Studies Towards the Total Synthesis of Eleutherobin and Other Marine Natural Products

by

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of the Requirements for the Degree of
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in the
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Abstract

The primary focus of the research described in this thesis relates to the development and application of new synthetic methodologies relevant for the concise construction of four natural products.

In Chapter 2, a discussion of our investigation of the total synthesis of eleutherobin (**1**) is disclosed. Eleutherobin (**1**), first isolated in 1997 from the rare soft coral *Eleutherobia sp*., is a member of a class of microtubule stabilising natural products. Although it displays potent cytotoxicity, its development as an anticancer drug has been hampered by the scarcity of material available from the natural source. In an effort to produce quantities of eleutherobin required for further biological testing, four conceptually unique approaches to eleutherobin were investigated which culminated in the development of an unprecedented palladium-catalysed α-arylation reaction/Friedel-Crafts cyclisation methodology for tetralone synthesis. This strategy permitted the production of multi-gram quantities of an advanced tetralone intermediate, and enabled the synthesis of a functionalised epoxyenone intermediate along our intended synthetic route. These investigations have provided a solid foundation for an eventual synthesis of eleutherobin that may also facilitate the evaluation of this natural product as an anticancer drug.

In Chapter 3, the total synthesis of two potent anthelmintic oxylipid natural products, isolated from *Notheia anomala*, is discussed. Specifically, a silver-mediated cyclisation of two chlorodiols afforded two diastereomeric styryl-tetrahydrofurans, which were rapidly elaborated into the desired natural products. In addition, these syntheses featured a remarkable example of inverse-temperature dependence in the diastereoselective addition of Grignard reagents to tetrahydrofurfurals. Ultimately, these natural products were prepared in six synthetic transformations in excellent overall yield and efficiency.

The last two topics presented in this thesis are contained in two separate appendices and highlight our interest in the synthesis of ecologically relevant natural products. In Appendix A, we report the synthesis and structure determination of the

unknown banana volatile, (3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate, and its olfactory recognition by the common fruit fly. The work presented in Appendix B focuses on the development of a scalable synthesis of mathuralure, the sex pheromone of the pink gypsy moth, *Lymantria mathura*, a potentially devastating invasive species.

Keywords: eleutherobin; natural products; total synthesis; antimitotic chemotherapeutics; *N*. *anomala* oxylipids; tetrahydrofurans

…Having reached this point in life, what chemist, facing the Periodic Table, or the monumental indices of Beilstein or Landolt, does not perceive scattered among them the sad tatters, or trophies, of his own professional past? He only has to leaf through any treatise and memories rise up in bunches: there is among us he who has tied his destiny, indelibly, to bromine or to propylene, or the -NCO group, or glutamic acid; and every chemistry student, faced by almost any treatise, should be aware that on one of those pages, perhaps in a single line, formula, or word, his future is written in indecipherable characters, which however, will become clear “afterward”: after success, error, or guilt, victory, or defeat. Every no longer young chemist, turning again to the *verhängnisvoll* page in that same treatise, is struck by love or disgust, delights or despairs…

- Primo Levi
  On carbon (from The Periodic Table)

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List of Abbreviations

°C	Degrees Celsius
δ	Chemical shift in ppm from tetramethylsilane
L	Levorotatory
D	Denotes position of olefin
$[\alpha]_D$	Specific rotation at the sodium D line (589 nm)
Ac	Acetyl
AIBN	2-2'-Azoisobutyronitrile
aq	aqueous
BAIB	[*Bis*(acetoxy)iodo]benzene
BCE	Before Common Era
BINAP	2,2′-*Bis*(diphenylphosphino)-1,1′-binaphthalene
br.	broad
Bu	Butyl
c	Concentration in g/mL
cat.	Catalytic amount
CDI	Carbonyldiimidazole
COSY	Correlation Spectroscopy
dba	Dibenzylideneacetone
D^{t}BPF	1,1'-bis(di-*tert*-butylphosphino)-ferrocene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl carbodiimide
DCE	Dichloroethane
DET	Diethyl tartrate
DFT	Density Functional Theory
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	*N*,*N*'-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
d.r.	Diastereomeric ratio
E	Entgegen (trans)
ee	Enantiomeric excess
equiv.	Equivalents

Et	Ethyl
Et_2O	Diethyl ether
FDA	Federal Drug Administration
GC	Gas chromatography
GC-EAD	Gas chromatography - Electroantennographic detection
Hex	Hexyl
HMBC	Heteronuclear Multiple Bond Correlation
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
i	Iso-
IC_{50}	Half maximal inhibitory concentration
LD_{50}	Lethal Dose, 50%
LDA	Lithium diisopropylamide
lit.	Literature
M	Molar
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mes	Mesityl
mmol	Millimole(s)
mol	Mole(s)
MOM	Methoxymethyl ether
Ms	Methanesulfonate
MS	Molecular Sieves
NCS	*N*-chlorosuccinimide
n	Nano
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
Nu	Nucleophile
p	Para
PCC	Pyridinium chlorochromate
pH	$-\log_{10}[H^+]$

Ph	Phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts-per-million
PIFA	phenyliodine bis(trifluoroacetate)
Piv	Pivaloyl
Pr	Propyl
PS	Polymer-supported
RCM	Ring closing metathesis
r.t.	Room temperature
SAR	Structure-activity relationship
sec	Secondary
SCUBA	Self-Contained Underwater Breathing Apparatus
t	Tertiary
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-butylhydroperoxide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
temp	Temperature
TES	Triethylsilyl
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	Tolyl
Ts	Toluenesulfonate
Z	Zusammen (*cis*)

1. Introduction

1.1. Thesis Overview

The primary focus of the research described in this thesis relates to the development of synthetic methods for the assembly of biologically active natural products. Specifically, this thesis focuses on the application of new synthetic strategies relevant for the concise construction of four natural products.

In *Chapter 2*, a discussion of our investigation of the total synthesis of eleutherobin (**1**) is disclosed. Eleutherobin (**1**), first isolated in 1997 from the rare soft coral *Eleutherobia sp*.,[1] is a member of a class of microtubule stabilising natural products. Although it displays potent microtubule stabilising activity (IC_{50} = 10 nM)[2] and cytotoxicity, its development as an anticancer drug has been hampered by the scarcity of material available from the natural source. Furthermore, previous synthetic efforts have failed to identify a concise route to eleutherobin, and consequently its promising biological activity has yet to be fully explored.[3–9] In an effort to produce quantities of eleutherobin required for further biological testing, studies directed at developing a scalable synthesis of this natural product were combined with the necessary development of new synthetic methods.

Specifically, four conceptually unique approaches to eleutherobin are discussed. The first involves the investigation of a Diels-Alder/fragmentation approach to the eleutherobin core. This work included a study of both inter- and intramolecular Diels-Alder reactions as well as the synthesis of three intramolecular Diels-Alder precursors designed to probe the effect of steric and electronic factors on the proposed Diels-Alder reaction. In an alternative approach, which centred on an oxidative dearomatisation reaction/fragmentation approach to the eleutherobin core, a benzocyclobutanol electrocyclic rearrangement reaction was investigated as a method to prepare the tetralone dearomatisation precursor. While several model tetralones were synthesised,

we were ultimately unsuccessful in constructing the intended tetralone that would lead to eleutherobin. Likewise, a palladium-catalysed cyclobutanol rearrangement strategy was also fruitless in preparing advanced intermediates *en route* to eleutherobin. However, we were successful in the construction of the targeted intermediates through the development of an unprecedented palladium-catalysed α-arylation reaction/Friedel-Crafts cyclisation strategy. This method permitted production of multi-gram quantities of the desired tetralone in 6 steps from commercially available materials. Finally, the dearomatisation and functionalisation of this tetralone was investigated, and eventually led to the construction of an epoxyenone intermediate through a 3-step sequence that included a BAIB mediated addition of water to a phenol, and the hydroxy-directed epoxidation of an enone. These investigations have provided a solid foundation for an eventual synthesis of eleutherobin that may also facilitate the evaluation of this natural product as an anticancer drug.

In *Chapter 3*, the total synthesis of two potent anthelmintic oxylipid natural products, isolated from *Notheia anomala*, is discussed. This work involved the application of a newly developed method for the preparation of substituted hydroxy-tetrahydrofurans, a key structural feature of both natural products. Specifically, a silver-mediated cyclisation of two chlorodiols afforded two diastereomeric styryl-tetrahydrofurans, which were rapidly elaborated into the desired natural products. In addition, these syntheses featured a remarkable example of inverse-temperature dependence in the diastereoselective addition of Grignard reagents to tetrahydrofurfurals. Moreover, a critical aspect of this work involved an in-depth optimisation of the key Grignard reaction, as well as a mechanistic study of this process using DFT calculations. Ultimately, these natural products were prepared in six synthetic transformations in excellent overall yield and efficiency.

The last two topics presented in this thesis are contained in two separate appendices. The research outlined in both these appendices highlight our interest in the synthesis of ecologically relevant natural products. In Appendix A, we report the synthesis and structure determination of the hitherto unknown banana volatile, (3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate, and its olfactory recognition by the common fruit fly. This synthesis relied on the application of a new method for the construction of β-hydroxyesters from alkynyl-chlorohydrins. The work presented in Appendix B focuses on

the development of a scalable synthesis of mathuralure, the sex pheromone of the pink gypsy moth, *Lymantria mathura*. Large quantities of this pheromone are required for use in baited traps as a means to monitor the population of this potentially devastating invasive species. Indeed, the success of this synthetic strategy relied on the ability to produce the quantities necessary to support the growing demand for this important semiochemical.

1.2. Introduction to Cancer and Chemotherapy

Cancer is a grouping of more than 100 diseases characterised by an uncontrolled growth of cells in the body. A report from the Canadian Cancer Society estimates that in 2012 there will be 186,400 new cases of cancer and over 75,700 deaths in Canada from cancer.[10] As a result, cancer remains one of the leading causes of premature death amongst Canadians. While mortality rates continue to fall due in large part to the continued development of more specific and efficacious treatments for this disease, incidence rates continue to rise. Consequently, the detection and treatment of all types of cancer is at the forefront of pharmaceutical research.

The term chemotherapy was first used by the German chemist Paul Ehrlich in the early 1900s, who defined it as the use of chemicals to treat disease. While it was his work on the development of arsenicals that led to a cure for syphilis, he had little success with respect to cancer, placing a sign over his door which read, “Give up all hope oh ye who enter.”[11] Cancer treatment predating the 1950’s was largely based on surgical therapies, with radiation therapy only becoming a tool after 1960. Unfortunately, both of these techniques fail to effectively cure metastatic cancers, which require treatment that can access every organ in the body. The beginning of chemotherapy as a treatment for cancer dates back to 1942, when Louis Goodman and Alfred Gilman studied the effects of nitrogen mustard on lymphoid tumours.[12] This research was inspired by autopsy reports from world war one indicating that exposure to sulphur mustard resulted in decreased lymph tissue. Based on this observation, they postulated that the structurally related nitrogen mustard (HN3) could cause remission of a lymphatic tumour.[13] While treatment of lymphatic tumours with nitrogen mustard did not lead to permanent regression, this seminal work demonstrated the concept that drugs could be

used in the treatment of cancer. Discovery of their mechanism of action as DNA alkylating agents, led to the development of a class of chemotherapeutic compounds and ultimately to the orally administered drugs cyclophosphamide and chlorambucil as prescribed courses of treatment for lymphomas and leukeamias.[13]

While normal cells spend a significant period of the cell cycle resting, waiting for cellular cues to begin cell division, cancerous cells grow without restraint, dividing and multiplying in an uncontrolled manner. The result is an increase in cellular metabolism and enhanced requirement for the building blocks of cellular processes (e.g., nucleic acids for DNA synthesis). Further progress in cancer therapy was made when researchers began to use the metabolic disparity between cancerous and healthy cells as a means of selectively targeting cancer cells in chemotherapeutic treatments. Ultimately, this strategy proved successful with the development and introduction of antifolate and purine analogue drugs methotrexate[14] and 6-mercaptopurine.[15]

This selective approach to chemotherapy was further exploited when two independent groups at the University of Western Ontario and Eli Lilly discovered the *Vinca* alkaloids.[16] These compounds were found to block proliferation of tumour cells, an effect attributed to their ability to inhibit microtubule polymerisation and therefore cell division.

1.2.1. Microtubules as a Target for Cancer Therapy

Since the discovery of the *Vinca* alkaloids, microtubules have become an important target for chemotherapeutic drugs. Of the compounds that entered clinical trials for the treatment of cancer between 2005 and 2007, 25% functioned by the interaction with microtubules.[17] In fact, it has been argued, "that microtubules represent the best cancer target to be identified so far, and it seems likely that drugs of this class will continue to be important chemotherapeutic agents, even as more selective approaches are developed."[18]

Microtubules are cytoskeletal protein polymers, critical for cell growth and division, motility, signalling, and the development and maintenance of cell shape. Microtubules are composed of α and β tubulin dimers that are arranged in long filamentous tubes, with the length of the microtubule being controlled by complex

polymerisation dynamics (Figure 1.1).[19] These microtubule dynamics, which are characterised by sporadic elongation and shortening, are crucial for many cellular processes, the most important of which is mitosis. At the beginning of mitosis, the cytoskeletal microtubule network is dismantled and replaced with highly dynamic spindle microtubules, which emanate from the microtubule organisation centres at the poles of the cell. These spindle microtubules are responsible for timely connection with the kinetochore on daughter chromatids, proper alignment of the chromatids at the metaphase plate, and synchronous separation of the chromosomes to opposite poles of the cell during anaphase. Since highly dynamic microtubules are required for all of these processes, an interference of microtubule polymerisation dynamics brought on by the action of antimitotic compounds, causes disruption of cell division and ultimately cell death by apoptosis. While the action of these compounds is expected to have a similar effect on healthy cells, the uncontrolled and rapid division of cancerous cells makes them more vulnerable to the affect of these chemotherapeutic agents.

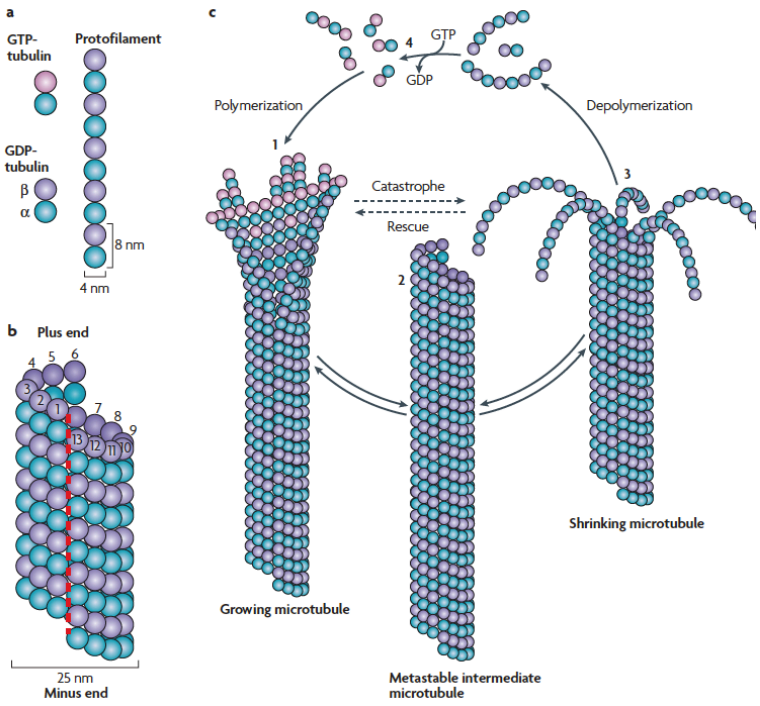
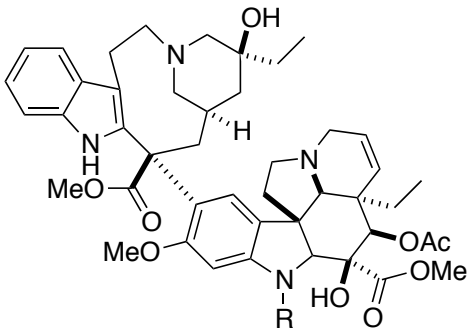


Figure 1.1 **Microtubule structure and its polymerisation dynamics.**[20]

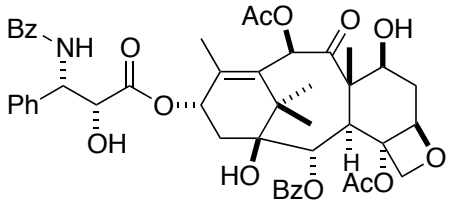
1.2.2. Development of Anitimitotics as Chemotherapuetic Agents

The *Vinca* alkaloids vinblastine (**2**) and vincristine (**3**), were isolated from the Madagascar periwinkle *Catharanthus roseus* (L.) G. Don (previously known as *Vinca rosea* L.) and consist of an upper catharanthine ring linked to a lower vindoline domain (Figure 1.2). Their therapeutic action is derived through the reversible binding to the "vinca domain" on β tubulin. At high concentrations these alkaloids induce depolymerisation of microtubules and destroy mitotic spindles. Conversely, at low concentrations, they are powerful suppressors of microtubule dynamics, blocking mitosis and inducing apoptosis (IC_{50} = 0.8 nM).[18] Because of their success in the treatment of childhood leukaemia they were considered "wonder drugs," and nearly 3 decades of use attests to this form of chemotherapy.[18]

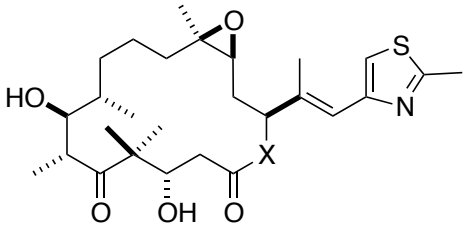
In addition to the *Vinca* alkaloids, a large number of compounds have been discovered which interfere with tubulin polymerisation dynamics and have shown potential utility in the treatment of cancer (Figure 1.2).[21–24] Perhaps the most well known of these compounds is Taxol (**4**), isolated in 1967 by Monroe Wall and Mansukh Wani from the bark of the Pacific yew tree.[25] Despite issues surrounding drug solubility and a significant supply crisis that initially impeded development, presently, Taxol has been used to treat over 1 million patients suffering with various forms of breast, ovarian, and lung cancers. Additionally, the success of Taxol has invigorated a search for new analogues or formulations to overcome its various shortcomings, and the FDA has now approved several for use.[26,27] In contrast to the *Vinca* alkaloids that inhibit microtubule polymerisation, the disruption of cell division by Taxol is attributed to the enhancement of microtubule assembly. Thus, interaction with the "taxol" binding site on β-tubulin stabilises the growth of microtubules, which results in a decrease in polymerisation dynamics and eventually leads to cell death.[28,29]



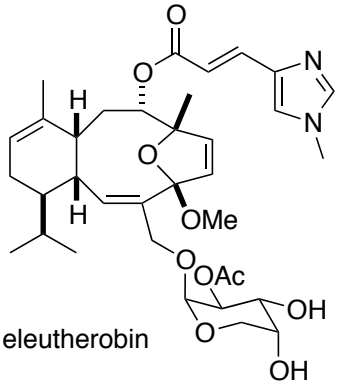
2: R = Me : vinblastine
3: R = CHO : vincristine



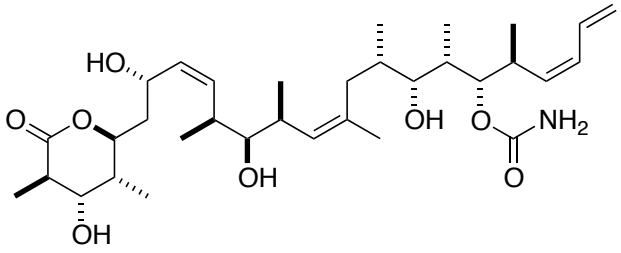
4: Taxol*TM*



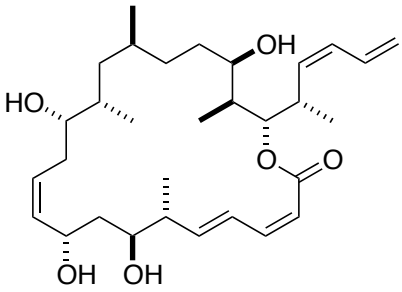
5: X = O : epothilone B
8: X = NH : ixabepilone B



1: eleutherobin



6: discodermolide



7: dictyostatin

Figure 1.2 Representative microtubule interactive natural products.

In recent years researchers have discovered several other natural products with taxol-like antimitotic activity. Some members of this growing class of natural products include epothilone B (**5**), discodermolide (**6**), dictyostatin (**7**), and eleutherobin (**1**). The epothilones were discovered as antifungal agents in 1986 as metabolites of the myxobacterium *Sorangium cellulosum*, but elicited little interest from the scientific community until their microtubule stabilising properties were identified.[30] While epothilone B is currently undergoing clinical trials, ixabepilone (**8**), a semi-synthetic lactam derivative with enhanced metabolic stability is currently used for the treatment of

advanced metastatic breast cancer. Notably, epothilone B and its derivatives display low susceptibility to drug resistance mechanisms such as drug efflux by P-glycoprotein, and are effective against taxol resistant forms of cancer.[31]

Discodermolide (**6**), isolated from the marine sponge *Discodermia dissolute*, entered clinical trials after a heroic total synthesis campaign by researchers at Novartis, which resulted in the production of 60 g of the natural product.[32–36] Despite the withdrawal of discodermolide from these trials as a result of its toxicity, the enormous effort invested in the production of discodermolide indicates that no crucially important compound is beyond reach for clinical evaluation.[37] While these examples illustrate the potential for this family of anticancer drugs, they also highlight the obstacles facing their development. Notwithstanding, the success of cancer chemotherapeutics is undeniable considering that in 2005, expenditures on cancer related chemotherapy drugs represented almost 5% of the worldwide market for pharmaceuticals (~US $22 Billion).[13] Furthermore, with 63% of anticancer drugs over the last 25 years being natural products or natural product inspired, it is of little surprise that researchers continue to turn to nature as a source of safer and more efficacious treatments for cancer.[38,39]

1.3. Introduction to Natural Products

Natural products are chemical compounds produced by living organisms. Because natural products often interact in biological systems, they have been used for a variety of purposes including drugs for the treatment of disease, chemical lures and pheromones in pest management and agriculture, and flavourings and additives for the food industry. Traditionally, terrestrial organisms such as plants, microorganisms, fungi, and insects have been the predominant source of natural products as a result of their accessibility. However, with the introduction of SCUBA in the 1960s, and further technological advances that allow researchers routine access to depths in excess of 330 meters, the marine environment is increasingly explored as a source of novel bioactive natural products.[40] With oceans representing 70% of the earth's surface, they are by far the largest habitat on the planet. Furthermore, while open waters are considered low in nutrients and desert like, the narrow ocean fringe and deep sea vents (representing less than 1% of the earth's surface) are home to the majority of the world's species.[41] As a

result of this intense concentration, these environments are highly competitive, leading to vast displays of biodiversity and adaptive techniques for survival. With respect to sessile invertebrate organisms, this has manifested itself in the production of structurally diverse secondary metabolites, which act as bioactive compounds for such purposes as reproduction, communication, or chemical defenses against overgrowth by competing species or ingestion by motile prey.[42] Consequently, the diverse nature and biological potential displayed by these compounds has made them a rich source of new lead structures in the search for drugs.

1.3.1. Natural Products as Drug Leads

Nature has long been a source of medicinal remedies, with plants forming the basis of sophisticated traditional medical systems for thousands of years.[43] In fact, ancient Egyptian, Chinese, and Greek literature dating back to 1500 BCE contains detailed descriptions for natural sources of medical remedies. The use of pure compounds as drugs can be traced back to the isolation of strychnine, colchicine, atropine, and morphine from commonly used plants and herbs, and commercialization of morphine as the first pure natural product in 1826. These advances were followed by the isolation of salicin, the active ingredient in willow bark by Johann Buchner, which eventually led to the development of Aspirin, the first semi-synthetic drug based on a natural product, by Bayer in 1899.[44] As the field of science has matured, so has our reliance on pharmaceuticals, with the global pharmaceutical market expected to reach over US $1 Trillion by 2014.[45] However, in light of these impressive figures, it has been estimated by the World Health Organization that approximately 80% of the world's inhabitants still rely mainly on traditional medicines for their primary health care.[43] Additionally, over 50% of all new drugs to enter the market between 1981 and 2006 were natural products or natural product derived, further highlighting the importance of natural products in the search for new pharmaceutical therapies.[38]

Despite their historical success, a number of obstacles face the continued development of natural products as leads for medicinal chemistry efforts. Recently, combinatorial techniques have begun to play a major role in drug discovery, owing to their compatibility with high throughput screening technology and the ability to rapidly produce large libraries of small molecules.[37] However, while combinatorial processes

represent an efficient means to explore the structure-activity relationships of lead candidates, and have succeeded in the optimisation of many recently approved agents, only one *de novo* combinatorial compound has been approved as a drug in the last 25 years.[38] Furthermore, not only do natural products occupy a broader and more "drug-like" chemical space compared to combinatorial libraries,[46] they are often viewed as a population of privileged structures, as illustrated by their ability to modulate and inhibit even the most challenging protein-protein interactions.[37]

A second obstacle facing the present use of natural products for drug discovery is the problem of supply. Since biologically active natural products are generally produced as secondary metabolites, often only very small quantities can be isolated from the natural source. While microbial and various plant products are amenable to culturing on productions scale, synthetic chemists are routinely tasked with supplying a source for scarce naturally occurring compounds. Although this challenge has contributed significantly to the field of organic synthesis, many natural products present a level of structural complexity that renders total synthesis efforts impractical, and the exciting biological potentials of these compounds are left unexplored. Therefore, it is only through the development of new synthetic methodologies that provide access to natural product skeletons can the promising properties of these compounds be fully investigated.

2. Studies Towards the Total Synthesis of Eleutherobin

2.1. Introduction to Eleutherobin and the Sarcodictyin Family of Natural Products

Marine organisms have attracted the attention of chemists for many decades due in large part to the diverse range of secondary metabolites that they produce. For example, octocorals, which are built of colonial polyps and characterised by their eight-fold radial symmetry, are prolific producers of terpenoid natural products with a broad range of biological activities.[47,48] Taxonomically, the subclass octocorallia (phylum Cnidaria, class Anthozoa) is comprised of six orders: Alcyonace (fleshy soft corals), Gorgonace (sea whips and sea fans), Pennatulace (sea pens and sea pansies), Helioporacea (blue-stony corals), Stolonifer (organ-pipe corals), and Telestacea.[49] As many octocorals do not produce substantial calcium carbonate skeletons, they are often referred to as soft corals. Due to their lack of a hard exoskeleton, octocorals have evolved chemical defenses in order to ensure their survival. As a result, vast arrays of isoprene-derived secondary metabolites have been isolated from these organisms, with a predominance of compounds that arise biosynthetically from the cembranoid diterpene skeleton **9** (Figure 2.1).[49]

Based on their proposed biosynthesis, cembranoid natural products can be classified into two main groups: the C3-C8 cyclised cembranoids (briaranes (**10**)) and the C2-C11 cyclised cembranoids.[50] Within the C2-C11 cyclised cembranoids there are 4 main categories: the cladiellins (eunicellins) (**11**), briarellins (**12**), asbestinins (**13**), and the sarcodictyins (**14**). A unique ether linkage between C2 and C9 characterises the cladiellins, briarellins, and asbestinins. Compared to the cladiellins, the briarellins and asbestinins also contain an additional seven-membered cyclic ether that connects C3 and C16. Moreover, the asbestinins are believed to be derived biosynthetically from the briarellins through a suprafacial 1,2-migration of the methyl group from C11 to C12.[50]

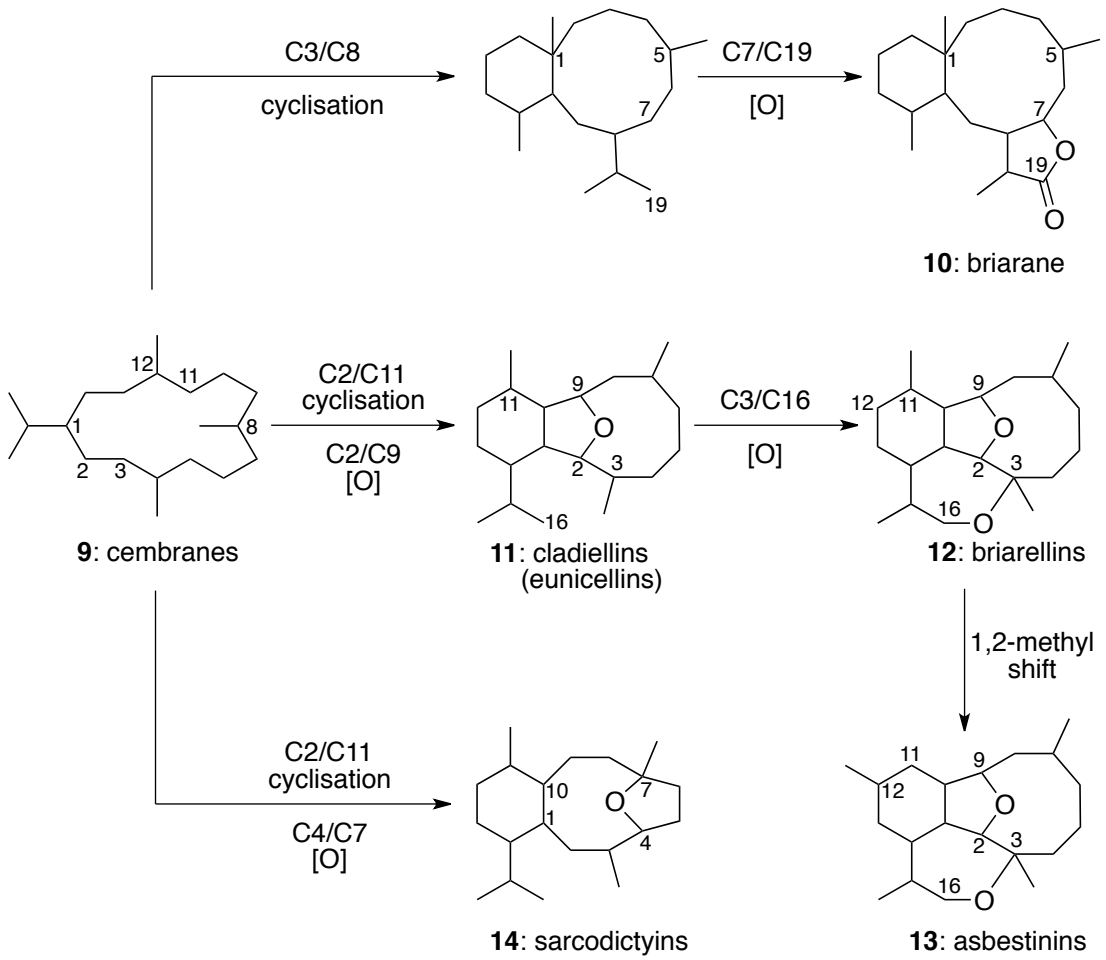
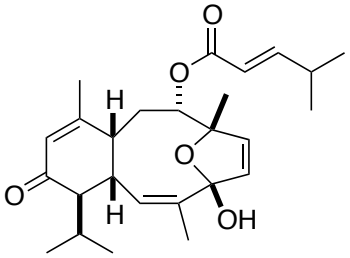


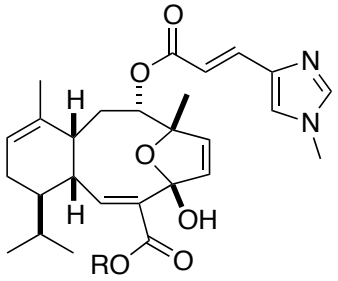
Figure 2.1 **Presumed biosynthesis of the known classes of oxygenated 2,11 and 3,8-cyclised cembranoids.**

The sarcodictyin family is comprised of three main groups: the valdivones, sarcodictyins, and eleuthosides. While relatively few members of the sarcodictyin family are known (15 members) compared to the other classes of cembranoid diterpenes, their interesting biological profiles have attracted significant attention from the chemical community over the past several decades (Figure 2.2). Structurally, members of the sarcodictyin family posses a bicyclo[8.4.0]tetradecane carbocyclic skeleton with an ether linkage connecting C4 and C7. All members contain a double bond between C2/C3 and C5/C6, and oxygenation at C4 and C8. While the eleuthosides and sarcodictyins (e.g., sarcodictyin A (**15**) and B (**16**))[51,52] feature an *N*-methylurocanic ester at C8, various other ester residues are found at this position in the valdivones (e.g., valdivone A (**17**)).[53] Although only three members of this family (eleuthosides A (**18**) and B (**19**) and

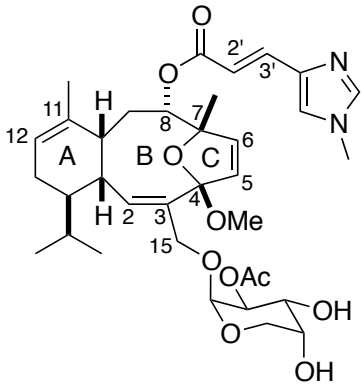
eleutherobin (**1**)) contain an arabinose sugar moiety attached to C15, they are generally referred to as the eleuthoside family of natural products.[54]



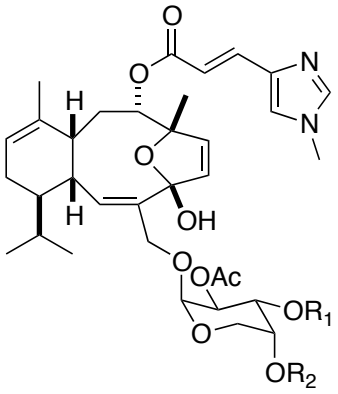
17: valdivone A



15: R = Me : sarcodictyin A
16: R = Et : sarcodictyin B



1: eleutherobin



18: R_1 = Ac, R_2 = H : eleuthoside A
19: R_1 = H, R_2 = Ac : eleuthoside B

Figure 2.2 **Representative members of the sarcodictyin family of natural products.**

The most notable member of the eleuthoside family of natural products is eleutherobin (**1**), which was isolated in 1997 from a rare alcyonacean, identified as an *Eleutherobia sp.* located near Bennett's Shoal in Western Australia.[1] In subsequent testing it showed significant cytotoxicity, potently inhibiting cancer cell proliferation in a variety of cancer cells lines (IC_{50} = 10-15 nM), and displaying retained activity towards taxol resistant carcinoma cells.[2] Additionally, when its mechanism of action was probed, eleutherobin was found to be an antimitotic agent, interfering with tubulin polymerisation dynamics in a taxol-like fashion. Specifically, eleutherobin (**1**) competes for the taxol binding site on tubulin,[55] which causes stabilisation of microtubules and results in mitotic arrest, apoptosis, and cell death.[56] Furthermore, sarcodictyin A (**15**) and B (**16**) also

posses taxol-like antimitotic properties, however, these compounds are reportedly 10-fold less potent than eleutherobin.[57]

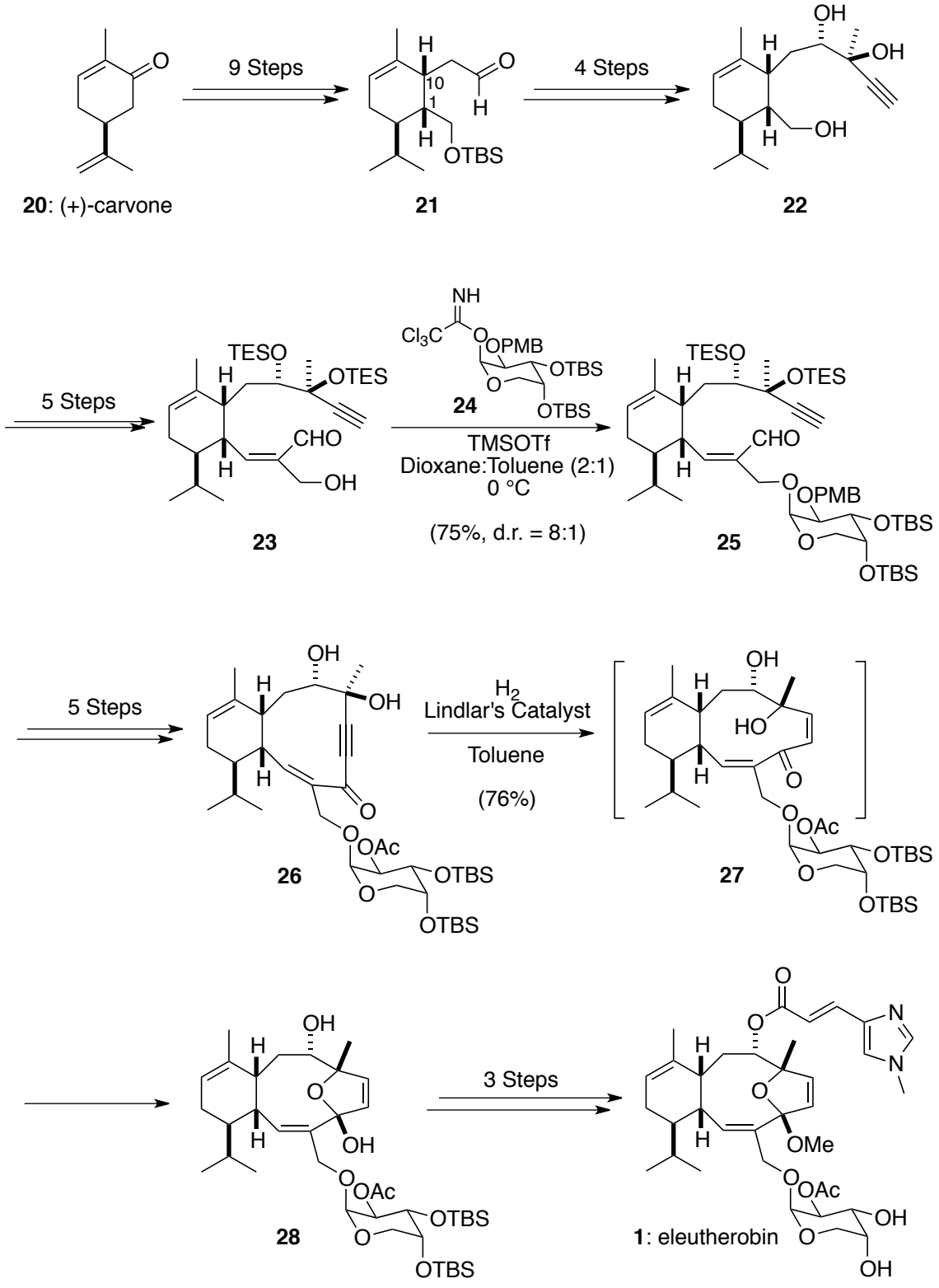
Although the syntheses of sarcodictyin A (**15**) and B (**16**), as well as eleuthoside A (**18**) and B (**19**) have been reported,[4,58] eleutherobin (**1**) has received the most attention due in large part to its promising biological profile, mechanism of action, and potential as a lead candidate for the clinical treatment of cancer. Despite these attributes, eleutherobin's development as an anti-cancer drug has been frustrated by the scarcity of material available from the natural source. To address this impasse, a number of research groups have invested considerable effort in the total synthesis of eleutherobin. Thus, while over 50 publications relating to its synthesis have appeared in the chemical literature, to date only 2 total syntheses and 1 formal synthesis have been reported.[3–9] Unfortunately, these efforts have failed to adequately address the problem of supply and eleutherobin's biological potential has yet to be fully realised.

2.1.1. Previous Syntheses of Eleutherobin

2.1.1.1. Nicolaou's Total Synthesis of Eleutherobin

Following the report of eleutherobin's antimitotic activity, Nicolaou and coworkers disclosed the first total synthesis of eleutherobin (**1**).[3,4] This synthesis commenced with the elaboration of (+)-carvone (**20**) to the silyl protected hydroxy-aldehyde **21** through a 9 step sequence that involved hydroxymethylation of **20** and a Claisen rearrangement to secure the C1-C10 *syn* stereochemistry (Scheme 2.1).[58] Exposure of aldehyde **21** to 1-ethoxyvinyllithium followed by acid catalysed hydrolysis gave two diastereomeric hydroxyketones that upon treatment with excess ethynylmagnesium bromide underwent stereoselective addition to afforded alkyne **22**. This latter material was then further elaborated to hydroxyaldehyde **23** by a 6 step sequence involving a Knoevenagel condensation and a series of functional group manipulations. Hydroxyaldehyde **23** was then treated with trichloroacetimidate **24** in the presence of a catalytic amount of TMSOTf to give an 8:1 ratio of glycosides favouring the desired β-anomer **25** in 75% isolated yield. Exposure of **25** to LiHMDS generated a lithium acetylide that subsequently underwent intramolecular addition to the aldehyde to furnish a propargyl alcohol and close the 10-membered ring. Diol **26** was then prepared through an oxidation followed by a series of protecting group manipulations. Hydrogenation of the

alkyne function over Lindlar's catalyst generated the *cis*-alkene **27** that subsequently led to formation of the acetal **28**, completing construction of the eleuthoside skeleton. Finally, installation of the *N*-methylurocanic ester and deprotection furnished eleutherobin (**1**). Following the preparation of this synthetic material, a thorough comparison of its spectroscopic and physical data with that of a natural sample confirmed the absolute stereochemistry as well as the relative stereochemical relationship between the carbohydrate and diterpenoid domain. Applying a similar set of conditions to those seen in the synthesis of eleutherobin, Nicolaou and co-workers also completed the total synthesis of sarcodictyin A (**15**) and B (**16**).[58,59] Overall, this synthetic strategy delivered 11 mg of eleutherobin in a combined yield of less than 1% over 28 steps. Key features of this work include a diastereoselective glycosylation reaction to install the arabinose moiety and an intramolecular acetylide addition to form the ten-membered ring (Scheme 2.1).

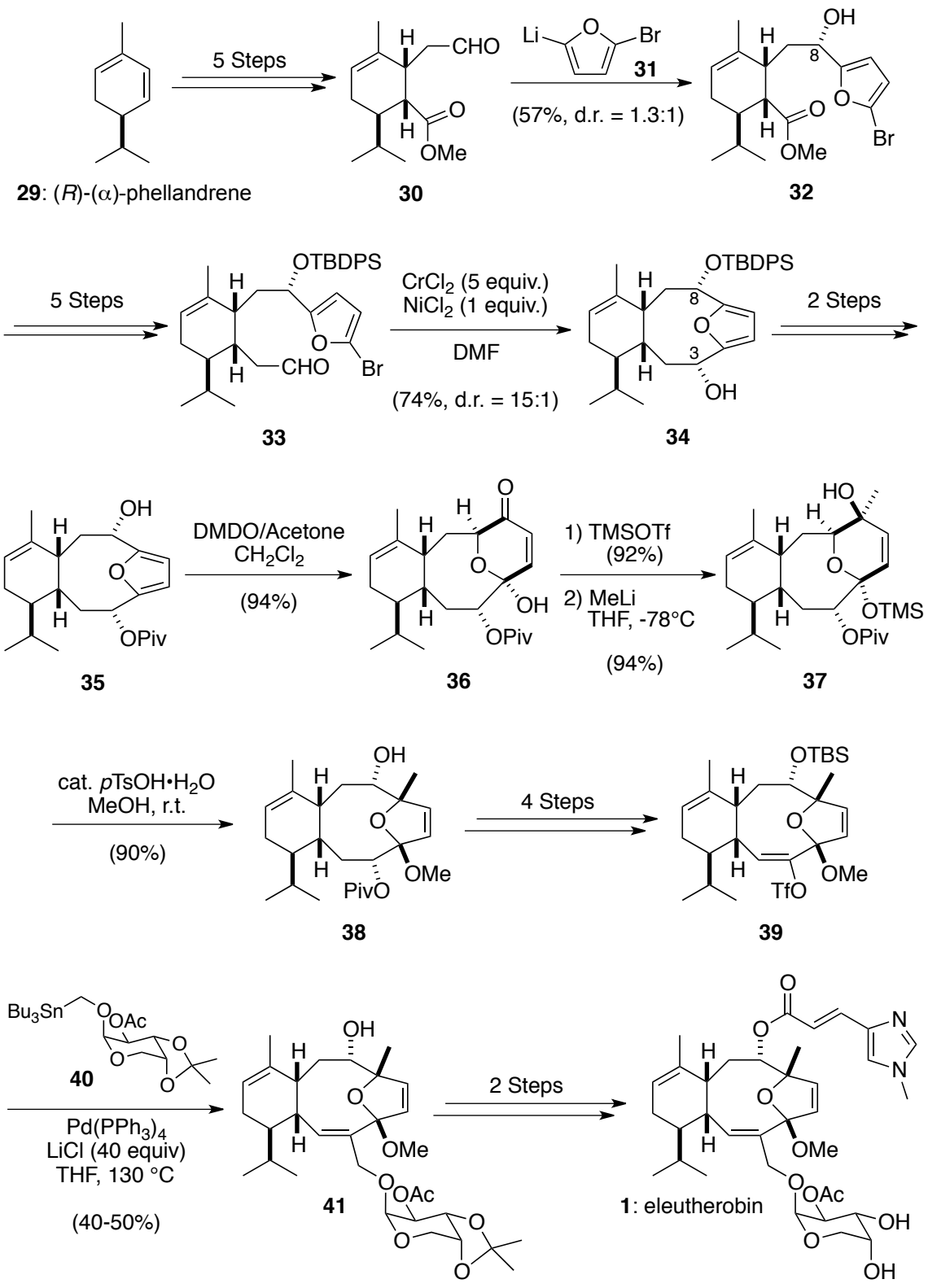


Scheme 2.1 Key transformations in Nicolaou's total synthesis of eleutherobin.

2.1.1.2. Danishefsky's Total Synthesis of Eleutherobin

Shortly after the initial report from Nicolaou, Danishefsky and co-workers disclosed an alternative total synthesis of eleutherobin (**1**).[5–7] This second synthesis initiated with the elaboration of (*R*)-(–)-phellandrene (**29**) through a 4 step sequence that included a [2+2] ketene cycloaddition followed by cyclobutanone functionalisation and fragmentation to afford aldehyde **30** (Scheme 2.2). Addition of 2-lithio-5-bromofuran (**31**) to **30** gave a diastereomeric mixture of alcohols **32** (d.r. = 1.3:1), in which the desired (8*S*)-diastereomer was isolated in 57% yield. This intermediate was then chain extended through a 5 step sequence that furnished bromoaldehyde **33** and set the stage for the key macrocyclisation reaction.

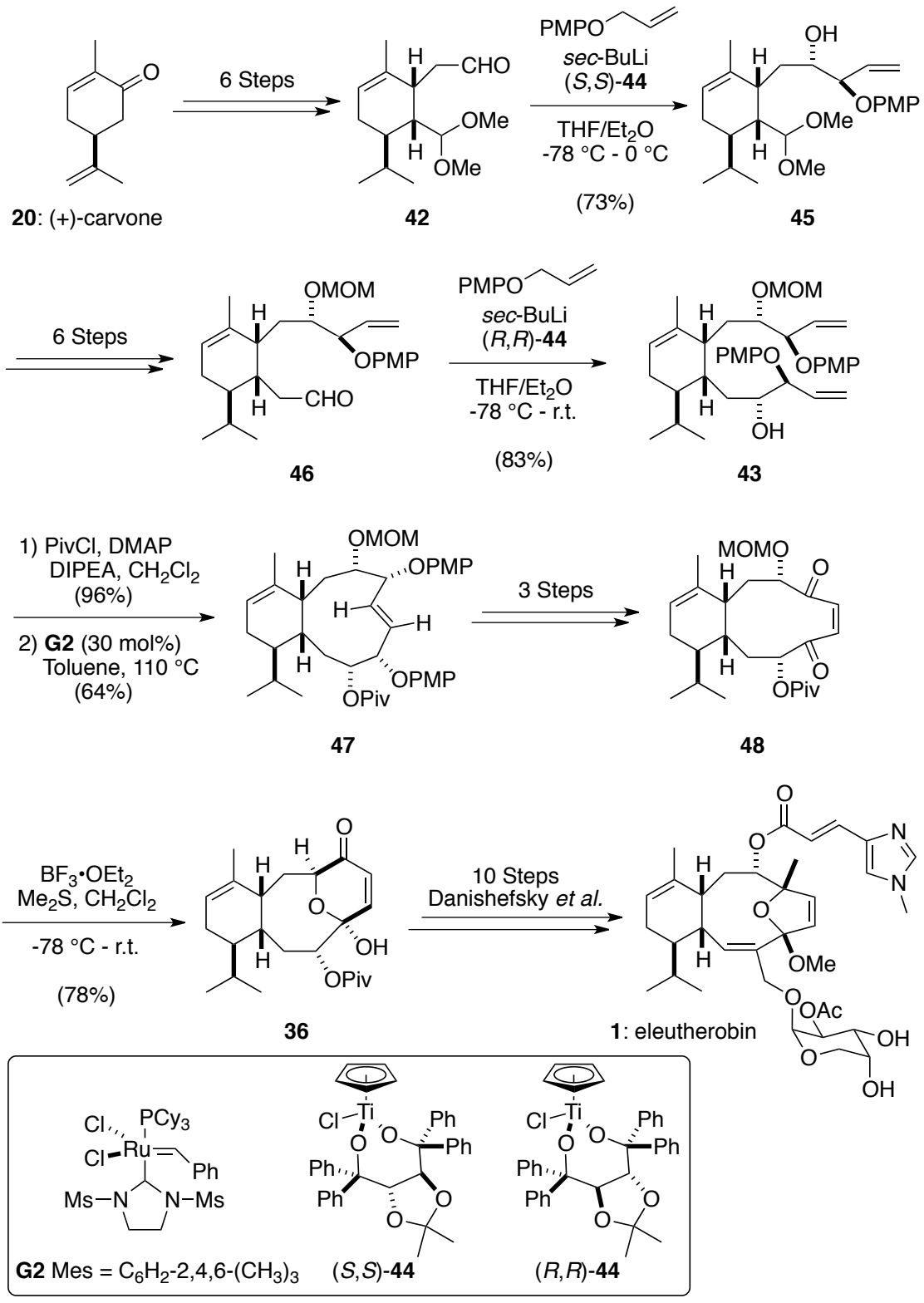
For this ring closure event, Danishefsky employed a $CrCl_2$-$NiCl_2$ mediated Nozaki-Hiyama-Kishi reductive cyclisation of **33** that afforded the macrocyclic furan **34** with excellent stereoselection for the (*R*)-diastereomer at C3 (d.r. = 15:1). Hydroxy-directed oxidation of furan **35** with DMDO gave the pyranose **36** in excellent yield. The ketal moiety was then protected as a silyl ether and treated with methyl lithium to afford the tertiary alcohol **37** in 86% yield over 2 steps. Upon treatment of **37** with a catalytic amount of acid in methanol, the pyranose function underwent a ring contraction, delivering the dihydroxy furan **38** and completing the diterpenoid core. Through a well-established sequence of functional group manipulations, **38** was converted to the vinyl triflate **39**. Realising that appending the carbohydrate domain through a standard glycosylation reaction would lead to low levels of diastereoselectivity,[6] Danishefsky employed a palladium-catalysed Stille coupling of the anomerically pure stannane **40** with the vinyl triflate **39** to afford **41**.[7] Finally, coupling of the *N*-methylurocanic ester and deprotection afforded eleutherobin (**1**). This synthesis provided 60 mg of eleutherobin in 25 consecutive steps with an overall yield of less than 1%. Central to this work was the use of a ketene [2+2] reaction to set the C1-C10 stereochemistry, a Nozaki-Hiyama-Kishi reductive cyclisation to close the 10 membered macrocycle, and a modified Stille coupling to install the carbohydrate domain (Scheme 2.2).



Scheme 2.2 **Key transformations in Danishefsky's total synthesis of eleutherobin.**

2.1.1.3. Gennari's Formal Total Synthesis of Eleutherobin

In 2005, Gennari and co-workers reported a third synthetic approach to eleutherobin (**1**).[8,9] Their synthesis initiated with the formation of the aldehyde **42** through a six step sequence that commenced with commercially available (+)-carvone (**20**).[60] Aldehyde **42** was then elaborated to diene **43** through 2 sequential Hafner-Duthaler oxyallylation reactions.[61] The first reaction, performed in the presence of titanium complex (*S*,*S*)-**44** afforded the desired product **45** as a single diastereomer in 73% yield. After a sequence of well-established reactions, homologated aldehyde **46** was then reacted under similar oxyallylation conditions, employing complex (*R*,*R*)-**44** to give diene **43** as a single diastereomer. After protection of the secondary alcohol as a pivalate ester, the diene was subjected to ring closing metathesis (RCM) conditions. To this end, treatment with Grubbs' second-generation RCM catalyst led to the kinetically favoured (*E*)-**47** macrocycle in 64% yield. Removal of the PMP protecting groups and oxidation of the allylic diol afforded an *E*-enedione that was isomerised to the thermodynamically more stable *Z*-isomer **48** following treatment with a catalytic amount of iodine. Removal of the MOM ether and spontaneous ketal formation gave the advanced intermediate **36** that displayed spectroscopic and physical data which was in full agreement to that previously reported by Danishefsky and co-workers.[6] Following the work of Danishefsky, this intermediate can be converted to eleutherobin in 10 additional steps and constitutes a formal total synthesis of eleutherobin (**1**). Overall, the Gennari synthesis gave advanced intermediate **36** in 20 steps with an overall yield of 4%. Key to this work was the use of 2 sequential oxyallylation reactions that set the stage for a ring closing metathesis reaction to close the 10 membered ring (Scheme 2.3).



Scheme 2.3 **Key transformations in Gennari's formal synthesis of eleutherobin.**

2.1.2. Structure Activity Relationship Studies on Eleutherobin

While the preceding discussion represents the state-of-the-art in eleuthoside synthesis, the overall number of steps, and generally low efficiency of these processes deter from their use in generating sufficient quantities of eleutherobin for preclinical evaluation. This work has, however, provided access to a number of synthetic analogues, and these congeners combined with those accessed through synthetic transformations performed on natural samples of eleutherobin have provided an initial glimpse into the relationship between structure and eleutherobin's antimitotic activity.[62]

As detailed in Figure 2.3, modifications to four key regions in the eleutherobin skeleton have provided insight into its microtubule stabilising pharmacophore. In particular, reactions performed on the A-ring demonstrate certain tolerability to polar groups on the α-face and a 10-100 fold decrease in activity when an epoxide or hydroxyl group is introduced to the β-face.[62] Unfortunately these few analogues represent the extent to which the carbon skeleton of eleutherobin has been probed for structure activity relationships. The remainder of the molecules studied are variants in which the eleutherobin periphery (*N*-methylurocanic ester, carbohydrate, and ketal domains) have undergone modification.[62–67] In this regard, ketal substitution showed very little effect on microtubule stabilisation, where all derivatives displayed potent activity. Studies on the *N*-methylurocanic ester domain showed that although olefin geometry has little effect on tubulin stabilisation,[64] the presence of the $\Delta^{2',3'}$ olefin was crucial for biological activity. Furthermore, it appears that both nitrogen atoms in the imidazole fragment are important, as replacement of one of these atoms with oxygen or sulphur resulted in decrease or loss of activity.[63] With respect to the carbohydrate domain, substitution of the C15 glycoside for a methyl or hydroxyl results in near loss of activity,[65] where replacement with a methyl ester or the β-anomer[67] of the arabinose leads to retained activity, indicating some degree of plasticity in this region. Surprisingly, this study also showed that although analogues that lacked an arabinose sugar moiety possessed some microtubule stabilising activity, the arabinose function was crucial for retained activity in taxol resistant cell lines.[67] These results highlight the subtle effects that structure plays in drug action and stresses the importance of structure activity relationship studies in the development of new active pharmaceutical agents.

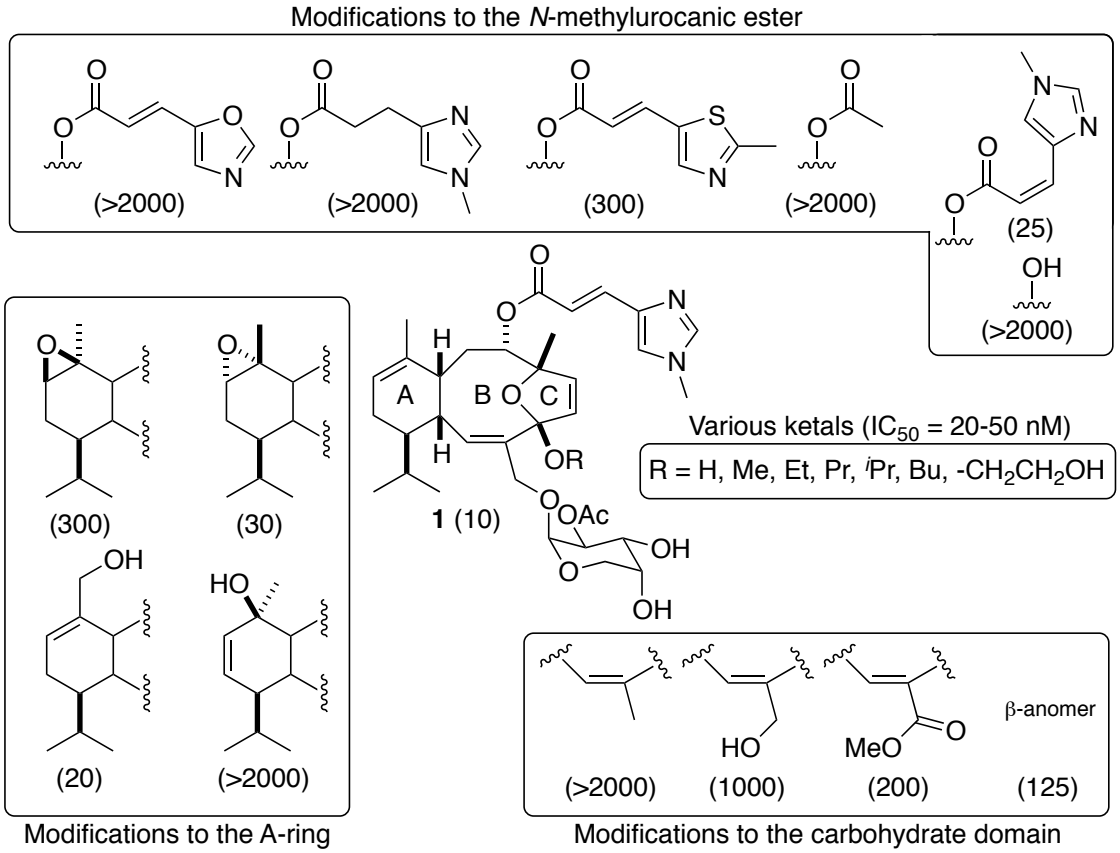


Figure 2.3 **Representative structural analogues of eleutherobin (number in parentheses represent IC_{50} values in nM).**

Based on these findings, efforts have been made to define a common pharmacophore model for microtubule stabilising agents.[68–70] Although these models correctly highlight the importance of the *N*-methylurocanic ester and carbohydrate domain, there remains little information regarding the structural importance of the carbocyclic skeleton. Therefore, the development and acceptance of a predictive model for antimitotic activity within the eleuthoside family will ultimately rely on the synthesis of new eleutherobin analogues that can systematically probe hypotheses on structure activity relationships.

2.1.3. Objectives

Despite displaying characteristics that strongly suggest eleutherobin has potential as an antimitotic agent, the primary challenge facing the progression of eleutherobin as an anticancer drug remains the lack of material. Although significant

effort has been invested in developing synthetic routes to overcome this issue, very little eleutherobin has been produced through total synthesis. While earlier reports represent important contributions to the field, questions remain regarding eleutherobin's toxicity, metabolic stability, mechanism of resistance, and the role of structure and conformation on microtubule stabilising activity. Therefore, the primary objective of our study is to develop a concise (<15 steps), flexible, and scalable synthesis of eleutherobin (**1**) from inexpensive and readily available materials that would allow for the production of sufficient quantities of material for preclinical evaluation. The remaining discussion in this chapter will focus on our investigation into the total synthesis of eleutherobin while striving to fulfill this ultimate objective.

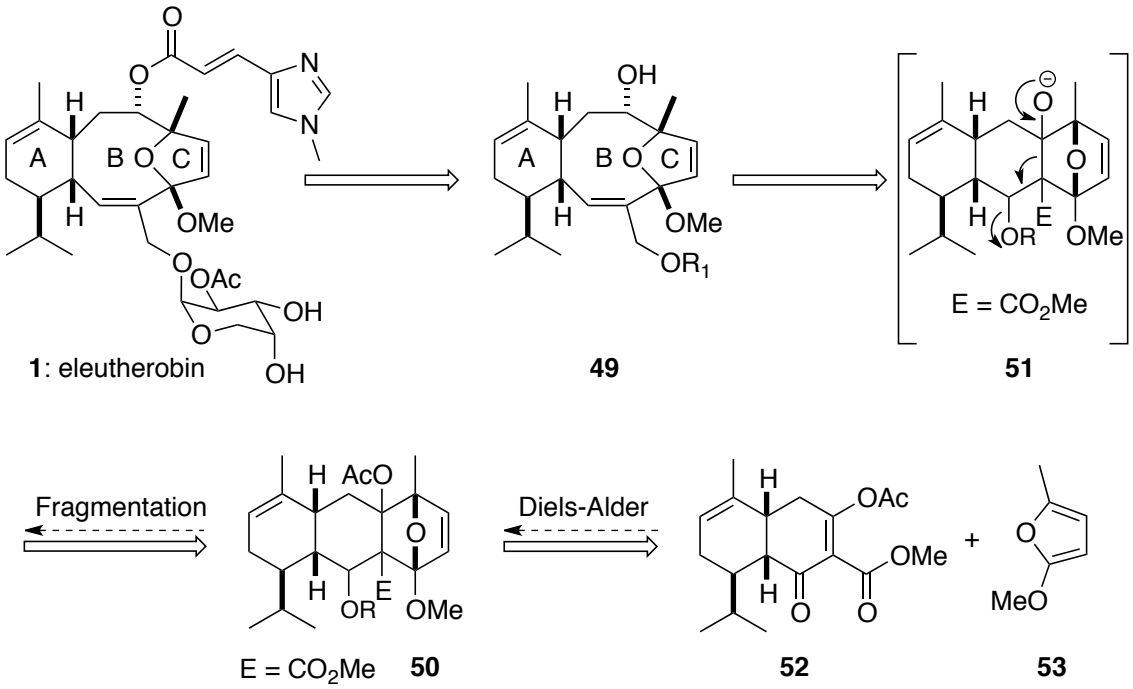
2.2. Initial Proposal: Diels-Alder/Fragmentation Strategy

2.2.1. Introduction

One of the most difficult aspects in eleuthoside synthesis is the formation of an appropriately functionalised 10-membered BC ring (Scheme 2.4). A survey of the successful syntheses of eleutherobin further highlights this obstacle, where more than half of the overall number of synthetic transformations were dedicated to construction of a correctly configured 10-membered ring from acyclic precursors. Bearing in mind our ultimate goal of a streamlined synthesis of eleutherobin, addressing this obstacle represents an important consideration. This section will discuss our studies into a Diels-Alder/fragmentation approach to access the core of eleutherobin, which we anticipated would overcome the complexities associated with the formation of the 10-membered ring.

Our initial proposal is outlined in Scheme 2.4. We hypothesised that the problematic 10-membered ring formation could be overcome through a synthetic plan that utilises bond cleavage of a functionalised decalin. Retrosynthetically, our strategy relies on late stage installation of the *N*-methylurocanic ester and arabinose moiety to the diterpenoid core of eleutherobin (**49**). It was expected that the fully functionalised core of eleutherobin could then be accessed from the oxatetracycle **50** through the

fragmentation of intermediate **51**. The former material would then be derived from a Diels-Alder reaction between enone **52** and 2-methoxy-5methylfuran (**53**).



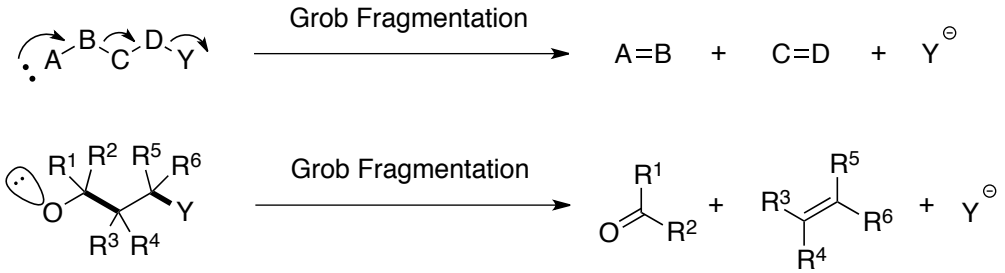
Scheme 2.4 Initial retrosynthetic analysis for eleutherobin.

This strategy would take advantage of the power of the Diels-Alder reaction to rapidly build structural complexity in a single step and draw on the extensive use of this well-known reaction in natural product total synthesis.[71,72] Diels-Alder [4+2] cycloadditions employing furans as the 4π diene component were some of the first reactions studied by Otto Diels and Kurt Alder during their development of this pericyclic reaction in the later part of the 1920s.[73,74] Consequently, it is of little surprise that the reaction of maleic anhydride with furan - a classic example of this prominent name reaction - is performed in many undergraduate organic chemistry laboratories. Since Diels and Alder's initial work, the use of furan Diels-Alder reactions has gained widespread use for the assembly of valuable synthetic targets and intermediates.[75] However, furans are known to have a high propensity towards retro-Diels-Alder reactions, which in many cases is problematic.[76,77] Additionally, the equilibrium position of furan Diels-Alder reactions are quite sensitive to temperature, solvent, and concentration, as well as the substitution pattern on both the furan and dienophile components.[78,79] These aspects, combined with furans aromatic nature and

consequently decreased reactivity make these reactions somewhat challenging. Nevertheless, several methods have been developed to address these issues such as the use of high-pressure,[80] Lewis-acid mediated reactions,[81,82] or utilising highly reactive dienophiles.

Although very few examples of furan Diels-Alder reactions between 2,5-disubstitued furans and tetra-substituted dienophiles exist in the literature, we were encouraged by the anticipated reactivity of our proposed system. Specifically, the presence of the electron withdrawing ketone and ester functions on the dienophile, as well as the electron donating methoxy substituent on the furan diene component was predicted to impart added reactivity to the two Diels-Alder components.

The successful execution of the proposed furan Diels-Alder reaction would then set the stage for a Grob fragmentation of the tricyclic Diels-Alder product **50**. Named after British chemist Cyril A. Grob, this reaction is described as a "fragmentation of a 1,3-diheterofunctionalised compound featuring a nucleophilic atom often called the nucleofuge, and leaving group, also called the electrofuge situated in a 1,3-relationship" (Figure 2.4).[83] Although this reaction bears Grob's name, the general process was reported almost 22 years earlier by several independent research groups, including pioneering work by Eschenmoser in 1952.[84,85] Several years later, Grob reported the fragmentation of 1,4-dibromocyclohexane,[86] after which time this reaction was known as the "Grob fragmentation" in somewhat "glaring disregard of earlier contributions."[83]



R^1, R^2 = alkyl, aryl, C=O
Y = OMs, OTs, Hal, $^+NR_3$

Figure 2.4 General reaction scheme for the Grob fragmentation.

Mechanistically, the Grob fragmentation can occur through either a stepwise mechanism (either cationic or anionic) or a concerted process. Which process is operative depends on a number of factors including the nature of the leaving group, and the ability of adjacent groups to stabilise a negative charge (Figure 2.5). With respect to the concerted process, there are strict structural and stereochemical requirements for the fragmentation to take place. Firstly, the lone pair of electrons on the oxygen must be *anti*-periplanar to the C2/C3 bond which helps donate electron density into the σ^* antibonding orbital thus weakening the fragmenting bond. Additionally, the C1/Y bond must be *anti*-periplanar to the C2/C3 bond to facilitate departure of the leaving group. This all *anti*-periplanar conformation maximizes orbital overlap in the transition state and is displayed in all the staggered conformations shown in the bottom of Figure 2.5. In this respect, the geometry of the newly formed olefin is set by the relative stereochemistry of the groups on C1 and C2.

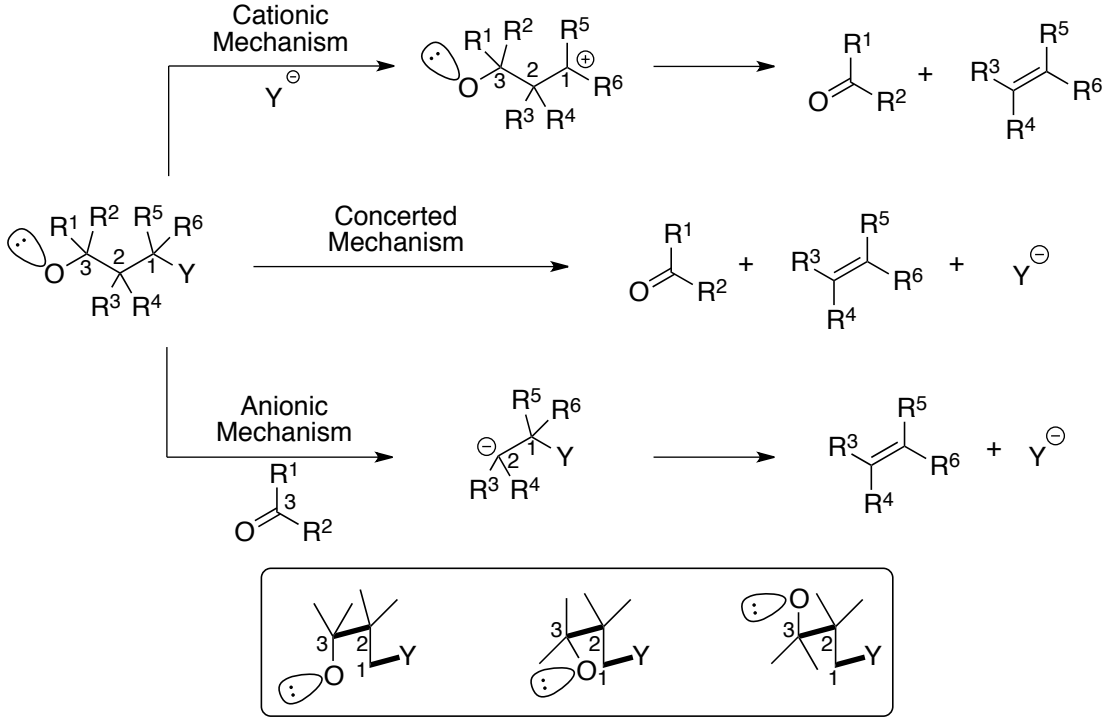
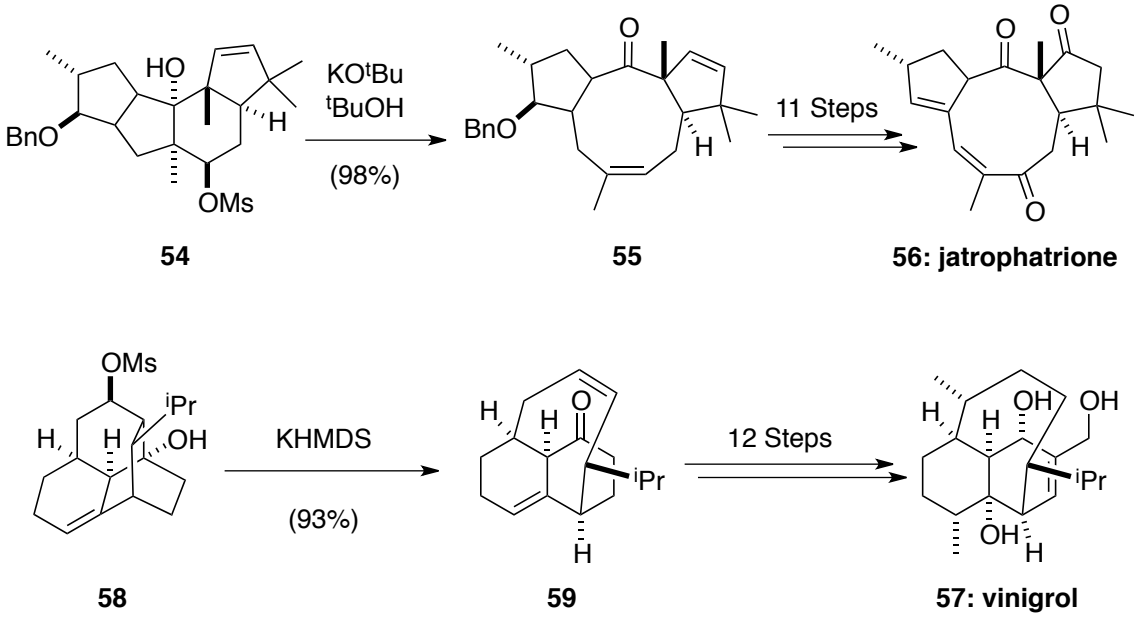


Figure 2.5 Mechanistic aspects of the Grob fragmentation.

As a testament to its synthetic utility, the Grob fragmentation has seen extensive use in natural product synthesis, particularly in the formation of synthetically challenging medium sized rings.[83] For example, Paquette reported a Grob fragmentation of

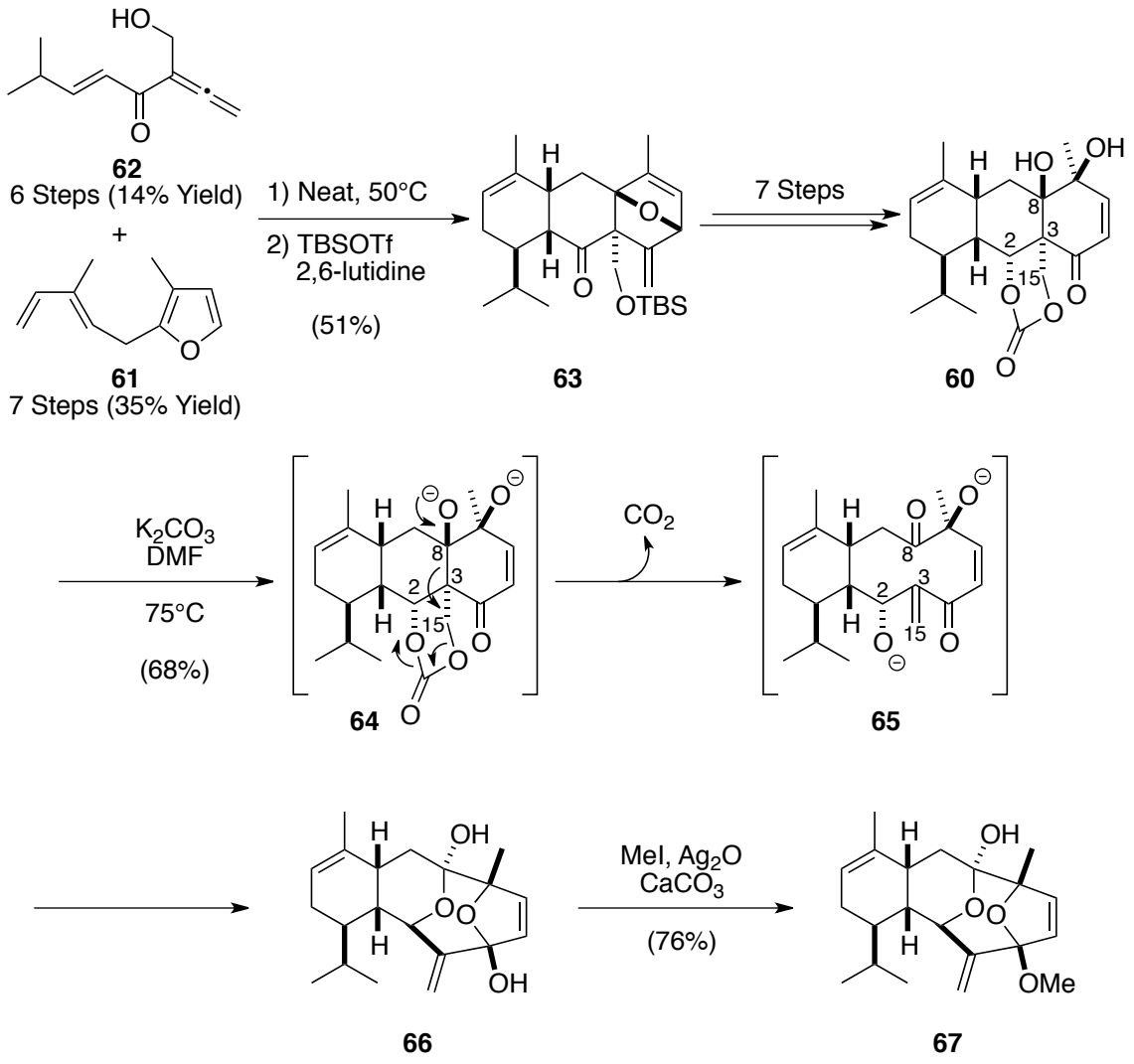
tetracyclic mesylate **54** which gave the tricyclic ketone **55** in nearly quantitative yield. This key reaction was used to install the 9-membered ring in their total synthesis of the tumour inhibitory agent jatrophatrione (**56**) (Scheme 2.5).[87] Additionally, Baran and co-workers recently reported a total synthesis of vinigrol (**57**) that utilises a Grob fragmentation of mesylate **58** to access **59**, the unusual 1,5-butanonaphthalene skeleton of this diterpenoid natural product.[88]



Scheme 2.5 Examples of the Grob fragmentation in total synthesis.

Our proposed Grob fragmentation is not the first time this strategic disconnection has been exploited in eleuthoside synthesis. Winkler and co-workers published a failed attempt towards the synthesis of eleutherobin that relied upon a Grob fragmentation of carbonate **60** as their key step *en route* to the 10-membered ring of eleutherobin (Scheme 2.6).[89] Winkler constructed the tricyclic fragmentation precursor through a tandem Diels-Alder reaction between dienylfuran **61** and ketene **62** that afforded racemic **63** after protection of the primary alcohol as the silyl ether. This compound was then elaborated to the carbonate fragmentation precursor **60** through a series of functional group manipulations that included oxidative cleavage of the exocyclic olefin, radical induced cleavage of the oxabicyclic ring, and hydroxy-directed epoxidation with concomitant epoxide opening to install the enone. Treatment of this latter material with potassium carbonate led to intermediate **64**, which induced a Grob fragmentation that

led to the formation of the 10-membered intermediate **65**. Subsequent ketalisation generated dihydrofuran **66**, which upon methylation of the ketal gave rise to **67**. Although this strategy was successful in fragmenting the fused decalin to a ring expanded cyclodecane, the elimination of the carbonate to give the exocyclic olefin between C3 and C15 instead of the desired $\Delta^{2,3}$ unsaturation ultimately led to the abandonment of this approach. However, despite the failure of this route to successfully deliver eleutherobin, this work serves as excellent precedence for our proposed fragmentation reaction.



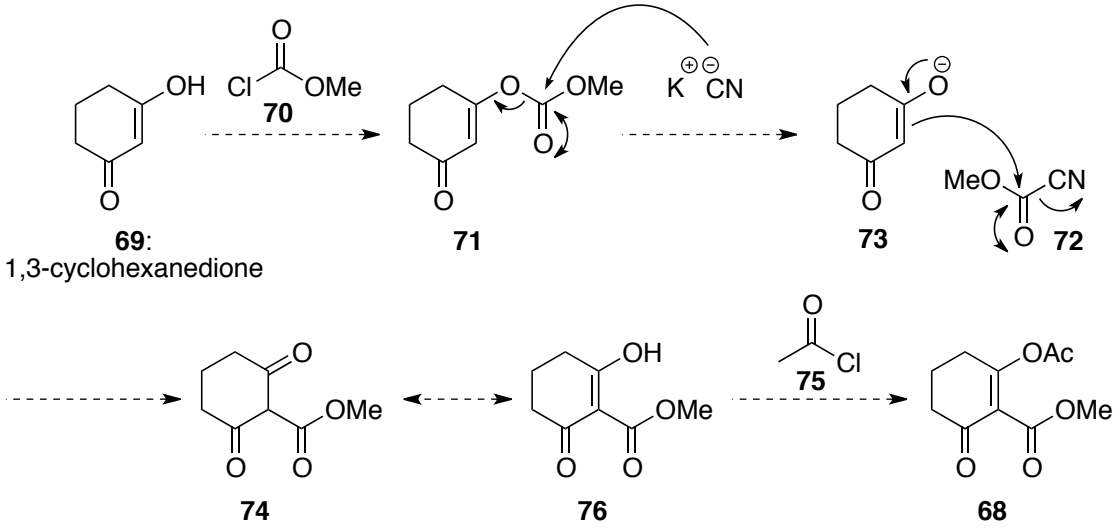
Scheme 2.6 Key transformations in Winkler's racemic Diels-Alder/fragmentation approach to eleutherobin.

2.2.2. Intermolecular Furan Diels-Alder Strategy

Based on the synthetic plan outlined above, our initial focus centred on the establishment of a proof of concept for the furan Diels-Alder reaction on a simplified dienophile. We reasoned that removal of the cyclohexene A ring from dienophile **52** would simplify the synthesis without significantly influencing the steric or electronic factors affecting the reaction outcome.

2.2.2.1. Synthesis of Model Dienophile 68

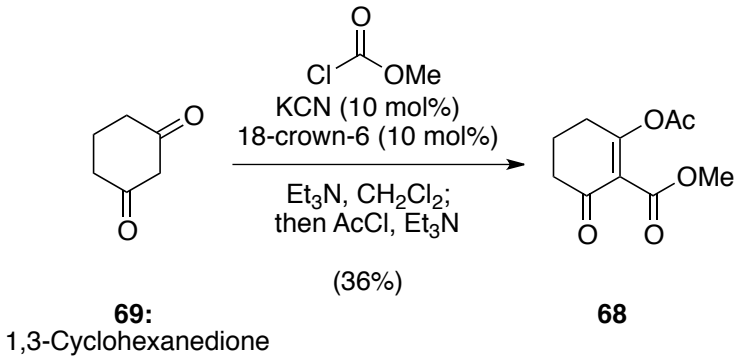
It was envisioned that model dienophile **68** could be derived through a cyanide catalysed rearrangement reaction (Scheme 2.7). Although this type of process has been exploited in the oxygen to carbon rearrangement of vinylogous esters, the subsequent rearrangement of vinylogous carbonates has not been reported.[90] The proposed mechanism is as follows. Reaction of 1,3-cyclohexandione (**69**) with methyl chloroformate (**70**) is expected to give vinylogous carbonate **71**. Nucleophilic addition of potassium cyanide on the carbonate would generate Mander's reagent (**72**)[91] *in situ* and enolate **73**. Subsequent carbon acylation would form the methoxycarbonylated dione **74** and regenerate the cyanide anion. Finally addition of acetyl chloride (**75**) to the vinylogous acid **76** would then afford dienophile **68**. While an alternative synthesis of **74** (3 steps, 80% overall yield) from 2,6-dimethoxybenzoic acid has been reported, the use of mercury salts and a Birch reduction detract from the synthetic appeal and scalability of this route.[92]



Scheme 2.7 Proposed synthesis of dienophile 68 through a cyanide catalysed rearrangement reaction.

Towards this end, treatment of 1,3-cyclohexanedione (**69**) with methyl chloroformate (**70**), in the presence of triethylamine and a catalytic amount of potassium cyanide generated the vinylogous acid **76** in a 1:1 ratio with **69** as determined by ^{1}H NMR spectroscopy. Unfortunately, the time needed to reach completion (> 3 days) was a considerable drawback to this process, however, addition of a catalytic amount of 18-

crown-6 decreased the reaction time needed to reach completion to 24 hours. Presumably 18-crown-6, which is well know to complex with potassium ions, gives a more nucleophilic source of cyanide anion and accelerates the consumption of the initially formed vinylogous carbonate **71**. Despite these results, attempts to isolate **76** were met with considerable difficulty. Not only is compound **76** water soluble, it is quite sensitive to acidic media, and readily undergoes decarboxylation at pH<2. In order to circumvent these difficulties, it was postulated that acetylation of vinylogous acid **76** prior to isolation would give a more tractable crude reaction mixture. Fortunately, reaction of 1,3-cyclohexanedione (**69**) under the previous described conditions followed after 24 hours by addition of triethylamine and acetyl chloride generated dienophile **68** in 36% yield (Scheme 2.8). Although the yield for this reaction is not ideal, the efficiency and synthetic ease with which this one-pot process gives access to compound **68** outweighs the drawbacks associated with the low isolated yield.



69: 1,3-Cyclohexanedione

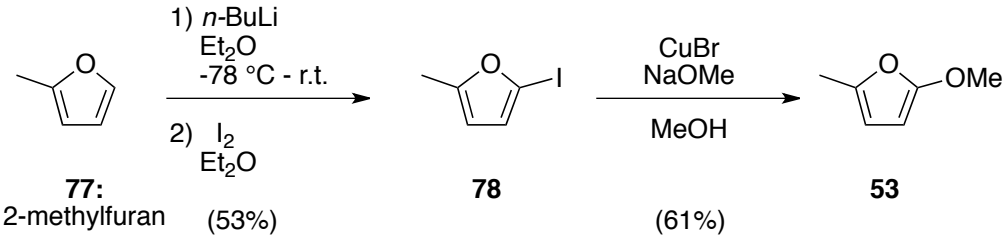
68

Scheme 2.8 Synthesis of model dienophile 68.

2.2.2.2. Synthesis of 2-Methoxy-5-methylfuran (53)

With dienophile **68** in hand, we turned our attention to the synthesis of 2-methoxy-5-methylfuran (**53**), the 4π-diene component of the proposed furan Diels-Alder reaction. While several reports refer to the use of 2-methoxy-5-methyfuran and even allude to its synthesis, none of these explicitly describe its experimental preparation.[93–95] Therefore, the synthesis of furan **53** relied on the utilisation of existing methods for the preparation of alkyl heteroaryl ethers from heteroaryl iodides.[96] Towards this end, reaction of 2-methylfuran (**77**) with *n*-butyllithium followed by treatment of the resulting lithium anion with iodine gave 2-iodo-5-methylfuran (**78**) in 53% yield (Scheme 2.9).

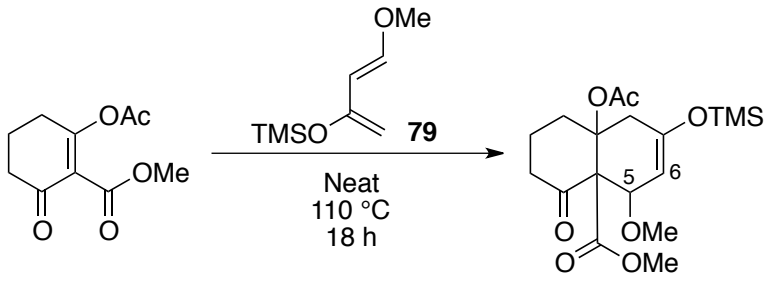
Refluxing a solution of **78** in freshly prepared sodium methoxide in the presence of copper(I) bromide gave 2-methoxy-5-methylfuran (**53**) in 61% isolated yield.



Scheme 2.9 Synthesis of 2-methoxy-5-methylfuran (53).

With the successful synthesis of model precursors **68** and **53**, we were poised to investigate the intermolecular furan Diels-Alder reaction of these two components. However, before attempting reactions with the furan **53**, it was deemed prudent to first study the reactivity of **68** with a model Diels-Alder diene.

For this investigation, Danishefsky's diene (**79)** was employed, due to its nucleophilic nature and reports of high levels of regioselectivity with unsymmetrical dienophiles.[97] Heating a neat solution of dienophile **68** with 10 equivalents of Danishefsky's diene (**79**) at 50 °C for several days gave only starting material and some products derived from hydrolysis of the silyl enol ether function in **79**. Increasing the temperature to 75 °C had no effect on the reaction outcome. However, when **68** and **79** were heated to 110 °C, full consumption and clean formation of the Diels-Alder adduct **80** was observed (Scheme 2.10). Inspection of the crude ^{1}H NMR spectrum revealed new resonances corresponding to the silyl enol ether and methoxy ether methine protons H6 and H5 at δ 5.15 (dd, 1H, *J* = 4.9, 1.9 Hz) and δ 4.25 (d, 1H, *J* = 4.9 Hz), respectively. Furthermore, the cyclohexane methylene protons that appeared between δ 2.66 – 2.41 (6H) and δ 1.88 – 1.71 (2H) displayed complex multiplicity, which was indicative of adjacent chirality being introduced into the previously achiral dienophile.



68 **80**

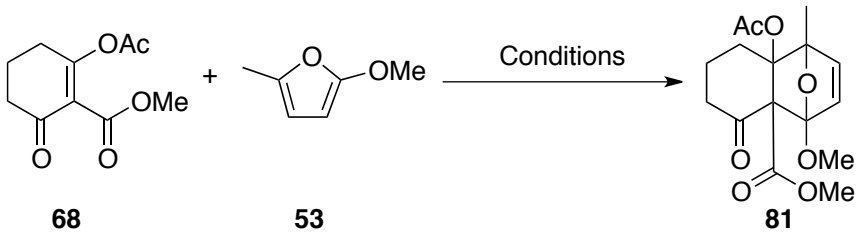
Scheme 2.10 Reaction of dienophile 68 with Danishefsky's diene.

2.2.2.3. Intermolecular Furan Diels-Alder Reactions

Cognisant of the decreased reactivity of **53** compared to Danishefsky's diene (**79**), but pleased with these results, we began our investigation into the formation of **81** through the proposed intermolecular furan Diels-Alder reaction between dienophile **68** and the furan **53**. The preliminary results of this study are summarised in Table 2.1.

Initial studies of the intermolecular furan Diels-Alder reaction focused on thermally promoted conditions due to the operational simplicity and traditional use of this method in Diels-Alder cycloadditions. While heating a mixture of the dienophile **68** and the furan **53** to 80 °C in toluene produced no reaction (entry 1), increasing the temperature to 110 °C led to complete consumption of the furan (entry 2). Although inspection of the crude ^{1}H NMR spectrum revealed no change in the signals corresponding to **68**, a new a set of doublets at δ 6.48 and δ 6.04 (d, 1H, *J* = 10.6 Hz) as well as two singlets at δ 3.77 (3H) and 2.33 (3H) appeared to have arisen from the furan. It was clear from the coupling constants that these protons no longer resided on a ring but were now part of a linear *cis*-olefin. Furthermore, the chemical shifts of the two singlets, along with their integration suggested a methyl ester, and methyl ketone respectively. Based on this information, it was deduced that furan **53** had been oxidised to ketoester **82** through the mechanism shown in Scheme 2.11. First, oxidation of furan leads to the oxo-bicycle **83**, which subsequently undergoes rearrangement to the carbonyl oxide **84**. The exact mechanism by which this latter compound is reduced to ketoester **82** is still of some contention, but it is believed that a dimerisation of the carbonyl oxide leads to intermediate **85** which decomposes to ketoester **82**.[98] Accordingly, the spectral data observed for **82** was in agreement with literature reported data for the oxidation of furan **53** with PCC.[99]

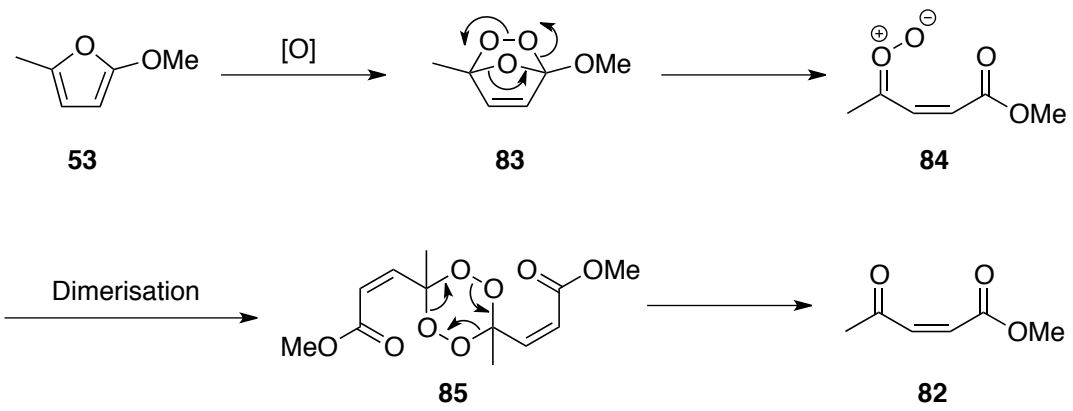
Table 2.1 Intermolecular Furan Diels-Alder Reactions



68 **53** **81**

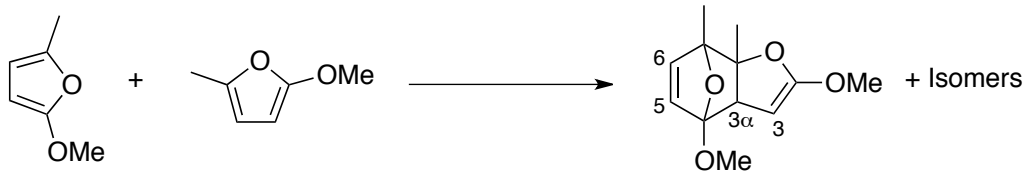
entry	solvent	Lewis-Acid	temp. (°C)	time (h)	result
1	toluene	-	80	48	no reaction
2	toluene	-	110	48	furan oxidation, ketoester **82**
3[a]	none	-	50	72	furan dimer **86** (trace)
4[a]	none	-	75	72	furan dimer **86** (trace)
5[a]	none	-	110	72	furan dimer **86** (trace)
6[a]	none	-	250	18	furan dimer **86** (trace)
7[b]	none	-	n.d.	2	furan dimer **86** (trace)
8[c]	CH_2Cl_2	$MgBr_2$	-78 - r.t.	8	no reaction
9[d]	CH_2Cl_2	BF_3•OEt_2	-78	6	1,4-addition/elimination product **87**
10[e]	CH_2Cl_2	$SnCl_4$	-78	2	1,4-addition/elimination product **87**
11[f]	CH_2Cl_2	$EtAlCl_2$	-78 - r.t.	4	chloride addition/elimination

[a] performed in a sealed screw-top vial with 5 equiv. of **53** and with the exclusion of oxygen. [b] performed in a standard home-use microwave oven in a sealed screw-top vial. [c] performed in CH_2Cl_2 with the addition of 3 equiv. of **53** and 2 equivalents of $MgBr_2$. [d] performed in CH_2Cl_2 with 10 equiv. of **53** and 2 equiv. of BF_3•OEt_2 in the presence of 4Å MS. [e] performed in CH_2Cl_2 with the addition of 3 equiv. of **53** and 1.5 equiv. of $SnCl_4$. [f] performed in CH_2Cl_2 with 1 equiv. of **53** and 1 equiv. of Et_2AlCl.



Scheme 2.11 Proposed mechanism of furan oxidation to ketoester 82.

Despite the slow degradation of **53** in previous reactions, no reaction of dienophile **68** was observed under the conditions employed. In subsequent reactions, neat conditions were utilised so as to avoid any deleterious oxygen present in the solvent, and to increase the interaction of the reacting components. When a solution of dienophile **68** and furan **53** were heated at various temperatures ranging from 50 °C to 250 °C (entry 3-7) we observed primarily the recovery of starting materials, with minor products representing less than 5% of the total crude mixture. Of particular interest in these minor components was the isolation of two compounds that displayed spectral data in agreement with the formation of the furan Diels-Alder dimer **86** (Scheme 2.12). The ^{1}H NMR spectrum of one isomer of **86** contained a set of doublets at δ 6.10 and δ 5.91 (d, 1H, *J* = 5.5 Hz) indicative of the dihydrofuran protons H5 and H6. Furthermore, a second set of doublets at δ 3.81 and 3.28 were consistent with the two-proton spin system of the ketene acetal proton H3 and bridgehead methine proton H3α. Finally, two sets of methoxy ether and methyl signals further enforced the dimeric nature of this substrate.



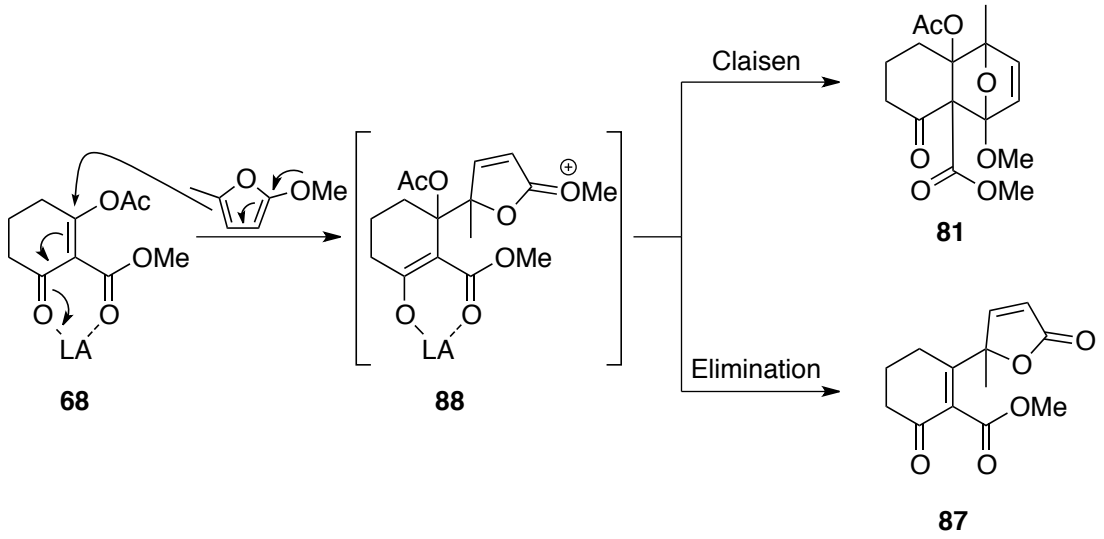
53 **53** **86**

Scheme 2.12 Diels-Alder dimerisation of furan 53.

In addition to the unusual formation of this dimer, no reaction between furan **53** and dienophile **68** was observed. In and effort to overcome the sluggish reactivity of furan dienes, Lewis-acid catalysis has been frequently employed in furan Diels-Alder reactions. Employing the weakly Lewis-acidic magnesium bromide, led to no reaction and recovery of starting materials after 8 hours (entry 8). Utilising BF_3•OEt_2 and $SnCl_4$ (entry 9-10) gave significant amounts of butenolide **87**, which comes from the proposed 1,4-addition/elimination sequence depicted in Scheme 2.13. Coordination of the 1,3-dicarbonyl by the Lewis-acid activates the β-position of the enone for nucleophilic attack by the furan leading to intermediate **88**. At this point, a Claisen condensation reaction of the resulting enolate with the pendant butenolide carbonyl would afford the Diels-Alder adduct **81**. In an alternative pathway, elimination of the β-acetoxy group would give **87**. Considering that the Diels-Alder reaction can proceed *via* a concerted or stepwise mechanism, the formation of **87** is indicative of this stepwise process where elimination of the acetoxy group from intermediate **88** is more facile than intramolecular Claisen condensation. The consequence of the acetoxy group positioning was highlighted in the reaction employing Et_2AlCl (entry 11), where substitution of the acetoxy group for chloride was observed, presumably proceeding through an intermediate analogous to **88**. Not surprisingly, this type of reactivity has been observed previously, where Lewis-acids were found to give exclusively 1,4-addition products in the reaction of cyclopentenones with similarly substituted furan dienes.[100]

Not only was the position of the acetoxy group problematic, the 1,3-dicarbonyl was also of concern. If a stepwise mechanism was operative, as was suggested by these studies, then the formation of intermediate **88** would result in a resonance-stabilised enolate, thus decreasing its reactivity and as such its propensity to undergo the Claisen addition step. As a result of the aforementioned difficulties, as well as our

failure to produce a Diels-Alder adduct by intermolecular means, we chose to abandon this model study.



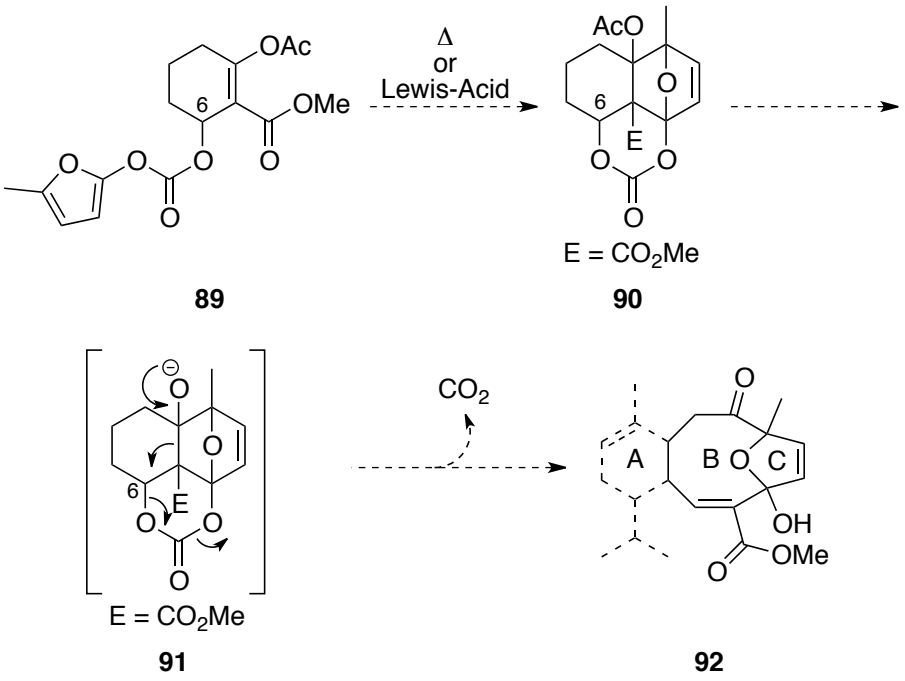
Scheme 2.13 Stepwise Diels-Alder mechanism leading to butenolide 87.

2.2.3. Intramolecular Furan Diels-Alder Reactions

Due to our lack of success in the execution of an intermolecular Diels-Alder reaction, we were forced to rethink our originally proposed strategy (Scheme 2.4). While still interested in exploring a furan Diels-Alder approach to eleutherobin, we chose to pursue an intramolecular variant, which could overcome some of the issues associated with our previous approach. In particular, by tethering the diene and dienophile, the reaction would expectedly benefit from lower activation entropy and increased reaction rate, due in large part to proximity effects that increase the effective concentration of reacting partners.[101] Additionally, the choice of tethering position would introduce the possibility of imparting asymmetry on the process, a necessary aspect in the eventual synthesis of eleutherobin. Despite these advantages however, the main challenge facing the feasibility of such an approach would be the preparation of an intramolecular furan Diels-Alder substrate.

Our revised model approach is described in Scheme 2.14. It was desirable that the intramolecular Diels-Alder substrate would feature the fewest possible structural changes to the substrates that were employed in the intermolecular approach. This aspect, combined with the intention to form a favourable sized ring in the cycloaddition

step led us to target the tethered Diels-Alder precursor **89**. Thus, it was believed that such a substrate could be prepared utilising the methods that were developed previously for the synthesis of dienophile **68**. Furthermore, the carbonate was considered advantageous because it would impose a low level of steric bulk on the transition state of the Diels-Alder reaction (**89** → **90**). Additionally, the carbonate function was expected to aid the subsequent Grob fragmentation reaction, activating the C6 oxygen as a leaving group, releasing carbon dioxide and affording access to the eleutherobin core (**91** → **92**). Choosing to tether the furan through the C6 oxygen in **89** would accomplish a necessary reduction in the oxidation state of this carbon, which would also allow for asymmetry to be introduced at C6 through employment of an enantioselective reduction method. In turn, the configuration of the C6 centre would impart facial selectivity on the requisite Diels-Alder reaction in what would ultimately lead to an enantioselective synthesis of eleutherobin (**1**).

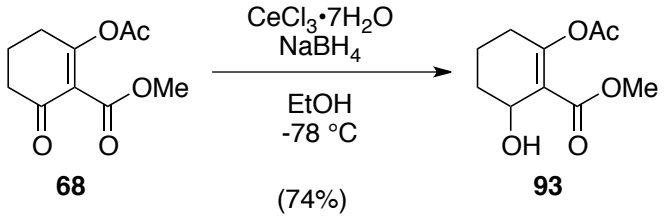


Scheme 2.14 Proposed intramolecular furan Diels-Alder/fragmentation route to the eleutherobin core.

2.2.3.1. Synthesis of Carbonate Tethered Diels-Alder Precursor 89

The next step in our study was the preparation of the carbonate tethered Diels-Alder precursor **89**. It was envisioned that reduction of the ketone function in **68** would

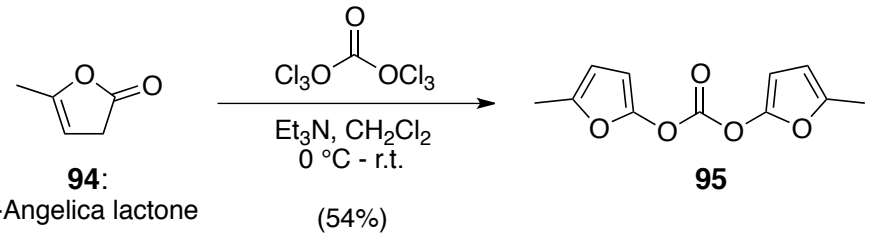
give access to the dienophilic portion of the tethered substrate. Towards this end, treatment of **68** under Luche reduction conditions ($CeCl_3 \cdot 7H_2O$, $NaBH_4$)[102] at -78 °C led to clean formation of the desired allylic alcohol **93** in 74% yield (Scheme 2.15). Notably, it was necessary to conduct this reaction at low temperature, as the yield of **93** eroded as the temperature of the reaction was increased. Subsequently, it was expected that activation of the allylic alcohol **93** as the corresponding chloroformate would facilitate its coupling to the furan portion of carbonate **89**. However utilising standard conditions for the preparation of chloroformates (triphosgene, Et_3N, CH_2Cl_2)[103] led to the formation of a considerable amount of by-products including dimers, and formation of dienes through chloroformate elimination. While it was possible to form analogous activated carbamates by reaction of alcohol **93** with CDI, subsequent coupling reactions were abortive due to attack of nucleophiles on the acetate carbonyl and elimination of the activated C6 allylic alcohol in a process similar to that shown in Scheme 2.18.



Scheme 2.15 Synthesis of allylic alcohol 93.

Our inability to activate the allylic alcohol led us to investigate an approach to carbonate **89** that would rely on reaction of **93** with an appropriately activated furan. Attempts to prepare the enol chlorofromate of α-angelica lactone (**94**) through its reaction with triphosgene gave several products with unclear structures. Eventually, through analysis of the spectral data (^1H NMR, ^{13}C NMR, IR, HRMS) derived from the major product, it was determined that this compound was not the expected chloroformate, but was in fact the *bis*-furan carbonate **95** shown in Scheme 2.16. While the majority of the data gave an ambiguous assignment, ultimately the structural determination of this compound relied on the mass spectral data which clearly showed a M+H signal at 223.0606 *m/z* which was consistent with the formula $C_{11}H_{11}O_5$. Although the synthetic utility of this bis-furan carbonate was unclear, it was encouraging to find that by altering the reaction stoichiometry it was possible to generate **95** in almost quantitative yield. While this compound could be purified by flash chromatography to

remove small impurities, its purification was accompanied by a substantial drop in the isolated yield (54%). Notably, thiophene variants of this carbonate have been prepared for use as coupling agents for the conversion of carboxylic acids to esters.[104] Whilst the authors of this previous work failed to form bis-furyl carbonate coupling agents similar to **95**, they did identify the synthetic potential of a furyl-activated ester for this conversion. Nonetheless, this work gave encouragement that carbonate **95** would be sufficiently activated to allow for the preparation of the intramolecular Diels-Alder precursor **89**.

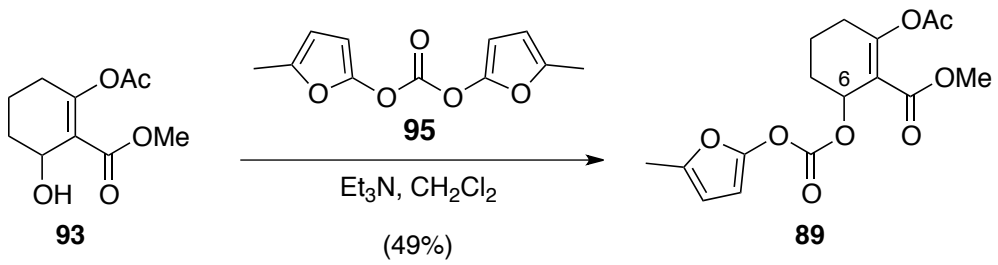


94:
α-Angelica lactone

95

Scheme 2.16 Synthesis of *bis*(5-methylfuran-2-yl) carbonate (95).

Through some experimentation, it was found that simply stirring allylic alcohol **93** with a large excess of carbonate **95** (7.5 equiv.) in the presence of triethylamine gave the desired carbonate **89** in 49% yield (Scheme 2.17). The ^{1}H NMR spectrum of the product displayed a diagnostic signal at δ 5.86 (br. t, 1H), corresponding to the deshielded carbonate C6 methine (Figure 2.6). Furthermore, the presence of 3 carbonyl signals in the ^{13}C NMR spectrum at δ 167.8, 163.9, and 163.1 were consistent with the 2 esters and carbonate function in **89**. Finally, the HRMS displayed a signal at 361.0916 m/z corresponding to a molecular formula of $C_{16}H_{18}NaO_8$ (M+Na), thus solidifying the structural assignment of the Diels-Alder precursor.



Scheme 2.17 Synthesis of carbonate 89.

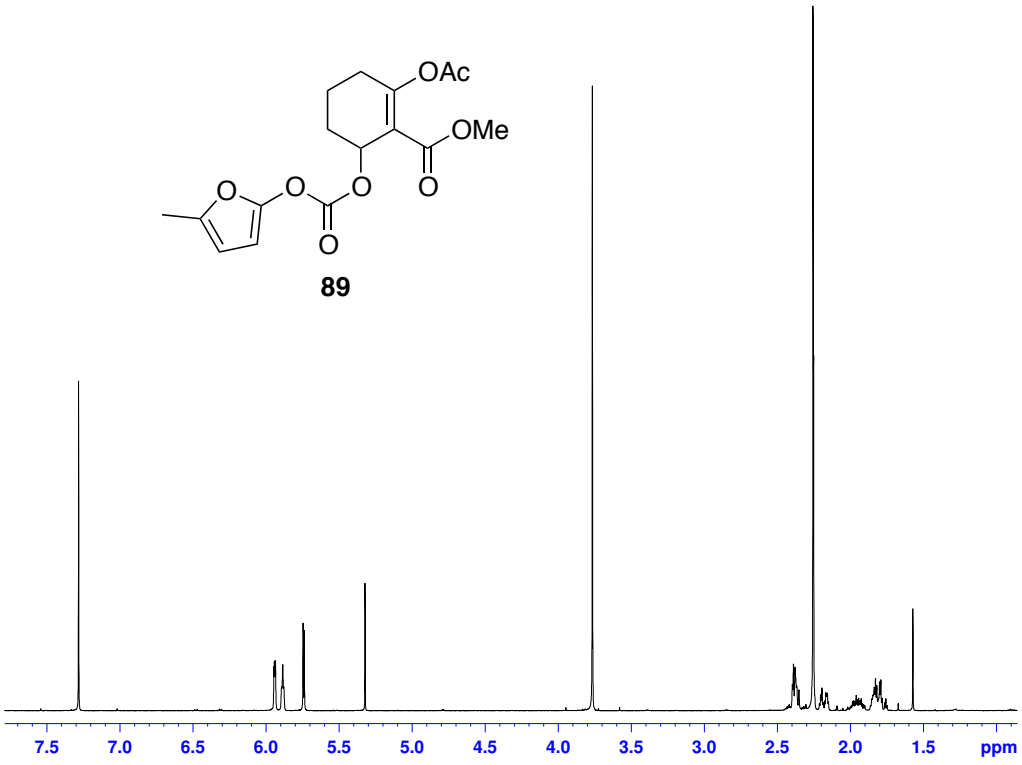


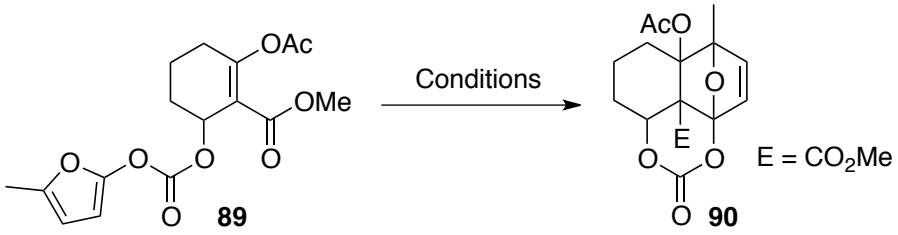
Figure 2.6 ^{1}H NMR spectrum of carbonate 89 recorded at 400 MHz in $CDCl_3$.

2.2.3.2. Intramolecular Furan Diels-Alder Reactions of Carbonate 89

Having secured the desired carbonate **89**, we began investigations of the intramolecular furan Diels-Alder reaction as described in Table 2.2. In an analogous manner to our study of intermolecular furan Diels-Alder reactions, we chose to first investigate the behaviour and stability of **89** under thermal conditions. Heating a solution of the carbonate **89** in either benzene or toluene resulted in no reaction and the isolation

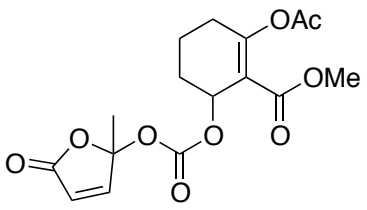
of starting material (entry 1-2). While increasing the temperature to 120 °C and extending the reaction time to 48 hours yielded mostly unreacted starting material, some small amounts (~25% conversion) of the two diastereomers of the butenolide carbonate **96** were isolated (Figure 2.7). The formation of this product is thought to arise from the oxidative degradation of the furan function of **89** followed by a rearrangement. While the exact mechanism by which this product forms is difficult to discern, one report of a similar process has been described utilising lead(IV) acetate to initiate the oxidation process.[105] Unfortunately, increasing the temperature through traditional or microwave heating resulted in decomposition of the carbonate (entry 4-6).

Table 2.2 Intramolecular Furan Diels-Alder Reactions of Carbonate 89



entry	solvent	Lewis-Acid	temp. (°C)	time	result
1	benzene	-	70	24 h	no Reaction
2	toluene	-	110	24 h	no Reaction
3[a]	xylenes	-	120	48 h	oxidation/rearrangement product **96**
4	diglyme	-	160	1.5 h	decomposition
5[a]	DCE	-	180	20 min.	decomposition
6[a]	DMF	-	200	10 min.	decomposition
7[b]	CH_2Cl_2	$MgBr_2$	-78 - r.t.	18 h	no reaction
8[b]	CH_2Cl_2	$EtAlCl_2$	-78	1 h	no reaction
9[b]	CH_2Cl_2	$ZnCl_2$	-78 - r.t.	5 h	butenolide **97**, enone **98**
10[b]	CH_2Cl_2	$BF_3 \cdot OEt_2$	-78	3 h	butenolide **100**
11[c]	CH_2Cl_2	ZnI_2	-20 - r.t.	18 h	butenolide **100**

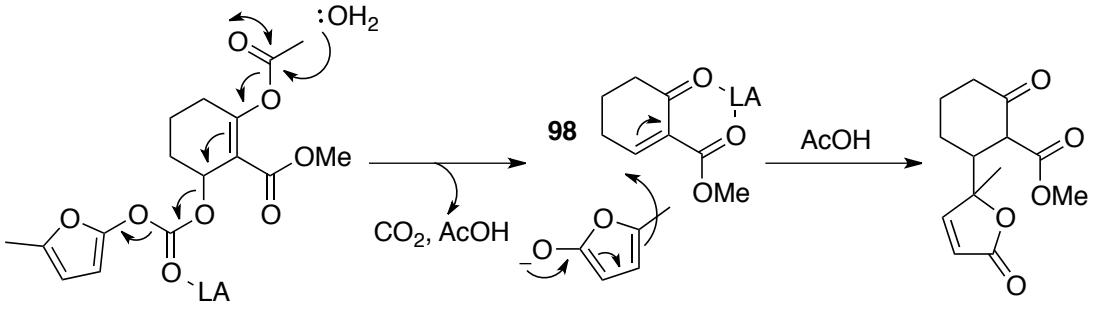
[a] performed in a Biotage microwave reactor. [b] performed in CH_2Cl_2 (0.05 M) with 1 equiv. of Lewis-acid. [c] performed in CH_2Cl_2 with 25 mol% ZnI_2 in the presence of 4Å MS.



96

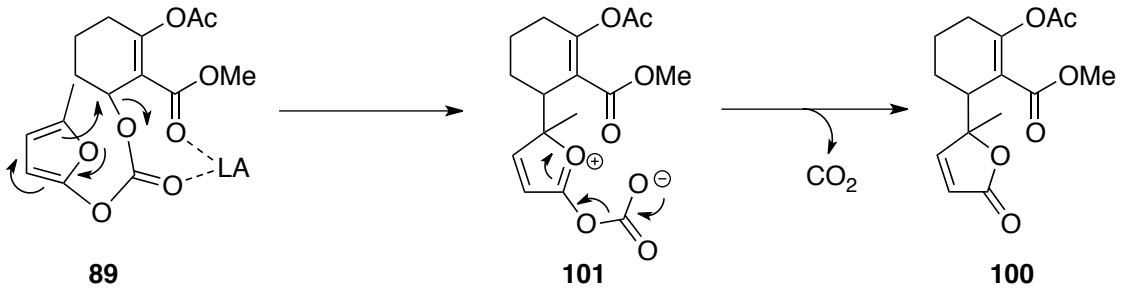
Figure 2.7 Structure of oxidised butenolide carbonate 96.

Due to the thermal instability of the carbonate at temperatures over 120 °C, we investigated the Lewis-acid catalysed intramolecular Diels-Alder reactions of this substrate. As was seen in the intermolecular reactions, treatment of **89** with weakly Lewis-acidic $MgBr_2$ resulted in no reaction (entry 7). Additionally, attempts to effect the desired transformation in the presence of Et_2AlCl at -78 °C also resulted in no reaction and isolation of starting material (entry 8). However, when carbonate **89** was treated with $ZnCl_2$ we observed complete consumption of the starting material within 5 hours. Analysis of the ^1H NMR spectrum obtained from the crude reaction mixture revealed the formation of two major products. One compound contained a set of doublets at δ 7.38 and 6.14 (d, 1H, *J* = 5.7 Hz), diagnostic for a butenolide, and the other displayed a triplet at δ 7.71. Separation of the two components by flash chromatography and interpretation of their spectral data revealed the presence of butenolide **97** and enone **98**, which we presumed were formed by the mechanism in Scheme 2.18. Coordination of the Lewis-acid to **89** initially activates the allylic carbonate function. Nucleophilic attack of water on the acetate - as was seen in the preparation of activated esters of allylic alcohol **93** (*vide supra*) - and elimination of the carbonate gives rise to the enone **98** and the enolate of α-angelica lactone **99**. Further coordination of the Lewis-acid to enone **98** activates this species towards nucleophilic attack by the enolate, leading to butenolide **97**.



Scheme 2.18 Mechanistic formation of butenolide 97.

Further investigations of the Diels-Alder reaction of carbonate **89** involved treatment of this substrate with ZnI_2 and BF_3•OEt_2 in separate experiments (entries 6 and 8), both of which led to a number of compounds that contained diagnostic butenolide resonances in the ^1H NMR spectrum. Although not all the compounds were identified, purification of the crude mixture led to the isolation of a single product whose spectral data was consistent with butenolide **100** (Scheme 2.19). Presumably, coordination of the Lewis-acid to the carbonate fuction in **89** activates this moiety towards displacement by the furan (**89** → **101**). Expulsion of the allylic carbonate is then followed by loss of CO_2, which generates the butenolide **100**.



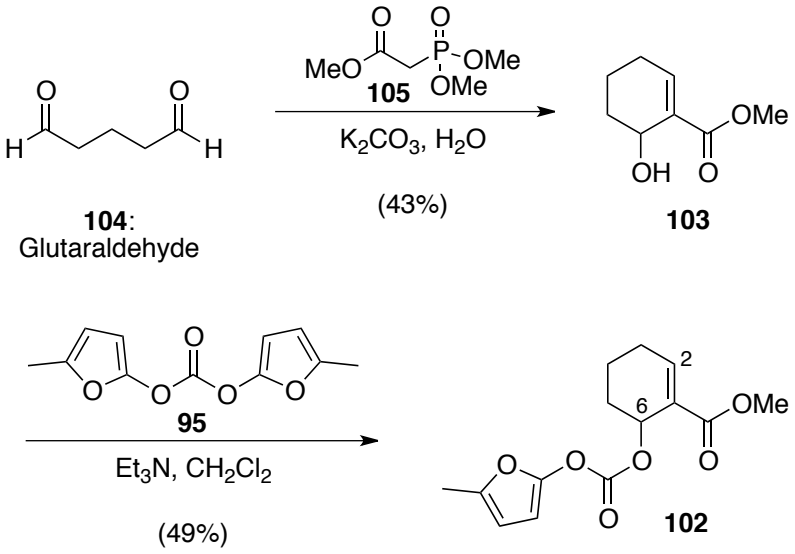
Scheme 2.19 Proposed mechanism for the formation of butenolide 100.

Although disappointing, several conclusions could be drawn from these results. First, while the furan function in the carbonate **89** was still mildly sensitive to oxidation, this reaction had been significantly reduced by its attachment to the carbonate. Unfortunately, attenuating the reactivity of the furan also resulted in a decreased proclivity to undergo a Diels-Alder reaction. Furthermore, it was clear from the Lewis-acid catalysed reactions that the Lewis-acids screened failed to activate the dienophilic

double bond. Instead, coordination to the carbonate resulted in the formation of the aforementioned by-products. Moreover, it was unclear to what extent the enol acetate imposes steric and electronic consequences that decrease the reactivity of the dienophilic double bond. Additionally, it appears that the enol acetate function in **89** is incompatible with many standard reaction conditions used to promote Diels-Alder reactions, and as a result, an investigation of the Diels-Alder reactions of a substrate lacking the acetate substituent was undertaken (*vide infra*).

2.2.3.3. Synthesis of Carbonate Tethered Diels-Alder Precursor 102

In order to further investigate the Diels-Alder strategy without the complications associated with the acetate group, we targeted carbonate **102**, in which the acetate moiety has been replaced with a hydrogen. The synthesis of **102** initiated with the preparation of hydroxyenoate **103** through the method reported by Trost and co-workers (Scheme 2.20).[106] Thus, an aqueous solution of glutaraldehyde (**104**) was treated with trimethyl phosphonoacetate (**105**) and potassium carbonate and allowed to react for 2 days, after which time hydroxyenoate **103** was isolated in 43% yield. Exposure of this material to *bis*-furan carbonate **95** and triethylamine in dichloromethane afforded the Diels-Alder precursor **102** in 49% yield. The ^{1}H NMR spectrum of this compound was similar to that of carbonate **89**, with the exception that the former contained a doublet of doublets at δ 7.31 (dd, 1H, *J* = 5.0, 2.7 Hz) which corresponds to the enoate methine H2. As expected, carbonate **102** displayed a broad singlet at δ 5.66 which was diagnostic for the carbonate C6 methine. Furthermore, the mass spectrum displayed a signal at 303.0838 m/z that was in agreement with a molecular formula of $C_{14}H_{16}NaO_6$ (M+Na).

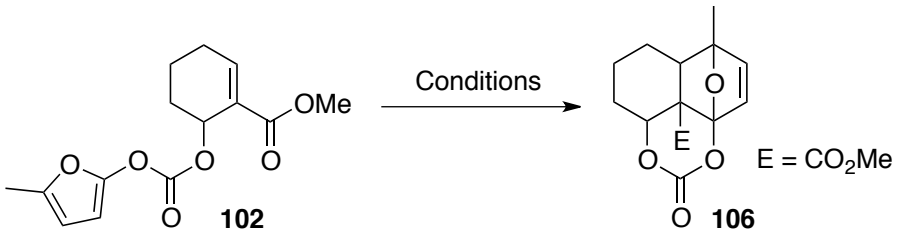


Scheme 2.20 Synthesis of carbonate 102.

2.2.3.4. Intramolecular Furan Diels-Alder Reactions of Carbonate 102

With Diels-Alder precursor **102** in hand, we proceeded with an investigation into the formation of the Diels-Alder adduct **106** as described in Table 2.3. Unfortunately, when a solution of carbonate **102** was heated in either benzene or toluene, no reaction was observed (entry 1-2). Reminiscent of our previous studies, as the temperature of the reaction was increased, we began to observe some degradation of the carbonate, and at 250 °C observed complete decomposition of the starting material (entries 3-4). Furthermore, microwave irradiation of carbonate **102** for several hours resulted in the formation of a complex mixture containing at least 4 compounds, all of which displayed diagnostic butenolide signals (entry 5). Despite the fact that the removal of the acetate function from **102** enhanced this compounds thermal stability, no indication of Diels-Alder adduct formation was observed under thermal conditions.

Table 2.3 Intramolecular Furan Diels-Alder Reactions of Carbonate 102



entry	solvent	Lewis-Acid	temp. (°C)	time	result
1	benzene	-	70	24 h	no Reaction
2	toluene	-	110	24 h	no Reaction
3[a]	*o*-dichlorobenzene	-	190	15 min.	SM and decomposition
4[a]	*o*-dichlorobenzene	-	250	20 min.	decomposition
5[a]	acetonitrile	-	150	6 h	complex mixture[b]
6[c]	CH_2Cl_2	$MgBr_2$	-78 - r.t.	8 h	no reaction
7[c]	CH_2Cl_2	$ZnCl_2$	-78 - r.t.	18 h	no reaction
8[c]	CH_2Cl_2	ZnI_2	-16 - r.t.	48 h	no reaction
9[c]	CH_2Cl_2	BF_3•OEt_2	-78 - 0	6 h	complex mixture[d]
10[c]	CH_2Cl_2	$EtAlCl_2$	-78 - r.t.	18 h	complex mixture[d]

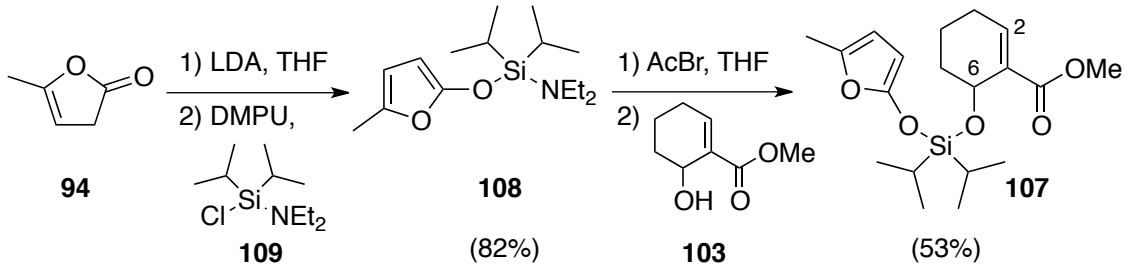
[a] performed in a CEM microwave reactor. [b] at least 4 sets of butenolide signals were observed in the crude ^{1}H NMR spectrum. [c] Reaction performed in CH_2Cl_2 (0.05M) with 1.5 equiv. of Lewis-acid. [d] The ^{1}H NMR spectrum of the crude mixture included several compounds with characteristic butenolide signals.

Unlike the reactions of its predecessor, carbonate **102** displayed increased stability towards mild Lewis-acids, showing no reaction when treated with $MgBr_2$ and zinc catalysts (entries 6-8). However, treatment with BF_3•OEt_2 or $EtAlCl_2$ (entries 9-10) resulted in the formation of complex mixtures of butenolides, presumably arising from similar processes to those observed for **89**. Unfortunately, **102** also failed to provide access to a Diels-Alder adduct and it was apparent that the carbonate tether was perhaps the source of much of our frustration. Not only is this group thermally labile, as evidenced by the thermal degradation of the two carbonate substrates, the Lewis-basicity of the carbonate moiety was likely forming preferential complexes with Lewis-acids, which resulted in decomposition and by-product formation. Additionally, as described by Parker and co-workers, Diels-Alder reactivity of tethered furan substrates is heavily dependant on the propensity of the substrate to adopt a reactive conformation.[107] Thus, substrates that contain ester moieties can be unreactive due to the non-competent

transoid conformation of the reactive groups about the ester linkage. Bearing this in mind, a third model system was prepared, in which the tethering carbonate group was replaced with a silicon atom.

2.2.3.5. Synthesis of a Silicon Tethered Diels-Alder Precursor

The use of a silicon atom to temporarily tether two reactive substrates has gained widespread use in synthetic chemistry due to its ease of introduction, stability to a wide range of reaction conditions, and ability to be easily removed or converted to a host of other desirable synthetic intermediates. Specifically, it has seen substantial use in intramolecular radical cyclisations,[108] Diels-Alder cycloadditions,[109,110] and a wide range of transition metal catalysed reactions including silicon tethered ring closing metatheses, and Pauson-Khand reactions.[101] We initially targeted the silicon tethered substrate **107**, which notably, does not include the intended acetate from the cyclohexene moiety. It was expected that the silicon tether would impart increased thermal stability, as well as decreased rigidity and greater degrees of freedom due to the longer Si-O bond length (1.63 Å for Si-O compared to 1.41 Å for C-O).[111] Furthermore, in Lewis-acid catalysed reactions, the silicon tether would render the ester carbonyl the most Lewis-basic site, activating the dienophilic bond and promoting the required Diels-Alder reaction.



Scheme 2.21 Synthesis of silicon tethered Diels-Alder substrate 107.

The preparation of the silicon tethered substrate **107** began with the synthesis of amino-silane **108** (Scheme 2.21). Following the method of Thomson and co-workers,[112] α-angelica lactone (**94**) was treated with LDA, and the resulting enolate was reacted with chloro-*N*,*N*-diethyl-1,1-diisopropylsilanamine (**109**)[113] and DMPU, which afforded amino-silane **108** in 82% yield (Scheme 2.21). Amino-silane **108** was then converted to the silicon-tethered substrate **107** through a two-step process that first involved formation of a silyl bromide, followed by addition to a cooled solution of hydroxyenoate **103** in the

presence of triethylamine in tetrahydrofuran. Following standard chromatographic purification, **107** was isolated in 53% yield. The ^{1}H NMR spectrum of **107** displayed a downfield doublet of doublets at δ 7.05 (dd, *J* = 4.7, 2.8 Hz, 1H) characteristic of the enoate hydrogen H2, as was seen in **102** (Figure 2.8). Also similar, was the shape of the silyl ether proton H6 that appeared at δ 4.96 (br. t, 1H, *J* = 2.9 Hz), although this resonance appeared more than 0.5 ppm downfield in the ^{1}H NMR spectrum of **102** due to the electron withdrawing properties of the carbonate. Other features of the spectral data included resonances attributed to the furan protons at δ 5.74 and 5.01, the methyl ester singlet at δ 3.69 (3H), and the isopropyl protons associated with the silicon tether at δ 1.28-1.11 (m, 2H) and 1.10-1.03 (m, 12H). Furthermore, the ^{13}C NMR spectrum displayed 19 signals, which is consistent with our structural assignment. With a synthesis of **107** in hand, we began to explore the Diels-Alder reactions of this substrate.

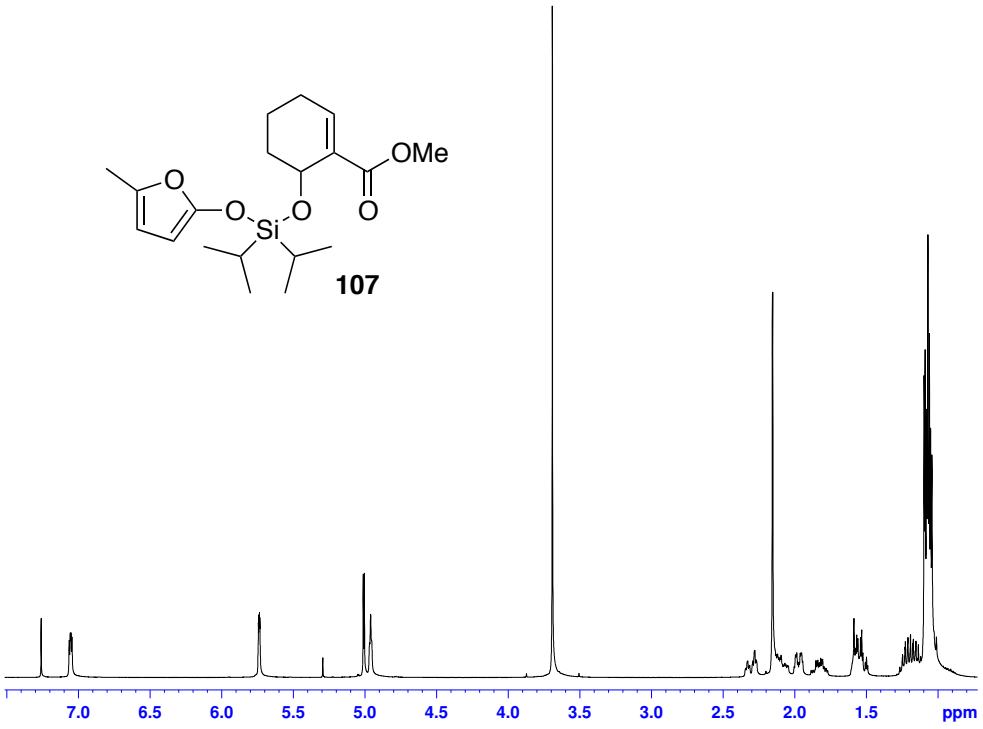
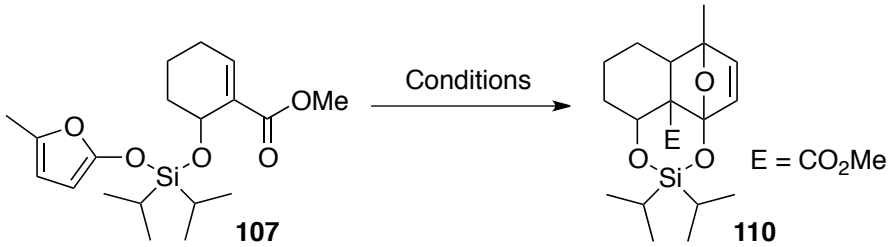


Figure 2.8 **^{1}H NMR spectrum of silicon tether 107 recorded at 400 MHz in $CDCl_3$.**

2.2.3.6. Intramolecular Furan Diels-Alder Reactions of Silicon Tether 107

As before, we began our investigations into the formation of the Diels-Alder adduct **110** with a screen of thermally promoted reaction conditions (Table 2.4). Although no reaction was seen when silicon tether **107** was heated in benzene, complete consumption of the starting material was observed upon heating in toluene for an extended period of time. Unfortunately, inspection of the crude ^{1}H NMR spectrum revealed two sets of doublets with coupling constants of J = 16.1 Hz and 12.1 Hz, which were indicative of furan oxidation. Not surprisingly, substitution of the carbonate linker for a silicon tether had increased the electron density within the furan ring, consequently rendering it more susceptible to oxidative degradation. Interestingly though, when a solution of **107** was heated in either DCE or acetonitrile under microwave conditions, no reaction was observed and the starting material was recovered. These results supported our proposal that replacement of the carbonate with a silicon tether would enhance the thermal stability of the substrate. Unfortunately, this increased stability was not accompanied by the observation of Diels-Alder adducts in the crude reaction mixtures.

Table 2.4 Intramolecular Furan Diels-Alder Reactions of Silicon Tether 107



107 **110**

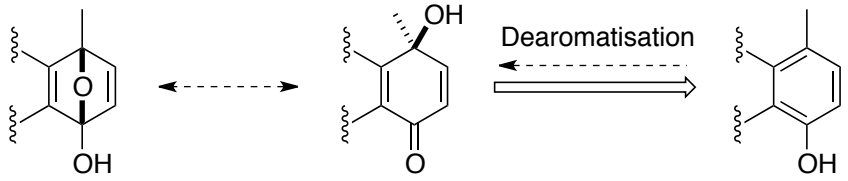
entry	solvent	Lewis-Acid	temp. (°C)	time (h)	result
1	benzene		70	24	no reaction
2	toluene		110	48	furan oxidation
3[a]	DCE		175	1.5	no reaction
4[a]	acetonitrile		150	2	no reaction
5[b]	CH_2Cl_2	$Ti(O^iPr)_4$	-78 - r.t.	48	slow hydrolysis
6[b]	CH_2Cl_2	$BF_3{\bullet}OEt_2$	-78 - r.t.	3	hydrolysis
7[c]	CH_2Cl_2	Et_2AlCl	-78 - r.t.	18	ethyl substitution and hydrolysis
8[b]	CH_2Cl_2	$ZnCl_2$	-20 - r.t.	2	hydrolysis
9[d]	THF	ZnI_2	-78	2	hydrolysis

[a] performed in a CEM microwave reactor. [b] reaction performed in CH_2Cl_2 (0.05M) with 30 mol% Lewis-acid. [c] reaction performed in CH_2Cl_2 (0.05M) with 1 equiv. Et_2AlCl. [d] reaction performed in THF (0.05M) with 30 mol% ZnI_2

Disappointingly, treatment of the tethered substrate with several Lewis-acids led to cleavage of the silicon tether and recovery of hydroxyenoate **103**. One exception was Et_2AlCl (entry 7), where incorporation of an ethyl group was observed, presumably arising from a transfer from the Lewis-acid. Ultimately the formation of this product was non-productive and no effort was invested in fully elucidating its structure. While it was predicted that the silyl-tether would be susceptible to acidic hydrolysis, the rapid rate that this substrate decomposed when subjected to Lewis-acids was unanticipated. As a result of this shortfall in addition to the lack of reactivity observed amongst all the intramolecular substrates tested, we were forced to abandon the furan Diels-Alder strategy.

2.3. Revised Proposal: Tetralone Dearomatisation Strategy

Due to the repeated failure of our efforts to install the C-ring dihydrofuran through a furan Diels-Alder reaction, we were forced to re-evaluate our proposed strategy. By realising that dihydrofuran moiety **111** could be viewed as a ketal isomer of dienone **112**, it was reasoned that oxidative dearomatisation of an appropriately functionalised phenol **113** could give access to dienone **112** (Figure 2.9). Using this approach it could be possible to employ a phenol as a dihydrofuran surrogate, overcoming the issues associated with the Diels-Alder strategy.

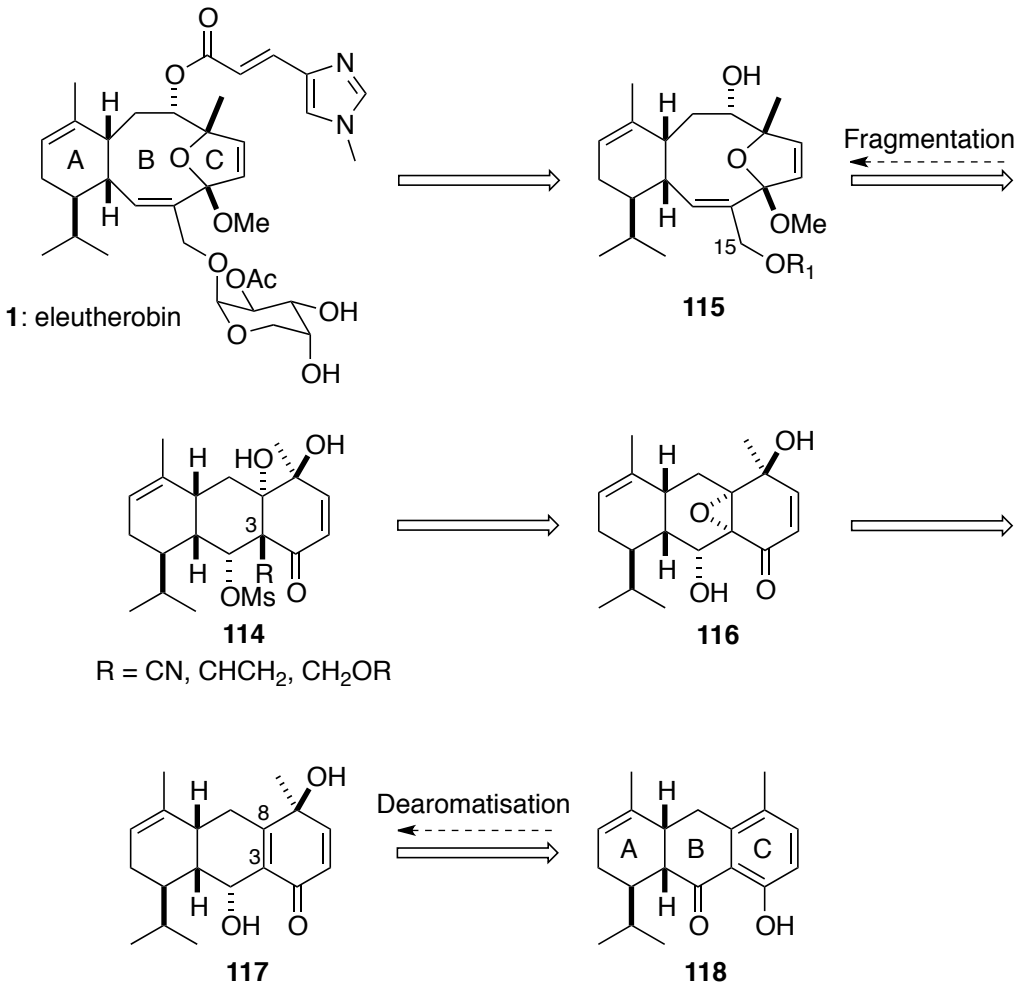


111 **112** **113**

Figure 2.9 Oxidative Dearomatisation Strategy.

Employing this conceptual approach, our revised retrosynthetic strategy is outlined in Scheme 2.22. It remained our contention that the eleutherobin 10-membered

ring could be accessed through a Grob fragmentation, and therefore we targeted mesylate **114** as our Grob fragmentation precursor. Fragmentation of **114** would give the intended decalone (not shown), which after spontaneous ketalisation and subsequent methylation would give the core ring system of eleutherobin **115**. Subsequent attachment of the urocanic ester, and arabinose moieties as in our previously proposed route would afford eleutherobin (**1**). Since employing a dearomatisation reaction would lead to a tetrasubstituted olefin between C3 and C8, it would be necessary to install the requisite functionality at these two positions. Towards this end, we envisioned a strategy that would employ epoxide **116**. This would install the required C8 hydroxyl group, as well as introduce a reactive α,β-epoxy ketone that could be exploited for the introduction of a one or two carbon R group (CN, CH_2OH, $CHCH_2$, etc.) that could be elaborated to the C15 hydroxy-methylene present in eleutherobin. Epoxyenone **116** could be accessed by a hydroxy-directed epoxidation of dienone **117**, which in turn could be derived through an oxidative dearomatisation reaction of tetralone **118**. Targeting tetralone **118** offered a number of advantages over our previously proposed route including the ease of handling and known stability of aromatic compounds, as well as the large number of synthetic methodologies that have been developed to access and functionalise these types of compounds. Furthermore, the use of a phenol oxidative dearomatisation as a key transformation *en route* to a fragmentation precursor held the benefit of being an extremely well studied and utilised process.



Scheme 2.22 Revised retrosynthetic strategy.

The dearomatisation of aromatic compounds has played an important role in the synthesis of complex natural products, and a number of methods exist to effect these types of processes.[114] Specifically, the oxidative dearomatisation of phenols offers a unique opportunity for synthetic chemists to access valuable cyclohexadienone structural motifs from their relatively simple phenolic counterparts (Figure 2.10). In a general sense, these reactions proceed through the action of a metal based 2-electron oxidant, whereby the nucleophilic phenol **119** is converted to the electrophilic resonance stabilised phenoxonium cation **120**. This intermediate can then be trapped by various carbon or heteroatom nucleophiles at the *ortho* or *para* position to afford the cyclohexadienone scaffold. The regioselectivity of the process is controlled not only by steric factors, but also electronic considerations imparted by the aromatic substituents

and their affect on the stability of the phenoxy cation. For example, phenols bearing an electron releasing alkoxy group at one of the *ortho* positions will lead to cyclohexa-2,4-dienones (**121**), while *para*-alkoxy substituted phenols afford cyclohexa-2,5-dienones (**122**).

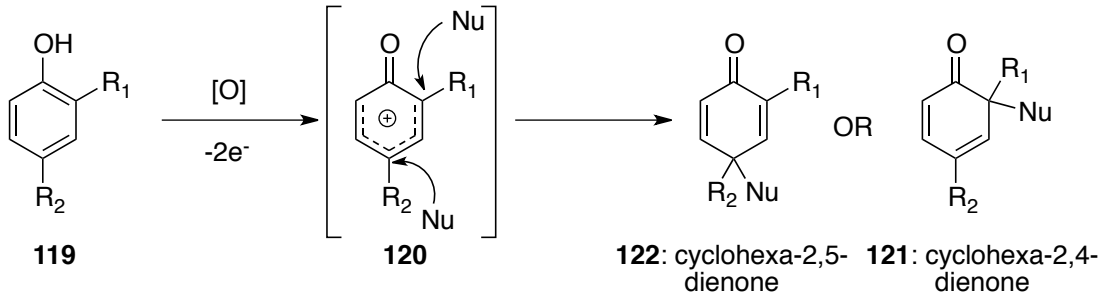
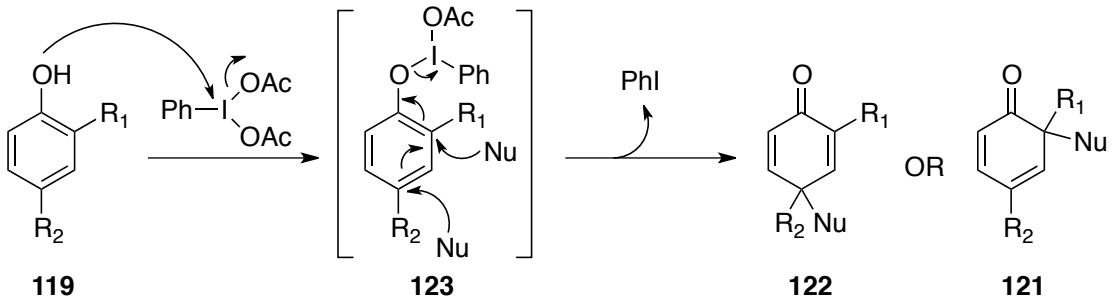


Figure 2.10 **General mechanistic aspects of the oxidative dearomatisation reaction of phenols.**

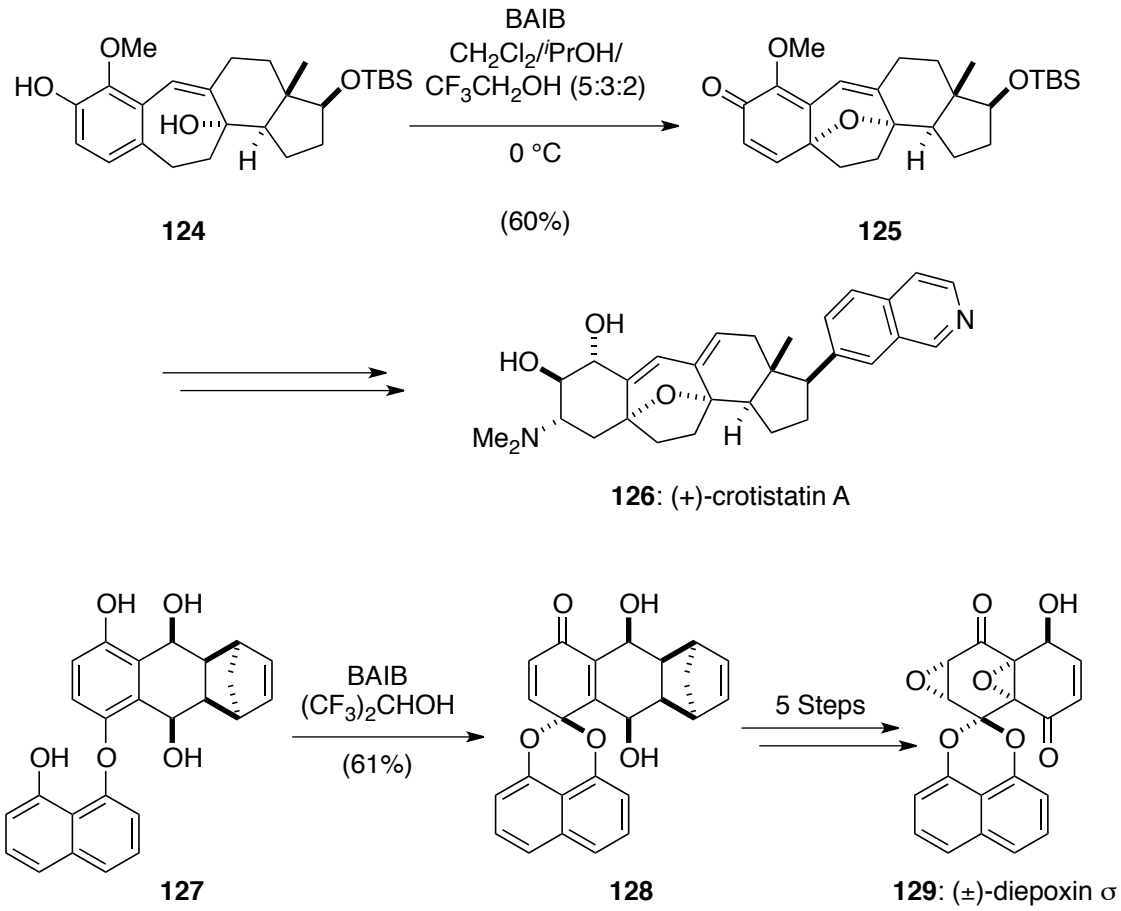
While this transformation can be effected by molecular oxygen[115] as well as a number of metal-based oxidants such as those based on thallium(III), lead(IV), or bismuth(V), the hypervalent iodine(III) reagents [*bis*(acetoxy)-iodo]benzene (BAIB) and [*bis*(trifluoroacetoxy)-iodo]benzene (PIFA) have become ubiquitous with this class of synthetic transformations.[116] Mechanistically, the iodine(III) atom first acts as an electrophilic centre, undergoing nucleophilic attack and ligand exchange by the phenolic oxygen (Scheme 2.23). This process creates an electrophilic arene **123**, which activates the *ortho* and *para* positions. Attack of a nucleophile at these centres results in the formation a carbonyl, reducing the iodine(III) centre to monovalent iodide (iodobenzene) and producing the cyclohexadienone skeleton. While this associative mechanism represents only one proposal, other possibilities have been postulated, including a free-radical mechanism, as well as a dissociative process proceeding through a discreet cation.[117]



Scheme 2.23 Mechanism of BAIB induced oxidative dearomatisation.

Owing to the efficiency of this reaction and synthetic utility of the formed products, the hypervalent iodine induced oxidative dearomatisation of phenols has found extensive use in natural product total synthesis.[116] A few examples of phenol dearomatisation with carbon-oxygen bond formation are shown in Scheme 2.24. Sarpong and co-workers relied on a BAIB-mediated intramolecular oxidative dearomatisation of the phenol **124**. This process furnished the dienone **125** and installed the oxabicyclo[3.2.1]octene moiety in their formal synthesis of the potent angiogenic inhibitor cortistatin A (**126**).[118] Not surprisingly, several analogous dearomatisation processes towards the oxapentacyclic core of this natural product were also reported, further highlighting the synthetic utility of this reaction. Additionally, Wipf and co-workers utilised a BAIB induced intramolecular oxidative dearomatisation of the diarylether **127** to afford the spiroacetal **128** in their total synthesis of diepoxin σ (**129**).

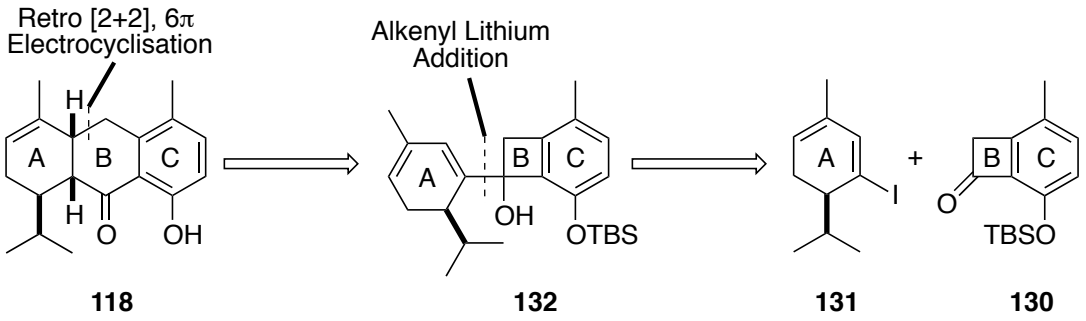
In the context of our synthesis, the regioselectivity of the process was expected to be controlled by the attachment of a ketone to the *ortho* position of tetralone **118**. This would significantly decrease the reactivity at the *ortho* position, rendering the reaction *para* selective. The diastereoselectivity of the reaction was expected to benefit from conformational bias imposed by the bowl like shape of the molecule. Specifically, steric shielding by the A-ring on the α-face of the molecule is expected to favour attack of the nucleophile on the desired top face of the aromatic ring.



Scheme 2.24 Examples of oxidative dearomatisation in total synthesis.

2.3.1. Proposed Tetralone Synthesis: Benzocyclobutanol Electrocyclic Ring Expansion Strategy

Having conceptualized an alternative strategy for the synthesis of eleutherobin that relied on the intermediacy of tetralone **118**, it was of importance to develop a concise route to this latter material. A retrosynthetic analysis for this compound is presented in Scheme 2.25. As depicted, our efforts focused on the formation of the B ring, as both the A and C rings are or can be readily accessed from commercially available materials. We initially envisioned a strategy in which the central 2 carbons of the B ring would originate from a benzocyclobutanone (e.g., **130**). It is reasonable to suggest that benzocyclobutanone could be coupled with dienyl iodide **131** to produce the benzocyclobutanol **132**, which would then undergo a sequential electrocyclic processes (i.e., retro [2+2] followed by 6π electrocyclisation) to afford ring expanded tetralone **118**.[119,120]

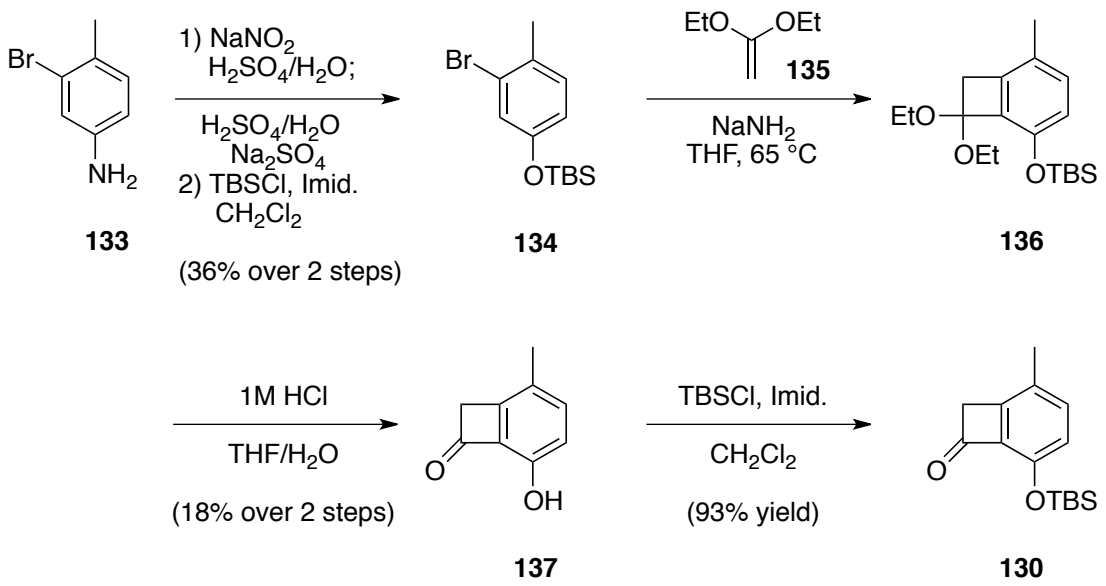


118 **132** **131** **130**

Scheme 2.25 Retrosynthesis of tetralone 118.

2.3.1.1. Synthesis of Benzocyclobutanone 130

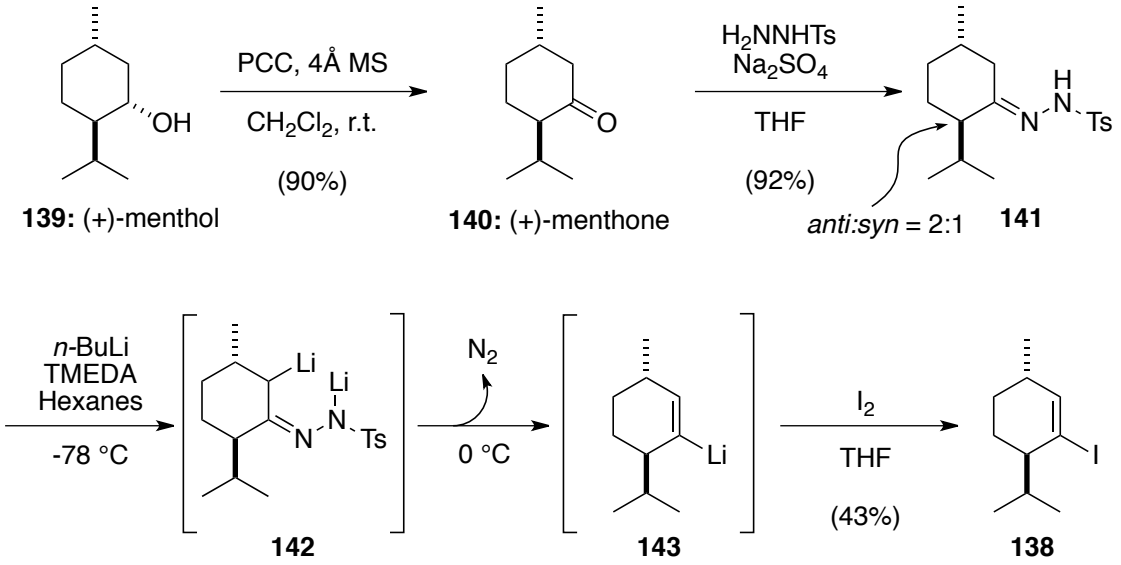
For the synthesis of benzocyclobutanone **130** we relied on existing methods reported in the literature for the synthesis of benzocyclobutanones, namely the [2+2] cycloaddition of ketene acetals with benzyne derivatives (Scheme 2.26).[121] Treatment of 3-bromo-4-methylaniline (**133**) with sodium nitrite in aqueous sulphuric acid gave an aryldiazonium, which upon hydrolysis of the diazonium function gave a phenol (not shown). Treatment of the crude phenol with TBSCl and imidazole in dichloromethane afforded the silyl protected phenol **134** in 36% yield over 2 steps. This latter compound was then subjected to a benzyne [2+2] cycloaddition through reaction with sodium amide and 1,1-diethoxyethylene (**135**)[122] to afford benzocyclobutanone diethoxy acetal **136**. Subsequent acetal hydrolysis gave phenol **137** which upon protection of the phenol provided the desired benzocyclobutanone **130** in 17% over 3 steps.



Scheme 2.26 Synthesis of benzocyclobutanone 130.

2.3.1.2. Synthesis of Model Vinyl Iodide 138

It was anticipated that the preparation of dienyl iodide **131** would provide certain synthetic challenges, and as such, a model system with a simplified A ring was initially targeted. Notably, the model alkenyl iodide **138** lacks the $\Delta^{11,12}$ olefin, but should be easily assembled from (+)-menthol (**139**), a readily accessible and commercially available chiral pool material (Scheme 2.27). Towards this end, (+)-menthol was subjected to oxidation with PCC to give (+)-menthone (**140**) in excellent yield (90%).[123] Subsequent formation of the tosyl hydrazone **141** was accomplished by treating (+)-menthone with tosyl hydrazine and Na_2SO_4 in tetrahydrofuran.[124] Although the yield for this process was excellent (92%), epimerisation of the α-isopropyl group was observed, resulting in a d.r. of 2:1 (*anti*:*syn*) as determined by ^{1}H NMR spectroscopy. Unfortunately, it was not possible to avoid the epimerisation process, even when a procedure was employed that purportedly circumvents this issue.[125] Nonetheless, subjecting this 2:1 mixture of hydrazones to a Shapiro reaction[125] with *n*-butyllithium in the presence of TMEDA gave dianion **142**, which upon warming to 0 °C resulted in expulsion of dinitrogen and formation of the alkenyl lithium **143**. Trapping of this latter substance with iodine afforded the alkenyl iodide **138** in 43% yield (d.r. = 2:1). Disappointingly, the mixture of diastereomeric alkenyl iodides was inseparable by column chromatography and was thus used in subsequent reactions in this form.

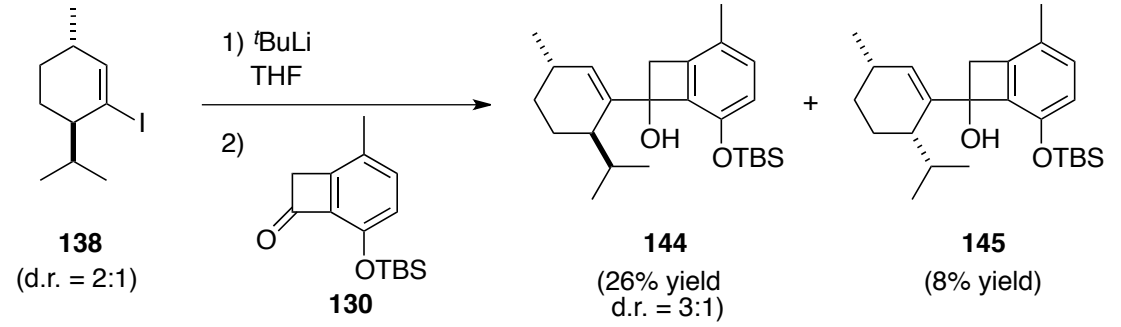


139: (+)-menthol **140:** (+)-menthone **141** **142** **143** **138**

Scheme 2.27 Synthesis of vinyl iodide 138.

2.3.1.3. Synthesis of Model Tetralones

Treatment of the diastereomeric mixture of alkenyl iodides **138** with *tert*-butyllithium formed the corresponding alkenyl lithium that reacted with benzocyclobutanone **130** to afford a complex mixture of products (Scheme 2.28). Purification of the mixture by column chromatography led to the isolation of benzocyclobutanol **144** (d.r. = 3:1), which was formed from the reaction of the *anti*-alkenyl iodide in 26% yield. Additionally a single diastereomer of benzocyclobutanol **145**, produced from the reaction of **130** with the *syn*-alkenyl iodide was isolated in 8% yield.

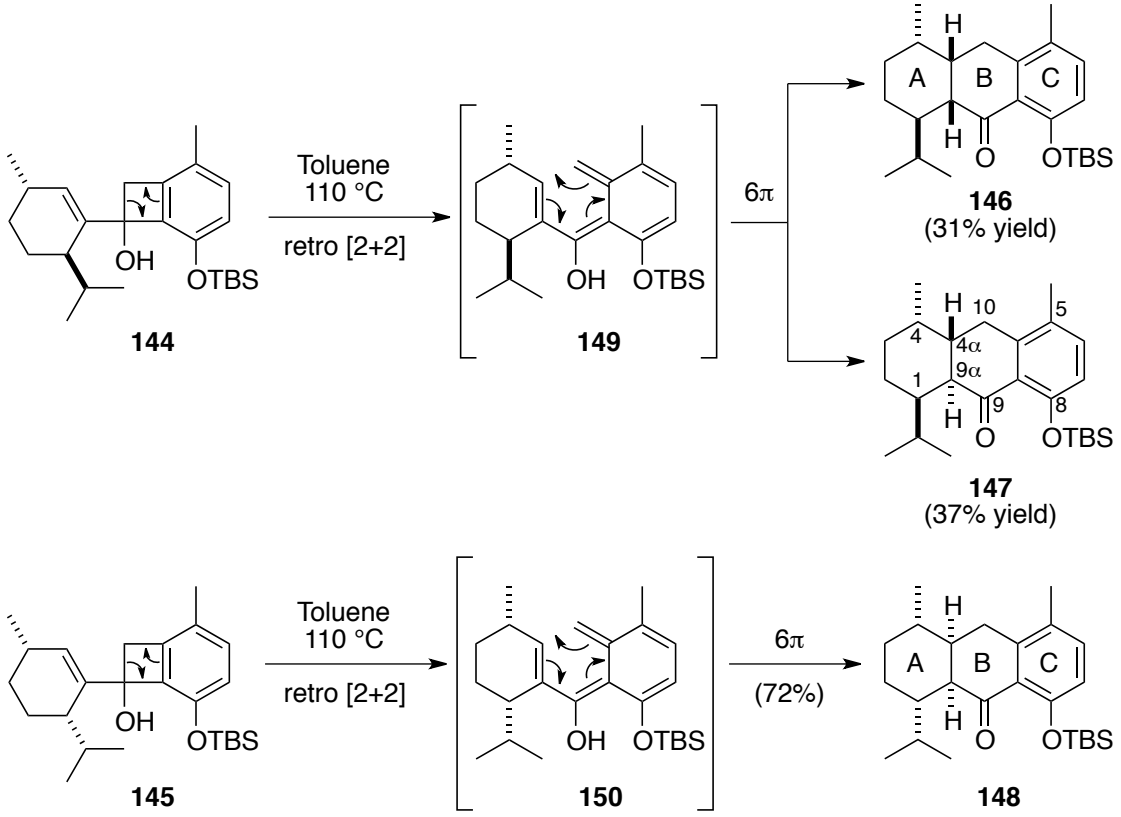


138 (d.r. = 2:1) **130** **144** (26% yield d.r. = 3:1) **145** (8% yield)

Scheme 2.28 Formation of benzocyclobutanols.

Finally, refluxing a solution of benzocyclobutanol **144** in toluene for 18 hours led to the formation of two diastereomeric tetralones **146** and **147** in a combined yield of

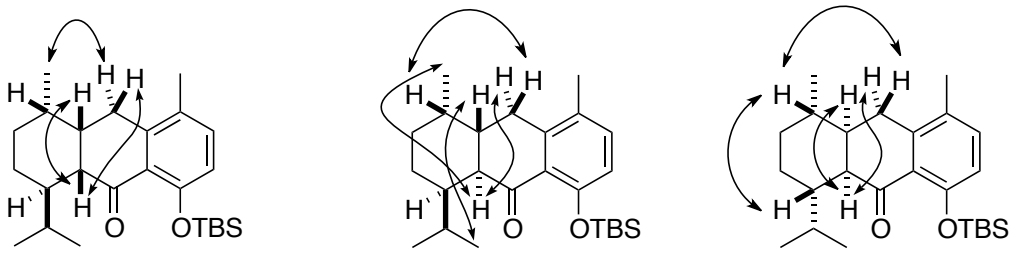
68% (Scheme 2.29). In a similar manner, heating a solution of benzocyclobutanol **145** in toluene for 18 hours afforded tetralone **148** as a single diastereomer in 72% yield. As described by Wallace and co-workers, thermal induced retro [2+2] electrocyclic ring opening of benzocyclobutenones initially gives rise to *o*-quinone methides (e.g., **149** and **150**), which subsequently undergo disrotatory 6π electrocyclic ring closure to afford ring expanded tetralones.[119,120]



Scheme 2.29 Synthesis of model tetralones via sequential electrocyclic reactions.

The structural assignment of tetralones **146**-**148** involved the subsequent analysis of their spectral data (^{1}H NMR, ^{13}C NMR, COSY, HSQC, 1D nOe). Each of the tetralones displayed similar spectral data with key features of the ^{1}H NMR spectrum including a pair of doublets corresponding to the 2 aromatic protons H6 and H7 (e.g., for **147** δ 7.11 and 6.64 (d, *J* = 8.3 Hz)), a set of proton resonances corresponding to the C10 methylene protons (e.g., for **147** δ 2.62 (dd, *J* = 15.0, 3.0 Hz) and 2.30 (dd, *J* = 15.0, 13.1 Hz)), one methyl singlet (e.g., for **147** δ 2.23 (3H)) for the phenyl methyl group

at C5, and 3 sets of methyl doublets corresponding to the aliphatic methyl and isopropyl groups respectively (e.g., for **147** δ 0.98 (d, 3H, *J* = 7.2 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), and 0.73 (d, 3H, *J* = 6.7 Hz)). Additionally, in the ^{13}C NMR spectrum, a resonance at δ 199.9 in **147** further supported the formation of an aryl ketone.



146 **147** **148**

Figure 2.11 Key nOe correlations for tetralones 146-148.

For the assignment of the relative configuration of the newly formed carbon chirality centres, we relied on the key nOe correlations shown in Figure 2.11. In all cases the newly formed C4α stereocentre was *syn* to the isopropyl group indicating this substituent imparts some control over the stereoselectivity of the 6π electrocyclisation. More specifically, rotation of the A ring in a direction which situates the isopropyl function away from the steric bulk of the molecule leads to enols **151** and **152**, establishing the relative configuration at C4α as shown (Figure 2.12). It was encouraging to find that the proposed sequence of transformations was not only synthetically feasible but also leads to a product with the correct relative stereochemistry for an eventual synthesis of eleutherobin (**1**). In this regard, the only structural aspect that remained unsolved was the installation of the $\Delta^{11,12}$ olefin. Therefore our next challenge was the synthesis of the desired dienyl iodide **131** that would subsequently lead to tetralone **118**.

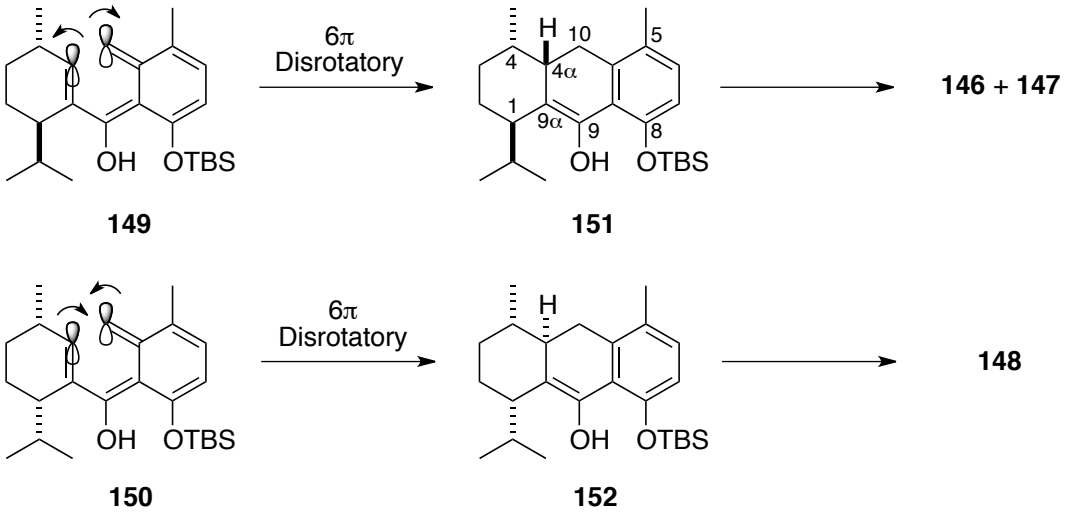
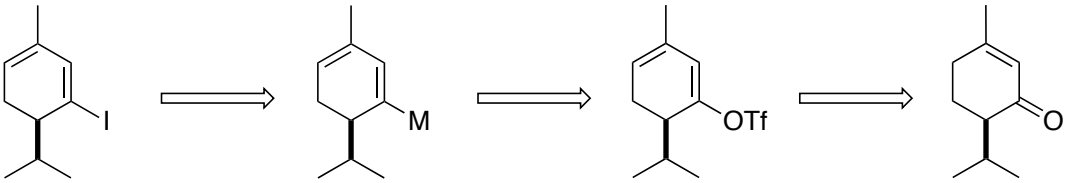


Figure 2.12 **Rationalisation for the stereochemical outcome of the tetralone electrocyclisation reaction.**

2.3.1.4. Synthesis of Dienyl Iodide 131

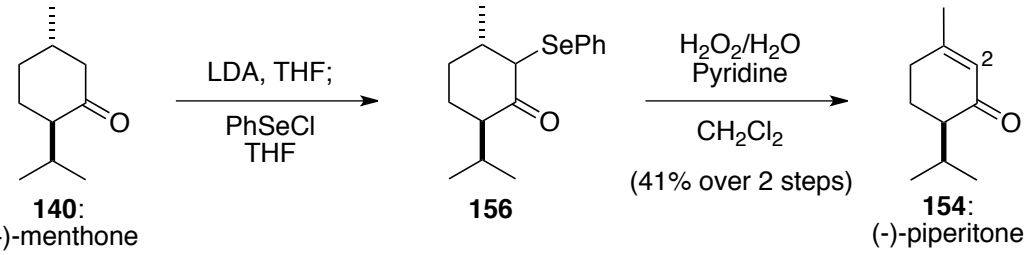
Our retrosynthetic analysis for dienyl iodide **131** is presented in Scheme 2.30. It was our contention that this material could be prepared through a metal-iodine exchange reaction performed on a metalated cyclohexadiene (e.g., **153**, where M = Sn, B, or Si). We envisioned this metalated diene could be derived from (-)-piperitone (**154**) through a coupling reaction performed on the corresponding dienyltriflate **155**. Furthermore, enantioenriched (-)-piperitone (**154**) could be derived from (+)-menthone (**140**) through the installation of an alkene.



Scheme 2.30 **Retrosynthesis of dienyl iodide 131.**

Following a report by Reich and co-workers,[126] (+)-menthone (**140**) was treated with LDA followed by phenylselenium chloride to give a mixture of the corresponding α-seleno ketones **156** (Scheme 2.31). Treatment of the crude α-seleno ketones with hydrogen peroxide induced selenide oxidation and elimination to afford (-)-piperitone

(**154**). The ^{1}H NMR spectral data recorded on **154** included a multiplet at δ 5.83 (m, 1H), corresponding to the enone hydrogen H2, as well as the diastereotopic methyl resonances corresponding to the isopropyl group at δ 0.94 (d, 3H, *J* = 7.0 Hz) and 0.85 (d, 3H, *J* = 7.0 Hz). The installation of the enone was further confirmed by the vinyl methyl signal at δ 1.92 (s, 3H). These values were in agreement with data reported in the literature for **154**.[127]



140:
(+)-menthone

156

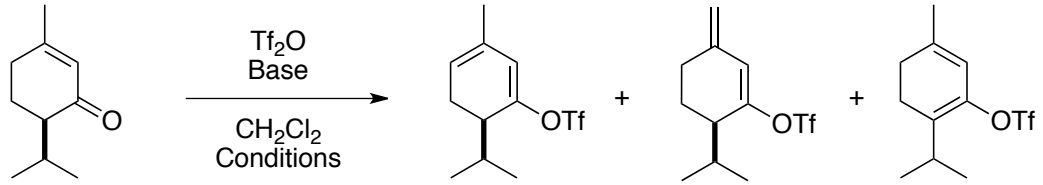
154:
(-)-piperitone

Scheme 2.31 Synthesis of (-)-piperitone (154).

The next step in our proposed sequence was formation of dienyl triflate **155** from piperitone (**154**). Despite the possible formation of 3 isomers (**155**, **157**, **158**), it was envisioned that formation of **155** could occur through treatment of piperitone with Tf_2O under basic conditions (Table 2.5). Towards this end, piperitone was treated with Tf_2O and lutidine in dichloromethane, which afforded a 1:5 mixture of dienyl triflates **155** and **157** respectively, in a combined yield of 51% (entry 1). When pyridine was employed as the base, the ratio of **155**:**157** changed to 2:3. This result highlights the importance of sterics in this reaction, as formation of the desired product involves removal of the more sterically encumbered methylene protons. While no reaction was observed at -78 °C, warming the reaction slowly from this temperature resulted in the exclusive formation of dienyl triflate **158** (entry 3). Alternatively, carrying out the reaction at room temperature led to a 1:1 ratio of dienyl triflates **155**:**157** (entry 4). Despite this reaction being quite sluggish (18 hours), simply changing the order of addition of reagents led to complete consumption of the starting material within one hour, and formation of the dienyl triflates **155** and **157** (1:1) in a combined isolated yield of 62% (entry 5). Although it was not possible to isomerise the double bond under a variety of conditions (formic acid, acetic acid, $MeSO_3H$, I_2), and the dienyl triflates were not distinguishable by TLC analysis, the two isomers **155** and **157** were readily separable by GC. Therefore it was possible to use GC analysis of flash chromatography fractions to identify enriched or indeed pure

fraction of **155** or **157**. Thus, purification of the sample by flash column chromatography (silica gel, hexanes) and analysis of the fractions by GC led to the isolation of clean dienyl triflate **155** (95% by GC) in 20% yield.

Table 2.5 Optimisation of Dienyl Triflate Formation

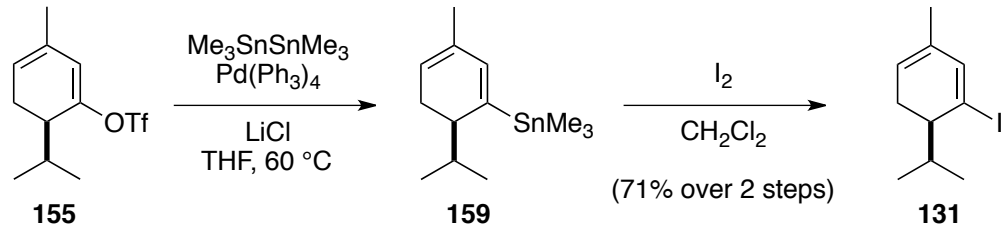


154: (-)-Piperitone **155** **157** **158**

entry	base (equiv.)	temp. (°C)	ratio 155:157:158[a] (% yield)[b]
1[c]	lutidine (2.0)	0 - r.t.	1:5:0 (51)
2[c]	pyridine (3.0)	0 - r.t.	2:3:0[f]
3[c]	pyridine (3.0)	-78 - r.t.	0:0:1[f]
4[c]	pyridine (3.0)	r.t.	1:1:0 (55)
5[d]	pyridine (3.0)	r.t.	1:1:0 (62) (20)[e]

[a] ratio determined by ^{1}H NMR spectroscopy. [b] Combined isolated yield after column chromatography (silica gel, 10:1 Hex:EtOAc) [c] solution of **154** in CH_2Cl_2 (0.1M) was added base followed by Tf_2O (2.0 equiv.). [d] solution of **154** in CH_2Cl_2 (0.1M) was added Tf_2O (2.0 equiv.) followed by pyridine. [e] Isolated yield of **155** after second purification by column chromatography (silica gel, hexanes) and analysis of column fractions by GC. [f] Yield not determined.

For the synthesis of an appropriate organometallic species which could undergo conversion to dienyl iodide **131**, we relied on established methods for the palladium catalysed coupling of enol triflates with dimetallic reagents.[128,129] While it was possible to form the pinacol boronate ester of **155** (*bis*(pinacolato)diboron, cat. $PdCl_2(PPh_3)_2$, PPh_3, KOPh, Toluene)[129] in good yield (79%), it was not possible to effect the desired boron-halide interconversion under a variety of conditions.[130–132] It was eventually found that dienyl iodide **131** could be formed from the corresponding organostannane **159** (Scheme 2.32).[133] Treatment of dienyl triflate **155** with catalytic $Pd(Ph_3)_4$, hexamethylditin, and lithium chloride in THF led to clean formation of stannane **159**. Exposure of the crude stannane to a solution of iodine in dichloromethane effected iodo-destannylation, affording dienyl iodide **131** in 71% over 2 steps.



155 **159** **131**

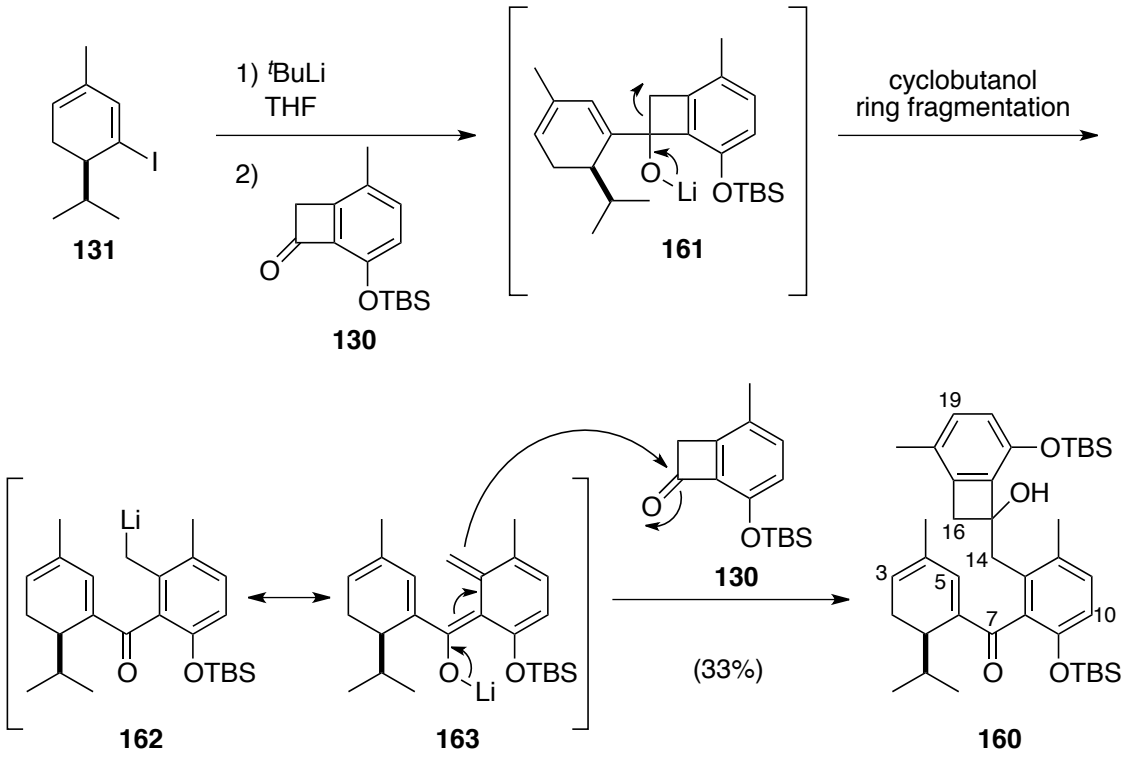
Scheme 2.32 Synthesis of dienyl iodide 131.

2.3.1.5. Attempted Coupling of Dienyl Iodide 131 and Benzocyclobutanone 130

With the successful preparation of dienyl iodide **131**, we were poised to construct the desired tetralone **118** through our previously validated sequential electrocyclic cascade (*vide supra*). Towards this end, treatment of **131** with *tert*-butyllithium formed the corresponding dienyl lithium that was subsequently reacted with benzocyclobutanone **130**. Purification of the crude mixture and analysis of the spectral data derived from the major product (^{1}H, ^{13}C, COSY, HSQC, HMBC) revealed the unexpected formation of enone benzocyclobutanol **160** in 33% yield (Scheme 2.33).

Presumably, initial attack of the dienyl lithium species on benzocyclobutanone **130** leads to the tetrahedral intermediate **161**, which upon spontaneous cyclobutanol fragmentation gives rise to enolate **162**. Vinylogous aldol reaction with a second equivalent of benzocyclobutanone **130** affords the observed product. Accordingly, the formation of **160** is perhaps not surprising given the known electronic effect of α-substituents on the sensitivity of cyclobutenols to ring opening reactions.[134,135] Key features of the spectral data included 4 sets of doublets between δ 7.05 and 6.46 corresponding to the 4 aromatic protons (H10, H11, H19, H20), as well as 2 sets of diastereotopic methylene resonances at δ 3.37 and 2.78 (d, *J* = 14.2Hz, H14), and δ 3.20 and 3.00 (d, *J* = 13.4 Hz, H16). An HMBC correlation displayed by both these latter two sets of protons resonances to the C15 carbinol signal at δ 79.0 provided insight into the dimeric nature of this substrate. Additionally, the observation of a ketone resonance in the ^{13}C spectrum at δ 201.4 and a proton resonance at δ 4.53 (s, 1H, OH) that lacked an HSQC correlation gave further confirmation of the nucleophilic attack of a ring-opened cyclobutanone onto a second molecule of benzocyclobutanone. Other diagnostic resonances included the two singlets at δ 6.28 (s, 1H, H5) and 5.76 (br. s, 1H, H3) corresponding to the vinyl protons, with the H5 proton resonance showing an HMBC

correlation to the C7 ketone. Finally the general observation of only one set of protons arising from the dienyl iodide **131** in contrast to the 2 sets of protons arising from benzocyclobutanone **130** further confirmed our structural assignment.

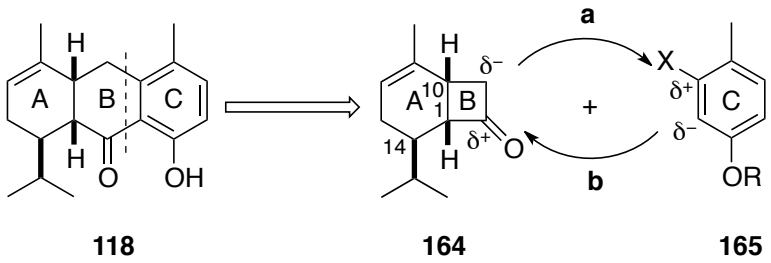


Scheme 2.33 Attempted coupling of dienyl iodide 131 and benzocyclobutanone 130.

Unfortunately, further attempts at this transformation were met with similarly disappointing results. Additionally, as our investigations of this general strategy progressed, several concerns emerged. First was the low yield of the benzyne [2+2] reaction, which made it difficult to produce significant quantities of **130**. Furthermore, the low overall efficiency in the preparation of dienyl iodide **131**, which required a laborious separation to obtain isomerically pure material, was a serious concern. Combined, these drawbacks affected our ability to progress material through the synthetic route, and impeded our investigations of the later stages of the strategy. More importantly, these issues were in direct contrast to our intended primary objective of a flexible, and scalable synthesis of eleutherobin (*vide supra*). Thus, the failed coupling of **131** and **130**, compounded with the inefficiencies discussed above forced us to abandon this strategy towards tetralone **118**.

2.3.2. Revised Tetralone Synthesis I: Palladium-Catalysed Cyclobutanol Ring Expansion

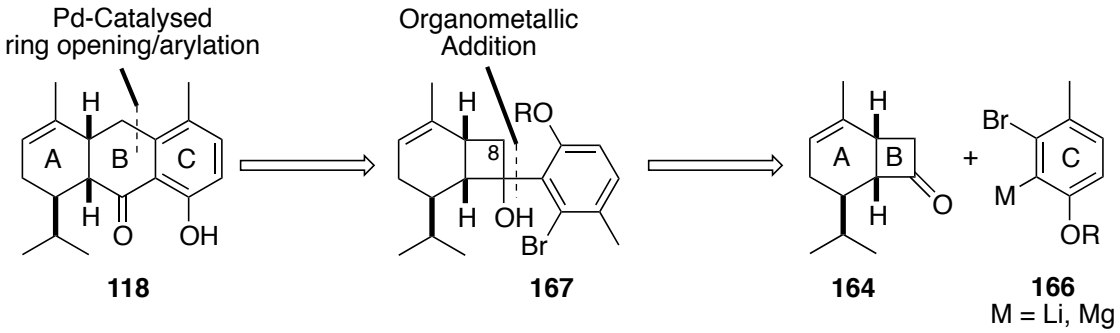
In designing a new synthetic approach to tetralone **118**, it remained our contention that the central B ring could be accessed through a formal ring expansion of a cyclobutanone. In our revised retrosynthetic approach it was surmised that tetralone **118** could be derived from the known cyclobutanone **164**[6] and a functionalised aromatic **165** through the general disconnections depicted in Figure 2.13. The use of cyclobutanone **164** was expected to provide greater stability with respect to electrocyclic ring opening as compared to benzocyclobutanone **130**. Furthermore, cyclobutanone **164** is available in both high enantio- and diastereoselectivity in 2 steps from commercially available materials, and contains the correct relative and absolute stereochemistry at C1, C10, and C14.



118 **164** **165**

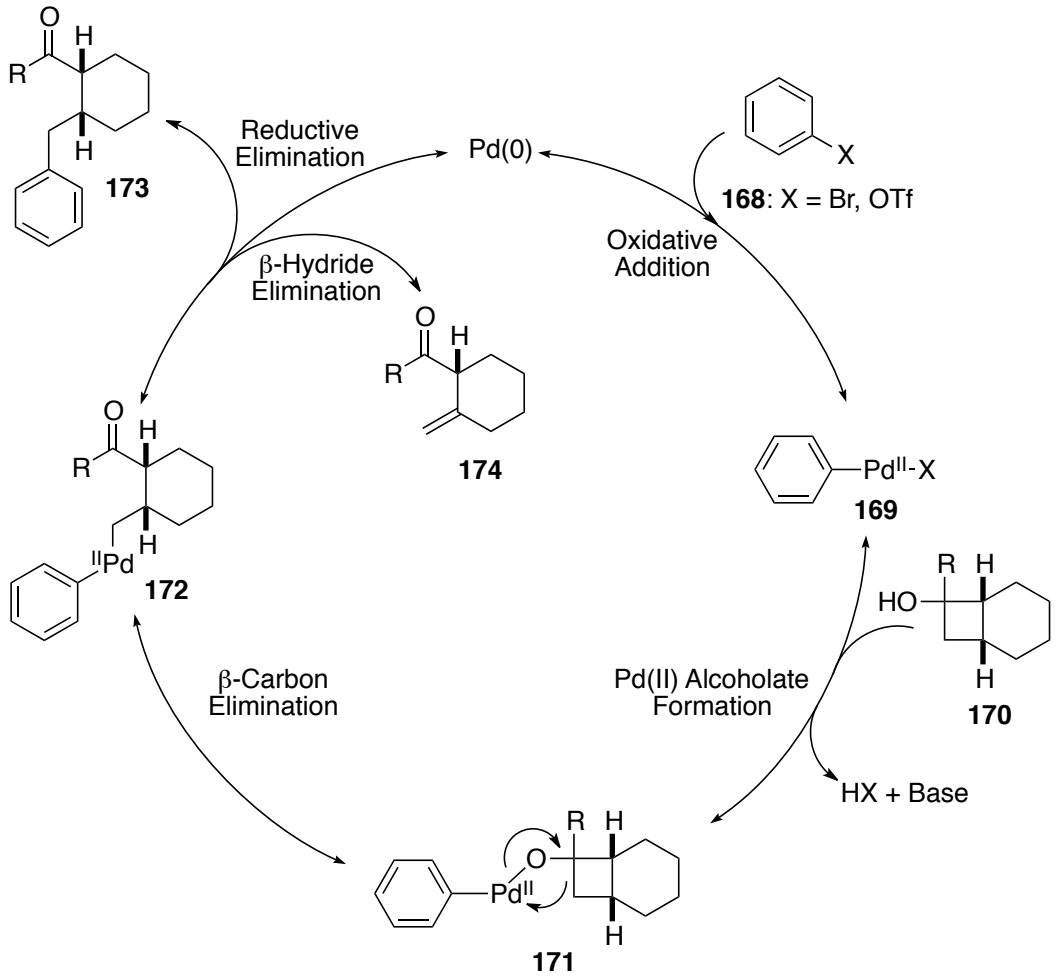
Figure 2.13 Polarity disconnections for tetralone 118.

Our revised synthetic strategy is outlined in Scheme 2.34. It was envisioned that the addition of an aryl lithium or Grignard reagent (e.g., **166**) to cyclobutanone **164** would give rise to cyclobutanol **167**, accomplishing the first disconnection of the general approach (**b** in Figure 2.13). To affect the subsequent ring expansion, we planned to utilise a palladium-catalysed reaction that would involve a fragmentation of the cyclobutane ring with concomitant C-C bond formation between the aryl group and C8 of the cyclobutanol.



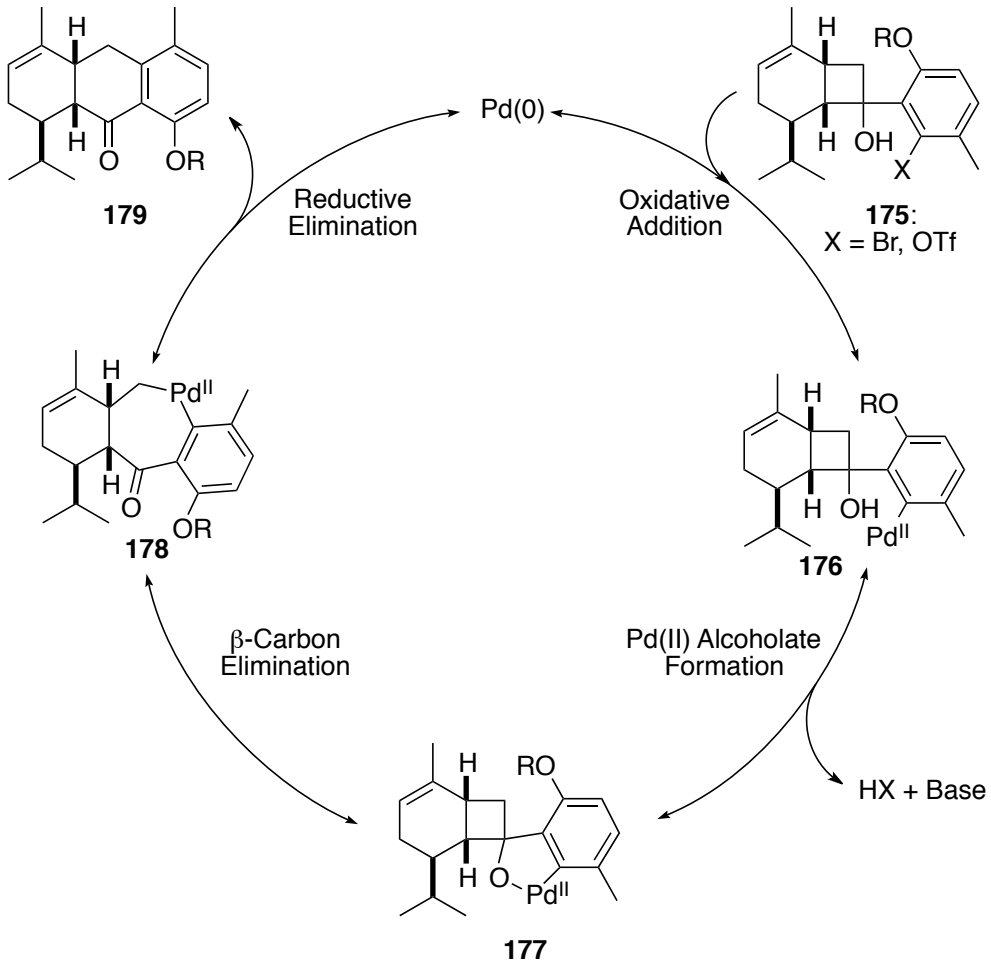
Scheme 2.34 Revised tetralone retrosynthesis.

Several palladium-catalysed processes that exploit the ring opening reactivity of cyclobutanols have recently been demonstrated that afford access to a wide range of structurally desirable motifs.[136] For example, Uemura and co-workers reported one example of such a process in which the arylation of cyclobutanols gives rise to γ-arylated ketones.[137] The proposed mechanism is depicted in Scheme 2.35. The palladium-catalysed process initiates with the oxidative insertion of a palladium (0) species into the aryl halide or triflate bond of **168**, which gives the palladium (II) intermediate **169**. Subsequent nucleophilic attack of cyclobutanol **170** onto the electrophilic palladium species affords the palladium alkoxide **171**. Fragmentation of the cyclobutane ring through a β-carbon elimination gives a primary alkyl palladium (II) species **172**, which can either undergo reductive elimination leading to the γ-arylketone **173** or β-hydride elimination to afford the β,γ-unsaturated ketone **174**. In this work, the choice of ligand is an important factor in determining the fate of the alkyl palladium (II) species **172**, with bulky phosphine ligands such as BINAP favouring the C-C bond forming pathway.[137] Additionally, reaction conditions leading directly to β,γ-unsaturated ketones have also been developed that involve a $Pd(OAc)_2$/pyridine/3Å MS catalyst system under an atmosphere of oxygen.[138]



Scheme 2.35 Proposed catalytic cycle for the palladium-catalysed arylation of cyclobutanols.

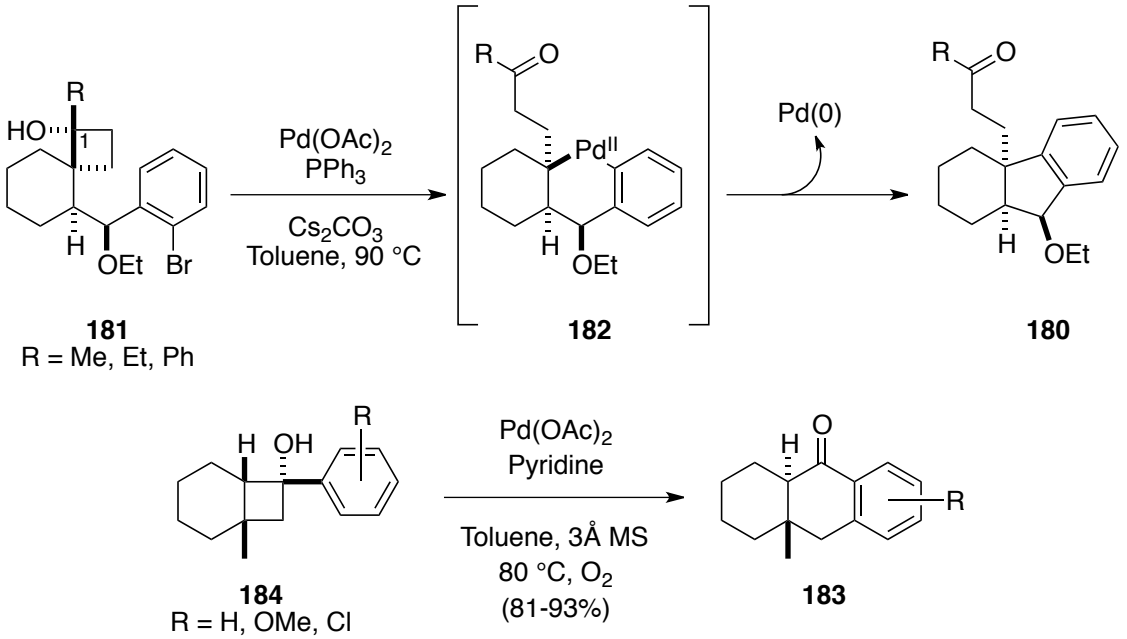
It was expected that an intramolecular application of this reaction that follows an analogous reaction mechanism could be exploited for the synthesis of tetralone **118** (Scheme 2.36). Following oxidative addition of palladium into the aromatic ring of **175**, internal palladium alkoxide formation of the intermediate **176** would lead to **177**. Subsequent β-carbon elimination would give rise to the palladacycle **178**, which upon reductive elimination would afford the tetralone **179** and regenerate the catalyst.



Scheme 2.36 Proposed mechanism of palladium-catalysed formation of tetralone 188.

While no examples of this specific transformation have been reported, a few accounts of the intramolecular palladium-catalysed arylation of cyclobutanols exist in the literature (Scheme 2.37). For example, Cha and co-workers reported the synthesis of five-membered ring carbocycles **180** by intramolecular palladium-catalysed ring opening of **181**.[139] In this process, ring cleavage of the more substituted C-C bond of the cyclobutanol gave rise to alkyl palladium **182,** which afforded the desired product upon reductive elimination. Notably, this reaction was particularly sensitive to the stereochemistry of the cyclobutanol hydroxyl group, with the C1 epimer leading only to products of dehalogenation, suggesting the reaction does not proceed via a cyclic palladium alcoholate (e.g., **177**). Additionally, Uemura has described the synthesis of tetralones **183** by aerobic oxidation of cyclobutanols **184** containing angular substituents.

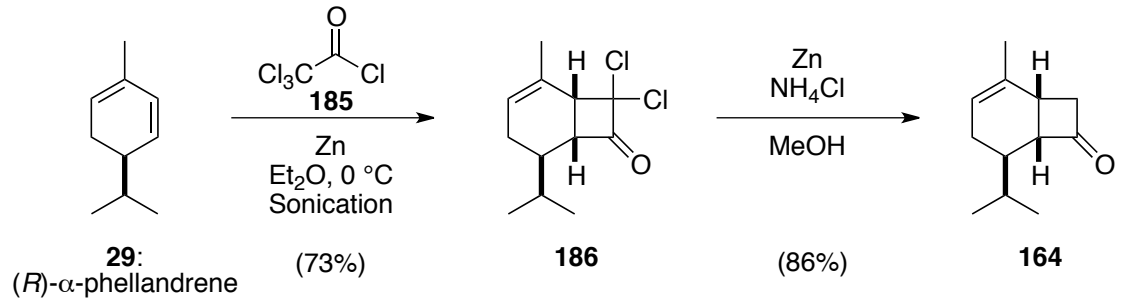
Without the possibility for β-hydride elimination, the alkyl palladium intermediates formed by β-carbon elimination of **184** undergo a 5-*exo*-trig cyclisation onto the aromatic ring. Subsequent β-hydride elimination restores aromaticity and gives rise to α-tetralones.[140]



Scheme 2.37 Examples of intramolecular palladium-catalysed arylation of cyclobutanols.

2.3.2.1. Synthesis of Cyclobutanols 189 and 191

To test the proposed intramolecular palladium-catalysed tetralone formation, it was first necessary to prepare the cyclobutanol precursors by addition of an aryl nucleophile to the cyclobutanone **164**. Following a report by Danishefsky and co-workers, cyclobutanone **164** was prepared as described in Scheme 2.38.[6] Thus, reaction of α-phellandrene (**29**) with dichloroketene (derived from the reaction of trichloroacetyl chloride (**185**) with zinc) afforded the dichlorocyclobutanone **186** in 73% yield. Subsequent dechlorination of the latter material with zinc in the presence of ammonium chloride in methanol afforded the cyclobutanone **164** in 86% yield.



29:
(*R*)-α-phellandrene

(73%)

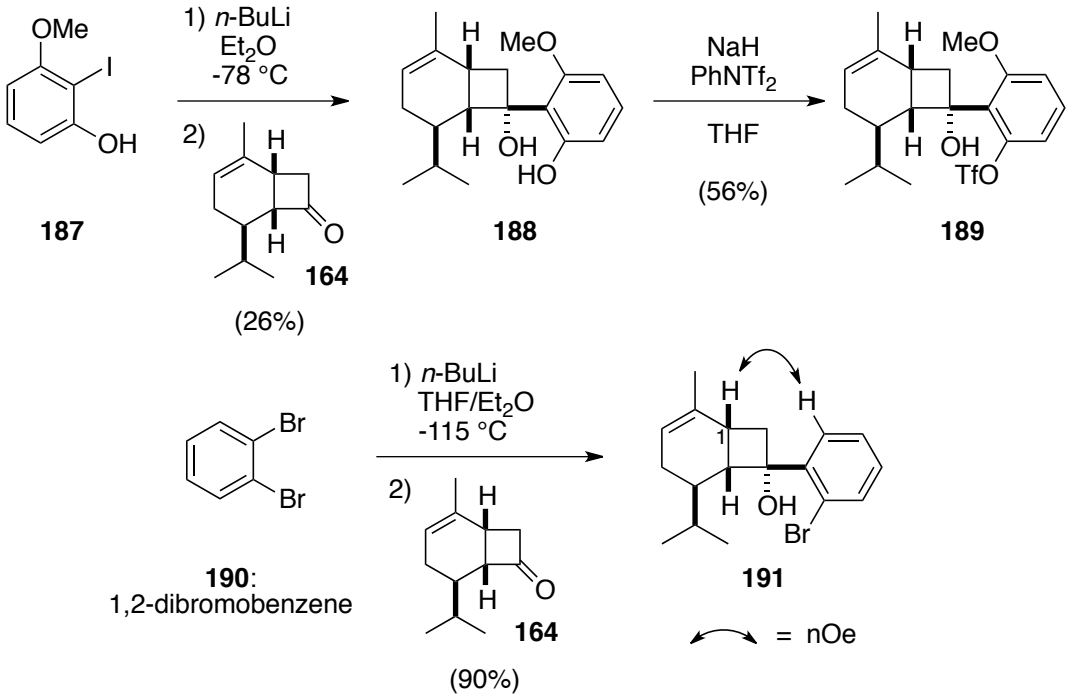
186

(86%)

164

Scheme 2.38 Synthesis of cyclobutanone 164.

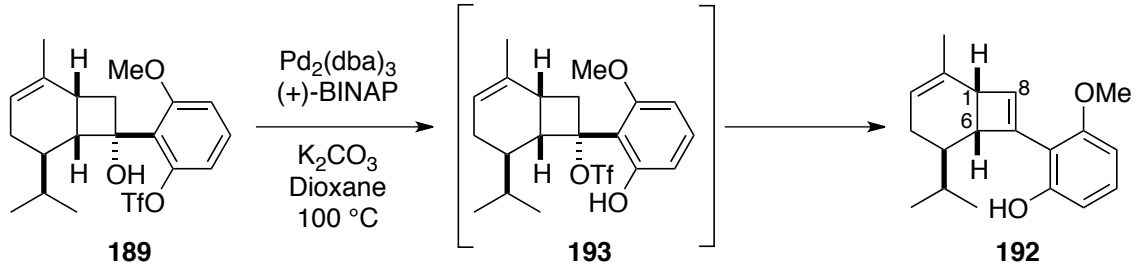
In order to explore the intramolecular palladium-catalysed reaction sequence discussed above, two cyclobutanol precursors were prepared, one containing an aryl bromide and the other an aryl triflate (Scheme 2.39). Towards this end, addition of the dianion derived from 3-methoxy-2-iodophenol (**187**)[141] to **164** gave the cyclobutanol **188** in 26% yield. The low yield of this process can be attributed to the formation of a cyclobutanone dimer, formed under the basic reaction conditions by an aldol reaction between two molecules of **164**. Treatment of cyclobutanol **188** with sodium hydride and *N*-phenylbistrifluoromethanesulfonamide afforded triflate **189** in 56% yield. In a similar manner, a single lithium-halogen exchange was carried out on 1,2-dibromobenzene (**190**) by treatment with *n*-butyllithium at -115 °C, conditions which preclude benzyne formation. Addition of this aryl lithium to cyclobutanone **164** gave rise to cyclobutanol **191** in excellent yield (90%). The stereochemistry of the newly formed carbon chirality centre in cyclobutanol **191** was assigned by 1D nOe experiments. Specifically, these experiments clearly showed a correlation between the aromatic hydrogen and the cyclobutanol H1, indicating attack of the nucleophile from the convex β-face of the cyclobutanone.



Scheme 2.39 Synthesis of Pd-catalysed arylation precursors.

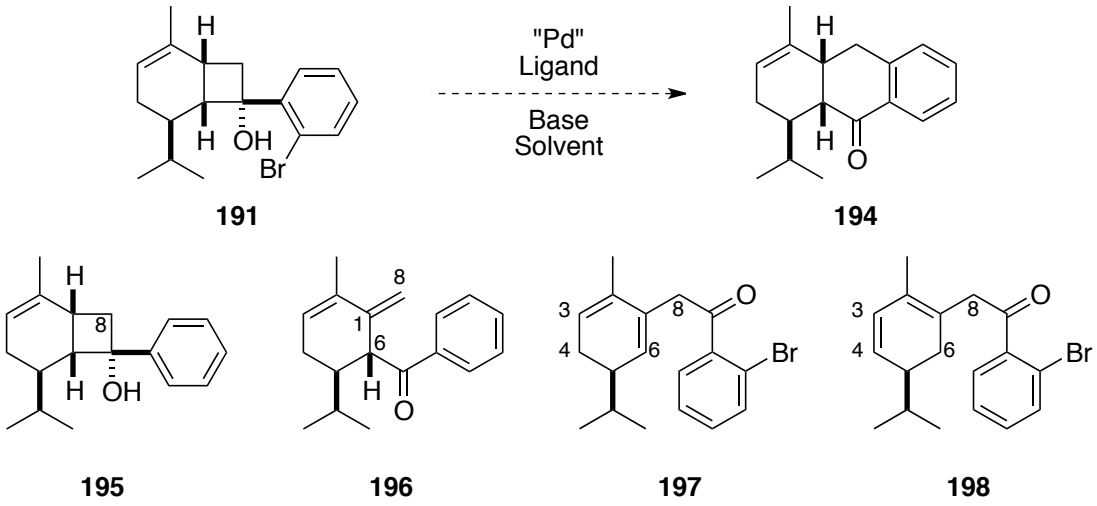
2.3.2.2. Palladium-Catalysed Reactions of Cyclobutanols 189 and 191

With the cyclobutanols **189** and **191** in hand, we began our investigation of the proposed palladium catalysed tetralone formation. Subjecting the triflate **189** to Uemura's conditions (Scheme 2.40) led to rapid consumption of the starting material and formation of cyclobutene **192**. This result suggests that under the necessarily basic reaction conditions, the triflate is transferred from the phenol to the cyclobutanol (**189** → **193**), an event which is followed by facile elimination of the tertiary triflate. Key features of the ^{1}H NMR spectrum recorded on **192** included 2 vinyl resonances at δ 5.51 and 5.40 corresponding to H8 and H3, respectively. Additionally, the phenol OH singlet at δ 5.66 (lacked an HSQC correlation) gave further evidence for the intramolecular transfer of the triflate from phenol to the tertiary alcohol. Unfortunately, lowering the reaction temperature did little to supress this undesired side reaction, as transformation of **189** to **192** required only 2 hours at 70 °C to reach 50% conversion. Since the reported palladium-catalysed cyclobutanol fragmentation reactions are slow (24 hours at 80 °C)[142] in comparison to cyclobutene formation, we decided to explore reactions of the cyclobutanol **191** that lacks the triflate function.



Scheme 2.40 Attempted Pd-catalysed arylation of 189.

When cyclobutanol **191** was subjected to a variety of reported cyclobutanol fragmentation reaction conditions that included various combinations of palladium sources (e.g., $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba_3)$, ligands (e.g., PPh_3, (+)-BINAP), bases (e.g., Cs_2CO_3, NaOAc, KOPh, NaOMe, KO^{t}Bu, pyridine) and solvents (e.g., toluene, DMF), formation of complex product mixtures were observed (Scheme 2.41). Unfortunately after careful separation and analysis of these products, there was no evidence for the formation of tetralone **194**. In an attempt to understand the failure of this reaction we characterised a number of the compounds isolated from the crude reaction mixtures. Analogous to reports by Cha,[139] debrominated cyclobutanol **195** was the major product of these reactions (*vide supra*). Key features of its ^{1}H NMR spectrum included 3 aromatic resonances at δ 7.57 (d, 2H, *J* = 7.3 Hz), 7.40 (t, 2H, *J* = 7.3 Hz), and 7.29 (t, 1H, *J* = 7.3 Hz) which are indicative of a mono-substituted benzene ring. Furthermore, a cyclobutanol signal in the ^{13}C NMR spectrum at δ 75.2 that displayed HMBC correlations to the cyclobutanol OH resonance at δ 1.92 as well as a cyclobutane H8 resonance at δ 2.13 supported the structural assignment.



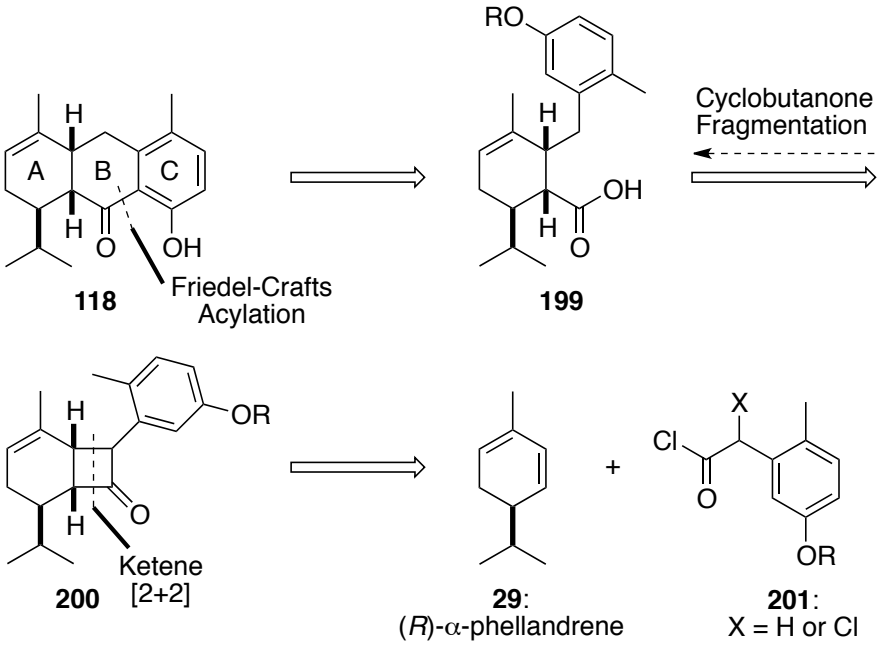
Scheme 2.41 Products isolated from attempted Pd-catalysed arylation of 191.

In addition to cyclobutanol **195**, the fragmented ketones **196**, **197**, and **198** were also isolated from this crude reaction mixture. The former compound displayed 4 resonances in the ^{1}H NMR spectrum at δ 5.66 (br. s, 1H), 5.12 (s, 1H), 4.71 (s, 1H), 4.30 (d, 1H, *J* = 6.0 Hz), corresponding to the H3 vinyl proton, H8 exocyclic methylene protons, and H6 methine respectively. Compounds **197** and **198** displayed similar spectral data. Confirmation of a fragmentation of the more substituted C-C bond of the cyclobutanol was established by the presence of 2 sets of diastereotopic H8 methylene resonances at δ 2.89 (d, 1H, *J* = 19.2 Hz) and 2.56 (d, 1H *J* = 19.2 Hz) for **197**, as well as δ 2.76 (d, 1H, *J* = 19.2 Hz) and 2.55 (d, 1H, *J* = 19.2 Hz) for **198**. Additionally, **197** also displayed 2 singlets at δ 5.68 and 5.25 corresponding to the H3 and H6 vinyl signals, respectively. In contrast, resonances indicative of the disubstituted *cis*-olefin in **198** were observed at δ 5.87 (dd, 1H, *J* = 5.4, 1.1 Hz) and δ 5.74 (d, 1H, *J* = 5.4 Hz) corresponding to H3 and H4, respectively. The observation of compounds containing brominated and debrominated aromatic rings suggests that they form concurrently through an intermolecular palladium catalysed process. For example, insertion of palladium (0) into aryl bromide **191** followed by palladium alkoxide formation and fragmentation with a second molecule of **191** could lead to the formation of **195** concurrently with **197**. Overall, the formation of these four compounds suggests that the 5-membered palladacycle formed by intramolecular palladium alcoholate formation is either too stable or sterically constrained to undergo β-carbon elimination. It was therefore reasoned that eliminating the potential for palladium alkoxide formation may

facilitate an intramolecular process. However, while cyclobutanol **191** was easily converted to its methyl ether (NaH, MeI, THF, 82%), employing a variety of reaction conditions typical for Pd-catalysed cyclobutanol fragmentation (*vide supra*) did not result in the production of the desired tetralone. Due to the failure of these reactions to provide access to tetralone scaffolds, we were forced to abandon this approach towards tetralone **118**.

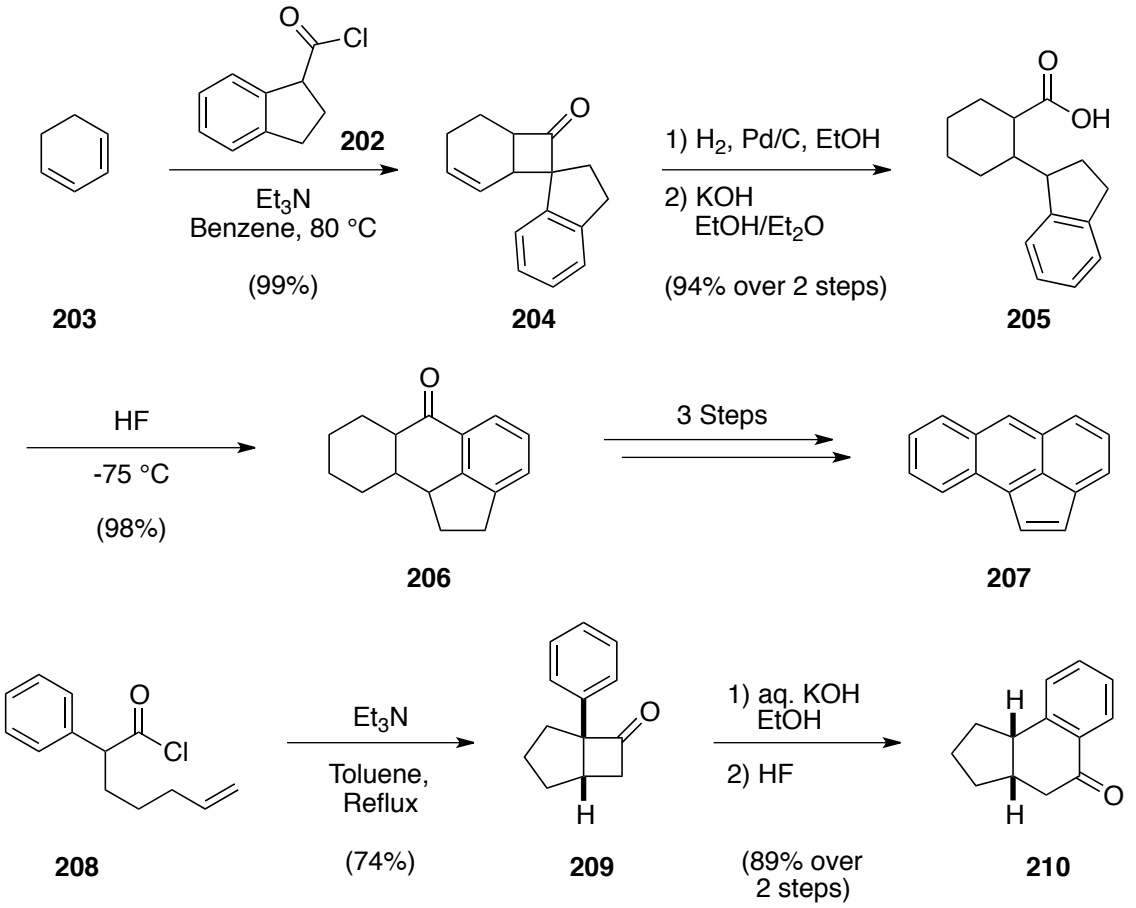
2.3.3. Revised Tetralone Synthesis II: Friedel-Crafts Acylation of γ-Arylacids

Based on the reasoning discussed in section 2.3.2, it remained our contention that tetralone **118** could be accessed through the general disconnections described in Figure 2.13. In this regard, a reversal of the bond forming events (i.e., **a** followed by **b** in Figure 2.13) would form the basis of our revised retrosynthetic analysis shown in Scheme 2.42. In our modified strategy, tetralone **118** would be accessed via a Friedel-Crafts acylation of γ-arylacid **199**. This latter compound could be derived through a base catalysed cyclobutanone fragmentation of α-arylcyclobutanone **200**, that in turn would be formed through a [2+2] cycloaddition between α-phellandrene (**29**) and the ketene derived from an appropriately substituted α-arylacylchloride **201**. This general strategy was expected to impart a number of important advantages over our previous route, including the robust and well-studied nature of ketene [2+2] and Friedel-Crafts acylation reactions.



Scheme 2.42 Revised retrosynthesis of tetralone 118.

Additionally, this sequence of transformations has been previously utilised for the construction of α-tetralones from arylcyclobutanones (Scheme 2.43). For example, Lee-Ruff and co-workers reported the synthesis of α-tetralones *en route* to polynuclear aromatic hydrocarbons.[143] Specifically, the ketene derived from treatment of 1-indanecarboxylic acid chloride (**202**) with triethylamine underwent [2+2] cycloaddition with 1,3-cyclohexadiene (**203**) to afford cyclobutanone **204** in quantitative yield. Following hydrogenation of the double bond, base promoted fragmentation of the cyclobutanone gave rise to carboxylic acid **205**. Treatment of this latter material with HF induced a Friedel-Crafts acylation giving the α-tetralone **206**, which after subsequent aromatisation afforded the polynuclear aromatic hydrocarbon **207**. In a subsequent example, intramolecular ketene [2+2] cycloaddition of **208** gave α-arylcyclobutanone **209**. Opening of the cyclobutanone under basic conditions and Friedel-Crafts acylation of the γ-arylacid with HF afforded the α-tetralone **210** in 89% yield.[144]

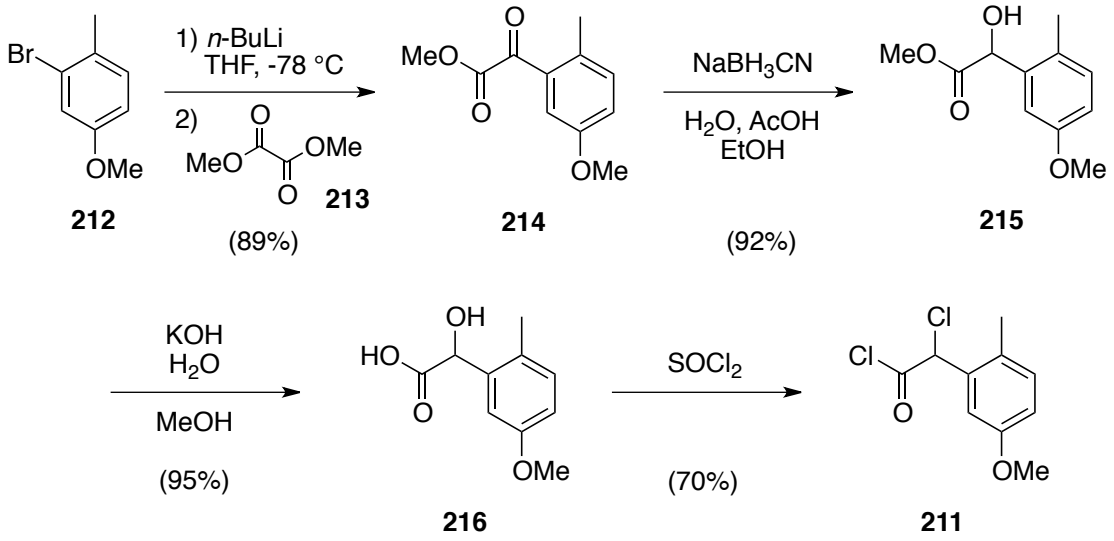


Scheme 2.43 Examples of ketene [2+2]/Friedel-Crafts reaction sequences leading to α-tetralones.

2.3.3.1. Ketene [2+2] Cycloaddition Approach to Tetralone 223

In an initial study of the proposed [2+2] cycloaddition reaction, phellandrene (**29**) was reacted with the ketene derived from both phenylacetyl chloride and α-chlorophenylacetyl chloride. From these reactions we learned that only the α-chloro functionalised ketene gave rise to [2+2] cycloaddition products. Therefore, in subsequent studies, α-chloroacylchloride **211** was targeted as the ketene [2+2] precursor that would lead to tetralone **118**. For the synthesis of **211** we relied upon reported methods for the preparation of α-chloroacylchlorides from α-hydroxyacids (Scheme 2.44).[145] Towards this end, bromide **212** (prepared in an analogous way to **134** in Scheme 2.26)[146] was transformed into the corresponding lithium anion by treatment with *n*-butyllithium. Following addition of dimethyl oxalate (**213**), ketoester **214** was isolated in 89% yield. Treatment of this latter material with sodium cyanoborohydride in a mixture of

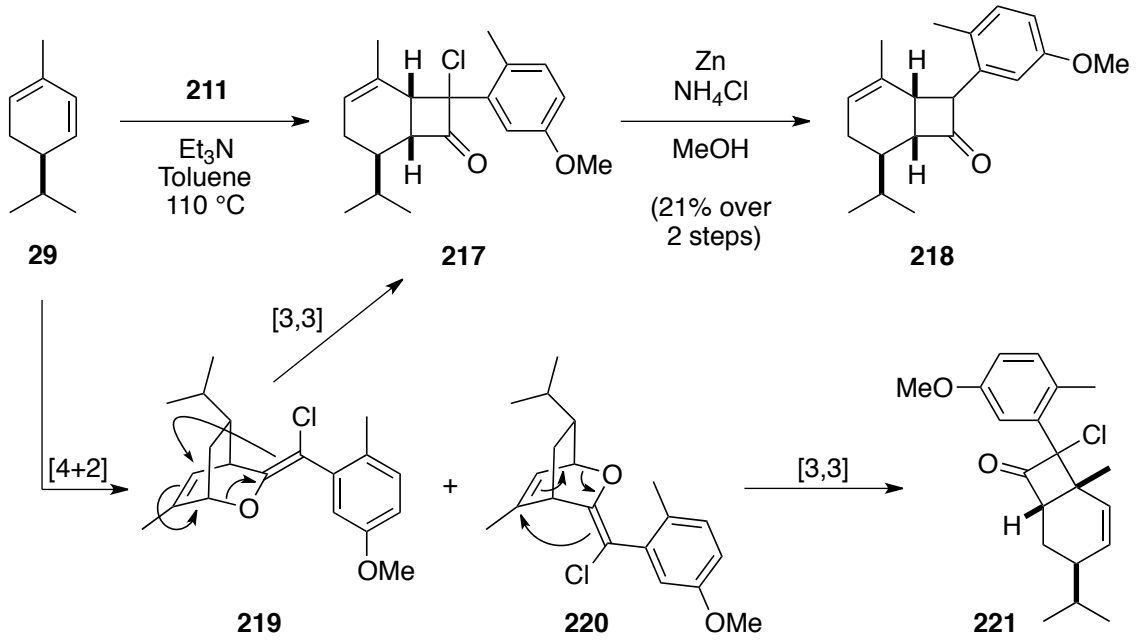
ethanol/water/acetic acid led to reduction of the ketone function and production of hydroxyester **215**. Saponification of the ester with aqueous potassium hydroxide in methanol gave hydroxyacid **216** in excellent yield. This latter material was then converted into the corresponding α-chloroacylchloride by the method reported by Fuson and co-workers, which involved stirring acid **216** in thionyl chloride.[145] After 2 hours at room temperature, full conversion to the corresponding α-chloroacid was observed by ^{1}H NMR spectroscopy. Heating the reaction to 60 °C for an additional 2 hours afforded the α-chloroacylchloride **211** in 70% yield after purification by distillation under reduced pressure. Notably, throughout this 6-step sequence (from aniline **133**) only a single purification of the final α-chloroacylchloride was required.



Scheme 2.44 Synthesis of α-chloroacylchloride 211.

With α-chloroacylchloride **211** in hand, it was found that dropwise addition of triethylamine to a refluxing solution of this material and α-phellandrene (**29**) in toluene delivered a complex mixture of products containing α-chlorocyclobutanone **217** (Scheme 2.45). Subjecting this mixture of products to the dechlorination conditions reported by Danishefsky afforded the α-arylcyclobutanone **218** in 21% yield over 2 steps.[6] Unfortunately, it was not possible to improve the yield of this process, as extensive optimisation (varying temperature, reaction times, stoichiometry, solvents, and concentration) led to only incremental changes in reaction yield. The low yield observed for the production of **217** was rationalised by the fact that ketene cycloadditions with

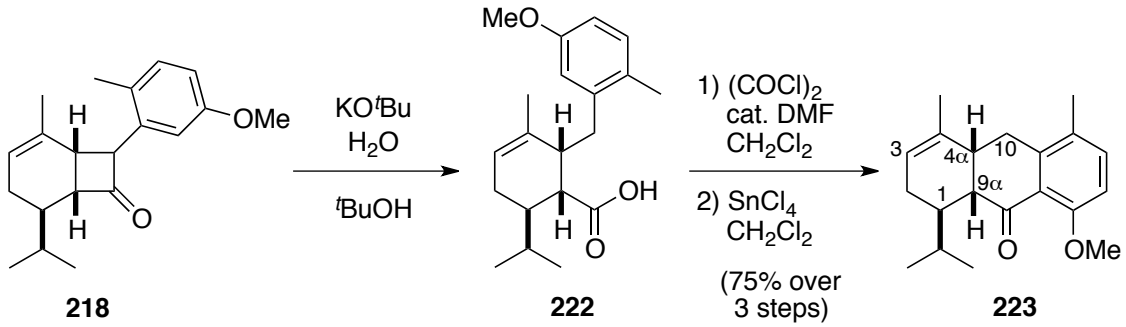
cyclic dienes often proceed through a step-wise process that first involves a [4+2] cycloaddition followed by a [3,3] sigmatropic rearrangement, providing an apparent [2+2] cycloaddition product.[147,148] As a result, it is possible to conceive of the formation and isolation of two regio-isomeric [4+2] adducts **219** and **220**. Rearrangement of the former would lead to the desired cyclobutanone **217**, while the latter [4+2] adduct would afford the regioisomeric compound **221** upon sigmatropic rearrangement. While the ^{1}H NMR spectrum recorded on purified samples of the proposed by-product **219** suggested the formation of this [4+2] adduct, we were unable to unambiguously assign the structure of this compound. In an attempt to initiate sigmatropic rearrangement of possible [4+2] adducts contained in the product mixture, crude reaction mixtures were either treated with Et_2AlCl[149] or heated under microwave irradiation.[150] While these efforts did lead to a change of product ratios, no increase in the relative quantity of chlorocyclobutanone **217** was observed.



Scheme 2.45 Synthesis of α-arylcyclobutanone 218.

Despite the low yield for the cyclobutanone formation sequence, investigations into the conversion of this material into the desired tetralone continued (Scheme 2.45). Thus, Haller-Bauer fragmentation[151] of the arylcyclobutanone following conditions reported by Chen and co-workers (KO^{t}Bu, H_2O, ^{t}BuOH)[152] gave γ-arylacid **222** in quantitative yield. Conversion of this material to the corresponding acid chloride and

treatment with tin(IV) chloride induced a Friedel-Crafts acylation that afforded tetralone **223** in 75% over 3 steps. Key features of the ^{1}H NMR spectrum of tetralone **223** included the two aromatic resonances at δ 6.95 and 6.41, and a broad singlet at δ 5.25 corresponding to the vinyl proton H3. Furthermore, two resonances at δ 2.61 (dd, 1H, *J* = 17.4, 6.5 Hz) and 2.56 (dd, 1H, *J* = 17.4, 8.5 Hz) that could be assigned to the diastereotopic C10 methylene protons, and the methoxy singlet at δ 3.41 (s, 3H) were also key elements of the ^{1}H NMR spectrum of **223**. Importantly, the ^{13}C NMR spectrum also displayed a signal at δ 199.9, corresponding to the C10 arylketone. Additionally, the HRMS displayed a peak at m/z 299.2013 that is in agreement with a molecular formula of $C_{20}H_{27}O_2$ (M+H). Finally, 1D nOe experiments performed on tetralone **223** showed a strong nOe correlation between H9α and H4α, confirming the *syn* stereochemistry of the ring junction.



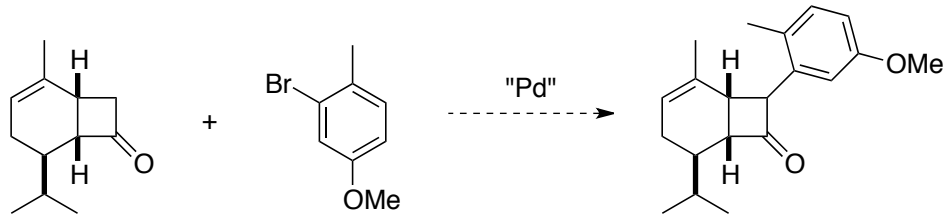
218 **222** **223**

Scheme 2.46 Synthesis of tetralone 223.

While the synthesis of tetralone **223** containing a fully functionalised A-ring in the correct stereochemical configuration was a significant achievement, the low overall yield of this route made it exceedingly difficult to access useful quantities of material and hindered our ability to investigate further steps along the intended route. In particular, the lengthy synthesis of α-chloroacylchloride **211** (6 steps), and the low yield of the ketene cycloaddition reaction represented significant detractors to this route. Thus, in order to fulfill the primary objective of a flexible, and scalable synthesis of eleutherobin, it would be necessary to develop a more succinct route that would allow for significant quantities of **223** to be produced.

2.3.3.2. Palladium-Catalysed α-Arylation Approach to α-Arylcyclobutanone 218

It was envisioned that a palladium-catalysed α-arylation reaction between cyclobutanone **164** and arylbromide **212** could give rapid access to α-arylcyclobutanone **218** (Figure 2.14). If realised, this strategy could greatly increase the overall efficiency of our route, eliminating 5 synthetic transformations and delivering **218** in 3 steps from commercially available materials. While no accounts of the α-arylation of cyclobutanones exist, several examples of palladium-catalysed α-arylation of linear as well as 5, 6, and 7 membered cyclic ketones have been reported.[153–155]

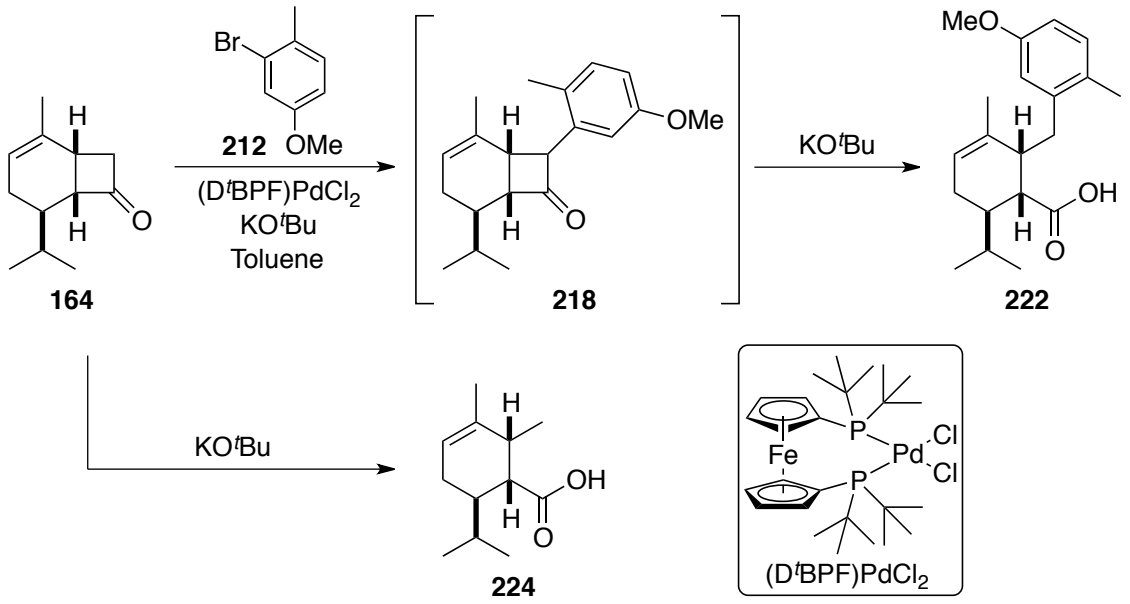


164 **212** **218**

Figure 2.14 Proposed palladium-catalysed α-arylation route to 218.

In our initial attempts to effect this unprecedented reaction, toluene solutions of **164** and **212** were stirred with combinations of several commercially available phosphine ligands (BINAP, P(^{t}Bu)$_3$, (2-Biphenyl)-di-*tert*-butylphosphine) and palladium sources (Pd(OAc)$_2$, Pd$_2$(dba)$_3$), according to procedures reported by Buchwald and Hartwig for the α-arylation of linear and cyclic ketones.[153,155] Unfortunately, these ligand/catalyst combinations failed to effect the desired transformation. Performing the reaction under conditions reported by Colacot and co-workers (D^{t}BPFPdCl$_2$, KO^{t}Bu, Toluene, 115 °C)[154] led to a 15% conversion of **164** to arylcyclobutanone **218** as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Scheme 2.47). Increasing the equivalents of base (KO^{t}Bu) employed from 1.1 to 2.2 equivalents gave a 45% conversion as determined by ^{1}H NMR spectroscopy and the isolation of arylcyclobutanone **218** in 15% yield as a mixture of diastereomers. Unfortunately, repetition of these conditions led to variable yields of **218**, with some reactions providing only minor quantities of product. Further investigation of this reaction revealed that fragmentation of arylcyclobutanone **218** under the basic reaction conditions also occurred, resulting in the formation of the arylacid **222** in 34% yield. While the

unexpected isolation of **222** was particularly fortuitous in our pursuit of tetralone **223**, fragmentation of the starting material and formation of acid **224** was also observed. In an attempt to avoid the fragmentation of the starting material **164**, the reaction was carried out under a variety of temperatures. However, even at room temperature, large quantities of **224** were observed, confirming the incompatibility of KO^{t}Bu with cyclobutanone **164**. While K_2CO_3 and K_3PO_4 were found to be ineffective at promoting the α-arylation process, the use of LiO^{t}Bu at room temperature led to the isolation of arylcyclobutanone **218** in 63% yield. Based on analysis of the ^{1}H NMR spectrum recorded on several crude reaction mixtures, it was apparent that LiO^{t}Bu causes an aldol dimerisation of cyclobutanone **164**, protecting the starting material from base induced fragmentation and reversibly releasing small concentrations of **164** that quickly react under the palladium-catalysed conditions. Furthermore, the formation of a cyclobutanone aldol adduct decreases the overall concentration of free base in solution, while the close association of the lithium counterion decreases the nucleophilicity of the base and inhibits fragmentation processes.

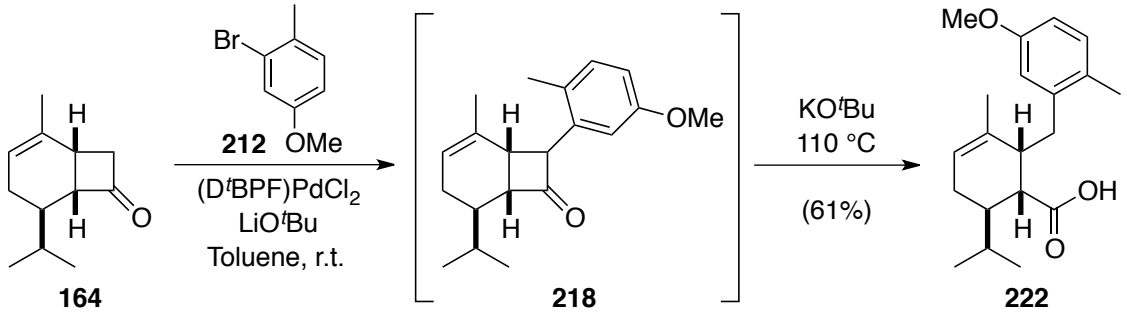


Scheme 2.47 Palladium-catalysed α-arylation of cyclobutanone 164.

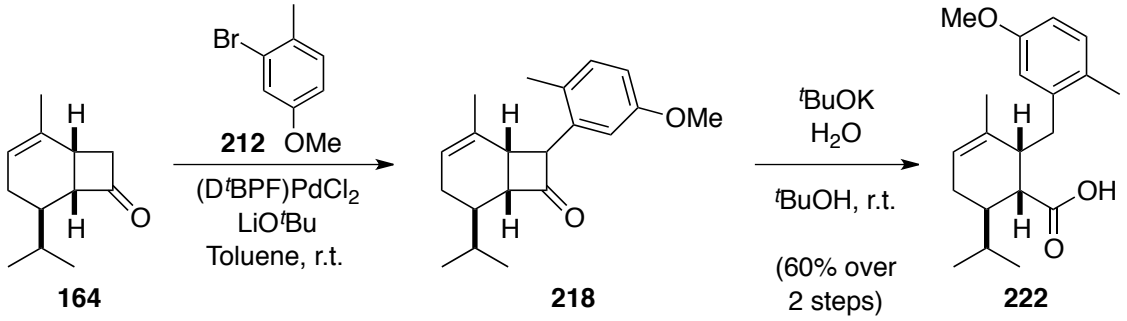
From a synthetic standpoint, the opportunity to access 2 structural scaffolds (e.g., **218** and **222**) through a single synthetic transformation represents a considerable advantage. Utilising the unique counter-ion effect uncovered in the previous

optimisation, we quickly developed two separate sets of reaction conditions to access either arylcyclobutanone **218** or arylacid **222** (Scheme 2.48). In a typical procedure, a solution of **164** and **212** in toluene was treated with D^{t}BPFPdCl$_2$ and LiO^{t}Bu at room temperature. Upon consumption of the starting materials (~5 hours as determined by TLC analysis), subjecting the mixture to standard work-up procedures produced arylcyclobutanone **218** in 63% yield. Conversely, treatment of the reaction mixture with KO^{t}Bu and heating to 110 °C for 24 hours induced cyclobutanone fragmentation and afforded arylacid **222** in 61% yield. Additionally, the crude arylcyclobutanone **218** could be subjected to the fragmentation conditions previously employed to give **222** in 60% over 2 steps.

One-Pot Procedure:



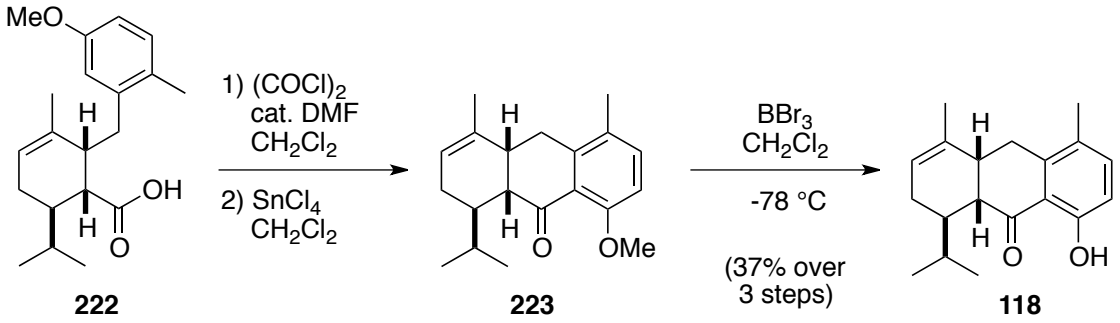
Two-Pot Procedure:



Scheme 2.48 Synthesis of γ-arylacid 222 by one and two pot palladium-catalysed methods.

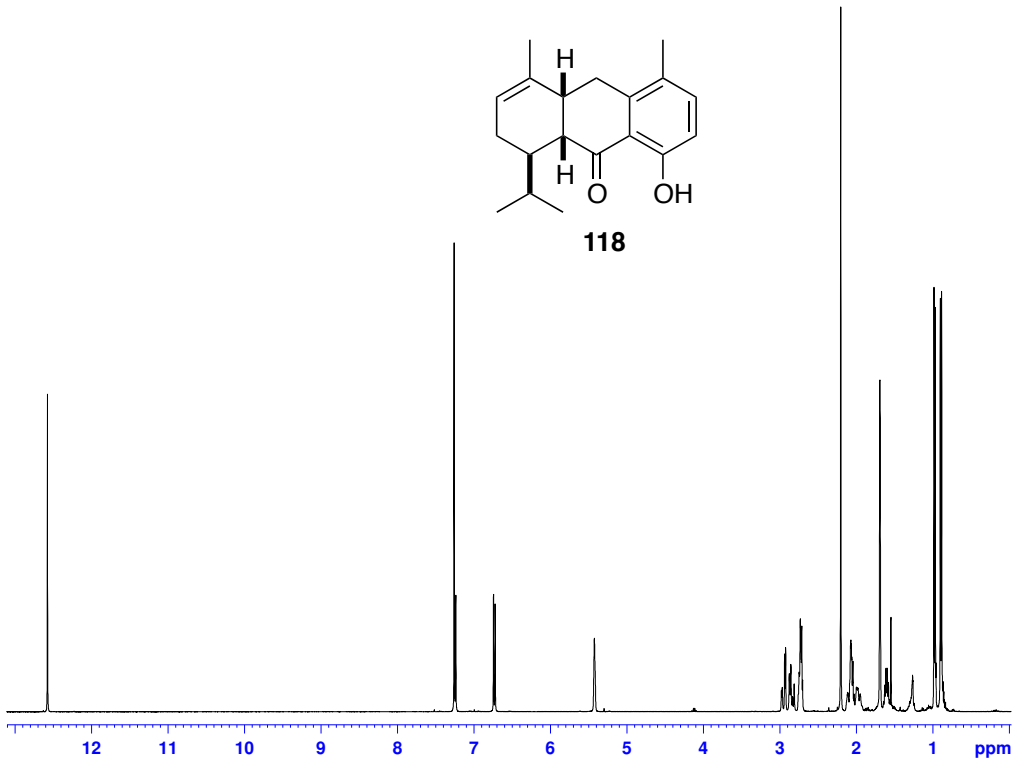
With this new process for the palladium catalysed construction of arylacid **222** in hand, we turned our attention to the formation of tetralone **118** (Scheme 2.49). Towards this end, conversion of **222** to the acid chloride and intramolecular Friedel-Crafts acylation according to our previously developed conditions (*vide supra*) afforded α-

tetralone **223**. Treatment of this latter compound with boron tribromide effected de-methylation of the phenol and gave rise to tetralone **118** in 37% over 3 steps. Disappointingly, the de-methylation reaction failed to progress to completion, delivering a 2:1 ratio of **118** to **223** as determined by analysis of ^{1}H NMR spectra recorded on the crude reaction mixtures. Utilising a large excess of boron tribromide failed to significantly alter the reaction outcome. Furthermore, while allowing the reaction to warm from -78 °C resulted in higher yields of tetralone **118**, epimerisation of the α-centre to the ketone was also observed (59% over 3 steps, d.r. = 4:1). Loss of the methyl group was confirmed by analysis of the ^{1}H NMR spectrum of tetralone **118**, which displayed a singlet at δ 12.60 corresponding to the hydrogen bonded phenolic proton (Figure 2.15). Additionally, the HRMS of **118** displayed a peak at m/z 285.1874 consistent with a molecular formula $C_{19}H_{25}O_2$ (M+H).



222 **223** **118**

Scheme 2.49 **Synthesis of tetralone 118 from γ-aryl acid 222.**

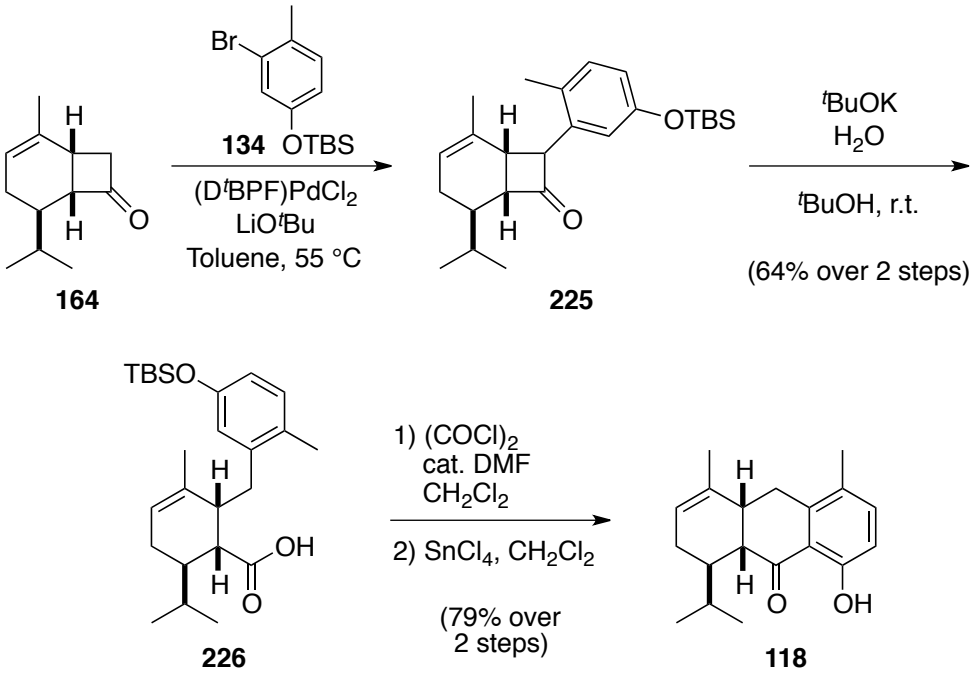


118

Figure 2.15 **^{1}H NMR spectrum of tetralone 118 recorded at 500 MHz in $CDCl_3$.**

It was envisioned that by utilising a phenol protecting group that could be removed under milder conditions, it would be possible to circumvent the difficulties associated with de-methylation of tetralone **223** and further increase the efficiency of our process. Repetition of the palladium-catalysed α-arylation with silyl-protected arylbromide **134** led to arylcyclobutanone **225** (Scheme 2.50). In this case a slightly

higher temperature (55 °C) was required to initiate the palladium-catalysed process. Fragmentation of the crude reaction mixture with KO^{t}Bu and H_2O in ^{t}BuOH afforded arylacid **226** in 64% over 2 steps. Formation of the acid chloride and treatment with tin(IV) chloride induced intramolecular Friedel-Crafts acylation with concomitant loss of the silyl protecting group, leading directly to tetralone **118** in 79% over 2 steps.



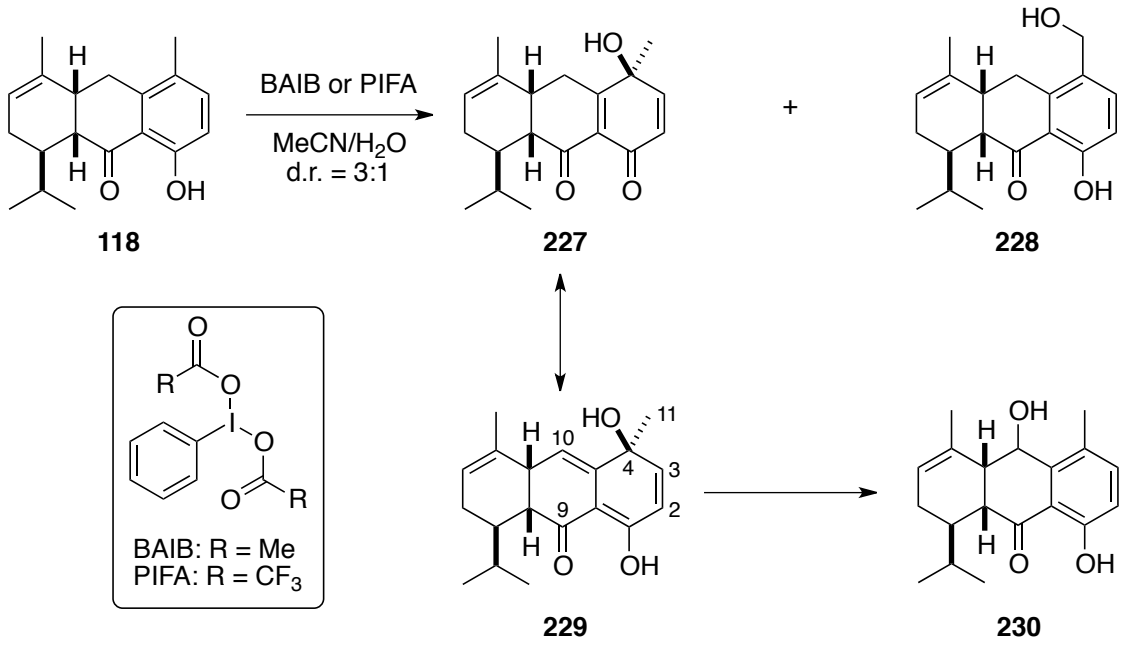
Scheme 2.50 Synthesis of tetralone 118 from silyl-protected aryl bromide 134.

The development of this unprecedented process for the α-arylation of cyclobutanones afforded a rapid and straightforward route to tetralone **118**. Employing this method, **118** could be produced in 6 steps from α-phellandrene (**29**) with an overall yield of 32%, and a reduction of 6 synthetic transformations from the ketene [2+2] strategy. Importantly, this method provided access to gram quantities of tetralone **118** and fulfilled our objective towards a scalable and flexible process for the synthesis of eleutherobin (**1**).

2.3.4. Tetralone Dearomatisation and Functionalisation

2.3.4.1. Tetralone Dearomatisation

With an optimised process for the synthesis of tetralone **118** in hand, we turned our attention to the dearomatisation of **118**, and further conversion of this advanced intermediate into the required Grob fragmentation precursor. Thus, treatment of **118** with BAIB in a mixture of acetonitrile and water resulted in the formation of dienedione **227** (d.r. = 3:1 as determined by ^{1}H NMR spectroscopy recorded on the crude reaction mixture) and a minor quantity of benzylic alcohol **228**, the latter of which is most likely formed through the intermediacy of a quinone methide derived from **227** (Scheme 2.51).[156] Despite the presence of **227** in crude reaction mixtures, purification of this compound by flash chromatography led to the tautomerisation of **227** and the isolation of two diastereomers of trienol **229** in addition to benzylic alcohol **230**.



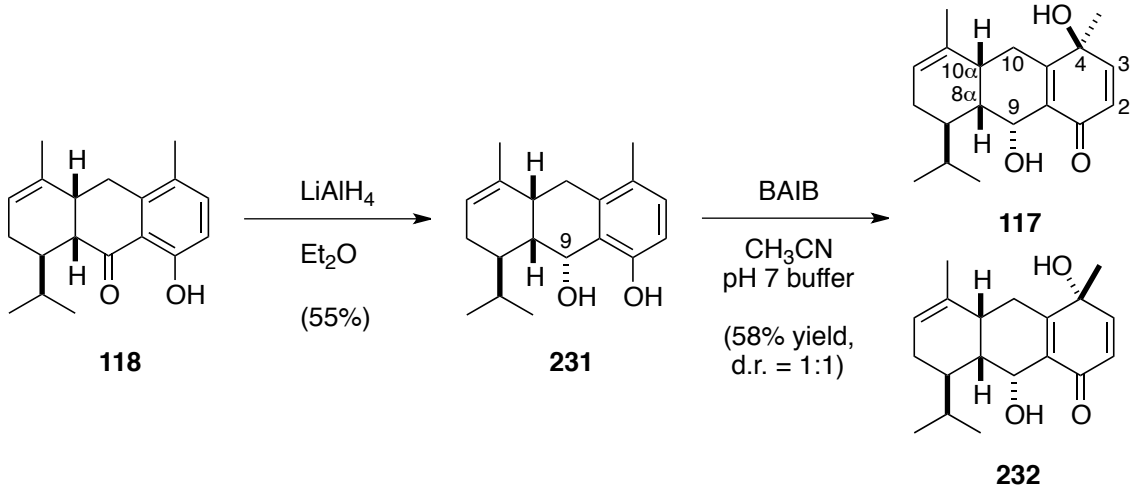
Scheme 2.51 Dearomatisation of tetralone 118.

The ^{1}H NMR spectrum recorded on the major diastereomer of **229** displayed two sets of doublets at δ 6.36 (d, 1H, *J* = 10.0 Hz) and 6.07 (d, 1H, *J* = 10.0 Hz), corresponding to the olefinic protons H2 and H3. An additional proton resonance at δ 6.04 (d, 1H, *J* = 5.1 Hz) which displayed an HSQC correlation to a carbon resonance at δ 121.2 (C10) gave further confirmation of the tautomerisation process. Furthermore, a

proton resonance at δ 14.60 (lacking an HSQC correlation) that displayed an HMBC correlation to the C9 ketone resonance in the ^{13}C NMR spectrum at δ 203.7 confirmed the presence of a hydrogen-bonded enol. Finally, the correlation of two singlets in the ^{1}H NMR spectrum at δ 1.83 (s, 1H, OH) and 1.42 (s, 3H, H11) to the C4 carbon signal δ 69.2 confirmed the installation of the hydroxyl group in the dearomatisation reaction and the formation of an oxidised benzene ring. Disappointingly, attempts to purify the desired product **227** utilising Iatrobeads (used for the purification of acid sensitive molecules) in place of silica gel, and/or adding triethylamine to eluent solvents did little to inhibit the tautomerisation (i.e., **227** → **229**). Additionally, while the formation of **229** was expected to be reversible, subjecting solutions of **229** to subsequent reactions (i.e., H_2O_2, NaOH, H_2O/MeOH or pyrrolidine, CH_2Cl_2) led only to the formation of **230**. This formal [1,3] sigmatropic rearrangement is most likely promoted by the favourable rearomatisation of the phenol ring as well as the intermediacy of a stabilised benzylic carbocation formed through ionisation of the tertiary hydroxyl group. Unfortunately, utilising PIFA to effect the dearomatisation reaction led directly to the formation of 4 diastereomers of **230**. Presumably, liberation of the more strongly acidic trifluoroacetic acid, catalyses both the tautomerisation and rearrangement processes, as well as promotes the epimerisation of the carbon chirality centre adjacent to the ketone in tetralone **118**. Disappointingly, removal of trifluoroacetic acid formed in the reaction through the addition of pH = 7 buffer only reduced the rate of the reaction while the outcome was largely unaffected.

Due to the tautomerisation of dienedione **227** and its subsequent rearrangement to **230**, it was reasoned that a reduction of the ketone function in **118** would obviate this process. This transformation would also effect a necessary oxidation state change required for preparation of the Grob fragmentation precursor as outlined in Scheme 2.22. Thus, treatment of tetralone **118** with lithium aluminum hydride in ether generated hydroxyphenol **231** in 55 % yield (Scheme 2.52). The presence of a proton resonance at δ 5.05 (dd, 1H, *J* = 7.7, 5.7 Hz) corresponding to the C9 proton as well as the observation of the C9 signal in the ^{13}C NMR spectrum at δ 73.5 confirmed the reduction of the ketone function. Despite observing a clean ^{1}H NMR spectrum for the crude reaction mixture, the modest isolated yield for this process was attributed to the acid sensitivity of hydroxyphenol **231**, which presumably decomposes via the formation of reactive *o*-quinone methides during chromatographic purification. Nonetheless,

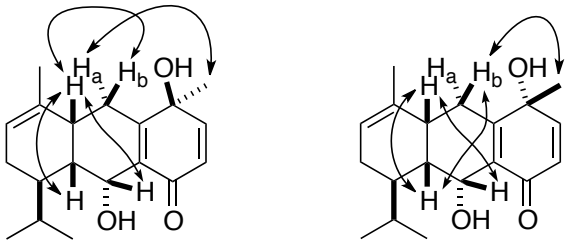
treatment of **231** with BAIB in a mixture of acetonitrile and water led to the formation of dienone **117** as well as an unidentified by-product most likely formed by acid catalysed decomposition of **232**. In order to reduce the decomposition of **232**, the reaction was carried out in a mixture of acetonitrile and pH = 7 buffer which resulted in the clean formation of dienone **117** and **232** (d.r. = 1:1 as determined by ^{1}H NMR spectroscopy). The two diastereomers were readily separated by flash chromatography and were isolated in a combined yield of 58%.



Scheme 2.52 Synthesis of dienone 117.

The structure of dienone **117** was unambiguously assigned through analysis of its spectral data (^{1}H NMR, ^{13}C NMR, COSY, 1D nOe, IR, HRMS). Key features of the ^{1}H NMR spectrum included two enone resonances at δ 6.90 (d, 1H, *J* = 9.9 Hz) and 6.14 (d, 1H, *J* = 9.9 Hz) corresponding to H3 and H2, respectively, a methyl singlet at δ 1.49 corresponding to the methyl group attached to the newly installed C4 tertiary alcohol, and the C9 allylic alcohol resonance at δ 4.82 (d, 1H, *J* = 3.2 Hz) (Figure 2.17). Furthermore, the ^{13}C NMR spectrum displayed a resonance at δ 186.9 indicative of a dienone carbonyl, as well as two carbon resonances at δ 70.0 and 69.1, assigned to the C4 and C9 carbons, respectively. In addition, the HRMS displayed a signal at m/z 325.1791, which is in agreement with a molecular formula of $C_{19}H_{26}NaO_3$ (M+Na). The IR spectrum of this material included a C=O stretching absorption at 1666 cm^{-1}, consistent with a dienone carbonyl. The diastereomeric dienone **232** displayed a similar set of spectroscopic data to that described above. For the assignment of the relative

configuration of the newly formed carbon chirality centres, we relied on the key nOe correlations depicted in Figure 2.16. In both **117** and **232** there was a strong nOe correlation between H8α and H10α confirming the *syn* stereochemistry of the ring junction. Additionally, an nOe correlation between H10α and H9 observed for both diastereomers confirmed the stereochemistry of the ketone reduction as α, with hydride addition proceeding from the β face of the tetralone. In **232**, an nOe correlation between $H10_b$ and both the C4 methyl as well as H8α confirmed the stereochemistry of the C4 methyl as β, indicating attack of water in the dearomatisation reaction from the bottom α–face of the aromatic ring. Conversely, an nOe correlation in **117** between $H10_a$ and the C4 methyl indicated the diastereomeric outcome of the dearomatisation reaction.



117 **232**

Figure 2.16 Key nOe correlations for dienone 117 and 232.

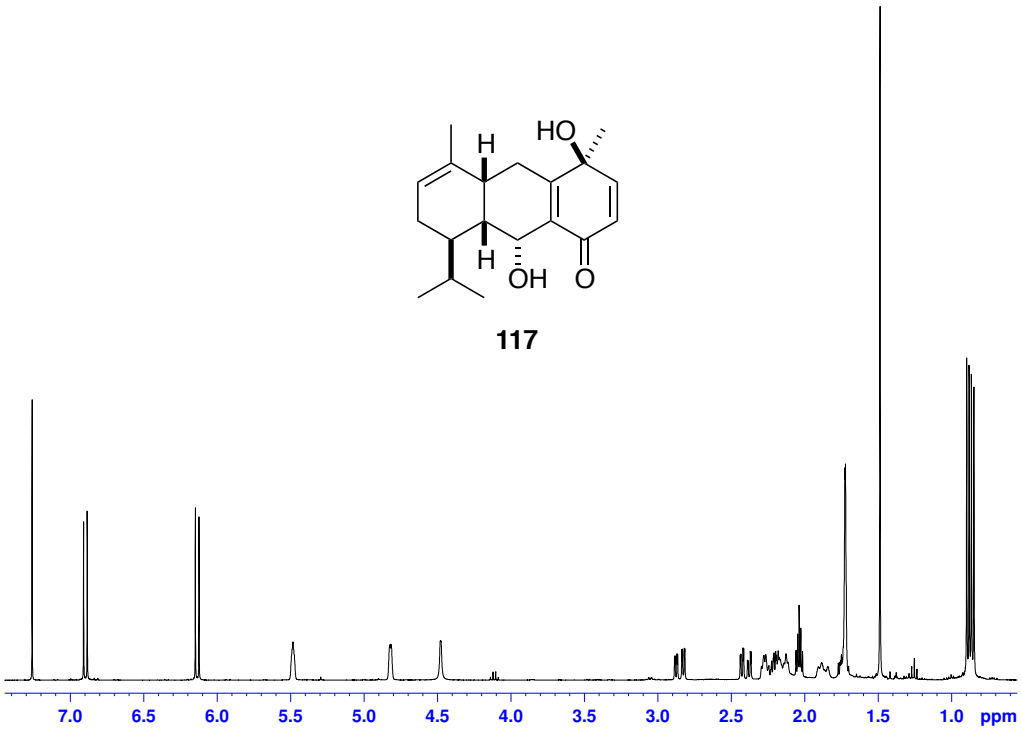
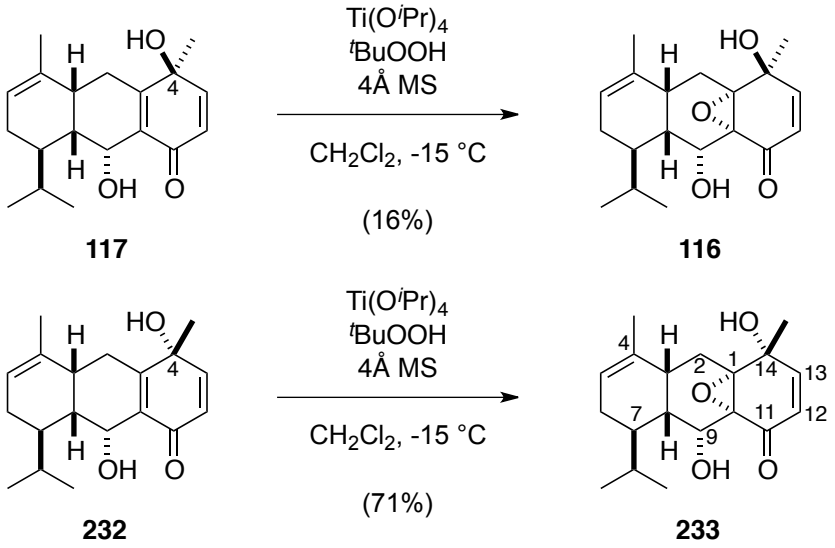


Figure 2.17 **^{1}H NMR spectrum of dienone 117 recorded at 400 MHz in $CDCl_3$.**

2.3.4.2. Hydroxy-directed Epoxidation of Dienones 117 and 232

With the two diastereomeric dienones **117** and **232** in hand, we turned our attention to epoxidation of the $\Delta^{4\alpha,9\alpha}$ enone olefin through a hydroxy-directed epoxidation. Towards this end, dichloromethane solutions of dienones **117** and **232** were treated with ^{t}BuOOH in the presence of a 4Å molecular sieves and a catalytic amount of titanium(IV) isopropoxide at -15 °C (Scheme 2.53).[157] While dienone **232** reacted cleanly under these conditions to give epoxyenone **233** in an isolated yield of 71%, dienone **117** afforded epoxyenone **116** in low yield (16%). The observed differences in the epoxidation of **117** and **232** can in part be rationalised by the steric shielding of the reactive α-face of the enone by the methyl group (A-value = 1.70)[158] in **117** as compared to the hydroxyl group (A-value = 0.87)[158] in **232**. As a result of these steric factors, a decrease in enone reactivity in **117** results in preferential epoxidation of the $\Delta^{5,6}$ olefin over the enone, giving rise to mixtures of mono- and bis-epoxyenones. Conversely, the hydroxyl group on the

α-face of **232** at C4 may act as a second directing group in the epoxidation, further increasing the reactivity of the tetrasubstituted enone olefin.



Scheme 2.53 Hydroxy-directed epoxidation of dienones 117 and 232.

The structure of epoxyenone **233** was assigned through analysis of its corresponding spectral data (^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC, HRMS, IR). The ^{1}H NMR spectrum of **233** displayed two doublets at δ 6.44 (d, 1H, *J* = 10.5 Hz) and 5.83 (d, 1H, *J* = 10.5 Hz) assigned to the two enone protons H12 and H13 (Figure 2.18). Also observed in the ^{1}H NMR spectrum was a broad singlet at δ 5.38 (br. s, 1H) corresponding to the olefinic proton H5, as well as a doublet of doublets at δ 4.70 (dd, 1H, *J* = 8.2, 5.9 Hz) and a doublet at δ 2.80, assigned to H9 and the OH resonance, respectively. Additionally, two singlets at δ 1.74 and 1.43 (3H) corresponding to the C4 and C14 methyl groups were observed. The ^{13}C NMR spectrum of **233** displayed a resonance at δ 195.4 corresponding to the enone carbonyl, four olefinic carbon resonances at δ 150.2, 136.0, 123.1, 122.9, as well as four oxygen substituted carbon resonances at δ 71.3, 69.5, 67.2, 65.0 corresponding to C14, C1, C9, and C10, respectively (assignments based on analysis of HSQC and HMBC experiments). The IR spectrum of **233** displayed a broad O-H stretching absorption at 3405 cm^{-1}, as well as a C=O stretching absorption at 1688 cm^{-1}. Furthermore, HRMS analysis showed a signal at m/z 319.1909 consistent with the molecular formula $C_{19}H_{27}O_4$ (M+Na).

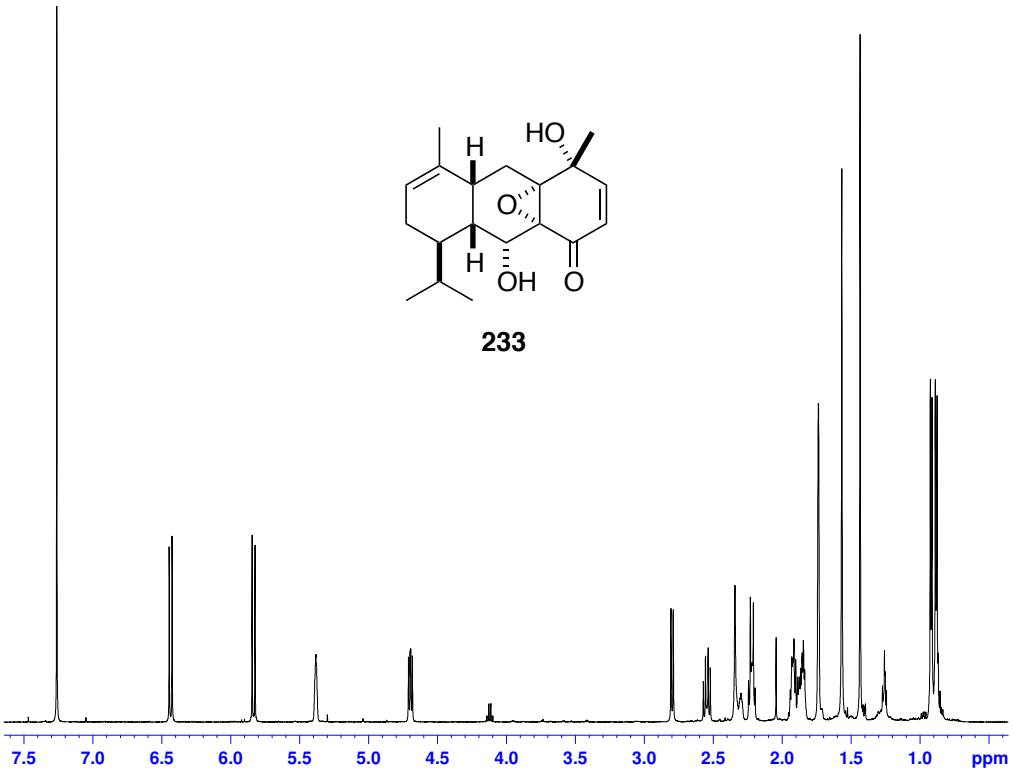
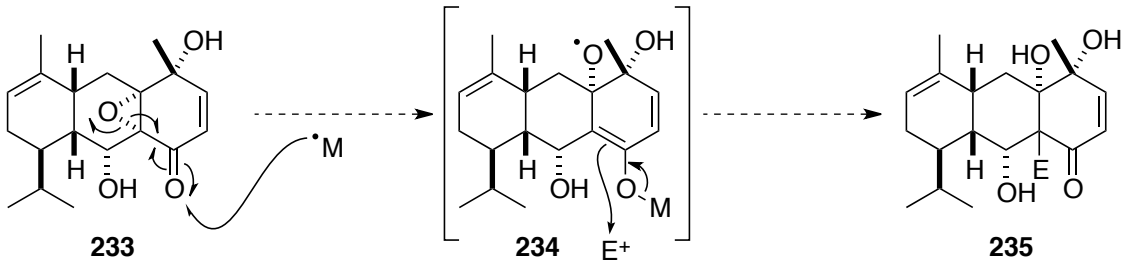


Figure 2.18 **^{1}H NMR spectrum of epoxyenone 233 recorded at 400 MHz in $CDCl_3$.**

Unfortunately, due to the low yield for the epoxidation of **117**, it was not possible to acquire significant quantities of **116** for further study. Therefore, despite its incorrect relative stereochemistry, in order to further investigate the planned synthetic route to eleutherobin, epoxyenone **233** was employed in future studies.

2.3.4.3. Reductive Epoxide Opening of Epoxyenone 233

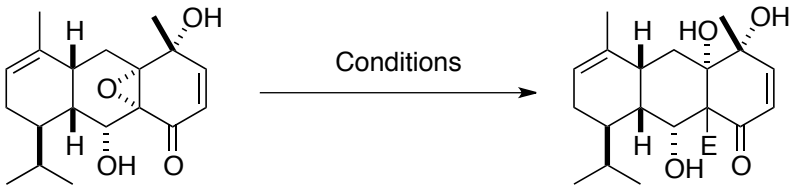
With epoxyenone **233** in hand, it was envisioned that opening of the epoxide through a radical process that proceeds through a one-electron reduction of the ketone function could lead to intermediate **234** (Scheme 2.54). This latter species, which incorporates an enolate, could then be exploited for the installation of the final carbon required for the eleutherobin skeleton (**234** → **235**).



Scheme 2.54 Proposed strategy for radical mediated opening/alkylation of epoxyenone 233.

In an attempt to effect the proposed reaction sequence, epoxyenone **233** was reacted under a variety of conditions as summarised in Table 2.6. Thus, treatment of epoxyenone **233** with low valent titanocene in a mixture of THF and methanol led only to products of decomposition (entry 1).[159] Reductive opening of the epoxide under dissolving metal conditions (Li, liq. NH_3) and quenching with methyl iodide resulted in a 1:1:2 mixture of **233**:**232**:**231** as determined by ^{1}H NMR spectroscopy recorded on the crude reaction mixture.[160,161] Presumably, enolate **234** undergoes facile elimination of the tertiary alcohol, leading to dienone **232**. Subsequent reduction of this latter substance and rearomatisation then generates the phenol **231**. Unfortunately, reaction of **233** with samarium diiodide and quenching with butanal led to similar product mixtures (entry 3).[162] When **233** was reacted with PhSeH (formed by the *in situ* reduction of $(PhSe)_2$ with $NaBH_4$) in the presence of AcOH and ethanol, a mixture of dienone **232** and a product derived from 1,4-addition of PhSeH to the enone was observed.[163] Repetition of this reaction in the absence of AcOH did little to change the reaction outcome, and led to the production of dienone **232** in addition to a product derived from $NaBH_4$ reduction of the enone carbonyl (entry 5).

Table 2.6 Attempted Reductive Epoxide Opening of Epoxyenone 233



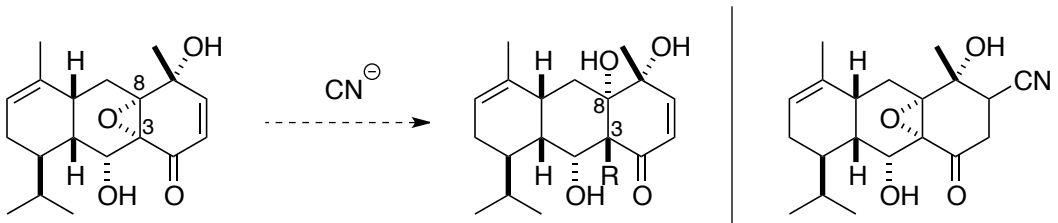
233 **235**

entry	conditions	electrophile	result
1	Cp_2TiCl_2, Zn, THF/MeOH	H	Decomposition
2	Li, $NH_{3(l)}$; then MeI	Me	**233** + **232** + **231** (1:1:2)[a]
3	SmI_2, THF; then butanal	$CH_3(CH_2)_2CHO$	**233** + **232** + **231** (2:4:1.5)[a]
4	$(PhSe)_2$, $NaBH_4$, AcOH, EtOH	H	PhSeH 1,4-Addition + **232** (1.5:1)[a]
5	$(PhSe)_2$, $NaBH_4$, EtOH	H	Reduced SM + **232** (1:3)[a]

[a] ratio determined by ^{1}H NMR spectroscopy recorded on crude reaction mixtures.

2.3.4.4. Cyanide Mediated Epoxide Opening of Epoxyenone 233

Due to the labile nature of intermediate **234** and our failure to open epoxide **233** through reductive reaction conditions, we turned our attention to the possibility of using cyanide as a nucleophile in an epoxide opening sequence. The addition of cyanide would install the requisite carbon at C3, as well as activate this carbon towards a retro-aldol fragmentation of the resulting cyanohydrin **236** (Scheme 2.55). Thus, epoxyenone **233** was treated under hydroxy-directed epoxide opening conditions (KCN, $Ti(O^iPr)_4$, TBAI in DMSO).[164] While similar reactions are reported to give regioselective opening of epoxy alcohols at the undesired C8 position, the neighbouring ketone was expected to enhance the reactivity of the desired C3 opening. Unfortunately, under these reaction conditions we observed formation of **237**, derived from 1,4-addition of cyanide to the enone. Subjecting **233** to conditions reported by Ma and co-workers (KCN and NH_4Cl in refluxing methanol)[165] for the cyanide mediated opening of a similar epoxyenone system resulted in a complex mixture of products with no evidence for the formation of the desired cyanohydrin **236**.

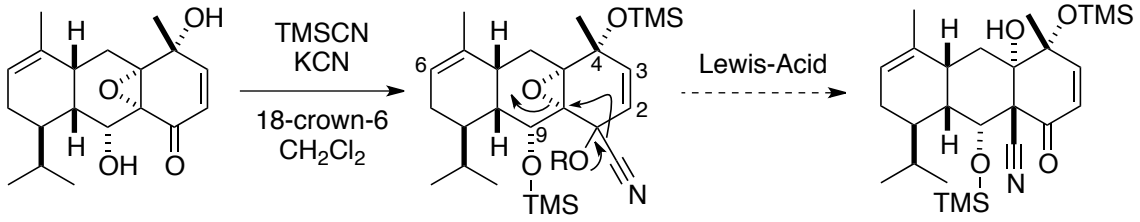


233 **236**: R = CN **237**

Scheme 2.55 Proposed cyanide opening of epoxyenone 233.

2.3.4.5. Semi-pinacol Rearrangement of Epoxyenone 233

As an alternative strategy, it was envisioned that a semi-pinacol rearrangement could give access to the desired structural motif for the planned Grob fragmentation. Towards this end, addition of a migratory group to the enone carbonyl would provide a tertiary alcohol (e.g., **238**, Scheme 2.56). Upon addition of a Lewis-acid, the migratory group could undergo a 1,2-shift, opening the epoxide and installing the requisite carbon in a regioselective manner (**238** → **239**). While there are no reports of the semi-pinacol rearrangement of epoxycyanohydrins such as **238**, the use of this reaction for the construction of quaternary carbon stereocentres is well documented.[166]



233 **238**: R = TMS **239**

Scheme 2.56 Proposed semi-pinacol type rearrangement of cyanohydrin 238.

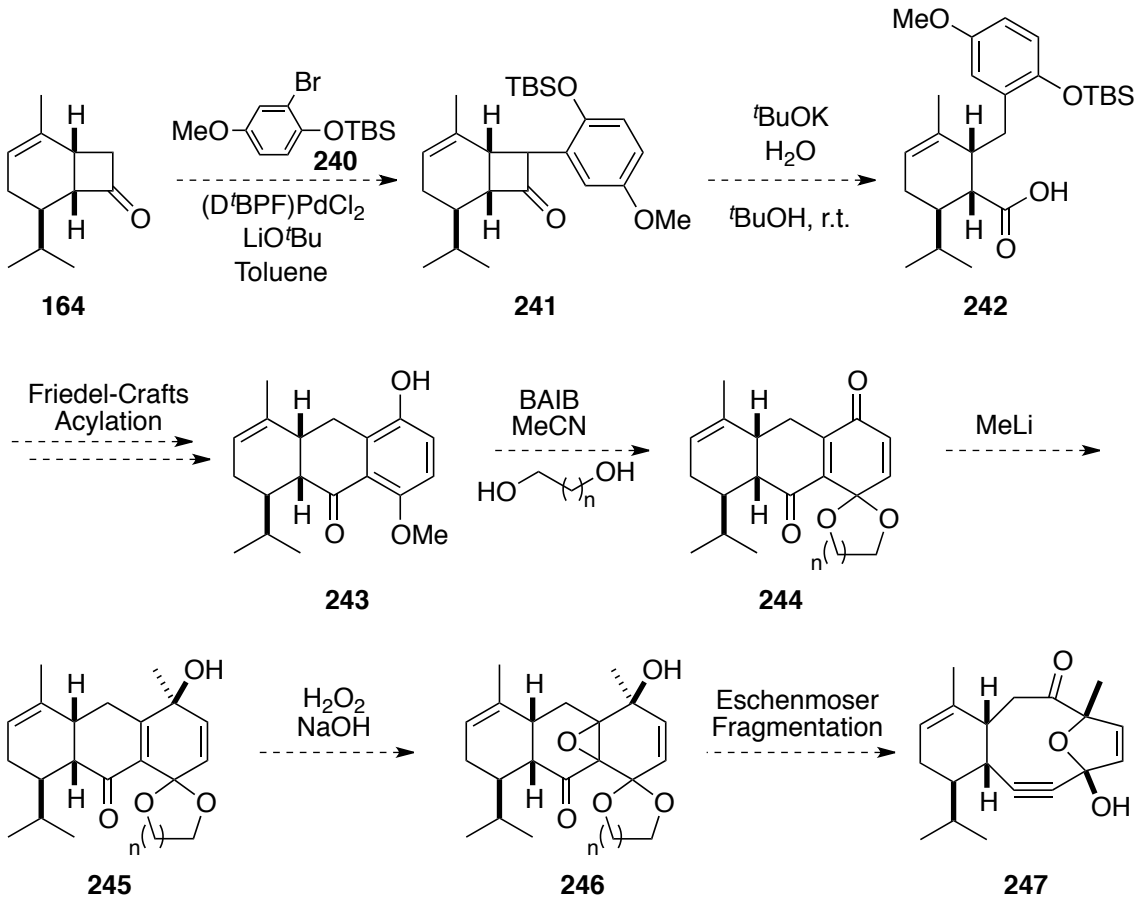
Towards this end, epoxyenone **233** was treated with TMSCN, and a catalytic amount of KCN and 18-crown-6 in dichloromethane, which resulted in the clean formation of cyanohydrin **238**. The ^{1}H NMR spectrum recorded on **238** displayed two doublets at δ 5.69 (d, 1H, *J* = 10.4 Hz) and 5.46 (d, 1H, *J* = 10.4 Hz), corresponding to the disubstituted *cis*-olefin protons H2 and H3. Also observed was a broad singlet at δ 5.38 (br. s, 1H), assigned to the olefinic proton H6, as well as a doublet at δ 4.45 (d, 1H, *J* = 2.4 Hz), corresponding to H9. Also observed were five singlets at δ 1.66 (s, 3H), 1.35 (s, 3H), 0.32 (s, 9H), 0.14 (s, 9H), and 0.10 (s, 9H), which were assigned to the two

methyl groups on C4 and C5, along with the three silyl ether groups at C1, C4 and C9. The structural assignment of cyanohydrin **238** was further confirmed by HRMS, which showed a signal at m/z 562.3197 corresponding to a molecular formula of $C_{29}H_{52}NO_4Si_3$ (M+H). Unfortunately, treatment of **238** with BF_3•OEt_2 or $TiCl_4$ did not lead to products of cyanide migration. Instead products arising from hydrolysis of the acid-sensitive cyanohydrin and TMS ethers, as well as elimination of the C9 secondary alcohol were observed. This result can be rationalised by preferential coordination of the Lewis-acid to the cyano function, resulting in its expulsion. Further hydrolysis of the TMS ethers by capricious acid leads to the other observed products.

2.4. Future Direction

While the syntheses of epoxyenones **117** and **232** represent a significant achievement in our development of a synthesis of eleutherobin, there still exist significant hurdles to overcome. Specifically, our inability to exploit epoxyenone **232** as an intermediate *en route* to a Grob fragmentation precursor represents a significant setback. Furthermore, the low levels of diastereoselectivity observed in the dearomatisation reaction would eventually need to be addressed in order to fulfill our objectives. In an attempt to overcome these and other concerns, a future approach to eleutherobin is presented in Scheme 2.57. Thus, employing our previously optimised process for the synthesis of tetralones from α-arylcyclobutanones, our synthesis would commence with the palladium-catalysed α-arylation of **164** with silyl protected-bromoanisole **240**. Fragmentation of the arylcyclobutanone **241** would give arylacid **242** which upon Friedel-Crafts acylation would afford tetralone **243**. Dearomatisation of the phenol in the presence of BAIB and a diol would give rise to the protected quinone **244**. This revised dearomatisation process presents several advantages. Not only is it expected that this modified system will benefit from the placement of the methoxy substituent, which increases the reactivity of the *para*-position and should increase the yield of the dearomatisation process, but the installation of a protected ketone differentiates the reactivity of the three olefins and two ketones in a strategic manner. Thus, addition of methyllithium to protected quinone **244** is expected to occur on the more sterically accessible and reactive quinone carbonyl giving protected quinol **245**.

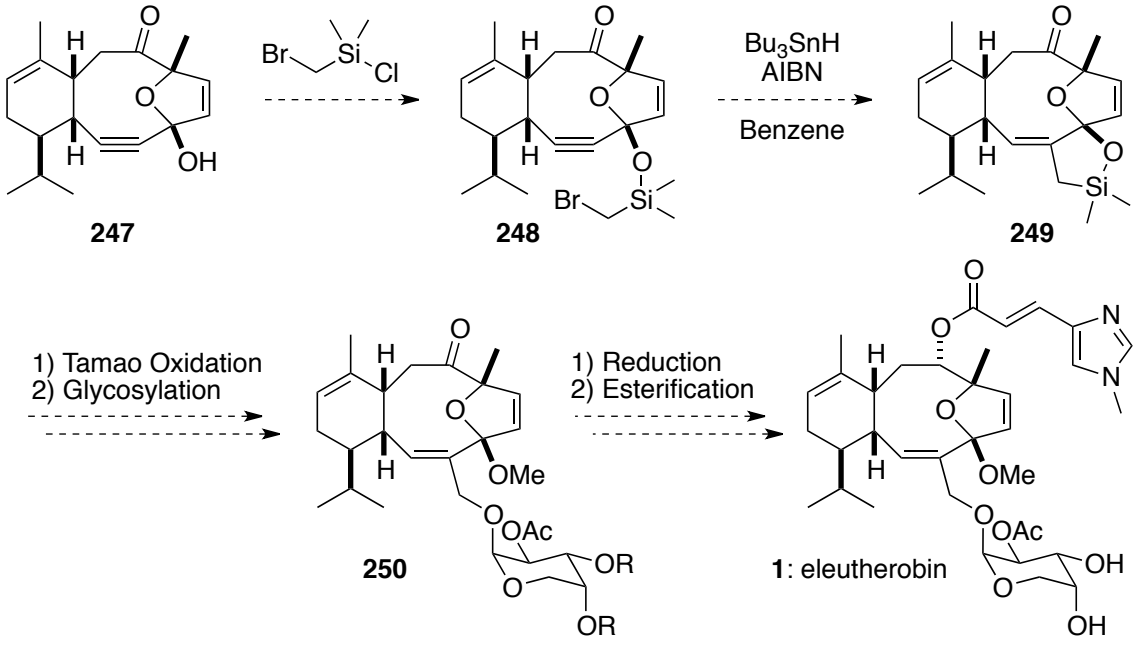
Furthermore, the stereochemistry of the addition can be controlled by the choice of a chiral diol in the dearomatisation step, if necessary.[167] The isolated enone can then undergo epoxidation under standard conditions to afford the epoxyketone **246**. Production of this latter material would then set the stage for an Eschenmoser fragmentation that would give access to the 10-membered ring of the eleutherobin skeleton. Subsequent ketal hydrolysis and hemi-ketal formation would afford alkyne **247**. The Eschenmoser fragmentation is expected to be well suited to this particular system, as its use is well documented on similar polycyclic frameworks.[168–170]



Scheme 2.57 Future synthetic approach to eleutherobin.

The remaining challenge of this conceptual approach would be functionalisation of the alkyne moiety in **247** in a regio- and stereospecific manner. In this regard, two possible strategies are proposed, the first of which is described in Scheme 2.58. Thus, treatment of alkyne **247** with (bromomethyl)dimethylsilylchloride would afford silylacetal

248. Subjecting this latter material to tributyltin hydride and AIBN would produce a silylmethyl radical that would undergo a 5-*exo*-*dig* cyclisation to afford **249**.[171] While the regioselectivity of the addition will be controlled by the kinetic preference for 5-membered ring formation,[172] hydrogen abstraction of the resulting vinyl radical could lead to mixtures of *E* and *Z* olefins. Tamao-Flemming oxidation would then install the requisite hydroxymethyl, which upon glycosylation with an appropriately protected sugar would afford **250**. Reduction of the carbonyl and installation of the urocanic ester would then furnish eleutherobin (**1**).

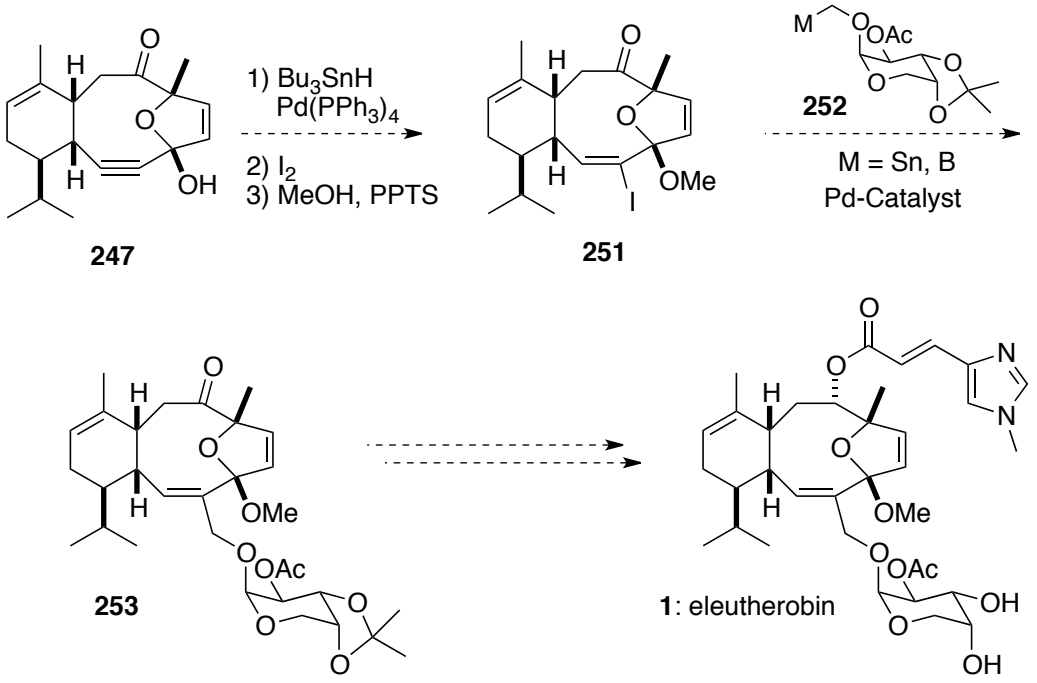


Scheme 2.58 End game approach through a silylmethyl radical cyclisation.

An alternative end-game approach is presented in Scheme 2.59. Thus, alkyne **247** could be subjected to a palladium-catalysed hydrostannylation reaction[173] which after iodo-destannylation and transketalisation would give vinyl iodide **251**. In this process, the geometry of the olefin would be controlled by the *syn*-addition of Sn-H to the alkyne. However, the regioselectivity of the addition, which is determined by both steric and electronic factors, may lead to mixtures of regioisomers. While this does present a concern, the choice of ketal functionality could be used to control the regiochemistry. Through the installation of a reactive vinyl iodide it would then be possible to employ an approach similar to that used by Danishefsky and co-workers, in which the sugar is installed through a palladium-catalysed sp^2-sp^3 coupling of vinyl

iodide **251** with a metalated arabinose (e.g., **252**) to afford **253**.[7] A series of straightforward transformations would then lead to eleutherobin (**1**).

The successful execution of either of these revised strategies should lead to the total synthesis of eleutherobin in 12-15 steps, a significant achievement given the pioneering syntheses ranged between 25-28 steps. Furthermore, it is expected that these synthetic efforts will fulfill our primary objective of a concise and scalable synthesis and would allow for the production of large quantities of eleutherobin (**1**). Ultimately, this method could then be used to support the biological investigation of eleutherobin's potentially useful antimitotic properties and facilitate its further preclinical evaluation.



Scheme 2.59 **End game approach through a palladium-catalysed coupling of a vinyl iodide with a metalated arabinose.**

2.5. Conclusions

In conclusion, this chapter has presented an overview of our synthetic advances towards the total synthesis of eleutherobin (**1**). Our efforts began with investigations into a furan Diels-Alder strategy to install the C-ring dihydrofuran. Despite significant effort, which included the synthesis of three intramolecular Diels-Alder precursors, we were

unable to produce any Diels-Alder adducts under a variety of thermal and Lewis-acid promoted conditions. In a revised strategy, we targeted an aromatic tetralone as an advanced intermediate *en route* to a Grob fragmentation precursor. While it proved possible to access tetralone model systems through a retro [2+2]/6π electrocyclic rearrangement of a benzocyclobutanol, our efforts were thwarted in the application of this strategy towards the intended tetralone. Despite a final setback in the application of a palladium-catalysed cyclobutanol rearrangement to access the tetralone intermediate, we were successful in preparing this compound through the development of a strategy which involved a ketene [2+2] cycloaddition, followed by a cyclobutanone fragmentation reaction and Friedel-Crafts cyclisation. This strategy was eventually refined through the development of an unprecedented palladium-catalysed α-arylation reaction of a cyclobutanone. The application of this reaction allowed for a 6-step reduction in the overall process, delivering gram quantities of the intermediate tetralone in 6 steps (32% overall yield) from commercially available α-phellandrene. Finally, through a 3-step sequence that included reduction of the tetralone carbonyl, BAIB mediated addition of water to a phenol, and hydroxy-directed epoxidation of the resulting enone, it was possible to further advance the tetralone along our intended route. While it was not possible synthesise a Grob fragmentation substrate or investigate this key reaction, the methods developed in this chapter have undoubtedly laid the groundwork for a successful synthesis of eleutherobin (**1**).

2.6. Experimental

General:

All reactions described were performed under an atmosphere of dry argon using oven dried glassware. Tetrahydrofuran was distilled over Na/benzophenone and dichloromethane was dried by distillation over CaH_2. All other solvents were used directly from EMD drysolv septum sealed bottles unless otherwise specified. Cold temperatures were maintained by the use of following reaction baths: -115 °C, EtOH-N_2(l); -78 °C, acetone-dry ice; temperatures between -40 °C to -20 °C were maintained with a Polyscience VLT-60A immersion chiller. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described

by Still.[174] Thin layer chromatography was carried out on commercial aluminum backed silica gel 60 plates (E. Merck, type 5554, thickness 0.2 mm). Visualization of chromatograms was accomplished using ultraviolet light (254 nm) followed by heating the plate after staining with one of the following solutions: (a) *p*-anisaldehyde in sulphuric acid-ethanol mixture (5% anisaldehyde v/v and 5% sulphuric acid v/v in ethanol); (b) 1% potassium permanganate w/v, 6.6% potassium carbonate w/v, and 1% v/v 10% sodium hydroxide in water. Concentration and removal of trace solvents was done via a Büchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Gas chromatography (GC) analysis was performed on a Hewlett Packard model 5890 gas chromatograph, equipped with a flame ionisation detector and a Cyclosil-B chiral column (30 m length, 0.320mm ID, 0.25um film).

NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance II 600 equipped with a QNP or TCI cryoprobe (600 MHz), Varian Inova 500 (500 MHz), Bruker Avance III 500 (500 MHz), or Bruker Avance III 400 (400 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (150 MHz), Bruker Avance III 500 (125 MHz), or Bruker Avance III 400 (100 MHz). Assignments of 1H and 13C NMR spectra are based on analysis of 1H-1H COSY, HSQC, HMBC and nOe spectra.

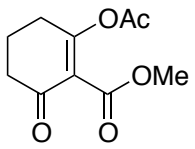
Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

Chemical ionisation (CI) mass spectra were recorded on a Varian 4000 mass spectrometer at 70 eV. High resolution fast atom bombardment (HR-FABMS) mass

spectra were recorded on a JEOL JMS-AX505HA mass spectrometer at 3 kV or an Agilent 6210 TOF LC/MS mass spectrometer.

Optical rotation was measured on a Perkin Elmer Polarimeter 341.

Preparation of methyl-2-acetoxy-6-oxocyclohex-1-enecarboxylate (68).



To a stirred solution of 1,3-cyclohexanedione (**69**) (5.00g, 44.6 mmol) in dichloromethane (100 mL) was added triethylamine (15.5 mL, 111 mmol), followed by methyl chloroformate (**70**) (3.80 mL, 49.4 mmol), potassium cyanide (726 mg, 11.1 mmol), and 18-crown-6 (2.95 g, 11.2 mmol). The resulting mixture was stirred for 24 hours and treated with triethylamine (12.4 mL, 89.2 mmol) and acetyl chloride (7.90 mL, 111 mmol). The reaction was stirred for an additional hour, after which time water (50 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give the crude enone. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes:ethyl acetate) afforded methyl-2-acetoxy-6-oxocyclohex-1-enecarboxylate (**68**) (3.40 g, 36%) as a pale yellow oil.

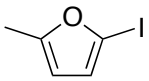
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.81 (s, 3H), 2.67 (t, 2H, *J* = 6.2 Hz), 2.49 (t, 2H, *J* = 6.5 Hz), 2.21 (s, 3H), 2.08 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 194.5, 168.8, 166.8, 163.7, 124.2, 52.4, 36.8, 28.8, 20.8, 20.3

IR (neat): 2970, 2901, 1773, 1732, 1675, 1650, 1359, 1238, 1153, 1046, 857 cm^{-1}

Exact mass calculated for $C_{10}H_{12}NaO_5$: 235.0577 (M+Na); found: 235.0575.

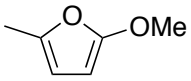
Preparation of 2-iodo-5-methylfuran (53).



To a cold (-78 °C), stirred solution of 2-methylfuran (**77**) (5.4 mL, 60 mmol) in ether (100 mL) was added *n*-butyllithium (2.5M in hexanes, 25.0 mL, 62.5 mmol). The resulting mixture was stirred at -78 °C for 30 minutes, 0 °C for 1 hour, and room temperature for 1.5 hours. The reaction mixture was then cooled to 0 °C and a solution of iodine (16.0 g, 63.0 mmol) in ether (50 mL) was added via cannula. The reaction mixture was warmed to room temperature and stirred for an additional 18 hours at which time a saturated aqueous solution of sodium thiosulphate (25 mL) and water (75 mL) were added. The layers were separated and the aqueous phase was extracted with ether (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and evaporated to give the crude furan **78**. Purification of the crude product by flash chromatography (silica gel, hexanes) afforded 2-iodo-5-methylfuran (**78**) (6.69 g, 53%) as a pale pink oil which displayed spectral data in agreement with literature reported values.[175]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.40 (d, 1H, *J* = 3.1 Hz), 5.91 (m, 1H), 2.34 (d, 3H, *J* = 0.7 Hz).

Preparation of 2-methoxy-5-methylfuran (53).



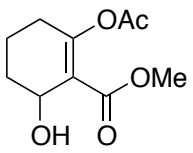
To a freshly prepared solution of sodium methoxide (made by the addition of sodium pieces (3.00 g, 103 mmol) to methanol (50 mL)), was added copper(I) bromide (690 mg, 4.81 mmol) and a solution of 2-iodo-5-methylfuran (**78**) (6.69 g, 32.3 mmol) in methanol (10 mL). The reaction mixture was heated to reflux for 18 hours after which time it was cooled, diluted with pentane (100 mL) and treated with a saturated aqueous solution of ammonium chloride (25 mL) and brine (75 mL). The layers were separated and the aqueous phase was extracted with pentane (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and the pentane was removed by distillation at atmospheric pressure to give crude 2-iodo-5-methylfuran (**53**). Purification

of the crude product by distillation (35 °C, 9 torr) afforded 2-methoxy-5-methylfuran (**53**) (2.21 g, 61%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.80 (m, 1H), 4.99 (d, 1H, *J* = 3.0 Hz), 3.80 (s, 3H), 2.19 (d, 3H, *J* = 1.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.3, 142.0, 106.0, 79.5, 57.7, 13.3.

Preparation of methyl-2-acetoxy-6-hydroxycyclohex-1-enecarboxylate (93).



To a cold (-78 °C), stirred solution of methyl-2-acetoxy-6-hydroxycyclohex-1-enecarboxylate (**68**) (623 mg, 2.93 mmol) in ethanol (60 mL) was added cerium(III) chloride heptahydrate (1.09 g, 2.93 mmol) followed immediately by sodium borohydride (110 mg, 2.91 mmol). The resulting mixture was stirred at -78 °C for 5 minutes after which time water (15 mL) was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate (50 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give the crude hydroxyenoate. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes:ethyl acetate) afforded methyl-2-acetoxy-6-hydroxycyclohex-1-enecarboxylate (**93**) (462 mg, 74%) as a pale yellow oil.

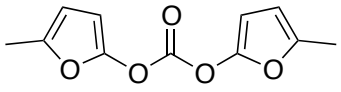
^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.69 (t, 1H, *J* = 3.7 Hz), 3.76 (s, 3H), 2.32-2.26 (m, 2H), 2.20 (s, 3H), 1.97-1.88 (m, 2H), 1.74-1.68 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.2, 165.9, 160.1, 119.7, 64.8, 51.9, 29.8, 29.3, 20.9, 17.1.

IR (neat): 3492, 2953, 1764, 1716, 1656, 1436, 1363, 1175, 1056, 908, 728 cm^{-1}

Exact mass calculated for $C_{10}H_{14}NaO_5$: 237.0733 (M+Na); found: 237.0734.

Preparation of *bis*(5-methylfuran-2-yl) carbonate (95).



To a stirred solution of α–angelica lactone (**94**) (1.40 mL, 15.6 mmol) in dichloromethane (50 mL) was added triethylamine (2.40 mL, 17.2 mmol). The resulting mixture was cooled to 0 °C and a solution of triphosgene (771 mg, 2.60 mmol) in dichloromethane (15 mL) was added dropwise over 15 minutes. The reaction mixture was stirred at 0 °C for 1 hour, then warmed to room temperature, stirred for an additional 2 hours and evaporated in vacuo. The residue was dissolved in ether (50 mL) and filtered through a pad of Celite®. The solvent was evaporated to give the crude carbonate **94**. Purification of the crude product by flash chromatography (silica gel, 10:1 hexanes:ethyl acetate) afforded *bis*(5-methylfuran-2-yl) carbonate (**95**) (941 mg, 54%) as a colourless oil.

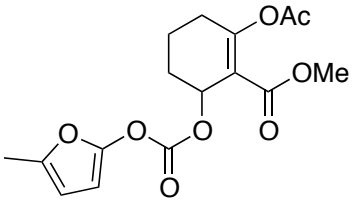
^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.95 (m, 1H), 5.82 (d, 1H, *J* = 3.2 Hz), 2.25 (s, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 148.3, 148.3, 145.8, 106.7, 93.0, 13.4.

IR (neat): 2957, 2927, 1810, 1739, 1628, 1578, 1436, 1186, 1023, 950, 780 cm^{-1}

Exact mass calculated for $C_{11}H_{11}O_5$: 223.0606 (M+H); found: 223.0610.

Preparation of methyl 2-acetoxy-6-({[(5-methylfuran-2-yl)oxy]carbonyl}oxy) cyclohex-1-enecarboxylate (89).



To a stirred solution of *bis*(5-methylfuran-2-yl) carbonate (**95**) (6.05 g, 27.3 mmol) and methyl-2-acetoxy-6-hydroxycyclohex-1-enecarboxylate (**93**) (777 mg, 3.63 mmol) in dichloromethane (35 mL) was added triethylamine (3.80 mL, 27.3 mmol). The mixture was stirred at room temperature for 16 hours at which time toluene (30 mL) was added and the solvent was evaporated to give the crude carbonate. Purification of the crude

product by flash chromatography (silica gel, 8:1 hexanes:ethyl acetate) afforded methyl 2-acetoxy-6-({[(5-methylfuran-2-yl)oxy]carbonyl}oxy)cyclohex-1-enecarboxylate (**89**) (600 mg, 49%).

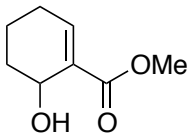
^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.92 (m, 1H), 5.86 (br. t, 1H), 5.72 (d, 1H, *J* = 3.0 Hz), 3.74 (s, 3H), 2.41-2.29 (m, 2H), 2.23 (s, 6H), 2.18-2.13 (m, 1H), 1.98-1.89 (m, 1H), 1.84-1.74 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.8, 163.9, 163.1, 151.1, 149.2, 145.4, 115.4, 106.6, 92.7, 72.7, 51.9, 29.6, 27.2, 21.0, 16.7, 13.4.

IR (neat): 2963, 2901, 1767, 1728, 1666, 1626, 1580, 1443, 1359, 1055, 787 cm^{-1}

Exact mass calculated for $C_{16}H_{18}NaO_8$: 361.0894 (M+Na); found: 361.0916.

Preparation of methyl-6-hydroxycyclohex-1-enecarboxylate (103).



Prepared according to the procedure reported by Trost and co-workers.[106] To a stirred solution of glutaraldehyde (25 wt.% in water, 8.50 mL, 22.1 mmol) in water (24 mL) was added trimethyl phosphonoacetate (2.40 mL, 16.6 mmol) and 2.4 mL of an aqueous solution of potassium carbonate (4.59 g, 33.2 mmol) in water (24 mL) dropwise over 2 hours. After the addition was complete, the remainder of the aqueous solution of potassium carbonate was added dropwise over 2 hours. The reaction mixture was stirred at room temperature for 2 days at which time an aqueous solution of 1M hydrochloric acid (25 mL) was added. The resulting solution was extracted with ether (3 x 40 mL) and the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and evaporated to give the crude hydroxyenoate. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded methyl-6-hydroxycyclohex-1-enecarboxylate (**103**) (1.11 g, 43%) as a pale yellow oil which exhibited spectral data which was in accordance with that reported in the literature.[106]

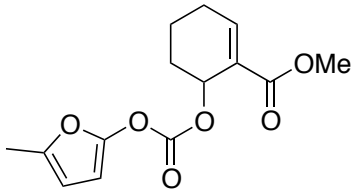
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.10 (t, 1H, *J* = 4.0 Hz), 4.53 (s, 1H), 3.77 (br. s, 3H), 3.06 (br. s, 1H), 2.33-2.08 (m, 2H), 1.88-1.54 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.78, 143.38, 131.98, 63.47, 51.74, 29.81, 26.07, 17.33.

IR (neat): 3450, 2951, 1712, 1647, 1437, 1261, 1243, 1051, 734 cm^{-1}

Exact mass calculated for $C_8H_{12}NaO_3$: 179.0679 (M+Na); found: 179.0663.

Preparation of methyl 6-({[(5-methylfuran-2-yl)oxy]carbonyl}oxy)cyclohex-1-enecarboxylate (102).



To a stirred solution of *bis*(5-methylfuran-2-yl) carbonate (**95**) (1.86 g, 8.38 mmol) and methyl 6-hydroxycyclohex-1-enecarboxylate (**103**) (203 mg, 1.30 mmol) in dichloromethane (15 mL) was added triethylamine (1.18 mL, 8.47 mmol). The mixture was stirred at room temperature for 18 hours at which time toluene (10 mL) was added and the solvent was evaporated to give the crude carbonate. Purification of the crude product by flash chromatography (silica gel, 8:1 hexanes:ethyl acetate) afforded methyl 2-acetoxy-6-({[(5-methylfuran-2-yl)oxy]carbonyl}oxy)cyclohex-1-enecarboxylate (**102**) (180 mg, 49%).

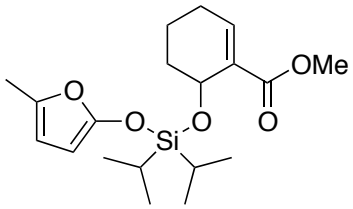
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (dd, *J* = 5.0, 2.7 Hz, 1H), 5.89 (m, 1H), 5.70 (d, 1H, *J* = 3.1 Hz), 5.66 (br. s, 1H), 3.75 (s, 3H), 2.43-2.33 (m, 1H), 2.20 (d, 3H, *J* = 0.8 Hz), 2.21-2.11 (m, 2H), 1.75-1.67 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.7, 151.0, 149.2, 146.9, 145.2, 127.3, 106.5, 92.5, 70.3, 51.8, 27.5, 25.6, 16.0, 13.3.

IR (neat): 2952, 2868, 1769, 1715, 1650, 1579, 1437, 1387, 1260, 1066, 933, 750 cm^{-1}

Exact mass calculated for $C_{14}H_{16}NaO_6$: 303.0839 (M+Na); found: 303.0838.

Preparation of methyl 6-({diisopropyl[(5-methylfuran-2-yl)oxy]silyl}oxy)cyclohex-1-enecarboxylate (107).



Prepared using a modification of the procedure described by Thomson.[112] To a cold (0 °C), solution of diisopropylamine (3.15 mL, 22.5 mmol) in dry tetrahydrofuran (30 mL) was added *n*-butyllithium (2.5 M in hexanes, 8.70 mL, 21.8 mmol). The mixture was stirred for 30 minutes at 0 °C, cooled to -78 °C and α–angelica lactone (**94**) (1.80 mL, 20.0 mmol) was added. After the mixture was stirred for 30 minutes, 1-chloro-*N*,*N*-diethyl-1,1-diisopropylsilanamine (**109**) (1.50 g, 6.76 mmol)[113] was added followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (5.75 mL, 47.6 mmol), and the reaction mixture was allowed to warm to room temperature over 18 hours. The solvent was removed in vacuo and the residue was dissolved in acetonitrile (100 mL) and extracted with pentane (3 x 75 mL). The combined pentane extracts were washed with acetonitrile (3 x 50 mL) and evaporated to give the crude aminosilane (**108**) (1.58 g, 82%), which was used immediately in the subsequent reaction and required no further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.74 (m, 1H), 4.95 (d, 1H, *J* = 3.0 Hz), 2.91 (q, 4H, *J* = 7.0 Hz), 2.16 (d, 3H, *J* = 1.0 Hz), 1.30-1.17 (m, 2H), 1.09 (app. d, 12H, *J* = 7.2 Hz), 0.99 (t, 6H, *J* = 7.0 Hz).

To a cold (0 °C), stirred solution of aminosilane **108** (1.07 g, 3.78 mmol) in tetrahydrofuran (10 mL) was added acetyl bromide (1.0 M in tetrahydrofuran, 3.80 mL, 3.80 mmol). The reaction mixture was stirred for 15 minutes and added via cannula to a cold (0 °C), stirred solution of methyl 6-hydroxycyclohex-1-enecarboxylate (**103**) (710 mg, 4.55 mmol) and triethylamine (0.79 mL, 5.67 mmol) in tetrahydrofuran (10 mL). The resulting mixture was allowed to warm to room temperature slowly over 4.5 hours. Hexanes (50 mL) were added and the mixture was filtered. The filtrate was then evaporated in vacuo to give the crude silicon tether **107**. Purification of the crude product

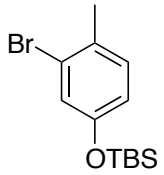
by flash chromatography (silica gel, 10:1 hexanes:ethyl acetate) gave methyl 6-({diisopropyl[(5-methylfuran-2-yl)oxy]silyl}oxy)cyclohex-1-enecarboxylate (**107**) (738 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.05 (dd, *J* = 4.7, 2.8 Hz, 1H), 5.74 (m, 1H), 5.01 (d, *J* = 3.0 Hz, 1H), 4.96 (br. t, *J* = 2.9 Hz, 1H), 3.69 (s, 3H), 2.30 (dtd, 1H, *J* = 2.1, 5.4, 20.0 Hz), 2.15 (d, *J* = 1.1 Hz, 3H), 2.15-2.04 (m, 1H), 2.01-1.94 (m, 1H), 1.89-1.76 (m, 1H), 1.62-1.48 (m, 2H), 1.28-1.11 (m, 2H), 1.10-1.03 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 154.4, 142.8, 141.0, 132.1, 106.1, 83.8, 63.4, 51.4, 31.2, 26.0, 17.1, 17.1, 17.0, 17.0, 15.8, 13.5, 12.4, 12.4.

Exact mass calculated for $C_{19}H_{31}O_5Si$: 367.1941 (M+H); found: 367.1945.

Preparation of 2-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-1-methylbenzene (134).



To a stirred suspension of 3-bromo-4-methylaniline (**133**) (2.50 g, 13.4 mmol) in water (12.5 mL), was slowly added concentrated sulphuric acid (3 mL). The resulting suspension was cooled to 0 °C and a solution of sodium nitrite (1.10 g, 15.9 mmol) in water (3.5 mL) was added dropwise at a rate which maintained the internal temperature below 5 °C. After the addition was complete the mixture was stirred for an additional 30 minutes upon which time urea (100 mg, 1.70 mmol) was added. The resulting mixture was added portion wise to a refluxing solution of sodium sulfate (5.0 g, 35.2 mmol) in sulphuric acid (7.5 mL) and water (3.8 mL) and stirred at this temperature for 2 hours. After the reaction mixture had cooled to room temperature the mixture was diluted with water (30 mL). Ether (50 mL) was added and the phases were separated. The aqueous phase was extracted with ether (2 x 30 mL) and the combined organic phases were washed with water (50 mL), and a 10% aqueous solution of sodium bicarbonate (50 mL). The crude phenol was then extracted from the organic phase by the addition of a 10% aqueous solution of sodium hydroxide (2 x 30 mL). The aqueous layer was acidified to pH < 2 with concentrated hydrochloric acid and extracted with ether (3 x 50 mL). The

combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give the crude phenol (1.50 g), which was used without further purification.

To a stirred solution of the crude phenol (1.50 g, 8.02 mmol) in dichloromethane (50 mL) was added imidazole (600 mg, 8.81 mmol) followed by *tert*-butyldimethylsilyl chloride (1.33 g, 8.82 mmol). The resulting mixture was stirred for 18 hours at room temperature after which time water (50 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 30 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude protected phenol. Purification of the crude product by flash chromatography (silica gel, hexanes) afforded 2-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-1-methylbenzene (**134**) (1.43 g, 35% over 2 steps) as a colourless oil.

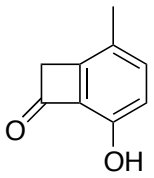
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.06 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.69 (dd, *J* = 8.2, 2.5 Hz, 1H), 2.31 (s, 3H), 0.97 (s, 10H), 0.18 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.2, 130.8, 130.4, 124.5, 123.9, 119.0, 25.6, 21.9, 18.2, -4.5.

IR (neat): 2956, 2859, 1601, 1557, 1489, 1463, 1284, 1251, 1196, 1030, 933, 837cm^{-1}

Exact mass calculated for $C_{13}H_{22}BrOSi$: 301.0623 (M+H); found: 301.0637.

Preparation of 5-hydroxy-2-methylbicyclo[4.2.0]octa-1,3,5-triene-7-one (137).



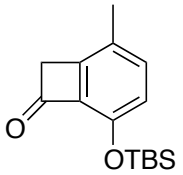
To a stirred suspension of sodium amide (371 mg, 9.51 mmol) in tetrahydrofuran (15 mL) was added 2-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-1-methylbenzene (**134**) (1.43 g, 4.75 mmol) and 1,1-diethoxyethylene (**135**)[122] (1.11 g, 9.55 mmol). The resulting mixture was heated to reflux for 3 hours, after which time it was cooled to 0 °C, water (10 mL) was added, and the phases were separated. The aqueous phase was extracted with

ether (3 x 20 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude cyclobutanone diethoxy acetal **136**, which was used without further purification.

To a stirred solution of the crude benzocyclobutanone diethoxy acetal **136** in tetrahydrofuran (45 mL) and water (10 mL) was added 5 drops of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 24 hours at which time the tetrahydrofuran was evaporated. The residue was extracted with ether (3 x 20 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude benzocyclobutanone. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes:ethyl acetate) afforded 5-hydroxy-2-methylbicyclo[4.2.0]octa-1,3,5-triene-7-one (**137**) (130 mg, 18% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, 1H, *J* = 8.3 Hz), 6.71 (d, 1H, *J* = 8.3 Hz), 3.83 (s, 2H), 2.25 (s, 3H).

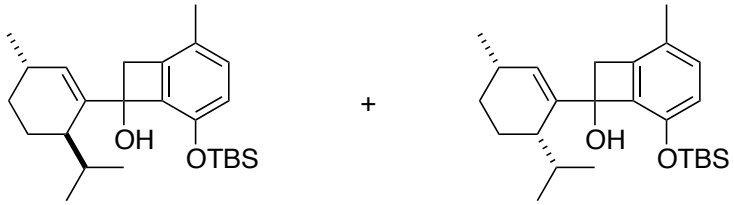
Preparation of 5-[(*tert*-butyldimethylsilyl)oxy]-2-methylbicyclo[4.2.0]octa-1,3,5-triene-7-one (130).



To a stirred solution of 5-hydroxy-2-methylbicyclo[4.2.0]octa-1,3,5-triene-7-one (**137**) (130 mg, 0.877 mmol) in dichloromethane (10 mL) was added *tert*-butyldimethylsilyl chloride (136 mg, 0.902 mmol) and imidazole (61 mg, 0.90 mmol). The resulting mixture was stirred at room temperature for 18 hours after which time water (10 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 x 15 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to afford 5-[(*tert*-butyldimethylsilyl)oxy]-2-methylbicyclo [4.2.0]octa-1,3,5-triene-7-one (**130**) (209 mg, 93%), which required no further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (d, 1H, *J* = 8.3 Hz), 6.66 (d, 1H, *J* = 8.3 Hz), 3.79 (s, 2H), 2.27 (s, 3H), 0.99 (s, 9H), 0.25 (s, 6H).

Preparation of [5-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-7-[(3*S*,6*R*)-3-methyl-6-(2-methylethyl)cyclohex-1-en-1-yl]bicyclo[4.2.0]octa-1,3,5-trien-7-ol (144) and [5-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-7-[(3*S*,6*S*)-3-methyl-6-(2-methylethyl)cyclohex-1-en-1-yl]bicyclo[4.2.0]octa-1,3,5-trien-7-ol (145).

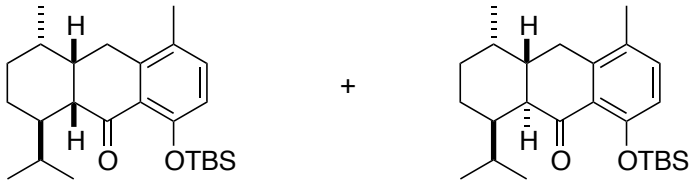


144 **145**

To a cold (-78 °C), stirred solution of (3*R*, 6*R*)-1-iodo-3-methyl-6-(2-methylethyl)cyclohex-1-ene **138**[125] (d.r. = 2:1) (119 mg, 0.451 mmol) in tetrahydrofuran (4.5 mL) was added *tert*-butyllithium (1.7M in pentane, 0.56 mL, 0.33 mmol). The resulting mixture was stirred at -78 °C for 30 minutes after which time a solution of 5-[(*tert*-butyldimethylsilyl)oxy]-2-methylbicyclo[4.2.0]octa-1,3,5-triene-7-one (**130**) (79 mg, 0.30 mmol) in tetrahydrofuran (3 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 30 minutes and treated with a saturated aqueous solution of ammonium chloride (5 mL). The mixture was diluted with ether (15 mL), then water (10 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 x 15 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to afford a crude mixture of benzocyclobutanols **144** and **145**. Purification of the crude material by flash column chromatography (silica gel, 40:1 hexanes:ethyl acetate) afforded [5-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-7-[(3*S*,6*R*)-3-methyl-6-(2-methylethyl)cyclohex-1-en-1-yl]bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**144**) (31 mg, 26%, d.r. = 3:1) and [5-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-7-[(3*S*,6*S*)-3-methyl-6-(2-methylethyl)cyclohex-1-en-1-yl]bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**145**) (9 mg, 8%).

^{1}H NMR for **145** (400 MHz, $CDCl_3$) δ: 6.95 (d, 1H, *J* = 8.3 Hz), 6.57 (d, 1H, *J* = 8.3 Hz), 5.63 (dd, 1H, *J* = 3.3, 1.6 Hz), 3.29 (d, 1H, *J* = 13.4 Hz), 3.09 (d, 1H, *J* = 13.4 Hz), 2.61 (m, 1H), 2.24 (m, 1H), 2.18 - 2.09 (m, 1H), 2.13 (s, 3H), 2.02 (s, 1H), 1.93 - 1.84 (m, 1H), 1.84 - 1.75 (m, 1H), 1.64 - 1.57 (m, 1H), 1.52 - 1.44 (m, 1H), 1.04 (d, 3H, *J* = 6.9 Hz), 0.95 (s, 9H), 0.87 (d, 3H, *J* = 7.0 Hz), 0.87 (d, 3H, *J* = 7.0 Hz), 0.20 (s, 3H), 0.19 (s, 3H).

Preparation of (1*R*,4*S*,4a*S*,9a*R*)-8-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethyl-1-(2-methylethyl)-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (146) and (1*R*,4*S*,4a*S*,9a*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethyl-1-(2-methylethyl)-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (147).



146 **147**

A stirred solution of [5-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-7-[(3*S*,6*R*)-3-methyl-6-(2-methylethyl)cyclohex-1-en-1-yl]bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**144**) (31 mg, 0.077 mmol) in toluene (1 mL) was heated to reflux for 18 hours. The reaction was cooled to room temperature and the solvent was evaporated to afford the crude tetralones **146** and **147** in a 1:1 ratio as determined by ^{1}H NMR spectroscopy. Purification of the crude material by flash chromatography (silica gel, 50:1 hexanes:ethyl acetate) afforded (1*R*,4*S*,4a*S*,9a*R*)-8-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethyl-1-(2-methylethyl)-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (**146**) (9.6 mg, 31%) and (1*R*,4*S*,4a*S*,9a*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethyl-1-(2-methylethyl)-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (**147**) (11.5 mg, 37%).

Data for (1*R*,4*S*,4a*S*,9a*R*)-8-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethyl-1-(2-methylethyl)-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (**146**)**:**

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.10 (d, 1H, *J* = 8.3 Hz), 6.63 (d, 1H, *J* = 8.1 Hz), 3.07 (d, 1H, *J* = 17.8 Hz), 3.00 (t, 1H, *J* = 3.8 Hz), 2.81 (dd, 1H, *J* = 17.7, 5.7 Hz), 2.40 – 2.29 (m, 1H), 2.19 (s, 3H), 1.74 (m, 4H), 1.43 – 1.34 (m, 1H), 1.32 – 1.23 (m, 1H), 1.00 (s, 9H), 0.95 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.19 (s, 3H), 0.14 (s, 3H).

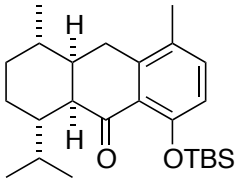
^{13}C NMR (150 MHz, $CDCl_3$) δ: 198.9, 153.6, 140.6, 134.2, 128.6, 126.1, 119.5, 50.1, 49.6, 46.1, 36.5, 30.2, 30.2, 29.4, 26.0, 25.9, 25.8, 22.3, 21.3, 20.1, 19.3, -4.2, -4.4.

Data for (1*R*,4*S*,4a*S*,9a*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethyl-1-(2-methylethyl)-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (**147**)**:**

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.11 (d, 1H, *J* = 8.3 Hz), 6.64 (d, 1H, *J* = 8.3 Hz), 2.62 (dd, 1H, *J* = 15.0, 3.0 Hz), 2.39 (dd, 1H, *J* = 13.1, 3.6 Hz), 2.30 (dd, 1H, *J* = 15.0, 13.1), 2.27 - 2.24 (m, 1H), 2.23 (s, 3H), 2.21 – 2.16 (m, 1H), 2.07 (m, 1H), 1.89 – 1.83 (m, 1H), 1.83 - 1.76 (m, 1H), 1.74 (ddd, 1H, *J* = 13.6, 5.9, 2.9 Hz), 1.66 (dt, 1H, *J* = 14.1, 3.8 Hz), 1.33 - 1.26 (m, 1H), 1.02 (s, 9H), 0.98 (d, 3H, *J* = 7.2 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), 0.73 (d, 3H, *J* = 6.7 Hz), 0.29 (s, 3H), 0.20 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 199.9, 153.8, 143.1, 134.3, 126.7, 125.9, 118.2, 50.7, 43.4, 34.8, 31.8, 30.7, 29.7, 27.3, 25.9, 25.6, 24.4, 23.1, 22.1, 19.2, 13.0, -4.0, -4.0.

Preparation of (1*S*,4*S*,4a*R*,9a*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethyl-1-(2-methylethyl)-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (148).

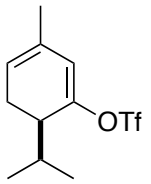


A stirred solution of [5-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-7-[(3*S*,6*S*)-3-methyl-6-(2-methylethyl)cyclohex-1-en-1-yl]bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**145**) (9.0 mg, 0.022 mmol) in toluene (1 mL) was heated to reflux for 18 hours. The reaction mixture was cooled to room temperature and the solvent evaporated to afford the crude tetralone **148**. Purification of the crude material by flash column chromatography (silica gel, 50:1 hexanes:ethyl acetate) afforded (1*S*,4*S*,4a*R*,9a*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethyl-1-(2-methylethyl)-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (**148**) (6.5 mg, 72%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.08 (d, 1H, *J* = 8.2 Hz), 6.62 (d, 1H, *J* = 8.2 Hz), 3.11 (dd, 1H, *J* = 18.3, 7.8 Hz), 2.93 (dd, 1H, *J* = 5.5, 4.1 Hz), 2.67 (d, 1H, *J* = 18.3 Hz), 2.46 (m, 1H), 2.38 (m, 1H), 2.18 (s, 3H), 1.92 – 1.82 (m, 2H), 1.64 – 1.57 (m, 3H), 0.99 (s, 9H), 0.97 – 0.95 (m, 1H), 0.95 (d, 3H, *J* = 6.6 Hz), 0.78 (d, 3H, *J* = 6.7 Hz), 0.67 (d, 3H, *J* = 7.4 Hz), 0.20 (s, 3H), 0.13 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 200.1, 152.9, 142.0, 133.7, 128.1, 127.5, 118.7, 49.0, 47.1, 41.4, 35.0, 33.7, 32.5, 29.7, 28.9, 26.0, 22.3, 21.3, 21.0, 19.2, 15.0, -4.1, -4.4.

Preparation of (6*R*)-3-methyl-6-(2-methylethyl)cyclohexa-1,3-dien-1-yl trifluoromethanesulfonate (155).



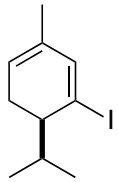
To a stirred solution of (-)-piperitone (**154**) (1.09 g, 7.16 mmol) in dichloromethane (70 mL) was added trifluoromethanesulfonic anhydride (2.40 mL, 14.3 mmol) followed by pyridine (1.70 mL, 21.1 mmol). The resulting mixture was stirred at room temperature for 1 hour at which time an aqueous solution of sodium bicarbonate (25 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic phases were washed with brine (35 mL), dried ($MgSO_4$) and concentrated to afford a crude mixture of dienyl triflates **155** and **157** in a 1:1 ratio as determined by ^{1}H NMR spectroscopy. Purification of the crude material by flash column chromatography (silica gel, 10:1 hexanes:ethyl acetate) afforded a 1:1 mixture of triflates **155** and **157** (1.27 g, 62%). Further purification by flash column chromatography (silica gel, hexanes) and analysis of the fractions by gas chromatography (Temperature program: initial temperature 70 °C, held for 2 minutes then increased by 10 °C per minute to 180 °C and held for 2 minutes. t_R = 16.2 min (**155**); 16.8 min (**157**)) gave (6*R*)-3-methyl-6-(2-methylethyl)cyclohexa-1,3-dien-1-yl trifluoromethanesulfonate (**155**) (320 mg, 16%). Subsequent purification of the remaining mixed fractions by the same method yielded an additional 80 mg of **155** to afford a combined yield of 400 mg, 20%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.83 (s, 1H), 5.38 (m, 1H), 2.64 - 2.53 (m, 1H), 2.42 - 2.32 (m, 1H), 2.27 (ddd, 1H, *J* = 9.9, 5.7, 3.8 Hz), 1.96 (app. octet, 1H, *J* = 6.8 Hz), 1.74 (m, 3H), 0.94 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 151.7, 128.3, 120.3, 118.6, 118.6 (q, *J* = 320 Hz), 42.0, 29.23, 26.6, 20.8, 20.0, 18.9.

IR (neat): 2964, 2876, 1652, 1466, 1417, 1245, 1203, 1140, 899, 819, 603 cm^{-1}

Preparation of (6*R*)-1-iodo-3-methyl-6-(2-methylethyl)cyclohexa-1,3-diene (131).



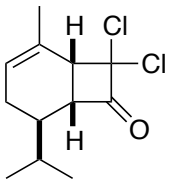
To a stirred solution of (6*R*)-3-methyl-6-(2-methylethyl)cyclohexa-1,3-dien-1-yl trifluoromethanesulfonate (**155**) (400 mg, 1.41 mmol) in tetrahydrofuran (14 mL) was added hexamethylditin (0.29 mL, 1.4 mmol), tetrakis(triphenylphosphine)palladium(0) (81 mg, 0.070 mmol), and lithium chloride (377 mg, 8.89 mmol). The resulting mixture was stirred at 60 °C for 18 hours after which time it was cooled, diluted with ether (15 mL), and treated with a saturated aqueous solution of sodium bicarbonate (15 mL). The phases were separated and the aqueous phase was extracted with ether (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated to afford the crude stannane **159**, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.95 (br. s, 1H, $^3J_{Sn-H}$ = 35.8 Hz), 5.39 (m, 1H), 2.22 - 2.08 (m, 3H), 1.75 (m, 1H), 1.69 (m, 3H), 0.92 (d, 3H, *J* = 6.8 Hz), 0.81 (d, 3H, *J* = 6.8 Hz), 0.14 (s, 9H, ^{119}Sn and ^{117}Sn satellites $^2J_{Sn-H}$ = 25.6, 26.8 Hz respectively).

To a cold (0 °C) stirred solution of crude stannane **159** in dichloromethane (18 mL) was added a solution of iodine (429 mg, 1.70 mmol) in dichloromethane (10 mL) dropwise over 10 minutes. The reaction mixture was stirred for an additional 5 minutes and treated with a saturated aqueous solution of sodium thiosulfate (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 15 mL), and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated to give the crude dienyl iodide. Purification of the crude product by flash chromatography (silica gel, hexanes) afforded (6*R*)-1-iodo-3-methyl-6-(2-methylethyl)cyclohexa-1,3-diene (**131**) (261 mg, 71% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.51 (s, 1H), 5.39 (m, 1H), 2.50 - 2.35 (m, 2H), 2.23 - 2.15 (m, 1H), 2.15 - 2.06 (m, 1H), 1.65 (m, 3H), 0.97 (d, 3H, *J* = 6.9 Hz), 0.85 (d, 3H, *J* = 6.9 Hz).

Preparation of (1*R*,5*R*,6*R*)-8,8-dichloro-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (186).



To a stirred solution of (*R*)-(–)-α-phellandrene (**29**) (10.0 mL, 66% purity, 40.0 mmol) in ether (100 mL) was added zinc (5.20 g, 80.0 mmol). The resulting suspension was cooled to 0 °C, sonicated, and a solution of trichloroacetyl chloride (6.8 mL, 60 mmol) in ether (40 mL) was added dropwise over 2 hours. After the addition was complete, the reaction mixture was stirred and agitated for an additional hour after which time the mixture was filtered through a pad of Celite® and evaporated in vacuo. The residue was dissolved in ether (100 mL), treated with a saturated aqueous solution of sodium bicarbonate (50 mL), and the phases were separated. The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give the crude dichlorocyclobutanone. Purification of the crude product by flash chromatography (silica gel, hexanes → 50:1 hexanes:ethyl acetate) afforded (1*R*,5*R*,6*R*)-8,8-dichloro-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**186**) (7.23 g, 73%) as a colourless oil.

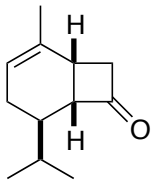
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 (m, 1H), 3.66 (dd, 1H, *J* = 7.9, 10.2 Hz), 3.28 (d, 1H, 10.3 Hz), 2.11-2.03 (m, 1H), 1.92-1.76 (m, 5H), 1.68 (m, 1H), 0.95 (d, 3H, *J* = 6.8 Hz), 0.88 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.1, 129.6, 125.7, 87.3, 56.9, 49.7, 38.4, 30.5, 24.7, 22.4, 20.7, 19.4.

IR (neat): 3040, 2962, 2873, 1804, 1463, 1440, 1071, 794 cm^{-1}

Exact mass calculated for $C_{12}H_{17}Cl_2O$: 247.0656 (M+H); found: 247.0695.

Preparation of (1*R*,5*R*,6*R*)-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (164).



To a stirred solution of (1*R*,5*R*,6*R*)-8,8-dichloro-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**186**) (2.62 g, 10.6 mmol) in methanol (40 mL) was added zinc (3.64 g, 55.7 mmol) and ammonium chloride (3.03 g, 56.6 mmol). The resulting suspension was stirred at room temperature for 24 hours after which time the mixture was filtered through a pad of Celite® and evaporated in vacuo. The residue was dissolved in ether (50 mL), treated with water (35 mL), and the phases were separated. The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give the crude cyclobutanone. Purification of the crude product by flash chromatography (silica gel, 30:1 hexanes:ethyl acetate) afforded (1*R*,5*R*,6*R*)-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**164**) (1.62 g, 86%) as a colourless oil.

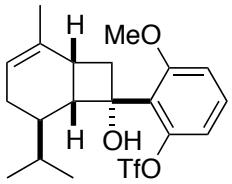
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.52(m, 1H), 3.39-3.35 (m, 1H), 3.24-3.17 (m, 1H), 2.75-2.67 (m, 2H), 2.09 (m, 1H), 1.80(m, 1H), 1.71-1.64 (m, 5H), 0.92 (d, 3H, *J* = 6.6 Hz), 0.87 (d, 3H, *J* = 6.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.3, 134.4, 122.3, 60.7, 51.0, 37.7, 30.5, 27.5, 24.9, 21.1, 20.8, 19.6.

IR (neat): 2960, 2929, 2873, 1778, 1464, 1368, 1084, 937, 804 cm^{-1}

Exact mass calculated for $C_{12}H_{19}O$: 179.1436 (M+H); found: 179.1439.

Preparation of 2-[(1*R*,5*R*,6*R*,7*S*)-7-hydroxy2-methyl-5-(2-methylethyl)bicyclo[4.2.0] oct-2-en-7-yl]-3-methoxyphenyl trifluoromethanesulfonate (189).



To a cold (-78 °C), stirred solution of 2-iodo-3-methoxyphenol (**187**)[141] (84 mg, 0.34 mmol) in ether (2.5 mL) was added *n*-butyllithium (2.5M in hexanes, 0.28 mL, 0.70 mmol). The resulting mixture was stirred at -78 °C for 45 minutes and then warmed to 0 °C for an additional 5 minutes. The reaction was cooled to -78 °C and a solution of (1*R*,5*R*,6*R*)-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**164**) (50 mg, 0.28 mmol) in ether (0.9 mL) was added. The resulting mixture was stirred at -78 °C for 1 hour, and warmed to 0 °C for an additional 30 minutes. The reaction was treated with water (10 mL), diluted with ether (10 mL) and the phases were separated. The aqueous phase was extracted with ether (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give the crude cyclobutanol. Purification of the crude product by flash chromatography (10:1 hexanes:ethyl acetate) afforded (1*R*, 5*R*, 6*R*, 7*S*)-7-(2-hydroxy-6-methoxyphenyl)-2-methyl-5-(2-methylethyl)bicyclo[4.2.0]oct-2-en-7-ol (**188**) (22 mg, 26%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 7.08 (t, 1H, *J* = 8.2 Hz), 6.49 (dd, 1H, *J* = 8.2, 1.1 Hz), 6.44 (dd, 1H, *J* = 8.2, 1.1 Hz), 5.61 (m, 1H), 3.84 (s, 3H), 3.37 (m, 1H), 3.30 (ddd, 1H, *J* = 12.5, 9.4, 1.3 Hz), 2.81 (s, 1H), 2.67 (m, 1H), 2.25 (dt, 1H, *J* = 16.5, 5.8 Hz), 1.97 (ddd, 1H, *J* = 12.5, 5.3, 0.7 Hz), 1.87 (m, 1H), 1.81 – 1.71 (m, 1H), 1.67 (br. s, 3H), 1.65 - 1.57 (m, 1H), 0.84 (d, 3H, *J* = 6.9 Hz), 0.78 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 157.3, 137.2, 128.5, 122.7, 116.8, 110.9, 103.0, 82.0, 55.5, 47.4, 42.8, 37.0, 33.0, 31.5, 25.4, 20.7, 19.8, 18.9.

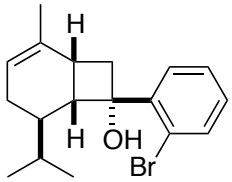
To a cold (0 °C) stirred solution of (1*R*, 5*R*, 6*R*, 7*S*)-7-(2-hydroxy-6-methoxyphenyl)-2-methyl-5-(2-methylethyl)bicyclo[4.2.0]oct-2-en-7-ol (**188**) (22 mg, 0.073 mmol) in tetrahydrofuran (1 mL) was added sodium hydride (60% dispersion in mineral oil, 3.0 mg, 0.075 mmol). The reaction was stirred for 5 minutes and *N*-phenylbis(trifluoromethanesulfonamide) (30 mg, 0.080 mmol) was added. The resulting mixture was stirred for 5 minutes, treated with water (5 mL) and diluted with ether (10 mL). The phases were separated and the aqueous phase was extracted with ether (3 x

10 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give the crude triflate. Purification of the crude product by flash chromatography (10:1 hexanes:ethyl acetate) afforded 2-[(1*R*,5*R*,6*R*,7*S*)-7-hydroxy2-methyl-5-(2-methylethyl)bicyclo[4.2.0]oct-2-en-7-yl]-3-methoxyphenyl trifluoromethanesulfonate (**189**) (18 mg, 56%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.29 (t, 1H, *J* = 8.3 Hz), 6.92 (d, 1H, *J* = 8.3 Hz), 6.89 (d, 1H, *J* = 8.3 Hz), 5.55 (br. s, 1H), 3.86 (s, 3H), 3.11 (dd, 1H, *J* = 8.0, 3.6 Hz), 2.94 (ddd, 1H, *J* = 12.2, 9.6, 1.2 Hz), 2.69 (s, 1H), 2.38 (m, 2H), 2.33 (dd, 1H, *J* = 12.7, 4.9 Hz), 2.19 (m, 1H), 1.95 (app. d, 1H, *J* = 18.0 Hz), 1.84 (m, 1H), 1.66 (s, 3H), 0.98 (d, 3H, *J* = 6.8 Hz), 0.81 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 158.4, 148.9, 136.1, 129.1, 127.2, 121.9, 118.4 (q, *J* = 320 Hz), 114.1, 111.0, 77.5, 55.6, 47.7, 41.5, 35.2, 32.7, 31.8, 23.9, 21.8, 20.6, 18.2.

Preparation of (1*R*, 5*R*, 6*S*, 7*S*)-7-(2-bromophenyl)-2-methyl-5-(2-methylethyl) bicyclo[4.2.0]oct-2-en-7-ol (191).



To a cold (-115 °C, liq. N_2/ethanol), stirred solution of 1,2-dibromobenzene (**190**) (0.45 mL, 3.78 mmol) in a 1:1 mixture of tetrahydrofuran:ether (30 mL) was added *n*-butyllithium (2.5M in hexanes, 1.50 mL, 3.75 mmol) dropwise over 10 minutes. The resulting mixture was stirred at -115 °C for an additional 20 minutes and a solution of (1*R*,5*R*,6*R*)-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**164**) (450 mg, 2.52 mmol) in tetrahydrofuran (3 mL) was added dropwise over 10 minutes. The reaction was stirred at -115 °C for 20 minutes after which time it was treated with ethanol (5 mL) and warmed to room temperature. The reaction mixture was treated with a saturated aqueous solution of ammonium chloride (15 mL), diluted with ether (15 mL), and the phases were separated. The aqueous phase was extracted with ether (3 x 15 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to give the crude cyclobutanol. Purification of the crude product by flash

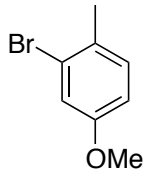
chromatography (20:1 hexanes:ethyl acetate) afforded (1*R*, 5*R*, 6*S*, 7*S*)-7-(2-bromophenyl)-2-methyl-5-(2-methylethyl)bicyclo[4.2.0]oct-2-en-7-ol (**191**) (759 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (dd, 1H, *J* = 7.9, 1.1 Hz), 7.59 (dd, 1H, *J* = 7.8, 1.4 Hz), 7.34 (td, 1H, *J* = 7.6, 1.2 Hz), 7.15 (td, 1H, *J* = 7.7, 1.6 Hz), 5.54 (br. s, 1H), 3.10 (td, 1H, *J* = 8.3, 2.8 Hz), 2.96 (ddd, 1H, *J* = 11.6, 8.3, 2.9 Hz), 2.82 (s, 1H), 2.37 – 2.16 (m, 3H), 2.16 – 2.01 (m, 2H), 1.85 – 1.75 (m, 1H), 1.60 (s, 3H), 0.99 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.7, 135.5, 134.8, 129.0, 127.3, 127.2, 122.8, 121.8, 77.5, 43.6, 42.4, 37.1, 30.8, 30.6, 23.6, 21.3, 20.1, 17.4.

Exact mass calculated for $C_{18}H_{24}BrO$: 335.1011 (M+H); found: 335.1015.

Preparation of 2-bromo-4-methoxy-1-methylbenzene (212).



Prepared according to the procedure reported by Wang and co-workers.[146] To a stirred suspension of 3-bromo-4-methylaniline (**133**) (10.0 g, 53.7 mmol) in water (50 mL), was slowly added concentrated sulphuric acid (12 mL). The resulting suspension was cooled to 0 °C and a solution of sodium nitrite (4.45 g, 64.5 mmol) in water (15 mL) was added dropwise at a rate which maintained the internal temperature below 5 °C. After the addition was complete the mixture was stirred for an additional 30 minutes upon which time urea (400 mg, 6.8 mmol) was added. The resulting mixture was added portion wise to a refluxing solution of sodium sulfate (20.0 g, 141 mmol) in sulphuric acid (30 mL) and water (15 mL), and the reaction was stirred at this temperature for 2 hours. After the reaction mixture had cooled to room temperature, ether (150 mL) was added and the phases were separated. The aqueous phase was extracted with ether (2 x 75 mL) and the combined organic phases were washed with water (150 mL), and a 10% aqueous solution of sodium bicarbonate (100 mL). The crude phenol was then extracted from the organic phase by the addition of a 10% aqueous solution of sodium hydroxide (2 x 100

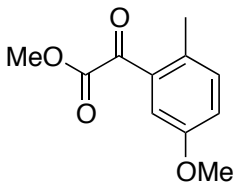
mL). The aqueous layer was acidified to pH < 2 with concentrated hydrochloric acid and extracted with ether (3 x 75 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to give the crude phenol (7.16 g) that was used without further purification.

To a stirred solution of the crude phenol (7.16 g, 38.3 mmol) in dimethyl sulfoxide (100 mL) was added potassium hydroxide (8.60 g, 153 mmol) and methyl iodide (4.7 mL, 75.5 mmol). The resulting mixture was stirred for 18 hours at room temperature after which time ether (100 mL) and water (100 mL) were added and the phases were separated. The aqueous phase was extracted with ether (2 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated to give the crude anisole. Purification of the crude product by flash chromatography (silica gel, 50:1 hexanes:ethyl acetate) afforded 2-bromo-4-methoxy-1-methylbenzene (**212**) (4.77 g, 44% over 2 steps) as a colourless oil. Spectral data obtained for **212** was in agreement with literature reported values.[146]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.12 (d, 1H, *J* = 8.4 Hz), 7.10 (d, 1H, *J* = 2.6 Hz), 6.77 (dd, 1H, *J* = 8.4, 2.6 Hz), 3.77 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.2, 131.0, 129.7, 124.9, 117.5, 113.4, 55.5, 21.8.

Preparation of methyl 2-(5-methoxy-2-methylphenyl)-2-oxoacetate (214).



To a cold (-78 °C), stirred solution of 2-bromo-4-methoxy-1-methylbenzene (**212**) (5.25 g, 26.1 mmol) in dry tetrahydrofuran (100 mL) was added *n*-butyllithium (2.46 M in hexanes, 11.7 mL, 28.8 mmol). The resulting mixture was stirred at -78 °C for 30 minutes after which time it was added via cannula to a cold (-78 °C), stirred suspension of dimethyl oxalate (3.39 g, 28.7 mmol) in tetrahydrofuran (40 mL) and ether (20 mL). After the addition was complete, the reaction mixture was stirred for an additional hour at -78 °C. The reaction was then treated with a saturated aqueous solution of ammonium

chloride (50 mL) and allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with ether (3 x 40 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and evaporated to give crude methyl 2-(5-methoxy-2-methylphenyl)-2-oxoacetate (**214**) (4.85 g, 89%) which was used without further purification.

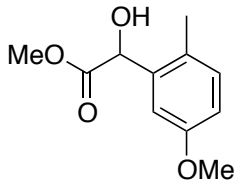
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (m, 2H), 7.05 (dd, 1H, *J* = 8.4, 2.7 Hz), 3.96 (s, 3H), 3.82 (s, 3H), 2.50 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 188.2, 164.7, 157.5, 133.2, 132.8, 132.0, 119.5, 116.9, 55.5, 52.8, 20.2

IR (neat): 2958, 1736, 1684, 1610, 1571, 1498, 1436, 1243, 1164, 994, 816 cm^{-1}

Exact mass calculated for $C_{11}H_{12}NaO_4$: 231.0628 (M+Na); found: 231.0622.

Preparation of methyl 2-hydroxy-2-(5-methoxy-2-methylphenyl)acetate (215).



To a stirred solution of methyl 2-(5-methoxy-2-methylphenyl)-2-oxoacetate (**214**) (4.66 g, 22.4 mmol) in a mixture of ethanol (60 mL), water (20 mL), and acetic acid (10 mL) was added sodium cyanoborohydride (1.68 g, 26.7 mmol). The resulting mixture was stirred for 10 minutes after which time the mixture was diluted with ethyl acetate (50 mL), and treated with a 1M aqueous solution of hydrochloric acid (10 mL) and water (10 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with a saturated aqueous solution of sodium bicarbonate (30 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated to give crude methyl 2-hydroxy-2-(5-methoxy-2-methylphenyl)acetate (**215**) (4.33 g, 92%) which was used without further purification.

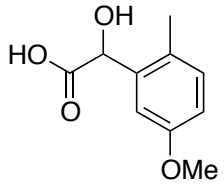
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.09 (d, 1H, *J* = 8.4 Hz), 6.86 (d, 1H, *J* = 2.7 Hz), 6.78 (dd, 1H, *J* = 8.4, 2.7 Hz), 5.35 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.6, 158.0, 137.4, 131.7, 128.2, 114.1, 112.1, 70.3, 55.3, 53.0, 18.3

IR (neat): 3425, 3008, 2955, 2929, 1728, 1611, 1502, 1436, 1245, 1111, 1035, 725 cm^{-1}

Exact mass calculated for $C_{11}H_{14}NaO_4$: 233.0784 (M+Na); found: 233.0787.

Preparation of 2-hydroxy-2-(5-methoxy-2-methylphenyl)acetic acid (216).



To a stirred solution of methyl 2-hydroxy-2-(5-methoxy-2-methylphenyl)acetate (**215**) (4.33 g, 20.6 mmol) in methanol (60 mL) was added a solution of potassium hydroxide (3.77 g, 67.2 mmol) in water (67 mL). The resulting mixture was stirred for 30 minutes at room temperature after which time the methanol was removed in vacuo and the aqueous residue was extracted with ethyl acetate (2 x 30 mL). The aqueous phase was adjusted to pH < 2 by the addition of a 1 M aqueous solution of hydrochloric acid and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and evaporated to give crude 2-hydroxy-2-(5-methoxy-2-methylphenyl)acetic acid (**216**) (3.84 g, 95%) which required no further purification.

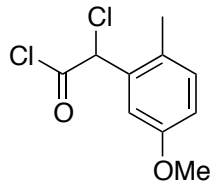
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.11 (d, 1H, *J* = 8.4 Hz), 6.91 (d, 1H, *J* = 2.6 Hz), 6.80 (dd, 1H, *J* = 8.4, 2.6 Hz), 5.42 (s, 1H), 3.78 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 176.2, 158.1, 136.8, 131.9, 128.2, 114.3, 112.1, 70.0, 55.3, 18.4.

IR (neat): 3417, 2971, 2901, 1708, 1610, 1502, 1438, 1245, 1036, 821 cm^{-1}

Exact mass calculated for $C_{10}H_{12}NaO_4$: 219.0628 (M+Na); found: 219.0618.

Preparation of 2-chloro-2-(5-methoxy-2-methylphenyl)acetyl chloride (211).

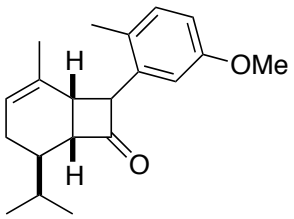


A solution of 2-hydroxy-2-(5-methoxy-2-methylphenyl)acetic acid (**216**) (1.36 g, 6.93 mmol) in thionyl chloride (5 mL) was stirred at room temperature for 2 hours after which time it was heated to 60 °C for an additional 2 hours. Thionyl chloride was removed in vacuo to give the crude chloroacylchloride. The crude product was purified by distillation (200 °C, 1 torr) to afford 2-chloro-2-(5-methoxy-2-methylphenyl)acetyl chloride (**211**) (1.13 g, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.16 (d, 1H, *J* = 8.4 Hz), 6.92 (d, 1H, *J* = 2.7 Hz), 6.88 (dd, 1H, *J* = 8.4, 2.7 Hz), 5.82 (s, 1H), 3.80 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 158.5, 132.7, 132.3, 128.4, 116.0, 113.6, 63.7, 55.4, 18.3.

Preparation of (1*S*,5*R*,6*R*,8*R*)-5-(2-methylethyl)-8-(5-methoxy-2-methylphenyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (218).



To a refluxing stirred solution of 2-chloro-2-(5-methoxy-2-methylphenyl)acetyl chloride (**211**) (750 mg, 3.22 mmol) and (*R*)-(–)-α-phellandrene (**29**) (396 mg, 66% purity, 1.61 mmol) in toluene (4.5 mL) was added a solution of triethylamine (0.54 mL, 3.9 mmol) in toluene (2.2 mL) dropwise over 1 hour. After the addition was complete, the reaction mixture was stirred for an additional 3 hours at reflux and then cooled and filtered. The filtrate was treated with water (30 mL), diluted with ethyl acetate (40 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 40 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to give the crude chlorocyclobutanone. Purification of the crude product by

flash chromatography (silica gel, 20:1 hexanes:ethyl acetate) afforded chlorocyclobutanone (**217**) (563 mg) that was contaminated with several other unidentified products.

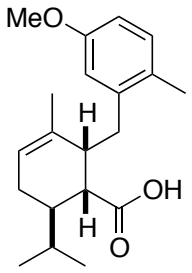
To a stirred solution of chlorocyclobutanone (**217**) (563 mg, 1.69 mmol) in methanol (15 mL) was added zinc (580 mg, 8.87 mmol) and ammonium chloride (484 mg, 9.05 mmol). The resulting suspension was stirred at room temperature for 24 hours after which time the mixture was filtered through a pad of Celite® and evaporated in vacuo. The residue was dissolved in ether (50 mL), treated with water (35 mL), and the phases were separated. The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give the crude cyclobutanone. Purification of the crude product by flash chromatography (silica gel, 20:1 hexanes:ethyl acetate) afforded (1*S*,5*R*,6*R*,8*R*)-5-(2-methylethyl)-8-(5-methoxy-2-methylphenyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**218**) (102 mg, 21% over 2 steps) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.00 (d, 1H, *J* = 7.8 Hz), 6.68 (m, 2H), 5.49 (app. d, 1H, *J* = 6.3 Hz), 4.73 (dd, 1H, *J* = 9.8, 2.2 Hz), 3.73 (s, 3H), 3.74-3.70 (m, 1H), 3.20 (t, 1H, *J* = 9.5 Hz), 2.31-2.24 (m, 1H), 2.25 (s, 3H), 2.06-2.00 (m, 1H), 1.97-1.92 (m, 1H), 1.61 (m, 1H), 1.04 (s, 3H), 0.92 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.9, 157.5, 133.7, 133.2, 130.1, 128.0, 123.1, 114.5, 112.6, 62.0, 58.7, 55.2, 35.6, 34.4, 30.1, 25.1, 22.6, 21.1, 20.9, 18.7.

Exact mass calculated for $C_{20}H_{27}O_2$: 299.2006 (M+H); found: 299.2002.

Preparation of (1*R*,2*R*,6*R*)-2-(5-methoxy-2-methylbenzyl)-6-(2-methylethyl)-3-methylcyclohex-3-enecarboxylic acid (222).



Method A (One-pot procedure):

To a stirred solution of (1*R*,5*R*,6*R*)-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**164**) (1.00 g, 5.61 mmol) and 2-bromo-4-methoxy-1-methylbenzene (**212**) (1.03 g, 5.12 mmol) in degassed toluene (8.0 mL) was added [1,1′-*bis*(di-*tert*-butylphosphino)-ferrocene]dichloropalladium(II) (166 mg, 0.255 mmol) followed by lithium *tert*-butoxide (1.0M in tetrahydrofuran, 12.3 mL, 12.3 mmol). The resulting mixture was stirred at room temperature for 5 hours and potassium *tert*-butoxide (1.26g, 11.2 mmol) was added. The resulting mixture was stirred at 110 °C for 16 hours after which time the reaction was diluted with ethyl acetate (30 mL), treated with a 1M aqueous solution of hydrochloric acid (20 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude acid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*R*,2*R*,6*R*)-2-(5-methoxy-2-methylbenzyl)-6-(2-methylethyl)-3-methylcyclohex-3-enecarboxylic acid (**222**) (929 mg, 61%) as a light yellow oil.

Method B (2-pot procedure):

To a stirred solution of (1*R*,5*R*,6*R*)-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**164**) (830 mg, 4.65 mmol) and 2-bromo-4-methoxy-1-methylbenzene (**212**) (851 mg, 4.23 mmol) in degassed toluene (6.5 mL) was added [1,1′-*bis*(di-*tert*-butylphosphino)-ferrocene]dichloropalladium(II) (138 mg, 0.21 mmol) followed by lithium *tert*-butoxide (1.0M in tetrahydrofuran, 10.2 mL, 10.2 mmol). The resulting mixture was stirred at room temperature for 5 hours after which time the reaction was diluted with ethyl acetate (30 mL). A 1M aqueous solution of hydrochloric acid (20 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 mL) and the combined organic phases were washed with brine (50 mL), dried

($MgSO_4$) and concentrated to give the crude α-arylcyclobutanone (**217**) that was used without further purification.

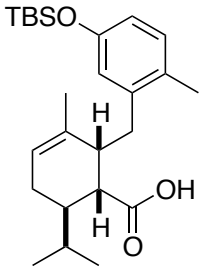
To a solution of crude α-arylcyclobutanone (**217**) (1.08g, 3.62 mmol) in *tert*-butanol (15 mL) was added water (65 μL, 3.62 mmol) and potassium *tert*-butoxide (812 mg, 7.24 mmol). The resulting mixture was stirred for 10 minutes, after which time the reaction was acidified to pH < 2 with a 1M aqueous solution of hydrochloric acid, diluted with ethyl acetate (30 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude acid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*R*,2*R*,6*R*)-2-(5-methoxy-2-methylbenzyl)-6-(2-methylethyl)-3-methylcyclohex-3-enecarboxylic acid (**222**) (803 mg, 60% over 2 steps).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.99 (d, 1H, *J* = 8.3 Hz), 6.67 (d, 1H, *J* = 2.5 Hz), 6.63 (dd, 1H, *J* = 8.3, 2.5 Hz), 5.37 (br. s, 1H), 3.73 (s, 3H), 2.91 (dd, 1H, *J* = 13.2, 4.8 Hz), 2.71 (dd, 1H, *J* = 13.2, 9.3 Hz), 2.65 (m, 2H), 2.20 (s, 3H), 2.18-2.10 (m, 2H), 2.09-2.01 (m, 1H), 1.93-1.85 (m, 1H), 1.30 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.8, 157.6, 140.1, 136.6, 130.9, 128.4, 121.4, 115.5, 111.3, 55.2, 47.0, 41.1, 34.8, 34.6, 28.1, 23.5, 23.2, 20.8, 18.5, 16.0.

Exact mass calculated for $C_{20}H_{29}O_3$: 317.2119 (M+H); found: 317.2111.

Preparation of (1*R*,2*R*,6*R*)-2-(5-[(*tert*-butyldimethylsilyl]oxy)-2-methylbenzyl)-6-(2-methylethyl)-3-methylcyclohex-3-eneoic acid (226).



To a stirred solution of (1*R*,5*R*,6*R*)-5-(2-methylethyl)-2-methylbicyclo[4.2.0]oct-2-en-7-one (**164**) (941 mg, 5.28 mmol) and 2-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-1-

methylbenzene (**134**) (1.45 g, 4.81 mmol) in degassed toluene (7.5 mL) was added [1,1′-*bis*(di-*tert*-butylphosphino)-ferrocene]dichloropalladium(II) (156 mg, 0.24 mmol) and lithium *tert*-butoxide (1.0M in tetrahydrofuran, 11.6 mL, 11.6 mmol). The resulting mixture was stirred at 55 °C for 4 hours after which time the reaction was diluted with ethyl acetate (30 mL), a 1M aqueous solution of hydrochloric acid (20 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude α-arylcyclobutanone (**225**) that was used without further purification.

To a stirred solution of the crude α-arylcyclobutanone (**225**) in *tert*-butanol (24 mL) was added water (86 μL, 4.8 mmol) and potassium *tert*-butoxide (1.07 mg, 9.54 mmol) and the mixture was stirred for 10 minutes. The reaction was then acidified with a 1M aqueous solution of hydrochloric acid to pH < 2, ethyl acetate (50 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude acid. Purification of the crude product by flash chromatography (silica gel, 5:1 hexanes:ethyl acetate) afforded (1*R*,2*R*,6*R*)-2-(5-[(*tert*-butyldimethylsilyl]oxy)-2-methylbenzyl)-6-(2-methylethyl)-3-methylcyclohex-3-eneoic acid (**226**) (1.128 g, 64% over 2 steps).

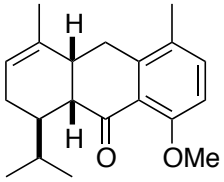
^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.94 (d, 1H, *J* = 8.0 Hz), 6.62-6.57 (m, 2H), 5.39 (br. s, 1H), 2.91 (q, 1H, *J* = 9.9 Hz), 2.71-2.62 (m, 3H), 2.21 (s, 3H), 2.20-2.17 (m, 1H), 2.17-2.04 (m, 2H), 1.97-1.86 (m, 1H), 1.28 (d, 3H, *J* = 1.4 Hz), 0.98 (s, 9H), 0.94 (d, 3H, *J* = 6.9 Hz), 0.82 (d, 3H, *J* = 6.8 Hz), 0.17 (app. d, 6H, *J* = 1.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.2, 153.5, 139.9, 136.7, 130.9, 129.0, 121.5, 121.4, 117.8, 47.2, 41.2, 34.6, 34.6, 28.2, 25.7, 23.4, 23.4, 20.8, 18.5, 18.2, 15.8, -4.4, -4.4.

IR (neat): 2957, 2929, 2858, 1744, 1702, 1607, 1497, 1254, 973, 866, 837, 779 cm^{-1}

Exact mass calculated for $C_{25}H_{41}O_3Si$: 417.2846 (M+H); found: 417.2825.

Preparation of (1*R*,4α*R*,9α*R*)-8-methoxy-4,5-dimethyl-1-(2-methylethyl)-1,2,4α,9,9α,10-hexahydroanthracen-9-one (223).



To a stirred solution of (1*R*,2*R*,6*R*)-2-(5-methoxy-2-methylbenzyl)-6-(2-methylethyl)-3-methylcyclohex-3-enecarboxylic acid (**222**) (18 mg, 0.054mmol) in dichloromethane (1 mL) was added *N*,*N*-dimethylformamide (1 drop) and oxalyl chloride (23 μL, 0.162mmol). The resulting mixture was stirred for 1 hour at room temperature after which time the solvent was removed in vacuo to afford the crude acid chloride which required no further purification.

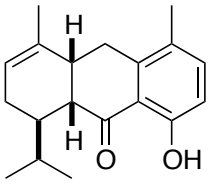
To a cold (0 °C) stirred solution of the crude acid chloride in dichloromethane (1 mL) was added tin(IV) chloride (0.5 M in dichloromethane, 0.13 mL, 0.065 mmol). The reaction mixture was stirred for 15 minutes after which time it was diluted with ethyl acetate (10 mL), treated with a saturated aqueous solution of sodium bicarbonate (5 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to give the crude tetralone. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*R*,4α*R*,9α*R*)-8-methoxy-4,5-dimethyl-1-(2-methylethyl)-1,2,4α,9,9α,10-hexahydroanthracen-9-one (**223**) (12 mg, 75% over 2 steps).

^{1}H NMR (600 MHz, C_6D_6) δ: 6.95 (dd, 1H, *J* = 8.4, 0.4 Hz), 6.41 (d, 1H, *J* = 8.4 Hz), 5.25 (br. s, 1H), 3.41 (s, 3H), 2.71 (dd, 1H, *J* = 9.7, 4.7 Hz), 2.61 (dd, 1H, *J* = 17.4, 6.5 Hz), 2.56 (dd, 1H, *J* = 17.4, 8.5 Hz), 2.42 (m, 1H), 2.14-2.09 (m, 1H), 1.99-1.94 (m, 1H), 1.94 (s, 3H), 1.84-1.75 (m, 2H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, C_6D_6) δ: 199.9, 158.8, 141.7, 135.6, 134.4, 127.1, 123.6, 122.3, 110.3, 55.7, 52.5, 37.3, 37.3, 30.6, 29.2, 25.2, 21.5, 20.9, 18.9, 17.5.

Exact mass calculated for $C_{20}H_{27}O_2$: 299.2011 (M+H); found: 299.2013.

Preparation of (1*R*,4α*R*,9α*R*)-8-hydroxy-4,5-dimethyl-1-(2-methylethyl)-1,2,4α,9,9α,10-hexahydroanthracen-9-one (118).



Method A (Prepared from 226):

To a stirred solution of (1*R*,2*R*,6*R*)-2-(5-[(*tert*-butyldimethylsilyl]oxy)-2-methylbenzyl)-6-(2-methylethyl)-3-methylcyclohex-3-eneoic acid (**226**) (1.107g, 2.66 mmol) in dichloromethane (20 mL) was added *N*,*N*-dimethylformamide (1 drop) and oxalyl chloride (0.67 mL, 7.92 mmol). The resulting mixture was stirred for 1 hour at room temperature after which time the solvent was removed in vacuo to afford the crude acid chloride, which required no further purification.

To a cold (0 °C), stirred solution of the acid chloride in dichloromethane (25 mL) was added tin(IV) chloride (0.31 mL, 2.64 mmol). The reaction mixture was stirred for 15 minutes after which time it was treated with a saturated aqueous solution of sodium bicarbonate (25 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 35 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give the crude tetralone. Purification of the crude product by flash chromatography (silica gel, 10:1 hexanes:ethyl acetate) afforded (1*R*,4α*R*,9α*R*)-8-hydroxy-4,5-dimethyl-1-(2-methylethyl)-1,2,4α,9,9α,10hexahydro-anthracen-9-one (**118**) (600 mg, 79% over 2 steps).

Method B (Prepared from 222):

To a stirred solution of (1*R*,2*R*,6*R*)-2-(5-methoxy-2-methylbenzyl)-6-(2-methylethyl)-3-methylcyclohex-3-enecarboxylic acid (**222**) (150 mg, 0.474 mmol) in dichloromethane (5 mL) was added *N*,*N*-dimethylformamide (1 drop) and oxalyl chloride (0.12 mL, 1.42 mmol). The resulting mixture was stirred for 1 hour at room temperature after which time the solvent was removed in vacuo to afford the crude acid chloride that was used without further purification.

To a cold (0 °C) stirred solution of acid chloride in dichloromethane (5 mL) was added tin(IV) chloride (1.0 M in dichloromethane, 0.52 mL, 0.52 mmol). The reaction mixture

was stirred for 15 minutes after which time it was diluted with ethyl acetate (25 mL), treated with a saturated aqueous solution of sodium bicarbonate (10 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to give the crude tetralone **223**, which was used without further purification.

To a cold (-78 °C), solution of tetralone **223** in dichloromethane (5 mL) was added boron tribromide (1.0 M in dichloromethane, 1.0 mL, 1.0 mmol). The reaction mixture was stirred for 45 minutes at -78 °C, treated with a saturated aqueous solution of sodium bicarbonate (10 mL), and allowed to warm to room temperature. The resulting mixture was diluted with ethyl acetate (25 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to give the crude tetralone. Purification of the crude product by flash chromatography (silica gel, 10:1 → 3:1 hexanes:ethyl acetate) afforded (1*R*,4α*R*,9α*R*)-8-hydroxy-4,5-dimethyl-1-(2-methylethyl)-1,2,4α,9,9α,10-hexahydroanthracen-9-one (**118**) (50 mg, 37% over 3 steps) and (1*R*,4α*R*,9α*R*)-8-methoxy-4,5-dimethyl-1-(2-methylethyl)-1,2,4α,9,9α,10-hexahydro anthracen-9-one (**223**) (40 mg, 29% over 3 steps).

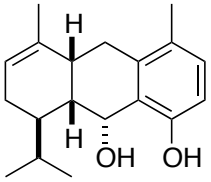
^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.57 (s, 1H), 7.25 (d, 1H, *J* = 8.4 Hz), 6.73 (d, 1H, *J* = 8.4 Hz), 5.43 (br. s, 1H), 2.95 (dd, 1H, *J* = 17.3, 4.8 Hz), 2.85 (dd, 1H, *J* = 17.3, 8.1 Hz), 2.76-2.69 (m, 2H), 2.20 (s, 3H), 2.14-1.92 (m, 3H), 1.69 (s, 3H), 1.61 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 208.0, 161.2, 140.4, 138.0, 134.4, 125.4, 122.8, 116.7, 115.0, 49.3, 36.8, 36.4, 29.5, 28.1, 24.8, 21.4, 21.0, 18.7, 17.5.

IR (neat): 3478, 2958, 2911, 2869, 1631, 1605, 1468, 1330, 1218, 778 cm^{-1}

Exact mass calculated for $C_{19}H_{25}O_2$: 285.1855 (M+H); found: 285.1874.

Preparation of (8*R*,8α*R*,9*R*,10α*R*)-4,5-dimethyl-8-(2-methylethyl)-7,8,8α,9,10,10α-hexahydroanthracene-1,9-diol (231).



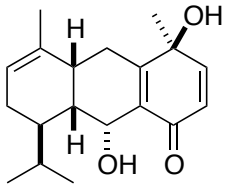
To a cold (0 °C), stirred suspension of lithium aluminum hydride (11 mg, 0.290 mmol) in ether (1.5 mL) was added a solution of (1*R*,4α*R*,9α*R*)-8-hydroxy-4,5-dimethyl-1-(2-methylethyl)-1,2,4α,9,9α,10-hexahydroanthracen-9-one (**118**) (42 mg, 0.148 mmol) in ether (0.5 mL). The resulting mixture was stirred for 10 minutes at 0 °C and treated with water (11 μL), followed by a 15% aqueous solution of sodium hydroxide (11 μL), and stirred for 5 minutes. Water (33 μL) was added and after 5 minutes the mixture was treated with anhydrous magnesium sulfate. The reaction mixture was filtered and concentrated to provide the crude hydroxyphenol. Purification of the crude product by flash chromatography (silica gel, 5:1 hexanes:ethyl acetate + 0.5% triethylamine) afforded (8*R*,8α*R*,9*R*,10α*R*)-4,5-dimethyl-8-(2-methylethyl)-7,8,8α,9,10,10α-hexahydroanthracene-1,9-diol (**231**) (23 mg, 55%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 6.98 (d, 1H, *J* = 8.1 Hz), 6.67 (d, 1H, *J* = 8.1 Hz), 5.50 (br. s, 1H), 5.05 (dd, 1H, *J* = 7.7, 5.7 Hz), 2.77 (dd, 1H, *J* = 17.6, 6.1 Hz), 2.69 (dd, 1H, *J* = 17.6, 6.6 Hz), 2.56 (d, 1H, *J* = 8.6 Hz), 2.48 (m, 1H), 2.27-2.19 (m, 1H), 2.16 (s, 3H), 2.17-2.14 (m, 1H), 2.02-1.86 (m, 3H), 1.63 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H).

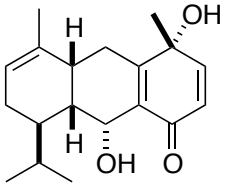
^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.7, 138.2, 134.0, 129.9, 126.7, 123.5, 122.1, 113.7, 73.5, 41.2, 37.8, 35.1, 30.4, 30.1, 26.3, 21.1, 20.7, 19.0, 18.5.

Exact mass calculated for $C_{19}H_{26}NaO_2$: 309.1830 (M+Na); found: 309.1834.

Preparation of (4*S*,8*R*,8α*R*,9*R*,10α*R*)-4,9-dihydroxy-4,5-dimethyl-8-(2-methylethyl)-1,4,7,8,8α,9,10,10α-octahydroanthracen-1-one (117) and (4*R*,8*R*,8α*R*,9*R*,10α*R*)-4,9-dihydroxy-4,5-dimethyl-8-(2-methylethyl)-1,4,7,8,8α,9,10,10α-octahydroanthracen-1-one (232).



+



117 **232**

To a cold (0 °C), stirred solution of (8*R*,8α*R*,9*R*,10α*R*)-4,5-dimethyl-8-(2-methylethyl)-7,8,8α,9,10,10α-hexahydroanthracene-1,9-diol (**231**) (36 mg, 0.126 mmol) in a mixture of acetonitrile (3.5 mL) and aqueous pH 7 buffer (0.9 mL) was added a solution of iodobenzene diacetate (46 mg, 0.143 mmol) in acetonitrile (3.5 mL) dropwise over 30 minutes. After the addition was complete, the resulting mixture was stirred for 30 minutes after which time it was diluted with ethyl acetate (15 mL), treated with water (10 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give the crude dienone (d.r. = 1:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes:ethyl acetate + 0.5% triethylamine) afforded (4*S*,8*R*,8α*R*,9*R*,10α*R*)-4,9-dihydroxy-4,5-dimethyl-8-(2-methylethyl)-1,4,7,8,8α,9,10,10α-octahydroanthracen-1-one (**117**) (12 mg, 32%) and its diastereomer (4*R*,8*R*,8α*R*,9*R*,10α*R*)-4,9-dihydroxy-4,5-dimethyl-8-(2-methylethyl)-1,4,7,8,8α,9,10,10α-octahydroanthracen-1-one (**232**) (10 mg, 26%) .

Data for (4*S*,8*R*,8α*R*,9*R*,10α*R*)-4,9-dihydroxy-4,5-dimethyl-8-(2-methylethyl)-1,4,7,8,8α,9,10,10α-octahydroanthracen-1-one **(117):**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90 (d, 1H, *J* = 9.9 Hz), 6.14 (d, 1H, *J* = 9.9 Hz), 5.48 (br. s, 1H), 4.82 (d, 1H, *J* = 3.2 Hz), 4.48 (d, 1H, *J* = 1.9 Hz), 2.85 (ddd, 1H, *J* = 19.8, 6.8, 1.6 Hz), 2.40 (ddd, 1H, *J* = 19.8, 7.7, 1.9 Hz), 2.27 (m, 1H), 2.24-2.10 (m, 3H), 2.04 (m, 1H), 1.92-1.83 (m, 1H), 1.77-1.73 (m, 1H), 1.72 (d, 3H, *J* = 1.5 Hz), 1.49 (s, 3H), 0.89 (d, 3H, *J* = 6.6 Hz), 0.86 (d, 3H, *J* = 6.9 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 186.9, 158.6, 152.5, 136.8, 131.9, 127.3, 122.8, 70.0, 69.1, 39.3, 37.5, 35.6, 29.5, 28.5, 26.8, 25.5, 21.4, 21.2, 17.4.

IR (cast film): 3382, 2959, 2906, 1666, 1614, 1444, 1290, 1084, 840, 737cm^{-1}

Exact mass calculated for $C_{19}H_{26}NaO_3$: 325.1780 (M+Na); found: 325.1791.

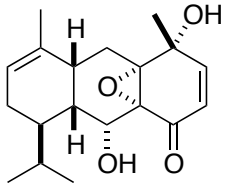
Data for (4*R*,8*R*,8α*R*,9*R*,10α*R*)-4,9-dihydroxy-4,5-dimethyl-8-(2-methylethyl)-1,4,7,8,8α,9,10,10α-octahydroanthracen-1-one (**232**):

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.89 (d, *J* = 9.9 Hz, 1H), 6.16 (d, *J* = 9.9 Hz, 1H), 5.55 (br. s, 1H), 4.77 (t, *J* = 4.5 Hz, 1H), 3.56 (d, *J* = 4.5 Hz, 1H), 2.84 (ddd, *J* = 18.9, 5.4, 1.0 Hz, 1H), 2.48 (ddd, *J* = 18.9, 6.9, 1.3 Hz, 1H), 2.40 (m, 1H), 2.29-2.18 (m, 1H), 2.07-1.81 (m, 4H), 1.73 (s, 3H), 1.46 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 185.8, 156.7, 152.1, 136.5, 132.6, 127.2, 124.0, 68.6, 68.1, 39.4, 38.5, 34.2, 30.6, 27.4, 26.4, 26.1, 21.0, 20.9, 18.7.

Exact mass calculated for $C_{19}H_{27}O_3$: 303.1960 (M+H); found: 303.1976.

Preparation of (1*R*,3*R*,7*R*,8*R*,9*R*,10*R*,14*R*)-9,14-dihydroxy-4,14-dimethyl-7-(2-methylethyl)-15-oxatetracyclo[8.4.1.0^{1,10}.0^{3,8}]pentadeca-4,12-dien-11-one (233).



To a flame dried round bottom flask containing activated powdered 4Å molecular sieves was added a solution of (4*R*,8*R*,8α*R*,9*R*,10α*R*)-4,9-dihydroxy-4,5-dimethyl-8-(2-methylethyl)-1,4,7,8,8α,9,10,10α-octahydroanthracen-1-one (**232**) (62 mg, 0.205 mmol), in dichloromethane (2.0 mL). The mixture was cooled to -20 °C and titanium(IV) isopropoxide (0.125 M in dichloromethane, 0.16 mL, 0.020 mmol) was added. The resulting mixture was stirred for 20 minutes after which time *tert*-butylhydroperoxide (1.375 M in dichloromethane, 0.19 mL, 0.261 mmol) was added dropwise over 10 minutes. The mixture was then warmed to -15 °C and stirred for 16 hours. A saturated aqueous solution of Rochelle's salt (2 mL) was added and the mixture was allowed to warm to room temperature. The mixture was diluted with ethyl acetate (15 mL), treated with water (10 mL), and the layers were separated. The aqueous phase was extracted

with ethyl acetate (2 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give the crude epoxyenone. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes:ethyl acetate + 0.5% triethylamine) afforded (1*R*,3*R*,7*R*,8*R*,9*R*,10*R*,14*R*)-9,14-dihydroxy-4,14-dimethyl-7-(2-methylethyl)-15-oxatetracyclo[8.4.1.$0^{1,10}$.$0^{3,8}$]pentadeca-4,12-dien-11-one (**233**) (46 mg, 71%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.44 (d, 1H, *J* = 10.5 Hz), 5.83 (d, 1H, *J* = 10.5 Hz), 5.38 (br. s, 1H), 4.70 (dd, 1H, *J* = 8.2, 5.9 Hz), 2.80 (d, 1H, *J* = 8.2 Hz), 2.55 (dd, 1H, *J* = 17.4, 7.8 Hz), 2.36-2.28 (m, 2H), 2.25-2.19 (m, 2H), 1.95-1.82 (m, 4H), 1.74 (s, 3H), 1.43 (s, 3H), 0.92 (d, *J* = 6.2 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 195.4, 150.2, 136.0, 123.1, 122.9, 71.3, 69.5, 67.2, 65.0, 38.9, 38.6, 33.4, 30.4, 26.9, 25.0, 24.5, 21.4, 21.1, 19.2.

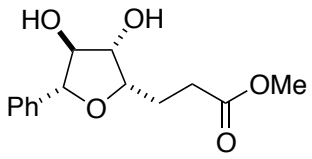
IR (cast film): 3405, 2960, 2870, 1688, 1673, 1440, 1368, 1265, 1086, 949, 736cm^{-1}

Exact mass calculated for $C_{19}H_{27}O_4$: 319.1909 (M+Na); found: 319.1909

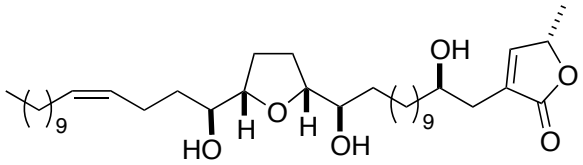
3. Total Synthesis of Marine Oxylipids from *Notheia Anomala*

3.1. Introduction

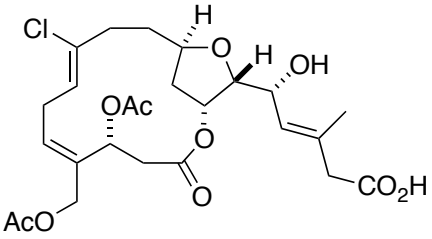
Sections of this chapter have been reproduced from our reports of this work in *Organic Letters*.[176,177] The tetrahydrofuran ring is one of the most prevalent heterocycles in natural products. Some representative natural product classes that feature this structural moiety include the *Goniothalamus* styryl lactones (e.g., (+)-goniothalesdiol (**254**), Figure 3.1),[178] and the annonaceous acetogenins (e.g., asiminenin A (**255**)).[179] More specifically, the 2,5-disubstituted-3-hydroxytetrahydrofuran core is present in well over 500 natural products that display a diversity of potentially useful biological activities. Some examples include: biselide A (**256**), a cytotoxic macrolide isolated from an Okinawan ascidian,[180] (-)-aplysiallene (**257**),[181,182] an ATPase inhibitor, and the anthelmintic oxylipids **258** and **259**, isolated from the brown algae *Notheia anomala*.[183,184] While several methods have been developed to access this important structural motif, these strategies often initiate with chiral pool materials and are consequently designed for the synthesis of a single configurational isomer. Consequently, these methods are not widely applicable to the production of naturally occurring and stereochemically differentiated tetrahydrofurans. Furthermore, many existing strategies rely heavily on protecting/functional group manipulations, which increase the total number of transformations required to access the target structure and detract from their synthetic utility.



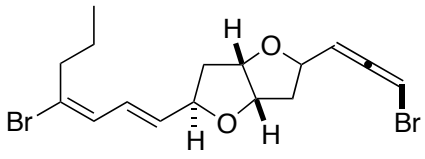
254: (+)-goniothalesdiol



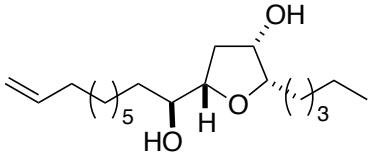
255: asiminenin A



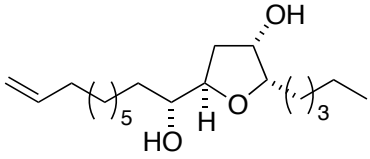
256: biselide A



257: (-)-aplysiallene



258: *Notheia anomala* oxylipid

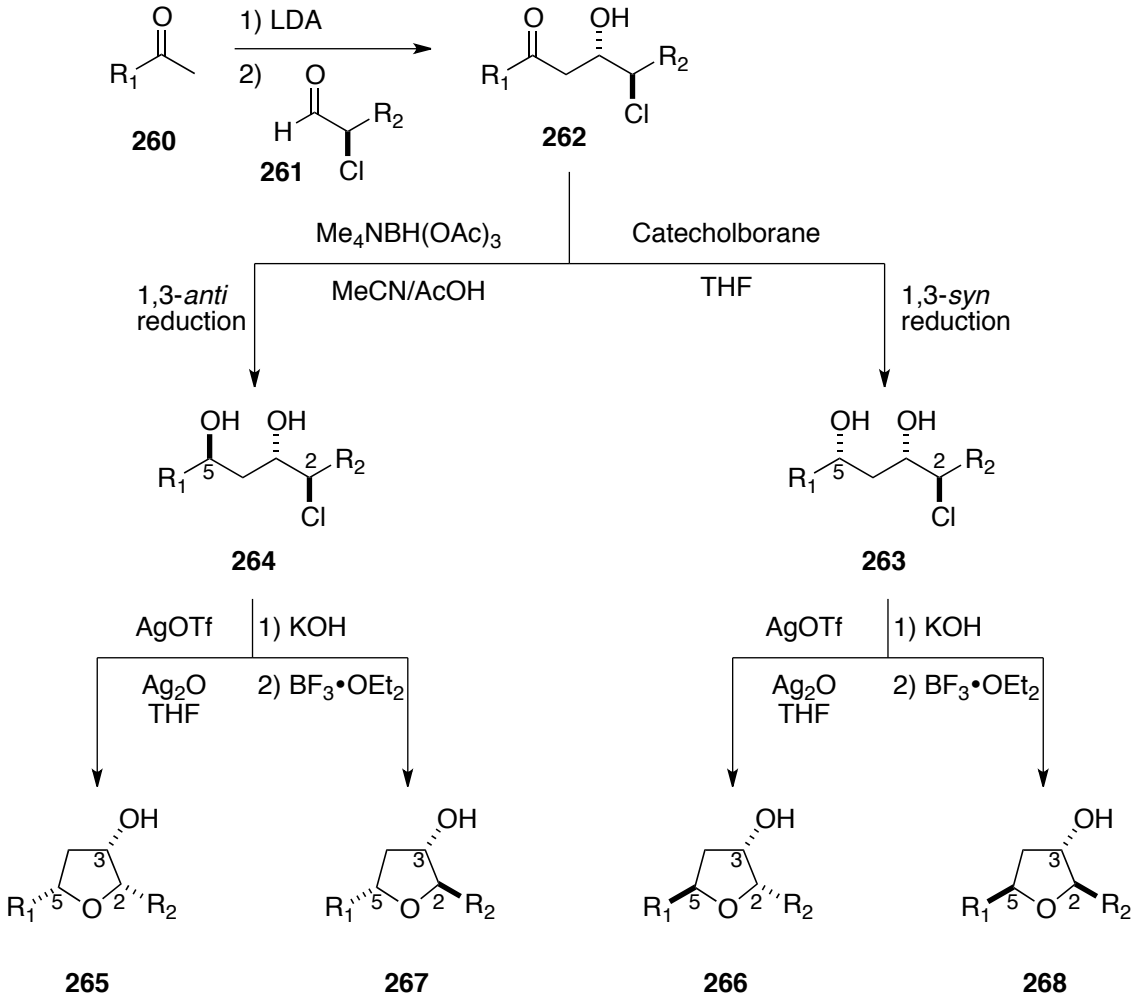


259: *Notheia anomala* oxylipid

Figure 3.1 Representative natural products containing a tetrahydrofuran core.

In order to address the inefficiencies of current strategies, Dr. Baldip Kang developed a concise and stereoselective method for the synthesis of all configuration isomers of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold.[176] As illustrated in Scheme 3.1, this approach initiates with the lithium aldol reaction between a methyl ketone **260** and an enantio-enriched α-chloroaldehyde **261**, the product of which is an *anti*-β-ketochlorohydrin **262** as predicted by the Cornforth model.[185] Stereoselective reduction of the ketone function in a 1,3-*syn*[186] or 1,3-*anti*[187] fashion delivers the diastereomeric chlorodiols **263** and **264**, respectively. Direct S_N2 displacement of the chloride by the C5 hydroxyl group through a novel AgOTf/Ag_2O mediated cyclisation[176] affords the 2,3-*syn* tetrahydrofurans **265** and **266**. Conversely, epoxidation of the chlorodiols with base gives epoxy alcohols (not shown), which upon treatment with Lewis-acid induces rearrangement to the 2,3-*anti* tetrahydrofurans **267** and **268**.[188] With these two complementary cyclisation strategies controlling the relative stereochemistry of the substituents at position 2 and 3 in the resulting tetrahydrofuran, and the

diastereoselective reduction controlling the stereochemistry at C5, all stereoisomers of this important scaffold are available from a single aldol adduct in 2-3 steps.



Scheme 3.1 Methodology developed to access all configurational isomers of the 2,5-disubstitued-3-hydroxytetrahydrofuran scaffold.

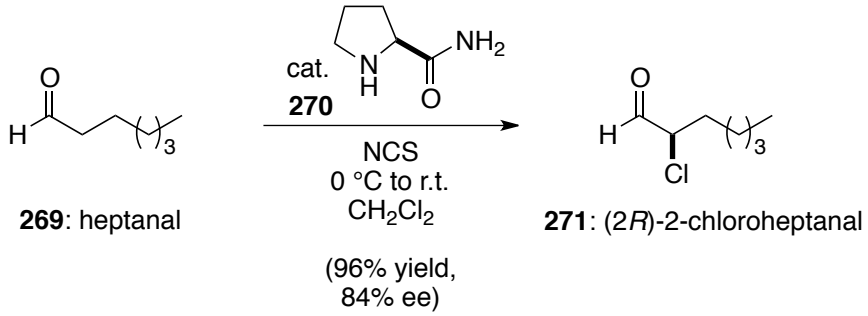
In order to demonstrate the synthetic utility of this newly developed methodology, a total synthesis of the two oxylipids **258** and **259** from *Notheia anomala* was initiated. These marine derived dihydroxytetrahydrofurans were originally isolated from the brown alga *Notheia anomala* located off the coast of southern Australia.[183,184] In subsequent testing, **259** was found to display potent and selective nematocidal activity against the free-living stages of the parasitic nematodes *Haemonchus contortus* and *Trichostrongylus colubriformis,* a major source of livestock loss in commercial production. Notably, the reported anthelmintic activity toward *H. contortus* (LD_{50} = 1.8

ppm)[183] and *T. colubriformis* (LD_{50} = 9.9 ppm)[183] was comparable to commercially available anthelmintics such as levamisole and closantel.[189] Despite the existence of commercially available anthelmintics, growing levels of observed drug resistance has reinvigorated the search for new nematocidal agents. Not only due to its biological profile, the synthesis of oxylipids **258** and **259** has attracted considerable attention from synthetic chemists as a target molecule capable of illustrating new synthetic methodologies relevant for the preparation of 2,5-disubstituted tetrahydrofurans. As a result, several total syntheses of these oxylipids exist in the literature, including four asymmetric syntheses of **258**[190–193] and eight asymmetric total syntheses of **259**.[191,192,194–199]

3.2. Results and Discussion

3.2.1. Synthesis of Chlorodiols 274 and 275

The synthesis of marine oxylipids **258** and **259** commenced with the α-chlorination of heptanal (**269**) as shown in Scheme 3.2. Following the procedure reported by Jørgensen and co-workers for the asymmetric α-chlorination of aldehydes, a solution of heptanal in dichloromethane was treated with 10 mol% L-prolinamide (**270**) and *N*-chlorosuccinimide, which afforded (2*R*)-2-chloroheptanal (**271**) in 96% yield and 84% ee.[200]



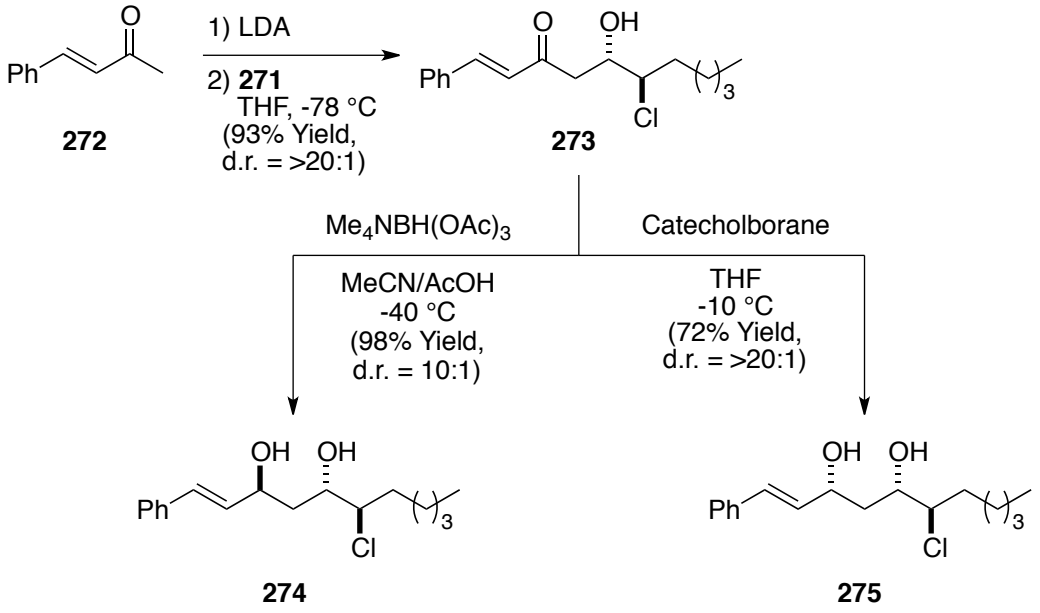
269: heptanal

271: (2*R*)-2-chloroheptanal

Scheme 3.2 Synthesis of α-chloroaldehyde 271.

Subjecting **271** to the lithium enolate derived from (*E*)-4-phenyl-but-3-ene-2-one (**272**) gave β-ketochlorohydrin **273** in excellent yield (93%) and diastereoselectivity (d.r. = >20:1, as determined by analysis of the ^{1}H NMR spectrum recorded on the crude

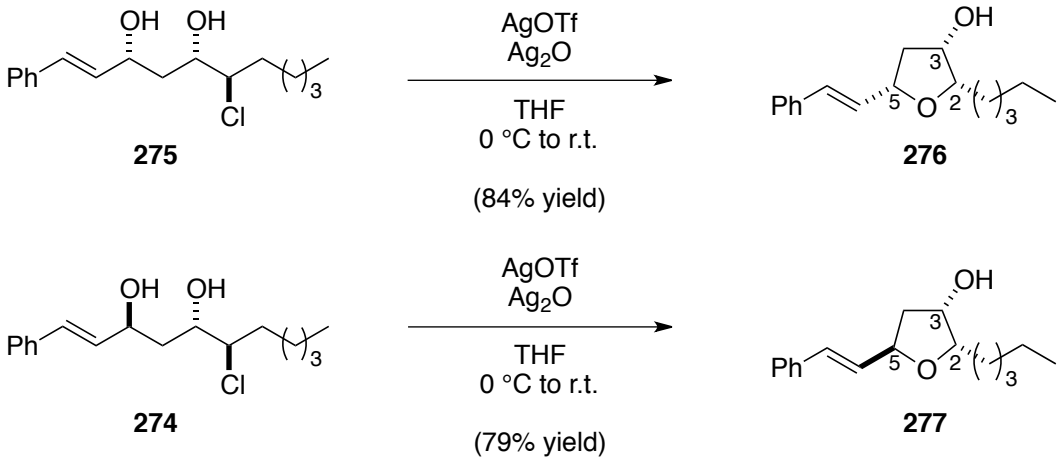
reaction mixture) (Scheme 3.3). Hydroxy-directed 1,3-*anti*-reduction of the carbonyl function by treatment of the latter material with $Me_4NBH(OAc)_3$ in a mixture of acetonitrile and acetic acid at -40 °C afforded the 1,3-*anti*-diol **274** in excellent yield and diastereocontrol.[187] Conversely, 1,3-*syn*-reduction with catecholborane in THF delivered the 1,3-*syn*-diol **275** in 72% yield.[186] The stereochemistry of the newly formed carbinol centres were assigned by conversion to the corresponding acetonide and subsequent analysis of their ^{13}C NMR spectrum following the method reported by Rychnovsky and co-workers (see experimental section 3.4).[201]



Scheme 3.3 Synthesis of chlorodiols 274 and 275.

3.2.2. Silver Cyclisation of Chlorodiols 274 and 275

With the chlorodiols **274** and **275** in hand, we turned our attention to the silver mediated cyclisation. Thus, treatment of **274** and **275** with a 1:1 mixture of silver(I) triflate and silver(I) oxide in THF afforded the diastereomeric styryl-tetrahydrofurans **276** and **277**, respectively (Scheme 3.4).



Scheme 3.4 Silver cyclisation of chlorodiols 274 and 275.

The stereochemistry of the tetrahydrofurans **276** and **277** was unambiguously assigned through the key nOe correlations shown in Figure 3.2. Notably, in $CDCl_3$, the tetrahydrofurans favoured a conformation dominated by an internal hydrogen bond between the C3 hydroxy group and furan oxygen. For example, **276** displayed nOe correlations between H5 and H2 as well as H5 and H3, placing all hydrogens on the β face of the tetrahydrofuran. Further supporting this all *syn* relationship was the observation of an nOe correlation between H4β and H2 as well as a correlation between H4α and the hydrogen bonded OH resonance. Conversely, **277** displayed nOe correlations between H2 and the olefinic proton, confirming the 2,5-stereochemistry as *anti*. A correlation between H5 and the OH resonance, as well as a correlation of this latter proton to H4α confirmed the relative stereochemistry of the 3,5-substituents as *anti*. This set of nOe correlations along with the observation of a correlation between H4β and H2 secured the absolute stereochemistry of the C3 hydroxyl group as β.

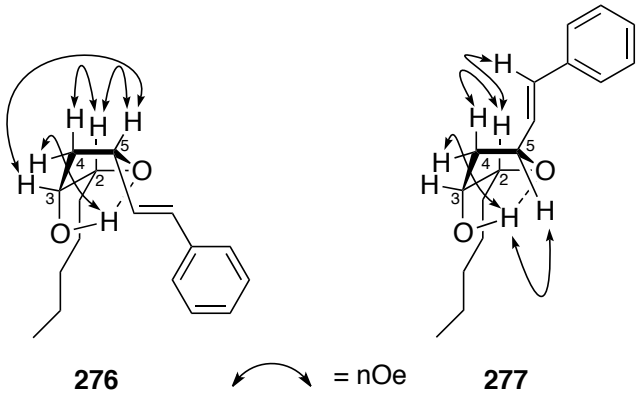
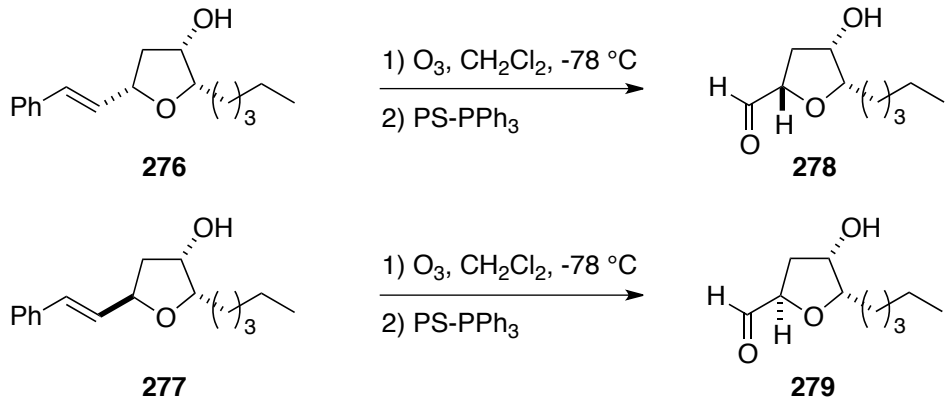


Figure 3.2 **Key nOe correlations observed for styryl-tetrahydrofurans 276 and 277.**

3.2.3. Preparation of Tetrahydrofurfurals 278 and 279

Oxidative cleavage of the alkene function in **276** with ozone and reductive workup with triphenylphosphine afforded tetrahydrofurfural **278** (Scheme 3.5). Unfortunately crude mixtures of **278** were found to readily decompose on silica gel. In an effort to remove triphenylphosphine oxide formed during reductive workup, polymer-supported triphenylphosphine was employed. Furthermore, it was found that stirring the reaction following the addition of the reducing agent led to a reduction in the purity of **278**, and complicated the filtration process. Therefore, addition of polymer-supported triphenylphosphine was followed by agitation on a wrist-action shaker[202] for one hour, at which time the mixture was filtered to give crude **278** that was used without further purification. Subjecting tetrahydrofuran **277** to an analogous set of reaction conditions led to the epimeric tetrahydrofurfural **279**.



Scheme 3.5 **Synthesis of tetrahydrofurfurals 278 and 279.**

3.2.4. Inverse Temperature Dependant Addition of Grignard Reagents to the Tetrahydrofurfural 278

The final step in the syntheses of both marine oxylipids **258** and **259** involved the addition of 8-nonenyl magnesium bromide to an unprotected 3-hydroxytetrahydrofurfural (e.g., **278** and **279**, Figure 3.3). During the optimisation of these processes we observed a remarkable example of inverse temperature dependence in the diastereoselective addition of Grignard reagents to tetrahydrofurfurals. The discovery of this inverse temperature dependent reaction, as well as mechanistic insights based on Kohn-Sham hybrid B3LYP calculations are described below.

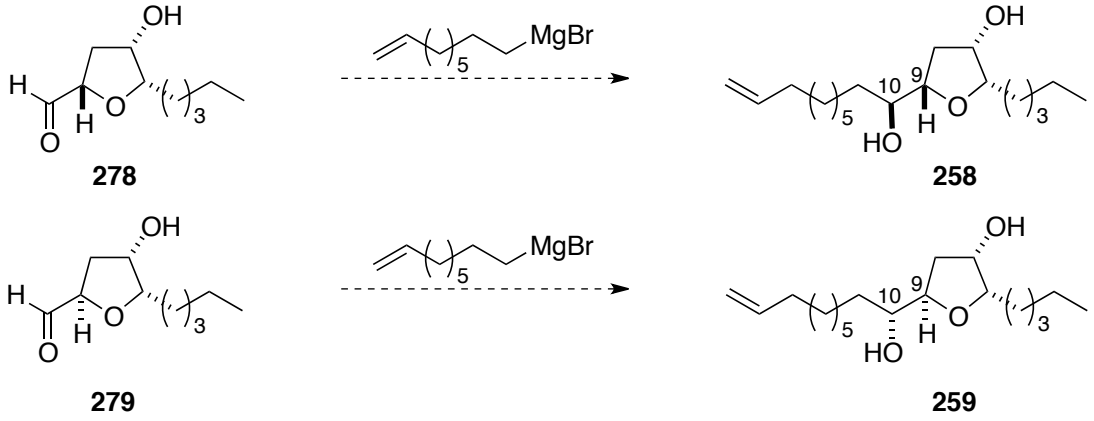
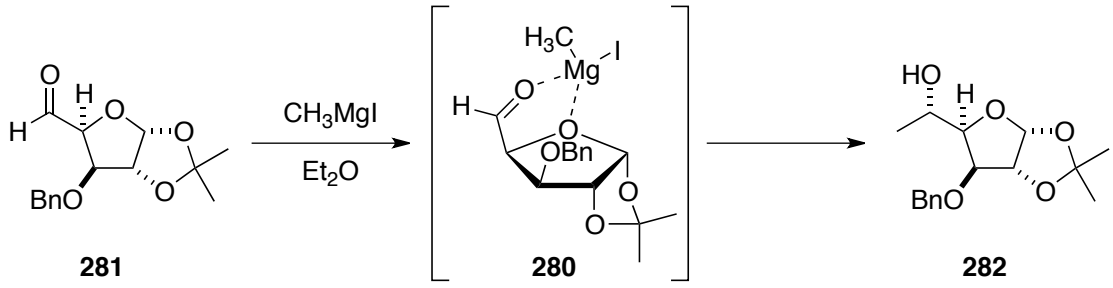


Figure 3.3 **Diastereoselective Grignard addition in the final step of the syntheses of marine oxylipids 258 and 259.**

The addition of organometallic reagents to tetrahydrofurfurals is a common method to access a host of tetrahydrofuran based natural products including the marine

oxylipids **258** and **259**. The diastereochemical outcome of these addition reactions are often rationalised by cyclic chelate models (e.g., **280**) similar to that originally proposed by Wolfrom and Hanessian[203] for the addition of methyl magnesium iodide to the protected dialdose **281** (Figure 3.4). In this latter instance, it was reasoned that coordination between the Grignard reagent and both the carbonyl and tetrahydrofuran ring oxygen directs nucleophilic attack to the less hindered *si* face of the aldehyde to provide **282** selectively. However, there are a number of exceptions to this model, and as a result, a thorough screen of both solvents[204,205] and organometallic reagents[204–207] is often required to optimise the diastereoselectivity of these processes.[208] The addition of organometallic reagents to oxygenated tetrahydrofurfurals (e.g., **281**) is further complicated by additional coordination sites, and consequently both the relative configuration[206] and choice of protecting group[207] for the oxygen substituents on the tetrahydrofuran ring play key roles in determining the degree and direction of stereoselection.



281 **280** **282**

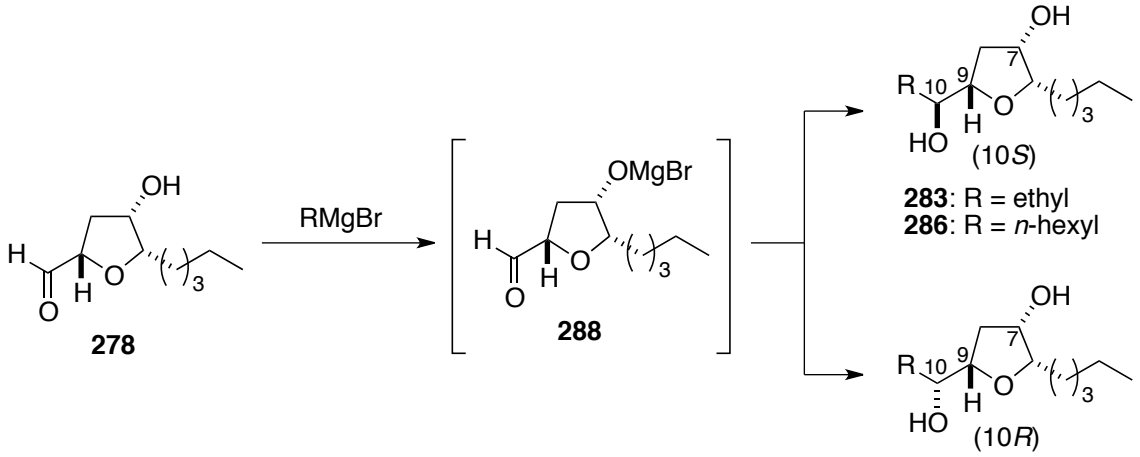
Figure 3.4 **Chelation model 280 for diastereoselective Grignard additions to tetrahydrofurfural 281.**

3.2.4.1. Diastereoselective Addition of Grignards to Tetrahydrofurfural 278 and 279

While the chelation model (e.g., **280**) predicts that addition of 8-nonenyl magnesium bromide to **278** would provide the desired 10*S* diastereomer **258**, we were aware that a similar reaction carried out on a protected analogue (i.e., **278**, OH = OBn) in THF affords a 4:1 mixture of diastereomeric alcohols favouring the undesired *R* configuration at C10.[193] Bearing this in mind, we set out to explore this process on the previously synthesised unprotected tetrahydrofurfural **278**, and focused our initial efforts on addition reactions involving EtMgBr. As summarized in Table 3.1, we observed a pronounced relationship between solvent and diastereoselectivity for this reaction. For

example, while the addition was non-selective in THF, the production of one diastereomer was favoured in non-coordinating solvents (entries 1-3).[209,210] Each of the reactions described in entries 1-3 were sluggish at -78 °C and were consequently allowed to gradually warm to room temperature to ensure complete consumption of the aldehyde **278**.

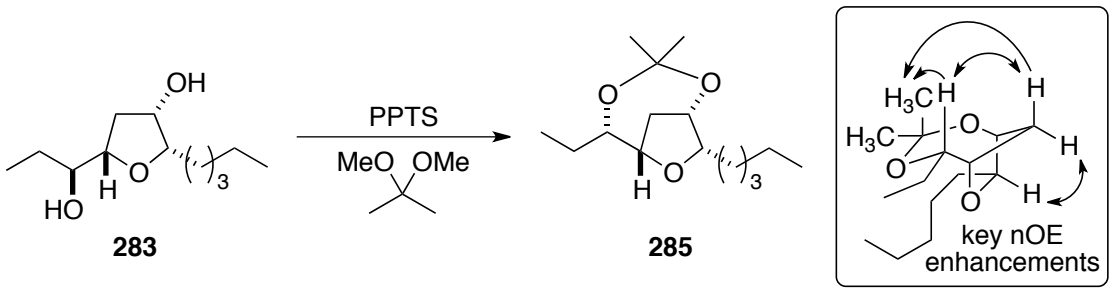
Table 3.1 Addition of Grignard Reagents to Aldehyde 278



entry	R	solvent	temp (°C)	products (ratio)[a]	% yield[b]
1	ethyl	THF	-78 to 20	**283**:**284** (1:1)	57
2	ethyl	$PhCH_3$	-78 to 20	**283**:**284** (2:1)	62
3	ethyl	CH_2Cl_2	-78 to 20	**283**:**284** (3.3:1)	67
4	ethyl	CH_2Cl_2	-40	**283**:**284** (1.3:1)	nd[c]
5	ethyl	CH_2Cl_2	-35	**283**:**284** (2:1)	42[d]
6	ethyl	CH_2Cl_2	20	**283**:**284** (5:1)	52
7	ethyl	DCE	20	**283**:**284** (5:1)	52
8	ethyl	DCE	20[e]	**283**:**284** (1:1)	nd[f]
9	ethyl	DCE	20[g]	**283**:**284** (5:1)	nd[f]
10	ethyl	DCE	40	**283**:**284** (5.1:1)	nd[f]
11	ethyl	DCE	60	**283**:**284** (5.8:1)	nd[f]
12	ethyl	DCE	83	**283**:**284** (8:1)	70
13	*n*-hexyl	DCE	40	**286**:**287** (3.6:1)	nd[f]
14	*n*-hexyl	DCE	83	**286**:**287** (8:1)	73

[a] ratio determined from analysis of ^{1}H NMR spectra of crude reaction mixtures. [b] combined isolated yield of both diastereomers over two steps from **276**. [c] after 20 hours the reaction had reached 60% conversion. [d] after 17 hours the reaction had reached 55% conversion. [e] 10 equivalents of 15-crown-5 was added. [f] yield not determined. [g] 10 equivalents of $MgBr_2$ was added.

The diastereomeric alcohols **283** and **284** proved to be separable by chromatography, and the major product from the reaction carried out in CH_2Cl_2 (entry 3) was converted to the corresponding acetonide **285** (Scheme 3.6). As indicated (see inset), a series of 1D nOe experiments carried out on this conformationally rigid acetonide permitted unambiguous assignment of the relative configuration of the newly formed carbinol chirality centre as 10*S*. Furthermore, in the ^{1}H NMR spectrum of **283** and **284** the protons at C10 resonate at δ 3.40 and δ 3.76 ppm, respectively. These chemical shift values are consistent with those reported for *threo* and *erythro* diastereomers of α-substituted 2-tetrahydrofuranmethanols.[211,212] Consequently, the major diastereomer produced from the addition of EtMgBr to the aldehyde **278** in CH_2Cl_2 (entry 3) was confidently assigned as the 10*S* diastereomer **283**.



Scheme 3.6 Synthesis of acetonide 285 and key nOe analysis.

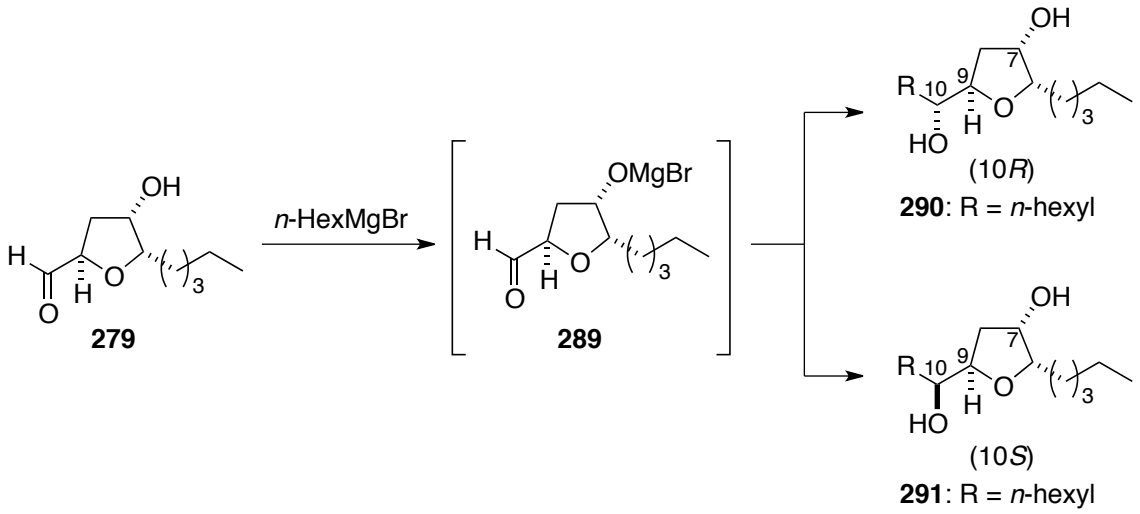
Surprisingly, repetition of the reaction described in entry 3 (Table 3.1) at -40 or -35 °C led to an erosion in diastereoselectivity, while at room temperature in either CH_2Cl_2 or DCE, the stereoselectivity was restored (entries 4-7). Addition of 15-crown-5 caused a significant decrease in the diastereomeric ratio, but $MgBr_2$ had little effect (entries 8 and 9), highlighting the importance of chelation in directing the Grignard addition to the *si* face of the aldehyde. Remarkably, further increases to the reaction temperature resulted in increased selectivity for the desired 10*S* diastereomer **283** (entries 10-12). In fact, in DCE at reflux (83 °C), **283** was produced[213–215] as the major component of an 8:1 mixture of diastereomers.[216,217] Notably, when a solution of **283** and **284** (8:1 mixture) in DCE was treated with EtMgBr and heated at reflux for 1 hour, there

was no change in the ratio of these substances. This result indicates that the diastereoselectivities summarized in Table 3.1 are not the result of a selective decomposition of **284** under the reaction conditions. A similar trend was observed using *n*-hexylmagnesium bromide in DCE leading to the diastereomeric alcohols **286** and **287** (entries 13 and 14).

On the basis of the results summarized in Table 3.1, it is clear that the formation of the 10*S* diastereomers **283**, and **286** are favoured in polar, non-coordinating solvents, consistent with a chelation-controlled addition.[218,219] Unfortunately, a series of ^{1}H NMR spectra recorded on a mixture of EtMgBr and **278** in CD_2Cl_2 at various temperatures (-50 °C to r.t.) failed to offer any additional insight into this unusual process. However, it is worth considering the nature of the Grignard reagent and the structure and solvation of the intermediate magnesium alkoxide **288** generated by deprotonation of the alcohol function in the tetrahydrofurfural **278**. More specifically, as the reaction temperature is decreased, a shift in the Schlenk equilibrium[220] that favours a more reactive[221] Et_2Mg species may account for the poor diastereocontrol. To test this theory, a commercially available solution of Bu_2Mg in heptane was added to **278** in DCE at room temperature and provided a 1.3:1 mixture of diastereomeric alcohols favouring the 10*S* diastereomer in low yield. Alternatively, temperature-dependent changes in the solvation and/or aggregation of the magnesium alkoxide **288** may account for the associated changes in diastereoselectivity.

Interestingly, as shown in Table 3.2, the stereoselective addition of *n*-hexylmagnesium bromide to the C9-epimeric trans-aldehyde **279** showed little dependence on solvent or temperature, suggesting the *cis*- relationship between the aldehyde and hydroxyl group in **278** is key to the temperature-dependent diastereoselectivity.

Table 3.2 Addition of Grignard Reagents to Aldehyde 279



entry	solvent	temp (°C)	products (ratio)[a]
1	THF	20	**290**:**291** (1.5:1)
2	Et_2O	20	**290**:**291** (1.8:1)
3	CH_2Cl_2	20	**290**:**291** (2.1:1)
4	DCE	40	**290**:**291** (2.3:1)
5	DCE	60	**290**:**291** (2.5:1)
6	DCE	83	**290**:**291** (2.4:1)

[a] ratio determined from analysis of ^{1}H NMR spectra of crude reaction mixtures.

3.2.4.2. DFT Calculations

Considering the diversity of factors[222–239] that may contribute to the results summarized in Table 3.1 and our incomplete understanding of the addition of organometallic reagents to oxygenated tetrahydrofurfurals (vide supra), we were intrigued as to whether or not DFT calculations would provide insight into the role played by the 3-hydroxy group in these reactions. Accordingly, Prof. Travis Dudding and Mr. Branden Fonovic (Brock University) initiated computations of the lowest energy first-order saddle points *pro*-(*S*)-**TS1** ($\Delta\Delta G$ = 0 kcal/mol) and *pro*-(*R*)-**TS1** ($\Delta\Delta G$ = 1.41 kcal/mol) that correspond to stereofacial additions of CH_3MgBr to the magnesium alkoxide derived from a *cis*-3-hydroxytetrahydrofurfural at the B3LYP/6-21G(d) level using the Gaussian 03 suite of programs (Figure 3.5).

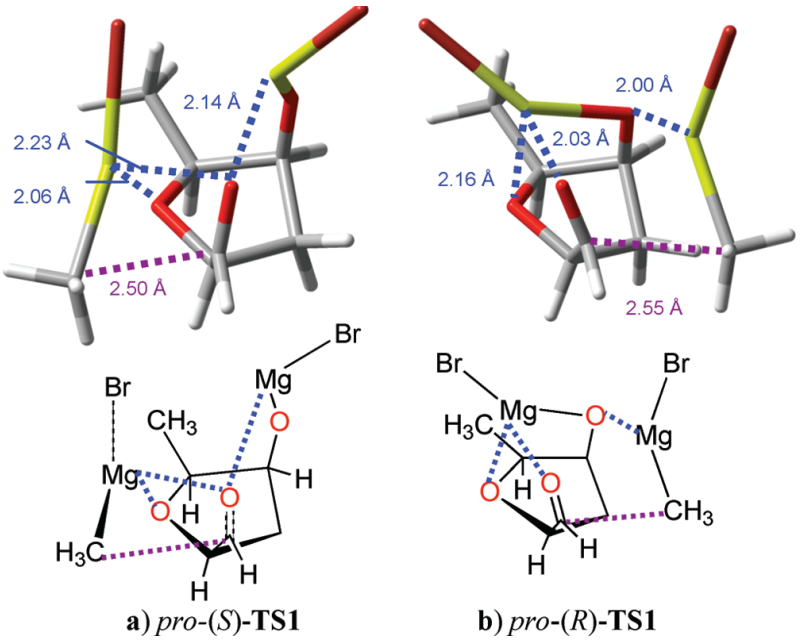


Figure 3.5 **Lowest energy transition structures corresponding to (a) *pro*-(*S*) and (b) *pro*-(*R*) additions of CH_3MgBr to the magnesium alkoxide of a *cis*-3-hydroxyetrahydrofurfural.**

As indicated in Figure 3.5, an intricate network of chelation modes was found in both transition structures that involved a γ-chelate between the magnesium alkoxide and the aldehyde oxygen measured at 2.14 Å in *pro*-(*S*)-**TS1** and 2.03 Å in *pro*-(*R*)-**TS1**. This chelation mode effectively locks the aldehyde and tetrahydrofuran oxygens in a *synclinal* orientation in *pro*-(*S*)-**TS1** (-54.0°) and a *synperiplanar* orientation in *pro*-(*R*)-**TS1** (-15.1°). Beyond the similarity of this γ-chelate, however, the two first-order saddle points were decidedly different. For example, a cyclic chelation mode consistent with **280**[203] (Figure 3.4) was found in *pro*-(*S*)-**TS1**, whereas *pro*-(*R*)-**TS1** contained a hybrid-type α/γ-chelate involving the aldehyde and tetrahydrofuran oxygens and the magnesium alkoxide, as well as an interaction between the magnesium alkoxide oxygen and the second equivalent of CH_3MgBr. Importantly, the calculated energetics correctly predict preferential formation of the 10*S* diastereomer (theoretical d.r. = 7.3:1, experimental d.r. = 8:1) and highlight the key role played by the magnesium alkoxide function in the low energy transition structure *pro*-(*S*)-**TS1**.

The low energy transition structures *pro*-(*R*)-**TS2** (ΔΔG = 0 kcal/mol) and *pro*-(*S*)-**TS2** (ΔΔG = 0.96 kcal/mol) (Figure 3.6), corresponding to CH_3MgBr addition to a *trans*-3-

hydroxytetrahydrofurfural, were also calculated. As a result of the positioning of the magnesium alkoxide and aldehyde functions on opposite faces of the tetrahydrofuran ring, these transition structures differed significantly from those discussed above (Figure 2). Notably, both *pro*-(*R*)-**TS2** and *pro*-(*S*)-**TS2** share nearly identical geometries, and both first-order saddle points possessed a chelate between the magnesium alkoxide and tetrahydrofuran oxygen and a cyclic five-membered ring coordination motif consistent with that proposed by Wolfrom and Hanessian (Figure 3.4).[203] Indeed, aside from the obvious facial selectivity of the Grignard reagent, the only major difference between these structures was the presence of a single van der Waals contact (2.32 Å) in *pro*-(*S*)-**TS2** associated with approach of CH_3MgBr from underneath the tetrahydrofuran ring. Again, these calculations correctly predict the preferential formation of the 10*R* diastereomer (theoretical d.r. = 3.9:1, experimental d.r. = 2.3:1), which is consistent with the sense and relative magnitude of diastereoselectivity observed in the addition of Grignard reagents to the *trans*-tetrahydrofurfural **279**.

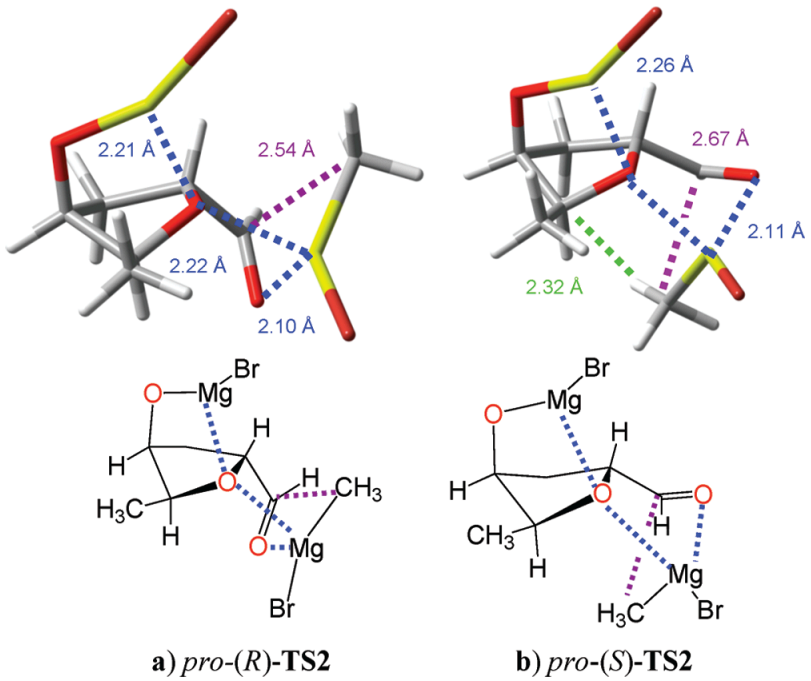
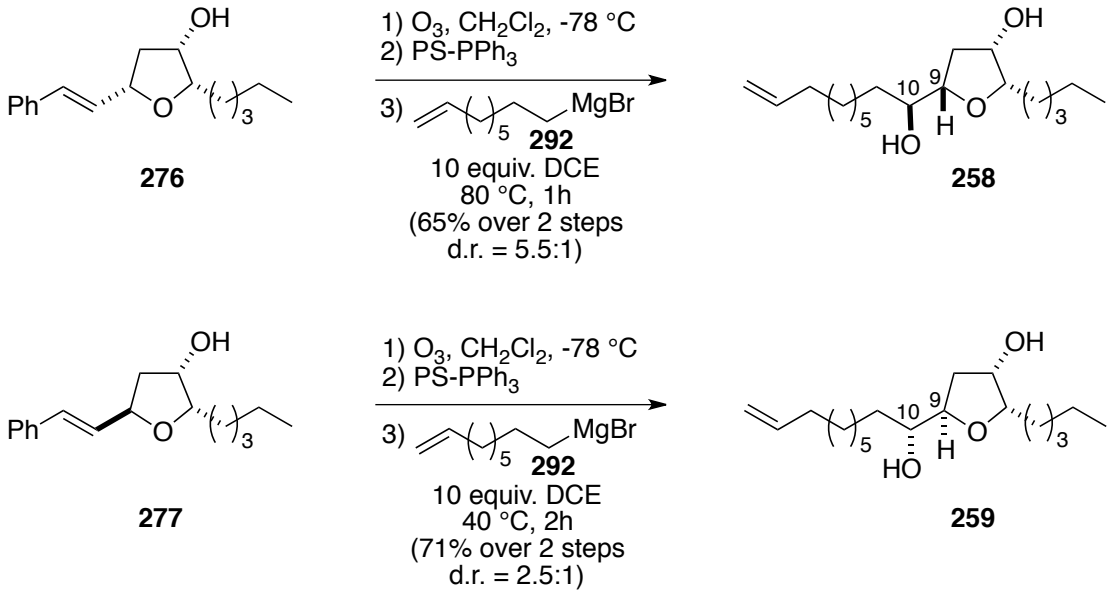


Figure 3.6 **Lowest energy transition structures corresponding to (a) *pro*-(*S*) and (b) *pro*-(*R*) additions of CH_3MgBr to the magnesium alkoxide of a *trans*-3-hydroxyetrahydrofurfural.**

3.2.5. Completion of the Total Synthesis of the Marine Oxylipids from *Notheia Anomala*

With an optimised set of conditions for the diastereoselective addition of Grignard reagents to tetrahydrofurfurals, we focused our efforts on the completion of the total synthesis of the *N. anomala* oxylipids. As depicted in Scheme 3.7, oxidative cleavage of the alkene function in **276** with ozone followed by reductive workup with polymer-supported triphenylphosphine (PS-PPh_3) and filtration provided the crude aldehyde **278**. Direct reaction of **278** with an excess of 8-nonenylmagnesium bromide (**292**)[240] in DCE at reflux provided (+)-**258** and its C10 epimer **293** as a separable 5.5:1 mixture of diastereomers. A similar sequence of reactions carried out on the tetrahydrofuran **277** afforded the C9/C10 epimeric natural product (+)-**259** and its C10 epimer **294** (d.r. = 2.5:1). The spectral data derived from these substances were in complete agreement with those reported in the literature (Figure 3.7).[193,196]



Scheme 3.7 **Synthesis of marine oxylipids 258 and 259.**

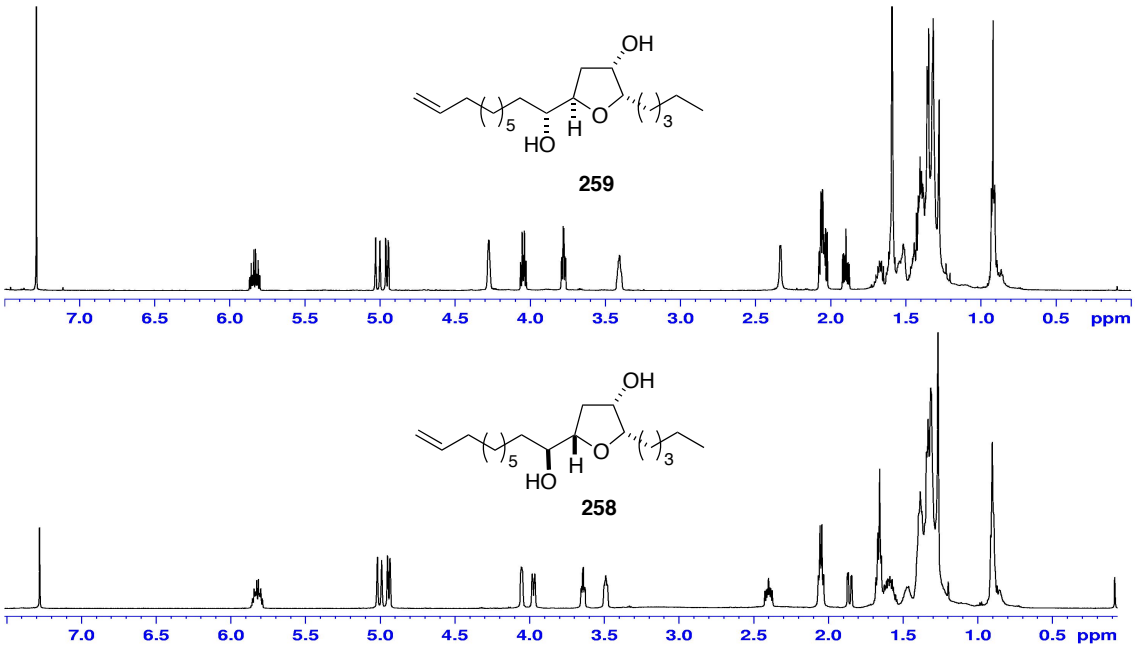


Figure 3.7 **^{1}H NMR spectrum of marine oxylipids 258 and 259 recorded at 600 MHz in $CDCl_3$.**

3.3. Conclusion

In conclusion, we have applied newly developed methods for the synthesis of 2,5-disubstituted-3-hydroxy-tetrahydrofurans to concise syntheses of the anthelmintic marine oxylipids **258** and **259**. The key features of this strategy involved the syntheses of two diastereomeric styryl-substituted tetrahydrofurans through a silver mediated cyclisation of two chlorodiols, which in turn were derived from a single aldol-adduct. Additionally, a remarkable example of inverse-temperature-dependent diastereoselectivity was observed while investigating the addition of Grignard reagents to a 3-hydroxytetrahydrofurfural in the final step of the synthesis. Notably, the optimised conditions for this process involve the addition of Grignard reagent to a solution of the tetrahydrofurfural **278** in DCE at reflux. While a temperature-dependent shift in the Schlenk equilibrium or change in solvation of the intermediate magnesium alkoxide may play an important role in this unusual process, it is clear that the *cis*-relationship between the alcohol and aldehyde functions on the tetrahydrofuran ring is paramount. Furthermore, on the basis of DFT calculations, a γ-chelate between the magnesium alkoxide and the aldehyde oxygen and an entropic preference for the *pro*-(*S*)-transition structure serve as the key factors responsible for the observed diastereoselectivity. Notably, the overall yield for **258** (37%) and **259** (26%) from heptanal and the total number of synthetic steps (6) required, compare very well with the reported asymmetric syntheses of these substances.

3.4. Experimental

General

All reactions described were performed under an atmosphere of dry argon using oven-dried glassware. Tetrahydrofuran, and dichloromethane were used directly from an MBraun Solvent Purifier System (MB-SP Series), and dichloroethane (DCE) was dried by distillation over CaH_2. Cold temperatures were maintained by the use of following reaction baths: -78 °C, acetone-dry ice; temperatures between -40 °C to -20 °C were maintained with a Polyscience VLT-60A immersion chiller. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[174] Thin layer chromatography was carried out on commercial

aluminum backed silica gel 60 plates (E. Merck, type 5554, thickness 0.2 mm). Visualization of chromatograms was accomplished using ultraviolet light (254 nm) followed by heating the plate after staining with one of the following solutions: (a) *p*-anisaldehyde in sulphuric acid-ethanol mixture (5% anisaldehyde v/v and 5% sulphuric acid v/v in ethanol); (b) 1% potassium permanganate w/v, 6.6% potassium carbonate w/v, and 1% v/v 10% sodium hydroxide in water. Concentration and removal of trace solvents was done via a Büchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Gas chromatography (GC) analysis was performed on a Hewlett Packard model 5890 gas chromatograph, equipped with a flame ionisation detector and a Cyclosil-B chiral column (30 m length, 0.320mm ID, 0.25um film).

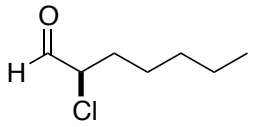
NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Varian Inova 500 (500 MHz), or Varian MercuryPlus (400 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (150 MHz) or Varian Inova 500 (125 MHz). Assignments of 1H and 13C NMR spectra are based on analysis of 1H-1H COSY, HMBC, HMQC and nOe spectra.

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

Chemical ionisation (CI) mass spectra were recorded on a Varian 4000 mass spectrometer at 70 eV. High resolution fast atom bombardment (HR-FABMS) mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer at 3 kV.

Optical rotation was measured on a Perkin Elmer Polarimeter 341.

Preparation of (2*R*)-2-chloroheptanal (271).



To a cold (0 °C), stirred solution of heptanal (11.42 g, 100 mmol) in dichloromethane (200 mL), was added L-prolinamide (1.14 g, 10 mmol) and *N*-chlorosuccinimide (13.35 g, 100 mmol). The reaction mixture was stirred for 1 hour and then allowed to slowly warm to room temperature over the course of 3 hours at which temperature it was stirred until complete consumption of heptanal (as determined by ^{1}H NMR spectroscopy). After this time, the mixture was diluted with pentane (200 mL), cooled to -78 °C, filtered through a fritted funnel, and concentrated on a rotary evaporator. The resulting oil was distilled under vacuum (1 mm Hg) at 40 °C to give (2*R*)-2-chloroheptanal (**271**) (14.2 g, 96% yield, 84% ee) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.49 (d, 1H, J = 2.4 Hz), 4.16 (ddd, 1H, J = 2.4, 5.4, 8.2 Hz), 1.97 (m, 1H), 1.82 (m, 1H), 1.57-1.41(m, 2H), 1.32 (m, 4H), 0.90 (t, 3H, J = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 195.6, 64.2, 32.2, 31.3, 25.4, 22.6, 14.1.

IR (neat): 2961, 2935, 2874, 1708, 1466, 1380, 1149, 1096 cm^{-1}

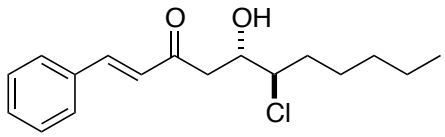
Exact mass calculated for $C_7H_{14}ClO$: 149.0733 (M+H); found: 149.0670 (M+H).

$[\alpha]_D^{25}$: 23.4° (c = 1.51, $CHCl_3$)

The enantiomeric excess of **271** was determined by chiral GC analysis of the epoxide derived from reduction and subsequent epoxidation of **271**. A solution of (2*R*)-2-chloroheptanal (**271**) (149 mg, 1 mmol) and sodium borohydride (76 mg, 2 mmol) in methanol (15 mL) was stirred at room temperature for 1 hour. The reaction mixture was treated with water (5 mL) and diluted with diethyl ether (15 mL) and the phases were separated. The organic phase was dried ($MgSO_4$) and concentrated to afford the corresponding alcohol. To the alcohol (25 mg, 0.18 mmol) in ethanol (3 mL) was added potassium hydroxide (15 mg, 0.26 mmol) and the reaction mixture was stirred for 1 hour. The resulting yellow solution was then diluted with pentane (10 mL) and washed with

brine (10 mL), dried ($MgSO_4$) and concentrated to afford (2*S*)-1,2-epoxyheptane. (Temperature program: 30 °C held for 35 minutes then increased by 5 °C per minute to 80 °C and run for 10 minutes. Retention time = 32.0 ((*R*)-enantiomer); 32.5 ((*S*)-enantiomer). $[\alpha]_D^{25}$: -9.2° (c = 1.0, $CHCl_3$) (lit. $[\alpha]_D^{25}$: -9.46° (c = 0.43, $CHCl_3$))[241]

Preparation of (1*E*,5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylundec-1-en-3-one (273).



To a cold (-78 °C), stirred solution of diisopropylamine (2.7 ml, 19.5 mmol) in tetrahydrofuran (100 mL) was added *n*-butyllithium (2.6 M in hexane, 7.5 mL 19.5 mmol). This solution was stirred for 45 minutes at -78 °C, warmed to 0 °C for 15 minutes and then cooled to -78 °C. To this solution was added a solution of *trans*-4-phenyl-3-buten-2-one (2.2 g, 15.0 mmol) in tetrahydrofuran (5 mL), and the resulting mixture was stirred for 45 minutes at -78 °C, warmed to -40 °C for 15 minutes and then cooled to -78 °C. After this time (2*R*)-2-chloroheptanal (**271**) (2.67 g, 18.0 mmol) in tetrahydrofuran (10 mL) was added dropwise over 12 minutes and the reaction mixture was stirred for 1 hour at -78 °C then treated with a saturated aqueous solution of ammonium chloride (15 mL) and allowed to warm to room temperature. The resulting mixture was diluted with ether (100 mL) and the phases were separated. The aqueous phase was extracted with ether (3 x 25 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give the crude chlorohydrin. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*E*,5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylundec-1-en-3-one (**273**) (3.90 g, 93%) as a white solid (m.p. = 51-53 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.61 (d, 1H, *J* = 16.1 Hz), 7.57 (m, 2H), 7.41 (m, 3H), 6.76 (d, 1H, *J* = 16.1 Hz), 4.21 (m, 1H), 3.98 (ddd, 1H, *J* = 3.1, 6.2, 9.4 Hz), 3.52 (d, 1H, *J* = 4.8 Hz), 3.12 (dd, 1H, *J* = 2.8, 17.4 Hz), 3.03 (dd, 1H, *J* = 8.5, 17.4 Hz) 1.95 (m, 1H), 1.70 (m, 1H), 1.63 (m, 1H), 1.42 (m, 1H), 1.33 (m, 4H), 0.90 (t, 3H, *J* = 7.0 Hz).

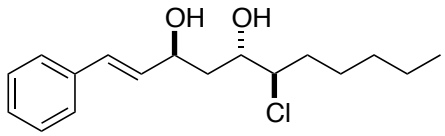
^{13}C NMR (150 MHz, $CDCl_3$) δ: 200.5, 144.3, 134.3, 131.1, 129.3, 128.7, 126.4, 71.4, 66.3, 43.0, 34.1, 31.5, 26.2, 22.7, 14.2.

IR (thin film): 3424, 2950, 2923, 2860, 1659, 1449, 1380, 1177, 1073 cm^{-1}

Exact mass calculated. for $C_{17}H_{24}ClO_2$: 295.1465 (M+H); found: 295.1468 (M+H).

$[\alpha]_D^{25}$: -11.1° (c= 1.51, CHCl3).

Preparation of (1*E*,3*S*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (274).



A solution of tetramethylammonium triacetoxyborohydride (714 mg, 2.7 mmol) dissolved in a 1:1.5 mixture of glacial acetic acid: acetonitrile (25 mL) was stirred at room temperature for 30 minutes and then cooled to -40 °C, (1*E*,5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylundec-1-en-3-one (**273**) (100 mg, 0.34 mmol) was added as a solution in acetonitrile (5 mL) and the resulting mixture was stirred for 24 hours at -40 °C. After this time, a saturated aqueous solution of sodium tartrate (10 ml) was slowly added and the reaction mixture was diluted with ethyl acetate (20 ml) and washed with brine (10 ml). The aqueous phases were extracted with ethyl acetate (4 x 15 ml) and the combined organic phases were dried ($MgSO_4$) and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*E*,3*S*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**274**) (98 mg, 98%, d.r. = 10:1) as a white solid (m.p. = 88-90°C).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 (d, 2H, *J* = 7.5Hz), 7.33 (t, 2H, *J* = 7.4 Hz), 7.25 (t, 1H, *J* = 7.3 Hz), 6.65 (d, 1H, *J* = 15.9 Hz), 6.28 (dd, 1H, *J* = 6.1, 15.9 Hz), 4.69 (m, 1H), 4.09 (dddd, 1H, *J* = 2.3, 4.6, 6.5, 9.1 Hz), 4.02 (m, 1H), 2.75 (dd, 1H, *J* = 1.4, 6.5 Hz), 2.33 (m, 1H), 1.97 (m, 1H), 1.85-1.79 (m, 2H), 1.73-1.58 (m, 2H), 1.43-1.24 (m, 5H), 0.90 (t, 3H, *J* = 7.0 Hz).

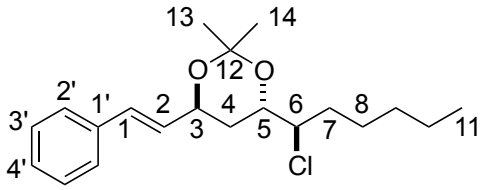
^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.7, 131.8, 130.5, 128.9, 128.0, 126.7, 72.0, 70.3, 68.4, 38.7, 33.4, 31.5, 26.5, 22.7, 14.2.

IR (thin film): 3406, 2955, 2927, 1646, 1049, 967 cm^{-1}

Exact mass calculated. for $C_{17}H_{26}ClO_2$: 297.1621 (M+H); found: 297.1614 (M+H).

The relative stereochemistry of the newly formed carbinol stereocentre was determined by analysis of the ^1H and ^{13}C NMR spectra derived from the corresponding acetonide.

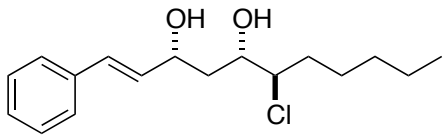
To a stirred solution of the diol (**274**) (10 mg, 0.034 mmol) in 2,2-dimethoxypropane (3 mL) at room temperature was added 2 drops of concentrated hydrochloric acid. After 4 hours, the reaction mixture was treated with a saturated aqueous solution of sodium bicarbonate (5 mL), diluted with diethyl ether (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 5 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in dichloromethane and passed through a short plug of silica gel to afford the acetonide.



^1H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.6 Hz, H-2'), 7.31 (t, 2H, *J* = 7.4 Hz, H-3'), 7.23 (tt, 1H, *J* = 1.1, 7.4 Hz, H-4'), 6.58 (d, 1H, *J* = 15.8 Hz, H-1), 6.23 (dd, 1H, *J* = 6.2, 15.8 Hz, H-2), 4.52 (m, 1H, H-3), 3.95 (td, 1H, *J* = 6.5, 8.7 Hz, H-5), 3.89 (m, 1H, Hz, H-6), 2.01 (m, 2H, H-7), 1.89 (m, 1H, H-4), 1.63 (m, 1H, H-4), 1.44 (s, 3H, H-13), 1.43 (s, 3H, H-14), 1.36 – 1.24 (m, 6H), 0.91 (t, 3H, *J* = 7.1 Hz, H-11).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.8 (C1'), 130.9 (C1), 129.6 (C2), 128.7 (C3'), 127.9 (C4'), 126.7 (C2'), 101.2 (C12), 69.6 (C5), 68.1 (C3), 65.8 (C6), 35.4 (C7), 34.1 (C4), 31.6, 25.9, 25.5 (C13), 24.9 (C14), 22.8, 14.2 (C11).

Preparation of (1*E*,3*R*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (275).



To a cold (-40 °C), stirred solution of (1*E*,5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylundec-1-en-3-one (**273**) (200 mg, 0.68 mmol) in dry tetrahydrofuran (5.5 mL) was added

catecholborane (1.0 M solution in tetrahydrofuran, 3.4 mL, 3.4 mmol). The reaction mixture was stirred for 24 hours then treated with a saturated aqueous solution of sodium tartrate (2 mL) and methanol (2 mL) and allowed to stir at room temperature for an additional 2 hours. The mixture was then diluted with diethyl ether (10 mL) and the phases were separated. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Excess catechol was removed by flash column chromatography (silica gel, 2:1:0.3 hexanes: dichloromethane: methanol) to provide the crude diol. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*E*,3*R*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**275**) (145 mg, 72%, d.r. = >20:1) as a white solid.

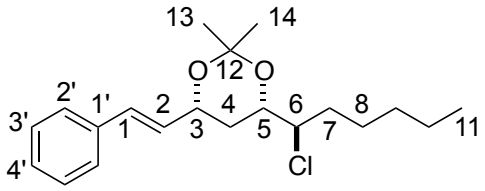
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.4 Hz), 7.32 (t, 2H, *J* = 7.4 Hz), 7.25 (t, 1H, *J* = 7.4 Hz), 6.63 (d, 1H, *J* = 16 Hz), 6.23 (dd, 1H, *J* = 6.7, 16 Hz), 4.58 (m, 1H), 4.01 (m, 1H), 3.93 (td, 1H, *J* = 3.5, 10.0), 3.36 (br. s, 1H), 2.97 (br. s, 1H), 1.92 (ddd, 1H, *J* = 2.3, 3.8, 14.5 Hz), 1.87-1.78 (m, 2H), 1.70 (m, 1H), 1.61 (m, 1H), 1.39 (m, 1H), 1.35 – 1.25 (m, 4H), 0.90 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.6, 131.5, 130.8, 128.8, 128.1, 126.7, 75.1, 73.3, 68.1, 39.3, 33.2, 31.5, 26.5, 22.7, 14.2.

IR (thin film): 3385, 2955, 2859, 1493, 1449, 967cm^{-1}

Exact mass calculated. for $C_{17}H_{26}ClO_2$: 297.1621 (M+H); found: 297.1640 (M+H).

The relative stereochemistry of the newly formed carbinol stereocentre was determined by analysis of the ^{1}H and ^{13}C NMR spectra derived from the corresponding acetonide.



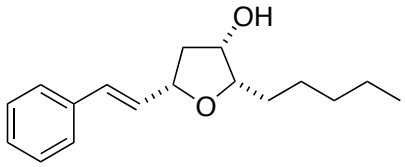
To a solution of the diol (**275**) (10 mg, 0.034 mmol) in 2,2-dimethoxypropane (3 mL) was added 2 drops of concentrated hydrochloric acid and the reaction mixture allowed to stir for 4 hours. After this time, the reaction mixture was treated with saturated aqueous

sodium bicarbonate (5 mL), diluted with diethyl ether (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 5 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in dichloromethane, passed through a short plug of silica gel and concentrated to afford the corresponding acetonide.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.2 Hz, H-2'), 7.30 (t, 2H, *J* = 7.4 Hz, H-3'), 7.23 (tt, 1H, *J* = 1.2, 7.4 Hz, H-4'), 6.62 (d, 1H, *J* = 15.9 Hz, H-1), 6.19 (dd, 1H, *J* = 6.3, 15.8 Hz, H-2), 4.54 (dddd, 1H, *J* = 1.1, 2.5, 6.3, 11.5 Hz, H-3), 3.92 (ddd, 1H, *J* = 2.3, 7.3, 11.3 Hz, H-5), 3.75 (m, 1H, H-6), 1.99 (td, 1H, *J* = 2.5, 12.9, H-7), 1.96 (m, 1H, H-4), 1.66 – 1.56 (m, 2H, H-4/H-8), 1.51 (s, 3H, H-13), 1.47 (s, 3H, H-14), 1.45–1.37 (m, 2H, H-7/H-8), 1.36 – 1.26 (m, 4H), 0.91 (t, 3H, *J* = 7.1 Hz, H-11).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.8 (C1'), 131.1 (C1), 129.8 (C2), 128.7 (C3'), 127.9 (C4'), 126.8 (C2'), 99.4 (C12), 72.0 (C5), 70.3 (C3), 65.7 (C6), 34.5 (C7), 33.7 (C4), 31.6, 30.2 (C13), 25.8, 22.7, 20.1 (C14), 14.2 (C11).

Preparation of (2S,3S,5S)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (276)



To a cold (0 °C), stirred solution of (1*E*,3*S*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**274**) (200 mg, 0.68 mmol) in tetrahydrofuran (15 mL) was added silver(I) oxide (274 mg, 1.36 mmol) and silver(I) trifluoromethanesulfonate (349 mg, 1.36 mmol). The resulting mixture was allowed to slowly warm to room temperature and stir for an additional 24 hours. After this time the reaction mixture was filtered through Celite®, diluted with diethyl ether (35 mL) and washed with saturated aqueous sodium bicarbonate (3 x 15 mL). The combined aqueous phases were extracted with diethyl ether (3 x 15 mL), and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (2*S*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**276**) (148 mg, 84%) as a white solid (m.p. = 63-65 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.2 Hz), 7.30 (t, 2H, *J* = 7.5 Hz), 7.23 (tt, 1H, *J* = 1.1, 7.2 Hz), 6.61 (d, 1H, *J* = 15.9 Hz), 6.31 (dd, 1H, *J* = 6.9, 15.9 Hz), 4.49 (m, 1H), 4.24 (m, 1H), 3.68 (dt, 1H, *J* = 2.3, 6.7 Hz), 2.52 (ddd, 1H, *J* = 5.9, 8.7, 14.2 Hz), 1.84 (ddd, 1H, *J* = 1.6, 5.6, 14.2), 1.77-1.65 (m, 2H), 1.57 (d, 1H, *J* = 7.4 Hz), 1.49 (m, 1H), 1.42 (m, 1H), 1.35 (m, 4H), 0.90 (t, 3H, *J* = 7.1 Hz).

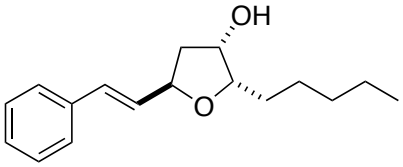
^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.5, 131.0, 130.8, 128.5, 127.6, 126.6, 83.7, 78.0, 73.2, 42.3, 32.0, 28.8, 26.0, 22.6, 14.0

IR (thin film): 3425, 2953, 2925, 2857, 1644, 1493, 1467, 1449, 1342, 1156, 1087 cm^{-1}

Exact mass calculated. for $C_{17}H_{24}O_2$: 260.1776 (M+); found: 260.1788 (M+).

$[\alpha]_D^{25}$: -11.8° (c: 8.0, $CHCl_3$).

Preparation of (2*S*,3*S*,5*R*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (277).



To a cold (0 °C), stirred solution of (1*E*,3*R*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**275**) (59 mg, 0.2 mmol) in tetrahydrofuran (3.6 mL) was added silver(I) oxide (46 mg, 0.2 mmol) and silver(I) trifluoromethanesulfonate (51 mg, 0.2 mmol). The resulting mixture was allowed to slowly warm to room temperature and stirred for an additional 48 hours. After this time the reaction mixture was filtered through Celite®, diluted with diethyl ether (25 mL) and washed with saturated aqueous sodium bicarbonate (3 x 15 mL). The combined aqueous phases were extracted with diethyl ether (3 x 15 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 4:1hexanes:ethyl acetate) afforded (2*S*,3*S*,5*R*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**277**) (40 mg, 77%) as a white solid (m.p. = 53-56 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.3 Hz), 7.30 (t, 2H, *J* = 7.5 Hz), 7.23 (tt, 1H, *J* = 1.2, 7.3 Hz), 6.58 (d, 1H, *J* = 15.8 Hz), 6.20 (dd, 1H, *J* = 7.1, 15.8 Hz), 4.83 (m,

1H), 4.31 (m, 1H), 3.92 (dt, 1H, *J* = 2.9, 6.9 Hz), 2.24 (ddd, 1H, *J* = 0.7, 6.4, 13.4 Hz), 1.98 (ddd, 1H, *J* = 4.5, 9.3, 13.4), 1.69 (m, 2H), 1.61 (m, 1H), 1.49 (m, 1H), 1.39 (m, 1H), 1.35 (m, 4H), 0.91 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.9, 130.8, 130.6, 128.7, 127.8, 126.7, 82.9, 77.8, 73.5, 42.6, 32.3, 29.3, 26.3, 22.8, 14.3.

IR (thin film): 3366, 2948, 2929, 2852, 1641, 1493, 1273, 1173, 1072 cm^{-1}

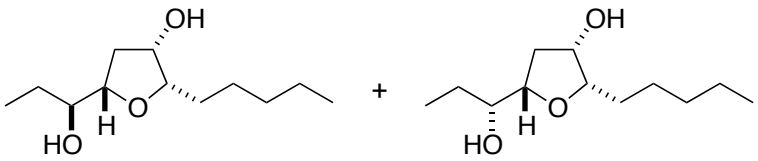
Exact mass calculated. for $C_{17}H_{24}O_2$: 260.1776 (M+); found: 260.1761 (M+).

$[\alpha]_D^{25}$: 21.0° (c = 1.0, $CHCl_3$).

General procedure for addition of Grignard reagents to tetrahydrofurfural (278).

To a stirred solution of aldehyde **278** in solvent (0.05 M), at the temperature specified in Table 3.1 was added alkyl magnesium bromide (10 equiv.). The resulting mixture was maintained at this temperature until complete consumption of starting material was achieved (unless otherwise noted). The reaction was then treated with water, diluted with diethyl ether, and the phases separated. The aqueous phase was extracted 3 times with diethyl ether and the combined organic layers were washed with brine, dried and concentrated to give the crude dihydroxytetrahydrofurans **283** and **284**, or **286** and **287**. Purification of the crude product was accomplished by flash chromatography.

Preparation of (3*S*,4*S*,6*S*,7*S*)-4,7-epoxydodec-3,6-diol (283) and (3*R*,4*S*,6*S*,7*S*)-4,7-epoxydodec-3,6-diol (284).



283 **284**

Into a cold (-78 °C), stirred solution of (2*S*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**276**) (50 mg, 0.19 mmol) in dichloromethane (5 mL) was bubbled ozone until the solution turned pale blue (~ 5 min). After this time, the reaction mixture was purged with nitrogen gas for 5 minutes to remove excess ozone. The reaction mixture was then

treated with polymer supported triphenylphosphine (3.0 mmol/g, 641 mg, 1.9 mmol) and shaken for 1 hour.[202] After this time, the mixture was filtered and the mother liquor was concentrated under high vacuum (1 torr) for 30 minutes to give the crude aldehyde **278**, which was used without further purification.

To a stirred solution of the aldehyde **278** in dichloroethane (3.5 mL) at 83 °C was added ethylmagnesium bromide (3.0 M solution in ether, 0.63 mL, 1.9 mmol) and the resulting mixture was maintained at this temperature for 1 hour. The reaction mixture was then treated with water (10 mL), cooled to room temperature, diluted with diethyl ether (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to give the crude dihydroxytetrahydrofurans **283** and **284** (d.r. = 8:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded a mixture of **283** and **284** (29 mg, 70% over 2 steps) as a clear oil. Separation of **283** and **284** by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (3*S*,4*S*,6*S*,7*S*)-4,7- epoxydodec-3,6-diol (**283**) and (3*R*,4*S*,6*S*,7*S*)-4,7-epoxydodec-3,6-diol (**284**) as clear oils.

Data for (3*S*,4*S*,6*S*,7*S*)-4,7-epoxydodec-3,6-diol (**283**):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.04 (dd, 1H, *J* = 2.5, 5.3 Hz), 3.99 (td, 1H, *J* = 2.6, 10.0 Hz), 3.61 (dt, 1H, *J* = 2.6, 6.9 Hz), 3.40 (dt, 1H, *J* = 2.1, 6.9 Hz), 3.18 (br. s, 1H), 2.39 (ddd, 1H, *J* = 5.5, 10.0, 14.2 Hz), 2.15 (br. s, 1H), 1.85 (dd, 1H, *J* = 3.4, 14.2 Hz), 1.67-1.60 (m, 6H), 1.41-1.31 (m, 4H), 1.00 (t, 3H, *J* = 7.4 Hz), 0.89 (t, 3H, *J* = 6.9 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 84.3, 78.5, 75.4, 71.5, 38.7, 32.0, 28.8, 27.3, 25.9, 22.6, 14.1, 10.5.

IR (thin film): 3369, 2956, 2928, 2856, 1462, 1378, 1290, 1186, 1139, 1090, 1063 cm^{-1}

Exact mass calculated. for $C_{12}H_{25}O_3$: 217.1804 (M+H); found: 217.1817 (M+H)

$[\alpha]_D^{25}$: +14.9° (c: 0.67, $CHCl_3$).

Data for (3*R*,4*S*,6*S*,7*S*)-4,7-epoxydodec-3,6-diol (**284**):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.03 (m, 2H), 3.76 (dt, 1H, J = 1.9, 6.8 Hz), 3.59 (dt, 1H, J = 2.5, 6.8 Hz), 3.27 (br. s, 1H), 2.42 (br. s, 1H), 2.19 (ddd, 1H, J = 5.4, 10.1, 14.4 Hz), 1.91 (dd, 1H, J = 3.4, 14.4 Hz), 1.68-1.64 (m, 2H), 1.43-1.28 (m, 8H), 0.98 (t, 3H, J = 7.5 Hz), 0.89 (t, 3H, J = 6.9 Hz)

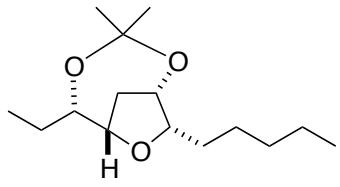
^{13}C NMR (150 MHz, $CDCl_3$) δ: 83.8, 79.6, 73.7, 71.2, 34.2, 32.0, 28.8, 26.3, 26.0, 22.6, 14.1, 10.4.

IR (thin film): 3384, 2976, 2939, 2867, 1454, 1388, 1282, 1197, 1114, 1040 cm^{-1}

Exact mass calculated. for $C_{12}H_{25}O_3$: 217.1804 (M+H); found: 217.1793 (M+H)

$[\alpha]_D^{25}$: +9.0° (c: 1.0, $CHCl_3$).

The relative stereochemistry of the newly formed carbinol stereocentre was determined by nOe analysis of the corresponding acetonide (Table 3.3).



285

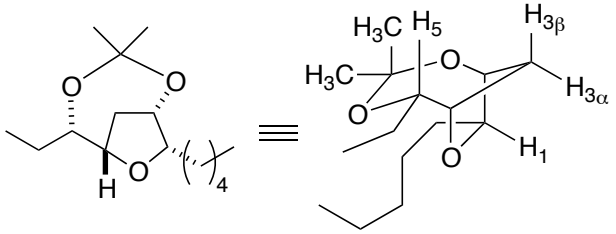
To a stirred solution of (3*S*,4*S*,6*S*,7*S*)-4,7-epoxydodec-3,6-diol (**283**) (10 mg, 0.046 mmol) in 2,2-dimethoxypropane (1 mL) at room temperature was added a crystal of pyridinium *p*-toluenesulfonate and molecular sieves. After 48 hours, the reaction mixture was treated with 1 drop of triethylamine, diluted with dichloromethane, passed through a small plug of silica gel and evaporated. Purification of the crude product by preparative TLC (silica gel, 3:1 hexanes:ethyl acetate) afforded acetonide **285** as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.31 (t, 1H, *J* = 4.6 Hz), 4.14 (d, 1H, *J* = 7.7 Hz), 3.82 (m, 1H), 3.39 (dd, 1H, *J* = 5.0, 8.4 Hz), 2.40 (d, 1H, *J* = 14.2 Hz), 2.13 (ddd, 1H, *J* = 5.2, 8.1, 14.2 Hz), 1.81-1.61 (m, 2H), 1.52 (s, 3H), 1.48 (s, 3H), 1.43-1.29 (m, 8H), 0.91 (t, 3H, *J* = 7.5 Hz), 0.88 (t, 3H, *J* = 6.9 Hz).

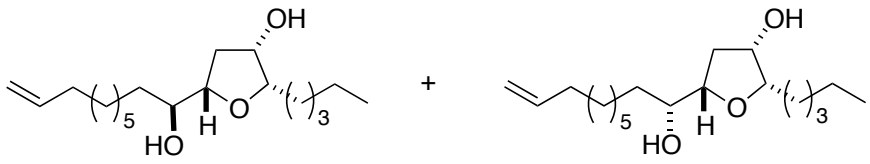
^{13}C NMR (150 MHz, $CDCl_3$) δ: 101.3, 85.5, 79.1, 76.6, 76.5, 35.5, 32.1, 32.0, 30.3, 26.0, 25.6, 25.5, 22.7, 14.1, 10.9.

Table 3.3 Selected nOe's observed for acetonide 285**.**

nOe Correlation	% nOe enhancement
$H_{3\beta}$-H_5	0.77
$H_{3\beta}$-CH_3	1.66
H_5-$H_{3\beta}$	0.59
H_5-CH_3	1.62
$H_{3\alpha}$-H_1	0.69
H_1-$H_{3\alpha}$	0.65



Preparation of (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-en-7,10-diol (258) and (6*S*,7*S*,9*S*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (293).



258 **293**

To a cold (-78 °C) stirred solution of (2*S*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**276**) (50 mg, 0.19 mmol) in dichloromethane (5mL) was bubbled ozone until the solution turned pale blue (~ 5 min). After this time, the reaction mixture was purged with nitrogen gas for 5 minutes to remove excess ozone. The reaction mixture was then treated with polymer supported triphenylphosphine (3.0 mmol/g, 641 mg, 1.9 mmol) and shaken for 1 hour.[202] After this time, the mixture was filtered and the mother liquor was concentrated under high vacuum (1 torr) for 30 minutes to give the crude aldehyde **278**, which was used without further purification.

To a stirred solution of the aldehyde **278** in dichloroethane (3.5 mL) at 83 °C was added 8-nonenylmagnesium bromide (**292**)[240] (0.4 M in ether, 4.8 mL, 1.9 mmol) and the resulting mixture was maintained at this temperature for 1 hour. The reaction mixture was then treated with water (10 mL), cooled to room temperature, diluted with diethyl ether (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (15

mL), dried ($MgSO_4$) and concentrated to give the crude dihydroxytetrahydrofurans **258** and its C10 epimer **293** (d.r. = 5.5:1 as determined by ^1H NMR spectroscopy). Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes:ethyl acetate) afforded a mixture of **258** and **293** (39 mg, 65% over 2 steps). Purification by flash chromatography (silica gel, 6:1 hexanes:ethyl acetate) afforded (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (**258**) as a white solid (m.p. = 32-35°C).

Data for (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-en-7,10-diol (**258**):

^1H NMR (600 MHz, $CDCl_3$) δ: 5.80 (tdd, 1H, *J* = 6.7, 10.2, 17.0 Hz), 4.99 (dd, 1H, *J* = 1.8, 17.0 Hz), 4.93 (dd, 1H, *J* = 1.8, 10.2 Hz), 4.03 (dd, 1H, *J* = 2.6, 5.3 Hz), 3.96 (td, 1H, *J* = 2.3, 9.9 Hz), 3.62 (dt, 1H, *J* = 2.6, 6.9 Hz), 3.47 (ddd, 1H, *J* = 2.2, 4.8, 7.3 Hz), 2.38 (ddd, 1H, *J* = 5.5, 10.0, 14.3), 2.03 (dd, 2H, *J* = 6.9, 14.2), 1.84 (dd, 1H, *J* = 3.4, 14.2Hz), 1.66-1.52 (m, 3H), 1.49-1.21 (m, 19H), 0.88 (t, 3H, *J* = 6.9 Hz).

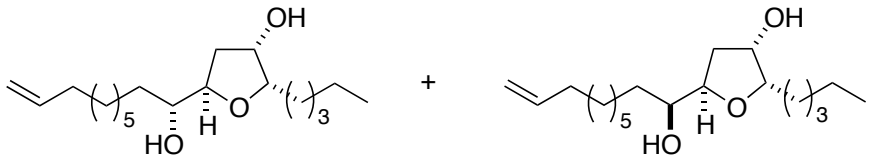
^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.2, 114.1, 84.3, 79.0, 73.9, 71.5, 38.7, 34.4, 33.8, 32.0, 29.5, 29.4, 29.0, 28.9, 28.7, 26.0, 25.9, 22.6, 14.0.

IR (thin film): 3387, 3077, 2927, 2855, 1641, 1465, 1377, 1289, 1184, 1129, 1090 cm^{-1}

Exact mass calculated. for $C_{19}H_{37}O_3$: 313.2743 (M+H); found: 313.2745 (M+H).

$[\alpha]_D^{25}$: +20.0° (c: 0.5, $CHCl_3$) (lit. $[\alpha]_D^{25}$: +24.3° (c: 0.3, $CHCl_3$)).[193]

Preparation of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (259) and (6*S*,7*S*,9*R*,10*S*)-6,9-epoxynonadec-18-en-7,10-diol (294).



259 **294**

To a cold (-78 °C), stirred solution of (2*S*,3*S*,5*R*)-2-pentyl-5-styryltetrahydrofuran-3-ol (**277**) (70 mg, 0.27 mmol) in dichloromethane (7 mL) was bubbled ozone until the solution turned pale blue (~ 5 min). After this time, the reaction mixture was purged with nitrogen gas for 5 minutes to remove excess ozone. The reaction mixture was then

treated with polymer supported triphenylphosphine (3.0mmol/g, 897 mg, 27.0 mmol) and shaken for 1 hour.[202] After this time, the mixture was filtered and the mother liquor was concentrated under high vacuum (1 torr) for 30 minutes to give the crude aldehyde **279**, which was used without further purification.

To a stirred solution of the aldehyde **279** in dichloroethane (5 mL) at 40 °C was added 8-nonenylmagnesium bromide (**292**)[240] (0.4 M solution in ether, 7 mL, 27.0 mmol) and the resulting mixture was maintained at this temperature for 2 hours. The reaction mixture was then treated with water (10 mL), diluted with diethyl ether (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to give the crude dihydroxytetrahydrofurans **259** and its C10 epimer **294** (d.r. = 2.5:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (**259**) (42 mg, 50% over 2 steps) as a white solid (m.p. = 51-54°C) and (6*S*,7*S*,9*R*,10*S*)-6,9-epoxynonadec-18-en-7,10-diol (**294**) (18 mg, 21% over 2 steps) as a white solid (m.p.= 71-73°C).

Data for (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (**259**):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.81 (tdd, 1H, *J* = 6.7, 10.2, 16.9 Hz), 4.99 (ddd, 1H, *J* = 1.9, 3.4, 16.9 Hz), 4.93 (dd, 1H, *J* = 1.9, 10.2 Hz), 4.25 (m, 1H), 4.02 (dt, 1H, *J* = 6.6, 9.0 Hz), 3.75 (dt, 1H, *J* = 2.7, 7.0 Hz), 3.38 (m, 1H), 2.31 (br. s, 1H), 2.05-2.00 (m, 3H), 1.88 (ddd, 1H, *J* = 4.6, 9.1, 13.5 Hz), 1.67-1.62 (m, 1H), 1.49-1.25 (m, 20H), 0.89 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.4, 114.4, 82.7, 80.4, 74.3, 73.7, 38.1, 34.0, 33.4, 32.2, 29.9, 29.6, 29.3, 29.1, 29.0, 26.2, 25.8, 22.8, 14.3.

IR (thin film): 3431, 2927, 2855, 1641, 1459, 1090cm^{-1}

Exact mass calculated. for $C_{19}H_{37}O_3$: 313.2743 (M+H); found: 313.2746 (M+H)

$[\alpha]_D^{25}$: 13.8° (c= 0.9, $CHCl_3$) (lit. $[\alpha]_D^{20}$: 15.0° (c= 1.0, $CHCl_3$)).[196]

Data for (6*S*,7*S*,9*R*,10*S*)-6,9-epoxynonadec-18-en-7,10-diol (**294**):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.80 (tdd, 1H, *J* = 6.7, 10.2, 16.9 Hz), 4.98 (ddd, 1H, *J* = 1.7, 3.4, 17.1 Hz), 4.92 (dd, 1H, *J* = 1.7, 10.2 Hz), 4.28 (m, 1H), 4.16 (ddd, 1H, *J* = 3.3, 5.9, 9.7 Hz), 3.84 (m, 2H), 2.11 (ddd, 1H, *J* = 4.5, 10.3, 13.3), 2.05-1.99 (m, 3H), 1.85 (dd, 1H, *J* = 6.1, 13.3 Hz), 1.65-1.20 (m, 21H), 0.89 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.4, 114.4, 83.8, 80.2, 73.5, 72.3, 34.4, 34.0, 32.5, 32.2, 29.8, 29.6, 29.4, 29.3, 29.1, 26.2, 26.1, 22.8, 14.2.

IR (thin film): 3415, 2925, 2853, 1635, 1467, 1091cm^{-1}

Exact mass calculated. for $C_{19}H_{37}O_3$: 313.2743 (M+H); found: 313.2725 (M+H).

$[\alpha]_D^{25}$: 14.5° (c= 1.1, $CHCl_3$) (lit. $[\alpha]_D^{25}$: 15.0° (c= 0.46, $CHCl_3$)).[197]

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(240) Wide variations in yield for this process were observed following different protocols for the formation of 8-nonenyl magnesium bromide. Ideally, 8-nonenyl magnesium bromide was prepared by the following procedure: To flame dried magnesium turnings (230 mg, 9.50 mmol) was added a solution of 1-bromo-8-nonene (390 mg, 1.90 mmol) in degassed ether (4.8 mL). The mixture was stirred for 30 minutes at room temperature after which time it was heated to reflux for an additional 2.5 hours.

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Appendices

Appendix A.

(3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate, a Banana Volatile and its Olfactory Recognition by the Common Fruit Fly Drosophila melanogaster

Fruit flies in the family Drosophilidae are a nuisance in homes, restaurants, fruit markets, and canneries, and wherever fruit and vegetable matter is left exposed.[1] Early research directed at identifying the natural volatiles that lure fruit flies to rotting organic material, with the intention of exploiting these compounds in commercial traps, led to the discovery of various attractants including ethanol, acetic acid, ethyl acetate, and acetaldehyde.[2] More recently, it was revealed that overripe mango fruit produces the fruit fly attractive volatiles ethanol, acetic acid, amyl acetate, 2-phenylethanol, and phenylethyl acetate.[3] It has also been demonstrated that *Drosophila melanogaster* is attracted by volatile compositions that include a short-chain carboxylic acid, a short-chain alcohol, a volatile aryl-substituted alcohol, a nitrogen compound, a sugar, a terpene, ethyl acetate, 2-phenylethyl acetate, and water.[4] Despite these discoveries, the development of effective means to remove *Drosophila* from areas of food preparation and storage remains an important challenge. Given that banana mash fermented by bakers' yeast has been used as a bait to attract fruit flies since the 1930s,[5] as a prelude to the development of an efficient semiochemical lure for *Drosophila,* we initiated an investigation of antenna-stimulating volatiles produced by ripening bananas.[6] The results of this study as well as the isolation, structural elucidation, and synthesis of (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate, a new natural product, are reported herein.

Approximately 50 ripening bananas were aerated individually for three days, and the volatile organic compounds were collected on Porapak Q (ethylvinylbenzene-divinylbenzene polymer) and subsequently extracted into pentane. Gas chromatographic-electroantennographic detection (GC-EAD) analyses[7] of the volatiles revealed that many components elicited a response from *D. melanogaster* antennae (Figure 1). With the exception of one compound, the structures of all antennal stimulatory volatile constituents were assigned on the basis of their characteristic retention indices and MS fragmentation patterns,[8] and assignments were confirmed by comparison with authentic standards. The behavioral activity of each candidate semiochemical is typically determined by preparing a synthetic blend that mimics in concentration and composition the antennal-stimulatory volatiles and by bioassaying this synthetic blend as well as blends from which specific compounds (e.g., alcohols, esters, or hydrocarbons) are eliminated.[9] While the structurally uncharacterised compound (t_R = 10.69 min, Figure 1) elicited a relatively weak antennal response (approximately 0.2 mV), this was not necessarily indicative of the compound's

behavioral significance.[10] Consequently, a confident structural assignment and synthetic source for this new candidate semiochemical were required. In its mass spectrum (Figure 2) the fragmentation ion *m*/*z* 89 was suggestive of a butyrate, which is commonly found in banana volatiles[6] and the molecular ion *m*/*z* 203 (M+H) was consistent with the chemical formula $C_{11}H_{22}O_3$, indicating an additional alcohol function. Moreover, the retention indices for this compound on DB-23 (1838), DB-5 (1347), DB-210 (1657), and DB-17 (1480) were consistent with those of a polar ester, such as a butyrate with an OH group in the alcohol or acid portion. While the fragmentation ion *m*/*z* 133 (loss of 69 from the molecular ion *m*/*z* 203) suggested an ester derived from pentanol, and *m*/*z* 45 further suggested a 2-pentyl ester,[11] the molecular mass of the candidate structure (2-pentyl hydroxybutyrate) deduced from the MS data was not a match with that of the unknown. With this in mind, the gas chromatographic retention indices for 2-heptyl-3-hydroxybutyrate, which has a molecular weight consistent with that of the unknown, were measured on DB-23 (1861), DB-5 (1345), DB-210 (1672), and DB-17 (1482) columns. These data closely resembled those of the unknown, but the mass spectrum of this substance lacked a strong *m*/*z* 89 ion. Considering that the MS information derived from the unknown appeared insufficient to assign a molecular structure and that many hydroxy esters seemed plausible, we decided to isolate this substance and to elucidate its molecular structure by ^{1}H NMR spectroscopy. Normal-phase flash chromatographic separation (Et_2O/pentane) of the crude mixture of volatiles followed by reversed-phase HPLC afforded a small amount (300 ng as determined by GC analysis with an internal standard) of this unidentified volatile. ^{1}H NMR spectroscopy with extended acquisition time (11 000 scans, 600 MHz TCI Cryoprobe) permitted the detection of a number of signals related to the natural product. However, the 300 ng sample also contained relatively large amounts of residual solvents and their associated impurities that masked key resonances. The presence of an ester function was suggested by a multiplet that resonated at δ 4.95 (acyloxy methine) and two doublets of doublets with resonances at δ 2.46 and 2.36 (α-methylene). Importantly, the multiplicity and splitting pattern of the latter two resonances were consistent with those of a β-hydroxy ester, and both signals showed a 1D TOCSY correlation to a multiplet that resonated at δ 3.96. On the basis of an additional 1D TOCSY correlation between the acyloxy methine proton and a methyl resonance at δ 1.20 (doublet), we were able to construct the partial structure depicted in Figure 3. Further observation of 1D TOCSY correlations from the acyloxy methine and carbinol protons to at least two methyl resonances centered around δ 0.90 reduced to 22 the number of potential structural isomers for the ester, but due to the limited amount of material, a confident structural assignment would ultimately rely on comparison with synthetic standards.

Antenna-stimulating compounds	t_R (min)
isobutyl acetate	2.00
ethyl btuyrate	2.49
butyl acetate	2.63
2-pentyl acetate	3.04
hexanol	3.31
isoamyl acetate	3.44
2-heptanol	3.77
isobutyl isobutyrate	3.96
2-hexyl acetate	4.39
isobutyl butyrate	4.61
3-butenyl butyrate	4.94
butyl butyrate	5.25
isoamyl isobutyrate	5.51
2-pentyl butyrate	5.69
2-heptyl acetate	5.94
3-methyl-1-butyl butyrate	6.25
2-phenylethanol	7.18
hexyl butyrate	8.38
unknown	10.69
methyl eugenol	11.46

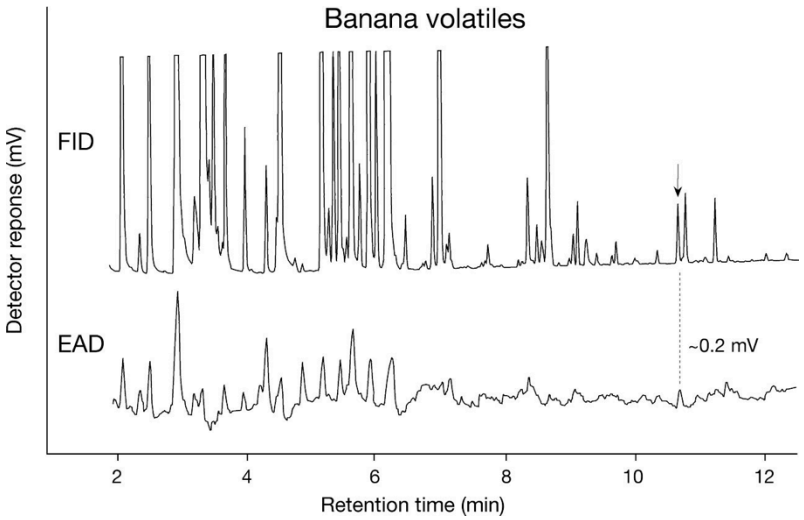


Figure 1 **Representative recording of flame ionisation detector (FID) and electroantennographic detector (EAD: *Drosophila melanogaster* antenna) responses to volatile organics collected from ripening bananas. Unidentified substance indicated with arrow (↓). Chromatography: DB-5 column; splitless injection, temperature of injection port and FID: 240 °C; temperature program: 1 min at 50 °C, then 10 °C/min to 280 °C.**

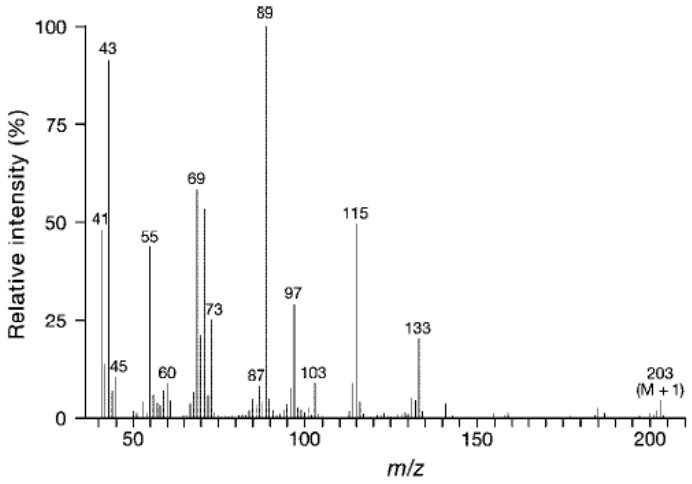


Figure 2 **Saturn 2000 ion trap mass spectrum of (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate (5).**

In order to gain further insight into the structure of this new volatile ester, the synthesis and spectroscopic analysis of a small family of synthetic β-hydroxy esters (MW = 202) was carried out. As detailed in Figure 3, acetylation of 2-butanol provided an acetate (not shown), the subsequent treatment of which with LDA followed by 2-methylbutanal afforded the β-hydroxy ester **2** as a mixture of diastereomers. Alternatively, acetylation of 3-methyl-2-pentanol or 2-pentanol followed by sequential treatment with LDA and propanal or isobutyraldehyde afforded the β-hydroxy esters **3** and **4**, respectively, as diastereomeric mixtures. While ^{1}H NMR spectra of esters **2**-**4** indicated that none of these substances possessed the connectivity of the natural product, similarities in the chemical shifts of the alkoxy fragment in **4** with those of the natural product suggested the latter substance was derived from 2-pentanol, which was consistent with the MS data (V*ide supra*). On the basis of this observation, the isomeric β-hydroxy ester **5** was synthesised, and the planar structure for the natural product was unambiguously assigned as 2-pentyl 3-hydroxyhexanoate. This is the first example of this compound as a synthetic or natural product.[12] As the four stereoisomers represented by **5** proved to be inseparable by HPLC, assignment of both the relative and absolute configuration of the natural product would require the stereoselective syntheses of these compounds.

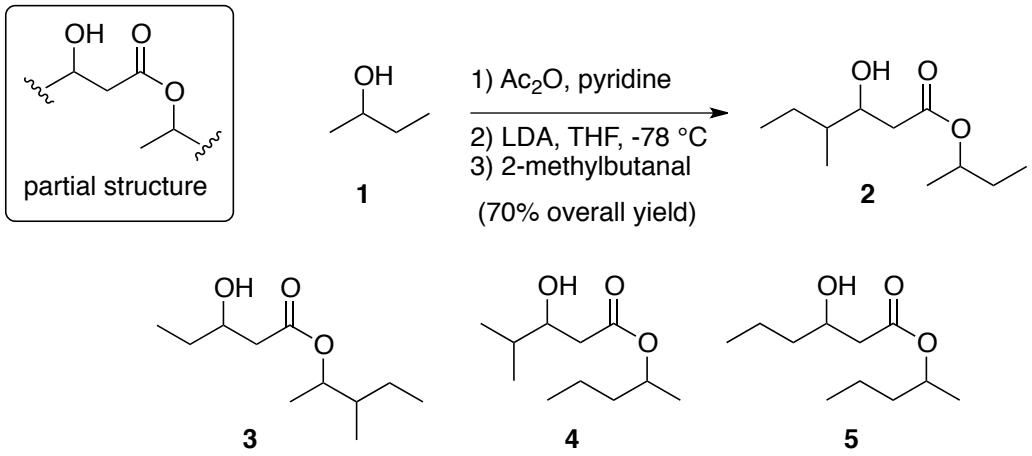
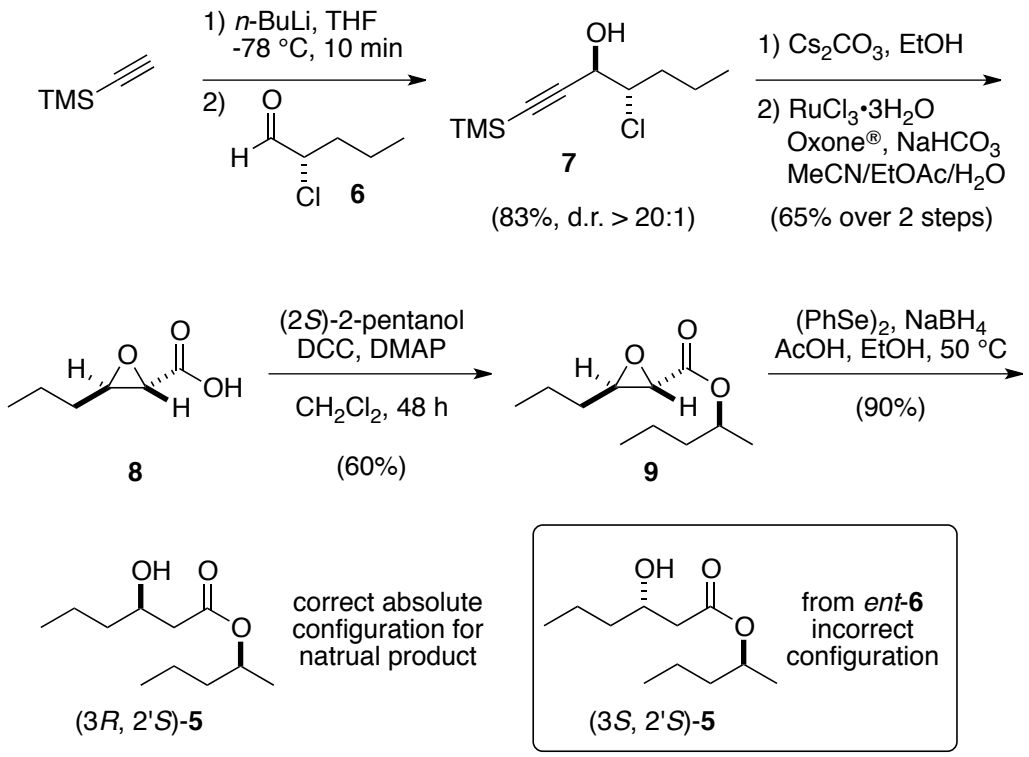


Figure 3 Synthesis and structures of candidate β-hydroxy esters 2-5.

Repetition of the synthesis of **5** starting with (*S*)-2-pentanol provided an inseparable mixture of diastereomeric hydroxy esters that, when compared to natural **5** by chiral GC,[13] confirmed the configuration of the acyloxy methine stereocentre as *S*. On the basis of this result, syntheses of both the *R*- and *S*-configured β-hydroxy esters were carried out. While the α,β-epoxy acid **8** required to access **5** is available via Sharpless asymmetric epoxidation of 2-hexen-1-ol followed by oxidation of the alcohol function,[14,15] an alternative route to this substance (Scheme 1) exploits methodology developed in one of our laboratories for the synthesis of *trans*-epoxides.[16] Thus, addition of the lithium anion derived from trimethylsilyl acetylene to (*S*)-2-chloropentanal (**6**) provided the chlorohydrin **7** in excellent yield (d.r. > 20:1). Following epoxide formation (Cs_2CO_3, EtOH), the alkyne function was oxidatively cleaved[17] to provide the desired α,β-epoxy acid **8** in good overall yield. Completion of the synthesis of the (*R*)-β-hydroxy ester involved esterification with (*S*)-2-pentanol and a subsequent regioselective reduction[18] of the epoxide. Following a similar sequence of reactions that started with (*R*)-2-chloropentanal, the (*S*)-β-hydroxy ester (3*S*,2*S*)-**5** (see inset in Scheme 1) was also constructed. Although the ^{1}H and ^{13}C NMR spectra derived from (3*R*,2*S*)-**5** and (3*S*,2*S*)-**5** were indistinguishable, chiral GC analysis[13] allowed confident configurational assignment of the natural product as (*S*)-2-pentyl (*R*)-3 hydroxyhexanoate.[19]



Scheme 1 Synthesis of (3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate.

In summary, the volatile organic compounds emitted from ripening bananas that elicit an antennal response from the common fruit fly, *D. melanogaster*, have been identified by a combination of GC-EAD analysis, MS, NMR spectroscopy, and synthesis. These efforts resulted in the isolation of sub-microgram quantities of the new antenna-stimulating ester (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate, the structural assignment of which was confirmed by synthesis. Notably, the stereoselective synthesis of this compound involved the development of a new method to access α,β-epoxy acids. Bioassaying the behavioral response of *D. melanogaster* to individual components and/or blends of the antenna-stimulating banana volatiles[9] identified in this study may lead to the development of effective lures for the common fruit fly.

Experimental

General

All reactions were performed under an atmosphere of dry argon using oven-dried glassware. Tetrahydrofuran, ether, and dichloromethane were used directly from an MBraun solvent purifier system (MB-SP Series). Commercial anhydrous ethanol (reagent grade) was used without further purification. Caledon pentane non-UV was distilled prior to use. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, silica gel 60). Chiral GC analyses were

performed on a Hewlett-Packard 5890 gas chromatograph equipped with a flame ionisation detector and a custom-made chiral GC column coated with a 1:1 mixture of heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin and OV-1701 (30 m length, 0.320 mm i.d., 0.25 *μ*m film).[13] NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Varian Inova 500 (500 MHz), or Varian MercuryPlus (400 MHz). Signal positions (δ) are given in parts per million from TMS and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR). Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Selected, characteristic absorption data are provided for each compound. Chemical ionisation (CI) mass spectra were recorded on a Varian 4000 mass spectrometer at 70 eV. High-resolution fast atom bombardment (HR-FABMS) mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer at 3 kV. Optical rotations were measured on a Perkin-Elmer polarimeter 341 at 589 nm.

Collection of volatiles from bananas. A single yellow-ripe banana was placed in a Pyrex glass aeration chamber (15.5 cm inner diameter (i.d.) x 20 cm). For 12 days, a water-driven aspirator drew purified air at 1 L/min through the chamber and a downstream Pyrex glass column (140 x 5 mm i.d.) filled with Porapak Q (50-80 mesh, Waters, Milford, MA, USA). Every 24 hours, volatiles were eluted from Porapak Q with 2 mL of freshly distilled pentane.

Analyses of volatiles. The volatile extracts eluted from the Porapak Q with pentane were concentrated to a volume of 1 mL and analyzed by coupled GC-EAD[7] employing a Hewlett-Packard (HP) 5890 gas chromatograph fitted with a GC column (30 m x 0.32 mm i.d.) coated with DB-5 (J&W Scientific, Folsom, CA). For GC-EAD recordings a fruit fly's head with both antennae intact was severed from the body and inserted into the opening of a glass capillary electrode (0.58 mm i.d. x 65 mm length) (A-M Systems, Inc., Calsborg, WA) filled with saline solution.[20] The tip of one antenna was removed by spring micro-scissors (Fine Science Tools Inc., North Vancouver, British Columbia, Canada) and then placed into the opening of the recording electrode mounted on a portable micromanipulator and positioned in front of a constant stream (250 mL/min) of warm (20 °C) non-humidified air (Praxair Canada Inc., Mississauga, Ontario, Canada), which delivered the GC column eluent through a custom-built interface kept a 250 °C. Antennal receptor potentials (measured in mV by a custom-built amplifier) elicited by specific compounds were recorded by a HP 3392A chart recorder. Identical retention times of compounds detected by the flame ionisation detector of the GC and by the insect antenna allowed assignment of antennal responses to specific compounds in the eluent. Volatiles that elicited responses from antennae were analyzed by GC-MS, employing a Varian Saturn 2000 ion trap

GC-MS fitted with a DB-5 column. As (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate occurred in greatest relative abundance between 24 and 48 hours, in 50 additional aerations of single bananas, volatiles were Porapak Q-collected for 3 days.

Isolation of (3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate. Single or combined Porapak Q volatile extracts were evaporated to dryness under a stream of N_2 (5 min). The samples were re-constituted in 100 µL of pentane and fractionated on silica gel (50 g) in a glass column (14 x 0.5 cm i.d.). After pre-rinsing the silica with pentane, the extract was applied and then successively eluted with 2 mL of pentane, 1 mL of pentane:ether (9:1) and 4 mL of pentane:ether (3:1). The pentane:ether (3:1) fraction was further purified by reverse phase HPLC (Nova Pak® C_{18}, 3.9 x 300 mm column) using a water:acetonitrile (2:3) mobile phase. (3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate eluted between 6.25-6.5 min.

General procedure for the synthesis of candidate β-hydroxy esters 2-4. Synthesis of 2-butyl 3-hydroxy-4-methylhexanoate (**2**).

To a cold (-78 °C) solution of diisopropylamine (0.66 mL, 4.7 mmol) in tetrahydrofuran (40 mL) was added *n*-butyllithium (2.5 M solution in hexanes, 1.9 mL, 4.7 mmol). The resulting solution was stirred at -78 °C for 30 minutes, then warmed to 0 °C and stirred for an additional 15 minutes. After this time, the slightly yellow solution was cooled to -78 °C and *sec*-butyl acetate (**1**) (500mg, 4.31mmol) was added and stirred for 15 minutes. 2-methyl-butanal (0.55 mL, 5.17 mmol) was then added and stirred for 30 minutes, after which time it was warmed to 0 °C, and treated with saturated aqueous ammonium chloride (10 mL). The reaction mixture was diluted with ether (20 mL) and the layers were separated. The aqueous layer was extracted with ether (3 x 10 mL), and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow oil. Purification of the crude material by flash chromatography (silica gel, 10:1 hexanes:ethyl acetate) afforded (2'-butyl)-3-hydroxy-4-methylhexanoate (**2**) as a mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.90 (sex, 4H, *J* = 6.3 Hz), 3.94 (m, 2H), 3.85 (m, 2H), 3.00 (dd, 2H, *J* = 3.9, 6.9 Hz), 2.83 (dd, 2H, *J* = 3.7, 7.7 Hz), 2.49-2.35 (m, 8H), 1.66-1.49 (m, 16H), 1.43 (m, 2H), 1.22 (d, 12H, 6.2 Hz), 1.17 (m, 4H), 0.93-0.88 (m, 36H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 173.2, 173.1, 173.1, 72.6, 72.6, 71.6, 71.5, 70.9, 70.9, 39.7, 39.7, 39.7, 39.0, 39.0, 38.1, 28.7, 25.4, 24.9, 19.3, 19.3, 14.3, 14.3, 13.7, 13.7, 11.6, 11.6, 11.4, 9.6.

IR (neat): 3494, 2967, 2878, 1714, 1463, 1380, 1278, 1183, 1095, 1061, 1028 cm^{-1}

Exact mass calculated for $C_{11}H_{23}O_3$: 203.1647 (M+H); found: 203.1651.

3-Methyl-2-pentyl 3-hydroxypentanoate (**3**) (mixture of four diastereomers) was prepared according to the general procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.87-4.78 (m, 4H), 3.85 (m, 4H), 3.16 (m, 4H), 2.42 (dd, 4H, *J* = 3.3, 16.2 Hz), 2.33 (ddd, 4H, *J* = 1.0, 8.9, 16.2 Hz), 1.57-1.34 (m, 16H), 1.13-1.01 (m, 16H), 0.90 (t, 12H, *J* = 7.5 Hz), 0.83 (m, 24H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 173.4, 173.4, 173.3, 173.3, 72.8, 72.7, 71.6, 71.6, 71.0, 71.0, 39.7, 39.7, 39.7, 39.0, 39.0, 38.1, 28.8, 25.5, 25.0, 19.5, 19.5, 14.4, 14.4, 13.9, 13.8, 11.8, 11.5, 9.7.

IR (neat): 3444, 2965, 2879, 1730, 1463, 1380, 1179, 1026, 983cm^{-1}

Exact mass calculated for $C_{11}H_{23}O_3$: 203.1647 (M+H); found: 203.1654.

2-Pentyl 3-hydroxy-4-methylpentanoate (**4**) (mixture of two diastereomers) was prepared according to the general procedure.

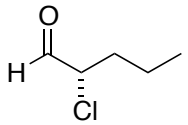
^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.96 (sex, 4H, *J* = 6.1 Hz), 3.76 (m, 4H), 3.00 (t, 4H, *J* = 3.9 Hz), 2.47 (dd, 4H, *J* = 2.4, 16.2 Hz), 2.37 (dd, 4H, *J* = 9.7, 16.2 Hz), 1.70 (m, 4H), 1.58 (m, 4H), 1.46 (m, 4H), 1.38-1.27 (m, 8H), 1.21 (dd, 12H, *J* = 0.7, 6.1 Hz), 0.95-0.89 (m, 36H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 173.2, 173.2, 72.7, 72.7, 71.3, 38.6, 38.0, 33.1, 20.0, 19.9, 18.6, 18.6, 18.3, 17.8, 17.8, 13.9.

IR (neat): 3466, 2961, 2875, 1731, 1468, 1382, 1327, 1282, 1186, 1121, 1106, 1056 cm^{-1}

Exact mass calculated for $C_{11}H_{23}O_3$: 203.1647 (M+H); found: 203.1653.

Preparation of (2*S*)-2-chloropentanal (6).



To a cold (0 °C), stirred solution of pentanal (430 mg, 5.0 mmol) in dichloromethane (20 mL), was added D-prolinamide (57.5 mg, 0.5 mmol) and *N*-chlorosuccinimide (870 mg, 6.5 mmol). The reaction mixture was stirred for 1 hour and then allowed to slowly warm to room temperature over the course of 3 hours at which temperature it was stirred until complete consumption of pentanal (as determined by ^{1}H NMR spectroscopy). After this time, the mixture was diluted with pentane (20 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice water bath. The resulting oil was dissolved in pentane (20 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice-water bath to give (2*S*)-2-chloropentanal (**6**) (600 mg, >97% yield, 85% enantiomeric excess) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.44 (d, 1H, *J* = 2.5 Hz), 4.14 (ddd, 1H, *J* = 2.5, 5.0, 7.5 Hz), 1.90 (m, 1H), 1.77 (m, 1H), 1.47 (m, 2H), 0.91 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.2, 63.6, 33.8, 18.7, 13.2.

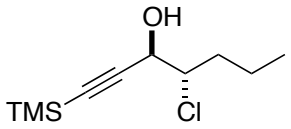
IR (neat): 2963, 2936, 2876, 2849, 1735, 1466, 1434, 1382, 1262, 1206, 1055 cm^{-1}

Exact mass calculated for $C_5H_{10}ClO$: 121.5868; found: 121.5870.

$[\alpha]_D^{25}$: -11.4° (c = 0.6, $CHCl_3$).

The enantiomeric excess of (**6**) was determined by chiral GC analysis of the alcohol derived from **6**. A solution of **6** (12 mg, 0.1 mmol) and sodium borohydride (10 mg, 0.25 mmol) in methanol (2 mL) was stirred at room temperature for 1 hour. The reaction mixture was then treated with water (1 mL) and diluted with diethyl ether (5 mL) and the phases were separated. The organic phase was dried ($MgSO_4$) and concentrated to afford (2*S*)-2-chloropentanol. (Temperature program: 70 °C held for 5 minutes then increased by 20 °C per minute until 150 °C and run for 30 minutes. Retention time = 21.0 ((*R*)-enantiomer); 21.8 ((*S*)-enantiomer).

Preparation of (3*R*,4*S*)-4-chloro-3-hydroxy-1-(trimethylsilyl)-1-heptyne (7).



To a cold (-78 °C), stirred solution of trimethylsilylacetylene (98mg, 1 mmol) in dry tetrahydrofuran (10 mL) was added *n*-butyllithium (1.84 M in hexanes, 0.54 mL, 1 mmol,). After 10 minutes, a solution of (2*S*)-2-chloropentanal (**6**) (132 mg, 1.1 mmol) in tetrahydrofuran (1.0 mL) was added and the resulting mixture was stirred for 10 minutes. After this time the solution was treated with saturated aqueous ammonium chloride (10 mL), diluted with ether (10 mL), and the phases were separated. The aqueous phase was extracted with ether (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give the crude chlorohydrin (>20:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash chromatography (silica gel, 15:1 hexanes:ethyl acetate) afforded (3*R*,4*S*)-4-chloro-3-hydroxy-1-(trimethylsilyl)-1-heptyne (**7**) (180 mg, 83%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.51 (dd, 1H, *J* = 3.5, 8.3 Hz), 4.03 (m, 1H), 2.43 (t, 1H, *J* = 8.3 Hz), 1.81 (m, 2H), 1.62 (m, 1H), 1.45 (m, 1H), 0.96 (t, 3H, *J* = 7.4 Hz), 0.19 (s, 9H).

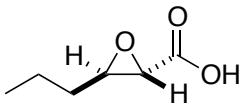
^{13}C NMR (150 MHz, $CDCl_3$) δ: 101.7, 92.0, 66.5, 66.4, 35.4, 19.7, 13.5, -0.3.

IR (neat): 3367, 2961, 2875, 2177, 1466, 1382, 1251, 1123 cm^{-1}

Exact mass calculated for $C_{10}H_{18}ClSi$: 201.0861 (M-OH); found: 201.0867.

$[\alpha]_D^{25}$: -11.1° (c = 8.7, $CHCl_3$).

Preparation of (2*R*,3*R*)-2,3-epoxy-hexanoic acid (8).



To a solution of (3*R*,4*S*)-4-chloro-3-hydroxy-1-(trimethylsilyl)-1-heptyne (**7**) (90 mg, 0.4 mmol) in ethanol (4 mL) was added Cs_2CO_3 (202 mg, 0.6 mmol) and stirred for 16 hours at room temperature. After this time, the reaction mixture was treated with water (5 mL), diluted with pentane (10 mL), and the phases were separated. The aqueous phase was extracted with pentane (3 x 10 mL) and the combined organic phases were washed with brine (3 x 15 mL), dried ($MgSO_4$), and concentrated to give the crude alkynylepoxide which was used without further purification.

To a cold (0 °C), solution of the crude alkynylepoxide dissolved in a 1.5:1:0.3 mixture of acetonitrile:water:ethyl acetate (11.5 mL) was added Oxone® (834 mg, 1.4 mmol) and sodium bicarbonate (342 mg, 4.1 mmol) and stirred for 5 minutes. At this time, ruthenium(III) chloride trihydrate (3 mg, 0.01 mmol) was added and the reaction stirred at 0 °C for 1 hour. The reaction mixture was then treated with 10% aqueous sodium bisulfite (10 mL), acidified with 2N aqueous hydrochloric acid to pH < 2, diluted with ethyl acetate (15 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated to provide the crude acid. Purification of the crude product by flash chromatography (Iatrobeads, 2.5% methanol in dichloromethane) afforded (2*R*,3*R*)-2,3-epoxy-hexanoic acid (**8**) (35 mg, 65% over 2 Steps) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.11 (br. s, 1H), 3.26 (s, 1H), 3.20 (t, 1H, *J* = 4.8 Hz), 1.68-1.46 (m, 4H), 0.98 (t, 3H, 7.4 Hz).

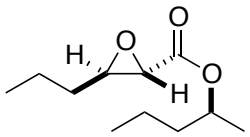
^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.8, 58.9, 52.5, 33.3, 19.0, 13.7.

IR (neat): 2963, 2876, 1730, 1462, 1383, 1198, 899cm^{-1}

Exact mass calculated for $C_6H_{11}O_3$: 131.0708 (M+H); found: 131.0703.

$[\alpha]_D^{25}$: 11.6° (c = 8.0, $CHCl_3$).

Preparation of (2*R*,3*R*,2'*S*)-(2'-pentyl)-2,3-epoxyhexanoate (9).



To a solution of (2*R*,3*R*)-2,3-epoxy-hexanoic acid (**8**) (100 mg, 0.77 mmol) in dichloromethane (10 mL) was added (2*S*)-2-pentanol (92 μL, 0.85 mmol), *N*,*N*'-dicyclohexyl-carbodiimide (238 mg, 1.2 mmol), and 4-dimethylaminopyridine (9 mg, 0.08 mmol). The resulting mixture was stirred at room temperature for 48 hours, after which time it was filtered through a plug of Celite® and concentrated to provide the crude ester. Purification of the crude product by flash chromatography (silica gel, dichloromethane) afforded (2*R*,3*R*,2'*S*)-(2'-pentyl)-2,3-expoxyhexanoate (**9**) (92 mg, 60%) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.00 (sex, 1H, *J* = 6.3 Hz), 3.18 (d, 1H, *J* = 1.9 Hz), 3.12 (dt, 1H, J = 1.9, 6.2 Hz), 1.67-1.45 (m, 6H), 1.33 (m, 2H), 1.23 (d, 3H, *J* = 6.3 Hz), 0.97 (t, 3H, *J* = 7.2 Hz), 0.91 (t, 3H, *J* = 7.3 Hz).

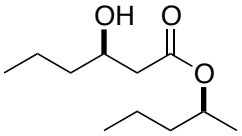
^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.0, 72.3, 58.2, 53.2, 37.9, 33.4, 19.8, 19.1, 18.6, 13.8, 13.7.

IR (neat): 2961, 2875, 1749, 1465, 1381, 1290, 1244, 1200, 1121 cm^{-1}

Exact mass calculated for $C_{11}H_{21}O_3$ (M+H): 201.1491; found: 201.1487.

$[\alpha]_D^{25}$: 14.3° (c = 10.0, $CHCl_3$).

Preparation of (3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate (5).



To a solution of diphenyldiselenide (47 mg, 0.15 mmol) in ethanol (2 mL) was added sodium borohydride (13 mg, 0.34 mmol). After gas evolution had subsided the reaction was cooled to 0 °C and acetic acid (12 μL, 0.4 mmol) was added. The reaction mixture was stirred for 5 minutes at which time a solution of epoxy ester (**9**) (20 mg, 0.1 mmol) in a 1:0.5 mixture of tetrahydrofuran: ethanol (1.5 mL) was added and the resulting mixture stirred at 50 °C for 24 hours. After this time, the reaction mixture was cooled, purged with air for 5 minutes and concentrated to provide the crude product. Purification by flash chromatography (silica gel, 15:1 hexanes:ethyl acetate) afforded (3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate (**5**) (18 mg, 90%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.97 (sex, 1H, *J* = 6.3 Hz), 4.00 (m, 1H), 3.01 (d, 1H, *J* = 3.8 Hz), 2.48 (dd, 1H, *J* = 2.9, 16.4 Hz), 2.38 (dd, 1H, *J* = 9.2, 16.4 Hz), 1.61-1.27 (m, 8H), 1.22 (d, 3H, *J* = 6.3 Hz), 0.93 (t, 3H, *J* = 7.2 Hz), 0.91 (t, 3H, 7.1 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 173.1, 71.5, 67.9, 41.7, 38.8, 38.2, 20.2, 18.9, 18.8, 14.2, 14.1.

IR (neat): 3450, 2932, 2874, 1731, 1466, 1379, 1176, 1120, 1019, 996 cm^{-1}

Exact mass calculated for $C_{11}H_{23}O_3$: 203.1647 (M+H); found: 203.1630.

$[\alpha]_D^{25}$: 3.4° (c = 10.0, $CHCl_3$).

The absolute stereochemistry of **5** was determined by analysis of the optical rotation of the diol derived from **5**. A solution of (3*R*,2'*S*)-(2'-pentyl)-3-hydroxyhexanoate (**5**) (8 mg, 0.04 mmol) in tetrahydrofuran (0.5 mL) was added lithium aluminum hydride (5 mg, 0.13 mmol) and stirred for 3 hours. After this time the reaction was treated with water (10 μL), 15% aqueous solution of sodium hydroxide (10 μL), and stirred for 5 minutes. Water (30 μL) was added and after 5 minutes the mixture was treated with anhydrous magnesium sulfate. The reaction mixture was filtered and concentrated to provide the crude diol. Purification by flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) afforded (3*R*)-1,3-hexanediol as a clear oil.

Observed $[\alpha]_D^{25}$: -9.2° (c = 2.4, EtOH). Lit. $[\alpha]_D^{25}$: -10.5° (c = 1.45, EtOH).[19]

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(10) For example see: Schwarz, J.; Gries, R.; Hillier, K.; Vickers, N.; Gries,G. *J. Chem. Ecol*. **2009**, *35*, 58.

(11) For the detection of 2-pentanol and esters derived from 2-pentanol in collections of banana volatiles see ref 6.

(12) The related ester ethyl 3-hydroxyhexanoate has been reported as a volatile component in bananas. However, its structure was only tentatively assigned using the NIST library (see ref 6b).

(13) GC analysis of **5** was carried out on a HP5890 GC equipped with a custom-made chiral GC column coated with a 1:1 mixture of heptakis(2,6-di-O-methyl-3-O-pentyl)-β-cyclodextrin and OV-1701 as described in: Gries, R.; Gries, G.; Khaskin, G.; King, S.; Olfert, O.;Kaminski, L.-A.; Lamb, R.; Bennett, R. *Naturwissenschaften* **2000**, *87*, 450. Temperature program: 100 °C isothermal. (3*R*,2*S*)-**5** t_R = 26.7 min; (3*S*,2*S*)-**5** t_R = 27.1 min; (3*R*,2*R*)-**5** and (3*S*,2*R*)-**5** t_R = 29.9 and 30.7 min.

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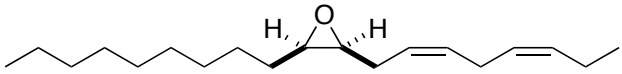
Appendix B.

Total Synthesis of the Pink Gypsy Moth *Lymantria mathura* Sex Pheromone (-)-Mathuralure

Introduction

The pink gypsy moth (*Lymantria mathura* Moore) is widespread in parts of Asia, India, and Russia.[1] Although it rarely reaches outbreak levels in these areas, the introduction of *L*. *mathura* into North America would threaten the integrity of forest ecosystems and presents the potential for widespread defoliation.[2] In recent years, egg masses of *L*. *mathura* have been detected on ships bound for North America, which has stimulated interest in the development of an efficient monitoring system for this potentially devastating insect pest. In this regard, gas chromatographic-electroantennographic detection (GC-EAD) and GC-mass spectrometric analysis of extracts from the abdominal tip pheromone glands of female *L*. *mathura* led to the identification of a 4:1 mixture of (2*R*,3*S*):(2*S*,3*R*)-2-nonyl-3-((2*Z*,5*Z*)-octa-2,5-dienyl)oxirane (**1**, (-)-mathuralure (Figure 1), as the major sex pheromone component.[3] Based on the effective employment of other insect sex pheromones for the early detection, monitoring, and/or eradication of pestiferous insects,[4] several synthetic strategies have been reported that provide access **1** and structurally related pheromones.[5-7] However, the development of a process capable of supplying the multi-gram quantities of **1** needed to support population monitoring studies of mathuralure (**1**) remains an important pursuit. Herein, we report an operationally simple, gram-scale synthesis of mathuralure (**1**) that can be used to support the growing demand for this pheromone.

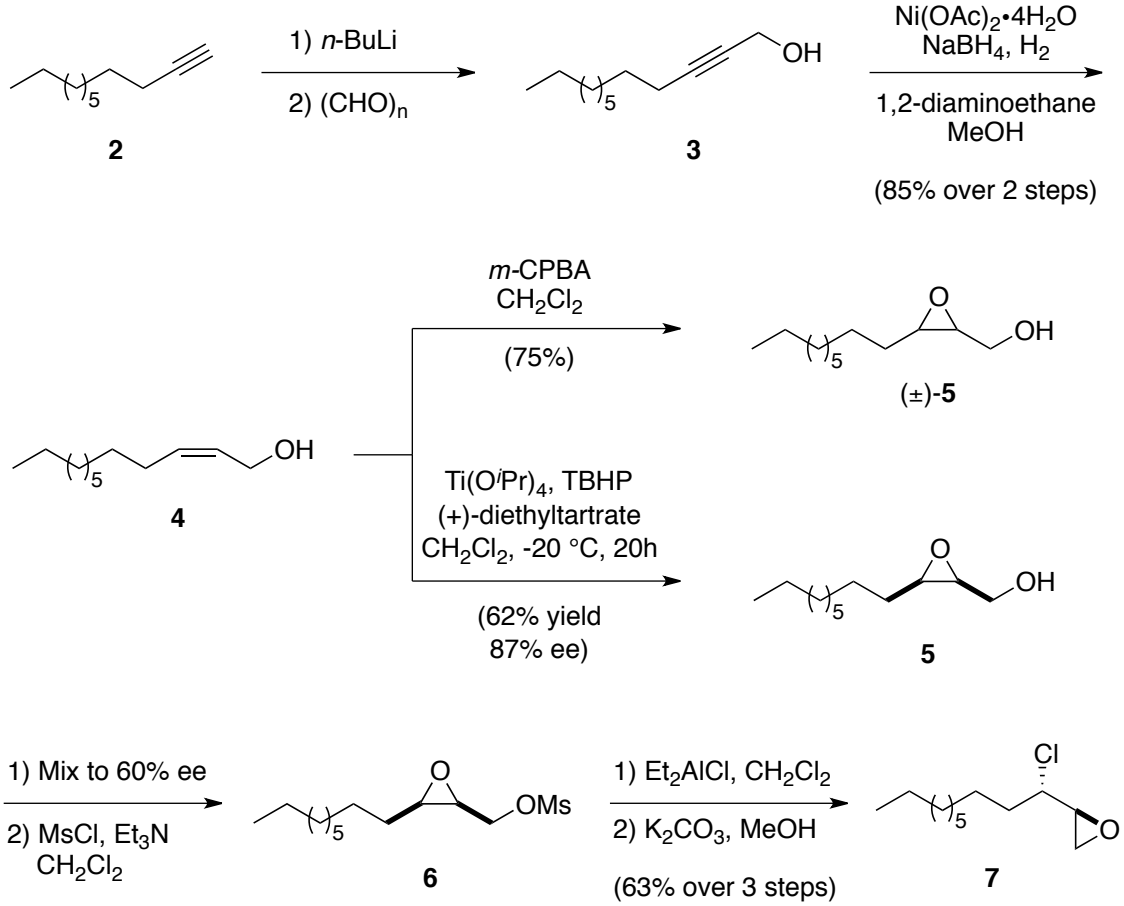


1: (-)-mathuralure

Figure 1 **(2*R*,3*S*)-2-nonyl-3-((2*Z*,5*Z*)-octa-2,5-dienyl)oxirane, (-)-mathuralure (1), the major sex pheromone component of the pink gypsy moth.**

As depicted in Scheme 1, the synthesis of **1** initiated with the hydroxymethylation of undecyne (**2**). Thus, treatment of **2** with *n*-BuLi followed by reaction of the resulting anion with paraformaldehyde furnished the propargyl alcohol **3**, which upon subsequent hydrogenation with P-2 Nickel catalyst[8] poisoned with 1,2-diaminoethane afforded *cis*-dodec-2-en-1-ol (**4**) in 85% over 2 steps.[9] Epoxidation of **4** with *m*-CPBA in dichloromethane then afforded racemic (±)-**5** in 75% yield. Alternatively, subjecting **4** to Sharpless epoxidation conditions[10] in the presence of

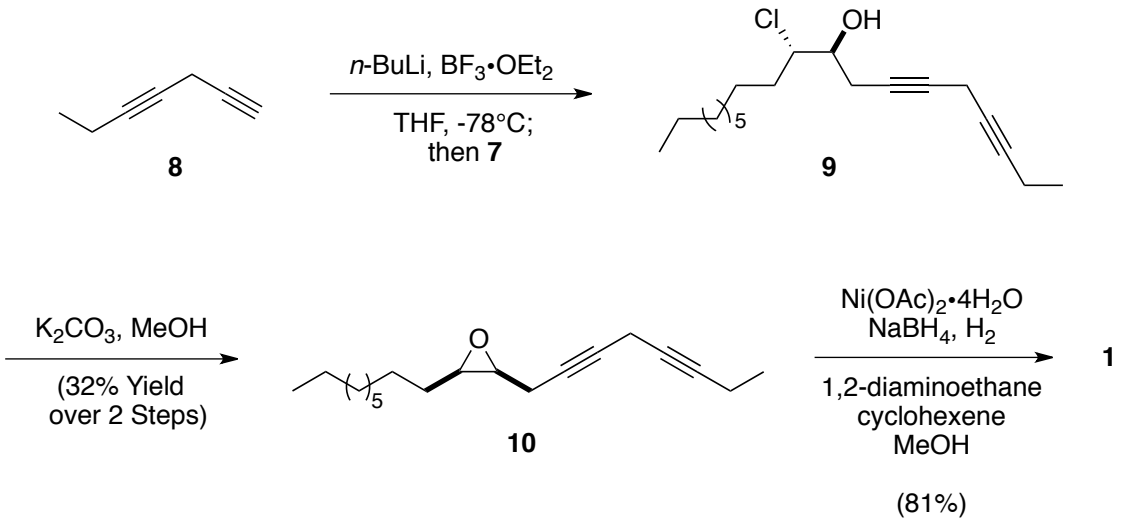
$Ti(O^iPr)_4$ and (+)-diethyl tartrate gave rise to **5** in 62% yield and 88% ee. With racemic and enantioenriched samples of **5** in hand, these materials were mixed in appropriate ratios to give epoxyalcohol **5** in 60% ee. Conversion of **5** to its corresponding mesylate **6** was then followed by regioselective opening of the epoxide by addition of Et_2AlCl.[11] The crude chlorohydrin (not shown) was subsequently treated with K_2CO_3, which effected epoxidation, affording epoxychloride **7** in 63% isolated yield over 3 steps. Notably, this route was carried out on >10 g scale without complication.



Scheme 1 Synthesis of epoxychloride 7.

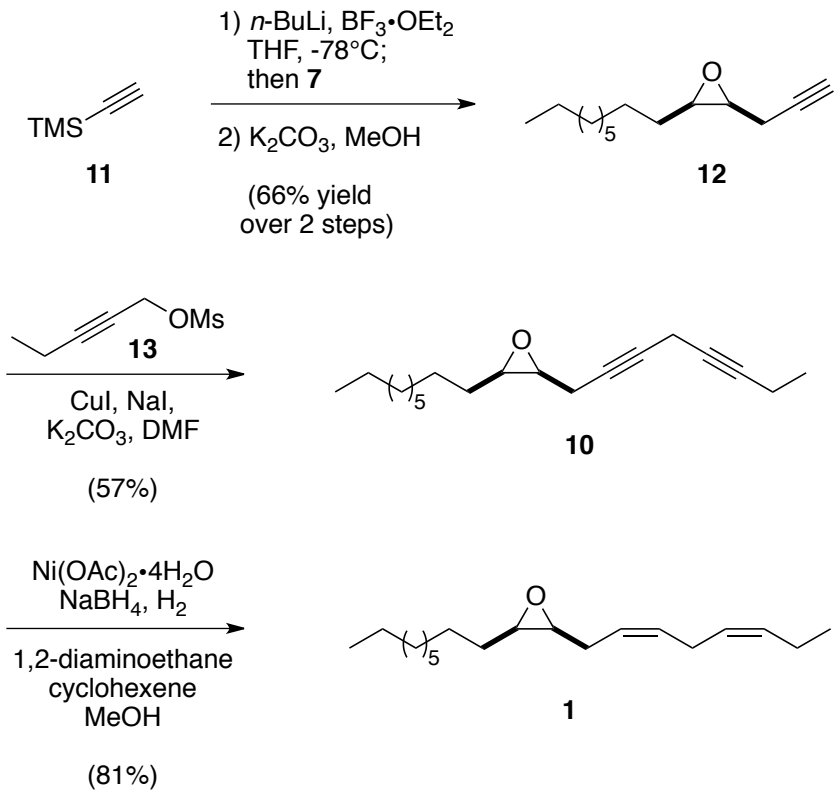
With epoxychloride **7** in hand, completion of the synthesis of mathuralure (**1**) then involved treatment of 1,4-heptadiyne (**8**)[12] with *n*-BuLi for 60 seconds, followed immediately by addition of BF_3•OEt_2 and epoxychloride **7**, which afforded chlorohydrin **9** (Scheme 2).[13] Notably, reaction of the diyne **8** with *n*-BuLi for periods of time greater than 60 seconds led to the production of significant amounts of by-products, seriously compromising the overall yield of the process and complicating the eventual purification of **1**.[14] Treatment of the crude product with K_2CO_3 in ethanol then effected epoxide formation, producing epoxydiyne **10** in 32% yield over 2 steps. Finally,

hydrogenation of the diyne moiety in **10** with H_2 and catalytic P-2 Nickel in the presence of 1,2-diaminoethane and cyclohexene[15] afforded (-)-mathuralure **1** in 81% yield. The addition of a large excess of cyclohexene to the reaction mixture was crucial to avoid over reduction of the resulting diene **1** and the production of side products that were difficult to separate from **1** and complicated the final purification process



Scheme 2 Synthesis of (-)-mathuralure (1).

Due to the low yield for the diyne addition step (i.e. **8** → **10**, Scheme 3), and issues concerning the stability and handling of **8** on larger scale, an alternative approach to mathuralure (**1**) was also developed that requires and additional chemical transformation but is more reliable, and provides **1** in higher overall yield. As depicted in Scheme 3, treatment of epoxychloride **7** with the lithium acetylide derived from addition of *n*-BuLi to trimethylsilylacetylene (**11**), resulted in formation of a chlorohydrin (not shown), that was directly treated with K_2CO_3 to afford epoxyalkyne **12** in 66% isolated yield over 2 steps. Subsequent coupling of propargylmesylate **13** with the terminal alkyne function in **12** in the presence of CuI afforded **10** in 57% yield.[16] Reduction of the diyne function in **10** with P-2 Nickel (*vide supra*), afforded (-)-mathuralure **1**. Notably, small amounts of over and/or under reduced impurities could be easily removed by final purification of **1** over 20% $AgNO_3$ impregnated silica gel.[17] Following this optimised process, (-)-mathuralure (**1**) was routinely produced with purity >95%, as determined by GC analysis,[18] and all spectral data recorded on synthetic **1** (^{1}H NMR, ^{13}C NMR, IR, HRMS, $[\alpha]_D$) were in complete agreement with that reported in the literature.[4b,19]



Scheme 3 Second generation synthesis of (-)-mathuralure (1).

In conclusion, we have developed a concise and scalable total synthesis of the *L. mathura* insect sex pheromone mathuralure (**1**). Key aspects of this synthesis include regioselective opening of an epoxymesylate to afford epoxychloride **7**, and the use of an alkylative epoxide rearrangement to furnish the epoxyalkynes **10** and **12**. Additionally the overall yield of **1** from undecyne (10% over 10 steps) compares well with that reported for previous synthesis of mathuralure **1**,[4b] and this strategy should also provide reliable access to several structurally related insect sex pheromones.[6,7] Importantly, following this process, multi-gram quantities of (-)-mathuralure have been prepared to support ongoing field testing of this material in pheromone-baited traps for *L. mathura.*

Experimental

General

All reactions described were performed under an atmosphere of dry argon using oven- dried glassware. THF was distilled over Na/benzophenone, and CH_2Cl_2 was dried by distillation over CaH_2. DMF and MeOH were used directly from EMD drysolv septum sealed bottles. Cold temperatures were maintained by the use of following reaction baths: -78 °C, acetone-dry ice; temperatures between -40 °C to -20 °C were maintained with a Polyscience VLT-60A immersion

chiller. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[20] Thin layer chromatography was carried out on commercial aluminum backed silica gel 60 plates (E. Merck, type 5554, thickness 0.2 mm). Visualization of chromatograms was accomplished using ultraviolet light (254 nm) followed by heating the plate after staining with one of the following solutions: (a) *p*-anisaldehyde in sulphuric acid-ethanol mixture (5% anisaldehyde v/v and 5% sulphuric acid v/v in ethanol); (b) 1% potassium permanganate w/v, 6.6% potassium carbonate w/v, and 1% v/v 10% sodium hydroxide in water. Concentration and removal of trace solvents was done via a Büchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Gas chromatography (GC) analysis was performed on a Hewlett Packard model 5890 gas chromatograph, equipped with a flame ionisation detector equipped with a custom-made chiral GC column coated with a 1:1 mixture of heptakis(2,6-di-O-methyl-3-O-pentyl)-β-cyclodextrin and OV-1701.[2]

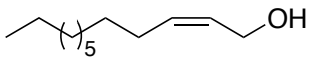
NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance II 600 equipped with a QNP or TCI cryoprobe (600 MHz), or Bruker Avance III 400 (400 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (150 MHz), or Bruker Avance III 400 (100 MHz). Assignments of 1H and 13C NMR spectra are based on analysis of 1H-1H COSY, HSQC, HMBC and nOe spectra.

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

Chemical ionisation (CI) mass spectra were recorded on a Varian 4000 mass spectrometer at 70 eV. High resolution fast atom bombardment (HR-FABMS) mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer at 3 kV or an Agilent 6210 TOF LC/MS mass spectrometer.

Optical rotation was measured on a Perkin Elmer Polarimeter 341.

Preparation of (*Z*)-dodec-2-en-1-ol (4)

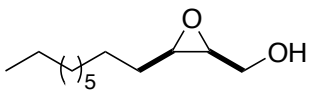


Prepared according to the procedure reported by Gansauer and co-workers.[9] To a cold (-78 °C) stirred solution of undec-1-yne (**2**) (10.0 g, 65.7 mmol) in THF (85 mL) was added *n*-butyllithium (2.4 M solution in hexanes, 27.4 mL, 65.7 mmol). The reaction mixture was stirred at this temperature for 40 min, after which time paraformaldehyde (1.97 g, 65.7 mmol) was added portion wise. The reaction mixture was stirred with gradual warming to rt over 20 h. Saturated aqueous NH_4Cl (20 mL) was then added, the mixture was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 100 mL) and combined organic phases were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated to give the crude propargyl alcohol that was used in the subsequent reaction without purification.

To a cold (0 °C) stirred solution of $Ni(OAc)_2 \bullet 4H_2O$ (3.25 g, 15.1 mmol) in MeOH (60 mL) was added $NaBH_4$ (570 mg, 15.1 mmol) (caution: vigorous gas evolution). The reaction was allowed to warm to rt and stirred for 5 min. After this time 1,2-diaminoethane (2.0 mL, 30.1 mmol) was added and the reaction mixture stirred for a further 5 min. A solution of crude dodec-2-yn-1-ol (11.0 g, 60.3 mmol) in MeOH (20 mL) was then added. The reaction vessel was evacuated and backfilled with hydrogen three times and the reaction mixture stirred under an atmosphere of hydrogen for 4 h. The reaction mixture was then filtered through a pad of Celite®, which was washed thoroughly with MeOH. The filtrate was evaporated under reduced pressure, and the residue diluted with Et_2O (300 mL). The organic phase was washed with H_2O (2 x 100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated to afford the crude product. The crude product was purified by flash chromatography (silica gel, 10:1 hexanes:EtOAc) and afforded (*Z*)-dodec-2-en-1-ol (**4**) (10.4 g, 85 % over 2 steps). The spectral data obtained for **4** was in agreement with literature reported values.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.62 (m, 2H), 4.19 (d, 2H, *J* = 6.5 Hz), 2.07 (m, 2H), 1.58 (br. s, 1H), 1.37-1.26 (m, 14H), 1.21 (t, 3H, *J* = 9.0 Hz).

Preparation of ((2*S*,3*R*)-3-nonyloxiran-2-yl)methanol (5)

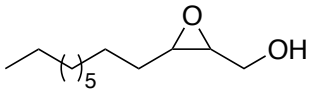


Prepared according to the procedure reported by Sharpless and co-workers.[10] To a cold (-20 °C) stirred suspension of activated 4Å MS in CH_2Cl_2 (250 mL) was added L-(+)-diethyl tartrate (2.83

mL, 16.5 mmol) and Ti(O^iPr)$_4$ (4.08 mL, 13.8 mmol). *tert*-butylhydrogenperoxide (5.25 M solution in hexanes, 26.3 mL, 137.9 mmol) was added and the resulting solution was stirred for 30 min. After this time, (*Z*)-dodec-2-en-1-ol (**4**) (12.7 g, 69 mmol) was added and the resulting mixture was stirred for 18 h at -20 °C. The reaction mixture was added to a beaker containing a cooled (0 °C) solution of $FeSO_4$ and tartaric acid[10] and the resulting mixture was stirred for 10 min. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were added to a cooled (0 °C) stirred solution of 30% NaOH in brine and the resulting mixture was stirred for 1h at 0 °C. The mixture was diluted with H_2O (50 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 40 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to afford the crude epoxide **5**. Purification of the crude product by flash chromatography (silica gel, 5:1 hexanes:EtOAc) afforded ((2*S*,3*R*)-3-nonyloxiran-2-yl)methanol (**5**) (8.57 g, 62 %, 88% ee) as a white solid.

The enantiomeric ratio of **5** ((2*S*,3*R*):(2*R*,3*S*) 94:6) was measured on a HP5890 GC equipped with a custom-made chiral GC column coated with a 1:1 mixture of heptakis(2,6-di-O-methyl-3-O-pentyl)-β-cyclodextrin and OV-1701.[22] Temperature program: 140 °C isothermal. (2*R*,3*S*) t_R = 34.5 min, (2*S*,3*R*) t_R = 35.4 min.

Preparation of (±)-(3-nonyloxiran-2-yl)methanol (±)-(5)



To a cold (0 °C) stirred solution of (*Z*)-dodec-2-en-1-ol (**4**) (8.00 g, 43.4 mmol) in CH_2Cl_2 (400 mL) was added *m*-CPBA (29.1 g, 130.1 mmol) portion wise over 30 min. The reaction mixture was stirred at 0 °C for 1 h, warmed to rt and stirred for a further 16 h. After this time the reaction mixture was poured into a saturated solution of $Na_2S_2O_3$, the phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were washed with a saturated solution of $NaHSO_3$ (100 mL), H_2O (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated to afford the crude epoxide **5**. The crude product was purified by flash chromatography (silica gel, 10:1 hexanes:EtOAc) to afford (±)-(3-nonyloxiran-2-yl)methanol (±)-(**5**) (6.5 g, 75 %) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.86 (m, 1H), 3.68 (m, 1H), 3.15 (dt, 1H, *J* = 7.0, 4.2 Hz), 3.03 (m, 1H), 1.90 (br. s, 1H), 1.63 - 1.20 (m, 16H), 0.87 (t, 3H, *J* = 7.0 Hz).

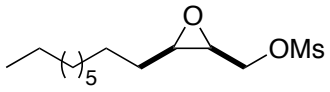
^{13}C NMR (150 MHz, $CDCl_3$) δ: 60.9, 57.3, 56.8, 31.9, 29.5, 29.5, 29.4, 29.3, 28.0, 26.6, 22.6, 14.1.

IR (neat): 3393, 2953, 2910, 2915, 2850, 1467, 1323, 1031, 850 cm^{-1}

Exact mass calculated for $C_{12}H_{25}O_2$: 201.1849 (M+H); found: 201.1851(M+H).

Racemic and enantiomerically enriched (3-nonyloxiran-2-yl)methanol (**5**) were mixed in a ratio to give an enantiomeric ratio of 80:20 (2*S*,3*R*):(2*R*,3*S*) (60% ee).

Preparation of ((2*S*,3*R*)-3-nonyloxiran-2-yl)methyl methanesulfonate (6)



To a cold (0 °C) stirred solution of ((2*S*,3*R*)-3-nonyloxiran-2-yl)methanol (**5**) (13.5 g, 67.8 mmol) and Et_3N (14.2 mL, 101.6 mmol) in CH_2Cl_2 (250 mL) was added methanesulfonyl chloride (6.8 mL, 88 mmol) dropwise over 10 min. The reaction mixture was stirred at 0 ºC for 30 min, at which time the reaction mixture was filtered. The filtrate washed with H_2O (100 mL), a 1M aqueous solution of HCl (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the crude mesylate **6** which was used in the subsequent reaction without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.45 (dd, 1H, *J* = 12.0, 4.0 Hz), 4.22 (dd, 1H, *J* = 12.0, 7.5 Hz), 3.26 (dt, 1H, *J* = 8.0, 4.0 Hz), 3.09 (s, 3H), 3.09-3.05 (m, 1H), 1.57-1.27 (m, 16H), 0.88 (t, 3H, *J* = 7.0 Hz).

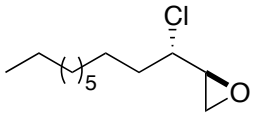
^{13}C NMR (100 MHz, $CDCl_3$) δ: 68.2, 56.8, 53.4, 37.9, 31.8, 29.4, 29.4, 29.3, 29.2, 27.9, 26.6, 22.6, 14.0.

IR (neat): 2920, 2358, 2337, 1259, 1359, 1175, 954 cm^{-1}.

Exact mass calculated for $C_{13}H_{26}SO_4$: 278.1558 (M+); found: 278.1552 (M+).

$[\alpha]_D^{25}$: -5.9 (c = 1.0, CH_2Cl_2).

Preparation of (*S*)-2-((*S*)-1-chlorodecyl)oxirane (7)



To a cold (-20 °C) stirred solution of ((2*S*,3*R*)-3-nonyloxiran-2-yl)methyl methanesulfonate (**6**) (18.9 g, 67.8 mmol) in CH_2Cl_2 (250 mL) was added Et_2AlCl (1M in hexane, 74.6 mL, 74.6 mmol) dropwise over 30 min. The reaction mixture was stirred at -20 °C for 4 h, at which time the reaction was quenched by drop-wise addition of a saturated aqueous solution of tartaric acid (50 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 100 mL).

The combined organic phases were washed successively with 1N HCl (100 mL), saturated aqueous solution of $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude chlorohydrin which was used in the subsequent reaction without purification.

To a stirred solution of the crude chlorohydrin in MeOH (400 mL) was added K_2CO_3 (14.1 g, 101.7 mmol). The reaction mixture was stirred at rt for 40 min, after which time the reaction mixture was filtered and concentrated under reduced pressure. The crude residue was dissolved in Et_2O (250 mL), and the organic phase was washed with H_2O (2 x 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated to afford the crude epoxychloride **7**. The crude product was purified by flash chromatography (silica gel, 20:1 hexanes:EtOAc) to afforded (*S*)-2-((*S*)-1-chlorodecyl)oxirane (**7**) (9.3 g, 63 % over 3 steps) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.88 (ddd, 1H, *J* = 8.5, 7.0, 5.5 Hz), 3.13 (ddd, 1H, *J* = 7.0, 4.0, 2.5 Hz), 2.90 (dd, 1H, *J* = 5.0, 4.0 Hz), 2.72 (dd, 1H, *J* = 5.0, 2.5 Hz), 1.88-1.73 (m, 2H), 1.60-1.50 (m, 1H), 1.47-1.39 (m, 1H), 1.33-1.23 (m, 12H), 0.88 (t, 3H, *J* = 7.0 Hz).

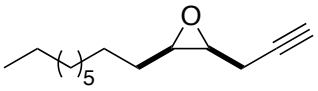
^{13}C NMR (100 MHz, $CDCl_3$) δ 63.4, 55.4, 47.1, 34.8, 31.9, 29.5, 29.4, 29.3, 29.1, 26.2, 22.7, 14.1

IR (neat): 2953, 2925, 2855, 1465, 1253 cm^{-1}

Exact mass calculated for $C_{12}H_{23}OCl$: 218.1446 (M+); found: 218.1437 (M+)

$[\alpha]_D^{25}$: -2.4° (c = 1.0, CH_2Cl_2)

Preparation of (2*R*,3*S*)-2-nonyl-3-(prop-2-ynyl)oxirane (12)



To a cold (-78 °C) stirred solution of trimethylsilylacetylene (**11**) (3.55 mL, 14.7 mmol) in THF (85 mL) was added *n*-butyllithium (2.5 M solution in hexanes, 9.4mL, 32 mmol). The reaction mixture was stirred for 5 min at which time BF_3•OEt_2 (2.89 mL, 23.4 mmol) was added. The reaction mixture was stirred for another 5 minute and a solution of (*S*)-2-((*S*)-1-chlorodecyl)oxirane (**7**) (2.70 g, 12.3 mmol) in THF (10 mL) was then added. The reaction mixture was stirred at -78 °C for 30 min, at which time a saturated aqueous solution of NH_4Cl (10 mL) was added, and the mixture was allowed to warm to rt. The aqueous phase was extracted with Et_2O (3 x 100 mL), and the combined organics phases were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude chlorohydrin that was used in the subsequent reaction without purification.

To a stirred solution of the chlorohydrin in MeOH (100 mL), was added K_2CO_3 (5.97 g, 43.2 mmol). The reaction mixture was stirred at rt for 5 h, at which time the reaction mixture was filtered and concentrated under reduced pressure. The crude residue was dissolved in Et_2O (250 mL), and the organic phase was washed with H_2O (2 x 100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated to afford the crude epoxyalkyne. The crude product was purified by flash chromatography (silica gel, 20:1 hexanes:EtOAc) to afford (2*R*,3*S*)-2-nonyl-3-(prop-2-ynyl)oxirane (**12**) (1.72 g, 66% over 2 steps) as a colourless oil.

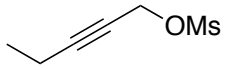
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.15 (ddd, 1H, *J* = 7.0, 5.5, 4.0 Hz), 2.99-2.95 (m, 1H), 2.58 (ddd, 1H, *J* = 17.0, 5.5, 2.5 Hz), 2.28 (ddd, 1H, *J* = 17.0, 7.0, 2.5 Hz), 2.05 (t, 1H, *J* = 2.5 Hz), 1.58-1.21 (m, 16H), 0.88 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 79.5, 70.3, 57.0, 54.8, 31.9, 29.5, 29.5, 29.5, 29.3, 27.5, 26.5, 22.7, 18.5, 14.1

IR (neat): 3313, 2955, 2925, 2855, 1465 cm^{-1}

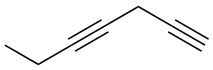
Exact mass calculated for $C_{14}H_{24}O$: 208.1835 (M+); found: 208.1827 (M+)

Preparation of pent-2-ynyl methanesulfonate (13)



To a cold (0 ºC) stirred solution of 2-pentyn-1-ol (**14**) (16.5 mL, 178 mmol) and Et_3N (37.0 mL, 267 mmol) in CH_2Cl_2 (250 mL) was added methanesulfonyl chloride (17.8 mL) dropwise over 15 min. The reaction mixture was then stirred at 0 ºC for a 45 min, after which time the mixture was filtered. The filtrate washed with H_2O (100 mL), a 1M aqueous solution of HCl (100 mL), and brine (100 mL), then dried ($MgSO_4$), and concentrated to give crude pent-2-ynyl methanesulfonate (**13**) (25.7 g, 89 %), which was used in the subsequent reaction without further purification. The spectral data obtained for **13** was in agreement with that reported for this compound.[23]

Preparation of hepta-1,4-diyne (8)



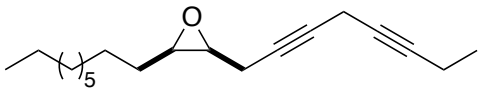
K_2CO_3 (42.6 g, 308 mmol), CuI (29.4 g, 154 mmol) and NaI (46.2 g, 308 mmol) were charged to a flask fitted with an overhead mechanical stirrer and the flask was then evacuated and backfilled with argon three times. DMF (270 mL) was then added, followed by a solution of pent-2-ynyl methanesulfonate (**13**) (25 g, 154 mmol) in DMF (80 mL), and trimethylsilylacetylene (**11**) (43.9 mL, 308 mmol). The resulting mixture was stirred at rt for 18 h then filtered. The filtrate was then diluted with Et_2O (500 mL) and washed with H_2O (250mL) and brine (7 x 250 mL), then dried

($MgSO_4$), and concentrated to afford the crude diyne, which was used in the subsequent reaction without further purification.

To a stirred solution of hepta-1,4-diynyltrimethylsilane (17.3 g, 105 mmol) in DMF (400 mL) was added KF•$2H_2O$ (29 .7 g, 316 mmol). The reaction mixture was stirred at rt for 4 h, after which time H_2O (100 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 200 mL), and the combined organic phases were washed with H_2O (3 x 200 mL) and brine (7 x 200 mL), then dried ($MgSO_4$) and concentrated under reduced pressure at 0 °C to afford the crude diyne **8**. Hepta-1,4-diyne (9.82 g, 70%) (**8**), which required no further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.15 (dt, 2H, *J* = 2.5, 2.5 Hz), 2.18 (qt, 2H, *J* = 7.5, 2.5 Hz), 2.06 (t, 1H, *J* = 2.5 Hz), 1.12 (t, 3H, *J* = 7.5 Hz).

Preparation of (2*R*,3*S*)-2-nonyl-3-(octa-2,5-diynyl)oxirane (10)



Method A (from **12**)**:** K_2CO_3 (2.40 g, 17.4 mmol), CuI (3.31 g, 17.4 mmol) and NaI (2.60 g, 17.4 mmol) were charged to a flask and the flask evacuated and backfilled with argon three times. DMF (80 mL) was then added, followed by a solution of (2*R*,3*S*)-2-nonyl-3-(prop-2-ynyl)oxirane (**7**) (1.81 g, 8.27 mmol) in DMF (10 mL), and pent-2-ynyl methanesulfonate (**13**) (4.22 g, 26.0 mmol). The reaction mixture was stirred at rt for 24 h, at which time the reaction mixture was filtered and the filtrate diluted with Et_2O (100 mL). The organic phase was washed with H_2O (50 mL), brine (7 x 50 mL), dried ($MgSO_4$), and concentrated to afford the crude epoxydiyne **10**. The crude product was purified by flash chromatography (silica gel, 20:1 hexanes:EtOAc) to afford (2*R*,3*S*)-2-nonyl-3-(octa-2,5-diynyl)oxirane (**10**) (1.35 g, 57 %). The spectral data obtained for **10** was in agreement with literature reported values.[5b]

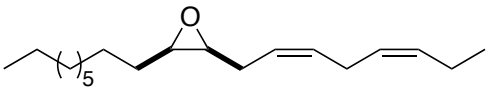
Method B (from **7**)**:** To a cold (-78 °C) stirred solution of hepta-1,4-diyne (**8**) (700 mg, 7.6 mmol) in THF (30 mL) was added *n*-butyllithium (2.4 M solution in hexanes, 2.98 mL, 7.6 mmol). The reaction mixture was stirred for 1 min at which time BF_3•OEt_2 (0.94 mL, 7.6 mmol) was added. The reaction mixture was stirred for 60 seconds at which time a solution of (*S*)-2-((*S*)-1-chlorodecyl)oxirane (**7**) (1.11 g, 5.06 mmol) in THF (10 mL) was added. The reaction mixture was stirred at -78 °C for 45 min, at which time a saturated aqueous solution of NH_4Cl (5 mL) was added, and the mixture was allowed to warm to rt. The aqueous phase was extracted with Et_2O (3 x 100 mL), and the combined organics phases were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude chlorohydrin **9** that was used in the subsequent reaction without purification.

To a stirred solution of the chlorohydrin **9** in MeOH (50 mL), was added K_2CO_3 (2.10 g, 15.2 mmol). The reaction mixture was stirred at rt for 5 h, at which time the reaction mixture was filtered and concentrated under reduced pressure. The crude residue was dissolved in Et_2O (250 mL), and the organic phase was washed with H_2O (2 x 100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated to afford the crude epoxydiyne **10**. The crude product was purified by flash chromatography (silica gel, 20:1 hexanes:EtOAc) to afford (2*R*,3*S*)-2-nonyl-3-(octa-2,5-diynyl)oxirane (**10**) (444 mg, 32 %). The spectral data obtained for **10** was in agreement with literature reported values.[5b]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.13 (m, 3H), 2.94 (m, 1H), 2.56 (ddt, 1H, *J* = 17.0, 5.5, 2.5 Hz), 2.27 (br. d, 1H, *J* = 7.0 Hz), 2.17 (m, 1H), 1.50 (m, 2H), 1.60-1.15 (m, 14H), 1.12 (t, 3H, *J* = 7.5 Hz), 0.88 (t, 3H, *J* = 6.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 82.0, 76.7, 75.4, 73.3, 57.1, 55.1, 31.9, 29.5, 29.5, 29.5, 29.3, 27.5, 26.5, 22.7, 18.8, 14.1, 13.8, 12.4, 9.7.

Preparation of (2*R*,3*S*)-2-nonyl-3-((2*Z*,5*Z*)-octa-2,5-dienyl)oxirane (**1**)



To a cold (0 °C) stirred solution of $Ni(OAc)_2$•$4H_2O$ (454 mg, 1.8 mmol) in MeOH (60 mL) was added $NaBH_4$ (69 mg, 1.8 mmol) (caution: vigorous gas evolution). The reaction was allowed to warm to rt and stirred for 5 min. After this time 1,2-diaminoethane (0.24 mL, 3.6 mmol) and cyclohexene (1.48 mL, 14.6 mmol) were added and the reaction mixture stirred for a further 5 min. A solution of (2*R*,3*S*)-2-nonyl-3-(octa-2,5-diynyl)oxirane (**10**) (1g, 3.6 mmol) in MeOH (20 mL) was then added. The reaction vessel was evacuated and backfilled with hydrogen 3 times and the reaction mixture stirred under an atmosphere of hydrogen for 4 h. The reaction mixture was then filtered through a pad of Celite®, which was washed thoroughly with MeOH. The filtrate was evaporated under reduced pressure, and the residue diluted with Et_2O (100 mL). The organic phase was washed with H_2O (2 x 50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated to afford the crude product. The crude product was purified by flash chromatography (20% $AgNO_3$/silica gel, 40:1 hexanes:EtOAc) to afford (2*R*,3*S*)-2-nonyl-3-((2*Z*,5*Z*)-octa-2,5-dienyl)oxirane (**1**) (803 mg, 81 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.55 – 5.37 (m, 3H), 5.34 – 5.26 (m, 1H), 2.97 – 2.90 (m, 2H), 2.81 (t, 2H, *J* = 7.0 Hz), 2.45 – 2.37 (m, 1H), 2.27 – 2.17 (m, 1H), 2.07 (dp, 2H, *J* = 7.6, 0.8 Hz), 1.54 – 1.22 (m, 16H), 0.98 (t, 3H, *J* = 7.5 Hz), 0.88 (t, 3H, *J* = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.2, 130.8, 126.7, 124.3, 57.2, 56.4, 31.9, 29.6, 29.5, 29.3, 27.8, 26.6, 26.3, 25.7, 22.7, 20.6, 14.2, 14.1.

IR (neat): 3013, 2959, 2924, 2854, 1730, 1463, 1380, 1272, 1070, 720 cm^{-1}

Exact mass calculated for $C_{19}H_{35}O$: 279.2682 (M+H); found: 279.2680 (M+H)

$[\alpha]_D^{25}$: -4.7° (c = 8.5, $CHCl_3$), lit. $[\alpha]_D^{25}$-4.3° (c = 1.15, $CHCl_3$)[5b]

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