemed 9-iodo-9-bicycloboranonane (9-I-9-BBN) to be the surest instantiation of this strategy to start with. Exposure of **4.41** to 9-I-9-BBN, however, led to no consumption of starting material over a 24 hour period. We thus turned to a procedure using cerium(III) chloride and sodium iodide published by the Marcantoni group, but this too failed to elicit any conversion of starting material (Scheme 4.24).

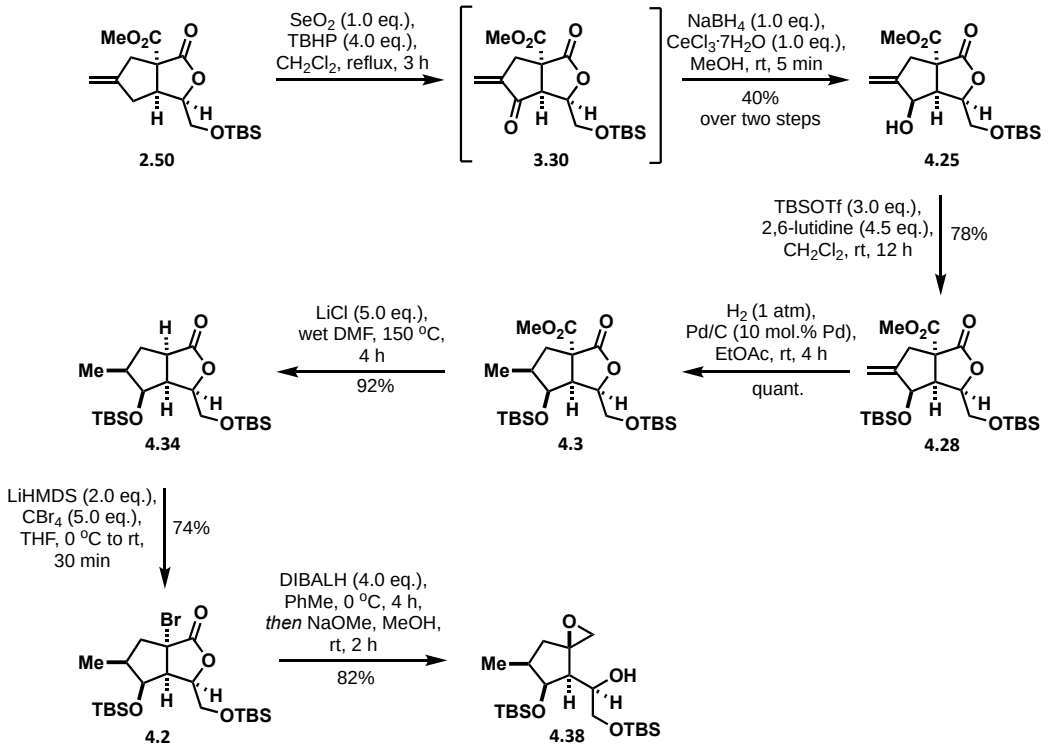


4.41

Scheme 4.24: Unsuccessful attempts to hydroiodinate alkyne **4.41**.

4.4.3 Chapter summary

In conclusion, we have developed a route from lactone **2.50** to epoxide **4.38** in a yield of 16% over seven steps. This sequence features a series of diastereoselective reductions which take advantage of the natural concavity of the oxabicyclo-[3.3.0]-octane ring system to achieve exquisite levels of stereocontrol; it concludes with an efficient reduction-cyclisation reaction to give spiro-epoxide **4.38**, establishing the fifth contiguous stereogenic centre in the jatrophane core and provide a useful handle for subsequent functionalisation (Scheme 4.25).



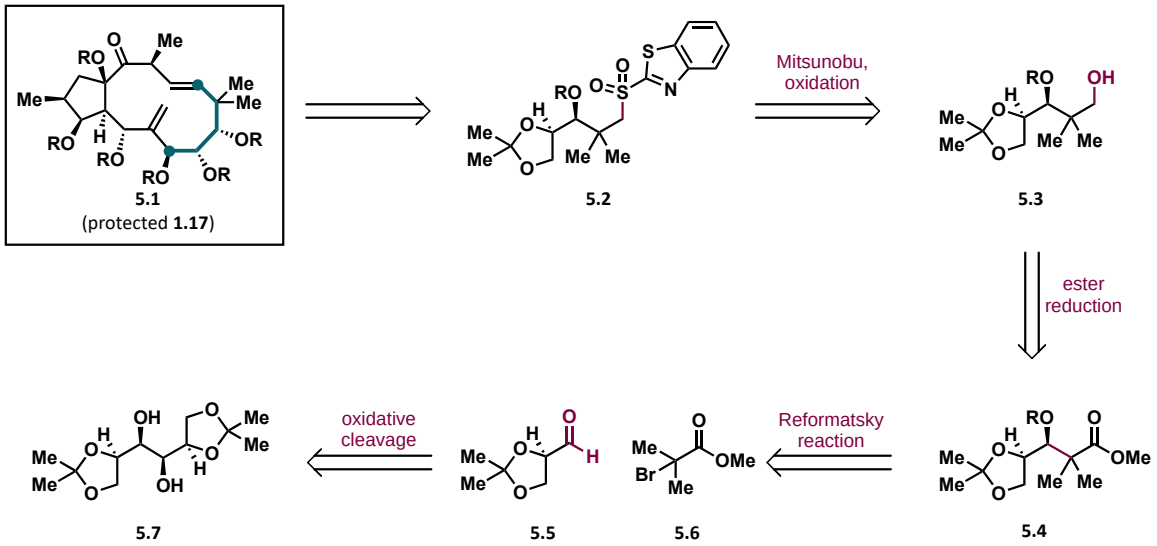
Scheme 4.25: Summary of the work covered in this chapter, resulting in epoxide **4.38.**

Chapter 5: Synthesis of the eastern fragment 5.2

5.1 Chapter introduction

The synthesis of the cyclopentane core **4.38**, discussed in the previous chapters, was the major challenge of the project and as such received the majority of our time and energy. However, as outlined in Section 1.5.2, our synthetic plan also featured 'eastern' fragment **5.2**. In that design, this open-chain fragment contains five of the atoms in the twelve-membered ring of the jatrophane skeleton, including the dimethylated quaternary carbon atom and two oxygen-bearing stereocentres; this chain is capped by an aryl sulfone on one end and a protected alcohol or aldehyde on the other end, enabling coupling to the cyclopentanoid fragment.

The stereogenic diol motif is perhaps retrosynthetically suggestive of the chemistry of Sharpless,[153] a canon which had thus far richly rewarded our solicitations; in spite of this, we elected to pursue the simpler, yet elegant, chiral pool-oriented strategy delineated below. In line with Dr Erin Shepherd's work on a homologue of this system (Scheme 1.12), the sulfone **5.2** would be installed *via* a Mitsunobu/oxidation sequence performed on alcohol **5.3**, accessed through the reduction of ester **5.4**. The stereodefined β-hydroxyester retron suggests the acquisition of the relative configuration through a Felkin-Nguyen[63] or Cornforth-Evans[154] stereocontrolled Reformatsky reaction[155] between methyl α-bromoisobutyrate **5.6** and glyceraldehyde acetonide **5.5**. The absolute stereochemistry would thus originate from that of **5.5**, the enantiopure synthesis of which is known to be accomplished by the oxidative cleavage of D-mannitol bisacetonide **5.7**.[156] This chapter will cover our investigation of this approach (Scheme 5.1).



Scheme 5.1: Strategy for the synthesis of 'eastern' fragment **5.2**, starting from chiral pool starting material D-mannitol acetonide **5.7**.

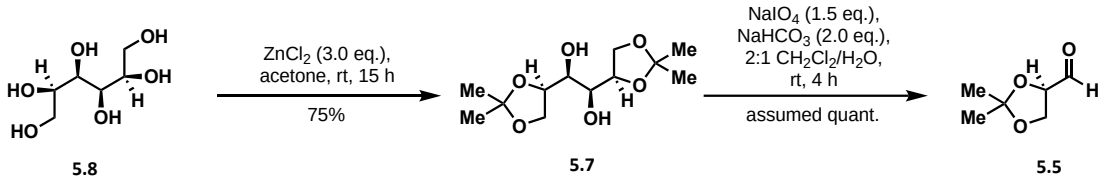
5.2 Reformatsky approach to ester 5.4

5.2.1 Synthesis of glyceraldehyde acetonide 5.5

The incorporation of two equivalents of acetone into D-mannitol **5.8** to deliver the bisacetonide **5.7** is a transformation which has abundant precedent in the synthetic literature. We initially followed the procedure of Yamauchi and co-workers,[157] using ten equivalents of zinc(II) chloride in dry acetone. Although this did indeed yield the desired product **5.7** in a high yield of 81%, the work-up protocol was somewhat impracticable on a larger (10.0 mmol or greater) scale; the addition of potassium carbonate solution at the end of the reaction resulted in the precipitation of copious amounts of zinc(II) carbonate in the form of a dense slurry, which necessitated a tedious and inefficient subsequent filtration step. As such, we turned instead to the work of Kroin and co-workers (Scheme 5.2),[156] which uses a more economical three equivalents of zinc(II) chloride resulting in a smoother purification protocol and an admittedly slightly diminished yield of 75% for **5.7**.

Having accessed **5.7**, we next sought to cleave the central diol in order to provide two equivalents of glyceraldehyde acetonide **5.5**. This was readily achieved using sodium periodate in a biphasic dichloromethane/aqueous sodium bicarbonate system, according to the conditions of Gálvez and

co-workers.[158] The crude aldehyde thus obtained was found to be essentially pure as a solution in dichloromethane and was carried forward immediately without additional purification.

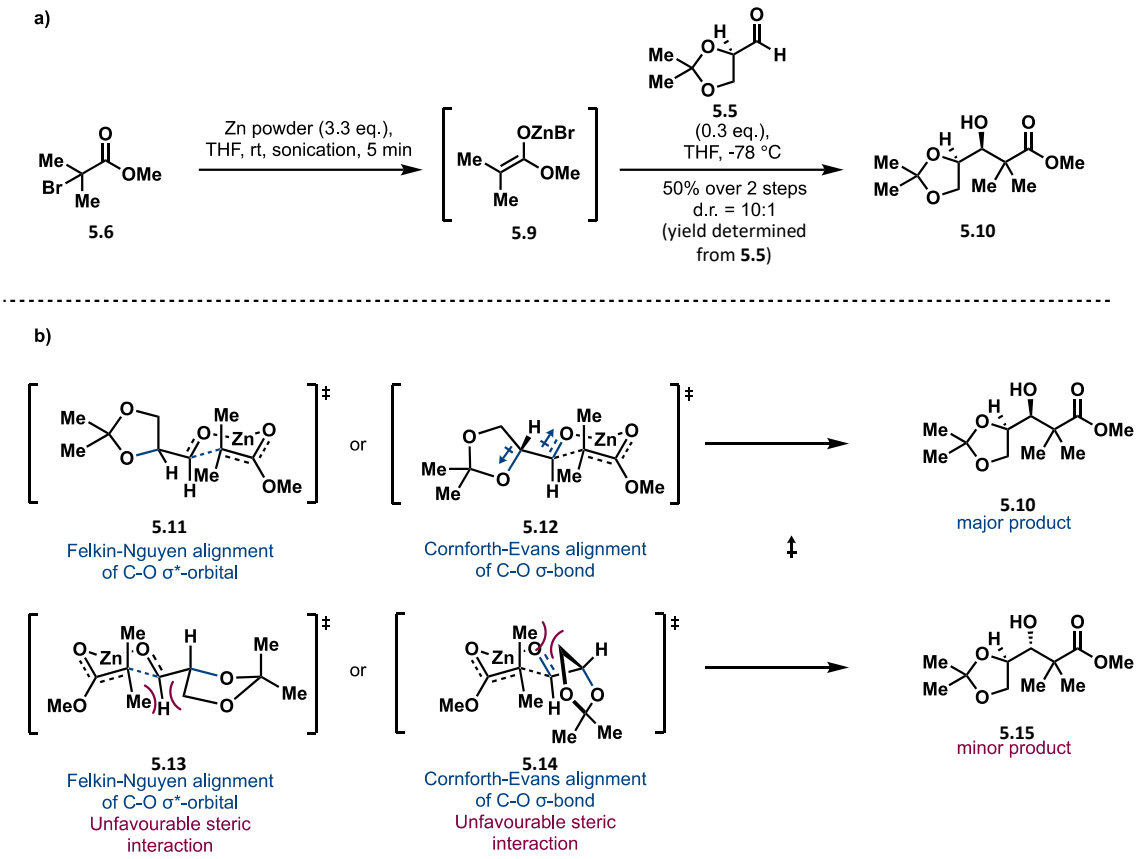


Scheme 5.2: Synthesis of glyceraldehyde acetonide **5.5** *via* the oxidative cleavage of D-mannitol acetonide **5.7**.

5.2.2 Reformatsky reaction of glyceraldehyde acetonide 5.5

We now turned our attention to the Reformatsky reaction of this aldehyde with methyl α-bromoisobutyrate **5.6**, a transformation which would establish the second stereocentre in the eastern fragment **5.2**. We chose the Reformatsky protocol on two bases: firstly, that the reaction of methyl **5.6** with zinc powder was the simplest protocol for generating a metal enolate operationally, and secondly, that the divalent zinc(II) cation would lead to well-defined Zimmerman-Traxler transition states **5.11**-**5.14** (Scheme 5.3),[159] thus enhancing the diastereoselectivity of the reaction. This choice was rewarded by the formation of methyl ester **5.10** with in a yield of 67%, in a 10:1 ratio with the minor diastereomer **5.15** (Scheme 5.3). It should be noted that the Reformatsky enolate **5.9** could only be successfully generated using zinc powder under sonication. We assert that the diastereoselectivity of this reaction can be rationalised within the Felkin-Nguyen or Cornforth-Evans models for the stereochemical outcome of nucleophilic addition to an α-chiral aldehyde (**5.11**-**5.14**). Within the Felkin-Nguyen paradigm, the most electrophilic conformations of the aldehyde are obtained through the perpendicular alignment of the C-O σ-bond of the α-carbon and the C-O π-bond of the carbonyl; nucleophilic attack occurs preferentially on the conformer in which the proton substituent, rather than the 1,3-dioxolane ring, occludes the Bürgi-Dunitz trajectory. The Cornforth-Evans model presents an even more compelling distinction between the two

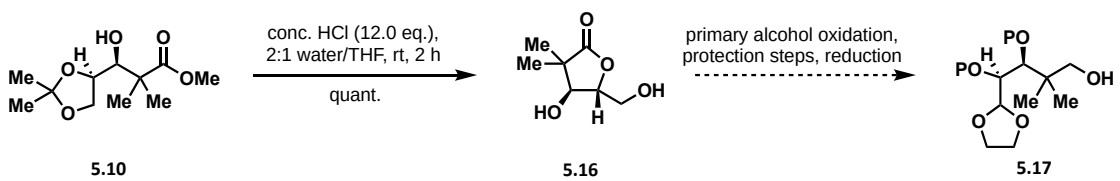
diastereomeric series: the most populated conformer of the α-chiral aldehyde is obtained *via* the opposed alignment of the relevant two C-O bonds and their respective dipoles; the nucleophile then attacks from the proton-bearing face rather than the 1,3-dioxolane bearing face.



Scheme 5.3: a) Reformatsky reaction of methyl α-bromoisobutyrate **5.6**, and glyceraldehyde acetonide **5.9**. **b)** Putative Felkin-Nguyen and Cornforth-Evans Zimmerman-Traxler transition states leading to major and minor products **5.10** and **5.15** respectively.

5.2.3 Proof of the relative stereochemistry of 5.10 by lactonisation to 5.16

Before proceeding with the synthesis, we endeavoured to demonstrate that the major diastereomer formed from this reaction was indeed the one predicted by the Zimmerman-Traxler transition state, required by the project, and depicted above as compound **5.10**. As such, the putative **5.10** was treated with dilute hydrochloric acid resulting in the formal loss of acetone and methanol and giving quantitative formation of lactone **5.16** as a crystalline solid (Scheme 5.4). The relative configuration of **5.16** was then assigned using a ^{1}H NOESY experiment, and that of **5.10** was correspondingly inferred (see Scheme 5.5 below). The protons of the hydroxymethyl group showed a stronger reciprocal NOE correlation to one of the diastereotopic methyl groups, suggesting that they occupied the same face; the other methyl group exhibited a stronger reciprocal NOE correlation to the hydroxyl proton of the secondary alcohol, indicating that the secondary alcohol is *trans*- to the hydroxymethyl group as shown. This is in keeping with the theory delineated in Scheme 5.3 and the results of Dr Erin Shepherd. We additionally determined that **5.16** could be obtained *via* the direct treatment of the crude Reformatsky reaction product with dilute hydrochloric acid, allowing for an entirely non-chromatographic preparation of analytically pure **5.16** from commercially available starting materials. The prospect of such a facile, scalable, and expeditious opening sequence to the eastern fragment led us to contemplate whether **5.16** could be efficiently integrated into the planned route. The realisation of this would require the oxidation of the primary alcohol to give protected aldehyde **5.17**, as the reduction of the lactone prior to such a transformation would lead to the need for extensive use of protecting groups and thus stray from efficiency.

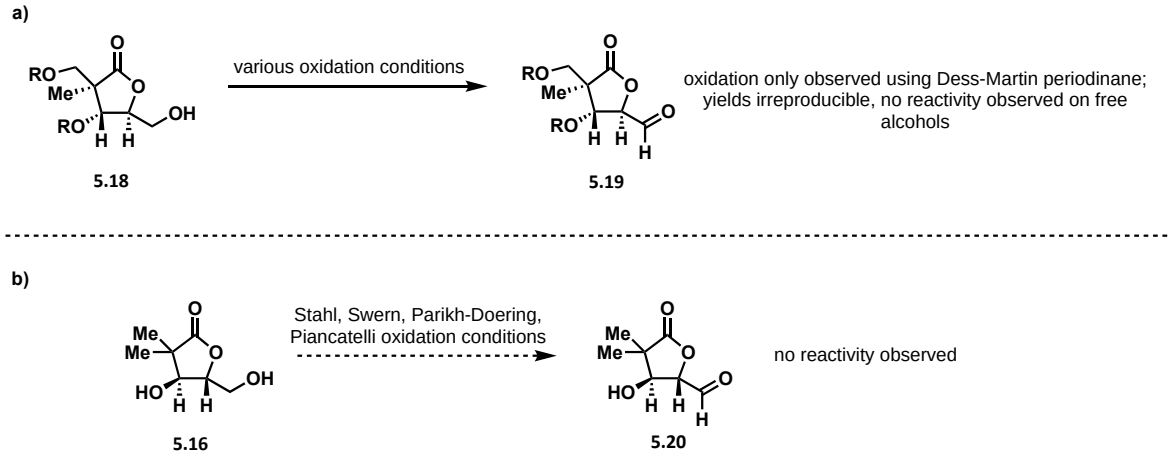


5.10 **5.16** **5.17**

Scheme 5.4: Acid-mediated lactonisation to give **5.16**, and prospective route to **5.17**.

Scheme 5.5: Selected NOESY correlations found in compound **5.16**.

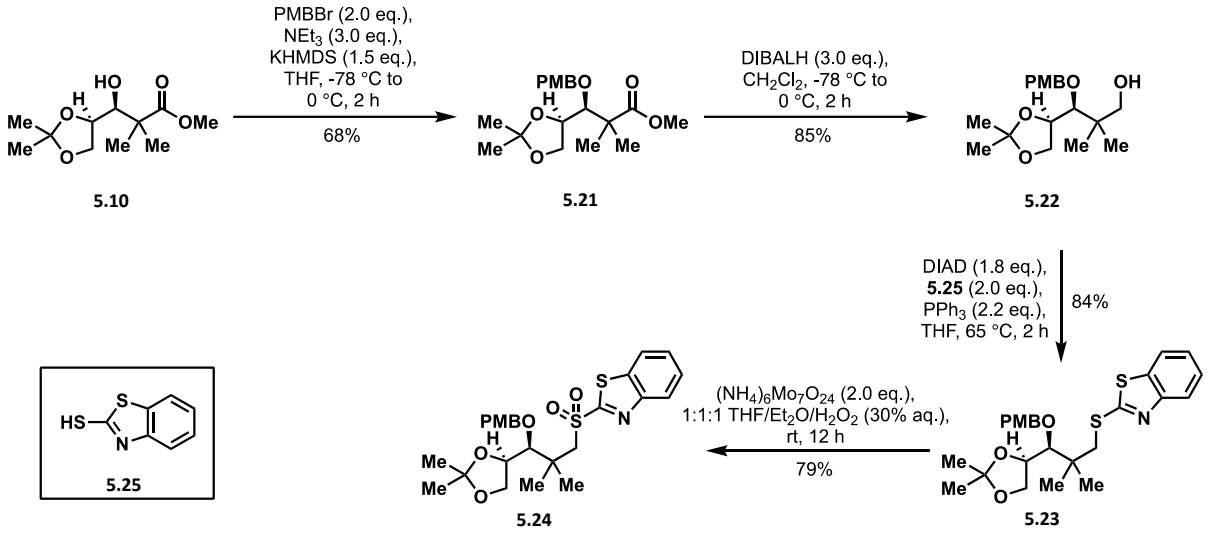
As such, **5.16** was subjected to a suite of standard alcohol oxidation conditions, with the goal of oxidising the primary alcohol selectively in the presence of the considerably more hindered secondary alcohol (Scheme 5.6). The Stahl,[142-144] Swern,[160] Parikh-Doering,[161] and Piancatelli[162] protocols all failed to elicit any reactivity whatsoever from **5.16**. This surprising inertia led us to consult the literature in a search for analogous systems; this led us to the work of Menche and co-workers on the total synthesis of a set of leupyrrin natural products.[163] During their investigations, the Menche group had attempted to oxidise **5.18** to **5.19** using a variety of procedures; in their publication, they note that **5.18** was 'very unreactive', requiring the use of Dess-Martin periodinane to obtain any product at all and even then in irreproducible yields. Given the apparent similarities between their system and ours, we elected to discontinue this line of investigation.



Scheme 5.6: a) Results from Menche and co-workers on the attempted oxidation of system **5.18**. **b)** Our unsuccessful attempts to oxidise **5.16**.

5.3 Synthesis of eastern fragment 5.24

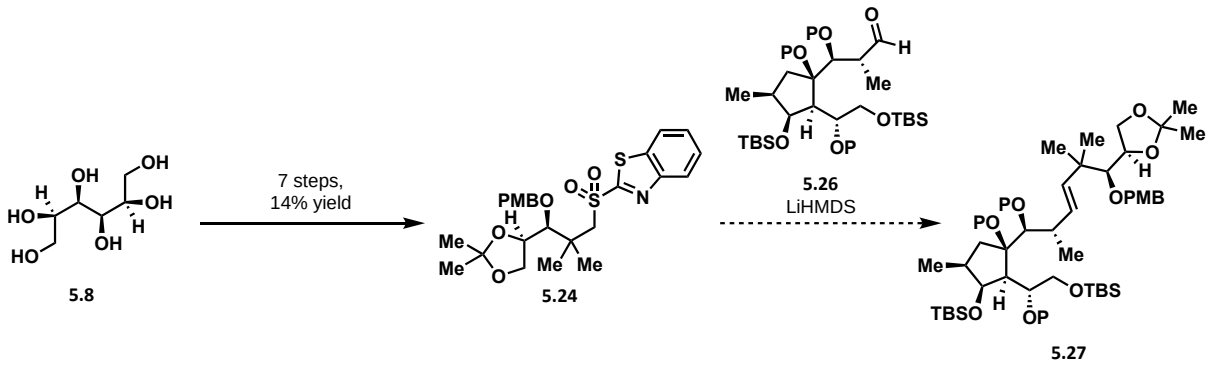
Having discarded the notion of proceeding from lactone **5.16**, we returned our attention to **5.10** and the matter of how to proceed thence. Taking Dr Erin Shepherd's route to **1.85** as a blueprint (delineated in Scheme 1.12), **5.10** was treated with freshly prepared *para*-methoxybenzyl bromide (PMBBr) in the presence of base, resulting in the formation of **5.21** in good yield. Reduction of the methyl ester group of **5.21** with DIBALH resulted in smooth conversion to primary alcohol **5.22**, again in high yield (Scheme 5.7). Subsequent Mitsunobu reaction with 2-mercaptobenzothiazole **5.25** proved facile in spite of the neopentylic substrate, resulting in thioether **5.23**. Oxidation with hydrogen peroxide in the presence of ammonium molybdate then gave the sulfone **5.24** in good yield.



Scheme 5.7: Elaboration of ester **5.10** to sulfone **5.24** through protection, reduction, substitution, and oxidation.

5.4 Chapter summary

In summary, the work in this chapter constitutes a short, efficient synthesis of fully protected eastern fragment **5.24** from the chiral pool starting material D-mannitol **5.8** in seven steps and a cumulative yield of 14% (Scheme 5.8). Material thus obtained would be suitable for Julia-Kocienski[164] coupling with prospective aldehyde **5.26** to give **5.27** in a continuation of this project.



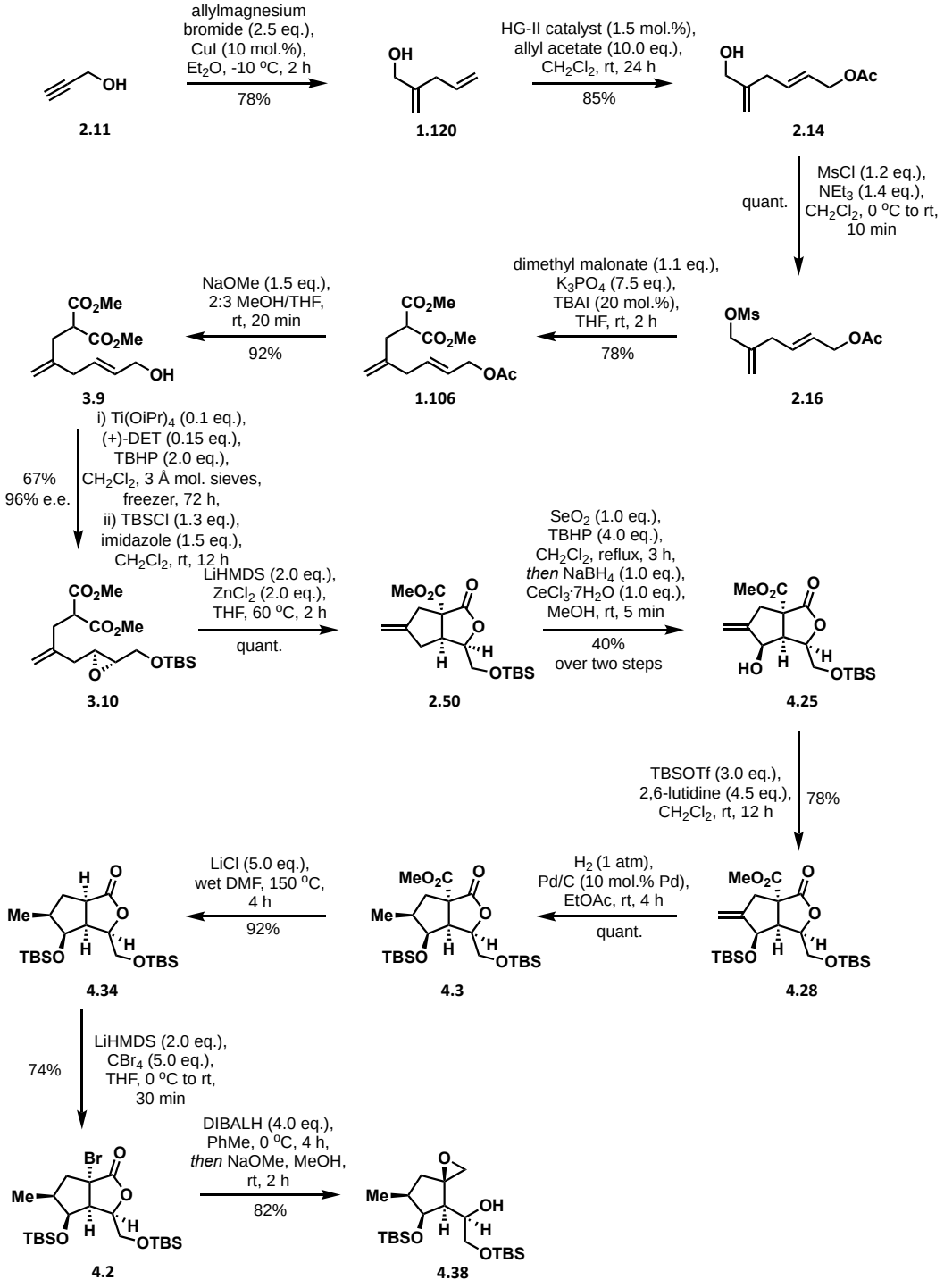
Scheme 5.8: Summary of the synthesis of **5.24** described in this chapter, and prospective incorporation of **5.24** into the synthesis of the jatrophanes by coupling with **5.26**.

Chapter 6: Conclusions and future work

6.1 Conclusion

In summary, we have made significant progress towards the synthesis of the jatrophane natural product **1.17**. The best route to our most advanced intermediate, **4.38**, is shown in Scheme 6.1. As described in Chapter 2 and Chapter 3, an open-chain molecule **1.106** was synthesised *via* an olefin metathesis and malonate alkylation. This compound was then easily converted into an allylic alcohol **3.9** which served as the substrate for a Sharpless asymmetric epoxidation to give **3.10** after protection, a transformation which gave a high level of enantioinduction into the synthesis. A subsequent tandem epoxide opening-lactonisation reaction assembled an oxabicyclo-[3.3.0]-octane skeleton in *cis*-fused cyclopentane lactone **2.50**. The increased steric hindrance inside the 'bowl' of this structure relative to the convex face enabled a series of highly diastereoselective transformations which accessed the relative configuration necessary for the project. Allylic oxidation followed by hydride reduction gave **4.25**; subsequent silylation gave **4.28**, which was hydrogenated to give **4.3**. A Krapcho decarboxylation gave **4.34**, and anionic bromination gave **4.2**. Reduction with DIBALH followed by treatment with sodium methoxide finally gave epoxide **4.38**. Thus we had accessed **4.38** in 16 steps in an overall yield of 6%. A number of possible alternatives for some of these transformations were explored, and this route was found to be the most successful and direct. Before the termination of this project, the route shown was conducted on asymmetric material, and data for enantioenriched intermediates were obtained.

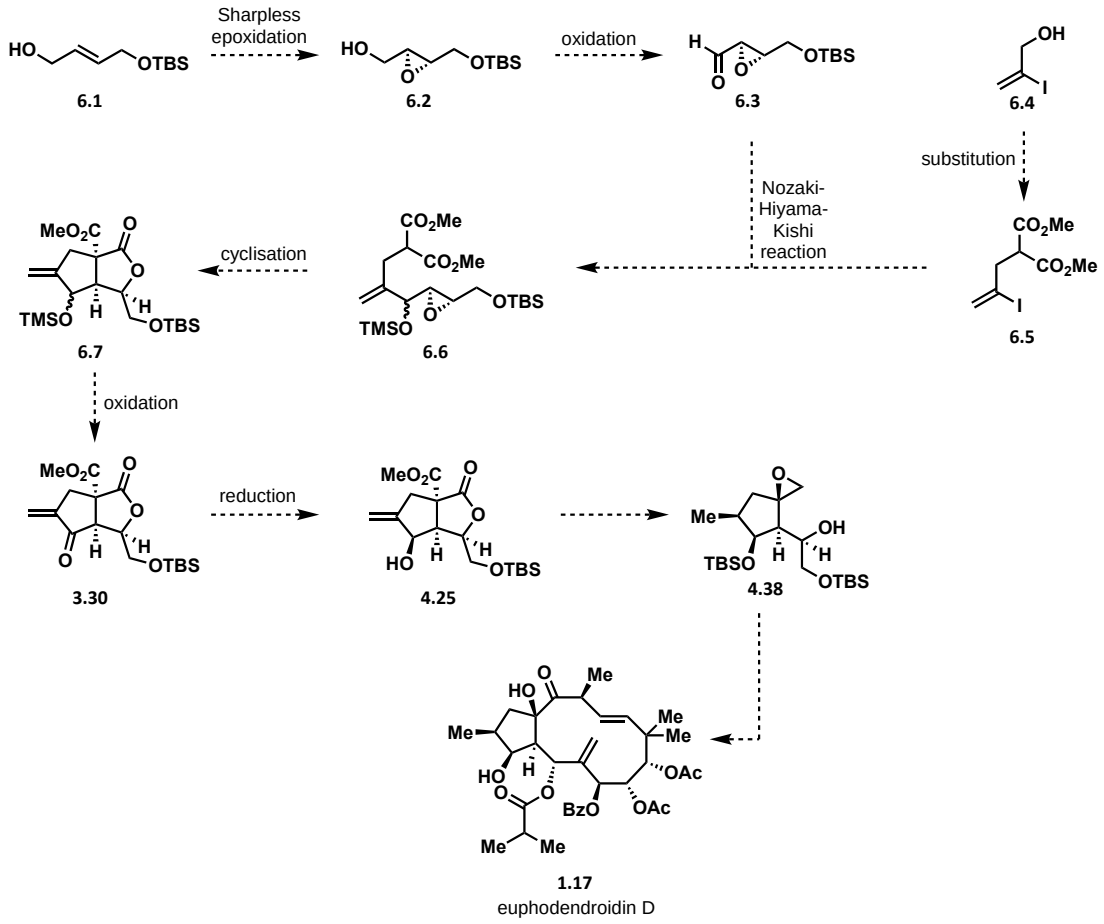
We also achieved the synthesis of eastern fragment **5.24**, which has just been described in Chapter 5 and so will not be reiterated here (Scheme 5.7, Scheme 5.8).



Scheme 6.1: The route to epoxide **4.38** developed over the course of this project, proceeding in a 6% yield over 16 steps.

6.2 Future work

Although the route shown above is adequate for the purpose of natural product synthesis, the allylic oxidation is a conspicuous weakness. Scheme 6.2 depicts an alternative route where the allylic alcohol is installed *via* the addition of a vinylmetallic species derived from building block **6.4** *via* iodide **6.5**, into an aldehyde **6.3**. **6.3** could be synthesised from building block **6.1** *via* a Sharpless epoxidation to give **6.2** followed by oxidation. This would give fragment **6.6** which is analogous to **3.2**, but with indeterminate stereochemistry. A sequence in line with that which has been developed in this thesis would then enable access to **4.38**. In addition to avoiding the low-yielding allylic oxidation step, this route would avoid the costly early-stage ruthenium-catalysed olefin metathesis and lower the overall step count of the route. Following this, the plan in Section 1.5 could be continued to further investigate the applicability of this chemistry to the total synthesis of the jatrophanes.

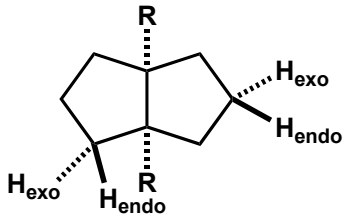


Scheme 6.2: Hypothetical third-generation route to the cyclopentane core **4.38** of euphodendroidin D **1.17** using the chemistry developed in this thesis.

Chapter 7: Experimental

7.1 General experimental

NMR spectra: Proton (^{1}H) and proton-decoupled carbon (^{13}C) NMR spectra were recorded on Bruker AV 600 (600/126 MHz), Bruker AV 500 (500/125 MHz), Bruker AV 400 (400/100 MHz) or Bruker DPX 200 (200/50 MHz) spectrometers. Proton and carbon chemical shifts are quoted in ppm and referenced to tetramethylsilane (δ = 0 ppm), with residual protonated solvent as an internal standard. Assignments were made by analysing chemical shifts, coupling constants, COSY, HSQC, HMBC, and NOESY data, and by comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (double doublet) and so on; these resonances are described as they were seen, rather than as a chemical interpretation would indicate (i.e. a resonance which would be chemically interpreted as a double doublet with two identical coupling constants would be described as a triplet). Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.1 Hz, and are averaged between corresponding coupling constants. Diastereotopic sets of protons are denoted H and H' where no stereochemical assignment could be made. Where a stereochemical assignment could be made on the basis of NOESY data, diastereotopic protons are either clearly labelled, or labelled H_{endo} and H_{exo} based on their orientation with respect to the *cis*-fused oxabicyclo-[3.3.0]-octane skeleton (Scheme 7.1). Nuclei attached to or part of an aromatic ring are either labelled H_{Ar} or C_{Ar}, or are clearly labelled where an assignment could be made.



Scheme 7.1: Explanation of stereochemical labels used in NMR assignments in this thesis.

Mass spectra: Low resolution mass spectra were recorded on a Fisons Platform spectrometer (electrospray). High resolution mass spectra were recorded by Mass Spectrometry Department staff at the Chemistry Research Laboratory, University of Oxford, using a Bruker Daltronics microTOF spectrometer (electrospray). *m/z* values are reported in Daltons with their percentage abundances and the formulae of relevant ions in parentheses. High resolution values are calculated to four decimal places from the molecular formula, all found values being within an acceptable tolerance.

Infrared spectra: Infrared spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer, using diamond ATR. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Melting points: Melting points were determined using a Griffin heated metal block apparatus and are uncorrected. Solids were crystallised from chromatography solvent except where stated.

Optical rotations: Optical rotations were measured using a Perkin-Elmer 241 polarimeter in a cell of 1 dm path length (l). Specific rotations denoted as $[\alpha]_D^T$ where T = temperature in °C, D refers to the 145 line of a sodium lamp (λ = 589 nm), and are calculated according to the equation below where α is the observed rotation: $[\alpha]_D^T = \frac{100a}{lc}$.

Chromatography: TLC was performed on Merck DC-Alufolien 60 F254 0.2 mm precoated plates and visualised using an acidic vanillin or basic potassium permanganate dips. Flash column chromatography was performed on Merck 60 silica (particle size 40–63 µm, pore diameter 60 Å) and the solvent system used is recorded in parentheses. HPLC analysis was performed in an Agilent 12000 series using a Chiracel OD column (9.4 x 250 mm, 10 µm beads).

Reactions: All reactions were carried out in flame-dried glassware under an inert atmosphere of nitrogen and employing standard techniques for handling air-sensitive materials unless specified. Solvents and commercially available reagents were dried and purified before use, as appropriate; where this was found to be necessary for a successful reaction outcome, it is clearly stated. Degassing was done by sparging with argon gas. All water used experimentally was deionised and the term 'brine' refers to a saturated solution of sodium chloride in water.

7.2 General preparations and purification procedures for reagents

2.45 – Bromodiethylsulfonium bromopentachloroantimonate (BDSB) had been previously synthesised by Dr Sam Chan in the Jonathan Burton group, who kindly provided a sample.

2.44 - Iododiethylsulfonium iodopentachloroantimonate (IDSI)

According to the procedure of Snyder[88]: Diethyl sulfide (0.54 mL, 5.00 mmol) was added dropwise over 2 minutes to a solution of iodine (635 mg, 2.50 mmol) in 1,2-dichloroethane (15 mL) at 0 °C, and the solution was stirred for 5 minutes. A solution of antimony pentachloride (1.0 M in dichloromethane, 5.00 mL, 5.00 mmol) was added dropwise over 1 minute, and the reaction was allowed to warm to room temperature and stirred for 2 hours. The stirrer bar was removed, hexane (4 mL) was layered on top of the solution, and the flask was carefully placed in a freezer and left for 48 hours. This led to the formation of orange crystals, which were isolated *via* filtration and washed twice with ice-cold hexane (1 mL), and dried under high vacuum prior to use without further purification (1.13 g, 3.50 mmol, 70% yield).

Cu/Al oxide

According to the modified procedure of Guerra[115]: Sodium carbonate (1.27 g, 12.00 mmol) and sodium hydroxide (5.20 g, 13.00 mmol) were dissolved in water (100 mL) to give a colourless solution. Copper(II) chloride (5.00 g, 40.00 mmol) and aluminium trichloride (2.20 g, 16.00 mmol) were dissolved in water (50 mL) to give a green solution. The basic solution was added dropwise to the copper-containing solution over 5 minutes, and the resulting blue suspension was heated to 70 °C for 24 hours, over which time the suspension turned black. The mixture was cooled to room temperature, filtered, and the black residue was washed with water. The residue was then dried under a stream of nitrogen at 110 °C for 3 hours, cooled to room temperature, ground to a uniform consistency in a mortar, and dried under high vacuum overnight.

3.59 *– a sample of manganese complex* ***3.59*** *was generously donated to Pol Hernández-Lladó in the Jonathan Burton group by the group of Miquel Costas; a small portion of this donation was kindly provided.*

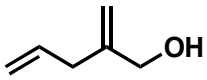
Palladium(II) acetate was recrystallised from benzene according to the procedure of White[165] prior for use in this project.

Molecular sieves were activated by heating to 200 ^{o}C under high vacuum for 12 hours.

Other preparations and purifications for reagents are given in the procedures for the compounds they were used to make.

7.3 Preparations for compounds and characterisation data

1.120 - 2-Methylenepent-4-en-1-ol



According to the procedure of Saux[74]: copper(I) iodide (6.10 g, 32.0 mmol) was suspended in dry, degassed diethyl ether (320 mL) in a multi-neck round-bottomed flask with a mechanical stirrer fitted, and the suspension was cooled to -10 °C. Propargyl alcohol (17.9 g, 18.6 mL, 320 mmol) was added, and then allylmagnesium bromide solution (1.0 M in diethyl ether, 800 mL, 800 mmol) was added dropwise *via* cannula over 10 minutes. The mixture was warmed to room temperature and stirred for 1 hour. After this time had elapsed, the reaction was cooled down to 0 °C and quenched by the dropwise addition of 50% aqueous ammonium chloride solution (800 mL) over 30 minutes. The organic phase was separated, and the aqueous phase was extracted three times with diethyl ether (500 mL). The combined organic fractions were washed with brine, dried over anhydrous magnesium sulfate, filtered, and the majority of the diethyl ether was removed under reduced pressure. The crude residue was distilled (b.p. = 84-85 °C at 34 mbar, lit. 84 °C at 33 mbar[74]) to give the product as a colourless oil (24.59 g, 250.6 mmol, 78% yield).

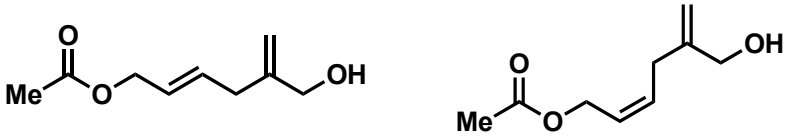
Data and spectra matched that previously reported in the literature.[74]

R.f: 0.28 (20% ethyl acetate in pentane, stains dark blue in vanillin dip, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.83 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, H_2C=C**H**R), 5.11 – 5.00 (m, 1H, **H**H'C=CHR), 5.10 – 5.00 (m, 2H, H**H'**C=CHR, **H**H'C=CR_2), 4.88 (q, *J* = 1.5 Hz, 1H, H**H'**C=CR_2), 4.04 (s, 2H, C**H_2**OH), 2.79 (d, *J* = 7.0 Hz, 2H, H_2C=CHC**H_2**R). Hydroxyl proton resonance not observed.

^{13}C NMR (151 MHz, $CDCl_3$): δ 147.4 (H_2C=**C**R_2), 135.9 (H_2C=**C**HR), 116.7 (H_2**C**=CHR), 110.7 (H_2**C**=CR_2), 65.9 (R**C**H_2OH), 38.0 (H_2C=CH**C**H_2R).

2.14 - (*E*)-5-(Hydroxymethyl)hexa-2,5-dien-1-yl acetate and **2.14'** - (*Z*)-5-(hydroxymethyl)hexa-2,5-dien-1-yl acetate



Compound **1.120** (3.93 g, 40.0 mmol) and allyl acetate (40.05 g, 43.16 mL, 400.0 mmol) were dissolved in dry, degassed dichloromethane (400 mL) under nitrogen. Hoveyda-Grubbs catalyst (2nd generation, also known as Hoveyda-Grubbs Catalyst® M720, **1.123**) (376 mg, 0.600 mmol) was added, and the solution was observed to turn a deep green colour which rapidly changed to a dark amber colour. The reaction was allowed to stir for 24 hours under nitrogen (supplied through a Schlenk manifold to allow for removal of the ethene by-product), after which dimethyl sulfoxide (0.38 mL) was added. The solution was allowed to stir for 12 hours, after which activated charcoal (20 g) was added. The mixture was allowed to stir for a further 12 hours, after which it was filtered through a pad of Celite™. Volatile organics were removed under reduced pressure, and the crude residue was purified *via* flash column chromatography, eluting with 5-20% acetone in pentane, in order to give the product as a colourless oil (5.24 g, 30.8 mmol, 77% yield, 10:1 ratio *E* to *Z*).

R.f: 0.15 (20% acetone in pentane, stains dark turquoise in vanillin dip, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.75 (dt, *J* = 15.3, 6.9 Hz, 1H, $AcOCH_2CH=C\mathbf{H}R$), 5.63 (dt, *J* = 15.3, 6.4 Hz, 1H, $AcOCH_2C\mathbf{H}=CHR$), 5.07 (br s, 1H, **H**H'$C=CR_2$), 4.89 (br s, 1H, H**H'**$C=CR_2$), 4.52 (dt, *J* = 6.4, 1.0 Hz, 2H, $AcOC\mathbf{H_2}CH=CR$), 4.05 (s, 2H, $HOC\mathbf{H_2}R$), 2.82 (d, *J* = 6.9 Hz, 2H, $AcOCH_2CH=CHC\mathbf{H_2}R$), 2.05 (s, 3H, $\mathbf{Me}CO_2R$). **Distinguishable minor diastereomer peaks**: 4.63 (d, *J* = 6.2 Hz, 2H, $AcOC\mathbf{H_2}CH=CR$), 2.89 (d, *J* = 6.9 Hz, 2H, $AcOCH_2CH=CHC\mathbf{H_2}R$). **Peak integral ratio for major:minor = 10:1**. Hydroxyl proton resonance not observed.

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.0 ($Me\mathbf{C}O_2R$), 147.0 ($H_2C=\mathbf{C}R_2$), 132.9 ($AcOCH_2CH=\mathbf{C}HR$), 126.1 ($AcOCH_2\mathbf{C}H=CHR$), 111.0 ($H_2\mathbf{C}=CR_2$), 65.7 ($HO\mathbf{C}H_2R$), 65.0 ($AcO\mathbf{C}H_2R$), 36.0 ($AcOCH_2CH=CH\mathbf{C}H_2R$), 21.1

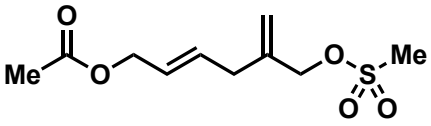
(**Me**CO_2R). **Distinguishable minor diastereomer peaks**: 131.9 (AcOCH_2CH=**C**HR), 125.4 (AcOCH_2**C**H=CHR), 60.3 (AcO**C**H_2R), 31.3 (AcOCH_2CH=CH**C**H_2R).

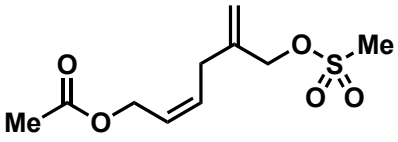
IR: (ν_{max}/cm^{-1} (thin film)) = 3416, 2932, 1737, 1432, 1382, 1026, 902.

LRMS (ESI^+): *m/z* = 193.0 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_9H_{14}O_3Na]^+$) = 193.0835; *m/z* found = 193.0837

2.16 - (*E*)-5-(((Methylsulfonyl)oxy)methyl)hexa-2,5-dien-1-yl acetate; and **2.16'** - (*Z*)-5-(((methylsulfonyl)oxy)methyl)hexa-2,5-dien-1-yl acetate





Mixture **2.14** (3.40 g, 20.0 mmol) and methanesulfonyl chloride (2.75 g, 1.86 mL, 24.0 mmol) were dissolved in dry dichloromethane (80 mL) in a flame-dried round-bottomed flask under nitrogen, and the resulting solution was cooled to 0 °C in an ice bath. Triethylamine (2.83 g, 3.90 mL, 28.00 mmol) was added dropwise over 1 minute. The reaction was allowed to stir for 10 minutes, after which time a white precipitate was observed to have formed. The mixture was allowed to warm to room temperature, was quenched by the addition of saturated aqueous sodium bicarbonate solution (40 mL) and water (40 mL), and stirred rapidly for 5 minutes. The reaction was transferred to a separating funnel, and the organic layer was separated. The aqueous layer was extracted three times with ethyl acetate (160 mL), and the combined organic extracts were washed with water, washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure to give the crude product as a pale yellow oil (4.97 g, 20.0 mmol, presumed quantitative yield, 10:1 ratio of *E* to *Z*). N.B: This product was observed to have a mild lachrymatory effect, and as such should be handled in sealed vessels when outside a fumehood, and should be concentrated on a rotary evaporator inside a fumehood.

R.f: 0.25 (20% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.77 (dt, *J* = 15.2, 6.8 Hz, 1H, $AcOCH_2CH$=**C**HR), 5.66 (dt, *J* = 15.2, 6.0 Hz, 1H, $AcOCH_2$**C**H=CHR), 5.23 (br s, 1H, **H**H'$C=CR_2$), 5.12 (br s, 1H, H**H'**$C=CR_2$), 4.64 (s, 2H, $MsOC$**H_2**R), 4.55 (d, *J* = 6.0 Hz, 2H, $AcOC$**H_2**R), 3.02 (s, 3H, **Me**SO_3R), 2.89 (d, *J* = 6.8 Hz, 2H, $AcOCH_2CH$=CHC**H_2**R), 2.06 (s, 3H, **Me**CO_2R). **Distinguishable minor diastereomer peaks**: 4.64 (d, *J* = 6.8 Hz, 2H, $AcOC$**H_2**R), 2.95 (d, *J* = 7.4 Hz, 2H, $AcOCH_2CH$=CHC**H_2**R). **Peak integral ratio for major:minor = 10:1**.

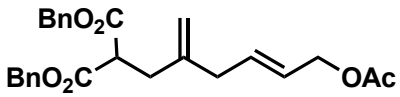
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.9 (Me**C**O_2R), 140.3 (H_2C=**C**R_2), 131.3 ($AcOCH_2CH$=**C**HR), 127.3 ($AcOCH_2$**C**H=CHR), 117.1 (H_2**C**=CR_2), 71.9 (MsO**C**H_2R), 64.7 (AcO**C**H_2R), 38.1 (**Me**SO_3R), 35.8 ($AcOCH_2CH$=CH**C**H_2R), 21.1 (**Me**CO_2R). **Distinguishable minor diastereomer peaks**: 130.4 ($AcOCH_2CH$=**C**HR), 126.6 ($AcOCH_2$**C**H=CHR), 60.1 (AcO**C**H_2R), 31.1 ($AcOCH_2CH$=CH**C**H_2R).

IR: (ν_{max}/cm^{-1} (thin film)) = 1735, 1437, 1352, 1173, 1024, 967, 834.

LRMS (ESI^+): *m/z* = 271.0 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{10}H_{16}O_5SNa]^+$) = 271.0611; *m/z* found = 271.0611

2.18 - Dibenzyl (*E*)-2-(6-acetoxy-2-methylenehex-4-en-1-yl)malonate;



Anhydrous tribasic potassium phosphate (having been further dried by heating at 150 °C under high vacuum overnight) (159 mg, 0.750 mmol) and tetrabutylammonium iodide (7.4 mg, 0.020 mmol) were suspended in dry, degassed tetrahydrofuran (0.10 mL). Dibenzyl malonate (31 mg, 0.027 mL, 0.11 mmol) was added, and a solution of mixture **2.16** (25 mg, 0.10 mmol) in dry, degassed tetrahydrofuran (0.10 mL) was added. The resulting pale yellow suspension was stirred rapidly for 2 hours at room temperature. After this time had elapsed, ethyl acetate (2 mL), saturated aqueous ammonium chloride solution (2 mL) and water (2 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under

reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 20% ethyl acetate in pentane, to give the product as a colourless oil (29 mg, 0.067 mmol, 67% yield).

R.f: 0.63 (30% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

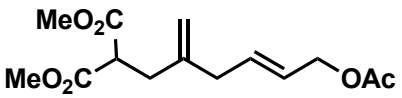
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 10H, **H**-Ar), 5.70 (dtt, *J* = 15.5, 6.6, 1.1 Hz, 1H, $AcOCH_2CH$=**C**HR), 5.58 (dtt, *J* = 15.5, 6.1, 1.1 Hz, 1H, $AcOCH_2$**C**H=CHR), 5.14 (s, 4H, (Ph**CH_2**O_2C)$_2$CHR), 4.78 (br s, 2H, **H**H'$C=CR_2$, H**H'**$C=CR_2$), 4.50 (dd, *J* = 6.1, 1.1 Hz, 2H, AcOC**H_2**R), 3.69 (t, *J* = 7.8 Hz, 1H, $(BnO_2C)_2$C**H**R), 2.75 (br d, *J* = 6.6 Hz, 2H, $AcOCH_2CH$=CHC**H_2**R), 2.66 (d, *J* = 7.8 Hz, 2H, $(BnO_2C)_2$CHC**H_2**R), 2.05 (s, 3H, **Me**CO_2R).

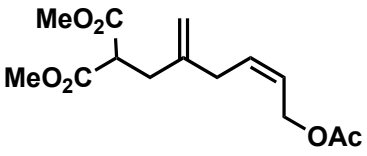
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.9 (Me**C**O_2R), 168.8 (2C, $(BnO_2$**C**$)_2$CHR), 143.6 (H_2C=**C**R_2), 135.4 (2C, RCO_2CH_2**C$_{Ar}$**), 132.7 ($AcOCH_2CH$=**C**HR), 128.7 (4C, **C$_{Ar}$**), 128.5 (2C, **C$_{Ar}$**), 128.4 (4C, **C$_{Ar}$**), 126.4 ($AcOCH_2$**C**H=CHR), 113.0 (H_2**C**$=CR_2$), 67.4 (2C, (Ph**C**H_2O_2C)$_2$CHR), 64.9 (AcO**C**H_2R), 50.7 ($(BnO_2C)_2$**C**HR), 39.1 ($AcOCH_2CH$=CH**C**H_2R), 34.8 ($(BnO_2C)_2$CH**C**H_2R), 21.1 (**Me**CO_2R).

IR: (ν_{max}/cm^{-1} (thin film)) = 2980, 1736, 1498, 1455, 1231, 1150, 1026.

HRMS (ESI^+): Predicted *m/z* ($[C_{26}H_{28}O_6Na]^+$) = 459.1778; *m/z* found = 459.1779.

1.106 - Dimethyl (*E*)-2-(6-acetoxy-2-methylenehex-4-en-1-yl)malonate and **1.106' -** dimethyl (*Z*)-2-(6-acetoxy-2-methylenehex-4-en-1-yl)malonate





Anhydrous tribasic potassium phosphate (having been further dried by heating at 150 °C under high vacuum overnight) (1.59 g, 7.50 mmol) and tetrabutylammonium iodide (74 mg, 0.20 mmol) were suspended in dry, degassed tetrahydrofuran (1.00 mL). Dimethyl malonate (313 mg, 0.275 mL, 1.10 mmol) was added, and a solution of mixture **2.16** (248 mg, 1.00 mmol) in dry, degassed tetrahydrofuran (1.00 mL) was added. The resulting pale yellow suspension was stirred rapidly for 2 hours at room temperature. After this time had elapsed, ethyl acetate (10 mL), saturated aqueous

ammonium chloride solution (10 mL) and water (10 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 20% ethyl acetate in pentane, to give the product as a colourless oil (244 mg, 0.823 mmol, 82% yield, 10:1 ratio of *E* to *Z*).

R.f: 0.50 (30% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.74 (dt, *J* = 15.2, 6.9 Hz, 1H, $AcOCH_2CH$=**C**HR), 5.60 (dt, *J* = 15.2, 6.2 Hz, 1H, $AcOCH_2$**C**H=CHR), 4.82 (br s, 1H, **H**H'$C=CR_2$), 4.80 (br s, 1H, H**H'**$C=CR_2$), 4.52 (d, *J* = 6.2 Hz, 2H, AcOC**H$_2$**R), 3.72 (s, 6H, (**Me**$O_2C)_2$CHR), 3.60 (t, *J* = 7.8 Hz, 1H, $(MeO_2C)_2$C**H**R), 2.77 (d, *J* = 6.9 Hz, 2H, $AcOCH_2CH$=CHC**H$_2$**R), 2.61 (d, *J* = 7.8 Hz, 2H, $(MeO_2C)_2$CHC**H$_2$**R), 2.05 (s, 3H, **Me**CO_2R). **Distinguishable minor diastereomer peaks**: 4.60 (d, *J* = 5.4 Hz, 2H, AcOC**H$_2$**R), 2.83 (d, *J* = 5.6 Hz, 2H, $AcOCH_2CH$=CHC**H$_2$**R). **Peak integral ratio for major:minor = 10:1**.

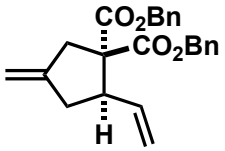
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.9 (Me**C**O_2R), 169.5 (2C, $(MeO_2$**C**$)_2$CHR), 143.7 (H_2C=**C**R_2), 132.7 ($AcOCH_2CH$=**C**HR), 126.4 ($AcOCH_2$**C**H=CHR), 112.8 (H_2**C**$=CR_2$), 64.9 (AcO**C**H_2R), 52.7 (2C, (**Me**$O_2C)_2$CHR), 50.4 ($(MeO_2C)_2$**C**HR), 39.1 ($AcOCH_2CH$=CH**C**H_2R), 34.8 ($(MeO_2C)_2$CH**C**H_2R), 21.1 (**Me**CO_2R). **Distinguishable minor diastereomer peaks**: 131.7 ($AcOCH_2CH$=**C**HR), 125.7 ($AcOCH_2$**C**H=CHR), 60.1 (AcO**C**H_2R), 34.2 ($AcOCH_2CH$=CH**C**H_2R).

IR: (ν_{max}/cm^{-1} (thin film)) = 1735, 1436, 1231, 1153, 1027, 975.

LRMS (ESI^+): *m/z* = 307.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{14}H_{20}O_6Na]^+$) = 307.1152; *m/z* found = 307.1153.

1.125 - (±)-Dibenzyl 4-methylene-2-vinylcyclopentane-1,1-dicarboxylate



Anhydrous tribasic potassium phosphate (having been further dried by heating at 150 °C under high vacuum overnight) (1.59 g, 7.50 mmol) and tetrabutylammonium iodide (74 mg, 0.20 mmol) were suspended in dry, degassed tetrahydrofuran (1.00 mL). Dibenzyl malonate (313 mg, 0.275 mL, 1.10 mmol) was added, and a solution of mixture **2.16** (248 mg, 1.00 mmol) in dry, degassed tetrahydrofuran (1.00 mL) was added. The resulting pale yellow suspension was stirred rapidly for 2 hours at room temperature. After this time, full consumption of **2.16** was observed by thin layer chromatography (20% ethyl acetate in pentane), and a solution of palladium(II) acetate (23 mg, 0.10 mmol) and triphenyl phosphine (79 mg, 0.30 mmol) in anhydrous, degassed tetrahydrofuran (8.00 mL) was added, and the resulting bright orange suspension was stirred rapidly for 12 hours at room temperature. After this time had elapsed, dichloromethane (10 mL), saturated aqueous ammonium chloride solution (10 mL) and water (10 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with dichloromethane (20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (256 mg, 0.681 mmol, 68% yield).

R.f: 0.73 (20% diethyl ether in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 –7.21 (m, 10H, **H**-Ar), 5.79 (ddd, *J* = 16.6, 10.4, 7.9 Hz, 1H, RC**H**=CH_2), 5.12 (br s, 2H, $RCO_2C\mathbf{H_2}Ph$), 5.07 (d, *J* = 12.3 Hz, 1H, $RCO_2C\mathbf{H}$H'Ph), 5.03 (d, *J* = 12.3 Hz, 1H, $RCO_2CH\mathbf{H'}Ph$), 5.03 (br d, *J* = 16.6 Hz, 1H, RCH=C**H**H'), 4.96 (br d, *J* = 10.4 Hz, 1H, RCH=CH**H'**), 4.91 (br s, 2H, $R_2C=C\mathbf{H_2}$), 3.34 (q, *J* = 7.9 Hz, 1H, $H_2C=C(R)CH_2C\mathbf{H}R_2$), 3.21 (dq, *J* = 17.3, 2.2 Hz, 1H,

H_2C=C(R)C**H**H'CR($CO_2Bn)_2$), 2.79 (dq, *J* = 17.3, 2.2 Hz, 1H, H_2C=C(R)CH**H'**CR($CO_2Bn)_2$), 2.67 (dq, *J* = 17.3, 2.1 Hz, 1H, H_2C=C(R)C**H**H'CHR_2), 2.43 (dq, *J* = 17.3, 2.1 Hz, 1H, H_2C=C(R)CH**H'**CHR_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.2 (R**C**O_2Bn), 169.9 (R**C**O_2Bn), 146.8 (R_2**C**=CH_2), 136.8 (RH**C**=CH_2), 135.6 (RCH_2-**C**$_{Ar}$), 135.5 (RCH_2-**C**$_{Ar}$), 128.6 (2C, **C**$_{Ar}$), 128.6 (2C, **C**$_{Ar}$), 128.4 (**C**$_{Ar}$), 128.4 (3C, **C**$_{Ar}$), 128.2 (2C, **C**$_{Ar}$), 116.7 (RHC=**C**H_2), 107.6 (R_2C=**C**H_2), 67.3 (RCO_2**C**H_2Ph), 67.1 (RCO_2**C**H_2Ph), 63.9 (($BnO_2C)_2$**C**R_2), 49.0 (H_2C=CH**C**HR), 40.2 (($BnO_2C)_2$CR**C**H_2), 37.2 (H_2C=CHC(R)H**C**H_2R).

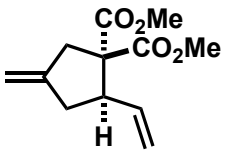
N.B: The NMR resonances corresponding to nuclei in the desymmetrised CO_2Bn groups were coincident to a significant extent in both ^{1}H and ^{13}C NMR spectra; this precluded a more precise assignment. NOESY data may have allowed for assignment of the benzylic CH_2 groups.

IR: (ν_{max}/cm^{-1} (thin film)) = 3034, 1731, 1498, 1455, 1231, 1162, 1029, 919, 738.

LRMS (ESI$^+$): *m/z* = 399.2 = [M+Na]$^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{24}H_{24}O_4$Na]$^+$) = 399.1567; *m/z* found = 399.1566.

1.102 - (±)-Dimethyl 4-methylene-2-vinylcyclopentane-1,1-dicarboxylate



Anhydrous tribasic potassium phosphate (having been further dried by heating at 150 °C under high vacuum overnight) (15.92 g, 75.00 mmol) and tetrabutylammonium iodide (741 mg, 2.00 mmol) were suspended in dry, degassed tetrahydrofuran (10.00 mL). Dimethyl malonate (1.45 g, 1.26 mL, 11.0 mmol) was added, and a solution of mixture **2.16** (2.48 g, 10.0 mmol) in dry, degassed tetrahydrofuran (10.00 mL) was added. The resulting pale yellow suspension was stirred rapidly for 2 hours at room temperature. After this time, full consumption of **2.16** was observed by thin layer chromatography (20% ethyl acetate in pentane), and a solution of palladium(II) acetate (225 mg, 1.00 mmol) and triphenyl phosphine (787 mg, 3.00 mmol) in anhydrous, degassed tetrahydrofuran (80.00 mL) was added, and the resulting bright orange suspension was stirred rapidly for 12 hours at room

temperature. After this time had elapsed, dichloromethane (200 mL), saturated aqueous ammonium chloride solution (100 mL) and water (100 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with dichloromethane (100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (1.58 g, 7.00 mmol, 70% yield).

R.f: 0.81 (20% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddd, *J* = 17.1, 10.3, 7.5 Hz, 1H, RC**H**=CH_2), 5.10 (dd, *J* = 17.1, 1.7 Hz, 1H, RCH=C**H**H'), 5.00 (dd, *J* = 10.3, 1.7 Hz, 1H, RCH=CH**H'**), 4.92 (m, 2H, R_2C=C**H_2**), 3.73 (s, 3H, RCO_2**Me**), 3.67 (s, 3H, RCO_2**Me**), 3.31 (q, *J* = 7.5 Hz, 1H, H_2C=C(R)CH_2C**H**R_2), 3.18 (dq, *J* = 17.3, 2.1 Hz, 1H, H_2C=C(R)C**H**H'CR(CO_2Me)$_2$), 2.76 (dq, *J* = 17.3, 2.1 Hz, 1H, H_2C=C(R)CH**H'**CR(CO_2Me)$_2$), 2.66 (ddq, *J* = 16.3, 7.5, 2.0 Hz, 1H, H_2C=C(R)C**H**H'CHR_2), 2.42 (ddq, *J* = 16.3, 7.5, 2.4 Hz, 1H, H_2C=C(R)CH**H'**CHR_2).

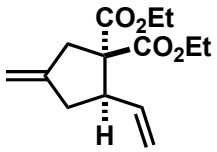
^{13}C NMR (151 MHz, $CDCl_3$): δ 171.8 (R**C**O_2Me), 170.4 (R**C**O_2Me), 146.8 (R_2**C**=CH_2), 136.8 (RH**C**=CH_2), 116.4 (RHC=**C**H_2), 107.4 (H_2**C**=CR_2), 63.8 (R_2**C**(CO_2Me)$_2$), 52.6 (RCO_2**Me**), 52.3 (RCO_2**Me**), 48.9 (H_2C=CH**C**HR_2), 39.9 (H_2C=C(R)**C**H_2CR(CO_2Me)$_2$), 37.1 (H_2C=C(R)**C**H_2CHR_2).

IR: (ν_{max}/cm^{-1} (thin film)) = 2981, 1731, 1435, 1275, 1164, 1070, 1044, 959.

LRMS (ESI$^+$): *m/z* = 247.0 = $[M+Na]^+$

HRMS (ESI$^+$): Predicted *m/z* ($[C_{12}H_{16}O_4Na]^+$) = 247.0941; *m/z* found = 247.0941.

2.21 - (±)-Diethyl 4-methylene-2-vinylcyclopentane-1,1-dicarboxylate



Anhydrous tribasic potassium phosphate (having been further dried by heating at 150 °C under high vacuum overnight) (159 mg, 0.750 mmol) and tetrabutylammonium iodide (7.4 mg, 0.020 mmol) were suspended in dry, degassed tetrahydrofuran (0.10 mL). Diethyl malonate (18 mg, 0.02 mL, 0.11 mmol) was added, and a solution of mixture **2.16** (25 mg, 0.10 mmol) in dry, degassed tetrahydrofuran (0.10 mL) was added. The resulting pale yellow suspension was stirred rapidly for 2 hours at room temperature. After this time, full consumption of **2.16** was observed by thin layer chromatography (20% ethyl acetate in pentane), and a solution of palladium(II) acetate (2.3 mg, 0.10 mmol) and triphenyl phosphine (7.9 mg, 0.30 mmol) in anhydrous, degassed tetrahydrofuran (0.80 mL) was added, and the resulting bright orange suspension was stirred rapidly for 12 hours at room temperature. After this time had elapsed, dichloromethane (2 mL), saturated aqueous ammonium chloride solution (2 mL) and water (5 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with dichloromethane (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (14 mg, 0.055 mmol, 55% yield).

R.f: 0.65 (20% diethyl ether in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (ddd, *J* = 17.1, 10.3, 7.5 Hz, 1H, RC**H**=CH_2), 5.09 (dt, *J* = 17.1, 1.5 Hz, 1H, RCH=C**H**H'), 5.03 (ddd, *J* = 10.3, 1.5, 1.0 Hz, 1H, RCH=CH**H'**), 4.91 (m, 2H, R_2C=C**H_2**), 4.26 – 4.07 (m, 4H, $R_2C(CO_2$**CH_2**$Me)_2$), 3.30 (br q, *J* = 7.5 Hz, 1H, H_2C=C(R)CH_2C**H**R_2), 3.22 – 3.11 (dq, *J* = 17.4, 2.2 Hz, 1H, H_2C=C(R)C**H**H'$CR(CO_2Et)_2$), 2.75 (dq, *J* = 17.4, 2.2 Hz, 1H, H_2C=C(R)CH**H'**$CR(CO_2Et)_2$), 2.67 (ddq, *J* =

16.3, 7.5, 2.0 Hz, 1H, H_2C=C(R)C**H**H'CHR_2), 2.43 (ddq, *J* = 16.3, 7.5, 2.2 Hz, 1H, H_2C=C(R)CH**H'**CHR_2), 1.24 (t, *J* = 7.1 Hz, 3H, RCO_2CH_2**Me**), 1.22 (t, *J* = 7.1 Hz, 3H, RCO_2CH_2**Me**).

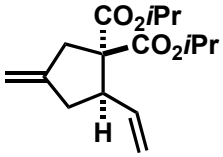
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.5 (R**C**O_2Et), 170.2 (R**C**O_2Et), 147.1 (R_2**C**=CH_2), 137.1 (RH**C**=CH_2), 116.4 (RHC=**C**H_2), 107.3 (H_2**C**=CR_2), 63.7 (R_2**C**$(CO_2Et)_2$), 61.5 (RCO_2**C**H_2Me), 61.3 (RCO_2**C**H_2Me), 48.9 (H_2C=CH**C**HR_2), 40.0 (H_2C=C(R)**C**$H_2CR(CO_2Et)_2$), 37.3 (H_2C=C(R)**C**H_2CHR_2), 14.3 (RCO_2CH_2**Me**), 14.2 (RCO_2CH_2**Me**).

IR: (ν_{max}/cm^{-1} (thin film)) = 2981, 1730, 1445, 1367, 1261, 1096, 1044, 919.

LRMS (ESI^+): *m/z* = 275.0 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{14}H_{21}O_4]^+$, $[M+H]^+$) = 253.1434; *m/z* found = 253.1436.

2.22 - (±)-Diisopropyl 4-methylene-2-vinylcyclopentane-1,1-dicarboxylate



Anhydrous tribasic potassium phosphate (having been further dried by heating at 150 °C under high vacuum overnight) (159 mg, 0.750 mmol) and tetrabutylammonium iodide (7.4 mg, 0.020 mmol) were suspended in dry, degassed tetrahydrofuran (0.10 mL). Diisopropyl malonate (21 mg, 0.021 mL, 0.11 mmol) was added, and a solution of mixture **2.16** (25 mg, 0.10 mmol) in dry, degassed tetrahydrofuran (0.10 mL) was added. The resulting pale yellow suspension was stirred rapidly for 2 hours at room temperature. After this time, full consumption of **2.16** was observed by thin layer chromatography (20% ethyl acetate in pentane), and a solution of palladium(II) acetate (2.3 mg, 0.10 mmol) and triphenyl phosphine (7.9 mg, 0.30 mmol) in anhydrous, degassed tetrahydrofuran (0.80 mL) was added, and the resulting bright orange suspension was stirred rapidly for 12 hours at room temperature. After this time had elapsed, dichloromethane (2 mL), saturated aqueous ammonium chloride solution (2 mL) and water (5 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with dichloromethane (5 mL). The combined organic

extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (9 mg, 0.03 mmol, 32% yield).

R.f: 0.71 (20% diethyl ether in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H, RC**H**=CH_2), 5.08 (dt, *J* = 17.1, 1.5 Hz, 1H, RCH=C**H**H'), 5.06 – 4.96 (m, 3H, RCH=CH**H'**, $R_2C(CO_2C\mathbf{H}Me_2)_\mathbf{2}$), 4.93 – 4.88 (m, 2H, $R_2C=C\mathbf{H_2}$), 3.30 (q, *J* = 7.6 Hz, 1H, $H_2C=C(R)CH_2C\mathbf{H}R_2$), 3.14 (dq, *J* = 17.2, 2.3 Hz, 1H, $H_2C=C(R)C\mathbf{H}H'CR(CO_2iPr)_2$), 2.72 (dq, *J* = 17.2, 2.2 Hz, 1H, $H_2C=C(R)CH\mathbf{H'}CR(CO_2iPr)_2$), 2.72 – 2.60 (m, 1H, $H_2C=C(R)C\mathbf{H}H'CHR_2$), 2.41 (ddq, *J* = 16.3, 7.6, 2.2 Hz, 1H, $H_2C=C(R)CH\mathbf{H'}CHR_2$), 1.22 (d, *J* = 6.2 Hz, 6H, $R_2C(CO_2CH\mathbf{Me_2})_2$), 1.20 (d, *J* = 6.2 Hz, 3H, $RCO_2CH\mathbf{Me}_2$), 1.19 (d, *J* = 6.2 Hz, 3H, $RCO_2CH\mathbf{Me}_2$).

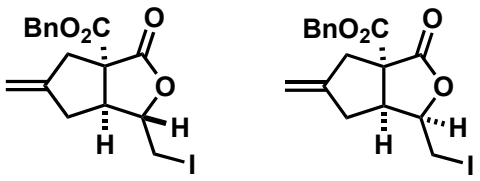
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.8 ($R\mathbf{C}O_2iPr$), 169.5 ($R\mathbf{C}O_2iPr$), 147.0 ($R_2\mathbf{C}=CH_2$), 137.0 ($RH\mathbf{C}=CH_2$), 116.1 ($RHC=\mathbf{C}H_2$), 107.0 ($H_2\mathbf{C}=CR_2$), 68.7 ($RCO_2\mathbf{C}HMe_2$), 68.6 ($RCO_2\mathbf{C}HMe_2$), 63.3 ($R_2\mathbf{C}(CO_2iPr)_2$), 48.6 ($H_2C=CH\mathbf{C}HR_2$), 39.9 ($H_2C=C(R)\mathbf{C}H_2CR(CO_2iPr)_2$), 37.2 ($H_2C=C(R)\mathbf{C}H_2CHR_2$), 21.7 ($RCO_2CH\mathbf{Me}_2$), 21.5 ($RCO_2CH\mathbf{Me}_2$), 21.5 ($RCO_2CH\mathbf{Me}_2$), 21.4 ($RCO_2CH\mathbf{Me}_2$).

IR: (ν_{max}/cm^{-1} (thin film)) = 2981, 1725, 1466, 1386, 1233, 1145, 1065, 1033, 885, 828.

LRMS (ESI^+): *m/z* = 303.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{16}H_{25}O_4]^+$,$[M+H]^+$) = 281.1747; *m/z* found = 281.1747.

2.38 - (±)-Benzyl (1*S*,3a*R*,6a*S*)-1-(iodomethyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate; **2.39 -** (±)-Benzyl (1*R*,3a*R*,6a*S*)-1-(iodomethyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Iodine (50 mg, 0.20 mmol) was dissolved in anhydrous dichloromethane (1.00 mL). Anhydrous sodium bicarbonate (25 mg, 0.30 mmol) was added to this solution, the flask was wrapped in foil to exclude light, and the mixture was stirred for 15 min at room temperature. **1.125** (38 mg, 0.10 mmol) was added, and the reaction was allowed to stir for 5 hours. After this time had elapsed, saturated aqueous sodium thiosulfate solution (1 mL), water (1 mL), and dichloromethane (2 mL) were added. The organic phase was separated, and the aqueous phase was extracted three times with dichloromethane (5 mL). The combined organic extracts were washed with saturated sodium thiosulfate solution, washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 10% ethyl acetate in pentane, to give the product as a yellow oil (33 mg, 0.080 mmol, 80%, 3:2 ratio of **2.39** to **2.38**).

Partial data for **2.38** and **2.39**:

R.f: 0.34 (20% diethyl ether in pentane, stains in potassium permanganate dip without heating).

Most of the NMR resonances could not be assigned due to peak overlap. The diagnostic resonances used in the assignment of the two diastereomers were those of the epimeric lactone protons. Across all compounds made in this series, lactone protons *endo*- with respect to the 'bowl' of the oxabicyclo-[3.3.0]-octane resonated around 4.2 ppm, whilst those *exo*- resonated around 4.8 ppm.

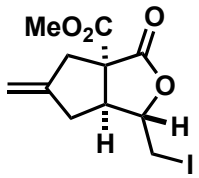
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.14 (m), 5.29 (s), 5.27 (d, *J* = 3.2 Hz), 5.24 (s), 5.21 (s), 5.18 (d, *J* = 1.1 Hz), 5.15 (d, *J* = 2.2 Hz), 5.11 – 5.09 (m), 4.98 – 4.89 (m), 4.99 (dt, *J* = 10.2, 3.8 Hz, $ICH_2C\mathbf{H}(OR)R$), 4.22 (ddd, *J* = 8.9, 4.8, 4.1 Hz, $ICH_2C\mathbf{H}(OR)R$), 3.91 (dd, *J* = 9.4, 5.2 Hz), 3.45 (dd, *J* = 10.0, 5.7 Hz), 3.41

– 3.01 (m), 2.89 (t, *J* = 9.7 Hz), 2.85 – 2.75 (m), 2.71 – 2.62 (m), 2.38 – 2.27 (m). **Peak integral ratio for major:minor = 3:2**.

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 174.3, 169.2, 168.6, 145.4, 145.4, 134.8, 134.8, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4., 109.8, 109.1, 84.1, 79.9, 68.2, 68.0, 63.6, 61.6, 50.0, 48.7, 39.9, 40.2, 39.3, 31.9, 5.5, -0.5.

HRMS (ESI^+): Predicted *m/z* ($[C_{17}H_{17}O_4INa]^+$) = 435.0064; *m/z* found = 435.0062

2.40 - (±)-Methyl (1*S*,3a*R*,6a*S*)-1-(iodomethyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate



Iodine (5.08 g, 20.0 mmol) was dissolved in dry dichloromethane (150 mL), and sodium bicarbonate (2.52 g, 30.0 mmol) was added. The resulting dark purple mixture was stirred for 1 hour, and the flask was covered in foil to exclude light. A solution of compound **1.102** (1.13 g, 5.00 mmol) in dry dichloromethane (50 mL) was added, and the reaction was stirred rapidly for 4.5 hours at room temperature. After this time had elapsed, saturated aqueous sodium thiosulfate (200 mL) was added, and the mixture was stirred for 1 hour. After this time had elapsed, water (100 mL) was added and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (200 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 10-20% ethyl acetate in pentane, to give the product as a colourless oil (1.29 g, 3.85 mmol, 77% yield).

R.f: 0.41 (20% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.97 – 4.95 (m, 2H, **H**H'C=CR_2, H**H'**C=CR_2), 4.23 (dt, *J* = 8.6, 4.9 Hz, 1H, ICH_2C**H**(OR)R), 3.80 (s, 3H, **Me**O_2CR), 3.42 (dd, *J* = 10.2, 4.9 Hz, 1H, IC**H**H'R), 3.31 (dd, *J* = 10.2, 8.6 Hz,

1H, ICH**H'**R), 3.18 (dtt, *J* = 16.6, 2.5, 1.3 Hz, 1H, H_2C=C(R)C**H**H'C(CO_2Me)COOR), 3.08 (ddd, *J* = 8.6, 4.4, 2.3 Hz, 1H, $ICH_2CH(OR)C\mathbf{H}R_2$), 2.81 (dddd, *J* = 16.3, 3.7, 2.5, 1.3 Hz, 1H, H_2C=C(R)C**H**H'CH(R)CH(OR)CH_2I), 2.82 – 2.74 (m, 1H, H_2C=C(R)CH**H'**C(CO_2Me)COOR), 2.37 – 2.31 (m, H_2C=C(R)CH**H'**CH(R)CH(OR)CH_2I).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.8 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 145.2 ($H_2C$=$\mathbf{C}R_2$), 109.7 ($H_2\mathbf{C}$=$CR_2$), 83.8 ($ICH_2\mathbf{C}H(OR)CHR_2$), 61.4 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.4 (**Me**$O_2$CR), 50.0 ($ICH_2CH(OR)\mathbf{C}HR_2$), 40.1 ($H_2C$=C(R)$\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 39.7 ($H_2C$=C(R)$\mathbf{C}H_2CH(R)CH(OR)CH_2$I), 5.5 ($I\mathbf{C}H_2R$).

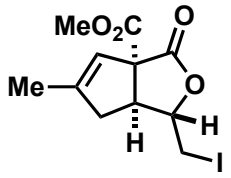
IR: (ν_{max}/cm^{-1} (thin film)) = 1776, 1739, 1433, 1340, 1143, 1018, 899.

LRMS (ESI$^+$): *m/z* = 359.0 = $[M+Na]^+$

HRMS (ESI$^+$): Predicted *m/z* ($[C_{11}H_{13}O_4INa]^+$) = 358.9751; *m/z* found = 358.9752.

HPLC data: flow rate: 1.0 mL/min, solvent: 5% IPA in hexane, retention times 20.0 minutes, 21.0 minutes; enantiomers unassigned.

2.42 - (±)-Methyl (1*S*,3a*R*,6a*S*)-1-(iodomethyl)-5-methyl-3-oxo-6,6a-dihydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate



Compound **2.42** was isolated as a product from the above procedure to form **2.40** from **1.102**, in varying yields.

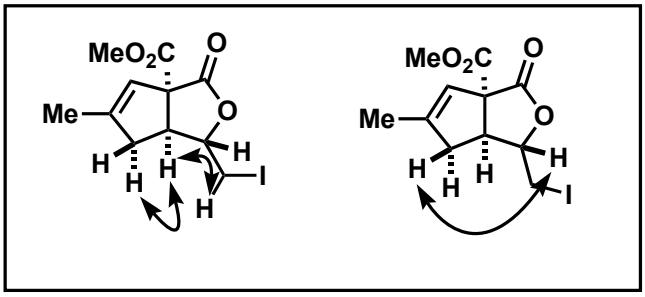
R.f: 0.40 (20% ethyl acetate in pentane, UV active, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.51 (br s, 1H, MeC(R)=C**H**R), 4.22 (dt, *J* = 8.4, 5.3 Hz, 1H, $ICH_2C\mathbf{H}(OR)R$), 3.80 (s, 3H, **Me**O_2CR), 3.47 (ddd, *J* = 10.2, 5.3 Hz, 1H, IC**H**H'R), 3.35 (dd, *J* = 10.2, 8.4 Hz, 1H, ICH**H'**R),

3.25 (ddd, *J* = 7.7, 5.3, 1.8 Hz, 1H, $ICH_2CH(OR)C\mathbf{H}R_2$), 2.88 (br dd, *J* = 17.4, 7.7 Hz, 1H, $\mathbf{H_{exo}}$), 2.35 (br d, *J* = 17.4, Hz, 1H, $\mathbf{H_{endo}}$), 1.83 (br s, 3H, **Me**C(R)=CHR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.9 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.5 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 145.6 (Me**C**(R)=CHC(R)(CO_2Me)CO_2R), 120.6 (MeC(R)=**C**HC(R)(CO_2Me)CO_2R), 84.6 ($ICH_2\mathbf{C}H(OR)CHR_2$), 69.4 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.2 (**Me**$O_2CR$), 49.4 ($ICH_2CH(OR)\mathbf{C}HR_2$), 43.7 (MeC(=CHR)$\mathbf{C}H_2CHR_2$), 16.2 (Me**C**(=CHR)$CH_2R$), 5.8 ($I\mathbf{C}H_2R$).

Key NOESY correlations used in assigning the relative configuration of 2.42:

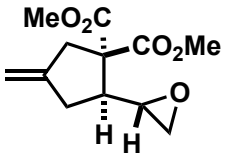


IR: (ν_{max}/cm^{-1} (thin film)) = 2953, 1772, 1731, 1435, 1037, 1009, 827.

LRMS (ESI^+): *m/z* = 359.0 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{11}H_{13}O_4INa]^+$) = 358.9751; *m/z* found = 358.9752.

2.46 - (±)-Methyl (1*R*,3a*R*,6a*S*)-1-(hydroxymethyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **2.40** (335 mg, 1.00 mmol) was dissolved in dry tetrahydrofuran (10.00 mL) and a solution of sodium methoxide (25% in methanol, 0.34 mL, 1.5 mmol) was added dropwise over 1 minute. The resulting colourless solution was stirred for 1 hour at room temperature. After this time had elapsed, saturated aqueous ammonium chloride solution (5 mL), water (5 mL), and ethyl acetate (10 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with ethyl

acetate (20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was used directly in the next reaction (241 mg, 1.00 mmol, quantitative yield).

R.f: 0.45 (20% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.95 (br s, 1H, **H**H'C=CR_2), 4.90 (br s, 1H, H**H'**C=CR_2), 3.76 (s, 3H, **Me**O_2CR), 3.74 (s, 3H, **Me**O_2CR), 3.25 (br d, *J* = 17.3 Hz, 1H, H_2C=C(R)C**H**H'C($CO_2Me)_2$R), 2.99 (ddd, *J* = 7.0, 4.0, 2.8 Hz, 1H, H_2C(O)C**H**R), 2.86 (dd, *J* = 17.3, 2.0 Hz, 1H, H_2C=C(R)CH**H'**C($CO_2Me)_2$R), 2.72 (dd, *J* = 5.0, 4.0 Hz, 1H, **H**H'C(O)CHR), 2.66 – 2.61 (m, 2H, H_2C=C(R)C**H**H'CH(R)CH(O)CH_2, H_2C=C(R)CH_2C**H**(R)CH(O)CH_2), 2.51 (dd, *J* = 5.0, 2.8 Hz, 1H, H**H'**C(O)CHR), 2.36 – 2.24 (m, 1H, H_2C=C(R)CH**H'**CH(R)CH(O)CH_2).

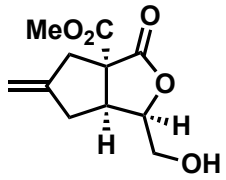
^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7 (R**C**O_2Me), 170.5 (R**C**O_2Me), 146.0 (H_2C=**C**R_2), 108.2 (H_2**C**=CR_2), 62.3 (R_2**C**($CO_2Me)_2$), 53.0 (**Me**O_2CR), 52.8 (**Me**O_2CR), 51.6 (H_2C(O)**C**HR), 47.8 (H_2C=C(R)CH_2**C**H(R)CH(O)CH_2), 45.6 (H_2**C**(O)CHR), 40.3 (H_2C=C(R)**C**H_2C($CO_2Me)_2$R), 33.8 (H_2C=C(R)**C**H_2CH(R)CH(O)CH_2).

IR: (ν_{max}/cm^{-1} (thin film)) = 2955, 1738, 1435, 1272, 1168, 1046, 898.

LRMS (ESI^+): *m/z* = 263.1 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{12}H_{16}O_5Na]^+$) = 263.0890; *m/z* found = 263.0891.

2.49 - Methyl (1*R*,3a*R*,6a*S*)-1-(hydroxymethyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



*From compound **2.50**:* compound **2.50** (113 mg, 0.500 mmol) was dissolved in dry tetrahydrofuran (5.00 mL). A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.75 mL, 0.75 mmol) was added, and the resulting colourless solution was stirred for 1 hour. After this time had elapsed, saturated aqueous ammonium chloride solution (5 mL), water (5 mL), and ethyl acetate (10 mL) were

added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (112 mg, 0.496 mmol, 99% yield).

*From compound **2.46**:* compound **2.46** (720 mg, 3.00 mmol) was dissolved in dry tetrahydrofuran (30 mL). A solution of iron(III) chloride (1.0 M in tetrahydrofuran, 1.05 mL, 1.05 mmol) was added, and the resulting orange solution was stirred at room temperature for 4 hours at room temperature. After this time had elapsed, dry methanol (15 mL) was added, and the reaction was allowed to stir overnight. After this time had elapsed, saturated aqueous sodium bicarbonate solution (10 mL) and water (10 mL) were added, causing the precipitation of a dark red solid, and the mixture was stirred for 5 minutes. The reaction was filtered through a plug of Celite™, ethyl acetate (30 mL) was added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (30 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (488 mg, 2.16 mmol, 72% yield).

R.f: 0.31 (60% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.92 (m, 2H, **HH'**C=CR_2), 4.85 (ddd, *J* = 7.5, 5.8, 4.2 Hz, 1H, $HOCH_2C$**H**(OR)R), 3.93 (dd, *J* = 12.1, 7.5 Hz, 1H, HOC**H**H'R), 3.80 (s, 3H, **Me**O_2CR), 3.79 (dd, *J* = 12.1, 4.2 Hz, 1H, HOCH**H'**R), 3.17 (ddd, *J* = 9.0, 8.0, 5.8 Hz, 1H, $HOCH_2CH(OR)C$**H**R_2), 3.07 (dq, 1H, *J* = 16.7 2.0 Hz, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.96 (br d, *J* = 16.7 Hz, 1H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R), 2.54 (ddq, *J* = 16.0, 9.0, 1.0 Hz, 1H, H_2C=C(R)C**H**H'CH(R)CH(OR)CH_2OH), 2.44 (ddq, *J* = 16.0, 8.0, 2.0 Hz, 1H, H_2C=C(R)CH**H'**CH(R)CH(OR)CH_2OH). Hydroxyl proton resonance not observed.

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.8 ($R_2C(CO_2Me)$**C**O_2R), 169.7 (R_2C(**C**O_2Me)CO_2R), 146.4 (H_2C=**C**R_2), 108.8 (H_2**C**=CR_2), 81.0 ($HOCH_2$**C**H(OR)CHR_2), 62.9 (R_2**C**(CO_2Me)CO_2R), 62.1 (HO**C**H_2R), 53.5 (**Me**O_2CR),

47.2 ($HOCH_2CH(OR)\mathbf{C}HR_2$), 39.2 ($H_2C=C(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 33.1 ($H_2C=C(R)\mathbf{C}H_2CH(R)CH(OR)CH_2OH$).

IR: (ν_{max}/cm^{-1} (thin film)) = 3457, 2957, 1774, 1739, 1435, 1361, 1107, 966.

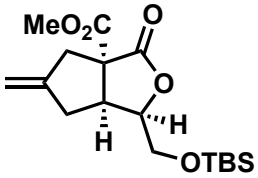
LRMS (ESI^+): *m/z* = 249.0 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{11}H_{14}O_5Na]^+$) = 249.0733; *m/z* found = 249.0733.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ -22.0 (c = 0.1 in $CHCl_3$).

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

2.50 - Methyl (1*R*,3a*R*,6a*S*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate



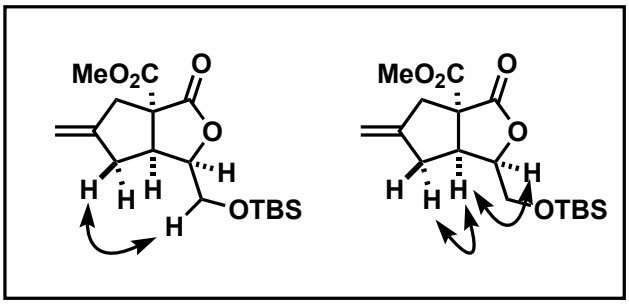
According to the modified procedure of Thompson[99]: compound **3.10** (1.86 g, 5.00 mmol) was dissolved in dry, degassed tetrahydrofuran (50 mL). A solution of lithium hexamethyldisilazide (1.0 M in toluene, 10.00 mL, 10.00 mmol) and a solution of zinc(II) chloride (1.0 M in diethyl ether, 10.00 mL, 10.00 mmol) were added, an air condenser was attached, and the resulting golden solution was stirred and heated to reflux for 2 hours, over which time the reaction mixture was observed to become cloudy. After this time had elapsed, the reaction was allowed to cool to room temperature, saturated aqueous ammonium chloride solution (25 mL), water (25 mL), and ethyl acetate (50 mL) were added, and the organic phase was separated. The aqueous layer was extracted three times with ethyl acetate (100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil which solidified upon standing in a freezer (1.70 g, 5.00 mmol, quantitative yield). Racemic material was a colourless oil.

R.f: 0.33 (20% diethyl ether in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.92 (m, 2H, **H**H'C=CR_2, H**H'**C=CR_2), 4.75 (q, *J* = 6.4 Hz, 1H, TBSOCH_2C**H**(OR)R), 3.93 (dd, *J* = 10.8, 6.4 Hz, 1H, TBSOC**H**H'R), 3.79 (s, 3H, **Me**O_2CR), 3.72 (dd, *J* = 10.8, 6.4 Hz, 1H, TBSOCH**H'**R), 3.15 (td, *J* = 8.7, 6.4 Hz, 1H, TBSOCH_2CH(OR)C**H**R_2), 3.07 (br d, *J* = 16.7 Hz, 1H, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.96 (d, *J* = 16.7 Hz, 1H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R), 2.54 (dd, J = 16.1, 9.0 Hz, 1H, H_2C=C(R)C**H**H'CH(R)CH(OR)CH_2OTBS), 2.45 (br dd, *J* = 16.1, 9.0 Hz, 1H, H_2C=C(R)CH**H'**CH(R)CH(OR)CH_2OTBS), 0.90 (s, 9H, **Me$_3$**CSiMe_2OR), 0.09 (s, 6H, Me_3CSi**Me$_2$**OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.1 (R_2C(CO_2Me)**C**O_2R), 170.0 (R_2C(**C**O_2Me)CO_2R), 146.7 (H_2C=**C**R_2), 108.5 (H_2**C**=CR_2), 80.2 (RCO_2**C**HR_2), 62.6 (R_2**C**(CO_2Me)CO_2R), 61.7 (TBSO**C**H_2R), 53.4 (**Me**O_2CR), 47.5 (TBSOCH_2CH(OR)**C**HR_2), 39.3 (H_2C=C(R)**C**H_2C(R)(CO_2Me)CO_2R), 33.0 (H_2C=C(R)**C**H_2CH(R)CH(OR)CH_2OTBS), 25.9 (3C, **Me$_3$**CSiMe_2OR), 18.3 (Me_3**C**SiMe$_2$OR), -5.3 (Me_3CSi**Me**$_2$OR), -5.4 (Me_3CSi**Me**$_2$OR).

Key NOESY correlations used in assigning the relative configuration of 2.50:



IR: (ν_{max}/cm^{-1} (thin film)) = 2954, 2930, 1780, 1742, 1472, 1054, 838.

LRMS (ESI$^+$): *m/z* = 363.2 = $[M+Na]^+$

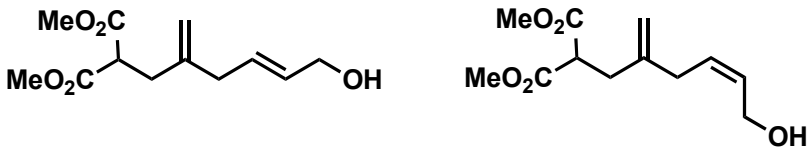
HRMS (ESI$^+$): Predicted *m/z* ($[C_{17}H_{28}O_5Si_1Na]^+$) = 363.1598; *m/z* found = 363.1599.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ +1.5 (c = 0.4 in $CHCl_3$).

Melting point of enantioenriched material: 25-26 °C.

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

3.9 - Dimethyl (*Z*)-2-(6-hydroxy-2-methylenehex-4-en-1-yl)malonate and **3.9'** dimethyl (*Z*)-2-(6-hydroxy-2-methylenehex-4-en-1-yl)malonate



Mixture **1.106** (853 mg, 3.00 mmol) was dissolved in a mixture of dry tetrahydrofuran (18.00 mL) and dry methanol (12.00 mL), and a solution of sodium methoxide (25% in methanol, 1.03 mL, 4.50 mmol) was added dropwise over 1 minute. The resulting colourless solution was stirred for 20 minutes at room temperature. After this time had elapsed, saturated aqueous ammonium chloride solution (15 mL), water (15 mL), and ethyl acetate (15 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (671 mg, 2.77 mmol, 92% yield, 10:1 ratio of *E* to *Z*).

R.f: 0.42 (50% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (dt, *J* = 15.6, 5.4 Hz, 1H, $HOCH_2$**C**H=CHR), 5.66 (dt, *J* = 15.6, 6.1 Hz, 1H, $HOCH_2CH$=**C**HR), 4.84 (br s, 1H, **H**H'$C=CR_2$), 4.81 (br s, 1H, H**H'**$C=CR_2$), 4.12 (dd, *J* = 7.1, 5.4 Hz, 2H, HOC**H$_2$**R), 3.74 (s, 6H, (**Me**$O_2C)_2$CHR), 3.63 (t, *J* = 7.8 Hz, 1H, $(MeO_2C)_2$C**H**R), 2.78 (d, *J* = 6.1 Hz, 2H, $HOCH_2CH$=CHC**H$_2$**R), 2.64 (d, *J* = 7.8 Hz, 2H, $(MeO_2C)_2$CHC**H$_2$**R), 1.26 (t, *J* = 7.1 Hz, 1H, **H**OCH_2R). **Distinguishable minor diastereomer peaks**: 4.19 (d, *J* = 6.8 Hz, 2H, HOC**H$_2$**R), 2.82 (d, *J* = 7.3 Hz, 2H, $HOCH_2CH$=CHC**H$_2$**R). **Peak integral ratio for major:minor = 10:1**.

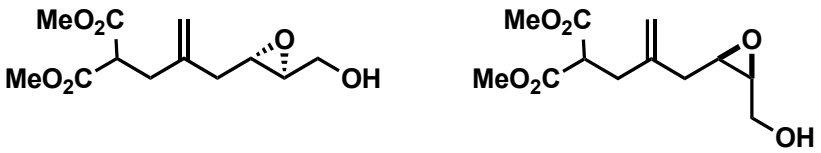
^{13}C NMR (126 MHz, $CDCl_3$): δ 169.6 (2C, $(MeO_2$**C**$)_2$CHR), 144.1 (H_2C=**C**R_2), 131.6 ($HOCH_2CH$=**C**HR), 129.8 ($HOCH_2CH$=**C**HR), 112.7 (H_2**C**$=CR_2$), 63.6 (HO**C**H_2R), 52.7 (2C, (**Me**$O_2C)_2$CHR), 50.5 $(MeO_2C)_2$**C**HR), 39.2 ($HOCH_2CH$=CH**C**H_2R), 34.8 ($(MeO_2C)_2$CH**C**H_2R). **Distinguishable minor diastereomer peaks**: 130.8 ($HOCH_2$**C**H=CHR), 129.4 ($HOCH_2CH$=**C**HR), 58.5 (HO**C**H_2R), 34.2 ($HOCH_2CH$=CH**C**H_2R).

IR: (ν_{max}/cm^{-1} (thin film)) = 3656, 2980, 1735, 1647, 1382, 1152, 1030, 971.

LRMS (ESI$^+$): *m/z* = 265.1 = $[M+Na]^+$

HRMS (ESI$^+$): Predicted *m/z* ($[C_{12}H_{18}O_5Na]^+$) = 265.1046; *m/z* found = 265.1048.

3.8 - Dimethyl 2-(2-(((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)methyl)allyl)malonate and **3.8'** - dimethyl 2-(2-(((2*R*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)methyl)allyl)malonate



Racemic: *According to the modified procedure of Itoh*[166]: mixture **3.9** (121 mg, 0.500 mmol) was dissolved in dry dichloromethane (4.00 mL) and a solution of vanadyl acetylacetonate (9.6 mg, 0.038 mmol) in dry dichloromethane (1.00 mL) was added to give a green solution. A solution of *tert*-butyl hydroperoxide (5.5 M in decane, 0.18 mL, 1.0 mmol) was added dropwise over 1 minute, and the resulting dark red solution was stirred for 6 hours at room temperature, over which time the colour of the solution faded to a pale red. After this time had elapsed, saturated aqueous ammonium chloride solution (5 mL), water (5 mL), and ethyl acetate (10 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 40-60% ethyl acetate in pentane, to give the product as a colourless oil (66 mg, 0.26 mmol, 51% yield; 10:1 ratio of **3.8** to **3.8'**).

Enantioselective: *According to the modified procedure of Sharpless*[97]: (+)-diethyl tartrate (0.22 mL, 1.3 mmol) was dissolved in dry dichloromethane (60 mL), and powdered activated 3 Å molecular sieves (600 mg) were added. The resulting mixture was cooled to -20 °C in an acetone bath (temperature maintained by the addition of dry ice), and stirred for 20 minutes. After this time had elapsed,

titanium(IV) isopropoxide (0.26 mL, 0.86 mmol) was added, and the reaction was stirred for a further 20 minutes. After this time had elapsed, a solution of *tert*-butyl hydroperoxide (5.5 M in decane, 3.44 mL, 17.2 mmol) was added, and the mixture was stirred for a further 20 minutes. After this time had elapsed, a solution of mixture **3.9** (2.09 g, 8.61 mmol) in dry dichloromethane (30 mL) was added, and the reaction was stirred for a further 20 minutes. After this time had elapsed, the flask was removed from the acetone bath and transferred to a freezer (the temperature of which was measured to be -24 °C), and allowed to stand for 72 hours. After this time had elapsed, saturated aqueous ammonium chloride solution (50 mL), water (50 mL), and ethyl acetate (100 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (200 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude product was used immediately in the subsequent reaction.

R.f: 0.21 (50% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.96 (br s, 1H, **H**H'C=CR_2), 4.90 (br s, 1H, H**H'**C=CR_2), 3.88 (m, 1H, HOC**H**H'R), 3.74 (s, 3H, (**Me**$O_2C)_2$CHR), 3.74 (s, 3H, (**Me**$O_2C)_2$CHR), 3.73 – 3.70 (m, 1H, HOCH**H'**R), 3.66 (t, *J* = 7.8 Hz, 1H, $(MeO_2C)_2$C**H**R), 3.06 (ddd, *J* = 6.2, 5.3, 2.3 Hz, 1H, $HOCH_2$CH(O)C**H**R), 2.95 (ddd, *J* = 4.1, 3.0, 2.3 Hz, 1H, $HOCH_2$C**H**(O)CHR), 2.70 (br d, *J* = 7.8 Hz, 2H, $(MeO_2C)_2$CHC**H$_2$**R), 2.33 (dd, *J* = 15.3, 6.2 Hz, 1H, $HOCH_2$CH(O)CHC**H**H'R), 2.28 (dd, *J* = 15.3, 5.3 Hz, 1H, $HOCH_2$CH(O)CHCH**H'**R), 1.74 (t, *J* = 5.4 Hz, 1H, **H**OCH_2R). **Distinguishable minor diastereomer peaks**: 3.20 (dt, *J* = 6.0, 4.3 Hz, 1H, $HOCH_2$C**H**(O)CHR), 3.16 (ddd, *J* = 6.7, 6.0, 4.2 Hz, 1H, $HOCH_2$CH(O)C**H**R). **Peak integral ratio for major:minor = 10:1**.

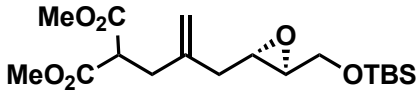
^{13}C NMR (151 MHz, $CDCl_3$): δ 169.5 ((MeO_2**C**$)_2$CHR), 169.5 ((MeO_2**C**$)_2$CHR), 141.8 (H_2C=**C**R_2), 113.9 (H_2**C**=CR_2), 61.7 (HO**C**H_2R), 58.3 ($HOCH_2$**C**H(O)CHR), 54.8 ($HOCH_2$CH(O)**C**HR), 52.8 ((**Me**$O_2C)_2$CHR), 52.8 ((**Me**$O_2C)_2$CHR), 50.4 (($MeO_2C)_2$**C**HR), 38.5 ($HOCH_2$CH(O)CH**C**H_2R), 35.3 (($MeO_2C)_2$CH**C**H_2R). **Distinguishable minor diastereomer peaks**: 56.4 ($HOCH_2$**C**H(O)CHR), 55.7 ($HOCH_2$CH(O)**C**HR).

IR: (ν_{max}/cm^{-1} (thin film)) = 3460, 1734, 1649, 1437, 1249, 1074, 1032, 734.

LRMS (ESI$^+$): *m/z* = 281.1 = [M+Na]$^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{12}H_{18}O_6Na$]$^+$) = 281.0996; *m/z* found = 281.0996.

3.10 - Dimethyl 2-(2-(((2*S*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)oxiran-2-yl)methyl)allyl)malonate



Mixture **3.8** (assumed 2.22 g, 8.61 mmol from the previous reaction) was dissolved dry dichloromethane (86 mL), and imidazole (762 mg, 12.9 mmol) and *tert*-butyldimethylsilyl chloride (1.69 g, 11.2 mmol) were added. The colourless solution was stirred for 12 hours at room temperature, over which time a white precipitate had formed. After this time had elapsed, saturated aqueous sodium bicarbonate solution (50 mL), water (50 mL), and dichloromethane (50 mL) were added and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (2.15 g, 5.77 mmol, 67% yield over two steps; quantitative yield observed from purified racemic starting material).

R.f: 0.42 (20% diethyl ether in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.97 (br s, 1H, **H**H'C=CR_2), 4.87 (br s, 1H, **H**H'C=CR_2), 3.79 (dd, *J* = 11.9, 3.7 Hz, 1H, TBSOC**H**H'R), 3.73 (s, 3H, (**Me**$O_2C)_2$CHR), 3.73 (s, 3H, (**Me**$O_2C)_2$CHR), 3.70 (dd, *J* = 11.9, 4.7 Hz, 1H, TBSOCH**H'**R), 3.65 (t, *J* = 7.9 Hz, 1H, $(MeO_2C)_2$C**H**R), 2.94 (td, *J* = 5.7, 2.2 Hz, 1H, TBSOCH_2CH(O)C**H**R), 2.87 (ddd, *J* = 4.7, 3.7, 2.2 Hz, 1H, TBSOCH_2C**H**(O)CHR), 2.69 (br d, *J* = 7.9 Hz, 2H, $(MeO_2C)_2$CHC**H_2**R), 2.28 (d, *J* = 5.7 Hz, 2H, HOCH_2CH(O)CHC**H_2**R), 0.89 (s, 9H, **Me_3**CSiMe_2OR), 0.07 (s, 3H, Me_3CSi**Me**$_2$OR), 0.06 (s, 3H, Me_3CSi**Me**$_2$OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.5 ($(MeO_2\mathbf{C})_2CHR$), 169.4 ($(MeO_2\mathbf{C})_2CHR$), 142.0 ($H_2C=\mathbf{C}R_2$), 113.7 ($H_2\mathbf{C}=CR_2$), 63.4 ($TBSO\mathbf{C}H_2R$), 58.6 ($TBSOCH_2\mathbf{C}H(O)CHR$), 54.8 ($TBSOCH_2CH(O)\mathbf{C}HR$), 52.7 ($(\mathbf{Me}O_2C)_2CHR$), 52.7 ($(\mathbf{Me}O_2C)_2CHR$), 50.4 ($(MeO_2C)_2\mathbf{C}HR$), 38.4 ($TBSOCH_2CH(O)CH\mathbf{C}H_2R$), 35.5 ($(MeO_2C)_2CH\mathbf{C}H_2R$), 26.0 (3C, $\mathbf{Me_3}CSiMe_2OR$), 18.5 ($Me_3\mathbf{C}SiMe_2OR$), -5.2 ($Me_3CSi\mathbf{Me}_2OR$), -5.2 ($Me_3CSi\mathbf{Me}_2OR$).

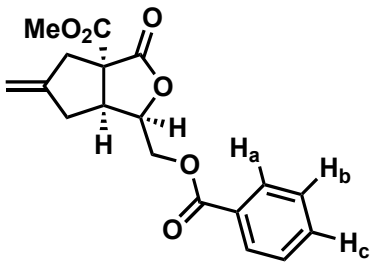
IR: (ν_{max}/cm^{-1} (thin film)) = 1739, 1462, 1072, 955, 913.

LRMS (ESI^+): *m/z* = 395.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{18}H_{32}O_6SiNa]^+$) = 395.1860; *m/z* found = 395.1859.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ -5.4 (c = 0.6 in $CHCl_3$). Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

3.18 - Methyl (1*R*,3a*R*,6a*S*)-1-((benzoyloxy)methyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate



Compound **2.49** (10 mg, 0.045 mmol) was dissolved in dry dichloromethane (0.50 mL), and the solution was cooled to 0 °C in an ice bath. 4-(Dimethylamino)pyridine (11 mg, 0.090 mmol) and benzoic anhydride (20 mg, 0.090 mmol) were added, and the colourless solution was stirred at room temperature for 12 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column

chromatography, eluting with 15% ethyl acetate in pentane, to give the product as a colourless oil (11 mg, 0.033 mmol, 74% yield).

R.f: 0.51 (30% ethyl acetate, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.6 Hz, 2H, **H_a**-Ar), 7.60 (t, *J* = 7.6 Hz, 1H, **H_b**-Ar), 7.46 (t, *J* = 7.6 Hz, 2H, **H_c**-Ar), 5.06 (ddd, *J* = 7.8, 5.7, 4.3 Hz, 1H, $BzOCH_2C\mathbf{H}(OR)R$), 4.97 (br t, *J* = 2.1 Hz, 1H, **H**H'$C=CR_2$), 4.95 (br t, *J* = 2.1 Hz, 1H, H**H'**$C=CR_2$), 4.58 (dd, *J* = 12.0, 4.3 Hz, 1H, $BzOC\mathbf{H}H'R$), 4.50 (dd, *J* = 12.0, 7.8 Hz, 1H, $BzOCH\mathbf{H'}R$), 3.81 (s, 3H, **Me**O_2CR), 3.25 (td, *J* = 8.7, 5.7 Hz, 1H, $BzOCH_2CH(OR)C\mathbf{H}R_2$), 3.10 (dq, *J* = 16.8, 2.1 Hz, 1H, $H_2C=C(R)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 3.01 (d, *J* = 16.3 Hz, 1H, $H_2C=C(R)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 2.63 (dd, *J* = 16.3, 8.7 Hz, 1H, $H_2C=C(R)C\mathbf{H}H'CH(R)CH(OR)CH_2OBz$), 2.47 (dd, *J* = 16.0, 8.7 Hz, 1H, $H_2C=C(R)CH\mathbf{H'}CH(R)CH(OR)CH_2OBz$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.6 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.5 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 166.2 ($Ph\mathbf{C}O_2R$), 145.9 ($H_2C=\mathbf{C}R_2$), 133.7 ($H_c$-$\mathbf{C_{Ar}}$), 130.0 (2C, H_a-$\mathbf{C_{Ar}}$), 129.4 (RO_2C-$\mathbf{C_{Ar}}$), 128.7 (2C, H_b-$\mathbf{C_{Ar}}$), 109.2 ($H_2\mathbf{C}=CR_2$), 78.0 ($BzOCH_2\mathbf{C}H(OR)R$), 63.4 ($BzO\mathbf{C}H_2R$), 62.7 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.6 (**Me**$O_2CR$), 47.4 ($BzOCH_2CH(OR)\mathbf{C}HR_2$), 39.1 ($H_2C=C(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 33.2 ($H_2C=C(R)\mathbf{C}H_2CH(R)CH(OR)CH_2OBz$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1781, 1729, 1723, 1273, 1122, 1026, 712.

LRMS (ESI^+): *m/z* = 353.0 = $[M+Na]^+$

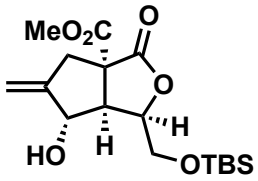
HRMS (ESI^+): Predicted *m/z* ($[C_{18}H_{18}O_6Na]^+$) = 353.0996; *m/z* found = 353.0995.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ -20.5 (c = 0.1 in $CHCl_3$).

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

HPLC data: flow rate: 1.0 mL/min, solvent: 3% IPA in hexane, retention times 75.0 minutes (1*R*, shown above), 80.0 minutes (1*S*).

3.2 - Methyl (1*R*,3a*R*,6*S*,6a*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the modified procedure of Wood[109]**:** compound **2.50** (409 mg, 1.20 mmol) was dissolved in dichloromethane (12.00 mL). Methanol (1.20 mL), water (0.12 mL), acetic acid (0.03 mL), and selenium dioxide (27 mg, 0.24 mmol) was added, a solution of *tert*-butyl hydroperoxide (5.5 M in decane, 0.55 mL, 3.0 mmol) was added, an air condenser was attached, and the colourless solution was heated to reflux for 4 hours. After this time had elapsed, the reaction was allowed to cool to room temperature, and volatile organics were evaporated under a stream of nitrogen. The crude residue was redissolved in methanol (15 mL), and potassium carbonate (166 mg, 1.20 mmol) was added. The resulting cloudy suspension was stirred for 1 hour, over which time a pale orange colour developed. After this time had elapsed, saturated aqueous ammonium chloride solution (10 mL), water (10 mL), and ethyl acetate (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 20% ethyl acetate in pentane, to give the product as a colourless oil (205 mg, 0.576 mmol, 48% yield).

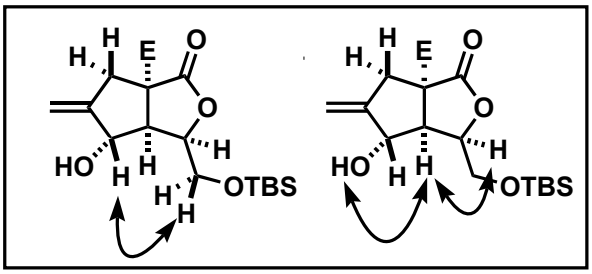
R.f: 0.45 (30% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.18 (br q, *J* = 2.3 Hz, 1H, **H**H'C=CR_2), 5.04 (q, *J* = 2.3 Hz, 1H, H**H'**C=CR_2), 4.81 (dt, *J* = 7.2, 5.1 Hz, 1H, TBSOCH_2C**H**(OR)R), 4.57 (br d, *J* = 8.5 Hz, 1H, H_2C=C(R)C**H**(OH)R), 4.13 (dd, *J* = 11.6, 5.1 Hz, 1H, TBSOC**H**H'R), 4.08 (dd, *J* = 11.6, 7.2 Hz, 1H, TBSOCH**H'**R), 3.80 (s, 3H, **Me**O_2CR), 3.32 (d, *J* = 3.2 Hz, 1H, H_2C=C(R)CH(O**H**)R), 3.23 (dq, *J* = 17.5, 1.8 Hz, 1H, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.95 – 2.87 (m, 2H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R,

TBSOCH$_2$CH(OR)C**H**R$_2$), 0.92 (s, 9H, **Me$_3$**CSiMe$_2$OR), 0.15 (s, 3H, Me$_3$CSi**Me**$_2$OR), 0.15 (s, 3H, Me$_3$CSi**Me**$_2$OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.7 (R$_2$C(CO$_2$Me)**C**O$_2$R), 169.4 (R$_2$C(**C**O$_2$Me)CO$_2$R), 147.7 (H$_2$C=**C**R$_2$), 107.9 (H$_2$**C**=CR$_2$), 78.3 (RCO$_2$**C**HR$_2$), 72.1 (H$_2$C=C(R)**C**H(OH)R), 61.6 (TBSO**C**H$_2$R), 57.9 (R$_2$**C**(CO$_2$Me)CO$_2$R), 55.6 (TBSOCH$_2$CH(OR)**C**HR$_2$), 53.7 (**Me**O$_2$CR), 35.0 (H$_2$C=C(R)**C**H$_2$C(R)(CO$_2$Me)CO$_2$R), 25.9 (3C, **Me$_3$**CSiMe$_2$OR), 18.4 (Me$_3$**C**SiMe$_2$OR), -5.3 (Me$_3$CSi**Me**$_2$OR), -5.3 (Me$_3$CSi**Me**$_2$OR).

Key NOE correlations involved in stereochemical assignment (E = CO$_2$Me):



IR: (ν_{max}/cm^{-1} (thin film)) = 3491, 2954, 1779, 1741, 1471, 1252, 1122, 838.

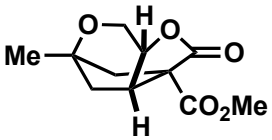
LRMS (ESI$^+$): *m/z* = 379.2 = [M+Na]$^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{17}H_{28}O_6Si_1Na$]$^+$) = 379.1547; *m/z* found = 379.1548.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ -3.0 (c = 0.1 in $CHCl_3$).

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

3.33 - (±)-Methyl (3a*S*,7a*R*)-5-methyl-2-oxotetrahydro-2*H*-3,5-methanofuro[2,3-c]pyran-3(3a*H*)-carboxylate



Compound **2.50** (6.8 mg, 0.020 mmol) was dissolved in chloroform (0.20 mL). *para*-Toluenesulfonic acid monohydrate (3.8 mg, 0.020 mmol) was added, and the colourless solution was stirred at room temperature for 2 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the

aqueous layer was extracted three times with ethyl acetate (2 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure to give the product as a colourless oil (4.5 mg, 0.020 mmol, 100% yield).

R.f: 0.30 (50% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.83 (dd, *J* = 9.1, 2.0 Hz, 1H, $R_2C(CO_2Me)CO_2C\mathbf{H}R_2$), 3.82 (dd, *J* = 13.3, 2.0 Hz, 1H, $MeCR_2OC\mathbf{H}H'R$), 3.79 (s, 3H, $\mathbf{Me}O_2CR$), 3.73 (d, *J* = 13.3 Hz, 1H, $MeCR_2OCH\mathbf{H'}R$), 3.47 (dd, *J* = 9.1, 4.7 Hz, 1H, $MeC(R)(OR)CH_2C\mathbf{H}R_2$), 2.49 (d, *J* = 14.0 Hz, 1H, $MeC(R)(OR)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 2.30 (dd, *J* = 14.0, 2.6 Hz, 1H, $MeC(R)(OR)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 2.13 (dd, *J* = 13.6, 2.6 Hz, 1H, $MeC(R)(OR)CH\mathbf{H'}CHR_2$), 1.64 (dd, *J* = 13.6, 4.7 Hz, 1H, $MeC(R)(OR)CH\mathbf{H'}CHR_2$), 1.39 (s, 3H, $\mathbf{Me}C(OR)R_2$).

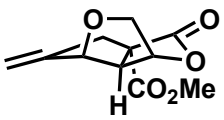
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.2 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 170.6 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 81.5 ($Me\mathbf{C}(OR)R_2$), 78.9 ($R_2C(CO_2Me)CO_2\mathbf{C}HR_2$), 63.4 ($MeCR_2O\mathbf{C}H_2R$), 58.6 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.5 ($\mathbf{Me}O_2CR$), 49.6 ($MeC(R)(OR)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 45.7 ($MeC(R)(OR)CH_2\mathbf{C}HR_2$), 34.7 ($MeC(R)(OR)\mathbf{C}H_2CHR_2$), 23.3 ($\mathbf{Me}C(OR)R_2$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1772, 1734, 1256, 1116, 1074.

LRMS (ESI^+): *m/z* = 249.1 = $[M+Na]^+$.

HRMS (ESI^+): Predicted *m/z* ($[C_{11}H_{14}O_5Na]^+$) = 249.0733; *m/z* found = 249.0734.

3.51 - (±)-Methyl (2a1*R*,4a*R*,6a*R*)-4-methylene-2-oxohexahydro-1,5-dioxacyclopenta[cd]pentalene-2a(2*H*)-carboxylate



Compound **3.2** (18 mg, 0.050 mmol) was dissolved in dry dichloromethane (0.50 mL), and the solution was cooled to 0 °C in an ice bath. Triethylamine (10 mg, 0.014 mL, 0.10 mmol) and methanesulfonyl chloride (8.6 mg, 0.006 mL, 0.075 mmol) were added, and the colourless solution was stirred and allowed to warm to room temperature over 2 hours. After this time had elapsed, saturated aqueous

sodium bicarbonate solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (11.0 mg, 0.049 mmol, 98% yield).

R.f: 0.41 (30% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 – 5.31 (m, 1H, **H**H'C=CR_2), 5.22 – 5.20 (m, 1H, H**H'**C=CR_2), 5.18 (dd, *J* = 7.0, 3.2 Hz, 1H, H_2C=C(R)CH(R)OCH_2C**H**(O_2CR)CHR_2), 4.64 (br d, *J* = 6.6 Hz, 1H, H_2C=C(R)C**H**(OR)R), 4.21 (d, *J* = 11.0 Hz, 1H, H_2C=C(R)CH(R)OC**H**H'R), 3.81 (s, 3H, **Me**O_2CR), 3.76 (dd, *J* = 11.0, 3.2 Hz, 1H, H_2C=C(R)CH(R)OCH**H'**R), 3.69 (t, *J* = 7.0 Hz, 1H, H_2C=C(R)CH(OR)C**H**R_2), 3.33 (dt, *J* = 17.2, 2.1 Hz, 1H, H_2C=C(R)C**H**H'R), 3.16 (dt, *J* = 17.3, 2.4 Hz, 1H, H_2C=C(R)CH**H'**R).

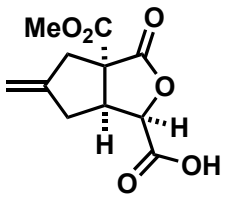
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7 ($R_2C(CO_2Me)$**C**O_2R), 169.7 (R_2C(**C**O_2Me)CO_2R), 146.3 (H_2C=**C**R_2), 114.2 (H_2**C**=CR_2), 87.5 (H_2C=C(R)**C**H(OR)R), 82.8 (H_2C=C(R)CH(R)OCH_2**C**H(O_2CR)$CHR)_2$, 74.3 (H_2C=C(R)CH(R)O**C**H_2R), 60.1 (R_2**C**(CO_2Me)CO_2R), 55.6 (H_2C=C(R)CH(OR)**C**HR_2), 53.7 (**Me**O_2CR), 39.7 (H_2C=C(R)**C**H_2R).

IR: (ν_{max}/cm^{-1} (thin film)) = 1774, 1742, 1435, 1354, 1153, 1006, 969.

LRMS (ESI^+): *m/z* = 247.0 = $[M+Na]^+$.

HRMS (ESI^+): Predicted *m/z* ($[C_{11}H_{12}O_5Na]^+$) = 247.0577; *m/z* found = 247.0578.

3.53 - (±)-(1*R*,3a*R*,6a*S*)-3a-(Methoxycarbonyl)-5-methylene-3-oxohexahydro-1*H*-cyclopenta[c]furan-1-carboxylic acid



According to the modified procedures of Martin[120] and Pinnick[121]: compound **2.49** (120 mg, 0.500 mmol) was dissolved in dry dichloromethane (5.00 mL), and stirred at room temperature. Sodium bicarbonate (210 mg, 2.50 mmol) and Dess-Martin periodinane (310 mg, 0.750 mmol) were added, and the resulting white suspension was stirred rapidly at room temperature for 1 hour. After this time had elapsed, the reaction was filtered through a plug of Celite™, saturated aqueous sodium bicarbonate solution (20 mL), water (20 mL), and ethyl acetate (50 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, to give a colourless oil as the crude residue.

This crude residue was redissolved in *tert*-butanol (3.50 mL) and stirred at room temperature. Amylene (1.50 mL), sodium dihydrogen phosphate (117 mg, 0.750 mmol), and sodium chlorite (135 mg, 1.50 mmol)) were added, and the resulting solution was stirred rapidly at room temperature for 2 hours, over which time a pale green colour was observed to develop and then fade. After this time had elapsed, saturated aqueous sodium bicarbonate solution (30 mL), water (20 mL), and ethyl acetate (50 mL) were added. The aqueous layer was separated, and the organic layer was extracted three times with water (20 mL). The combined aqueous extracts were acidified to pH 2 with sulfate buffer (pH = 2), and were extracted three times with ethyl acetate (50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, to the crude product as a colourless oil (75 mg, 0.31 mmol, 62%).

R.f: 0.30 (30% methanol in dichloromethane).

^{1}H NMR (600 MHz, d_6-DMSO): δ 5.26 (d, *J* = 6.6 Hz, 1H, $HO_2CC\mathbf{H}(OR)R$), 4.90 (br s, 1H, $\mathbf{H}H'C=CR_2$), 4.89 (br s, 1H, $H\mathbf{H'}C=CR_2$), 3.74 (s, 3H, $\mathbf{Me}O_2CR$), 3.54 (dt, *J* = 9.8, 6.6 Hz, 1H, $HO_2CCH(OR)C\mathbf{H}R_2$), 3.00 (br d, *J* = 16.3 Hz, 1H, $H_2C=C(R)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 2.78 (br d, *J* = 16.3 Hz, 1H, $H_2C=C(R)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 2.69 (dd, *J* = 16.7, 9.8 Hz, 1H, $H_2C=C(R)C\mathbf{H}H'CH(R)CH(OR)CO_2H$), 2.20 – 2.11 (m, 1H, $H_2C=C(R)CH\mathbf{H'}CH(R)CH(OR)CO_2H$). Hydroxyl proton resonance not observed.

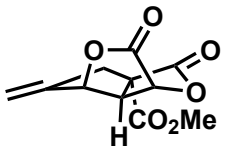
^{13}C NMR (151 MHz, d_6-DMSO): δ 174.0 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 168.6 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 168.5 ($R\mathbf{C}O_2H$), 145.9 ($H_2C=\mathbf{C}R_2$), 108.5 ($H_2\mathbf{C}=CR_2$), 77.6 ($HO_2C\mathbf{C}H(OR)CHR_2$), 61.6 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.3 ($\mathbf{Me}O_2CR$), 46.1 ($HO_2CCH(OR)\mathbf{C}HR_2$), 40.1 ($H_2C=C(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 34.2 ($H_2C=C(R)\mathbf{C}H_2CH(R)CH(OR)CO_2H$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1780, 1745.

LRMS (ESI^+): *m/z* = 263.1 = $[M+Na]^+$

HRMS (ESI^-): Predicted *m/z* ($[C_{11}H_{11}O_6]^-$) = 239.0561; *m/z* found = 239.0565.

3.54 - (±)-Methyl (2a1*R*,4a*R*,6a*R*)-4-methylene-2,6-dioxohexahydro-1,5-dioxacyclopenta[cd]pentalene-2a(2*H*)-carboxylate



According to the modified procedure of Piestruszka[167]: compound **3.53** (28 mg, 0.12 mmol) was dissolved in dry ethyl acetate (2.00 mL). White's catalyst **3.44** (12 mg, 0.023 mmol), freshly recrystallised benzoquinone (19 mg, 0.18 mmol), and powdered activated 4 Å molecular sieves (5 mg) were added, and the resulting crimson suspension was heated to 40 °C and stirred for 4 days. After this time had elapsed, the reaction was filtered through a plug of Celite™, volatile organics were removed under reduced pressure, and the crude product was purified rapidly *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (1.4 mg, 0.0060 mmol, 2% yield).

Partial data for **3.54**:

R.f: 0.45 (60% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

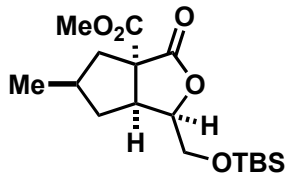
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.44 (br q, *J* = 2.0 Hz, **H**H'C=CR_2), 5.37 (br q, *J* = 2.0 Hz, 1H, H**H'**C=CR_2), 5.36 (br d, *J* = 8.7 Hz, 1H, H_2C=C(R)C**H**(O_2CR)R), 5.05 (d, *J* = 8.7 Hz, 1H, H_2C=C(R)CH(R)O_2CC**H**(O_2CR)CHR_2), 4.01 (t, *J* = 8.7 Hz, 1H, H_2C=C(R)CH(O_2CR)C**H**R_2), 3.84 (s, 3H, **Me**O_2CR), 3.26 (dt, *J* = 16.2, 2.0 Hz, 1H, H_2C=C(R)CH(R)OC**H**H'R), 3.05 (dt, *J* = 16.2, 2.0 Hz, 1H, H_2C=C(R)CH(R)OCH**H'**R).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.5 ($R_2C(CO_2Me)$**C**O_2R), 169.4 (H_2C=C(R)CH(R)O_2**C**CH(O_2CR)CHR_2), 167.9 (R_2C(**C**O_2Me)CO_2R), 143.3 (H_2C=**C**R_2), 116.3 (H_2**C**=CR_2), 82.6 (H_2C=C(R)**C**H(R)O_2CR), 74.5 (H_2C=C(R)CH(R)O_2C**C**H(O_2CR)CHR_2), 58.7 (R_2**C**(CO_2Me)CO_2R), 54.1 (**Me**O_2CR), 48.5 (H_2C=C(R)CH(R)O_2CCH(O_2CR)**C**HR_2), 39.8 (H_2C=C(R)**C**H_2R).

IR: (ν_{max}/cm^{-1} (thin film)) = 1784, 1746, 1437, 1229, 1145, 1025, 930.

LRMS (ESI^+): *m/z* = 239.0 = $[M+H]^+$.

3.55 - (±)-Methyl (1*R*,3a*R*,5*R*,6a*S*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **2.50** (34 mg, 0.10 mmol) was dissolved in ethyl acetate (1.00 mL), the solution was sparged with nitrogen, and palladium on carbon (10% palladium by weight, 11 mg, 0.010 mmol palladium) was added. The suspension was sparged with nitrogen, then sparged with hydrogen, the flask was fitted with a three-skinned hydrogen balloon, and the mixture was stirred rapidly for 4 hours. After this time had elapsed, the hydrogen balloon was removed, and the flask was opened to the atmosphere. The mixture was filtered through a pad of Celite™, volatile organics were removed under reduced

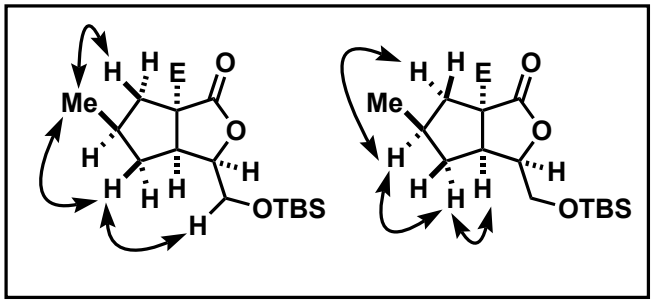
pressure, and the crude product was purified *via* flash column chromatography, eluting with 20% diethyl ether in pentane, to give the product as a colourless oil (31 mg, 0.091 mmol, 91% yield).

R.f: 0.33 (20% diethyl ether in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.70 (q, *J* = 6.2 Hz, 1H, TBSOCH$_2$C**H**(OR)R), 3.90 (dd, *J* = 10.7, 6.2 Hz, 1H, TBSOC**H**H'R), 3.78 (s, 3H, **Me**O$_2$CR), 3.72 (dd, *J* = 10.7, 6.2 Hz, 1H, TBSOCH**H'**R), 3.03 (dt, *J* = 12.0, 6.2 Hz, 1H, TBSOCH$_2$CH(OR)C**H**R$_2$), 2.69 (dd, *J* = 13.9, 7.7 Hz, 1H, MeCH(R)C**H$_{exo}$**H$_{endo}$C(R)(CO$_2$Me)CO$_2$R), 2.19 – 2.06 (m, 1H, MeC**H**R$_2$), 1.92 (dd, *J* = 12.0, 6.0 Hz, 1H, MeCH(R)C**H$_{exo}$**H$_{endo}$CH(R)CH(OR)CH$_2$OTBS), 1.66 (dd, *J* = 13.9, 10.9 Hz, 1H, MeCH(R)CH$_{exo}$**H$_{endo}$**C(R)(CO$_2$Me)CO$_2$R), 1.27 – 1.18 (q, *J* = 12.0 Hz, 1H, MeCH(R)CH$_{exo}$**H$_{endo}$**CH(R)CH(OR)CH$_2$OTBS), 1.04 (d, *J* = 6.2 Hz, 3H, **Me**CHR$_2$), 0.90 (s, 9H, **Me$_3$**CSiMe$_2$OR), 0.09 (s, 3H, Me$_3$CSi**Me**$_2$OR), 0.08 (s, 3H, Me$_3$CSi**Me**$_2$OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.3 (R$_2$C(CO$_2$Me)**C**O$_2$R), 170.8 (R$_2$C(**C**O$_2$Me)CO$_2$R), 80.0 (RCO$_2$**C**HR$_2$), 62.9 (R$_2$**C**(CO$_2$Me)CO$_2$R), 62.0 (TBSO**C**H$_2$R), 53.3 (**Me**O$_2$CR), 50.1 (TBSOCH$_2$CH(OR)**C**HR$_2$), 41.3 (MeCH(R)**C**H$_2$C(R)(CO$_2$Me)CO$_2$R), 36.4 (Me**C**HR$_2$), 35.8 (MeCH(R)**C**H$_2$CH(R)CH(OR)CH$_2$OTBS), 25.9 (3C, **Me$_3$**CSiMe$_2$OR), 18.8 (**Me**CHR$_2$), 18.4 (Me$_3$**C**SiMe$_2$OR), -5.2 (Me$_3$CSi**Me**$_2$OR), -5.4 (Me$_3$CSi**Me**$_2$OR).

Key NOE correlations involved in stereochemical assignment (E = CO$_2$Me):

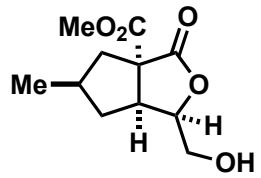


IR: (ν_{max}/cm^{-1} (thin film)) = 1778, 1743, 1258, 1116, 838.

LRMS (ESI$^+$): *m/z* = 365.2 = [M+Na]$^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{17}H_{31}O_5Si$]$^+$, [M+H]$^+$) = 343.1935; *m/z* found = 343.1938.

3.56 - (±)-Methyl (1*R*,3a*R*,5*R*,6a*S*)-1-(hydroxymethyl)-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.55** (29 mg, 0.085 mmol) was dissolved in dry tetrahydrofuran (0.85 mL), and the reaction was cooled to 0 °C in an ice bath. A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.13 mL, 0.13 mmol) was added, and the colourless solution was stirred and allowed to warm to room temperature over 30 minutes. After this time had elapsed, saturated aqueous ammonium chloride solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (15 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (17 mg, 0.074 mmol, 87% yield).

R.f: 0.31 (60% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.79 (ddd, *J* = 7.9, 6.0, 4.1 Hz, 1H, $HOCH_2C\mathbf{H}(OR)R$), 3.92 (dd, *J* = 12.2, 7.9 Hz, 1H, HOC**H**H'R), 3.78 (s, 3H, **Me**O_2CR), 3.76 (dd, *J* = 12.2, 4.1 Hz, 1H, HOCH**H'**R), 3.03 (dt, *J* = 11.9, 6.0 Hz, 1H, $HOCH_2CH(OR)C\mathbf{H}R_2$), 2.70 (dd, *J* = 13.9, 7.8 Hz, 1H, MeCH(R)C**H**H'C(R)$(CO_2Me)CO_2R$), 2.12 (ddddd, *J* = 11.9, 10.9, 7.8, 6.5, 5.3 Hz, 1H, MeC**H**R_2), 1.95 – 1.85 (m, 1H, MeCH(R)CH**H'**C(R)$(CO_2Me)CO_2R$), 1.67 (dd, *J* = 11.9, 10.9 Hz, 1H, MeCH(R)C**H**H'CH(R)$CH(OR)CH_2OH$), 1.23 (q, *J* = 11.9 Hz, 1H, MeCH(R)CH**H'**CH(R)$CH(OR)CH_2OH$), 1.05 (d, *J* = 6.5 Hz, 3H, **Me**CHR_2). Hydroxyl proton resonance not observed.

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.9 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 170.5 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 80.7 ($RCO_2\mathbf{C}HR_2$), 63.2 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 62.4 (HO**C**$H_2R$), 53.4 (**Me**$O_2CR$), 49.8 ($HOCH_2CH(OR)\mathbf{C}HR_2$), 41.2

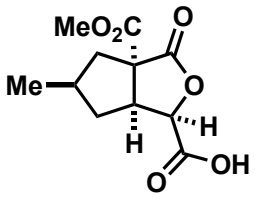
(MeCH(R)**C**H_2C(R)(CO_2Me)CO_2R), 36.6 (Me**C**HR_2), 35.8 (MeCH(R)**C**H_2CH(R)CH(OR)CH_2OH), 18.7 (**Me**CHR_2).

IR: (ν_{max}/cm^{-1} (thin film)) = 3546, 1772, 1740, 1104, 997.

LRMS (ESI^+): *m/z* = 251.1 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{11}H_{17}O_5]^+$, $[M+H]^+$) = 229.1071; *m/z* found = 229.1072.

3.58 - (±)-(1*R*,3a*R*,5*R*,6a*S*)-3a-(Methoxycarbonyl)-5-methyl-3-oxohexahydro-1*H*-cyclopenta[c]furan-1-carboxylic acid



According to the modified procedures of Martin[120] and Pinnick[121]: compound **3.56** (12 mg, 0.050 mmol) was dissolved in dry dichloromethane (0.50 mL), and stirred at room temperature. Sodium bicarbonate (21 mg, 0.25 mmol) and Dess-Martin periodinane (31 mg, 0.075 mmol) were added, and the resulting white suspension was stirred rapidly at room temperature for 1 hour. After this time had elapsed, the reaction was filtered through a plug of Celite™, saturated aqueous sodium bicarbonate solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, to give a colourless oil as the crude residue.

This crude residue was redissolved in *tert*-butanol (0.35 mL) and stirred at room temperature. Amylene (0.15 mL), sodium dihydrogen phosphate (12 mg, 0.075 mmol), and sodium chlorite (14 mg, 0.15 mmol)) were added, and the resulting solution was stirred rapidly at room temperature for 2 hours, over which time a pale green colour was observed to develop and then fade. After this time had elapsed, saturated aqueous sodium bicarbonate solution (3 mL), water (2 mL), and ethyl acetate (5 mL) were added. The aqueous layer was separated, and the organic layer was extracted three times

with water (2 mL). The combined aqueous extracts were acidified to pH 2 with sulfate buffer (pH = 2), and were extracted three times with ethyl acetate (5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, to the crude product as a colourless oil (8.3 mg, 0.034 mmol, 68%).

R.f: 0.30 (30% methanol in dichloromethane).

^{1}H NMR (600 MHz, d_6-DMSO): δ 5.18 (d, *J* = 6.9 Hz, 1H, $HO_2CC\mathbf{H}(OR)R$), 3.72 (s, 3H, $\mathbf{Me}O_2CR$), 3.41 (dt, *J* = 11.9, 6.9 Hz, 1H, $HO_2CCH(OR)C\mathbf{H}R_2$), 2.57 (dd, *J* = 13.5, 7.6 Hz, 1H, $MeCH(R)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 2.12 – 2.01 (m, 1H, $MeC\mathbf{H}R_2$), 1.93 (dddd, *J* = 11.9, 6.9, 5.1 Hz, 1H, $MeCH(R)C\mathbf{H}H'CH(R)CH(OR)CO_2H$), 1.50 (dd, *J* = 13.5, 10.8 Hz, 1H, $MeCH(R)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 1.02 (q, *J* = 11.9 Hz, 1H, $MeCH(R)C\mathbf{H}H'CH(R)CH(OR)CO_2H$), 0.96 (d, *J* = 6.6 Hz, 3H, $\mathbf{Me}CHR_2$). Hydroxyl proton resonance not observed.

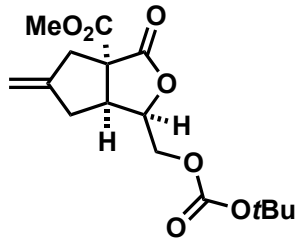
^{13}C NMR (151 MHz, d_6-DMSO): δ 174.9 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.5 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 168.6 ($R\mathbf{C}O_2H$), 76.5 ($RCO_2\mathbf{C}HR_2$), 61.7 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.2 ($\mathbf{Me}O_2CR$), 48.5 ($HO_2CCH(OR)\mathbf{C}HR_2$), 40.7 ($MeCH(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 37.0 ($Me\mathbf{C}HR_2$), 35.3 ($MeCH(R)\mathbf{C}H_2CH(R)CH(OR)CO_2H$), 18.3 ($\mathbf{Me}CHR_2$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1780, 1745.

LRMS (ESI^+): *m/z* = 265.1 = $[M+Na]^+$

HRMS (ESI^-): Predicted *m/z* ($[C_{11}H_{13}O_6]^-$) = 241.0718; *m/z* found = 241.0714.

3.19 - (±)-Methyl (1*R*,3a*R*,6a*S*)-1-(((*tert*-butoxycarbonyl)oxy)methyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **2.49** (113 mg, 0.500 mmol) was dissolved in dry dichloromethane (5.00 mL), and the solution was cooled to 0 °C in an ice bath. 4-(Dimethylamino)pyridine (183 mg, 1.50 mmol) and di-*tert*-butyl dicarbonate (164 mg, 0.750 mmol) were added, and the colourless solution was stirred and allowed to warm to room temperature over 12 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (5 mL), water (5 mL), and ethyl acetate (15 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (15 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 30% ethyl acetate in pentane, to give the product as a colourless oil (139 mg, 0.426 mmol, 85% yield).

R.f: 0.68 (40% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.98 – 4.88 (m, 3H, $BocOCH_2C\mathbf{H}(OR)R$, $\mathbf{HH'}C{=}CR_2$), 4.33 (dd, *J* = 11.8, 7.6 Hz, 1H, BocOC**H**H'R), 4.22 (dd, *J* = 11.8, 4.7 Hz, 1H, BocOCH**H'**R), 3.79 (s, 3H, $\mathbf{Me}O_2CR$), 3.18 (td, *J* = 8.7, 5.7 Hz, 1H, $BocOCH_2CH(OR)C\mathbf{H}R_2$), 3.08 (dq, *J* = 16.9, 2.1 Hz, 1H, $H_2C{=}C(R)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 3.98 (br d, *J* = 16.9 Hz, 1H, $H_2C{=}C(R)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 2.57 (ddq, *J* = 16.0, 9.0, 1.5 Hz, 1H, $H_2C{=}C(R)C\mathbf{H}H'CH(R)CH(OR)CH_2OBoc$), 2.38 (ddq, *J* = 16.0, 9.0, 2.0 Hz, 1H, $H_2C{=}C(R)CH\mathbf{H'}CH(R)CH(OR)CH_2OBoc$), 1.50 (s, 9H, $\mathbf{Me_3}COCO_2R$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.5 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 153.1 ($Me_3CO\mathbf{C}O_2R$), 145.9 ($H_2C{=}\mathbf{C}R_2$), 109.1 ($H_2\mathbf{C}{=}CR_2$), 83.3 ($Me_3\mathbf{C}OCO_2R$), 77.6 ($BocOCH_2\mathbf{C}H(OR)CHR_2$), 65.2 ($BocO\mathbf{C}H_2R$),

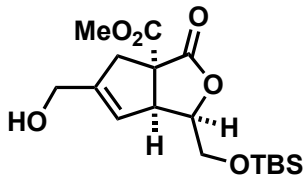
62.6 (R_2**C**(CO_2Me)CO_2R), 53.5 (**Me**O_2CR), 47.3 (BocOCH_2CH(OR)**C**HR_2), 39.0 (H_2C=C(R)**C**H_2C(R)(CO_2Me)CO_2R), 33.1 (H_2C=C(R)**C**H_2CH(R)CH(OR)CH_2OBoc), 27.9 (3C, **Me**$_3$COCO_2R).

IR: (ν_{max}/cm^{-1} (thin film)) = 1782, 1745, 1280, 1158, 857.

LRMS (ESI^+): *m/z* = 349.2 = $[M+Na]^+$; 293.0 = $[M-H_2C=CMe_2+Na]^+$;

HRMS (ESI^+): Predicted *m/z* ($[C_{16}H_{22}O_7Na]^+$) = 349.1258; *m/z* found = 349.1256.

3.67 - (±)-Methyl (1*R*,3a*R*,6a*S*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(hydroxymethyl)-3-oxo-4,6a-dihydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the procedure of Li[128]: compound **2.50** (3.4 mg, 0.010 mmol) was dissolved in dry dichloroethane (0.50 mL). Tetraphenylporphyrin (0.6 mg, 0.001 mmol) was added, the solution was sparged with oxygen for 15 minutes, and the flask was fitted with an oxygen balloon. The resulting deep violet solution was irradiated using a 30 W compact fluorescent light (at a distance of 1 cm) and stirred for 4 days. After this time had elapsed, the light source was removed, triphenylphosphine (5.2 mg, 0.020 mmol) was added, and the reaction was stirred for a further 30 minutes. The volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a pale green oil (1.7 mg, 0.0046 mmol, 46% yield).

R.f: 0.45 (30% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.53 – 5.50 (m, 1H, HOCH_2C(R)=C**H**CHR_2), 4.76 (q, *J* = 6.4 Hz, 1H, TBSOCH_2C**H**(OR)R), 4.28 – 4.15 (m, 2H, HOC**H$_2$**R), 3.92 (dd, *J* = 10.6, 6.2 Hz, 1H, TBSOC**H**H'R), 3.82 – 3.81 (m, 1H, TBSOCH_2CH(OR)C**H**R_2), 3.81 (s, 3H, **Me**O_2CR), 3.72 (dd, *J* = 10.6, 7.0 Hz, 1H, TBSOCH**H'**R), 3.16 (dtt, *J* = 16.9, 2.3, 1.2 Hz, 1H, HOCH_2C(=CHR)C**H**H'C(R)(CO_2Me)CO_2R), 2.96 (dq, *J* = 16.9, 1.4 Hz,

1H, $HOCH_2C(=CHR)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 0.90 (s, 9H, $\mathbf{Me_3}CSiMe_2OR$), 0.10 (s, 3H, $Me_3CSi\mathbf{Me}_2OR$), 0.09 (s, 3H, $Me_3CSi\mathbf{Me}_2OR$). Hydroxyl proton resonance not observed.

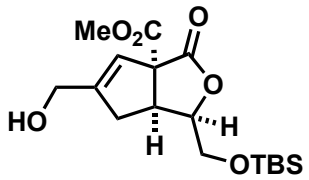
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.6 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.4 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 146.7 ($HOCH_2\mathbf{C}(R)=CHCHR_2$), 119.4 ($HOCH_2C(R)=\mathbf{C}HCHR_2$), 81.2 ($TBSOCH_2\mathbf{C}H(OR)CHR_2$), 62.3 ($TBSO\mathbf{C}H_2CH(OR)CHR_2$), 61.4 ($HO\mathbf{C}H_2R$), 61.2 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 54.4 ($TBSOCH_2CH(OR)\mathbf{C}HR_2$), 53.4 ($\mathbf{Me}O_2CR$), 39.9 ($HOCH_2C(=CHR)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 25.9 (3C, $\mathbf{Me_3}CSiMe_2OR$), 18.3 ($Me_3\mathbf{C}SiMe_2OR$), -5.2 ($Me_3CSi\mathbf{Me}_2OR$), -5.3 ($Me_3CSi\mathbf{Me}_2OR$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1770, 1739.

LRMS (ESI^+): *m/z* = 379.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{17}H_{28}O_6SiNa]^+$) = 379.1457; *m/z* found = 379.1459.

3.66 - (±)-Methyl (1*R*,3a*R*,6a*S*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(hydroxymethyl)-3-oxo-6,6a-dihydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.66** was isolated as a product from the above procedure to form **3.67** from **2.50**, in a yield of (0.4 mg, 0.001 mmol, 10% yield).

R.f: 0.42 (30% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.83 – 5.80 (m, 1H, $HOCH_2C(R)=C\mathbf{H}C(R)(CO_2Me)CO_2R$), 4.82 (td, *J* = 7.0, 5.4 Hz, 1H, $TBSOCH_2C\mathbf{H}(OR)R$), 4.22 (br s, 2H, $HOC\mathbf{H_2}R$), 3.96 (dd, *J* = 11.0, 5.4 Hz, 1H, $TBSOC\mathbf{H}H'R$), 3.81 (s, 3H, $\mathbf{Me}O_2CR$), 3.78 (dd, *J* = 11.0, 7.0 Hz, 1H, $TBSOCH\mathbf{H'}R$), 3.57 (ddd, *J* = 9.5, 7.0, 5.4 Hz, 1H, $TBSOCH_2CH(OR)C\mathbf{H}R_2$), 2.75 – 2.68 (m, 1H, $HOCH_2C(=CHR)C\mathbf{H}H'CHR_2$), 2.64 – 2.58 (br dd, *J* = 17.3, 9.5 Hz, 1H, $HOCH_2C(=CHR)CH\mathbf{H'}CHR_2$), 0.89 (s, 9H, $\mathbf{Me_3}CSiMe_2OR$), 0.10 (s, 3H, $Me_3CSi\mathbf{Me}_2OR$), 0.09 (s, 3H, $Me_3CSi\mathbf{Me}_2OR$). Hydroxyl proton resonance not observed.

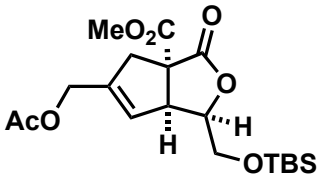
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.8 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 149.4 ($HOCH_2\mathbf{C}(R)=CHC(R)(CO_2Me)CO_2R$), 121.2 ($HOCH_2C(R)=\mathbf{C}HC(R)(CO_2Me)CO_2R$), 80.3 ($TBSOCH_2\mathbf{C}H(OR)CHR_2$), 68.7 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 62.3 ($TBSO\mathbf{C}H_2CH(OR)CHR_2$), 61.3 ($HO\mathbf{C}H_2R$), 53.4 ($\mathbf{Me}O_2CR$), 46.3 ($TBSOCH_2CH(OR)\mathbf{C}HR_2$), 32.9 ($HOCH_2C(=CHR)\mathbf{C}H_2CHR_2$), 25.9 (3C, $\mathbf{Me_3}CSiMe_2OR$), 18.3 ($Me_3\mathbf{C}SiMe_2OR$), -5.3 ($Me_3CSi\mathbf{Me}_2OR$), -5.3 ($Me_3CSi\mathbf{Me}_2OR$).

IR: (ν_{max}/cm^{-1} (thin film)) = 3385, 1767, 1737.

LRMS (ESI^+): *m/z* = 379.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{17}H_{28}O_6SiNa]^+$) = 379.1457; *m/z* found = 379.1459.

3.76 - (±)-Methyl (1*R*,3a*R*,6a*S*)-5-(acetoxymethyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-oxo-4,6a-dihydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the modified procedure of Stahl[129]: compound **2.50** (34 mg, 0.10 mmol) was dissolved in dry dioxane (0.75 mL) and acetic acid (0.25 mL). Palladium(II) acetate (2.2 mg, 0.010 mmol), sodium acetate (1.6 mg, 0.020 mmol), and 4,5-diazafluoren-9-one (1.8 mg, 0.010 mmol) were added, and the flask was fitted with an oxygen balloon. The resulting golden solution was heated to 70 °C, at which temperature the colour of the solution was observed to change from golden to deep orange over 30 minutes; the reaction was stirred at this temperature for 18 hours. After this time had elapsed, the reaction was cooled to room temperature, volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 20% ethyl acetate in pentane, to give the product as a colourless oil (27 mg, 0.068 mmol, 68% yield).

R.f: 0.32 (20% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.56 – 5.52 (m, 1H, $AcOCH_2C(R)=C\mathbf{H}CHR_2$), 4.76 (dt, *J* = 7.3, 6.1 Hz, 1H, $TBSOCH_2C\mathbf{H}(OR)R$), 4.61 (br s, 2H, $AcOC\mathbf{H_2}R$), 3.92 (dd, *J* = 10.5, 5.9 Hz, 1H, $TBSOC\mathbf{H}H'R$), 3.83 – 3.81

(m, 1H, TBSOCH$_2$CH(OR)C**H**R$_2$), 3.80 (s, 3H, **Me**O$_2$CR), 3.69 (dd, *J* = 10.5, 7.3 Hz, 1H, TBSOCH**H'**R), 3.17 (dtt, *J* = 17.0, 2.3, 1.2 Hz, 1H, AcOCH$_2$C(=CHR)C**H**H'C(R)(CO$_2$Me)CO$_2$R), 2.97 (dt, *J* = 17.0, 1.9 Hz, 1H, AcOCH$_2$C(=CHR)CH**H'**C(R)(CO$_2$Me)CO$_2$R), 2.08 (s, 3H, **Me**CO$_2$CH$_2$R), 0.90 (s, 9H, **Me$_3$**CSiMe$_2$OR), 0.09 (s, 3H, Me$_3$CSi**Me**$_2$OR), 0.09 (s, 3H, Me$_3$CSi**Me**$_2$OR).

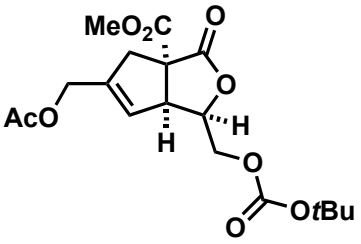
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4 (R$_2$C(CO$_2$Me)**C**O$_2$R), 170.6 (Me**C**O$_2$CH$_2$R), 169.2 (R$_2$C(**C**O$_2$Me)CO$_2$R), 141.4 (AcOCH$_2$**C**(R)=CHCHR$_2$), 122.5 (AcOCH$_2$C(R)=**C**HCHR$_2$), 80.9 (TBSOCH$_2$**C**H(OR)CHR$_2$), 62.1 (TBSO**C**H$_2$CH(OR)CHR$_2$), 62.0 (AcO**C**H$_2$R), 61.1 (R$_2$**C**(CO$_2$Me)CO$_2$R), 54.5 (TBSOCH$_2$CH(OR)**C**HR$_2$), 53.4 (**Me**O$_2$CR), 40.2 (AcOCH$_2$C(=CHR)**C**H$_2$C(R)(CO$_2$Me)CO$_2$R), 25.9 (3C, **Me$_3$**CSiMe$_2$OR), 20.9 (**Me**CO$_2$CH$_2$R), 18.3 (Me$_3$**C**SiMe$_2$OR), -5.3 (Me$_3$CSi**Me**$_2$OR), -5.4 (Me$_3$CSi**Me**$_2$OR).

IR: (ν_{max}/cm^{-1} (thin film)) = 1780, 1744, 1031.

LRMS (ESI$^+$): *m/z* = 421.2 = [M+Na]$^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{19}H_{30}O_7SiNa$]$^+$) = 421.1653; *m/z* found = 421.1652.

3.78 - (±)-Methyl (1*R*,3a*R*,6a*S*)-5-(acetoxymethyl)-1-(((*tert*-butoxycarbonyl)oxy)methyl)-3-oxo-4,6a-dihydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the modified procedure of Stahl[129]: compound **3.19** (33 mg, 0.10 mmol) was dissolved in dry dioxane (0.75 mL) and acetic acid (0.25 mL). Palladium(II) acetate (2.2 mg, 0.010 mmol), sodium acetate (1.6 mg, 0.020 mmol), and 4,5-diazafluoren-9-one (1.8 mg, 0.010 mmol) were added, and the flask was fitted with an oxygen balloon. The resulting golden solution was heated to 70 °C, at which temperature the colour of the solution was observed to change from golden to deep orange over 30 minutes; the reaction was stirred at this temperature for 18 hours. After this time had elapsed, the reaction was cooled to room temperature, volatile organics were removed under reduced pressure,

and the crude product was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (24 mg, 0.063 mmol, 63% yield).

R.f: 0.18 (20% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.47 – 5.45 (m, 1H, $AcOCH_2C(R)=C\mathbf{H}CHR_2$), 4.97 (ddd, *J* = 7.5, 6.3, 5.1 Hz, 1H, $BocOCH_2C\mathbf{H}(OR)R$), 4.61 (br s, 2H, $AcOC\mathbf{H_2}R$), 4.29 (dd, *J* = 11.6, 7.5 Hz, 1H, $BocOC\mathbf{H}H'R$), 4.25 (dd, *J* = 11.7, 5.1 Hz, 1H, $BocOCH\mathbf{H'}R$), 3.86 (dq, *J* = 6.3, 2.1 Hz, 1H, $BocOCH_2CH(OR)C\mathbf{H}R_2$), 3.80 (s, 3H, $\mathbf{Me}O_2CR$), 3.20 (br d, *J* = 17.2 Hz, 1H, $AcOCH_2C(=CHR)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 3.00 (br d, *J* = 17.2 Hz, 1H, $AcOCH_2C(=CHR)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 2.10 (s, 3H, $\mathbf{Me}CO_2CH_2R$), 1.50 (s, 9H, $\mathbf{Me_3}COCO_2R$).

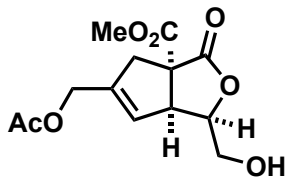
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.7 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 170.6 ($Me\mathbf{C}O_2CH_2R$), 168.7 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 153.1 ($Me_3CO\mathbf{C}O_2R$), 142.9 ($AcOCH_2\mathbf{C}(R)=CHCHR_2$), 120.8 ($AcOCH_2C(R)=\mathbf{C}HCHR_2$), 83.4 ($Me_3\mathbf{C}OCO_2R$), 78.6 ($BocOCH_2\mathbf{C}H(OR)CHR_2$), 65.6 ($BocO\mathbf{C}H_2CH(OR)CHR_2$), 61.8 ($AcO\mathbf{C}H_2R$), 61.0 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 54.0 ($BocOCH_2CH(OR)\mathbf{C}HR_2$), 53.6 ($\mathbf{Me}O_2CR$), 40.2 ($AcOCH_2C(=CHR)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 27.9 (3C, $\mathbf{Me_3}COCO_2R$), 20.9 ($\mathbf{Me}CO_2CH_2R$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1782, 1742, 1370.

LRMS (ESI^+): *m/z* = 351.0 = $[M\text{-}H_2C{=}CMe_2{+}Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{18}H_{24}O_9Na]^+$, $[M+Na]^+$) = 407.1307; *m/z* found = 407.1313.

3.89 - (±)-Methyl (1*R*,3a*R*,6a*S*)-5-(acetoxymethyl)-1-(hydroxymethyl)-3-oxo-4,6a-dihydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate



Compound **3.78** (3.8 mg, 0.010 mmol) was dissolved in dry dichloromethane (0.10 mL) and the resulting solution was cooled to 0 °C in an ice bath. Boron trifluoride diethyl etherate (0.001 mL, 0.01 mmol) was added, and the reaction was allowed to stir for 5 minutes. After this time had elapsed, saturated aqueous sodium bicarbonate solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were

added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure to give the product as a colourless oil (2.2 mg, 0.0079 mmol, 79% yield).

R.f: 0.30 (60% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

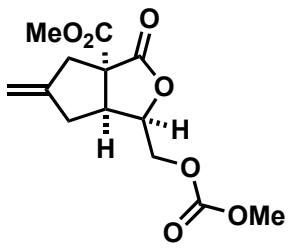
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.50 (br s, 1H, $AcOCH_2C(R)=C\mathbf{H}CHR_2$), 4.87 (td, *J* = 6.9, 4.7 Hz, 1H, $HOCH_2C\mathbf{H}(OR)R$), 4.61 (br s, 2H, $AcOC\mathbf{H_2}R$), 3.89 (dd, *J* = 12.0, 6.9 Hz, 1H, HOC**H**H'R), 3.86 (dd, *J* = 12.0, 4.7 Hz, 1H, HOCH**H'**R), 3.83 (td, *J* = 4.7, 2.1 Hz, 1H, $HOCH_2CH(OR)C\mathbf{H}R_2$), 3.81 (s, 3H, **Me**$O_2CR$), 3.17 (br d, *J* = 17.2 Hz, 1H, $AcOCH_2C(=CHR)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 2.99 (br d, *J* = 17.2 Hz, 1H, $AcOCH_2C(=CHR)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 2.09 (s, 3H, **Me**$CO_2CH_2R$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.9 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 170.5 (Me**C**$O_2CH_2R$), 168.8 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 141.6 ($AcOCH_2\mathbf{C}(R)=CHCHR_2$), 121.7 ($AcOCH_2C(R)=\mathbf{C}HCHR_2$), 81.7 ($HOCH_2\mathbf{C}H(OR)CHR_2$), 62.4 ($HO\mathbf{C}H_2CH(OR)CHR_2$), 61.8 ($AcO\mathbf{C}H_2R$), 61.2 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.8 ($BocOCH_2CH(OR)\mathbf{C}HR_2$), 53.4 (**Me**$O_2CR$), 40.0 ($AcOCH_2C(=CHR)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 20.8 (**Me**$CO_2CH_2R$).

IR: (ν_{max}/cm^{-1} (thin film)) = 3566, 1772, 1734.

HRMS (ESI^+): Predicted *m/z* ($[C_{13}H_{16}O_7Na]^+$) = 307.0788; *m/z* found = 307.0789.

3.20 - (±)-Methyl (1*R*,3a*R*,6a*S*)-1-(((methoxycarbonyl)oxy)methyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **2.49** (68 mg, 0.25 mmol) was dissolved in dry dichloromethane (2.50 mL), and the solution was cooled to 0 °C in an ice bath. 4-(Dimethylamino)pyridine (92 mg, 0.75 mmol) and methyl chloroformate (35 mg, 0.03 mL, 0.38 mmol) were added, and the colourless solution was stirred and

allowed to warm to room temperature over 12 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (3 mL), water (3 mL), and ethyl acetate (10 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 30% ethyl acetate in pentane, to give the product as a colourless oil (50 mg, 0.18 mmol, 72% yield).

R.f: 0.52 (50% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.96 – 4.93 (m, 3H, $MeOCO_2CH_2C\mathbf{H}(OR)R$, **HH'**$C=CR_2$), 4.40 (dd, *J* = 11.8, 7.6 Hz, 1H, $MeOCO_2C\mathbf{H}H'R$), 4.30 (dd, *J* = 11.8, 4.7 Hz, 1H, $MeOCO_2CH\mathbf{H'}R$), 3.82 (s, 3H, **Me**OCO_2CH_2R), 3.80 (s, 3H, **Me**O_2CR), 3.19 (td, *J* = 8.7, 5.7 Hz, 1H, $MeOCO_2CH_2CH(OR)C\mathbf{H}R_2$), 3.13 – 3.03 (dq, *J* = 17.0, 1.9 Hz, 1H, $H_2C=C(R)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 2.98 (d, *J* = 17.0 Hz, 1H, $H_2C=C(R)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 2.58 (ddq, *J* = 16.0, 8.7, 1.6 Hz, 1H, $H_2C=C(R)C\mathbf{H}H'CH(R)CH(OR)CH_2OCO_2Me$), 2.38 (br dd, *J* = 16.0, 8.7 Hz, 1H, $H_2C=C(R)CH\mathbf{H'}CH(R)CH(OR)CH_2OCO_2Me$).

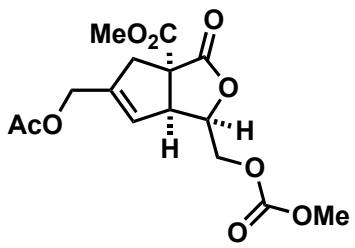
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.3 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.4 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 155.4 ($MeO\mathbf{C}O_2R$), 145.8 ($H_2C=\mathbf{C}R_2$), 109.2 ($H_2\mathbf{C}=CR_2$), 77.4 ($MeOCO_2CH_2\mathbf{C}H(OR)CHR_2$), 66.1 ($MeOCO_2\mathbf{C}H_2R$), 62.6 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 55.4 (**Me**$OCO_2R$), 53.6 (**Me**$O_2CR$), 47.2 ($MeOCO_2CH_2CH(OR)\mathbf{C}HR_2$), 39.0 ($H_2C=C(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 33.1 ($H_2C=C(R)\mathbf{C}H_2CH(R)CH(OR)CH_2OCO_2Me$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1780, 1747, 1275, 1059, 790.

LRMS (ESI^+): *m/z* = 307.0 = $[M+Na]^+$.

HRMS (ESI^+): Predicted *m/z* ($[C_{13}H_{16}O_7Na]^+$) = 307.0788; *m/z* found = 307.0788.

3.91 - (±)-Methyl (1*R*,3a*R*,6a*S*)-5-(acetoxymethyl)-1-(((methoxycarbonyl)oxy)methyl)-3-oxo-4,6a-dihydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the modified procedure of Stahl[129]: compound **3.20** (29 mg, 0.10 mmol) was dissolved in dry dioxane (0.75 mL) and acetic acid (0.25 mL). Palladium(II) acetate (2.2 mg, 0.010 mmol), sodium acetate (1.6 mg, 0.020 mmol), and 4,5-diazafluoren-9-one (1.8 mg, 0.010 mmol) were added, and the flask was fitted with an oxygen balloon. The resulting golden solution was heated to 70 °C, at which temperature the colour of the solution was observed to change from golden to deep orange over 30 minutes; the reaction was stirred at this temperature for 18 hours. After this time had elapsed, the reaction was cooled to room temperature, volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (18 mg, 0.051 mmol, 51% yield).

R.f: 0.23 (40% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.47 – 5.45 (m, 1H, $AcOCH_2C(R)=C\mathbf{H}CHR_2$), 4.98 (ddd, *J* = 7.3, 6.3, 5.3 Hz, 1H, $MeOCO_2CH_2C\mathbf{H}(OR)R$), 4.62 (br s, 2H, $AcOC\mathbf{H_2}R$), 4.36 (dd, *J* = 11.7, 7.3 Hz, 1H, $MeOCO_2C\mathbf{H}$'R), 4.33 (dd, *J* = 11.7, 5.3 Hz, 1H, $MeOCO_2CH\mathbf{H'}R$), 3.86 (ddt, *J* = 6.3, 3.9, 2.0 Hz, 1H, $MeOCO_2CH_2CH(OR)C\mathbf{H}R_2$), 3.83 (s, 3H, $\mathbf{Me}OCO_2CH_2R$), 3.81 (s, 3H, $\mathbf{Me}O_2CR$), 3.18 (br d, *J* = 17.2, Hz, 1H, $AcOCH_2C(=CHR)C\mathbf{H}$H'C(R)$(CO_2Me)CO_2R$), 3.00 (dt, *J* = 17.2, 2.0 Hz, 1H, $AcOCH_2C(=CHR)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 2.10 (s, 3H, $\mathbf{Me}CO_2CH_2R$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.6 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 170.6 ($Me\mathbf{C}O_2CH_2R$), 168.7 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 155.5 ($MeO\mathbf{C}O_2R$), 143.1 ($AcOCH_2\mathbf{C}(R)=CHCHR_2$), 120.7 ($AcOCH_2C(R)=\mathbf{C}HCHR_2$), 78.3 ($MeOCO_2CH_2\mathbf{C}H(OR)CHR_2$), 66.5 ($MeOCO_2\mathbf{C}H_2CH(OR)CHR_2$), 61.8 ($AcO\mathbf{C}H_2C$), 61.0 ($R_2\mathbf{C}(CO_2Me)CO_2R$),

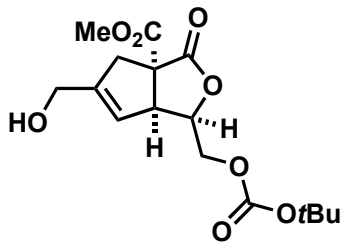
55.4 (**Me**OCO_2R), 53.9 ($MeOCO_2CH_2CH(OR)$**C**HR_2), 53.6 (**Me**O_2CR), 40.2 ($AcOCH_2C(=CHR)$**C**$H_2C(R)(CO_2Me)CO_2R$), 20.9 (**Me**CO_2CH_2R).

IR: (ν_{max}/cm^{-1} (thin film)) = 1772, 1745, 1443, 977.

LRMS (ESI^+): *m/z* = 365.0 = $[M+Na]^+$.

HRMS (ESI^+): Predicted *m/z* ($[C_{15}H_{18}O_9Na]^+$) = 365.0843; *m/z* found = 365.0843.

3.70 - (±)-Methyl (1*R*,3a*R*,6a*S*)-1-(((*tert*-butoxycarbonyl)oxy)methyl)-5-(hydroxymethyl)-3-oxo-4,6a-dihydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.78** (3.8 mg, 0.010 mmol) was dissolved in dry methanol (1.00 mL) and potassium carbonate (2.1 mg, 0.015 mmol) was added. The resulting suspension was stirred at room temperature for 30 minutes. After this time had elapsed, saturated ammonium chloride solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added, and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 20% ethyl acetate in pentane, to give the product as a colourless oil (2.7 mg, 0.0080 mmol, 80% yield).

R.f: 0.43 (30% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.45 (br s, 1H, $HOCH_2C(R)=C$**H**CHR_2), 4.96 (ddd, *J* = 7.5, 6.2, 5.4 Hz, 1H, $BocOCH_2C$**H**(OR)R), 4.30 (dd, *J* = 16.6, 7.5 Hz, 1H, BocOC**H**H'R), 4.26 (dd, *J* = 16.6, 5.4 Hz, 1H, BocOCH**H'**R), 4.22 (br d, *J* = 15.0 Hz, 1H, HOC**H**H'R), 4.20 (br d, *J* = 15.0 Hz, 1H, HOCH**H'**R), 3.85 (ddd, *J* = 6.2, 4.6, 2.4 Hz, 1H, $BocOCH_2CH(OR)C$**H**R_2), 3.80 (s, 3H, **Me**O_2CR), 3.17 (br d, *J* = 17.0 Hz, 1H, $HOCH_2C(=CHR)C$**H**H'C(R)$(CO_2Me)CO_2R$), 2.96 (br d, *J* = 17.0 Hz, 1H,

$HOCH_2C(=CHR)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 1.50 (s, 9H, $\mathbf{Me_3}COCO_2R$). Hydroxyl proton resonance not observed.

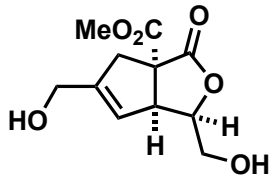
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.0 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 168.9 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 153.1 ($Me_3CO\mathbf{C}O_2R$), 148.0 ($HOCH_2\mathbf{C}(R)=CHCHR_2$), 118.0 ($HOCH_2C(R)=\mathbf{C}HCHR_2$), 83.3 ($Me_3\mathbf{C}OCO_2R$), 78.7 ($BocOCH_2\mathbf{C}H(OR)CHR_2$), 65.7 ($BocO\mathbf{C}H_2CH(OR)CHR_2$), 61.3 ($HO\mathbf{C}H_2R$), 61.1 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.9 ($BocOCH_2CH(OR)\mathbf{C}HR_2$), 53.5 ($\mathbf{Me}O_2CR$), 39.8 ($HOCH_2C(=CHR)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 27.9 (3C, $\mathbf{Me_3}COCO_2R$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1781, 1742, 1155, 1039.

LRMS (ESI$^+$): *m/z* = 309.0 = $[M\text{-}H_2C{=}CMe_2{+}Na]^+$;

HRMS (ESI$^+$): Predicted *m/z* ($[C_{16}H_{22}O_8Na]^+$, $[M+Na]^+$) = 365.1207; *m/z* found = 365.1206.

3.92 - (±)-Methyl (1*R*,3a*R*,6a*S*)-1,5-bis(hydroxymethyl)-3-oxo-4,6a-dihydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.92** was isolated as a product from the above procedure to form **3.70** from **3.78** (0.3 mg, 0.001 mmol, 11% yield).

R.f: 0.20 (70% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.48 (br s, 1H, $HOCH_2C(R)=C\mathbf{H}CHR_2$), 4.87 (td, *J* = 6.7, 4.6 Hz, 1H, $HOCH_2C\mathbf{H}(OR)R$), 4.21 (m, 2H, $HOC\mathbf{H}H'C(R)=CHR$, $HOCH\mathbf{H'}C(R)=CHR$), 3.88 (m, 2H, $HOC\mathbf{H}H'CH(OR)R$), $HOCH\mathbf{H'}CH(OR)R$), 3.81 (s, 3H, $\mathbf{Me}O_2CR$), 3.81 (m, 1H, $HOCH_2CH(OR)C\mathbf{H}R_2$), 3.15 (d, *J* = 17.0 Hz, 1H, $HOCH_2C(=CHR)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$), 2.96 (d, *J* = 17.0 Hz, 1H, $HOCH_2C(=CHR)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 1.93 (dd, *J* = 7.4, 5.0 Hz, 1H, $\mathbf{H}OCHH'CH(OR)R$), 1.67 (t, *J* = 5.8 Hz, 1H, $\mathbf{H}OCHH'C(R)=CHR$).

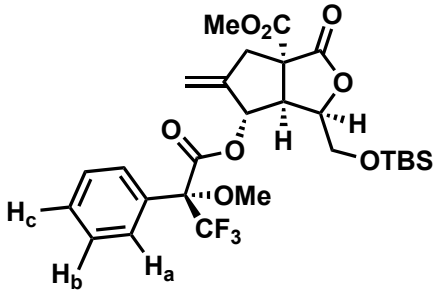
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.2 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 147.0 ($HOCH_2\mathbf{C}(R)=CHCHR_2$), 118.7 ($HOCH_2C(R)=\mathbf{C}HCHR_2$), 82.1 ($HOCH_2\mathbf{C}H(OR)CHR_2$), 62.7 ($HO\mathbf{C}H_2CH(OR)CHR_2$), 61.5 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 61.3 ($HO\mathbf{C}H_2C(R)=CHR$), 53.9 ($HOCH_2CH(OR)\mathbf{C}HR_2$), 53.5 ($\mathbf{Me}O_2CR$), 39.8 ($HOCH_2C(=CHR)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$).

IR: (ν_{max}/cm^{-1} (thin film)) = 3347, 1771, 1730.

LRMS (ESI^+): *m/z* = 265.0 = $[M+Na]^+$.

HRMS (ESI^+): Predicted *m/z* ($[C_{11}H_{14}O_6Na]^+$) = 265.0683; *m/z* found = 265.0683.

3.98 - Methyl (1*R*,3a*R*,6*S*,6a*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylene-3-oxo-6-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)tetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the modified procedure of Ward[135]: (*R*)-MTPA **3.94** (8.0 mg, 0.033 mmol) was dissolved in dry hexane (1.30 mL), and the solution was stirred at room temperature. Oxalyl chloride (0.012 mL, 0.13 mmol) and *N,N*-dimethylformamide (0.003 mL, 0.030 mmol) were added, and the resulting colourless solution was stirred for 1 hour, over which time a white precipitate was observed to form. After this time had elapsed, the reaction mixture was filtered through a plug of cotton wool, and the volatile organics were removed under reduced pressure to give a colourless oily residue.

This residue was redissolved in dry dichloromethane (0.25 mL), and the solution was stirred at room temperature. A solution of alcohol **3.2** (4.0 mg, 0.011 mmol) in dry dichloromethane (0.25 mL) and 4-(dimethylamino)pyridine (7.0 mg, 0.055 mmol) were added, and the resulting colourless solution was stirred for 2 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (1

mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 15% diethyl ether in pentane, to give the product as a colourless oil (4.9 mg, 0.0090 mmol, 79% yield).

R.f: 0.37 (20% ethyl acetate in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.54 – 7.50 (m, 2H, **H_a**-Ar), 7.46 – 7.42 (m, 3H, **H_b**-Ar, **H_c**-Ar), 5.98 (d, *J* = 2.0 Hz, 1H, H_2C=C(R)C**H**(OMTPA)R), 5.31 – 5.28 (m, 1H, **H**H'=CR_2), 5.25 (dt, *J* = 2.5, 1.2 Hz, 1H, H**H'**=CR_2), 4.84 (ddd, *J* = 8.0, 5.9, 4.5 Hz, 1H, TBSOCH_2C**H**(OR)R), 4.09 (dd, *J* = 11.4, 4.5 Hz, 1H, TBSOC**H**H'R), 3.95 (dd, *J* = 11.4, 5.9 Hz, 1H, TBSOCH**H'**R), 3.80 (s, 3H, **Me**O_2CR), 3.53 (s, 3H, ArO**Me**), 3.33 (dd, *J* = 8.0, 2.0 Hz, 1H, TBSOCH_2CH(OR)C**H**R_2), 3.21 – 3.11 (m, 1H, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.94 (br d, *J* = 15.9 Hz, 1H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R), 0.93 (s, 9H, **Me_3**C$SiMe_2$OR), 0.14 (s, 3H, Me_3CSi**Me**$_2$OR), 0.12 (s, 3H, Me_3CSi**Me**$_2$OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.6 (R_2C(CO_2Me)**C**O_2R), 168.7 (R_2C(**C**O_2Me)CO_2R), 165.8 (PhC(CF_3)(OMe)**C**O_2R), 143.9 (H_2C=**C**R_2), 131.7 (RO_2C-**C_{Ar}**), 129.8 (H_c-**C_{Ar}**), 128.5 (2C, H_b-**C_{Ar}**), 127.3 (2C, H_a-**C_{Ar}**), 123.2 (q, *J* = 290 Hz, F_3**C**R), 115.6 (H_2**C**=CR_2), 84.7 (q, *J* = 30 Hz, F_3C**C**R_3), 79.0 (RCO_2**C**HR_2), 78.5 (H_2C=C(R)**C**H(OMTPA)R), 61.4 (TBSO**C**H_2R), 60.6 (R_2**C**(CO_2Me)CO_2R), 55.4 (ArO**Me**), 53.5 (**Me**O_2CR), 53.2 (TBSOCH_2CH(OR)**C**HR_2), 38.0 (H_2C=C(R)**C**H_2C(R)(CO_2Me)CO_2R), 25.7 (3C, **Me_3**C$SiMe_2$OR), 18.3 (Me_3**C**$SiMe_2$OR), -5.4 (Me_3CSi**Me**$_2$OR), -5.6 (Me_3CSi**Me**$_2$OR).

^{19}F NMR (565 MHz, $CDCl_3$): δ -71.7 (**F_3**CR).

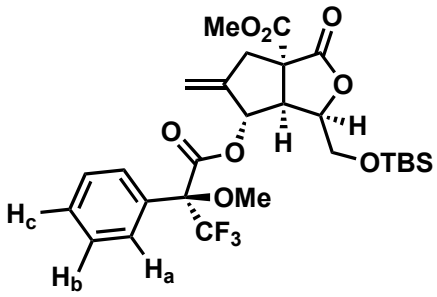
IR: (ν_{max}/cm^{-1} (thin film)) = 2955, 1783, 1749, 1437, 1124, 1016, 968, 838.

LRMS (ESI^+): *m/z* = 595.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{27}H_{35}O_8F_3SiNa]^+$) = 595.1942; *m/z* found = 595.1946.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ +1.5 (c = 0.1 in $CHCl_3$).

3.99 - Methyl (1*R*,3a*R*,6*S*,6a*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylene-3-oxo-6-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)tetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the modified procedure of Ward[135]: (*S*)-MTPA **3.95** (8.0 mg, 0.033 mmol) was dissolved in dry hexane (1.30 mL), and the solution was stirred at room temperature. Oxalyl chloride (0.012 mL, 0.13 mmol) and *N,N*-dimethylformamide (0.003 mL, 0.03 mmol) were added, and the resulting colourless solution was stirred for 1 hour, over which time a white precipitate was observed to form. After this time had elapsed, the reaction mixture was filtered through a plug of cotton wool, and the volatile organics were removed under reduced pressure to give a colourless oily residue.

This residue was redissolved in dry dichloromethane (0.25 mL), and the solution was stirred at room temperature. A solution of alcohol **3.2** (4.0 mg, 0.011 mmol) in dry dichloromethane (0.25 mL) and 4-(dimethylamino)pyridine (7.0 mg, 0.055 mmol) were added, and the resulting colourless solution was stirred for 2 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 15% diethyl ether in pentane, to give the product as a colourless oil (3.3 mg, 0.0061 mmol, 52% yield).

R.f: 0.39 (20% ethyl acetate in pentane)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 – 7.46 (m, 2H, **H_a**-Ar), 7.44 – 7.38 (m, 3H, **H_b**-Ar, **H_c**-Ar), 5.99 (br s, 1H, H_2C=C(R)C**H**(OMTPA)R), 5.32 (br d, *J* = 2.3 Hz, 1H, **H**H'=CR_2), 5.26 (br d, *J* = 2.3 Hz, 1H, H**H'**=CR_2), 4.80 (dt, *J* = 8.1, 5.0 Hz, 1H, TBSOCH_2C**H**(OR)R), 4.02 (dd, *J* = 11.5, 4.5 Hz, 1H, TBSOC**H**H'R), 3.93 (dd, *J* = 11.5, 5.5 Hz, 1H, TBSOCH**H'**R), 3.75 (s, 3H, **Me**O_2CR), 3.52 (s, 3H, ArO**Me**), 3.24 – 3.21 (m, 3H, TBSOCH_2CH(OR)C**H**R_2, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.94 (d, *J* = 16.0 Hz, 1H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R), 0.90 (s, 9H, **Me$_3$**CSiMe_2OR), 0.11 (s, 3H, Me_3CSi**Me**$_2$OR), 0.10 (s, 3H, Me_3CSi**Me**$_2$OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.8 (R_2C(CO_2Me)**C**O_2R), 168.8 (R_2C(**C**O_2Me)CO_2R), 166.0 (PhC(CF_3)(OMe)**C**O_2R), 144.3 (H_2C=**C**R_2), 131.9 (RO_2C-**C_{Ar}**), 129.9 (H_c-**C_{Ar}**), 128.7 (2C, H_b-**C_{Ar}**), 127.4 (2C, H_a-**C_{Ar}**), 123.4 (q, *J* = 290 Hz, F_3**C**R), 115.8 (H_2**C**=CR_2), 84.6 (d, *J* = 30 Hz, F_3C**C**R_3), 79.3 (RCO_2**C**HR_2), 78.6 (H_2C=C(R)**C**H(OMTPA)R), 61.6 (TBSO**C**H_2R), 60.8 (R_2**C**(CO_2Me)CO_2R), 55.5 (ArO**Me**), 53.6 (**Me**O_2CR), 53.5 (TBSOCH_2CH(OR)**C**HR_2), 38.2 (H_2C=C(R)**C**H_2C(R)(CO_2Me)CO_2R), 25.9 (3C, **Me$_3$**CSiMe_2OR), 18.5 (Me_3**C**SiMe$_2$OR), -5.3 (Me_3CSi**Me**$_2$OR), -5.4 (Me_3CSi**Me**$_2$OR).

^{19}F NMR (565 MHz, $CDCl_3$): δ -71.4 (**F_3**CR).

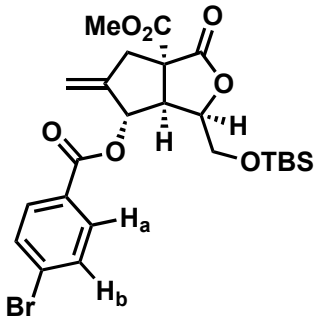
IR: (ν_{max}/cm^{-1} (thin film)) = 2954, 1784, 1749, 1251, 1125, 1017, 838.

LRMS (ESI^+): *m/z* = 595.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{27}H_{35}O_8F_3SiNa]^+$) = 595.1942; *m/z* found = 595.1945.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ -31.5 (c = 0.1 in $CHCl_3$).

SI1 - Methyl (1*R*,3a*R*,6*S*,6a*R*)-6-((4-bromobenzoyl)oxy)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.2** (4.0 mg, 0.011 mmol) was dissolved in dry dichloromethane (0.25 mL). 4-(Dimethylamino)pyridine (7.0 mg, 0.055 mmol) and bromobenzoyl chloride (7.0 mg, 0.033 mmol) were added and the resulting colourless solution was stirred for 2 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (3.8 mg, 0.0069 mmol, 64% yield).

R.f: 0.43 (20% ethyl acetate in pentane)

^{1}H NMR (600 MHz, $CDCl_3$): δ δ 7.86 (br d, *J* = 8.5 Hz, 2H, **H_a**-Ar), 7.59 (br d, *J* = 8.5 Hz, 2H, **H_b**-Ar), 5.93 (br s, 1H, H_2C=C(R)C**H**(O_2CAr)R), 5.25 (br d, *J* = 2.0 Hz, 1H, **H**H'=CR_2), 5.22 (br d, *J* = 2.0 Hz, 1H, H**H'**=CR_2), 4.85 (dt, *J* = 7.5, 5.0 Hz, 1H, TBSOCH_2C**H**(OR)R), 4.10 (dd, *J* = 11.5, 5.0 Hz, 1H, TBSOC**H**H'R), 4.01 (dd, *J* = 11.5, 5.0 Hz, 1H, TBSOCH**H'**R), 3.82 (s, 3H, **Me**O_2CR), 3.38 – 3.28 (m, 2H, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R, TBSOCH_2CH(OR)C**H**R_2), 3.00 (d, *J* = 16.2 Hz, 1H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R), 0.84 (s, 9H, **Me$_3$**CSiMe_2OR), 0.08 (s, 3H, Me_3CSi**Me**$_2$OR), 0.05 (s, 3H, Me_3CSi**Me**$_2$OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 169.3 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 165.1 ($Ar\mathbf{C}O_2R$), 144.9 ($H_2C=\mathbf{C}R_2$), 132.0 (2C, H_a-$\mathbf{C}_{Ar}$), 131.4 (2C, H_b-$\mathbf{C}_{Ar}$), 128.8 (Br-$\mathbf{C}_{Ar}$), 128.7 (RO_2C-$\mathbf{C}_{Ar}$), 114.0 ($H_2\mathbf{C}=CR_2$), 79.8 ($RCO_2\mathbf{C}HR_2$), 76.5 ($H_2C=C(R)\mathbf{C}H(O_2CAr)R$), 61.7 ($TBSO\mathbf{C}H_2R$), 60.3 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.9 ($TBSOCH_2CH(OR)\mathbf{C}HR_2$), 53.7 ($\mathbf{Me}O_2CR$), 37.9 ($H_2C=C(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 25.9 (3C, $\mathbf{Me_3}CSiMe_2OR$), 18.4 ($Me_3\mathbf{C}SiMe_2OR$), -5.3 ($Me_3CSi\mathbf{Me}_2OR$), -5.4 ($Me_3CSi\mathbf{Me}_2OR$).

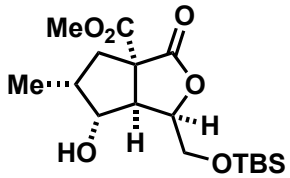
IR: (ν_{max}/cm^{-1} (thin film)) = 2957, 1783, 1735, 1730, 1262, 1059, 1012.

LRMS (ESI^+): *m/z* = 561.0, 563.0 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z*s ($[C_{24}H_{31}O_7SiBrNa]^+$) = 561.0915 (50%), 563.0896 (50%); *m/z* found = 561.0914 (50%), 563.0893 (50%).

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ -8.0 (c = 0.05 in $CHCl_3$).

4.12 - (±)-Methyl (1*R*,3a*R*,5*R*,6*R*,6a*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



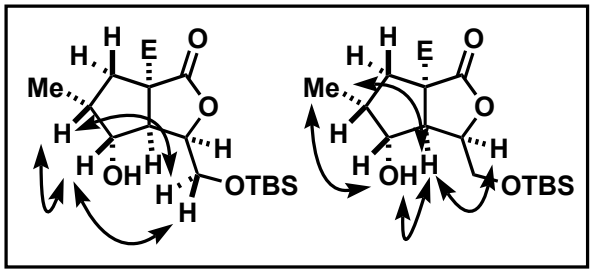
Compound **3.2** (36 mg, 0.10 mmol) was dissolved in ethyl acetate (1.20 mL), the solution was sparged with nitrogen, and palladium on carbon (10% palladium by weight, 11 mg, 0.010 mmol palladium) was added. The suspension was sparged with nitrogen, then sparged with hydrogen, the flask was fitted with a three-skinned hydrogen balloon, and the mixture was stirred rapidly for 4 hours. After this time had elapsed, the hydrogen balloon was removed, and the flask was opened to the atmosphere. The mixture was filtered through a pad of Celite™, volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 5-20% ethyl acetate in pentane, to give the product as a colourless oil (27 mg, 0.074 mmol, 74% yield).

R.f: 0.47 (30% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.75 (td, *J* = 6.8, 4.8 Hz, 1H, TBSOCH$_2$C**H**(OR)R), 4.28 (t, *J* = 5.3 Hz, 1H, MeCH(R)C**H**(OH)R), 4.02 (dd, *J* = 11.4, 4.8 Hz, 1H, TBSOC**H**H'R), 3.97 (dd, *J* = 11.4, 6.8 Hz, 1H, TBSOCH**H'**R), 3.79 (s, 3H, **Me**O$_2$CR), 3.08 (dd, *J* = 6.8, 5.3 Hz, 1H, MeCH(R)CH(OH)C**H**R$_2$), 2.54 (br s, 1H, MeCH(R)CH(O**H**)R), 2.31 – 2.29 (m, 2H, MeCH(R)C**H**H'C(R)(CO$_2$Me)CO$_2$R, MeCH(R)CH**H'**C(R)(CO$_2$Me)CO$_2$R), 2.16 – 2.11 (qd, *J* = 7.0, 5.3 Hz, 1H, MeC**H**R$_2$), 1.03 (d, *J* = 7.0 Hz, 3H, **Me**CHR$_2$), 0.91 (s, 9H, **Me$_3$**CSiMe$_2$OR), 0.12 (s, 3H, Me$_3$CSi**Me**$_2$OR), 0.12 (s, 3H, Me$_3$CSi**Me**$_2$OR).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.6 (R$_2$C(CO$_2$Me)**C**O$_2$R), 170.0 (R$_2$C(**C**O$_2$Me)CO$_2$R), 78.6 (RCO$_2$**C**HR$_2$), 74.4 (MeCH(R)**C**H(OH)R), 61.6 (R$_2$**C**(CO$_2$Me)CO$_2$R), 60.7 (TBSO**C**H$_2$R), 55.0 (TBSOCH$_2$CH(OR)**C**HR$_2$), 53.5 (**Me**O$_2$CR), 38.6 (Me**C**HR$_2$), 37.4 (MeCH(R)**C**H$_2$C(R)(CO$_2$Me)CO$_2$R), 25.9 (3C, **Me$_3$**CSiMe$_2$OR), 18.4 (Me$_3$**C**SiMe$_2$OR), 13.0 (**Me**CHR$_2$), -5.4 (2C, Me$_3$CSi**Me$_2$**OR).

Key NOE correlations involved in stereochemical assignment (E = CO$_2$Me):

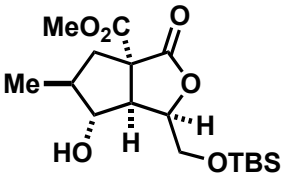


IR: (ν_{max}/cm^{-1} (thin film)) = 3480, 1777, 1741, 1461, 1435, 1360, 1047.

LRMS (ESI$^+$): *m/z* = 381.2 = [M+Na]$^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{17}H_{30}O_6Si_1Na$]$^+$) = 381.1704; *m/z* found = 381.1704.

3.1 - (±)-Methyl (1*R*,3a*R*,5*S*,6*R*,6a*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.2** (36 mg, 0.10 mmol) was dissolved in dichloromethane (1.50 mL), the solution was sparged with nitrogen, and Crabtree's catalyst (16 mg, 0.020 mmol) was added. The resulting orange

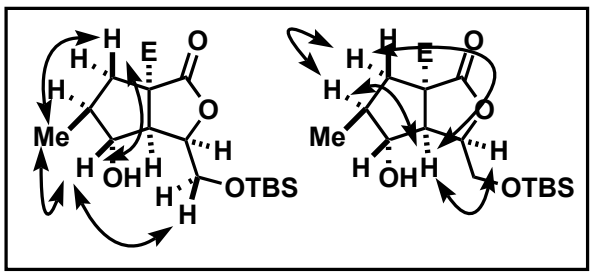
solution was stirred at room temperature, and the flask was fitted with a single-skinned balloon (which had been previously inflated at least once) filled with a 4:1 mixture of nitrogen and hydrogen, and the mixture was stirred rapidly for 1 hour. After this time had elapsed, the hydrogen balloon was removed, and the flask was opened to the atmosphere. The mixture was filtered through a pad of Celite™, volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 20% ethyl acetate in pentane, to give the product as a colourless oil (33 mg, 0.091 mmol, 91% yield).

R.f: 0.43 (30% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.73 (dt, *J* = 8.4, 5.5 Hz, 1H, $TBSOCH_2C\mathbf{H}(OR)R$), 4.11 (dd, *J* = 11.3, 5.5 Hz, 1H, TBSOC**H**H'R), 4.02 (dd, *J* = 11.3, 8.4 Hz, 1H, TBSOCH**H'**R), 3.80 (s, 3H, **Me**O_2CR), 3.67 (ddd, *J* = 10.5, 9.3, 1.9 Hz, 1H, $MeCH(R)C\mathbf{H}(OH)R$), 3.61 (d, *J* = 1.9 Hz, 1H, $MeCH(R)CH(O\mathbf{H})R$), 2.95 (dd, *J* = 9.3, 5.5 Hz, 1H, $MeCH(R)CH(OH)C\mathbf{H}R_2$), 2.74 (dd, *J* = 14.2, 8.2 Hz, 1H, $MeCH(R)C\mathbf{H}_{exo}H_{endo}C(R)(CO_2Me)CO_2R$), 2.10 – 1.99 (m, 1H, $MeC\mathbf{H}R_2$), 1.63 (dd, *J* = 14.2, 11.9 Hz, 1H, $MeCH(R)CH_{exo}\mathbf{H}_{endo}C(R)(CO_2Me)CO_2R$), 1.09 (d, *J* = 6.5 Hz, 3H, **Me**CHR_2), 0.92 (s, 9H, $\mathbf{Me_3}CSiMe_2OR$), 0.15 (s, 6H, $Me_3CSi\mathbf{Me_2}OR$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.4 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 170.1 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 77.8 ($RCO_2\mathbf{C}HR_2$), 76.8 ($MeCH(R)\mathbf{C}H(OH)R$), 61.5 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 58.1 ($TBSO\mathbf{C}H_2R$), 56.4 ($TBSOCH_2CH(OR)\mathbf{C}HR_2$), 53.5 (**Me**$O_2CR$), 41.4 (Me**C**$HR_2$), 36.7 ($MeCH(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 25.8 (3C, $\mathbf{Me_3}CSiMe_2OR$), 18.3 ($Me_3\mathbf{C}SiMe_2OR$), 16.3 (**Me**CHR_2), -5.3 ($Me_3CSi\mathbf{Me}_2OR$), -5.4 ($Me_3CSi\mathbf{Me}_2OR$).

Key NOE correlations involved in stereochemical assignment (E = CO_2Me):

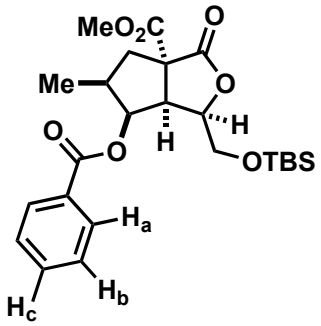


IR: (ν_{max}/cm^{-1} (thin film)) = 3481, 1776, 1742, 1168, 1004.

LRMS (ESI^+): *m/z* = 381.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{17}H_{30}O_6Si_1Na]^+$) = 381.1704; *m/z* found = 381.1704.

4.16 - (±)-Methyl (1*R*,3a*R*,5*S*,6*S*,6a*R*)-6-(benzoyloxy)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.1** (18 mg, 0.050 mmol) was dissolved in dry, degassed toluene (0.50 mL). Benzoic acid (31 mg, 0.25 mmol), triphenylphosphine (66 mg, 0.25 mmol), and diisopropylazodicarboxylate (51 mg, 0.25 mmol) were added, the resulting pale yellow solution was heated to 110 °C and stirred for 72 hours. After this time had elapsed, the reaction was allowed to cool to room temperature, saturated aqueous sodium bicarbonate solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (18s mg, 0.039 mmol, 78% yield).

R.f: 0.42 (20% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 – 7.95 (m, 2H, **H_a**-Ar), 7.63 – 7.55 (m, 1H, **H_c**-Ar), 7.53 – 7.41 (m, 2H, **H_c**-Ar), 5.74 (t, *J* = 4.0 Hz, 1H, MeCH(R)C**H**(OBz)R), 4.82 (ddd, *J* = 7.3, 6.1, 5.1 Hz, 1H, TBSOCH$_2$C**H**(OR)R), 3.86 (dd, *J* = 11.1, 7.3 Hz, 1H, TBSOC**H**H'R), 3.84 (s, 3H, **Me**O_2CR), 3.71 (dd, *J* = 11.1, 5.1 Hz, 1H, TBSOCH**H'**R), 3.26 (dd, *J* = 6.1, 4.0 Hz, 1H, MeCH(R)CH(OBz)C**H**R_2), 2.70 (dd, *J* = 13.7, 8.2 Hz, 1H, MeCH(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.47 – 2.32 (m, 1H, MeC**H**R_2), 2.11 (dd, *J* = 13.7, 11.9 Hz, 1H, MeCH(R)CH**H'**C(R)(CO_2Me)CO_2R), 0.96 (d, *J* = 6.7 Hz, 2H, **Me**CHR_2), 0.79 (s, 9H, **Me_3**CSiMe_2OR), -0.10 (s, 3H, Me_3CSi**Me**$_2$OR), -0.13 (s, 3H, Me_3CSi**Me**$_2$OR).

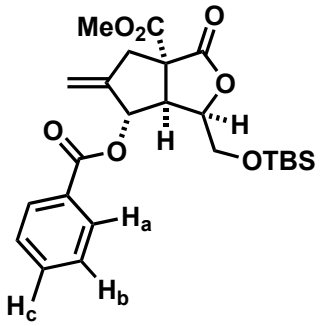
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.1 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 170.3 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 165.3 ($Ph\mathbf{C}O_2R$), 133.6 ($H_c$-$\mathbf{C}_{Ar}$), 129.8 (2C, H_a-$\mathbf{C}_{Ar}$), 128.8 (RO_2C-$\mathbf{C}_{Ar}$), 128.7 (2C, H_b-$\mathbf{C}_{Ar}$), 80.2 ($RCO_2\mathbf{C}HR_2$), 78.1 (MeCH(R)**C**H(OBz)R), 61.6 ($TBSO\mathbf{C}H_2R$), 61.3 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 53.4 ($\mathbf{Me}O_2CR$), 53.3 ($TBSOCH_2CH(OR)\mathbf{C}HR_2$), 41.4 ($Me\mathbf{C}HR_2$), 37.9 ($MeCH(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 25.7 (3C, $\mathbf{Me}_3CSiMe_2OR$), 18.1 ($Me_3\mathbf{C}SiMe_2OR$), 13.3 ($\mathbf{Me}CHR_2$), -5.7 ($Me_3CSi\mathbf{Me}_2OR$), -5.8 ($Me_3CSi\mathbf{Me}_2OR$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1787, 1725, 1687, 706.

LRMS (ESI^+): *m/z* = 485.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{24}H_{34}O_7SiNa]^+$) = 485.1996; *m/z* found = 485.1996.

4.23 - (±)-Methyl (1*R*,3a*R*,6*S*,6a*R*)-6-(benzoyloxy)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.2** (4.0 mg, 0.011 mmol) was dissolved in dry dichloromethane (0.25 mL). 4-(Dimethylamino)pyridine (2.7 mg, 0.022 mmol) and benzoic anhydride (5.0 mg, 0.022 mmol) were added and the resulting colourless solution was stirred for 12 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (4.1 mg, 0.0090 mmol, 81% yield).

R.f: 0.42 (20% ethyl acetate in pentane, stains in potassium permanganate deep without heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 – 7.99 (m, 2H, **H_a**-Ar), 7.63 – 7.54 (m, 1H, **H_c**-Ar), 7.52 – 7.40 (m, 2H, **H_b**-Ar), 5.93 (dq, *J* = 2.8, 1.5 Hz, 1H, H_2C=C(R)C**H**(OBz)R), 5.25 (q, *J* = 1.5 Hz, 1H, **H**H'=CR_2), 5.22 (q, *J* = 1.5 Hz, 1H, H**H'**=CR_2), 4.86 (dt, *J* = 7.5, 5.0 Hz, 1H, TBSOCH_2C**H**(OR)R), 4.11 (dd, *J* = 11.5, 5.0 Hz, 1H, TBSOC**H**H'R), 4.03 (dd, *J* = 11.5, 5.0 Hz, 1H, TBSOCH**H'**R), 3.82 (s, 3H, **Me**O_2CR), 3.44 – 3.29 (m, 2H, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R, TBSOCH_2CH(OR)C**H**R_2), 3.01 (dt, *J* = 16.1, 1.5 Hz, 1H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R), 0.84 (s, 9H, **Me_3**CSiMe_2OR), 0.08 (s, 3H, Me_3CSi**Me**$_2$OR), 0.04 (s, 3H, Me_3CSi**Me**$_2$OR).

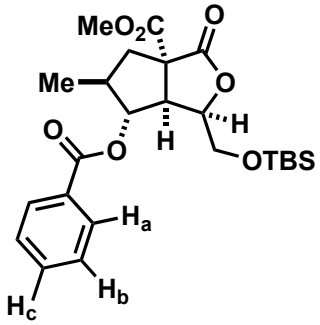
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1 (R_2C(CO_2Me)**C**O_2R), 169.4 (R_2C(**C**O_2Me)CO_2R), 165.9 (Ph**C**O_2R), 145.1 (H_2C=**C**R_2), 133.6 (H_c-**C_{Ar}**), 129.9 (2C, H_a-**C_{Ar}**), 129.8 (RO_2C-**C_{Ar}**), 128.6 (2C, H_b-**C_{Ar}**), 113.7 (H_2**C**=CR_2), 80.0 (RCO_2**C**HR_2), 76.1 (H_2C=C(R)**C**H(OBz)R), 61.8 (TBSO**C**H_2R), 60.2 (R_2**C**(CO_2Me)CO_2R), 53.9 (TBSOCH_2CH(OR)**C**HR_2), 53.7 (**Me**O_2CR), 37.8 (H_2C=C(R)**C**H_2C(R)(CO_2Me)CO_2R), 25.9 (3C, **Me_3**CSiMe_2OR), 18.4 (Me_3**C**SiMe$_2$OR), -5.3 (Me_3CSi**Me**$_2$OR), -5.4 (Me_3CSi**Me**$_2$OR).

IR: (ν_{max}/cm^{-1} (thin film)) = 1783, 1747, 1722, 1472, 1251, 1109, 837, 712.

LRMS (ESI^+): *m/z* = 483.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{24}H_{32}O_7SiNa]^+$) = 483.1810; *m/z* found = 483.1804.

4.24 - (±)-Methyl (1*R*,3a*R*,5*S*,6*R*,6a*R*)-6-(benzoyloxy)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **3.1** (3.9 mg, 0.010 mmol) was dissolved in dry dichloromethane (0.10 mL). 4-Dimethylaminopyridine (2.4 mg, 0.020 mmol) and benzoic anhydride (4.5 mg, 0.020 mmol) were added and the resulting colourless solution was stirred for 12 hours. After this time had elapsed, the

reaction was allowed to cool to room temperature, saturated aqueous sodium bicarbonate solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (3.2 mg, 0.0070 mmol, 70% yield).

R.f: 0.44 (20% ethyl acetate in pentane, stains in potassium permanganate deep with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 – 7.95 (m, 2H, **H_a**-Ar), 7.62 – 7.55 (m, 1H, **H_c**-Ar), 7.49 – 7.40 (m, 2H, **H_b**-Ar), 5.20 (dd, *J* = 8.7, 6.5 Hz, 1H, MeCH(R)C**H**(OBz)R), 4.82 (dt, *J* = 8.0, 4.5 Hz, 1H, TBSOCH$_2$C**H**(OR)R), 4.18 (dd, *J* = 11.8, 4.5 Hz, 1H, TBSOC**H**H'R), 3.96 (dd, *J* = 11.8, 4.5 Hz, 1H, TBSOCH**H'**R), 3.81 (s, 3H, **Me**O_2CR), 3.37 (dd, *J* = 8.0, 6.5 Hz, 1H, MeCH(R)CH(OBz)C**H**R_2), 2.75 (dd, *J* = 13.6, 7.5 Hz, 1H, MeCH(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.47 – 2.39 (m, 1H, MeC**H**R_2), 1.93 (dd, *J* = 13.6, 11.4 Hz, 1H, MeCH(R)CH**H'**C(R)(CO_2Me)CO_2R), 1.11 (d, *J* = 6.7 Hz, 3H, **Me**CHR_2), 0.83 (s, 9H, **Me$_3$**CSiMe_2OR), 0.05 (s, 3H, Me_3CSi**Me**$_2$OR), 0.01 (s, 3H, Me_3CSi**Me**$_2$OR).

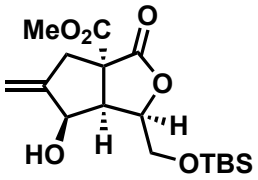
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.6 (R_2C(CO_2Me)**C**O_2R), 170.3 (R_2C(**C**O_2Me)CO_2R), 166.2 (Ph**C**O_2R), 133.5 (H_c-**C$_{Ar}$**), 129.9 (2C, H_a-**C$_{Ar}$**), 129.7 (RO_2C-**C$_{Ar}$**), 128.6 (2C, H_b-**C$_{Ar}$**), 80.4 (RCO_2**C**HR_2), 80.2 (MeCH(R)**C**H(OBz)R), 62.1 (TBSO**C**H_2R), 59.8 (R_2**C**(CO_2Me)CO_2R), 54.1 (TBSOCH$_2$CH(OR)**C**HR_2), 53.6 (**Me**O_2CR), 42.0 (Me**C**HR_2), 37.0 (MeCH(R)**C**H_2C(R)(CO_2Me)CO_2R), 26.0 (3C, **Me$_3$**CSiMe_2OR), 18.6 (Me_3**C**SiMe$_2$OR), 16.3 (**Me**CHR_2), -5.3 (Me_3CSi**Me**$_2$OR), -5.4 (Me_3CSi**Me**$_2$OR).

IR: (ν_{max}/cm^{-1} (thin film)) = 1781, 1746, 1721, 1452, 1127, 1109, 835, 781, 712.

LRMS (ESI$^+$): *m/z* = 485.2 = [M+Na]$^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{24}H_{34}O_7$SiNa]$^+$) = 485.1996; *m/z* found = 485.1996.

4.25 - Methyl (1*R*,3a*R*,6*R*,6a*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **2.50** (1.03 g, 3.00 mmol) was dissolved in dichloromethane (30 mL). Selenium dioxide (333 mg, 3.00 mmol) was added, a solution of *tert*-butyl hydroperoxide (5.5 M in decane, 2.18 mL, 12.0 mmol) was added dropwise over 1 minute, an air condenser was attached, and the colourless solution was heated to reflux for 3 hours. After this time had elapsed, the reaction was allowed to cool to room temperature, filtered through a plug of Celite™, and water (50 mL), and ethyl acetate (50 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was redissolved in methanol. Cerium trichloride heptahydrate (1.12 g, 3.00 mmol) and sodium borohydride (114 mg, 3.00 mmol) were added, and the resulting reaction was stirred for 5 minutes at room temperature. After this time had elapsed, ammonium chloride (30 mL), water (30 mL), and ethyl acetate (50 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude residue was purified *via* flash column chromatography, eluting with 20% ethyl acetate in pentane, to give the product as a waxy white solid (427 mg, 1.21 mmol, 40% yield). Racemic material was a colourless oil.

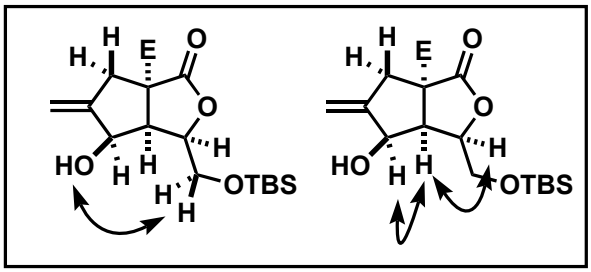
R.f: 0.43 (30% ethyl acetate in pentane, stains in potassium permanganate deep without heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.18 (br s, 1H, **H**H'C=CR_2), 4.99 (br s, 1H, H**H'**C=CR_2), 4.78 (ddd, *J* = 6.0, 4.6, 3.1 Hz, 1H, TBSOCH_2C**H**(OR)R), 4.57 (dd, *J* = 4.6, 2.5 Hz, 1H, H_2C=C(R)C**H**(OH)R), 4.24 (dd, *J* = 11.9, 4.6 Hz, 1H, TBSOC**H**H'R), 4.06 (dd, *J* = 11.9, 3.1 Hz, 1H, TBSOCH**H'**R), 3.89 (br d, *J* = 2.5 Hz, 1H,

H_2C=C(R)CH(O**H**)R), 3.79 (s, 3H, **Me**O_2CR), 3.20 (dt, *J* = 16.8, 2.5 Hz, 1H, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R), 3.05 – 2.98 (m, 2H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R, TBSOCH_2CH(OR)C**H**R_2), 0.93 (s, 9H, **Me**$_3$CSiMe_2OR), 0.16 (s, 3H, Me_3CSi**Me**$_2$OR), 0.14 (s, 3H, Me_3CSi**Me**$_2$OR).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7 (R_2C(CO_2Me)**C**O_2R), 170.3 (R_2C(**C**O_2Me)CO_2R), 149.6 (H_2C=**C**R_2), 109.9 (H_2**C**=CR_2), 79.6 (RCO_2**C**HR_2), 76.3 (H_2C=C(R)**C**H(OH)R), 61.5 (TBSO**C**H_2R), 60.7 (R_2**C**(CO_2Me)CO_2R), 53.7 (TBSOCH_2CH(OR)**C**HR_2), 53.6 (**Me**O_2CR), 35.5 (H_2C=C(R)**C**H_2C(R)(CO_2Me)CO_2R), 25.9 (3C, **Me**$_3$CSiMe_2OR), 18.5 (Me_3**C**SiMe_2OR), -5.4 (Me_3CSi**Me**$_2$OR), -5.5 (Me_3CSi**Me**$_2$OR).

Key NOE correlations involved in stereochemical assignment (E = CO_2Me):



IR: (ν_{max}/cm^{-1} (thin film)) = 3370, 1777, 1739, 1462, 1389, 1254, 1121, 954, 838, 780.

LRMS (ESI$^+$): *m/z* = 379.2 = $[M+Na]^+$

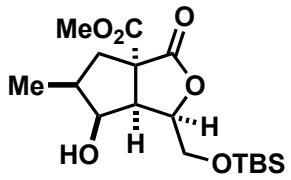
HRMS (ESI$^+$): Predicted *m/z* ($[C_{17}H_{28}O_6Si_1Na]^+$) = 379.1547; *m/z* found = 379.1548.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ -23.5 (c = 0.35 in $CHCl_3$).

Melting point of enantioenriched material: 82-83 °C.

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

4.27 - (±)-Methyl (1*R*,3a*R*,5*S*,6*S*,6a*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



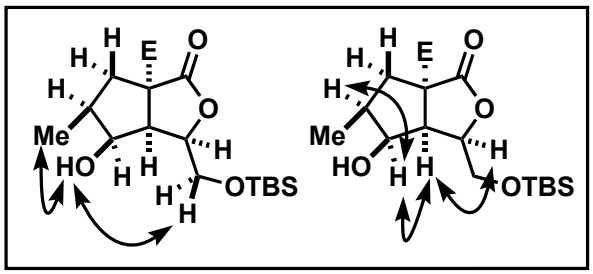
Compound **4.25** (36 mg, 0.10 mmol) was dissolved in ethyl acetate (1.20 mL), the solution was sparged with nitrogen, and palladium on carbon (10% palladium by weight, 11 mg, 0.010 mmol palladium) was added. The suspension was sparged with nitrogen, then sparged with hydrogen, the flask was fitted with a three-skinned hydrogen balloon, and the mixture was stirred rapidly for 4 hours. After this time had elapsed, the hydrogen balloon was removed, and the flask was opened to the atmosphere. The mixture was filtered through a pad of Celite™, volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 5-20% ethyl acetate in pentane, to give the product as a colourless oil (8 mg, 0.02 mmol, 21% yield) alongside compound **4.26** (23 mg, 0.065 mmol, 65% yield).

R.f: 0.42 (30% ethyl acetate in pentane, stains in potassium permanganate deep with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.66 (ddd, *J* = 5.9, 3.7, 2.5 Hz, 1H, $TBSOCH_2C\mathbf{H}(OR)R$), 4.28 (dd, *J* = 12.2, 3.7 Hz, 1H, TBSOC**H**H'R), 4.14 (br s, 1H, $MeCH(R)C\mathbf{H}(OH)R$), 4.01 (dd, *J* = 12.2, 2.5 Hz, 1H, TBSOCH**H'**R), 3.80 (br s, 1H, $MeCH(R)CH(O\mathbf{H})R$), 3.77 (s, 3H, $\mathbf{Me}O_2CR$), 2.88 (dd, *J* = 5.9, 3.1 Hz, 1H, $MeCH(R)CH(OH)C\mathbf{H}R_2$), 2.48 (dd, *J* = 11.0, 5.4 Hz, 1H, MeCH(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.24 – 2.07 (m, 2H, $MeC\mathbf{H}R_2$, MeCH(R)CH**H'**C(R)(CO_2Me)CO_2R), 1.06 (d, *J* = 6.3 Hz, 3H, $\mathbf{Me}CHR_2$), 0.92 (s, 9H, $\mathbf{Me_3}CSiMe_2OR$), 0.15 (s, 3H, $Me_3CSi\mathbf{Me}_2OR$), 0.15 (s, 3H, $Me_3CSi\mathbf{Me}_2OR$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.6 ($R_2C(CO_2Me)\mathbf{C}O_2R$), 171.3 ($R_2C(\mathbf{C}O_2Me)CO_2R$), 79.0 ($RCO_2\mathbf{C}HR_2$), 75.8 ($MeCH(R)\mathbf{C}H(OH)R$), 61.9 ($R_2\mathbf{C}(CO_2Me)CO_2R$), 61.6 ($TBSO\mathbf{C}H_2R$), 57.0 ($TBSOCH_2CH(OR)\mathbf{C}HR_2$), 53.3 ($\mathbf{Me}O_2CR$), 41.3 ($Me\mathbf{C}HR_2$), 37.2 ($MeCH(R)\mathbf{C}H_2C(R)(CO_2Me)CO_2R$), 25.9 (3C, $\mathbf{Me_3}CSiMe_2OR$), 18.5 ($Me_3\mathbf{C}SiMe_2OR$), 13.1 ($\mathbf{Me}CHR_2$), -5.5 ($Me_3CSi\mathbf{Me}_2OR$), -5.6 ($Me_3CSi\mathbf{Me}_2OR$).

Key NOE correlations involved in stereochemical assignment (E = CO_2Me):

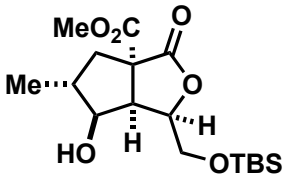


IR: (ν_{max}/cm^{-1} (thin film)) = 2955, 1775, 1738, 1461, 1253, 1118, 1000, 836, 779.

LRMS (ESI^+): *m/z* = 381.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{17}H_{30}O_6Si_1Na]^+$) = 381.1704; *m/z* found = 381.1704.

4.26 - (±)-Methyl (1*R*,3a*R*,5*R*,6*S*,6a*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



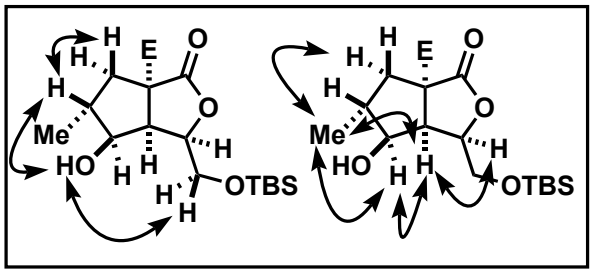
Compound **4.25** (36 mg, 0.10 mmol) was dissolved in ethyl acetate (1.20 mL), the solution was sparged with nitrogen, and palladium on carbon (10% palladium by weight, 11 mg, 0.010 mmol palladium) was added. A single crystal of tetrakis(acetonitrile)copper(I) tetrafluoroborate and a single crystal of 2,2'-bipyridine were dissolved in ethyl acetate (1.000 mL), and 0.050 mL of this solution was added to the reaction. The suspension was sparged with nitrogen, then sparged with hydrogen, the flask was fitted with a three-skinned hydrogen balloon, and the mixture was stirred rapidly for 8 hours. After this time had elapsed, the hydrogen balloon was removed, and the flask was opened to the atmosphere. The mixture was filtered through a pad of Celite™, volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 5-20% ethyl acetate in pentane, to give the product as a colourless oil (33 mg, 0.091 mmol, 91% yield).

R.f: 0.40 (30% ethyl acetate in pentane, stains in potassium permanganate deep with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.72 (ddd, *J* = 6.3, 3.8, 1.9 Hz, 1H, TBSOCH$_2$C**H**(OR)R), 4.41 (d, *J* = 4.0 Hz, 1H, MeCH(R)CH(O**H**)R), 4.28 (dd, *J* = 12.3, 3.8 Hz, 1H, TBSOC**H**H'R), 4.03 (dd, *J* = 12.3, 1.9 Hz, 1H, TBSOCH**H'**R), 3.99 (br q, *J* = 4.0 Hz, 1H, MeCH(R)C**H**(OH)R), 3.78 (s, 3H, **Me**O$_2$CR), 3.10 (dd, *J* = 6.3, 4.0 Hz, 1H, MeCH(R)CH(OH)C**H**R$_2$), 2.66 (dd, *J* = 13.6, 7.0 Hz, 1H, MeCH(R)C**H$_{endo}$**H$_{exo}$C(R)(CO$_2$Me)CO$_2$R), 2.20 (m, 1H, MeC**H**R$_2$), 2.00 (dd, *J* = 13.6, 4.2 Hz, 1H, MeCH(R)CH$_{endo}$**H$_{exo}$**C(R)(CO$_2$Me)CO$_2$R), 0.98 (d, *J* = 7.0 Hz, 3H, **Me**CHR$_2$), 0.93 (s, 9H, **Me$_3$**CSiMe$_2$OR), 0.16 (s, 3H, Me$_3$CSi**Me**$_2$OR), 0.15 (s, 3H, Me$_3$CSi**Me**$_2$OR).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5 (R$_2$C(CO$_2$Me)**C**O$_2$R), 171.0 (R$_2$C(**C**O$_2$Me)CO$_2$R), 79.4 (MeCH(R)**C**H(OH)R), 79.0 (RCO$_2$**C**HR$_2$), 61.4 (R$_2$**C**(CO$_2$Me)CO$_2$R), 61.3 (TBSO**C**H$_2$R), 53.4 (**Me**O$_2$CR), 52.7 (TBSOCH$_2$CH(OR)**C**HR$_2$), 41.7 (Me**C**HR$_2$), 37.7 (MeCH(R)**C**H$_2$C(R)(CO$_2$Me)CO$_2$R), 25.9 (3C, **Me$_3$**CSiMe$_2$OR), 18.6 (Me$_3$**C**SiMe$_2$OR), 17.5 (**Me**CHR$_2$), -5.4 (Me$_3$CSi**Me**$_2$OR), -5.6 (Me$_3$CSi**Me**$_2$OR).

Key NOE correlations involved in stereochemical assignment (E = CO$_2$Me):

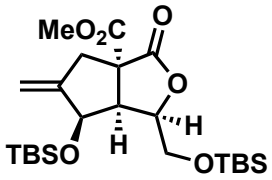


IR: (ν_{max}/cm^{-1} (thin film)) = 1775, 1737, 1461, 1000, 836, 779.

LRMS (ESI$^+$): *m/z* = 381.2 = [M+Na]$^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{17}H_{30}O_6Si_1Na$]$^+$) = 381.1704; *m/z* found = 381.1704.

4.28 - Methyl (1*R*,3a*R*,6*R*,6a*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylene-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **4.25** (179 mg, 0.500 mmol) was dissolved in dry dichloromethane (5.00 mL). 2,6-Lutidine (241 mg, 0.26 mL, 2.25 mmol) was added, *tert*-butyldimethylsilyl trifluormethanesulfonate (397 mg, 0.35 mL, 1.50 mmol) was added, and the resulting colourless solution was stirred at room temperature for 12 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (5 mL), water (5 mL), and ethyl acetate (10 mL) were added, and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and volatile organics were removed under reduced pressure. The crude residue was purified *via* flash column chromatography, eluting with 20% diethyl ether in pentane, to give the product as a white solid (184 mg, 0.391 mmol, 78% yield). Racemic material was a colourless oil.

R.f: 0.49 (40% diethyl ether in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.07 (br s, 1H, **H**H'=CR_2), 4.97 (br s, H**H'**=CR_2), 4.76 (q, *J* = 6.0 Hz, 1H, $TBSOCH_2C$**H**(OR)R), 4.54 (d, *J* = 4.1 Hz, 1H, H_2C=C(R)C**H**(OTBS)R), 4.15 (dd, *J* = 10.7, 6.0 Hz, 1H, TBSOC**H**H'R), 4.07 (dd, *J* = 10.7, 6.0 Hz, 1H, TBSOCH**H'**R), 3.79 (s, 3H, **Me**O_2CR), 3.08 (br d, *J* = 16.4 Hz, 1H, H_2C=C(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.95 (d, *J* = 16.4 Hz, 1H, H_2C=C(R)CH**H'**C(R)(CO_2Me)CO_2R), 2.91 (dd, *J* = 6.0, 4.1 Hz, 1H, $TBSOCH_2CH(OR)C$**H**R_2), 0.90 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.87 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.10 (s, 3H, Me_3CSi**Me**$_2OR$), 0.09 (s, 6H, Me_3CSi**Me**$_2OR$, Me_3CSi**Me**$_2OR$), 0.05 (s, 3H, Me_3CSi**Me**$_2OR$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.6 ($R_2C(CO_2Me)$**C**O_2R), 170.6 (R_2C(**C**O_2Me)CO_2R), 150.1 (H_2C=**C**R_2), 110.4 (H_2**C**=CR_2), 81.0 (RCO_2**C**HR_2), 77.5 (H_2C=C(R)**C**H(OTBS)R), 62.2 (TBSO**C**H_2R), 60.1 (R_2**C**(CO_2Me)CO_2R), 53.5 (2C, **Me**O_2CR, $TBSOCH_2CH(OR)$**C**HR_2), 35.8 (H_2C=C(R)**C**H_2C(R)(CO_2Me)CO_2R),

26.0 (3C, **Me$_3$**CSiMe$_2$OR), 25.8 (3C, **Me$_3$**CSiMe$_2$OR), 18.3 (Me$_3$**C**SiMe$_2$OR), 18.1 (Me$_3$**C**SiMe$_2$OR), -3.8 (Me$_3$CSi**Me**$_2$OR), -4.9 (Me$_3$CSi**Me**$_2$OR), -5.0 (Me$_3$CSi**Me**$_2$OR), -5.2 (Me$_3$CSi**Me**$_2$OR).

IR: (ν_{max}/cm^{-1} (thin film)) = 2857, 1781, 1737, 1472, 1103, 1066, 1005, 837, 777.

LRMS (ESI$^+$): *m/z* = 493.2 = [M+Na]$^+$

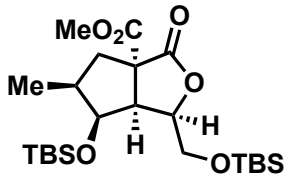
HRMS (ESI$^+$): Predicted *m/z* ([$C_{23}H_{42}O_6Si_2Na$]$^+$) = 493.2412; *m/z* found = 493.2408.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ -16.5 (c = 0.6 in $CHCl_3$).

Melting point of enantioenriched material: 40-41 °C.

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

4.3 - Methyl (1*R*,3a*R*,5*S*,6*S*,6a*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **4.28** (94 mg, 0.20 mmol) was dissolved in ethyl acetate (2.50 mL), the solution was sparged with nitrogen, and palladium on carbon (10% palladium by weight, 21 mg, 0.020 mmol palladium) was added. The suspension was sparged with nitrogen, then sparged with hydrogen, the flask was fitted with a three-skinned hydrogen balloon, and the mixture was stirred rapidly for 4 hours. After this time had elapsed, the hydrogen balloon was removed, and the flask was opened to the atmosphere. The mixture was filtered through a pad of Celite™, volatile organics were removed under reduced pressure to give the product as a white solid (94 mg, 0.20 mmol, 100% yield). Racemic material was a colourless oil.

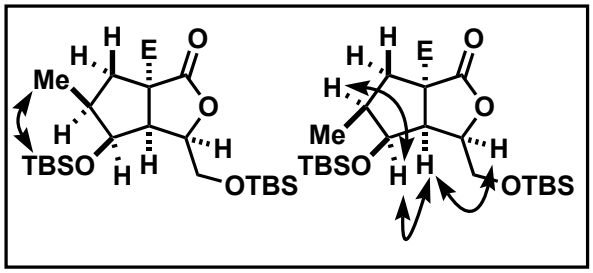
R.f: 0.49 (40% diethyl ether in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.67 (ddd, *J* = 7.2, 6.3, 5.3 Hz, 1H, TBSOCH$_2$C**H**(OR)R), 4.31 (dd, *J* = 4.7, 2.7 Hz, 1H, MeCH(R)C**H**(OTBS)R), 4.10 (dd, *J* = 11.2, 7.2 Hz, 1H, TBSOC**H**H'R), 4.00 (dd, *J* = 11.2, 5.3 Hz, 1H, TBSOCH**H'**R), 3.78 (s, 3H, **Me**O$_2$CR), 2.97 (dd, *J* = 6.3, 4.7 Hz, 1H, MeCH(R)CH(OTBS)C**H**R$_2$), 2.44 – 2.34

(dd, *J* = 10.5, 5.5 Hz, 1H, MeCH(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.14 – 2.04 (m, 2H, MeC**H**R_2, MeCH(R)CH**H'**C(R)(CO_2Me)CO_2R), 0.99 (d, *J* = 6.6 Hz, 3H, **Me**CHR_2), 0.91 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.90 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.13 (s, 3H, Me_3CSi**Me**$_2OR$), 0.09 (s, 3H, Me_3CSi**Me**$_2OR$), 0.09 (s, 3H, Me_3CSi**Me**$_2OR$), 0.09 (s, 3H, Me_3CSi**Me**$_2OR$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.4 ($R_2C(CO_2Me)$**C**O_2R), 171.3 (R_2C(**C**O_2Me)CO_2R), 81.4 (RCO_2**C**HR_2), 77.7 (MeCH(R)**C**H(OTBS)R), 62.5 (TBSO**C**H_2R), 60.7 (R_2**C**(CO_2Me)CO_2R), 54.6 ($TBSOCH_2CH(OR)$**C**HR_2), 53.4 (**Me**O_2CR), 41.8 (Me**C**HR_2), 37.1 (MeCH(R)**C**$H_2C(R)(CO_2Me)CO_2R$), 26.2 (3C, **Me$_3$**$CSiMe_2OR$), 26.0 (3C, **Me$_3$**$CSiMe_2OR$), 18.5 (Me_3**C**$SiMe_2OR$), 18.3 (Me_3**C**$SiMe_2OR$), 14.5 (**Me**CHR_2), -2.1 (Me_3CSi**Me**$_2OR$), -3.6 (Me_3CSi**Me**$_2OR$), -4.9 (Me_3CSi**Me**$_2OR$), -5.0 (Me_3CSi**Me**$_2OR$).

Key NOE correlations involved in stereochemical assignment (E = CO_2Me):



IR: (ν_{max}/cm^{-1} (thin film)) = 1782, 1740, 1463, 1028, 838, 776.

LRMS (ESI^+): *m/z* = 495.3 = $[M+Na]^+$

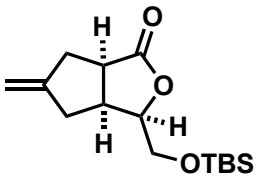
HRMS (ESI^+): Predicted *m/z* ($[C_{23}H_{45}O_6Si_2]^+$) = 473.2749; *m/z* found = 473.2747.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ +1.0 (c = 0.35 in $CHCl_3$).

Melting point of enantioenriched material: 43-44 °C.

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

4.30 - (±)-(3*R*,3a*S*,6a*R*)-3-(((*ter*t-Butyldimethylsilyl)oxy)methyl)-5-methylenehexahydro-1*H*-cyclopenta[c]furan-1-one



Compound **2.50** (170 mg, 0.500 mmol) and anhydrous lithium chloride (106 mg, 2.50 mmol) were dissolved in dry, degassed *N*,*N*-dimethylformamide (5.00 mL) under nitrogen. Water (0.05 mL) was added, an air condenser was attached, and the solution was heated to reflux for 4 hours, over the course of which the colour of the reaction turned from colourless to yellow. The reaction was allowed to cool to room temperature, and the majority of the volatile organics were removed under a stream of dry nitrogen overnight. The crude residue was redissolved in diethyl ether (10 mL) and water (10 mL), and this mixture was transferred to a separating funnel. The organic layer was separated, and the aqueous layer was extracted three times with diethyl ether (10 mL). The combined organic extracts were washed twice with water, washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (122 mg, 0.432 mmol, 86% yield).

R.f: 0.33 (20% diethyl ether in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.92 – 4.90 (m, 1H, **H**H'C=CR_2), 4.89 – 4.85 (m, 1H, H**H'**C=CR_2), 4.58 (q, *J* = 6.0 Hz, 1H, TBSOCH_2C**H**(OR)R), 3.91 (dd, *J* = 10.8, 6.0 Hz, 1H, TBSOC**H**H'R), 3.72 (dd, *J* = 10.8, 6.0 Hz, 1H, TBSOCH**H'**R), 3.15 (ddd, *J* = 10.2, 8.7, 2.5 Hz, 1H, RO_2CC**H**R_2), 2.97 (qd, *J* = 8.7, 6.0 Hz, 1H, TBSOCH_2CH(OR)C**H**R_2), 2.80 – 2.73 (m, 1H, H_2C=C(R)C**H**H'CH(R)CO_2R), 2.68 – 2.59 (m, 1H, H_2C=C(R)CH**H'**CH(R)CO_2R), 2.41 (dd, *J* = 16.1, 8.7 Hz, 1H, H_2C=C(R)C**H**H'CH(R)CH(OR)CH_2OTBS), 2.37 – 2.29 (dd, *J* = 16.1, 8.7 Hz, 1H, H_2C=C(R)CH**H'**CH(R)CH(OR)CH_2OTBS), 0.90 (s, 9H, **Me$_3$**CSiMe_2OR), 0.09 (s, 6H, Me_3CSi**Me$_2$**OR).

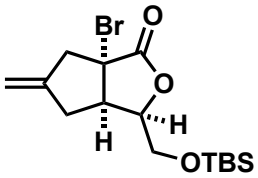
^{13}C NMR (151 MHz, $CDCl_3$): δ 179.5 ($R\mathbf{C}O_2R$), 148.8 ($H_2C=\mathbf{C}R_2$), 107.8 ($H_2\mathbf{C}=CR_2$), 80.5, ($RCO_2\mathbf{C}HR_2$), 62.2 ($TBSO\mathbf{C}H_2R$), 46.2 ($RO_2C\mathbf{C}HR_2$), 42.1 ($TBSOCH_2CH(OR)\mathbf{C}HR_2$), 34.1 ($H_2C=C(R)\mathbf{C}H_2CH(R)CO_2R$), 32.3 ($H_2C=C(R)\mathbf{C}H_2CH(R)CH(OR)CH_2OTBS$), 25.9 (3C, $\mathbf{Me_3}CSiMe_2OR$), 18.4 ($Me_3\mathbf{C}SiMe_2OR$), -5.2 ($Me_3CSi\mathbf{Me}_2OR$), -5.4 ($Me_3CSi\mathbf{Me}_2OR$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1775, 1119, 838.

LRMS (ESI^+): *m/z* = 305.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{15}H_{27}O_3Si_1]^+$, $[M+H]^+$) = 283.1724; *m/z* found = 283.1723

4.31 - (±)-(3*R*,3a*R*,6a*S*)-6a-Bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylenehexahydro-1*H*-cyclopenta[c]furan-1-one



Compound **4.30** (28 mg, 0.10 mmol) was dissolved in dry, degassed tetrahydrofuran (1.00 mL) under nitrogen. Carbon tetrabromide (166 mg, 0.500 mmol) was added, and the resulting solution was cooled to 0 °C. A solution of lithium hexamethyldisilazide (1.0 M in toluene, 0.20 mL, 0.20 mmol) was added dropwise over 30 seconds; during this addition the colour of the solution was observed to change from colourless to brown. The solution was allowed to warm to room temperature over 30 minutes. After this time had elapsed, saturated aqueous ammonium chloride solution (3 mL), water (3 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (25 mg, 0.070 mmol, 70% yield).

R.f: 0.40 (10% diethyl ether in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.99 – 4.90 (m, 2H, **H**H'C=CR_2, H**H'**C=CR_2), 4.80 (td, *J* = 6.5, 4.8 Hz, 1H, TBSOCH_2C**H**(OR)R), 3.98 (dd, *J* = 10.8, 6.5 Hz, 1H, TBSOC**H**H'R), 3.73 (dd, *J* = 10.8, 6.5 Hz, 1H, TBSOCH**H'**R), 3.36 (br d, *J* = 17.3, 1.6 Hz, 1H, H_2C=C(R)C**H**H'CBr(R)CO_2R), 3.07 (td, *J* = 9.4, 4.8 Hz, 1H, TBSOCH_2CH(OR)C**H**R_2), 2.96 (dq, *J* = 17.3, 2.4 Hz, 1H, H_2C=C(R)CH**H'**CBr(R)CO_2R), 2.55 (ddq, *J* = 16.8, 9.4, 1.7 Hz, 1H, H_2C=C(R)C**H**H'CH(R)CH(OR)CH_2OTBS), 2.36 (ddt, *J* = 16.8, 9.4, 2.4 Hz, 1H, H_2C=C(R)CH**H'**CH(R)CH(OR)CH_2OTBS), 0.90 (s, 9H, **Me$_3$**CSiMe_2OR), 0.10 (s, 3H, Me_3CSi**Me**$_2$OR), 0.09 (s, 3H, Me_3CSi**Me**$_2$OR).

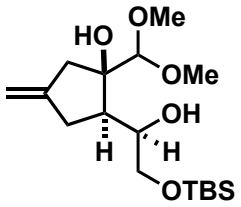
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5 (R**C**O_2R), 144.6 (H_2C=**C**R_2), 109.5 (H_2**C**=CR_2), 78.8 (RCO_2**C**HR_2), 61.4 (TBSO**C**H_2R), 57.9 (RO_2C**C**BrR_2), 51.9 (TBSOCH_2CH(OR)**C**HR_2), 44.6 (H_2C=C(R)**C**H_2CBr(R)CO_2R), 31.7 (H_2C=C(R)**C**H_2CH(R)CH(OR)CH_2OTBS), 25.9 (3C, **Me$_3$**CSiMe_2OR), 18.3 (Me_3**C**SiMe_2OR), -5.3 (Me_3CSi**Me**$_2$OR), -5.4 (Me_3CSi**Me**$_2$OR).

IR: (ν_{max}/cm^{-1} (thin film)) = 1782, 1121, 839.

LRMS (ESI$^+$): *m/z* = 383.1, 385.1 = $[M+Na]^+$

HRMS (ESI$^+$): Predicted *m/z* ($[C_{15}H_{25}O_3BrSiNa]^+$) = 383.0649, 385.0628; *m/z* found = 383.0648 (50%), 385.0627 (50%).

4.33 - (±)-(1*R*,2*R*)-2-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxyethyl)-1-(dimethoxymethyl)-4-methylenecyclopentan-1-ol



Compound **4.31** (18 mg, 0.050 mmol) was dissolved in dry, degassed tetrahydrofuran (0.50 mL) under nitrogen, and the resulting solution was cooled to -78 °C. A solution of diisobutylaluminium hydride (1.0 M in hexane, 0.20 mL, 0.20 mmol) was added dropwise over 1 minute, and the resulting colourless solution was stirred at -78 °C for 12 hours. After this time had elapsed, methanol (0.50 mL) and sodium

methoxide (25% by weight in methanol, 0.10 mL, 0.45 mmol) were added, and the reaction was allowed to warm to room temperature over 2 hours. After this time had elapsed, saturated aqueous ammonium chloride solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (12 mg, 0.34 mmol, 67% yield).

R.f: (40% diethyl ether in pentane, stains in potassium permanganate dip upon heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.93 (dd, *J* = 2.8, 1.4 Hz, 1H, **H**H'C=CR_2), 4.90 (dd, *J* = 2.8, 1.5 Hz, 1H, H**H'**C=CR_2), 4.30 (s, 1H, $(MeO)_2C$**H**R), 4.18 (td, *J* = 6.1, 2.5 Hz, 1H, $TBSOCH_2C$**H**(OH)R), 3.58 (dd, *J* = 9.7, 6.1 Hz, 1H, TBSOC**H**H'R), 3.56 (s, 3H, (**Me**O)$_2$CHR), 3.55 (s, 3H, (**Me**O)$_2$CHR), 3.49 (s, 1H, $(MeO)_2CHC(O$**H**$)R_2$) 3.46 (dd, *J* = 9.7, 6.1 Hz, 1H, TBSOCH**H'**R), 3.34 (d, *J* = 2.5 Hz, 1H, $TBSOCH_2CH(O$**H**$)$R), 2.83 – 2.72 (m, 1H, H_2C=C(R)C**H**H'CH(R)CH(OH)CH_2OTBS), 2.71 – 2.61 (m, 1H, H_2C=C(R)C**H**H'C(OH)(R)CH$(OMe)_2$), 2.35 – 2.30 (m, 2H, $TBSOCH_2CH(OH)C$**H**R_2, H_2C=C(R)CH**H'**CH(R)CH(OH)CH_2OTBS), 2.27 (br d, *J* = 16.7 Hz, 1H, H_2C=C(R)CH**H'**C(OH)(R)CH$(OMe)_2$), 0.90 (s, 9H, **Me$_3$**$CSiMe_2$OR), 0.07 (s, 6H, Me_3CSi**Me$_2$**OR).

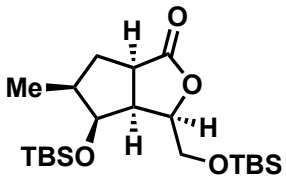
^{13}C NMR (151 MHz, $CDCl_3$): δ 148.4 (H_2C=**C**R_2), 108.8 ($(MeO)_2$**C**HR), 107.3 (H_2**C**=CR_2), 85.1 ($(MeO)_2CH$**C**$(OH)R_2$), 70.8 ($TBSOCH_2$**C**H(OH)R), 65.6 (TBSO**C**H_2R), 58.6 ((**Me**O)$_2$CHR), 58.1 ((**Me**O)$_2$CHR), 43.7 ($TBSOCH_2CH(OH)$**C**HR_2), 43.1 (H_2C=C(R)**C**$H_2C(OH)$(R)CH$(OMe)_2$), 29.7 (H_2C=C(R)**C**H_2CH(R)CH(OH)CH_2OTBS), 26.0 (3C, **Me$_3$**$CSiMe_2$OR), 18.4 (Me_3**C**$SiMe_2$OR), -5.2 (Me_3CSi**Me**$_2$OR), -5.3 (Me_3CSi**Me**$_2$OR).

IR: (ν_{max}/cm^{-1} (thin film)) = 3384, 1079.

LRMS (ESI$^+$): *m/z* = 369.2 = $[M+Na]^+$

HRMS (ESI$^+$): Predicted *m/z* ([$C_{17}H_{34}O_5SiNa$]$^+$) = 369.2068; *m/z* found = 369.2068.

4.34 - (3*R*,3a*S*,4*S*,5*S*,6a*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylhexahydro-1*H*-cyclopenta[*c*]furan-1-one



Compound **4.3** (94 mg, 0.20 mmol) and anhydrous lithium chloride (42 mg, 1.0 mmol) were dissolved in dry, degassed *N*,*N*-dimethylformamide (2.00 mL) under nitrogen. Water (0.02 mL) was added, an air condenser was attached, and the solution was heated to reflux for 4 hours, over the course of which the colour of the reaction turned from colourless to dark brown. The reaction was allowed to cool to room temperature, and the majority of the volatile organics were removed under a stream of dry nitrogen overnight. The crude residue was redissolved in diethyl ether (10 mL) and water (10 mL), and this mixture was transferred to a separating funnel. The organic layer was separated, and the aqueous layer was extracted three times with diethyl ether (20 mL). The combined organic extracts were washed twice with water, washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a white solid (76 mg, 0.18 mmol, 92% yield). Racemic material was a colourless oil.

R.f: 0.52 (40% diethyl ether in pentane, stains in potassium permanganate dip upon heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.54 (td, *J* = 6.5, 5.3 Hz, 1H, TBSOCH_2C**H**(OR)R), 4.20 (dd, *J* = 4.4, 3.1 Hz, 1H, MeCH(R)C**H**(OTBS)R), 4.09 (dd, *J* = 11.2, 6.5 Hz, 1H, TBSOC**H**H'R), 4.00 (dd, *J* = 11.2, 5.3 Hz, 1H, TBSOCH**H'**R), 3.03 (td, *J* = 9.4, 4.4 Hz, 1H, RO_2CC**H**R_2), 2.77 (ddd, *J* = 9.4, 6.5, 4.4 Hz, 1H, TBSOCH_2CH(OR)C**H**R_2), 2.03 (ddd, *J* = 12.5, 9.5, 6.9 Hz, 1H, MeCH(R)C**H**H'C(R)HCO_2R), 1.94 (dtd, *J* = 9.5, 6.9, 3.1 Hz, 1H, MeC**H**R_2), 1.80 (ddd, *J* = 12.5, 9.5, 4.4 Hz, 1H, MeCH(R)CH**H'**C(R)HCO_2R), 0.97 (d, *J* = 6.9

Hz, 3H, **Me**CHR_2), 0.91 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.90 (s, 9H **Me$_3$**$CSiMe_2OR$), 0.12 (s, 3H Me_3CSi**Me$_2$**OR), 0.08 (s, 9H, Me_3CSi**Me$_2$**OR).

^{13}C NMR (126 MHz, $CDCl_3$): δ 180.0 (R**C**O_2R), 81.8 (RCO_2**C**HR_2), 76.9 (TBSO**C**HR_2), 62.8 (TBSO**C**H_2R), 48.9 (TBSOCH_2CH(OR)**C**HR_2), 43.9 (R_2**C**HCO_2R), 41.9 (Me**C**HR_2), 31.7 (R**C**H_2CHRCO_2R), 26.2 (3C, **Me**$_3CSiMe_2OR$), 26.0 (3C, **Me**$_3CSiMe_2OR$), 18.4 (Me_3**C**$SiMe_2OR$), 18.3 (Me_3**C**$SiMe_2OR$), 15.0 (**Me**CHR_2), -2.0 (Me_3CSi**Me**$_2$OR), -3.6 (Me_3CSi**Me**$_2$OR), -4.9 (Me_3CSi**Me**$_2$OR), -5.0 (Me_3CSi**Me**$_2$OR).

IR: (ν_{max}/cm^{-1} (thin film)) = 1773, 1463, 1362, 1138, 1115, 1071, 837, 775.

LRMS (ESI$^+$): *m/z* = 437.2 = $[M+Na]^+$

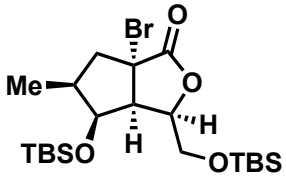
HRMS (ESI$^+$): Predicted *m/z* ($[C_{21}H_{42}O_4Si_2Na]^+$) = 437.2514; *m/z* found = 437.2510.

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ +0.7 (c = 0.7 in $CHCl_3$).

Melting point of enantioenriched material: 50-51 °C.

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

4.2 - (3*R*,3a*S*,4*S*,5*S*,6a*S*)-6a-Bromo-4-((*tert*-butyldimethylsilyl)oxy)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylhexahydro-1*H*-cyclopenta[c]furan-1-one



Compound **4.34** (41 mg, 0.10 mmol) was dissolved in dry, degassed tetrahydrofuran (1.00 mL) under nitrogen. Carbon tetrabromide (166 mg, 0.500 mmol) was added, and the resulting solution was cooled to 0 °C. A solution of lithium hexamethyldisilazide (0.5 M in toluene, 0.40 mL, 0.20 mmol) was added dropwise over 30 seconds, during the course of which the colour of the solution was observed to change from colourless to brown. The solution was allowed to warm to room temperature over 30 minutes. After this time had elapsed, saturated aqueous ammonium chloride solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed

with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 5% diethyl ether in pentane, to give the product as a colourless oil (36 mg, 0.074 mmol, 74% yield).

R.f: 0.48 (10% diethyl ether in pentane, stains in potassium permanganate dip upon heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.74 (br q, *J* = 6.2 Hz, 1H, $TBSOCH_2C\mathbf{H}(OR)R$), 4.23 (dd, *J* = 4.0, 3.0 Hz, 1H, $MeCH(R)C\mathbf{H}(OTBS)R$), 4.11 (dd, *J* = 10.9, 6.2 Hz, 1H, $TBSOC\mathbf{H}H'R$), 3.98 (dd, *J* = 10.9, 6.2 Hz, 1H, $TBSOCH\mathbf{H'}R$), 2.86 (dd, *J* = 6.2, 4.0 Hz, 1H, $TBSOCH_2CH(OR)C\mathbf{H}R_2$), 2.50 – 2.30 (m, 3H, $MeCH(R)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$, $MeCH(R)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$, $MeC\mathbf{H}R_2$), 0.99 (d, *J* = 6.6 Hz, 3H, $\mathbf{Me}CHR_2$), 0.91 (s, 9H, $\mathbf{Me_3}CSiMe_2OR$), 0.89 (s, 9H, $\mathbf{Me_3}CSiMe_2OR$), 0.13 (s, 3H, $Me_3CSi\mathbf{Me_2}OR$), 0.10 (s, 3H, $Me_3CSi\mathbf{Me_2}OR$), 0.10 (s, 3H, $Me_3CSi\mathbf{Me_2}OR$), 0.09 (s, 3H, $Me_3CSi\mathbf{Me_2}OR$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.9 ($R\mathbf{C}O_2R$), 79.4 ($RCO_2\mathbf{C}HR_2$), 76.9 ($MeCH(R)\mathbf{C}H(OTBS)R$), 61.6 ($TBSO\mathbf{C}H_2R$), 60.2 ($TBSOCH_2CH(OR)\mathbf{C}HR_2$), 58.8 ($R_2\mathbf{C}BrCO_2R$), 42.8 ($MeCH(R)\mathbf{C}H_2CBr(R)CO_2R$), 41.5 ($Me\mathbf{C}HR_2$), 26.1 (3C, $\mathbf{Me_3}CSiMe_2OR$), 25.9 (3C, $\mathbf{Me_3}CSiMe_2OR$), 18.4 ($Me_3\mathbf{C}SiMe_2OR$), 18.3 ($Me_3\mathbf{C}SiMe_2OR$), 14.7 ($\mathbf{Me}CHR_2$), -1.7 ($Me_3CSi\mathbf{Me}_2OR$), -3.6 ($Me_3CSi\mathbf{Me}_2OR$), -4.9 ($Me_3CSi\mathbf{Me}_2OR$), -5.0 ($Me_3CSi\mathbf{Me}_2OR$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1773, 1463, 1161, 1138, 1035, 836, 775.

LRMS (ESI^+): *m/z* = 515.2, 517.2 = $[M+Na]^+$

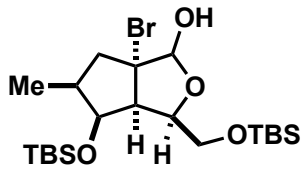
HRMS (ESI^+): Predicted *m/z* ($[C_{21}H_{41}O_4BrSi_2Na]^+$) = 515.1619, 517.1600; *m/z* found = 515.1619 (50%), 517.1600 (50%).

Specific rotation for enantioenriched material: $[\alpha]_D^{25}$ +1.5 (c = 0.25 in $CHCl_3$).

Melting point of enantioenriched material: 52-53 °C.

Racemic and enantioenriched data had the same physical and spectroscopic properties otherwise.

4.35 - (±)-(3*R*,3a*S*,4*S*,5*S*,6a*S*)-6a-Bromo-4-((t*ert*-butyldimethylsilyl)oxy)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methylhexahydro-1*H*-cyclopenta[c]furan-1-ol



Compound **4.2** (4.9 mg, 0.010 mmol) was dissolved in dry, degassed toluene (0.10 mL) under nitrogen, and the resulting solution was cooled to 0 °C. A solution of diisobutylaluminium hydride (1.0 M in hexane, 0.04 mL, 0.04 mmol) was added dropwise over 30 seconds. The solution was allowed to warm to room temperature over 20 minutes. After this time had elapsed, saturated aqueous ammonium chloride solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (3 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 5% diethyl ether in pentane, to give the product as a colourless oil (2.9 mg, 0.0058 mmol, 58% yield).

Partial data for **4.35**:

R.f: 0.48 (40% diethyl ether in pentane, stains in potassium permanganate dip upon heating).

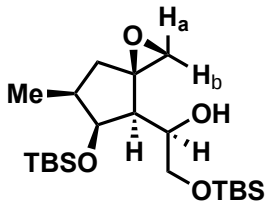
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.40 (d, *J* = 12.7 Hz, 1H, $R_2CBrC\mathbf{H}(OH)OR$), 5.13 (d, *J* = 12.7 Hz, 1H, $R_2CBrCH(O\mathbf{H})OR$), 4.39 (dt, *J* = 8.1, 6.6 Hz, 1H, $TBSOCH_2C\mathbf{H}(OR)R$), 4.16 (t, *J* = 3.4 Hz, 1H, $MeCH(R)C\mathbf{H}(OTBS)R$), 3.91 (dd, *J* = 9.9, 6.2 Hz, 1H, $TBSOC\mathbf{H}H'R$), 3.87 (dd, *J* = 9.9, 8.1 Hz, 1H, $TBSOCH\mathbf{H'}R$), 2.87 (dd, *J* = 6.2, 4.1 Hz, 1H, $TBSOCH_2CH(OR)C\mathbf{H}R_2$), 2.53 – 2.40 (m, 2H, $MeCH(R)C\mathbf{H}H'C(R)(CO_2Me)CO_2R$, $MeC\mathbf{H}R_2$), 2.38 – 2.27 (m, 1H, $MeCH(R)CH\mathbf{H'}C(R)(CO_2Me)CO_2R$), 0.99 (d, *J* = 7.0 Hz, 3H, $\mathbf{Me}CHR_2$), 0.96 (s, 9H, $\mathbf{Me_3}CSiMe_2OR$), 0.90 (s, 9H, $\mathbf{Me_3}CSiMe_2OR$), 0.22 (s, 3H, $Me_3CSi\mathbf{Me_2}OR$), 0.16 (s, 3H, $Me_3CSi\mathbf{Me_2}OR$), 0.08 (s, 3H, $Me_3CSi\mathbf{Me_2}OR$), 0.07 (s, 3H, $Me_3CSi\mathbf{Me_2}OR$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 105.4 (R_2CBr**C**H(OH)OR), 78.0 ($R_2CBrCH(OH)O$**C**HR_2), 77.0 (MeCH(R)**C**H(OTBS)R), 72.5 (R_2**C**BrCH(OH)OR), 63.5 ($TBSOCH_2CH(OR)$**C**HR_2), 62.5 (TBSO**C**H_2R), 42.5 (Me**C**HR_2), 42.3 (MeCH(R)**C**H_2CBr(R)CH(OH)OR), 26.4 (3C, **Me$_3$**$CSiMe_2OR$), 26.0 (3C, **Me$_3$**$CSiMe_2OR$), 18.4 (Me_3**C**$SiMe_2OR$), 18.3 (Me_3**C**$SiMe_2OR$), 14.8 (**Me**CHR_2), -1.9 (Me_3CSi**Me**$_2OR$), -3.4 (Me_3CSi**Me**$_2OR$), -4.0 (Me_3CSi**Me**$_2OR$), -4.9 (Me_3CSi**Me**$_2OR$).

IR: (ν_{max}/cm^{-1} (thin film)) = 3373, 1472, 1361, 835, 775, 732.

LRMS (ESI^+): *m/z* = 517.2, 519.2 = $[M+Na]^+$

4.38 - (*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-((3*R*,4*S*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-methyl-1-oxaspiro[2.4]heptan-4-yl)ethan-1-ol



Compound **4.2** (246 mg, 0.500 mmol) was dissolved in dry, degassed toluene (5.00 mL) under nitrogen, and the resulting solution was cooled to 0 °C. A solution of diisobutylaluminium hydride (1.0 M in hexane, 2.00 mL, 2.00 mmol) was added dropwise over 30 seconds. The solution was allowed to warm to room temperature over 4 hours. After this time had elapsed, saturated aqueous ammonium chloride solution (10 mL), water (10 mL), and ethyl acetate (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure to give a crude residue.

This crude residue was dissolved in dry tetrahydrofuran (2.50 mL). Methanol (0.50 mL) and sodium methoxide (25% by weight in methanol, 1.00 mL, 4.77 mmol) were added, and the reaction was allowed to warm to room temperature over 2 hours. After this time had elapsed, saturated aqueous

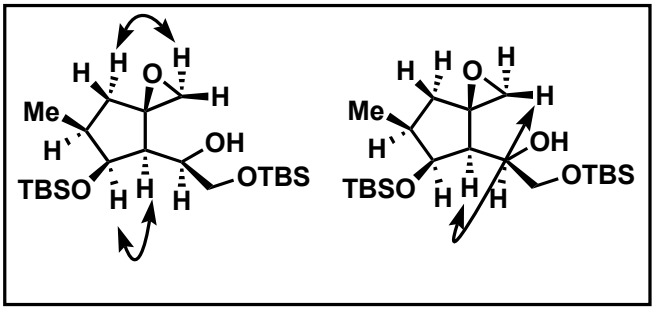
ammonium chloride solution (10 mL), water (10 mL), and ethyl acetate (25 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% ethyl acetate in pentane, to give the product as a colourless oil (164 mg, 0.395 mmol, 79% yield).

R.f: 0.60 (30% ethyl acetate in pentane, stains in potassium permanganate dip upon heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.27 (t, *J* = 3.0 Hz, 1H, MeCH(R)C**H**(OTBS)R), 3.74 (ddt, *J* = 8.5, 6.1, 4.0 Hz, 1H, TBSOCH$_2$C**H**(OH)R), 3.64 (dd, *J* = 9.8, 4.0 Hz, 1H, TBSOC**H**H'R), 3.38 (dd, *J* = 9.8, 6.1 Hz, 1H, TBSOCH**H'**R), 2.64 (d, *J* = 4.8 Hz, 1H, R$_2$COC**H$_a$**H$_b$), 2.63 (d, *J* = 4.0 Hz, 1H, TBSOCH$_2$CH(O**H**)R), 2.58 (d, *J* = 4.8 Hz, 1H, R$_2$COCH$_a$**H$_b$**), 2.21 (dd, *J* = 8.5, 3.0 Hz, 1H, TBSOCH$_2$CH(OH)C**H**R$_2$), 1.93 – 1.89 (m, 3H, MeCH(R)C**H**H'C(OR)R$_2$, MeCH(R)CH**H'**C(OR)R$_2$, MeC**H**R$_2$), 1.04 (d, *J* = 5.9 Hz, 3H, **Me**CHR$_2$), 0.94 (s, 9H, **Me$_3$**CSiMe$_2$OR), 0.89 (s, 9H, **Me$_3$**CSiMe$_2$OR), 0.15 (s, 3H, Me$_3$CSi**Me$_2$**OR), 0.10 (s, 3H, Me$_3$CSi**Me$_2$**OR), 0.06 (s, 3H, Me$_3$CSi**Me$_2$**OR), 0.06 (s, 3H, Me$_3$CSi**Me$_2$**OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 77.0 (MeCH(R)**C**H(OTBS)R), 68.5 (TBSOCH$_2$**C**H(OH)R), 65.1 (TBSO**C**H$_2$R), 62.6 (R$_2$**C**OCH$_2$), 50.6 (R$_2$CO**C**H$_2$), 49.9 (TBSOCH$_2$CH(OH)**C**HR$_2$), 39.1 (MeCH(R)**C**H$_2$C(OR)R$_2$), 38.3 (Me**C**HR$_2$), 26.4 (3C, **Me$_3$**CSiMe$_2$OR), 26.0 (3C, **Me$_3$**CSiMe$_2$OR), 18.6 (Me$_3$**C**SiMe$_2$OR), 18.4 (Me$_3$**C**SiMe$_2$OR), 15.2 (**Me**CHR$_2$), -3.7 (Me$_3$CSi**Me**$_2$OR), -4.1 (Me$_3$CSi**Me**$_2$OR), -5.1 (Me$_3$CSi**Me**$_2$OR), -5.2 (Me$_3$CSi**Me**$_2$OR).

Key NOE correlations involved in stereochemical assignment:

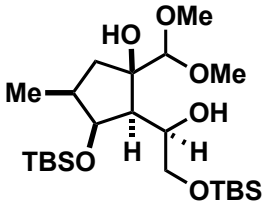


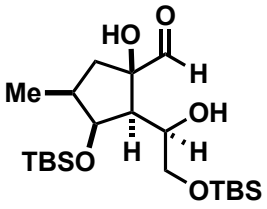
IR: (ν_{max}/cm^{-1} (thin film)) = 3567, 1472, 1388, 1254, 835.

LRMS (ESI$^+$): *m/z* = 439.2 = $[M+Na]^+$

HRMS (ESI$^+$): Predicted *m/z* ($[C_{21}H_{45}O_4Si_2]^+$, $[M+H]^+$) = 417.2851; *m/z* found = 417.2847.

4.1 - (±)-(1*R*,2*S*,3*S*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyethyl)-1-(dimethoxymethyl)-4-methylcyclopentan-1-ol; **4.36** - (±)-(1*R*,2*S*,3*S*,4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyethyl)-1-hydroxy-4-methylcyclopentane-1-carbaldehyde;





Compound **4.35** (10 mg, 0.020 mmol) was dissolved in dry tetrahydrofuran (0.10 mL). Methanol (0.10 mL) and sodium methoxide (25% by weight in methanol, 0.04 mL, 0.18 mmol) were added, and the reaction was allowed to warm to room temperature over 2 hours. After this time had elapsed, saturated aqueous ammonium chloride solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% ethyl acetate in pentane, to give a 5:2 mixture of the products as a colourless oil (5.1 mg combined 0.010 mmol, 51%).

R.f: 0.43 (20% diethyl ether in pentane, stains in potassium permanganate dip upon heating).

NMR data for 4.1:

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.30 (t, *J* = 3.0 Hz, 1H, MeCH(R)C**H**(OTBS)R), 4.11 (s, 1H, $(MeO)_2C$**H**R), 3.94 (m, 2H, $TBSOCH_2C$**H**(OH)R, TBSOC**H**H'R), 3.57 (dd, *J* = 9.7, 8.7 Hz, 1H, TBSOCH**H'**R), 3.55 (s, 3H, (**Me**O)$_2$CHR), 3.46 (s, 3H, (**Me**O)$_2$CHR), 3.06 (s, 1H, $(MeO)_2CHC(O$**H**$)R_2$), 2.79 (d, *J* = 3.0 Hz, 1H, $TBSOCH_2CH(O$**H**)R), 2.45 (dd, *J* = 13.9, 8.7 Hz, 1H, MeCH(R)C**H**H'C(OH)R_2), 1.96 (dd, *J* = 8.7, 3.0 Hz, 1H, $TBSOCH_2CH(OH)C$**H**R_2), 1.81 – 1.73 (m, 1H, MeC**H**R_2), 1.47 – 1.37 (m, 1H, MeCH(R)CH**H'**C(OH)R_2), 0.99 (d, *J* = 6.8 Hz, 3H, **Me**CHR_2), 0.92 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.92 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.17 (s, 3H, Me_3CSi**Me**$_2$OR), 0.11 (s, 9H, Me_3CSi**Me$_2$**OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 109.1 ($(MeO)_2$**C**HR), 83.7 ($(MeO)_2CH$**C**$(OH)R_2$), 79.1 (MeCH(R)**C**H(OTBS)R), 69.0 ($TBSOCH_2$**C**H(OH)R), 66.2 (TBSO**C**H_2R), 58.7 ((**Me**O)$_2$CHR), 57.4 ((**Me**O)$_2$CHR), 52.7 ($TBSOCH_2CH(OH)$**C**HR_2), 44.0 (MeCH(R)**C**$H_2C(OH)R_2$), 38.5 (Me**C**HR_2), 26.4 (3C, **Me$_3$**$CSiMe_2OR$), 26.1 (3C, **Me$_3$**$CSiMe_2OR$), 18.6 (Me_3**C**$SiMe_2OR$), 18.4 (Me_3**C**$SiMe_2OR$), 15.5 (**Me**CHR_2), -3.9 (Me_3CSi**Me**$_2$OR), -4.2 (Me_3CSi**Me**$_2$OR), -5.0 (Me_3CSi**Me**$_2$OR), -5.0 (Me_3CSi**Me**$_2$OR).

NMR data for 4.36:

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.53 (s, 1H, O**H**CR), 4.39 (t, *J* = 2.9 Hz, 1H, , MeCH(R)C**H**(OTBS)R), 3.90 – 3.83 (m, 1H, $TBSOCH_2C$**H**(OH)R), 3.62 (dd, *J* = 9.9, 3.3 Hz, 1H, TBSOC**H**H'R), 3.51 (s, 1H, $OHCC(O$**H**$)R_2$), 3.33 (dd, *J* = 9.9, 6.0 Hz, 1H, TBSOCH**H'**R), 2.36 (m, 2H, $TBSOCH_2CH(O$**H**)R, MeCH(R)C**H**H'C(OH)R_2), 2.11 (m, 1H, MeC**H**R_2), 1.99 (dd, *J* = 10.2, 2.9 Hz, 1H, $TBSOCH_2CH(OH)C$**H**R_2), 1.60 (dd, *J* = 14.5, 10.5 Hz, 1H, MeCH(R)CH**H'**C(OH)R_2), 1.06 (d, *J* = 6.8 Hz, 3H, **Me**CHR_2), 0.95 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.94 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.20 (s, 3H, Me_3CSi**Me**$_2$OR), 0.15 (s, 3H, Me_3CSi**Me**$_2$OR), 0.13 (s, 3H, Me_3CSi**Me**$_2$OR), 0.05 (s, 3H, Me_3CSi**Me**$_2$OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 203.1 (OH**C**R), 85.8 (OHC**C**$(OH)R_2$), 78.6 (MeCH(R)**C**H(OTBS)R), 67.5 ($TBSOCH_2$**C**H(OH)R), 65.7 (TBSO**C**H_2R), 55.2 ($TBSOCH_2CH(OH)$**C**HR_2), 46.5 (MeCH(R)**C**$H_2C(OR)R_2$), 39.1 (Me**C**HR_2), 26.3 (3C, **Me$_3$**$CSiMe_2OR$), 26.0 (3C, **Me$_3$**$CSiMe_2OR$), 18.4 (Me_3**C**$SiMe_2OR$), 18.4

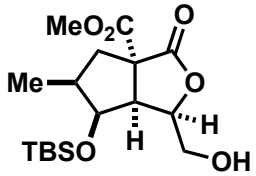
(Me_3**C**$SiMe_2OR$), 15.2 (**Me**CHR_2), -3.7 (Me_3CSi**Me**$_2OR$), -4.0 (Me_3CSi**Me**$_2OR$), -4.1 (Me_3CSi**Me**$_2OR$), -4.5 (Me_3CSi**Me**$_2OR$).

IR: (ν_{max}/cm^{-1} (thin film)) = 3568, 1740.

LRMS (ESI^+): *m/z* = 501.2 = [M(**4.1**)+Na]$^+$; 455.2 = [M(**4.36**)+Na]$^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{23}H_{50}O_6Si_2Na]^+$) = 501.3038; *m/z* found = 501.3038. Predicted *m/z* ($[C_{21}H_{44}O_5Si_2Na]^+$) = 455.2619; *m/z* found = 455.2619.

4.39 - (±)-Methyl (1*R*,3a*R*,5*S*,6*S*,6a*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-(hydroxymethyl)-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



Compound **4.3** (47 mg, 0.10 mmol) was dissolved in methanol (1.00 mL) and cooled to 0 °C. *para*-Toluenesulfonic acid (38 mg, 0.020 mmol) was added, and the resulting colourless solution was stirred at room temperature for 4 hours. After this time had elapsed, saturated aqueous sodium bicarbonate solution (2 mL), water (2 mL), and ethyl acetate (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 40% ethyl acetate in pentane, to give the product as a colourless oil (36 mg, 0.10 mmol, 100% yield).

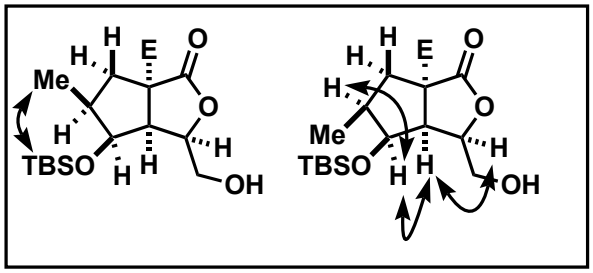
R.f: 24% (40% ethyl acetate in pentane, stains in potassium permanganate dip upon heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.79 (td, *J* = 7.0, 4.2 Hz, 1H, $HOCH_2C$**H**(OR)R), 4.37 (dd, *J* = 7.0, 4.1 Hz, 1H, MeCH(R)C**H**(OTBS)R), 4.17 (dd, *J* = 12.5, 7.0 Hz, 1H, HOC**H**H'R), 3.92 (dd, *J* = 12.5, 4.2 Hz, 1H, HOCH**H'**R), 3.78 (s, 3H, **Me**O_2CR), 3.06 (t, *J* = 7.0 Hz, 1H, MeCH(R)CH(OTBS)C**H**R_2), 2.41 (dd, *J* = 12.8, 7.0 Hz, 1H,

MeCH(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.20 – 2.10 (m, 2H, MeC**H**R_2, MeCH(R)CH**H'**C(R)(CO_2Me)CO_2R), 0.98 (d, *J* = 6.9 Hz, 3H, **Me**CHR_2), 0.93 (s, 9H, Me_3CSi**Me**$_2$OR), 0.15 (s, 3H, Me_3CSi**Me**$_2$OR), 0.12 (s, 3H, Me_3CSi**Me**$_2$OR). Hydroxyl proton resonance not observed.

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.3 (R_2C(CO_2Me)**C**O_2R), 170.7 (R_2C(**C**O_2Me)CO_2R), 81.4 (RCO_2**C**HR_2), 77.9 (MeCH(R)**C**H(OTBS)R), 61.8 (HO**C**H_2R), 60.7 (R_2**C**(CO_2Me)CO_2R), 53.5 (**Me**O_2CR), 52.4 (HOCH_2CH(OR)**C**HR_2), 40.5 (Me**C**HR_2), 36.8 (MeCH(R)**C**H_2C(R)(CO_2Me)CO_2R), 26.1 (3C, **Me$_3$**CSiMe_2OR), 18.5 (Me_3**C**SiMe_2OR), 14.2 (**Me**CHR_2), -3.0 (Me_3CSi**Me**$_2$OR), -4.1 (Me_3CSi**Me**$_2$OR).

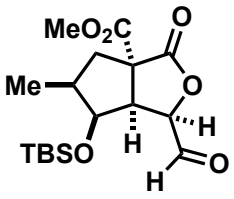
Key NOE correlations involved in stereochemical assignment (E = CO_2Me):



IR: (ν_{max}/cm^{-1} (thin film)) = 3454, 1776, 1737, 1258, 1150, 685.

HRMS (ESI$^+$): Predicted mass ([$C_{17}H_{31}O_6Si$]$^+$, [M+H]$^+$) = 359.1884; mass found = 359.1886.

4.40 - (±)-Methyl (1*R*,3a*R*,5*S*,6*S*,6a*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-formyl-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the modified procedure of Martin[120]: compound **4.39** (18 mg, 0.050 mmol) was dissolved in dry dichloromethane (0.50 mL). Sodium bicarbonate (21 mg, 0.25 mmol) and Dess-Martin periodinane (32 mg, 0.075 mmol) were added, and the white suspension was stirred rapidly at room temperature for 1 hour. After this time had elapsed, the reaction was filtered through a plug of Celite™, saturated aqueous sodium bicarbonate solution (2 mL), water (2 mL), and ethyl acetate (5

mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, to give the product as a colourless oil (18 mg, 0.050 mmol, 100% yield).

R.f: 0.25 (50% ethyl acetate in pentane, stains in potassium permanganate dip upon heating).

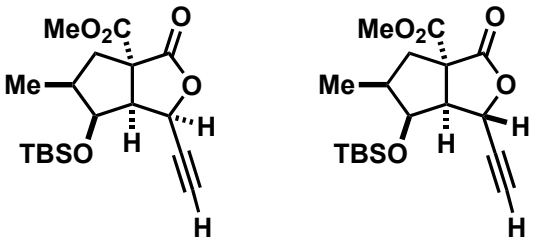
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.98 (d, *J* = 0.9 Hz, 1H, RC**H**O), 4.88 (dd, *J* = 7.3, 0.9 Hz, 1H, OCHC**H**(OR)R), 4.28 (dd, *J* = 4.7, 2.9 Hz, 1H, MeCH(R)C**H**(OTBS)R), 3.79 (s, 3H, **Me**O_2CR), 3.42 (dd, *J* = 7.3, 4.7 Hz, 1H, MeCH(R)CH(OTBS)C**H**R_2), 2.56 – 2.43 (m, 1H, MeCH(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.19 – 2.01 (m, 2H, MeC**H**R_2, MeCH(R)CH**H'**C(R)(CO_2Me)CO_2R), 1.01 (d, *J* = 6.2 Hz, 3H, **Me**CHR_2), 0.90 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.07 (s, 3H, Me_3CSi**Me**$_2$OR), 0.04 (s, 3H, Me_3CSi**Me**$_2$OR).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.6 (R**C**HO), 174.0 ($R_2C(CO_2Me)$**C**O_2R), 170.2 (R_2C(**C**O_2Me)CO_2R), 81.2 (RCO_2**C**HR_2), 76.6 (MeCH(R)**C**H(OTBS)R), 60.0 (R_2**C**(CO_2Me)CO_2R), 57.4 (OCHCH(OR)**C**HR_2), 53.6 (**Me**O_2CR), 40.9 (Me**C**HR_2), 36.9 (MeCH(R)**C**H_2C(R)(CO_2Me)CO_2R), 26.2 (3C, **Me$_3$**$CSiMe_2OR$), 18.5 (Me_3**C**$SiMe_2OR$), 14.6 (**Me**CHR_2), -2.5 (Me_3CSi**Me**$_2$OR), -3.2 (Me_3CSi**Me**$_2$OR).

IR: (ν_{max}/cm^{-1} (thin film)) = 1789, 1736, 1102, 1005, 807, 745.

HRMS (ESI^+): Predicted *m/z* ($[C_{17}H_{28}O_6SiNa]^+$) = 379.1547; *m/z* found = 379.1548.

4.41 - (±)-Methyl (1*R*,3a*R*,5*S*,6*S*,6a*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethynyl-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate; **4.44** - (±)-methyl (1*S*,3a*R*,5*S*,6*S*,6a*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethynyl-5-methyl-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate



According to the modified procedure of Bestmann[152]: Compound **4.40** (3.6 mg, 0.011 mmol) was dissolved in dry methanol (0.10 mL). Ohira-Bestmann reagent **4.45** (4.2 mg, 0.022 mmol) was added, and the resulting yellow solution was stirred at room temperature. Potassium carbonate (4.6 mg, 0.033 mmol) was added, and the reaction was stirred rapidly at room temperature for 30 minutes. After this time had elapsed saturated aqueous ammonium chloride solution (1 mL), water (1 mL), and ethyl acetate (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (2 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 30% diethyl ether in pentane, to give the product as a colourless oil (2.8 mg, 0.0080 mmol, 71% yield 5:1 ratio of **4.41** to **4.44**).

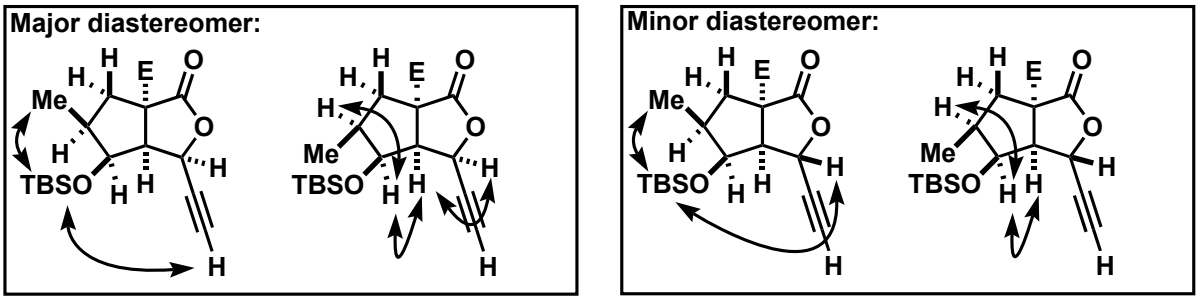
R.f: 0.28 (30% diethyl ether in pentane, stains in potassium permanganate dip upon heating).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.36 (dd, *J* = 5.8, 2.7 Hz, 1H, HC≡CC**H**(OR)R), 4.36 (t, *J* = 3.0 Hz, 1H, MeCH(R)C**H**(OTBS)R), 3.78 (s, 3H, **Me**O_2CR), 3.03 (dd, *J* = 5.8, 3.0 Hz, 1H, MeCH(R)CH(OTBS)C**H**R_2), 2.61 (d, *J* = 2.7 Hz, 1H, **H**C≡CR), 2.47 – 2.43 (m, 1H, MeCH(R)C**H**H'C(R)(CO_2Me)CO_2R), 2.14 – 2.04 (m, 2H, MeC**H**R_2, MeCH(R)CH**H'**C(R)(CO_2Me)CO_2R), 1.04 (d, *J* = 6.4 Hz, 3H, **Me**CHR_2), 0.92 (s, 9H, **Me**$_3$CSiMe_2OR), 0.20 (s, 3H, Me_3CSi**Me**$_2$OR), 0.11 (s, 3H, Me_3CSi**Me**$_2$OR). **Distinguishable minor diastereomer peaks**: 5.16 (t, *J* = 2.1 Hz, 1H, HC≡CC**H**(OR)R), 4.19 (dd, *J* = 5.2, 3.7 Hz, 1H,

MeCH(R)C**H**(OTBS)R), 3.79 (s, 3H, **Me**O_2CR), 3.21 (dd, *J* = 5.2, 2.1 Hz, 1H, MeCH(R)CH(OTBS)C**H**R_2), 2.61 (d, *J* = 2.1 Hz, 1H, **H**C≡CR), 2.22 – 2.18 (m, 1H, MeC**H**R_2), 1.98 (dd, *J* = 13.2, 10.4 Hz, 1H, MeCH(R)C**H**H'C(R)(CO_2Me)CO_2R), 0.98 (d, *J* = 6.9 Hz, 3H, **Me**CHR_2), 0.90 (s, 9H, **Me$_3$**$CSiMe_2OR$), 0.11 (s, 3H, Me_3CSi**Me**$_2$OR), 0.09 (s, 3H, Me_3CSi**Me**$_2$OR). **Peak integral ratio for major:minor = 5:1**.

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.9 (R_2C(CO_2Me)**C**O_2R), 170.7 (R_2C(**C**O_2Me)CO_2R), 78.7 (H**C**≡CR), 78.0 (HC≡**C**R), 77.7 (MeCH(R)**C**H(OTBS)R), 67.5 (HC≡CCH(OR)**C**HR_2), 59.9 (R_2**C**(CO_2Me)CO_2R), 57.5 (HC≡CCH(OR)**C**HR_2), 53.5 (**Me**O_2CR), 42.1 (Me**C**HR_2), 37.4 (MeCH(R)**C**H_2C(R)(CO_2Me)CO_2R), 26.6 (3C, **Me$_3$**$CSiMe_2OR$), 18.7 (Me_3**C**$SiMe_2OR$), 14.8 (**Me**CHR_2), -1.5 (Me_3CSi**Me**$_2$OR), -2.8 (Me_3CSi**Me**$_2$OR). **Distinguishable minor diastereomer peaks**: δ 175.0 (R_2C(CO_2Me)**C**O_2R), 171.4 (R_2C(**C**O_2Me)CO_2R), 80.5 (HC≡**C**R), 76.5 (MeCH(R)**C**H(OTBS)R), 75.6 (H**C**≡CR), 66.6 (HC≡CCH(OR)**C**HR_2), 59.1 (HC≡CCH(OR)**C**HR_2), 59.0 (R_2**C**(CO_2Me)CO_2R), 53.3 (**Me**O_2CR), 41.5 (Me**C**HR_2), 38.5 (MeCH(R)**C**H_2C(R)(CO_2Me)CO_2R), 25.9 (3C, **Me$_3$**$CSiMe_2OR$), 18.1 (Me_3**C**$SiMe_2OR$), 13.8 (**Me**CHR_2), -4.0 (Me_3CSi**Me**$_2$OR), -4.2 (Me_3CSi**Me**$_2$OR).

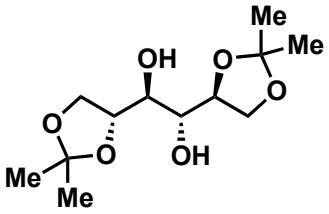
Key NOE correlations involved in stereochemical assignment (E = CO_2Me):



IR: (ν_{max}/cm^{-1} (thin film)) = 3269, 1785, 1740, 1025, 991, 880, 810.

HRMS (ESI$^+$): Predicted *m/z* ($[C_{18}H_{28}O_5SiNa]^+$) = 375.1598; *m/z* found = 375.1604.

5.7 - (1*S*,2*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol



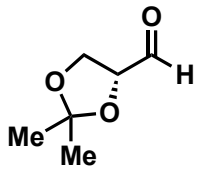
According to the modified procedure of Kroin[156]: anhydrous zinc chloride (40.89 g, 30.00 mmol) was dissolved in dry acetone (500 mL). D-mannitol **5.8** (18.20 g, 10.00 mmol) was added, and the resulting colourless solution was stirred at room temperature for 15 hours. After this time had elapsed, saturated aqueous potassium carbonate solution (40 mL) was added slowly whilst the reaction was stirred rapidly; stirring was continued for 1 hour as a white suspension formed. Ethyl acetate (200 mL) was added, the mixture was filtered to remove solids, and the filter cake was washed with ethyl acetate. Volatile organics were removed under reduced pressure, the crude residue was redissolved in dichloromethane (200 mL) and water (200 mL). The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane (200 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude residue was suspended in hexane (100 mL) and transferred to a freezer for 2 weeks. After this time had elapsed, the mixture was warmed to room temperature, filtered, and washed with hexane to give the product as a white solid (1.97 g, 7.51 mmol, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.22 – 4.15 (m, 2H), 4.12 (dd, *J* = 8.5, 6.3 Hz, 2H), 3.97 (dd, *J* = 8.6, 5.6 Hz, 2H), 3.75 (d, *J* = 6.6 Hz, 2H), 2.61 (d, *J* = 19.2 Hz, 2H), 1.42 (s, 6H), 1.36 (s, 6H).

Melting point: 111-112 °C (120-122 °C lit.[168]).

Other data and spectra matched those reported in the literature.[168]

5.5 - (*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde



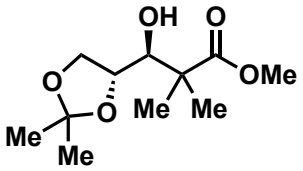
According to the modified procedure of Gálvez[158]**: 5.5** (1.31 g, 5.00 mmol) was dissolved in dichloromethane (50 mL). Saturated aqueous sodium bicarbonate solution (10 mL) was added, and the resulting biphasic mixture was stirred rapidly at room temperature. A solution of sodium periodate (1.60 g, 7.50 mmol) in water (16 mL) was added dropwise over 1 minute, and rapid stirring was continued for 4 hours at room temperature. After this time had elapsed, dichloromethane (100 mL) and water (50 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane (100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were carefully removed under reduced pressure to give the crude product as a solution in dichloromethane. This crude product was used immediately in subsequent procedures without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (d, *J* = 1.9 Hz, 1H, RC**H**O), 4.32 (ddd, *J* = 7.4, 4.7, 1.9 Hz, 1H, OHCC**H**(OR)CH_2OR), 4.10 (dd, *J* = 8.8, 7.4 Hz, 1H, OHCCH(OR)C**H**H'OR), 4.03 (dd, *J* = 8.8, 4.7 Hz, 1H, OHCCH(OR)CH**H'**OR), 1.42 (s, 3H, **Me**Me'C$(OR)_2$), 1.35 (s, 3H, Me**Me'**C$(OR)_2$).

LRMS (ESI^+): *m/z* = 153.0 = $[M+Na]^+$

Other data and spectra matched those reported in the literature.[156]

5.10 - Methyl (*S*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoate



Procedure for activating zinc dust: Zinc dust (50.00 g, 764.8 mmol) was added to an aqueous solution of hydrochloric acid (2% concentrated HCl by weight, 200 mL), and the resulting suspension was stirred rapidly for 1 minute. The mixture was filtered, and the metallic residue was washed twice with distilled water (200 mL), twice with ethanol (200 mL), and once with dry diethyl ether (200 mL). The resulting metallic chunks were then dried under a stream of nitrogen, dried under high vacuum, and then powdered with a pestle in a mortar. The resulting grey powder was then stored in a stoppered flask under an inert atmosphere.

Procedure for preparing Reformatsky reagent 5.9: Activated zinc dust (6.54 g, 100 mmol) was suspended in dry, degassed tetrahydrofuran (80 mL), and stirred. Methyl α-bromoisobutyrate **5.6** (3.88 mL, 5.43 g, 30.0 mmol) was added dropwise over 2 minutes, and the mixture was sonicated for 3 minutes. After this time had elapsed, consumption of methyl α-bromoisobutyrate **5.6** was confirmed by TLC analysis and the mixture was cooled to -78 °C for use in the procedure below.

Compound **5.5** (crude from the procedure above, assumed 10.00 mmol) was dissolved in tetrahydrofuran (20 mL). The resulting colourless solution was added to the Reformatsky reagent **5.9** at -78 °C as prepared above, and the reaction was stirred for 2 hours. After this time had elapsed, the reaction was allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (50 mL) was added, the mixture was stirred for a further 10 minutes, and the mixture was filtered. Water (50 mL), and ethyl acetate (50 mL) were added to the filtrate, the organic phase was separated, and the aqueous layer was extracted three times with ethyl acetate (100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column

chromatography, eluting with 10-30% ethyl acetate in pentane, to give the product as a colourless oil (1.06 g, 4.61 mmol, 45% yield).

R.f: 0.35 (30% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.09 – 4.03 (m, 2H, $MeO_2CCMe_2CH(OH)C$**H**$(OR)CH_2OR$, $MeO_2CCMe_2CH(OH)CH(OR)C$**H**H'OR), 3.98 – 3.91 (m, 1H, $MeO_2CCMe_2CH(OH)CH(OR)CH$**H'**OR), 3.83 (d, *J* = 5.4 Hz, 1H, MeO_2CCMe_2C**H**$(OH)CH(OR)CH_2OR$), 3.70 (s, 3H, **Me**O_2CR), 1.38 (s, 3H, **Me**Me'$C(OR)_2$), 1.33 (s, 3H, Me**Me'**$C(OR)_2$), 1.25 (s, 6H, MeO_2CC**Me**Me'R, MeO_2CCMe**Me'**R). Hydroxyl resonance not observed

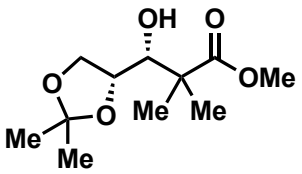
^{13}C NMR (126 MHz, $CDCl_3$): δ 177.7 (MeO_2**C**R), 109.1 (Me_2**C**$(OR)_2$), 76.9 ($MeO_2CCMe_2CH(OH)$**C**$H(OR)CH_2OR$), 76.2 (MeO_2CCMe_2**C**$H(OH)CH(OR)CH_2OR$), 67.0 ($MeO_2CCMe_2CH(OH)CH(OR)$**C**H_2OR), 52.2 (**Me**O_2CR), 46.2 (MeO_2C**C**Me_2R), 26.6 (**Me**$_2C(OR)_2$), 25.5 (**Me**$_2C(OR)_2$), 21.8 (MeO_2CC**Me**$_2R$), 21.5 (MeO_2CC**Me**$_2R$).

IR: (ν_{max}/cm^{-1} (thin film)) = 3479, 1721, 1470, 1213, 1057.

LRMS (ESI^+): *m/z* = 255.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{11}H_{20}O_5Na]^+$) = 255.1203; *m/z* found = 255.1203.

5.15 - Methyl (*R*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoate



Compound **5.15** was isolated as a product from the above procedure to form **5.10** from **5.5**, in a yield of (101 mg, 0.396 mmol, 5% yield) contaminated by approximately 25% of **5.10**.

Partial data for **5.15**:

R.f: 0.31 (30% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.18 (m, 1H, $MeO_2CCMe_2CH(OH)C$**H**$(OR)CH_2OR$), 4.02 (dd, *J* = 8.0, 6.6 Hz, 1H, $MeO_2CCMe_2CH(OH)CH(OR)C$**H**H'OR), 3.86 (t, *J* = 7.8 Hz, 1H, $MeO_2CCMe_2CH(OH)CH(OR)CH$**H'**OR),

3.68 (s, 3H, **Me**O_2CR), 3.52 (dd, *J* = 9.4, 2.2 Hz, 1H, MeO_2CCMe_2C**H**(OH)CH(OR)CH_2OR), 2.99 (d, *J* = 9.4 Hz, 1H, MeO_2CCMe_2CH(O**H**)CH(OR)CH_2OR), 1.39 (s, 3H, **Me**Me'C$(OR)_2$), 1.34 (s, 3H, Me**Me'**C$(OR)_2$), 1.24 (s, 3H, MeO_2CC**Me**Me'R), 1.24 (s, 3H, MeO_2CCMe**Me'**R).

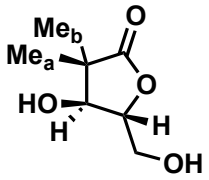
^{13}C NMR (126 MHz, $CDCl_3$): δ 177.2 (MeO_2**C**R), 109.7 (Me_2**C**$(OR)_2$), 75.3 (MeO_2CCMe_2**C**H(OH)CH(OR)CH_2OR), 74.7 (MeO_2CCMe_2CH(OH)**C**H(OR)CH_2OR), 67.2 (MeO_2CCMe_2CH(OH)CH(OR)**C**H_2OR), 52.1 (**Me**O_2CR), 46.3 (MeO_2**C**CMe_2R), 26.3 (**Me**$_2$C$(OR)_2$), 25.7 (**Me**$_2$C$(OR)_2$), 22.5 (MeO_2CC**Me**$_2$R), 21.9 (MeO_2CC**Me**$_2$R).

IR: (ν_{max}/cm^{-1} (thin film)) = 3471, 1723.

LRMS (ESI$^+$): *m/z* = 255.2 = $[M+Na]^+$

HRMS (ESI$^+$): Predicted *m/z* ($[C_{11}H_{20}O_5Na]^+$) = 255.1203; *m/z* found = 255.1203.

5.16 - (4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)-3,3-dimethyldihydrofuran-2(3*H*)-one



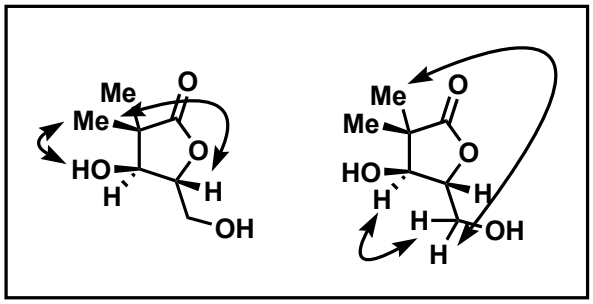
Compound **5.10** (232 mg, 1.000 mmol) was dissolved in tetrahydrofuran (3.50 mL). Water (6.50 mL) was added, and the resulting mixture was stirred and cooled to 0 °C. Concentrated hydrochloric acid (1.00 mL) was added, and the reaction was allowed to warm to room temperature over 2 hours. After this time had elapsed ethyl acetate (20 mL) was added, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were carefully removed under reduced pressure to give the product as a white solid (160 g, 1.00 mmol, 100% yield).

R.f: 0.40 (ethyl acetate, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, acetone): δ 4.77 (br s, 1H, $HOCH_2CH(OR)CH(O\mathbf{H})R$), 4.15 – 4.12 (m, 2H, $HOCH_2CH(OR)C\mathbf{H}(OH)R$, $HOCH_2C\mathbf{H}(OR)CH(OH)R$), 4.11 (t, *J* = 6.0 Hz, 1H, $\mathbf{H}OCH_2R$), 3.94 (dd, *J* = 12.6, 6.0 Hz, 1H, HOC**H**H'R), 3.71 (m, 1H, HOCH**H'**R), 1.18 (s, 3H, $HOCH_2CH(OR)CH(OH)CMe_a\mathbf{Me_b}CO_2R$), 1.14 (s, 3H, $HOCH_2CH(OR)CH(OH)C\mathbf{Me_a}Me_bCO_2R$).

^{13}C NMR (126 MHz, acetone): δ 180.3 ($HOCH_2CH(OR)CH(OH)CMe_2\mathbf{C}O_2R$), 83.3 ($HOCH_2CH(OR)\mathbf{C}H(OH)R$), 75.0 ($HOCH_2\mathbf{C}H(OR)CH(OH)R$), 61.3 ($HO\mathbf{C}H_2CH(OR)CH(OH)R$), 44.2 ($HOCH_2CH(OR)CH(OH)\mathbf{C}Me_2CO_2R$), 23.0 ($HOCH_2CH(OR)CH(OH)CMe_a\mathbf{Me_b}CO_2R$), 18.5 ($HOCH_2CH(OR)CH(OH)C\mathbf{Me_a}Me_bCO_2R$).

Key NOE correlations involved in stereochemical assignment:



IR: (ν_{max}/cm^{-1} (thin film)) = 3416, 1755, 1101, 1037.

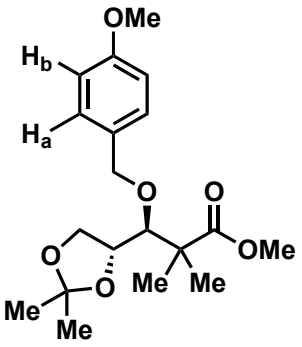
LRMS (ESI$^+$): *m/z* = 183.0 = $[M+Na]^+$

HRMS (ESI$^+$): Predicted *m/z* ($[C_7H_{12}O_4Na]^+$) = 183.0628; *m/z* found = 183.0629.

Specific rotation: $[\alpha]_D^{25}$ 54.0 (c = 0.1 in $CHCl_3$).

Melting point: 108-109 °C.

5.21 - Methyl (*S*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-((4-methoxybenzyl)oxy)-2,2-dimethylpropanoate



Procedure for preparing 4-methoxybenzyl bromide: *according to the modified procedure of Burke[169]:* hydrogen bromide (48% in water, 1.70 mL) was added to diethyl ether (2.50 mL) and a solution of 4-methoxybenzyl alcohol (1.38 g, 10.0 mmol) in diethyl ether (2.50 mL) was added dropwise over 3 minutes. The resulting mixture was stirred rapidly at room temperature for 1 hour. After this time had elapsed, saturated aqueous sodium bicarbonate solution (20 mL) was added dropwise over 5 minutes. Water (20 mL), and diethyl ether (40 mL) were added, the organic layer was separated, and the aqueous layer was extracted three times with diethyl ether (50 mL). The combined organic extracts were washed with water, washed with saturated aqueous sodium bromide solution, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were carefully removed under reduced pressure to give the crude product as a colourless oil (1.97 g, 9.82 mmol, 98% yield). The crude product was used immediately in subsequent procedures without further purification.

*According to the modified procedure of Burke[169]***:** compound **5.10** (581 mg, 2.50 mmol) was dissolved in tetrahydrofuran (25 mL). Triethylamine (1.04 mL, 7.50 mmol) and freshly prepared 4-methoxybenzyl bromide (0.71 mL, 5.00 mmol) were added, and the resulting colourless solution was cooled to -78 °C. A solution of potassium hexamethyldisilazide (0.5 M in toluene, 7.50 mL, 3.75 mmol) was added dropwise over 30 seconds, and the reaction was stirred for 15 minutes. After this time had elapsed, the reaction was allowed to warm to room temperature and stirred for a further 30 minutes. After this time had elapsed, saturated aqueous sodium bicarbonate solution (15 mL) was added and the mixture was stirred rapidly for a further 30 minutes. Diethyl ether (50 mL) was added, the organic

layer was separated, and the aqueous layer was extracted three times with diethyl ether (50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 5-10% diethyl ether in pentane, to give the product as a colourless oil (600 mg, 1.71 mmol, 68% yield).

R.f: 0.31 (10% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.6 Hz, 2H, **H_a-Ar**), 6.87 (d, *J* = 8.6 Hz, 2H, **H_b-Ar**), 4.70 (d, *J* = 10.8 Hz, 1H, Ar-C**H**H'OR), 4.55 (d, *J* = 10.8 Hz, 1H, Ar-CH**H'**OR), 4.13 (td, *J* = 6.7, 4.3 Hz, 1H, $MeO_2CCMe_2CH(OR)C$**H**$(OR)CH_2OR$), 4.04 – 3.90 (m, 3H, MeO_2CCMe_2C**H**$(OR)CH(OR)CH_2OR$, $MeO_2CCMe_2CH(OR)CH(OR)C$**H**H'OR, $MeO_2CCMe_2CH(OR)CH(OR)CH$**H'**OR), 3.80 (s, 3H, **Me**OAr), 3.65 (s, 3H, **Me**O_2CR), 1.41 (s, 3H, **Me**Me'$C(OR)_2$), 1.32 (s, 3H, Me**Me'**$C(OR)_2$), 1.22 (s, 3H, MeO_2CC**Me**Me'R), 1.17 (s, 3H, MeO_2CCMe**Me'**R).

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.7 (MeO_2**C**R), 159.1 (MeO-**C_{Ar}**), 130.6 ($ROCH_2$-**C_{Ar}**), 129.2 (2C, H_a-**C_{Ar}**), 113.7 (2C, H_b-**C_{Ar}**), 108.2 (Me_2**C**$(OR)_2$), 83.4 (MeO_2CCMe_2**C**H(OR)CH(OR)CH_2OR), 76.5 ($MeO_2CCMe_2CH(OR)$**C**H$(OR)CH_2OR$), 75.1 (RO**C**H_2Ar), 66.0 ($MeO_2CCMe_2CH(OR)CH(OR)$**C**H_2OR), 55.3 (**Me**O-Ar), 51.8 (**Me**O_2CR), 46.5 (MeO_2C**C**Me_2R), 26.3 (**Me**$_2C(OR)_2$), 24.8 (**Me**$_2C(OR)_2$), 22.6 (MeO_2CC**Me**$_2R$), 20.3 (MeO_2CC**Me**$_2R$).

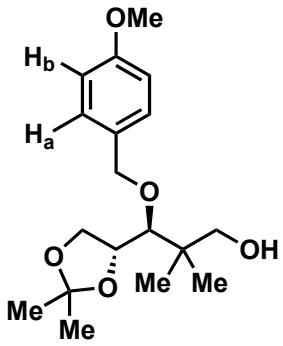
IR: (ν_{max}/cm^{-1} (thin film)) = 1746, 1277, 1256.

LRMS (ESI^+): *m/z* = 375.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{19}H_{28}O_6Na]^+$) = 375.1778; *m/z* found = 375.1778.

Specific rotation: $[\alpha]_D^{25}$ 8.5 (c = 0.1 in $CHCl_3$).

5.22 - (*S*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-((4-methoxybenzyl)oxy)-2,2-dimethylpropan-1-ol



Compound **5.21** (486 mg, 1.50 mmol) was dissolved in dry dichloromethane (15 mL) under nitrogen, and the resulting solution was cooled to -78 °C. A solution of diisobutylaluminium hydride (1.0 M in hexane, 5.00 mL, 5.00 mmol) was added dropwise over 1 minute. The solution was allowed to warm to 0 °C over 1 hour. After this time had elapsed, the solution was allowed to warm to room temperature, and saturated aqueous sodium potassium tartrate solution (5 mL), saturated aqueous ammonium chloride solution (1 mL), and ethyl acetate (10 mL) were added, and the mixture was stirred rapidly for 12 hours. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 30% ethyl acetate in pentane, to give the product as a colourless oil (415 mg, 1.28 mmol, 85% yield).

R.f: 0.15 (30% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.6 Hz, 2H, **H_a**-Ar), 6.88 (d, *J* = 8.6 Hz, 2H, **H_b**-Ar), 4.79 (d, *J* = 10.7 Hz, 1H, Ar-C**H**H'OR), 4.57 (d, *J* = 10.7 Hz, 1H, Ar-CH**H'**OR), 4.31 (td, *J* = 7.5, 3.4 Hz, 1H, $HOCH_2CMe_2CH(OR)C$**H**$(OR)CH_2OR$), 4.06 (t, *J* = 7.5 Hz, 1H, $HOCH_2CMe_2CH(OR)CH(OR)C$**H**H'OR), 4.02 (t, *J* = 7.5 Hz, 1H, $HOCH_2CMe_2CH(OR)CH(OR)CH$**H'**OR), 3.80 (s, 3H, **Me**OAr), 3.64 (d, *J* = 3.4 Hz, 1H, $HOCH_2CMe_2C$**H**$(OR)CH(OR)CH_2OR$), 3.37 (m, 2H, HOC**H**H'R, HOCH**H'**R), 1.48 (s, 3H, **Me**Me'$C(OR)_2$), 1.37 (s, 3H, Me**Me'**$C(OR)_2$), 0.96 (s, 3H, $HOCH_2C$**Me**Me'R), 0.89 (s, 3H, $HOCH_2CMe$**Me'**R). Hydroxyl proton resonance not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.5 (MeO-**C_{Ar}**), 130.5 ($ROCH_2$-**C_{Ar}**), 129.7 (2C, H_a-**C_{Ar}**), 114.0 (2C, H_b-**C_{Ar}**), 108.2 (Me_2**C**$(OR)_2$), 84.8 ($HOCH_2CMe_2$**C**H(OR)CH(OR)CH_2OR), 76.8 ($HOCH_2CMe_2CH(OR)$**C**H(OR)CH_2OR), 75.3 (RO**C**H_2Ar), 71.1 (HO**C**H_2R), 65.6 ($HOCH_2CMe_2CH(OR)CH(OR)$**C**H_2OR), 55.4 (**Me**O-Ar), 39.2 ($HOCH_2$**C**Me_2R), 26.6 (**Me**$_2$C$(OR)_2$), 25.0 (**Me**$_2$C$(OR)_2$), 22.4 ($HOCH_2C$**Me**$_2R$), 21.4 ($HOCH_2C$**Me**$_2R$).

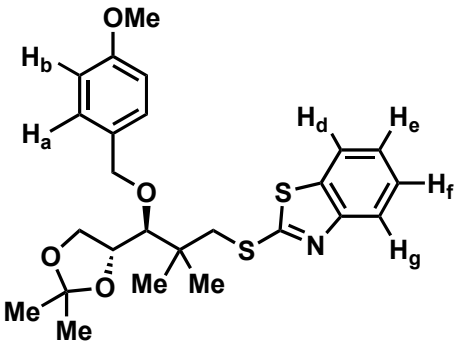
IR: (ν_{max}/cm^{-1} (thin film)) = 3446, 2982, 1515, 1059, 1037.

LRMS (ESI^+): *m/z* = 347.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{18}H_{28}O_5Na]^+$) = 347.1829; *m/z* found = 347.1829.

Specific rotation: $[\alpha]_D^{25}$ 5.5 (c = 0.1 in $CHCl_3$).

5.23 - 2-(((*S*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-((4-methoxybenzyl)oxy)-2,2-dimethylpropyl)thio)benzo[d]thiazole



Compound **5.22** (374 mg, 1.15 mmol) was dissolved in dry tetrahydrofuran (11.5 mL) under nitrogen. Triphenylphosphine (604 mg, 2.30 mmol) was added, and the resulting solution was stirred and cooled to 0 °C. Diisopropylazodicarboxylate (0.407 mL, 2.070 mmol) was added, and the reaction was stirred for 15 minutes. 2-Mercaptobenzothiazole **5.25** (423 mg, 2.53 mmol) was added, and the resulting solution was heated to 60 °C and stirred for 3 hours. After this time had elapsed, the solution was allowed to cool to room temperature, and ethyl acetate (10 mL) and water (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with aqueous hydrogen peroxide (15% hydrogen peroxide by weight), washed with saturated aqueous sodium thiosulfate solution, washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced

pressure, and the crude product was purified *via* flash column chromatography, eluting with 10% diethyl ether in pentane, to give the product as a colourless oil (458 mg, 0.966 mmol, 84% yield).

R.f: 0.27 (20% diethyl ether in pentane, stains in potassium permanganate dip without heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (br d, *J* = 8.1 Hz, 1H, **H_g**-Ar), 7.73 (br d, *J* = 7.9 Hz, 1H, **H_d**-Ar), 7.40 (ddd, *J* = 8.1, 7.4, 1.2 Hz, 1H, **H_f**-Ar), 7.29 – 7.27 (m, 3H, **H_e**-Ar, **H_a**-Ar), 6.88 – 6.75 (m, 2H, **H_b**-Ar), 4.83 (d, *J* = 10.6 Hz, 1H, Ar-C**H**H'OR), 4.55 (d, *J* = 10.6 Hz, 1H, Ar-CH**H'**OR), 4.36 (ddd, *J* = 7.8, 6.6, 2.8 Hz, 1H, $ArSCH_2CMe_2CH(OR)C$**H**$(OR)CH_2OR$), 4.07 (t, *J* = 7.8 Hz, 1H, $ArSCH_2CMe_2CH(OR)CH(OR)C$**H**H'OR), 4.02 (dd, *J* = 7.8, 6.6 Hz, 1H, $ArSCH_2CMe_2CH(OR)CH(OR)C$**H**H'OR), 3.77 (s, 3H, **Me**OAr), 3.75 (d, *J* = 2.8 Hz, 1H, $ArSCH_2CMe_2C$**H**$(OR)CH(OR)CH_2OR$), 3.59 (d, *J* = 12.6 Hz, 1H, ArSC**H**H'R), 3.47 (d, *J* = 12.6 Hz, 1H, ArSCH**H'**R), 1.47 (s, 3H, **Me**Me'$C(OR)_2$), 1.36 (s, 3H, Me**Me'**$C(OR)_2$), 1.11 (s, 3H, $ArSCH_2C$**Me**Me'R), 1.04 (s, 3H, $ArSCH_2CMe$**Me'**R).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.0 (RCH_2S-**C_{Ar}**), 159.3 (MeO-**C_{Ar}**), 153.0 ($(RS)_2C$=N-**C_{Ar}**), 135.3 (RSC(=NR)S-**C_{Ar}**), 130.9 ($ROCH_2$-**C_{Ar}**), 129.6 (2C, H_a-**C_{Ar}**), 126.2 (H_f-**C_{Ar}**), 124.3 (H_e-**C_{Ar}**), 121.5 (H_g-**C_{Ar}**), 121.1 (H_d-**C_{Ar}**), 113.8 (2C, H_b-**C_{Ar}**), 108.1 (Me_2**C**$(OR)_2$), 83.5 ($ArSCH_2CMe_2$**C**$H(OR)CH(OR)CH_2OR$), 76.8 ($ArSCH_2CMe_2CH(OR)$**C**$H(OR)CH_2OR$), 75.3 (RO**C**H_2Ar), 65.4 ($ArSCH_2CMe_2CH(OR)CH(OR)$**C**H_2OR), 55.4 (**Me**O-Ar), 43.7 (ArS**C**H_2R), 39.4 ($ArSCH_2$**C**Me_2R), 26.6 (**Me**$_2$C$(OR)_2$), 25.1 (**Me**$_2$C$(OR)_2$), 24.2 ($ArSCH_2C$**Me**$_2$R), 23.5 ($ArSCH_2C$**Me**$_2$R).

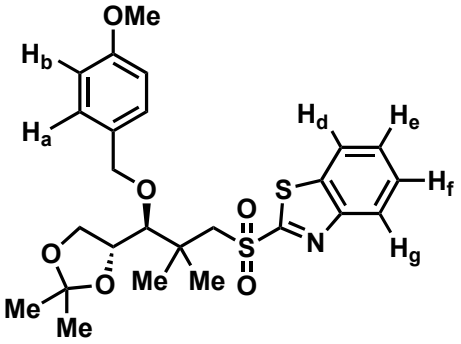
IR: (ν_{max}/cm^{-1} (thin film)) = 2984, 1612.

LRMS (ESI^+): *m/z* = 496.3 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{25}H_{32}O_4NS_2]^+$, $[M+H]^+$) = 474.1767; *m/z* found = 474.1766.

Specific rotation: $[\alpha]_D^{25}$ 2.0 (c = 0.1 in $CHCl_3$).

5.24 - 2-(((*S*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-((4-methoxybenzyl)oxy)-2,2-dimethylpropyl)sulfonyl)benzo[d]thiazole



Compound **5.23** (426 mg, 0.900 mmol) was dissolved in dry tetrahydrofuran (0.90 mL). Ethanol (0.90 mL) was added, and the resulting solution was stirred and cooled to 0 °C. Ammonium molybdate tetrahydrate (2.68 g, 2.30 mmol) was dissolved in an aqueous solution of hydrogen peroxide (15% hydrogen peroxide by weight, 0.90 mL), the resulting yellow solution was added dropwise to the solution of compound **5.23** over 5 minutes, and the reaction was stirred for 12 hours. After this time had elapsed, the solution was allowed to warm to room temperature, and ethyl acetate (20 mL) and water (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with saturated aqueous sodium thiosulfate solution, washed with saturated aqueous sodium bicarbonate solution, washed with brine, dried over anhydrous magnesium sulfate, and filtered. Volatile organics were removed under reduced pressure, and the crude product was purified *via* flash column chromatography, eluting with 20% ethyl acetate in pentane, to give the product as a colourless oil (360 mg, 0.711 mmol, 79% yield).

R.f: 0.30 (20% ethyl acetate in pentane, stains in potassium permanganate dip with heating).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (br d, *J* = 8.4 Hz, 1H, **H_g**-Ar), 8.02 (br d, *J* = 8.0 Hz, 1H, **H_d**-Ar), 7.64 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H, **H_f**-Ar), 7.59 (ddd, *J* = 8.0, 7.2, 1.3 Hz, 1H, **H_e**-Ar), 7.29 – 7.26 (m, 2H, **H_a**-Ar), 6.84 – 6.79 (m, 2H, **H_b**-Ar), 4.79 (d, *J* = 10.7 Hz, 1H, Ar-C**H**H'OR), 4.64 (d, *J* = 10.7 Hz, 1H, Ar-CH**H'**OR), 4.30 (td, *J* = 7.0, 3.7 Hz, 1H, $ArSO_2CH_2CMe_2CH(OR)C$**H**$(OR)CH_2OR$), 3.99 (m, 2H, $ArSO_2CH_2CMe_2CH(OR)CH(OR)C$**H**H'OR, $ArSO_2CH_2CMe_2CH(OR)CH(OR)CH$**H'**OR), 3.95 (d, *J* = 3.7 Hz, 1H,

$ArSO_2CH_2CMe_2C$**H**$(OR)CH(OR)CH_2OR$), 3.79 (d, *J* = 14.3 Hz, 1H, $ArSO_2C$**H**H'R), 3.76 (s, 3H, **Me**OAr), 3.62 (d, *J* = 14.3 Hz, 1H, $ArSO_2CH$**H'**R), 1.47 (s, 3H, **Me**Me'$C(OR)_2$), 1.35 (s, 3H, Me**Me'**$C(OR)_2$), 1.34 (s, 3H, $ArSO_2CH_2C$**Me**Me'R), 1.18 (s, 3H, $ArSO_2CH_2CMe$**Me'**R).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.1 (RCH_2SO_2-**C_{Ar}**), 159.4 (MeO-**C_{Ar}**), 152.7 ($RSO_2C(SR)$=N-**C_{Ar}**), 136.9 ($RSO_2C(=NR)S$-**C_{Ar}**), 130.6 ($ROCH_2$-**C_{Ar}**), 129.8 (2C, H_a-**C_{Ar}**), 128.1 (H_f-**C_{Ar}**), 127.7 (H_e-**C_{Ar}**), 125.5 (H_g-**C_{Ar}**), 122.5 (H_d-**C_{Ar}**), 113.9 (2C, H_b-**C_{Ar}**), 108.5 (Me_2**C**$(OR)_2$), 83.6 ($ArSO_2CH_2CMe_2$**C**H(OR)CH(OR)CH_2OR), 76.3 ($ArSO_2CH_2CMe_2CH(OR)$**C**H(OR)CH_2OR), 75.1 (RO**C**H_2Ar), 65.9 ($ArSO_2CH_2CMe_2CH(OR)CH(OR)$**C**$H_2OR$), 61.9 ($ArSO_2$**C**$H_2CMe_2CH(OR)CH(OR)CH_2OR$), 55.4 (**Me**O-Ar), 39.8 ($ArSO_2CH_2$**C**Me_2R), 26.6 (**Me**$_2C(OR)_2$), 25.1 (**Me**$_2C(OR)_2$), 24.3 ($ArSO_2CH_2C$**Me**$_2R$), 24.1 ($ArSO_2CH_2C$**Me**$_2R$).

IR: (ν_{max}/cm^{-1} (thin film)) = 1612, 1514, 1472, 1380, 1248, 1149.

LRMS (ESI^+): *m/z* = 528.2 = $[M+Na]^+$

HRMS (ESI^+): Predicted *m/z* ($[C_{25}H_{31}O_6NS_2Na]^+$) = 528.1485; *m/z* found = 528.1483.

Specific rotation: $[\alpha]_D^{25}$ 14.0 (c = 0.1 in $CHCl_3$).

Bibliography

1. Nicolaou, K. C., The art and science of constructing the molecules of nature. *Proceedings of the National Academy of Sciences* **2004,** *101* (33), 11928-11928.

2. Wöhler, F., Ueber künstliche Bildung des Harnstoffs. *Annalen der Physik und Chemie* **1828,** *88* (2), 253-256.

3. Kolbe, H., Beiträge zur Kenntniss der gepaarten Verbindungen. *Annalen der Chemie und Pharmacie* **1845,** *54* (2), 145-188.

4. Kinne-Saffran, E.; Kinne, R. K. H., Vitalism and Synthesis of Urea. *American Journal of Nephrology* **1999,** *19* (2), 290-294.

5. Mahdi, J. G.; Mahdi, A. J.; Mahdi, A. J.; Bowen, I. D., The historical analysis of aspirin discovery, its relation to the willow tree and antiproliferative and anticancer potential. *Cell Proliferation* **2006,** *39* (2), 147-155.

6. Robinson, R., LXIII.—A synthesis of tropinone. *J. Chem. Soc., Trans.* **1917,** *111* (0), 762-768.

7. Woodward, R. B.; Doering, W. E., THE TOTAL SYNTHESIS OF QUININE1. *Journal of the American Chemical Society* **1944,** *66* (5), 849-849.

8. Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S., First total synthesis of taxol. 1. Functionalization of the B ring. *Journal of the American Chemical Society* **1994,** *116* (4), 1597-1598.

9. Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S., First total synthesis of taxol. 2. Completion of the C and D rings. *Journal of the American Chemical Society* **1994,** *116* (4), 1599-1600.

10. Yoo, H.-D.; Nam, S.-J.; Chin, Y.-W.; Kim, M.-S., Misassigned natural products and their revised structures. *Archives of Pharmacal Research* **2016,** *39* (2), 143-153.

11. Hetzler, B. E.; Trauner, D.; Lawrence, A. L., Natural product anticipation through synthesis. *Nature Reviews Chemistry* **2022,** *6* (3), 170-181.

12. Sam Chan, H. S.; Nguyen, Q. N. N.; Paton, R. S.; Burton, J. W., Synthesis, Characterization, and Reactivity of Complex Tricyclic Oxonium Ions, Proposed Intermediates in Natural Product Biosynthesis. *Journal of the American Chemical Society* **2019,** *141* (40), 15951-15962.

13. Lietava, J., Medicinal plants in a Middle Paleolithic grave Shanidar IV? *Journal of Ethnopharmacology* **1992,** *35* (3), 263-266.

14. Wongso, H., Natural product-based Radiopharmaceuticals:Focus on curcumin and its analogs, flavonoids, and marine peptides. *Journal of Pharmaceutical Analysis* **2021** (in press).

15. Cragg, G. M.; Newman, D. J.; Snader, K. M., Natural Products in Drug Discovery and Development. *Journal of Natural Products* **1997,** *60* (1), 52-60.

16. Newman, D. J.; Cragg, G. M.; Snader, K. M., Natural Products as Sources of New Drugs over the Period 1981−2002. *Journal of Natural Products* **2003,** *66* (7), 1022-1037.

17. Newman, D. J.; Cragg, G. M., Natural Products as Sources of New Drugs over the Last 25 Years. *Journal of Natural Products* **2007,** *70* (3), 461-477.

18. Newman, D. J.; Cragg, G. M., Natural Products As Sources of New Drugs over the 30 Years from 1981 to 2010. *Journal of Natural Products* **2012,** *75* (3), 311-335.

19. Newman, D. J.; Cragg, G. M., Natural Products as Sources of New Drugs from 1981 to 2014. *Journal of Natural Products* **2016,** *79* (3), 629-661.

20. Newman, D. J.; Cragg, G. M., Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *Journal of Natural Products* **2020,** *83* (3), 770-803.

21. Baran, P. S., Natural Product Total Synthesis: As Exciting as Ever and Here To Stay. *Journal of the American Chemical Society* **2018,** *140* (14), 4751-4755.

22. Rinner, U., Progress in the Preparation of Jatrophane Diterpenes. *European Journal of Organic Chemistry* **2015,** *2015* (15), 3197-3219.

23. Vasas, A.; Hohmann, J., Euphorbia Diterpenes: Isolation, Structure, Biological Activity, and Synthesis (2008–2012). *Chemical Reviews* **2014,** *114* (17), 8579-8612.

24. Adolf, W.; Hecker, E., Diterpenoid Irritants and Cocarcinogens in Euphorbiaceae and Thymelaeaceae: Structural Relationships in View of their Biogenesis. *Israel Journal of Chemistry* **1977,** *16* (1), 75-83.

25. Fattahian, M.; Ghanadian, M.; Ali, Z.; Khan, I. A., Jatrophane and rearranged jatrophane-type diterpenes: biogenesis, structure, isolation, biological activity and SARs (1984–2019). *Phytochemistry Reviews* **2020,** *19* (2), 265-336.

26. Kemboi, D.; Siwe-Noundou, X.; Krause, R. W. M.; Langat, M. K.; Tembu, V. J., Euphorbia Diterpenes: An Update of Isolation, Structure, Pharmacological Activities and Structure–Activity Relationship. *Molecules* **2021,** *26* (16), 5055.

27. Corea, G.; Fattorusso, E.; Lanzotti, V.; Taglialatela-Scafati, O.; Appendino, G.; Ballero, M.; Simon, P.-N.; Dumontet, C.; Di Pietro, A., Jatrophane Diterpenes as P-Glycoprotein Inhibitors. First Insights of Structure−Activity Relationships and Discovery of a New, Powerful Lead. *Journal of Medicinal Chemistry* **2003,** *46* (15), 3395-3402.

28. Corea, G.; Fattorusso, E.; Lanzotti, V.; Motti, R.; Simon, P.-N.; Dumontet, C.; Di Pietro, A., Jatrophane Diterpenes as Modulators of Multidrug Resistance. Advances of Structure−Activity

Relationships and Discovery of the Potent Lead Pepluanin A. *Journal of Medicinal Chemistry* **2004,** *47* (4), 988-992.

29. Corea, G.; Di Pietro, A.; Dumontet, C.; Fattorusso, E.; Lanzotti, V., Jatrophane diterpenes from Euphorbia spp. as modulators of multidrug resistance in cancer therapy. *Phytochemistry Reviews* **2009,** *8* (2), 431-447.

30. Appendino, G.; Jakupovic, S.; Tron, G. C.; Jakupovic, J.; Milon, V.; Ballero, M., Macrocyclic Diterpenoids fromEuphorbiasemiperfoliata. *Journal of Natural Products* **1998,** *61* (6), 749-756.

31. Jakupovic, J.; Morgenstern, T.; Marco, J. A.; Berendsohn, W., Diterpenes from Euphorbia paralias. *Phytochemistry* **1998,** *47* (8), 1611-1619.

32. Ferreira, R. J.; Dos Santos, D. J. V. A.; Ferreira, M.-J. U.; Guedes, R. C., Toward a Better Pharmacophore Description of P-Glycoprotein Modulators, Based on Macrocyclic Diterpenes from Euphorbia Species. *Journal of Chemical Information and Modeling* **2011,** *51* (6), 1315-1324.

33. Nielsen, D.; Skovsgaard, T., P-glycoprotein as multidrug transporter: a critical review of current multidrug resistant cell lines. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1992,** *1139* (3), 169-183.

34. Xiang, Z.-N.; Tong, Q.-L.; Su, J.-C.; Hu, Z.-F.; Zhao, N.; Xia, R.-F.; Wu, J.-L.; Chen, C.; Chen, J.-C.; Wan, L.-S., Diterpenoids with Rearranged 9(10→11)-abeo-10,12-Cyclojatrophane Skeleton and the First (15S)-Jatrophane from Euphorbia helioscopia: Structural Elucidation, Biomimetic Conversion, and Their Immunosuppressive Effects. *Organic Letters* **2021**.

35. Smith, A. B.; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W., A strategy for the total synthesis of jatrophone: synthesis of normethyljatrophone. *Journal of the American Chemical Society* **1981,** *103* (1), 219-222.

36. Smith, A. B.; Lupo, A. T.; Ohba, M.; Chen, K., Total synthesis of (+)-hydroxyjatrophone A and (+)-hydroxyjatrophone B. *Journal of the American Chemical Society* **1989,** *111* (17), 6648-6656.

37. Gyorkos, A. C.; Stille, J. K.; Hegedus, L. S., The total synthesis of (.+-.)-epi-jatrophone and (.+-.)-jatrophone using palladium-catalyzed carbonylative coupling of vinyl triflates with vinyl stannanes as the macrocycle-forming step. *Journal of the American Chemical Society* **1990,** *112* (23), 8465-8472.

38. Han, Q.; Wiemer, D. F., Total synthesis of (+)-jatrophone. *Journal of the American Chemical Society* **1992,** *114* (20), 7692-7697.

39. Helmboldt, H.; Rehbein, J.; Hiersemann, M., Enantioselective synthesis of the C-14 to C-5 cyclopentane segment of jatrophane diterpenes. *Tetrahedron Letters* **2004,** *45* (2), 289-292.

40. Helmboldt, H.; Hiersemann, M., Synthetic Studies toward Jatrophane Diterpenes from Euphorbia characias. Enantioselective Synthesis of (−)-15-O-Acetyl-3-O-propionyl-17-norcharaciol. *The Journal of Organic Chemistry* **2009,** *74* (4), 1698-1708.

41. Schnabel, C.; Hiersemann, M., Total Synthesis of Jatrophane Diterpenes from Euphorbia characias. *Organic Letters* **2009,** *11* (12), 2555-2558.

42. Mulzer, J.; Gilbert, M.; Galkina, A., Toward the Total Syntheses of Pepluanin A and Euphosalicin: Concise Route to a Highly Oxygenated Cyclopentane as a Common Intermediate. *Synlett* **2004,** *2004* (14), 2558-2562.

43. Mulzer, J.; Giester, G.; Gilbert, M., Toward a Total Synthesis of Macrocyclic Jatrophane Diterpenes - Concise Route to a Highly Functionalized Cyclopentane Key Intermediate. *Helvetica Chimica Acta* **2005,** *88* (6), 1560-1579.

44. Curran, T. T.; Hay, D. A., Resolution of cis-4-O-TBS-2-Cyclopenten-1,4-diol. *Tetrahedron: Asymmetry* **1996,** *7* (10), 2791-2792.

45. Lentsch, C.; Rinner, U., General Synthesis of Highly Functionalized Cyclopentane Segments for the Preparation of Jatrophane Diterpenes. *Organic Letters* **2009,** *11* (22), 5326-5328.

46. Rinner, U.; Lentsch, C.; Fürst, R., Enyne Metathesis Approach towards the Cyclopentane Motif of Jatrophane Diterpenes. *Synlett* **2013,** *24* (20), 2665-2670.

47. Lentsch, C.; Fürst, R.; Mulzer, J.; Rinner, U., Jatrophane Diterpenes: Preparation of the Western Fragment of Pl-3. *European Journal of Organic Chemistry* **2014,** *2014* (5), 919-923.

48. Shimokawa, K.; Takamura, H.; Uemura, D., Concise synthesis of a highly functionalized cyclopentane segment: toward the total synthesis of kansuinine A. *Tetrahedron Letters* **2007,** *48* (32), 5623-5625.

49. Mohan, P.; Koushik, K.; Fuertes, M. J., Efforts toward the total synthesis of a jatrophane diterpene. *Tetrahedron Letters* **2012,** *53* (22), 2730-2732.

50. Mohan, P.; Fuertes, M. J., Synthesis of vinyliodides: progress toward the total synthesis of a jatrophane diterpene. *Tetrahedron Letters* **2013,** *54* (30), 3919-3925.

51. Mohan, P.; Koushik, K.; Fuertes, M. J., Synthetic studies directed toward the total synthesis of a jatrophane diterpene. *Tetrahedron Letters* **2015,** *56* (1), 61-65.

52. Fürst, R.; Rinner, U., Synthesis of an Advanced Intermediate of the Jatrophane Diterpene Pl-4: A Dibromide Coupling Approach. *The Journal of Organic Chemistry* **2013,** *78* (17), 8748-8758.

53. Rinner, U.; Fürst, R.; Lentsch, C., Synthetic Studies towards an Advanced Precursor of the Jatrophane Diterpene Pl-4. *Synthesis* **2013,** *46* (03), 357-367.

54. Davies, J. J.; Krulle, T. M.; Burton, J. W., Total Synthesis of 7,11-Cyclobotryococca-5,12,26-triene Using an Oxidative Radical Cyclization as a Key Step. *Organic Letters* **2010,** *12* (12), 2738-2741.

55. Ferrara, S. J.; Burton, J. W., A Short Synthesis of Aphanamol I in Both Racemic and Enantiopure Forms. *Chemistry - A European Journal* **2016,** *22* (33), 11597-11600.

56. Ainsua Martinez, S.; Gillard, M.; Chany, A.-C.; Burton, J. W., Short total syntheses of the avenaciolide family of natural products. *Tetrahedron* **2018,** *74* (38), 5012-5021.

57. Marx, L. B.; Burton, J. W., A Total Synthesis of Salinosporamide A. *Chemistry - A European Journal* **2018,** *24* (26), 6747-6754.

58. Shepherd, E. Anionic oxidative cyclisations; development and application to the Jatrophane natural products. Oxford University, 2016.

59. Shepherd, E. D.; Hallside, M. S.; Sutro, J. L.; Thompson, A.; Hutchings, M.; Burton, J. W., Synthesis of the cyclopentane core of pepluanin A. *Tetrahedron* **2020,** *76* (11), 130981.

60. Barton, D. H. R.; Crich, D.; Motherwell, W. B., New and improved methods for the radical decarboxylation of acids. *Journal of the Chemical Society, Chemical Communications* **1983,** (17), 939.

61. Abiko, A.; Liu, J.-F.; Masamune, S., The Anti-Selective Boron-Mediated Asymmetric Aldol Reaction of Carboxylic Esters. *Journal of the American Chemical Society* **1997,** *119* (10), 2586-2587.

62. Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H., Grignard-type carbonyl addition of allyl halides by means of chromous salt. A chemospecific synthesis of homoallyl alcohols. *Journal of the American Chemical Society* **1977,** *99* (9), 3179-3181.

63. Chérest, M.; Felkin, H.; Prudent, N., Torsional strain involving partial bonds. The stereochemistry of the lithium aluminium hydride reduction of some simple open-chain ketones. *Tetrahedron Letters* **1968,** *9* (18), 2199-2204.

64. Mitsunobu, O.; Yamada, M., Preparation of Esters of Carboxylic and Phosphoric AcidviaQuaternary Phosphonium Salts. *Bulletin of the Chemical Society of Japan* **1967,** *40* (10), 2380-2382.

65. Barton, D. H. R.; O'Brien, R. E.; Sternhell, S., 88. A new reaction of hydrazones. *Journal of the Chemical Society (Resumed)* **1962**, 470.

66. Crabtree, R. H.; Davis, M. W., Occurrence and origin of a pronounced directing effect of a hydroxyl group in hydrogenation with [Ir(cod)P(C6H11)3(py)]PF6. *Organometallics* **1983,** *2* (5), 681-682.

67. Bian, J.; Van Wingerden, M.; Ready, J. M., Enantioselective Total Synthesis of (+)- and (−)-Nigellamine A2. *Journal of the American Chemical Society* **2006,** *128* (23), 7428-7429.

68. Sousa, B., Unpublished work. University of Oxford: 2016-2017.

69. Jimenez, N., Unpublished work. University of Oxford: 2018.

70. Petruncio, G.; Shellnutt, Z.; Elahi-Mohassel, S.; Alishetty, S.; Paige, M., Skipped dienes in natural product synthesis. *Natural Product Reports* **2021,** *12* (38), 2187-2213.

71. Sato, T.; Suto, T.; Nagashima, Y.; Mukai, S.; Chida, N., Total Synthesis of Skipped Diene Natural Products. *Asian Journal of Organic Chemistry* **2021,** *10* (10), 2486-2502.

72. Del Valle, L.; Stille, J. K.; Hegedus, L. S., Palladium-catalyzed coupling of allylic acetates with aryl- and vinylstannanes. *The Journal of Organic Chemistry* **1990,** *55* (10), 3019-3023.

73. Trost, B. M.; Probst, G. D.; Schoop, A., Ruthenium-Catalyzed Alder Ene Type Reactions. A Formal Synthesis of Alternaric Acid. *Journal of the American Chemical Society* **1998,** *120* (36), 9228-9236.

74. Duboudin, J. G.; Jousseaume, B.; Saux, A., Reactifs de grignard vinyliques γ fonctionnels. *Journal of Organometallic Chemistry* **1979,** *168* (1), 1-11.

75. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H., Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *Journal of the American Chemical Society* **2000,** *122* (34), 8168-8179.

76. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H., A General Model for Selectivity in Olefin Cross Metathesis. *Journal of the American Chemical Society* **2003,** *125* (37), 11360-11370.

77. Voigtritter, K.; Ghorai, S.; Lipshutz, B. H., Rate Enhanced Olefin Cross-Metathesis Reactions: The Copper Iodide Effect. *The Journal of Organic Chemistry* **2011,** *76* (11), 4697-4702.

78. Lin, Y. A.; Davis, B. G., The allylic chalcogen effect in olefin metathesis. *Beilstein Journal of Organic Chemistry* **2010,** *6*, 1219-1228.

79. Cho, J. H.; Kim, B. M., An Efficient Method for Removal of Ruthenium Byproducts from Olefin Metathesis Reactions. *Organic Letters* **2003,** *5* (4), 531-533.

80. King, J. F., Return of sulfenes. *Accounts of Chemical Research* **1975,** *8* (1), 10-17.

81. Ding, R.; He, Y.; Wang, X.; Xu, J.; Chen, Y.; Feng, M.; Qi, C., Treatment of Alcohols with Tosyl Chloride Does Not always Lead to the Formation of Tosylates. *Molecules* **2011,** *16* (7), 5665-5673.

82. Itoh, T.; Nagata, K.; Sano, D., Catalytic Asymmetric Alkylation of α-Cyanocarboxylates Using a Phase-Transfer Catalyst. *Synlett* **2007,** *2007* (04), 0547-0550.

83. Kanemitsu, T.; Koga, S.; Nagano, D.; Miyazaki, M.; Nagata, K.; Itoh, T., Asymmetric Alkylation of Malonic Diester Under Phase-Transfer Conditions. *ACS Catalysis* **2011,** *1* (10), 1331-1335.

84. Trost, B. M.; Crawley, M. L., Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chemical Reviews* **2003,** *103* (8), 2921-2944.

85. Brown, M. Palladium-catalysed synthesis of indanes. University of Oxford, 2021.

86. Golden, D. M.; Egger, K. W.; Benson, S. W., Iodine-Catalyzed Isomerization of Olefins. I. Thermodynamic Data from Equilibrium Studies of Positional and Geometrical Isomerization of 1-Butene and 2-Butene. *Journal of the American Chemical Society* **1964,** *86* (24), 5416-5420.

87. Marković, D.; Varela-Álvarez, A.; Sordo, J. A.; Vogel, P., Mechanism of the Diphenyldisulfone-Catalyzed Isomerization of Alkenes. Origin of the Chemoselectivity: Experimental and Quantum Chemistry Studies. *Journal of the American Chemical Society* **2006,** *128* (24), 7782-7795.

88. Snyder, S. A.; Treitler, D. S.; Brucks, A. P., Simple Reagents for Direct Halonium-Induced Polyene Cyclizations. *Journal of the American Chemical Society* **2010,** *132* (40), 14303-14314.

89. Barrett, J. W.; Linstead, R. P., 138. Fused carbon rings. Part X. Some fundamental properties of the 0 : 3 : 3-bicyclooctane ring. *Journal of the Chemical Society (Resumed)* **1936**, 611.

90. Mihovilovic, M. D.; Bianchi, D. A.; Rudroff, F., Accessing tetrahydrofuran-based natural products by microbial Baeyer–Villiger biooxidation. *Chemical Communications* **2006,** (30), 3214-3216.

91. Koch, G.; Pfaltz, A., Chiral phosphinooxazolines as ligands in asymmetric catalysis: Intramolecular Pd-catalyzed allylic alkylation. *Tetrahedron: Asymmetry* **1996,** *7* (8), 2213-2216.

92. Helmchen, G.; Pfaltz, A., Phosphinooxazolines: A New Class of Versatile, Modular P,N-Ligands for Asymmetric Catalysis. *Accounts of Chemical Research* **2000,** *33* (6), 336-345.

93. Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F., Identification of the Effective Palladium(0) Catalytic Species Generated in Situ from Mixtures of $Pd(dba)_2$ and Bidentate Phosphine Ligands. Determination of Their Rates and Mechanism in Oxidative Addition. *Journal of the American Chemical Society* **1997,** *119* (22), 5176-5185.

94. Bruno, N. C.; Tudge, M. T.; Buchwald, S. L., Design and preparation of new palladium precatalysts for C–C and C–N cross-coupling reactions. *Chemical Science* **2013,** *4* (3), 916-920.

95. Streiff, S.; Welter, C.; Schelwies, M.; Lipowsky, G.; Miller, N.; Helmchen, G., Carbocycles via enantioselective inter- and intramolecular iridium-catalysed allylic alkylations. *Chemical Communications* **2005,** (23), 2957.

96. Baldwin, J. E., Rules for ring closure. *Journal of the Chemical Society, Chemical Communications* **1976,** (18), 734.

97. Sharpless, K. B.; Michaelson, R. C., High stereo- and regioselectivities in the transition metal catalyzed epoxidations of olefinic alcohols by tert-butyl hydroperoxide. *Journal of the American Chemical Society* **1973,** *95* (18), 6136-6137.

98. Salomone, A.; Capriati, V.; Florio, S.; Luisi, R., Michael Addition of Ortho-Lithiated Aryloxiranes to α,β-Unsaturated Malonates: Synthesis of Tetrahydroindenofuranones. *Organic Letters* **2008,** *10* (10), 1947-1950.

99. Thompson, W. J.; Ball, R. G.; Darke, P. L.; Zugay, J. A.; Thies, J. E., Stereoselective synthesis of the hydroxyethylene isostere of the HIV protease (Tyr-Pro) cleavage site. *Tetrahedron Letters* **1992,** *33* (21), 2957-2960.

100. Dale, J. A.; Mosher, H. S., Nuclear magnetic resonance enantiomer regents. Configurational correlations via nuclear magnetic resonance chemical shifts of diastereomeric mandelate, O-methylmandelate, and .alpha.-methoxy-.alpha.-trifluoromethylphenylacetate (MTPA) esters. *Journal of the American Chemical Society* **1973,** *95* (2), 512-519.

101. Kharasch, M. S.; Sosnovsky, G., The reactions of t-butyl perbenzoate and olefins—a stereospecific reaction. *Journal of the American Chemical Society* **1958,** *80* (3), 756-756.

102. Sharpless, K. B.; Lauer, R. F., Selenium dioxide oxidation of olefins. Evidence for the intermediacy of allylseleninic acids. *Journal of the American Chemical Society* **1972,** *94* (20), 7154-7155.

103. Riley, H. L.; Morley, J. F.; Friend, N. A. C., 255. Selenium dioxide, a new oxidising agent. Part I. Its reaction with aldehydes and ketones. *Journal of the Chemical Society (Resumed)* **1932**, 1875.

104. Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jensen, H. P., Selenium dioxide oxidations of olefins. Trapping of the allylic seleninic acid intermediate as a seleninolactone. *Journal of the American Chemical Society* **1973,** *95* (23), 7917-7919.

105. Stephenson, L. M.; Speth, D. R., Mechanism of allylic hydroxylation by selenium dioxide. *The Journal of Organic Chemistry* **1979,** *44* (25), 4683-4689.

106. Singleton, D. A.; Hang, C., Isotope Effects and the Mechanism of Allylic Hydroxylation of Alkenes with Selenium Dioxide. *The Journal of Organic Chemistry* **2000,** *65* (22), 7554-7560.

107. Köppel, C.; Baudisch, H.; Beyer, K. H.; Klöppel, I.; Schneider, P. V., Fatal Poisoning with Selenium Dioxide. *Journal of Toxicology: Clinical Toxicology* **1986,** *24* (1), 21-35.

108. Umbreit, M. A.; Sharpless, K. B., Allylic oxidation of olefins by catalytic and stoichiometric selenium dioxide with tert-butyl hydroperoxide. *Journal of the American Chemical Society* **1977,** *99* (16), 5526-5528.

109. Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L., Total Synthesis of Ingenol. *Journal of the American Chemical Society* **2004,** *126* (50), 16300-16301.

110. Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T., In Situ Generated Bulky Palladium Hydride Complexes as Catalysts for the Efficient Isomerization of Olefins. Selective Transformation of Terminal Alkenes to 2-Alkenes. *Journal of the American Chemical Society* **2010,** *132* (23), 7998-8009.

111. Aldea, L.; García, J. I.; Mayoral, J. A., Multiphase enantioselective Kharasch–Sosnovsky allylic oxidation based on neoteric solvents and copper complexes of ditopic ligands. *Dalton Transactions* **2012,** *41* (27), 8285.

112. Kawasaki, K.-I.; Katsuki, T., Enantioselective allylic oxidation of cycloalkenes by using Cu(II)-tris(oxazoline) complex as a catalyst. *Tetrahedron* **1997,** *53* (18), 6337-6350.

113. Corey, E. J.; Lee, J., Enantioselective total synthesis of oleanolic acid, erythrodiol, .beta.-amyrin, and other pentacyclic triterpenes from a common intermediate. *Journal of the American Chemical Society* **1993,** *115* (19), 8873-8874.

114. Beckwith, A. L. J.; Zavitsas, A. A., Allylic oxidations by peroxy esters catalyzed by copper salts. The potential for stereoselective syntheses. *Journal of the American Chemical Society* **1986,** *108* (26), 8230-8234.

115. García-Cabeza, A. L.; Marín-Barrios, R.; Moreno-Dorado, F. J.; Ortega, M. J.; Massanet, G. M.; Guerra, F. M., Allylic Oxidation of Alkenes Catalyzed by a Copper–Aluminum Mixed Oxide. *Organic Letters* **2014,** *16* (6), 1598-1601.

116. Chen, M. S.; White, M. C., A Sulfoxide-Promoted, Catalytic Method for the Regioselective Synthesis of Allylic Acetates from Monosubstituted Olefins via C−H Oxidation. *Journal of the American Chemical Society* **2004,** *126* (5), 1346-1347.

117. Hansson, S.; Heumann, A.; Rein, T.; Aakermark, B., Preparation of allylic acetates from simple alkenes by palladium(II)-catalyzed acetoxylation. *The Journal of Organic Chemistry* **1990,** *55* (3), 975-984.

118. Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C., Macrolactonization via Hydrocarbon Oxidation. *Journal of the American Chemical Society* **2006,** *128* (28), 9032-9033.

119. Skhiri, A.; Nagae, H.; Tsurugi, H.; Seki, M.; Mashima, K., Effects of Silver Carbonate and p-Nitrobenzoic Acid for Accelerating Palladium-Catalyzed Allylic C–H Acyloxylation. *Organic Letters* **2021,** *23* (18), 7044-7048.

120. Dess, D. B.; Martin, J. C., Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *The Journal of Organic Chemistry* **1983,** *48* (22), 4155-4156.

121. Bal, B. S.; Childers, W. E.; Pinnick, H. W., Oxidation of α,β-un saturated aldehydes. *Tetrahedron* **1981,** *37* (11), 2091-2096.

122. Covell, D. J.; White, M. C., A Chiral Lewis Acid Strategy for Enantioselective Allylic C□H Oxidation. *Angewandte Chemie International Edition* **2008,** *47* (34), 6448-6451.

123. Cianfanelli, M.; Olivo, G.; Milan, M.; Klein Gebbink, R. J. M.; Ribas, X.; Bietti, M.; Costas, M., Enantioselective C–H Lactonization of Unactivated Methylenes Directed by Carboxylic Acids. *Journal of the American Chemical Society* **2020,** *142* (3), 1584-1593.

124. White, M. C. C., Mark S., A predictably selective aliphatic C-H oxidation reaction for complex molecule synthesis. *Science* **2007,** *318* (5851), 783-787.

125. Schenck, G. N. O., Zur Theorie der photosensibilisierten Reaktion mit molekularem Sauerstoff. *Die Naturwissenschaften* **1948,** *35* (1), 28-29.

126. Bayer, P.; Pérez-Ruiz, R.; Jacobi Von Wangelin, A., Stereoselective Photooxidations by the Schenck Ene Reaction. *ChemPhotoChem* **2018,** *2* (7), 559-570.

127. Prein, M.; Adam, W., The Schenck Ene Reaction: Diastereoselective Oxyfunctionalization with Singlet Oxygen in Synthetic Applications. *Angewandte Chemie International Edition in English* **1996,** *35* (5), 477-494.

128. Hu, Y.-J.; Gu, C.-C.; Wang, X.-F.; Min, L.; Li, C.-C., Asymmetric Total Synthesis of Taxol. *Journal of the American Chemical Society* **2021,** *143* (42), 17862-17870.

129. Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S., Allylic C−H Acetoxylation with a 4,5-Diazafluorenone-Ligated Palladium Catalyst: A Ligand-Based Strategy To Achieve Aerobic Catalytic Turnover. *Journal of the American Chemical Society* **2010,** *132* (43), 15116-15119.

130. Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K., Carbonate extension. A versatile procedure for functionalization of acyclic homoallylic alcohols with moderate stereocontrol. *The Journal of Organic Chemistry* **1982,** *47* (21), 4013-4018.

131. Upadhyaya, K.; Subedi, Y. P.; Crich, D., Direct Experimental Characterization of a Bridged Bicyclic Glycosyl Dioxacarbenium Ion by 1 H and 13 C NMR Spectroscopy: Importance of Conformation on Participation by Distal Esters. *Angewandte Chemie International Edition* **2021,** *60* (48), 25397-25403.

132. Bonney, K. J.; Braddock, D. C., A Unifying Stereochemical Analysis for the Formation of Halogenated C15-Acetogenin Medium-Ring Ethers FromLaurenciaSpecies via Intramolecular Bromonium Ion Assisted Epoxide Ring-Opening and Experimental Corroboration with a Model Epoxide. *The Journal of Organic Chemistry* **2012,** *77* (21), 9574-9584.

133. Cornil, J.; Gonnard, L.; Guérinot, A.; Reymond, S.; Cossy, J., Lewis Acid Catalyzed Synthesis of Cyclic Carbonates, Precursors of 1,2- and 1,3-Diols. *European Journal of Organic Chemistry* **2014,** *2014* (23), 4958-4962.

134. Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H., Absolute configurations of marine diterpenes possessing a xenicane skeleton. An application of an advanced mosher's method. *Tetrahedron Letters* **1989,** *30* (24), 3147-3150.

135. Ward, D. E.; Rhee, C. K., A simple method for the microscale preparation of mosher's acid chloride. *Tetrahedron Letters* **1991,** *32* (49), 7165-7166.

136. Hoye, T. R.; Jeffrey, C. S.; Shao, F., Mosher ester analysis for the determination of absolute configuration of stereogenic (chiral) carbinol carbons. *Nature Protocols* **2007,** *2* (10), 2451-2458.

137. Crabtree, R. H.; Morris, G. E., Some diolefin complexes of iridium(I) and a trans-influence series for the complexes [IrCl(cod)L]. *Journal of Organometallic Chemistry* **1977,** *135* (3), 395-403.

138. Crabtree, R. H.; Felkin, H.; Morris, G. E., Cationic iridium diolefin complexes as alkene hydrogenation catalysts and the isolation of some related hydrido complexes. *Journal of Organometallic Chemistry* **1977,** *141* (2), 205-215.

139. Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J., Total Synthesis of (−)-Himalensine A. *Journal of the American Chemical Society* **2017,** *139* (49), 17755-17758.

140. Crabtree, R., Iridium compounds in catalysis. *Accounts of Chemical Research* **1979,** *12* (9), 331-337.

141. But, T. Y. S.; Toy, P. H., The Mitsunobu Reaction: Origin, Mechanism, Improvements, and Applications. *Chemistry – An Asian Journal* **2007,** *2* (11), 1340-1355.

142. Hoover, J. M.; Stahl, S. S., Highly Practical Copper(I)/TEMPO Catalyst System for Chemoselective Aerobic Oxidation of Primary Alcohols. *Journal of the American Chemical Society* **2011,** *133* (42), 16901-16910.

143. Hoover, J. M.; Ryland, B. L.; Stahl, S. S., Mechanism of Copper(I)/TEMPO-Catalyzed Aerobic Alcohol Oxidation. *Journal of the American Chemical Society* **2013,** *135* (6), 2357-2367.

144. Steves, J. E.; Stahl, S. S., Copper(I)/ABNO-Catalyzed Aerobic Alcohol Oxidation: Alleviating Steric and Electronic Constraints of Cu/TEMPO Catalyst Systems. *Journal of the American Chemical Society* **2013,** *135* (42), 15742-15745.

145. Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P., Reduction of natural enones in the presence of cerium trichloride. *Journal of the Chemical Society, Chemical Communications* **1978,** *0* (14), 601-602.

146. Luche, J. L., Lanthanides in organic chemistry. 1. Selective 1,2 reductions of conjugated ketones. *Journal of the American Chemical Society* **1978,** *100* (7), 2226-2227.

147. Albers, P.; Pietsch, J.; Parker, S. F., Poisoning and deactivation of palladium catalysts. *Journal of Molecular Catalysis A: Chemical* **2001,** *173* (1-2), 275-286.

148. Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E.; Lovey, A. J.; Stephens, W. P., Synthetic applications and mechanism studies of the decarbalkoxylations of geminal diesters and related systems effected in dimethyl sulfoxide by water and/or by water with added salts. *The Journal of Organic Chemistry* **1978,** *43* (1), 138-147.

149. Corey, E. J.; Fuchs, P. L., A synthetic method for formyl→ethynyl conversion. *Tetrahedron Letters* **1972,** *13* (36), 3769-3772.

150. Desai, N. B.; McKelvie, N.; Ramirez, F., A New Synthesis of 1,1-Dibromoolefins *via* Phosphine-Dibromomethylenes. the Reaction of Triphenylphosphine with Carbon Tetrabromide. *Journal of the American Chemical Society* **1962,** *84* (9), 1745-1747.

151. Ohira, S., Methanolysis of Dimethyl (1-Diazo-2-oxopropyl) Phosphonate: Generation of Dimethyl (Diazomethyl) Phosphonate and Reaction with Carbonyl Compounds. *Synthetic Communications* **1989,** *19* (3-4), 561-564.

152. Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J., An Improved One-pot Procedure for the Synthesis of Alkynes from Aldehydes. *Synlett* **1996,** *1996* (06), 521-522.

153. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B., Asymmetric dihydroxylation via ligand-accelerated catalysis. *Journal of the American Chemical Society* **1988,** *110* (6), 1968-1970.

154. Evans, D. A.; Siska, S. J.; Cee, V. J., Resurrecting the Cornforth Model for Carbonyl Addition: Studies on the Origin of 1,2-Asymmetric Induction in Enolate Additions to Heteroatom-Substituted Aldehydes. *Angewandte Chemie International Edition* **2003,** *42* (15), 1761-1765.

155. Reformatsky, S., Neue Synthese zweiatomiger einbasischer Säuren aus den Ketonen. *Berichte der deutschen chemischen Gesellschaft* **1887,** *20* (1), 1210-1211.

156. Hertel, L. W.; Grossman, C. S.; Kroin, J. S., Preparation and Storage of (R)-2,3-O-Isopropylideneglyceraldehyde (D-Glyceraldehyde Acetonide). *Synthetic Communications* **1991,** *21* (2), 151-154.

157. Yamauchi, K.; Une, F.; Tabata, S.; Kinoshita, M., Synthesis of glycerophosphonolipids containing aminoalkylphosphonic acids. *Journal of the Chemical Society, Perkin Transactions 1* **1986**, 765.

158. Etayo, P.; Badorrey, R.; Díaz-De-Villegas, M. D.; Gálvez, J. A., Chiral Amino Diol Derivatives as New Modular Organocatalysts for the Enantioselective α-Chlorination of Cyclic β-Keto Esters. *Advanced Synthesis & Catalysis* **2010,** *352* (18), 3329-3338.

159. Zimmerman, H. E.; Traxler, M. D., The Stereochemistry of the Ivanov and Reformatsky Reactions. I. *Journal of the American Chemical Society* **1957,** *79* (8), 1920-1923.

160. Omura, K.; Swern, D., Oxidation of alcohols by “activated” dimethyl sulfoxide. a preparative, steric and mechanistic study. *Tetrahedron* **1978,** *34* (11), 1651-1660.

161. Parikh, J. R.; Doering, W. V. E., Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide. *Journal of the American Chemical Society* **1967,** *89* (21), 5505-5507.

162. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G., A Versatile and Highly Selective Hypervalent Iodine (III)/2,2,6,6-Tetramethyl-1-piperidinyloxyl-Mediated Oxidation of Alcohols to Carbonyl Compounds. *The Journal of Organic Chemistry* **1997,** *62* (20), 6974-6977.

163. Thiede, S.; Wosniok, P. R.; Herkommer, D.; Debnar, T.; Tian, M.; Wang, T.; Schrempp, M.; Menche, D., Total Synthesis of Leupyrrins A1and B1, Highly Potent Antifungal Agents from the MyxobacteriumSorangium cellulosum. *Chemistry - A European Journal* **2017,** *23* (14), 3300-3320.

164. Blakemore, P. R., The modified Julia olefination: alkene synthesis via the condensation of metallated heteroarylalkylsulfones with carbonyl compounds. *Journal of the Chemical Society, Perkin Transactions 1* **2002,** (23), 2563-2585.

165. Stang, E. M.; Christina White, M., Total synthesis and study of 6-deoxyerythronolide B by late-stage C–H oxidation. *Nature Chemistry* **2009,** *1* (7), 547-551.

166. Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S., Vanadium-catalyzed epoxidation of cyclic allylic alcohols. Stereoselectivity and stereocontrol mechanism. *Journal of the American Chemical Society* **1979,** *101* (1), 159-169.

167. Pietruszka, J.; Bischop, M., Synthesis of Vinyllactones via Allylic Oxidation of Alkenoic Acids. *Synlett* **2011,** *2011* (18), 2689-2692.

168. Kuszmann, J.; Tomori, É.; Meerwald, I., The synthesis of 1,2:5,6-di-O-isopropylidene-d-mannitol: a comparative study. *Carbohydrate Research* **1984,** *128* (1), 87-99.

169. Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P., Synthetic Studies of Antitumor Macrolide Rhizoxin: Stereoselective Syntheses of the C(1)−C(9) and C(12)−C(26) Subunits. *The Journal of Organic Chemistry* **1998,** *63* (20), 6952-6967.