

Synthesis of Eleutherobin-Like Potential Microtubule Stabilising Agents

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ASLIB Abstract

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This thesis describes synthetic studies towards the tricyclic terpene framework of the cytotoxic natural product eleutherobin, and the investigation of biocatalytic methodology towards late-stage functionalisation of the structure.

Chapter 1 provides an introduction to the biomedical significance of the natural product and to the various synthetic studies reported to date.

Chapter 2 explores intramolecular Diels–Alder approaches to the construction of the nine- and six- membered rings present in the natural product.

Chapter 3 describes alternative approaches to the eleutherobin core structure, leading to a formal synthesis of the natural product. The synthetic sequence developed is applied to the preparation of a small library of furanoid analogues of eleutherobin.

Chapter 4 details the development of methodology for the one-pot preparation of (*E*)-4-methylhexa-3,5-dien-1-ol, and its use in an intermolecular Diels–Alder / lactonisation sequence to achieve enantioselective preparation of an important lactone building block.

Chapter 5 describes studies on the mP450-mediated oxidation of various eleuthoside structures obtained.

Finally, Chapter 6 details the construction of an electrochemical flow cell, and its use for the anodic oxidation of furfuryl alcohol derivatives.

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SPIRIT. We are immortal, and do not forget;
We are eternal; and to us the past
Is as the future, present. Art thou answer'd?
MANFRED. Ye mock me—but the power which brought ye here
Hath made you mine. Slaves, scoff not at my will!
The mind, the spirit, the Promethean spark,
The lightning of my being, is as bright,
Pervading, and far darting as your own,
And shall not yield to yours, though coop'd in clay!

– Lord Byron, *Manfred*, 1.1.154–162

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Abbreviations

18-C-6	18-crown-6,1,4,7,10,13,16-hexaoxacyclooctadecane
Å	Ångström, 10^{-10} m
μm	micrometre, 10^{-6} m
μW	microwave irradiation
Ac	acetyl
ADP	adenosine diphosphate
Alk	alkyl
ATP	adenosine triphosphate
aq.	aqueous
BHT	butylated hydroxytoluene
BINOL	1,1’-bi-2-naphthol
Bn	benzyl
b.r.s.m.	based on recovered starting material
Bu	butyl
Bz	benzoyl
ca.	circa (approximately)
CAN	ceric ammonium nitrate
cat.	catalytic amount, catalyst
CI	chemical ionisation
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	day
dba	dibenzylideneacetone

DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DET	diethyltartrate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutyl aluminum hydride
DIPEA	diisopropyl ethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMDO	dimethyl dioxirane
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DTBP	2,5-di-*tert*-butylpyridine
d.r.	diastereomeric ratio
equiv	equivalent
ESI	electrospray ionisation
Et	ethyl
et al.	and others
FAD	flavin adenine nucleotide
FEP	fluorinated ethylene propylene

FMN	flavin mononucleotide
FI	field ionisation
g	gram
GC	gas chromatography
GDP	guanosine diphosphate
GTP	guanosine triphosphate
hν	(ultraviolet) irradiation
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
h	hour
HSQC	heteronuclear single-quantum coherence
i-	iso-
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
IMDA	intramolecular Diels–Alder
IR	infrared
J	coupling constant
KHMDS	potassium *bis*-(trimethylsilyl)amide
L	litre
LA	Lewis acid
LDA	lithium diisopropylamide
LiHMDS	lithium *bis*-(trimethylsilyl)amide
lit.	literature value

LUMO	lowest unoccupied molecular orbital
M	mole/litre
m/z	mass/charge ratio
m-CPBA	3-chloroperbenzoic acid
mP450	mutant cytochrome P450
Me	methyl
Mes	mesityl
mg	milligram
MHz	megahertz
mL	millilitre
mmol	millimole
mol	mole
MOM	methoxymethyl
m.p.	melting point
MS	molecular sieves, mass spectrometry
Ms	methanesulfonyl
MVK	methyl vinyl ketone (3-buten-2-one)
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NaHMDS	sodium *bis*-(trimethylsilyl)amide
NHK	Nozaki–Hiyama–Kishi
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate

PDC	pyridinium dichromate
PEEK	polyether ether ketone
Ph	phenyl
PG	protecting group
PMB	4-methoxybenzyl
PMMA	poly(methyl methacrylate)
PMP	4-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
PTFE	polytetrafluoroethylene
Pr	propyl
quant.	quantitative
RCM	ring-closing metathesis
R_f	retention factor
rpm	repetitions per minute
RT	room temperature
s-	sec-
sat.	saturated
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEBA	benzyltriethylammonium chloride
TES	triethylsilyl
Tf	trifluoromethanesulfonyl

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
tol.	toluene
Ts	4-toluenesulfonyl
vs.	versus
v/v	volume-to-volume ratio

Chapter 1: Introduction

Natural Products as drugs

Since the early days of civilisation humanity has taken advantage of the biological activity inherent in many natural products by using them as therapeutic agents: extracts of the opium poppy (*Papaver somniferum*) have been utilised since the time of ancient Summeria as painkillers and sedatives, these effects now known to derive from alkaloids, such as morphine, present in the plant. The bark of trees of the genus *Cinchona*, containing quinine, have been historically used as antimalarial medication. Salicin, derived from the bark of *Salix alba* (willow tree) possesses anti-inflammatory properties and led to the discovery of acetylsalicylic acid (aspirin). Recently, analysis of the bones of ancient Nubians showed that they regularly consumed tetracycline, an antibiotic, potentially *via* beer made from grain contaminated by bacteria of the genus *Streptomyces*.[1]

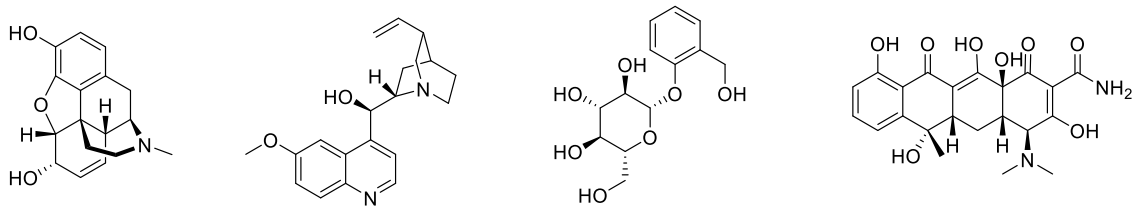


Figure 1. Examples of historically significant natural products.

In modern times, natural products maintain an important position in pharmacology; of the new drugs approved by the FDA in the period 1981–2010, 34% were natural products or their derivatives.[2] An important property that sets apart natural products from man-made compounds is their structural complexity: their complex carbon frameworks are usually rigid and highly three-dimensional by virtue of the high proportion of sp^3 hybridised carbon atoms they contain; this enables the modulation of biological targets traditionally considered difficult, such as protein-protein interactions. In comparison, the structures of *de novo*

designed drugs are typically flatter and more flexible, largely due to considerations of synthetic accessibility.

Despite their potential, the screening of natural products in the drug discovery process is hindered by the low quantities obtainable from natural sources, the long and laborious synthetic routes required for their preparation, as well as the difficult access to analogues; in recent years a number of novel approaches emerged for the synthesis of libraries of so-called "natural product-like" compounds, inspired by natural product structures and aimed at more efficiently probing chemical space.[3,4]

Natural Products in cancer chemotherapy

A survey of the small molecules currently used as drugs reveals that natural products or their close analogues account for a large proportion of anticancer and anti-infective agents; this can be linked to the postulated natural function of many as cytotoxic agents. With regards to anticancer therapy specifically, 49% of the small molecules approved in the period from 1940 to 2014 are natural products or their direct derivatives.[5] Their mechanism of action often involves the direct or indirect induction of DNA damage, which leads to apoptosis of rapidly dividing cells. Examples include mitomycin C, which is a DNA cross-linker by virtue of its aziridine ring;[6] irinotecan and topotecan, derivatives of camptothecin, which inhibit topoisomerase I causing lethal strand breaks;[7] etoposide, a derivative of podophyllotoxin, which acts as a topoisomerase II poison, again causing DNA strand breaks;[7] and doxorubicin and related anthracyclines, which intercalate between DNA bases.[8] A different mechanism of cytotoxic activity is found in compounds that interact with microtubules to halt the mitotic process; a closer examination of this mode of action requires a more detailed description of the biochemistry of microtubules.

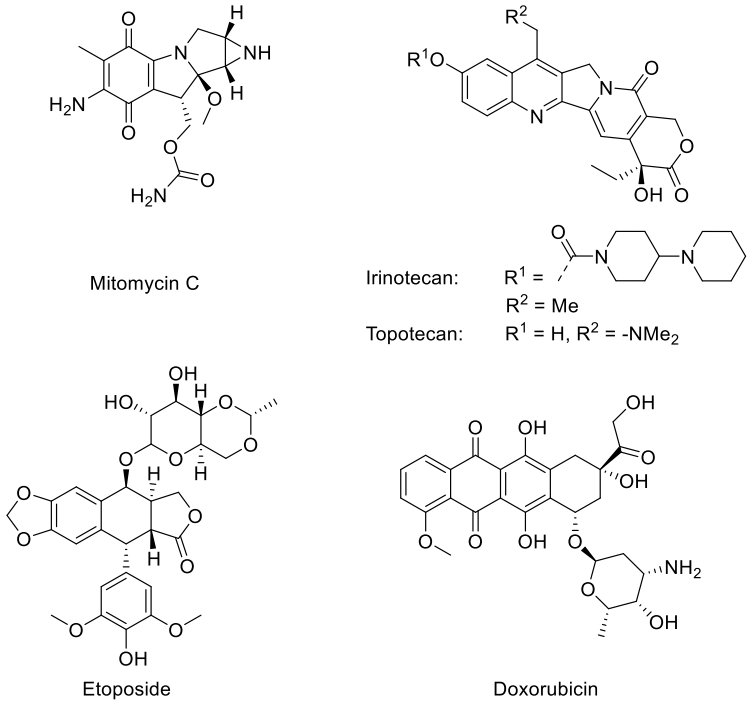


Figure 2. Examples of DNA-targeting natural products used in cancer therapy.

Microtubule structure and function

Microtubules are a key constituent of the eukaryotic cell, specifically a component of the cytoskeleton. Aside from their structural role in maintaining the cell's shape, they are involved in a number of other processes, such as in signalling, in intracellular transport and in the process of mitosis;[9] this latter function is what makes them a significant target in cancer therapy.

From a structural point of view, microtubules are long polymeric filamentous tubes, formed from the repetition of a dimeric unit composed of two proteins, α and β tubulin. The filament formed from the linear association of the tubulin heterodimers is called a *protofilament* (Figure 3a). The dimers are also associated laterally in a spiral fashion to form the walls of the microtubule, with each turn of the spiral comprising 13 dimers[9] (Figure 3b). The inner core of the microtubule is termed the *lumen*.

In the cytoplasm, microtubules are in a dynamic state, being subject to both lengthening *via* addition of tubulin dimers and shortening *via* rapid depolymerisation. They are said to be *polarised*, with the end bearing an exposed α tubulin subunit termed the (−) end and the opposite one, corresponding to a β subunit, the (+) end; elongation takes place preferentially at the latter. α and β tubulin bind a unit of GTP each, and while the GTP bound to the α subunit is stable, the corresponding molecule bound to β tubulin is rapidly hydrolysed to GDP and phosphate upon association of the free dimer with the polymer; this GDP is not exchangeable as long as the β tubulin is embedded in the polymer, while the inorganic phosphate dissociates. Microtubule polymerisation dynamics are thought to be governed by the existence, in the (+) end, of a single layer of β subunits bound to either GTP or GDP and phosphate called the GTP cap.[10]

The currently accepted model posits that tubulin-GTP assumes a "straight" conformation and associates to form protofilaments and thus microtubules; upon GTP hydrolysis the conformation of the dimer changes to a strained "curved" form that is unfavourable to the polymerised state, yet the dimer is still embedded in the microtubule as long as the GTP cap is present in the (+) end, and the structure can continue to grow (Figure 3c). If instead the GTP cap is lost, then the unstable inner part depolymerises and the microtubule shortens.[10] This dynamic behaviour is called *dynamic instability*;[11] the transition from a phase of growth or pause to one of shortening, as described above, is called a *catastrophe*, while the opposite process is called a *rescue*. A second behaviour called *treadmilling* refers to growth on one end of the microtubule accompanied by shortening of the other end.[12]

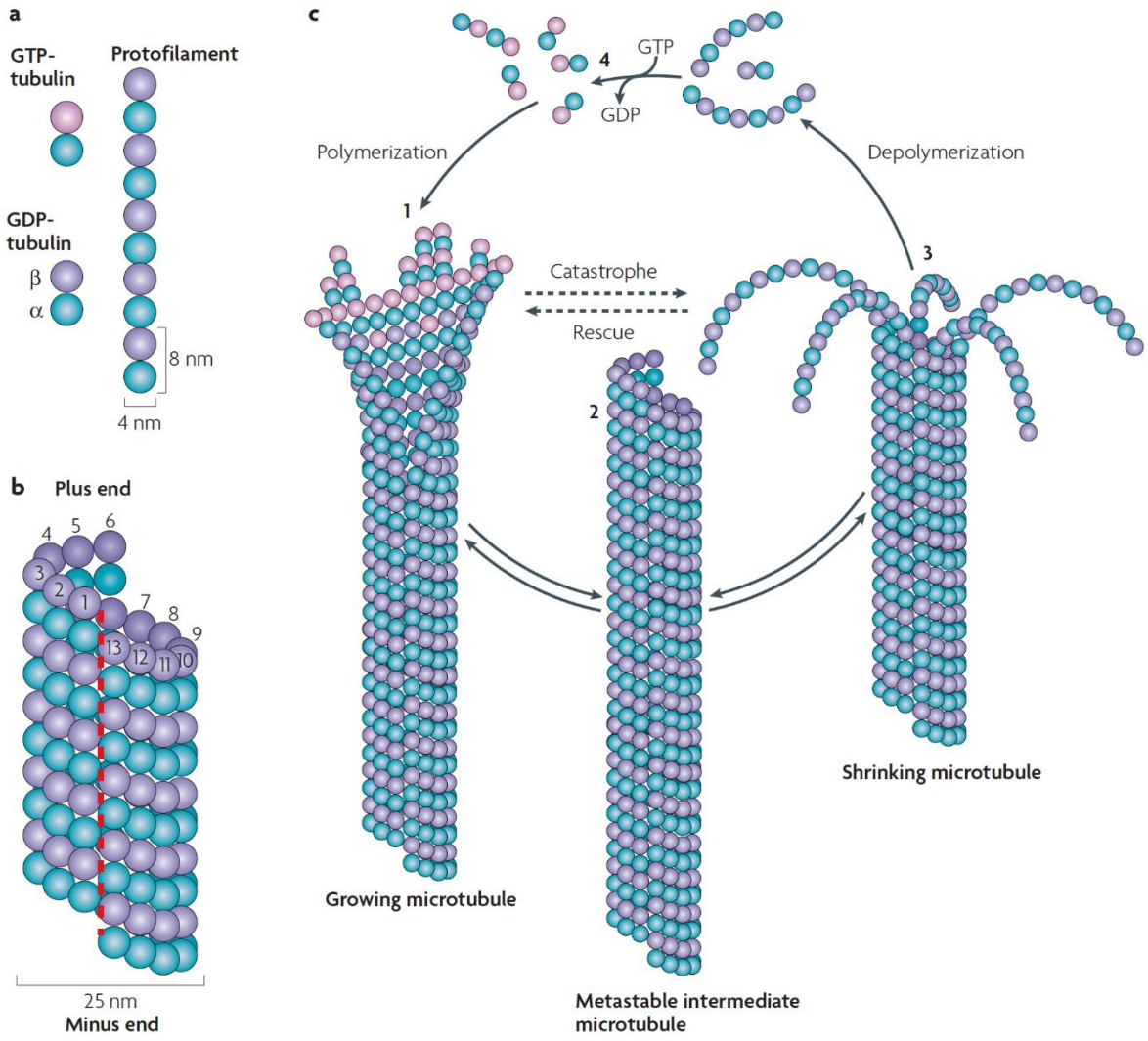


Figure 3. a: Association of tubulin dimers into protofilaments; b: microtubule structure; c: microtubule dynamics. Image adapted from Akhmanova and Steinmetz, 2008.[13]

The crystal structure of the tubulin dimer has been solved, and the density maps for α and β tubulin found to be very similar.[14,15,16] Each consists of 12 α helices (H1 to H12) and two β sheets (of 6 and 4 strands, B1 to B10). Each monomer contains what is called a Rossmann fold, a particular arrangement of β sheets characteristic of nucleotide binding proteins. A detailed view of the longitudinal and lateral interactions of the tubulin subunits within the microtubule was provided by a study by Nogales *et al.*,[17] in which docking of the dimer crystal structure into a map of the microtubule allowed the construction of a high resolution model.

The dynamic behaviour of the microtubules is of crucial importance to the process of mitosis, where they are anchored to the kinetochores of the condensed chromosomes and then drive the proper positioning of the sister chromatids on the metaphase plate. After the separation of the sister chromatids, microtubules pull the newly formed daughter chromosomes to opposite poles of the cell, at the same time lengthening the cell in preparation for the post-mitotic separation.[18]

Microtubule targeting natural products

Given the integral role of microtubules in mitosis, it is not surprising that agents that interfere with microtubule dynamics can impede the process. A number of natural products have been identified that interact with tubulin, and many act as mitotic poisons; such compounds that target dividing cells are of interest as potential anticancer agents. Though this mechanism of action is not inherently selective toward cancerous cells, these generally divide far more rapidly than healthy cells and thus are especially susceptible.

Antimitotic compounds that interact with tubulin can be classified in one of two categories, based on their effect on microtubule formation: microtubule destabilising agents, which inhibit microtubule formation, and microtubule stabilising agents, which stabilise microtubules and inhibit depolymerisation. It has been suggested that this distinction may not be accurate with regards to the mechanism of the antimitotic action of such compounds, as the typical therapeutic concentrations of both microtubule stabilising and destabilising drugs are lower than what would be necessary to affect polymer mass, and that the main effect instead derives from their effect on microtubule dynamics.[9] In general, suppression of microtubule dynamics by antimitotic drugs prevents progression from metaphase to anaphase, and the mitotically blocked cell eventually undergoes apoptosis.[19]

Microtubule destabilising agents

The first microtubule destabilising agents to be discovered are the *Vinca* alkaloids, isolated from the leaves of *Catharanthus roseus* (periwinkle); their anticancer potential was first discovered by groups at Eli Lilly[20] and at the University of Western Ontario,[21] and since then they have entered the clinic as drugs for the treatment of various malignancies. It has been determined that they bind to the β subunit of dimeric tubulin, in what is called the *Vinca domain*.[22] Other microtubule-destabilising agents include eribulin (Halaven®), a simplified analogue of the natural product halichondrin B,[23] the dolastatins, small linear peptides with remarkable antimitotic activity but considerable toxicity in *in vivo* studies,[24] and colchicine, extracted from flowers of the genus *Colchicum* and used therapeutically to treat gout.[25]

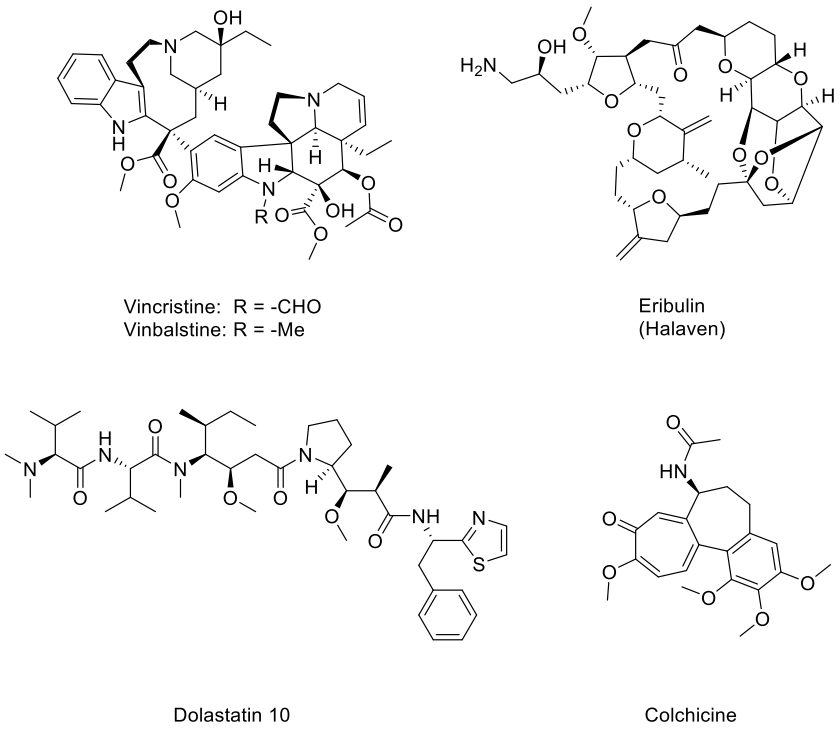


Figure 4. Examples of microtubule destabilising agents.

Microtubule stabilising agents

The first compound found to possess this mode of action was paclitaxel (taxol), isolated in 1967 from the Pacific Yew tree and found to display promising anticancer activity.[26] In 1979

Horwitz *et al*. demonstrated that this activity was due to microtubule stabilisation,[27] in contrast to the destabilising action of the *Vinca* alkaloids. The epothilones are another class of natural products, isolated from the myxobacterium *Sorangium cellulosum*, that demonstrate such activity; they have been shown to bind to the taxol site on β tubulin.[28] Their comparatively simpler structure has made them attractive targets for medicinal chemistry studies, with various analogues undergoing clinical trials.[29] Finally, eleutherobin and related natural products were found to possess promising cytotoxic properties; they will be examined in detail later on in this text.

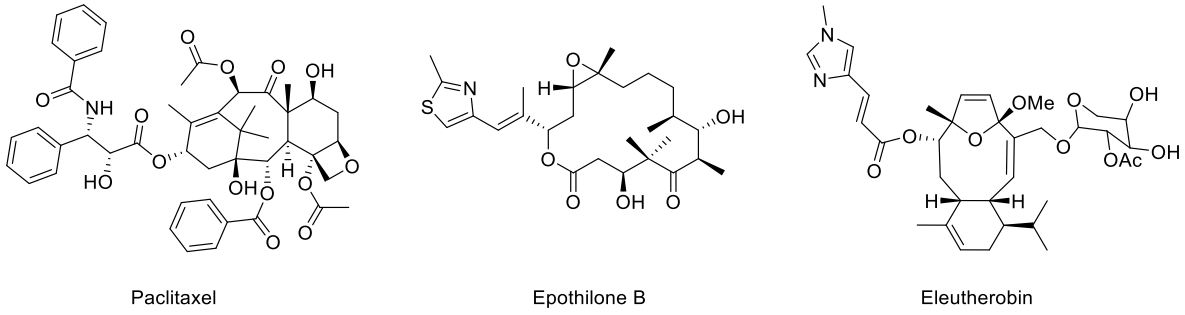


Figure 5. Examples of microtubule stabilising compounds.

Taxol: History and mechanism of action

Given the therapeutic potential of taxol, an intense research effort was mounted towards its total synthesis, which was first achieved by the Holton group[30,31] and independently by the Nicolaou group.[32] Numerous further total syntheses have emerged in the meantime, and despite their importance towards medicinal chemistry studies on the compound, their complexity has made them impractical for large-scale production of taxol. Instead, semi-synthetic approaches have been employed to this end; the first such approach, described by the Potier group, starts from 10-deacetylbaccatin which is isolated in large quantities from the European yew tree (*Taxus baccata*).[33] Paclitaxel was granted FDA approval in 1992; a close analogue, docetaxel, was approved shortly afterwards in 1995.

Paclitaxel binds to β tubulin, on the luminal side of assembled microtubules (Figure 6); its affinity for soluble tubulin is much lower.[14] The exact mechanism through which the compound gains access to its binding site on the inside surface of the microtubule is subject to debate, with one theory suggesting passage through small pores on the microtubule surface.[34] Binding of paclitaxel to tubulin induces a conformational change that increases its affinity for its neighbouring tubulin dimers thus stabilising the microtubule; its binding site is known from crystallographic studies to consist of the S9-S10 loop and portions of S7 and helixes H1, H6 and H7.[15] Taxol binding shifts a structure called the *M-loop*, known to be important in interprotofilament interaction, to a position more favourable towards microtubule stabilisation. In fact, α tubulin possesses an extra 8 amino acid residues in the B9-B10 loop in correspondence to the taxol binding site in β tubulin, with a stabilising effect on the M-loop; it is thought that taxol binding mimics the structural effect of these additional residues.[35]

Higher resolution structures of taxol bound to tubulin give some insight into the specific interactions that govern binding (Figure 7):[16] the N' and 3' phenyl rings take part in hydrophobic interaction with Val23; the 3'-phenyl ring by itself contacts Ala233, Ser236, and Phe 272. The amide nitrogen is involved in a hydrogen bond with Asp26. The 2-phenyl ring forms hydrophobic contacts with a pocket formed by Leu217, Leu219, His229 and Leu230. Thr276 on the M-loop interacts with the oxetane ring, while Pro274, Leu275, Ser277 and Arg278 are also thought to be involved in binding. The crystallographic data are complemented by mutant cell studies from the Giannakakou group[36,37] and by photoaffinity labelling studies from the Horwitz group.[38,39,40,41]

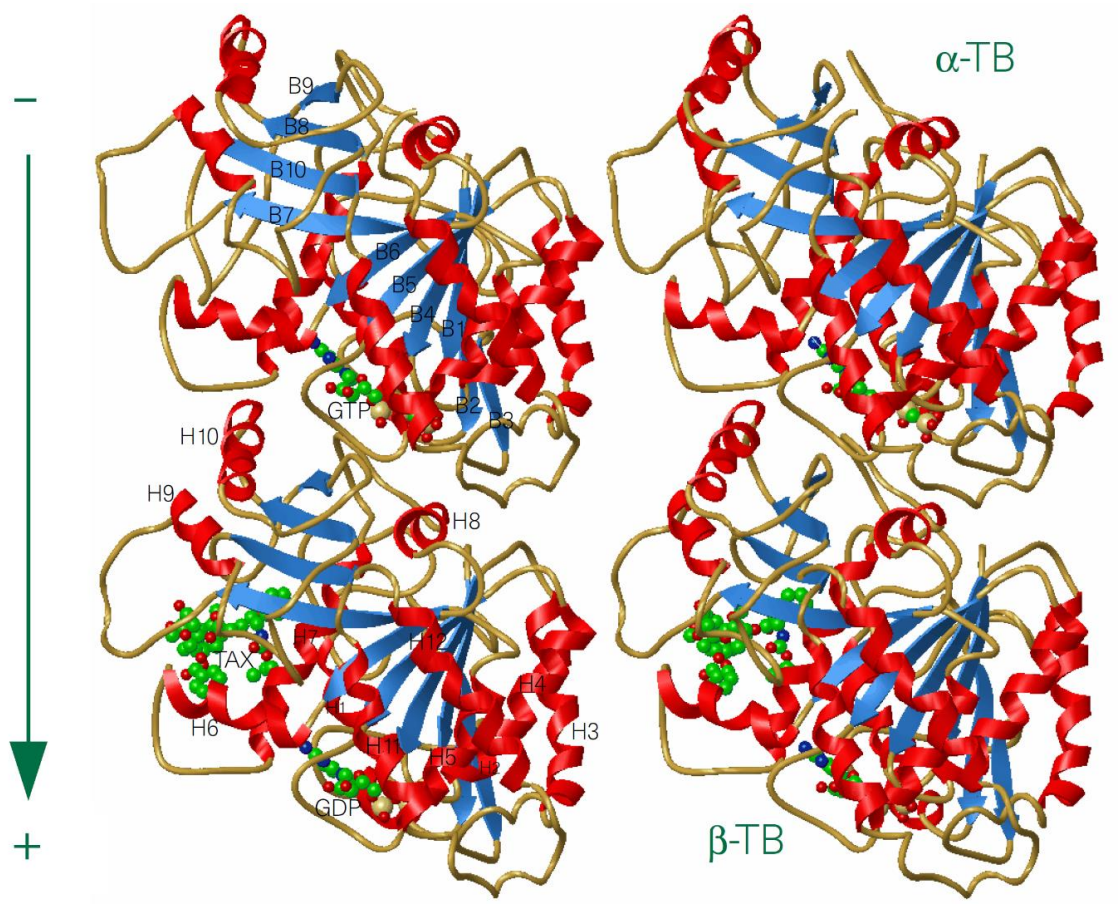


Figure 6. Crystallographic structure of taxol bound to the tubulin dimer. Image reproduced from Nogales *et al.*, 1998.[15]

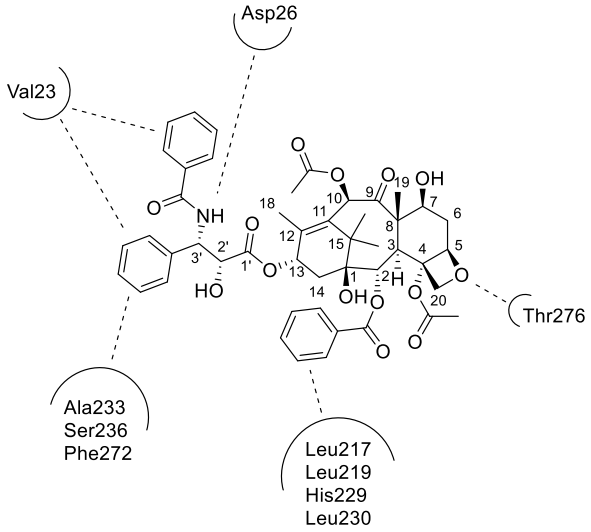


Figure 7. Paclitaxel numbering system and interactions with β tubulin as determined *via* crystallographic studies.

Eleutherobin and related natural products

Eleutherobin (Figure 8) was isolated from the soft coral *Eleutherobia sp.* in the Indian Ocean near west Australia, and found to possess cytotoxic activity comparable to that of taxol by acting as a microtubule stabiliser;[42,43,44] The eleuthosides are closely related natural products, isolated from *Eleutherobia aurea* near the coast of south Africa.[45] The sarcodictyins, also structurally related, were isolated in 1987 from the Mediterranean coral *Sarcodictyon roseum*;[46,47] their taxol-like action was reported in 1997.[48] Finally, the valdivones, isolated from the coral *Alcyonium valdivae*, display anti-inflammatory properties.[49]

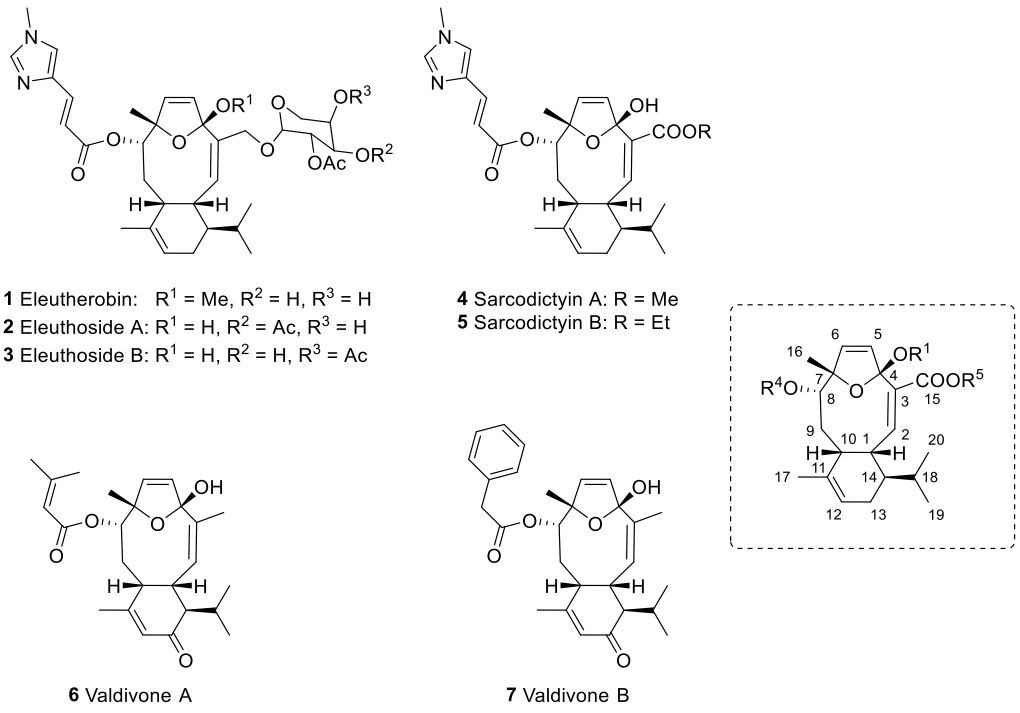


Figure 8. Left: Eleutherobin and related natural products. Right: Sarcodictyin numbering system.

These natural products, here referred to collectively as the sarcodictyins, are a subclass of diterpenes possessing the cembrane skeleton; three other groups of diterpenes have been identified to possess this general structure,[50] namely the cladiellins (also known as eunicellins), the briarellins and the asbestinins. This has led to the proposal by Faulkner[51] that

these four groups of natural products arise biosynthetically from the cembrane skeleton (Figure 9): C2-C11 cyclisation leads to cladiellins and sarcodictyins; intramolecular etherification of the cladiellin framework provides access to the briarellins, and subsequent 1,2-methyl shift gives rise to the asbestinins.

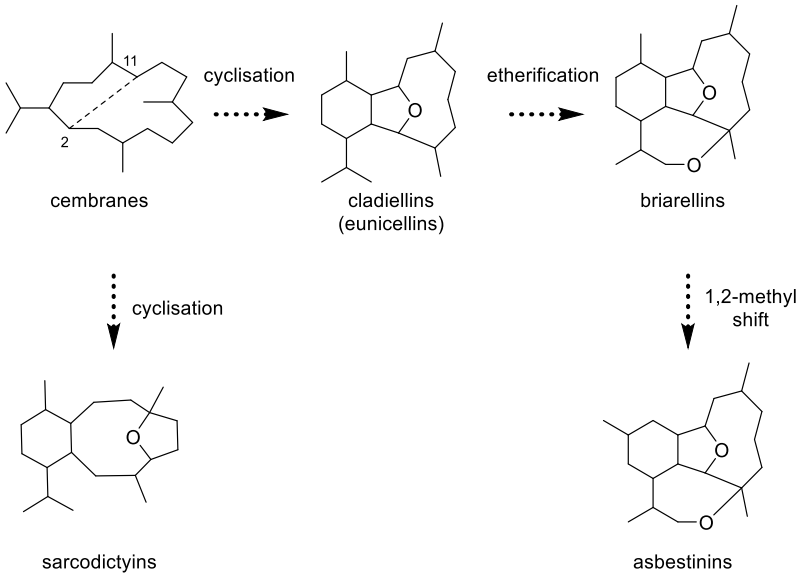


Figure 9. Faulkner's biosynthetic proposal.

Britton and colleagues have presented evidence[52] that the methyl acetal in eleutherobin is an isolation artifact arising from the use of methanol as an extraction solvent in the isolation process. In the same study the authors report the isolation of the diterpenoid caribaeorane from *Erythropodium caribaeorum*, which they propose is an intermediate in the biosynthesis of the sarcodictyins (Figure 10).

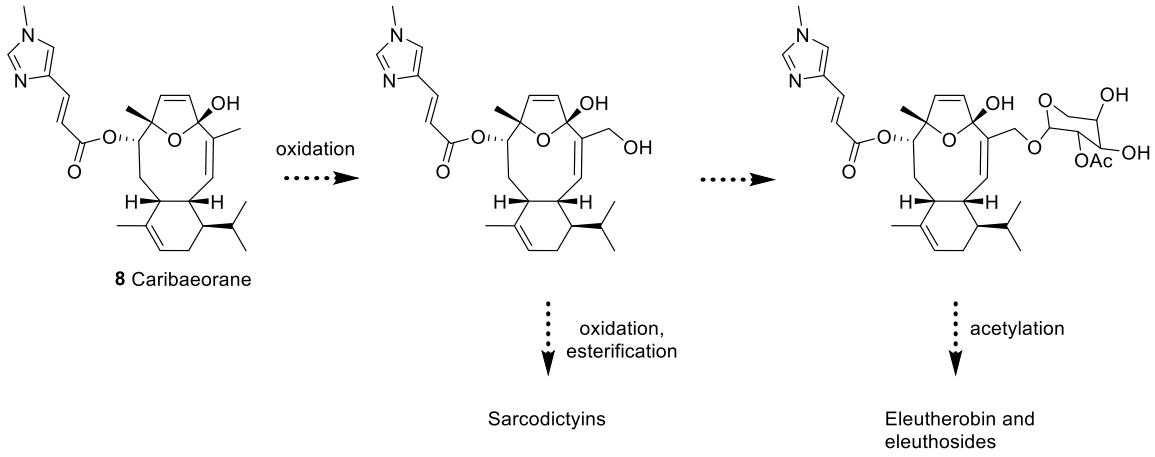


Figure 10. Britton and colleagues' biosynthetic proposal.

Medicinal chemistry studies on eleutherobin and the sarcodictyins

Understanding the binding mode of eleutherobin is an important part of the effort to derive a common pharmacophore for microtubule stabilising agents. In a study by Ojima *et al.*[53] superposition of eleutherobin with a number of other microtubule stabilising compounds indicated that the *N*-methyl urocanic acid residue on eleutherobin is important for its activity and corresponds to the amide substituent on the C13 side chain of taxol, whereas the sugar moiety was judged to be expendable. Molecular modelling studies of a sarcodictyin A analogue[37] indicated that the importance of the *N*-methyl urocanic ester side chain lies in its interaction with Phe270 of β tubulin, and that the oxygen bridge in eleutherobin could be involved in hydrogen bonding and in this manner correspond to the oxetane oxygen in taxol. The same study also provided a possible explanation for the observation that the sarcodictyins maintain activity against a number of epothilone resistant cells expressing mutant tubulin: the methyl group at C7 is found to take part in an unfavourable interaction with the hydroxyl group of Thr274, which becomes a favourable hydrophobic interaction in $274^{Thr\rightarrow Ile}$ mutants.

Nicolaou *et al*. have synthesised a library of sarcodictyin analogues;[54] compounds bearing an acetyl group in place of the *N*-methyl urocanic ester at C8 exhibited far lower microtubule stabilising activity, again demonstrating the importance of the side chain. Substitution of the

ester group at C15 with a primary alcohol, fluoride, acetate, benzoate, azide or *N*-phenyl carbamate all led to a decrease in activity. Variation in the size of the alkyl group on the acetal led only to small changes in activity. The Nicolaou group also reported the synthesis of a solid-phase combinatorial library of sarcodictyin analogues,[55] making use of the acetal as the anchoring point; here as well the variation focused on the side chains at C8 and C15 as well as the acetal. The methyl-urocanic ester was again deemed indispensable, while with regards to the C15 side chain it was found that ester groups were superior to amides.

Britton *et al*. effected a number of chemical modifications on the natural product to give a number of varied products (Figure 11);[56] compound **9** maintained antimitotic activity, as did α epoxide **10**, while β epoxide **11** demonstrated 10-fold lower activity. Analogues **12** and **13**, bearing bulkier substituents on the acetal carbon, also demonstrated antimitotic activity comparable to eleutherobin. Reduction of the double bonds on the five and six membered rings to give **14** led to a modest decrease in activity, while compound **15**, where the double bond on the *N*-methyl urocanic acid residue is reduced instead, proved far less active.

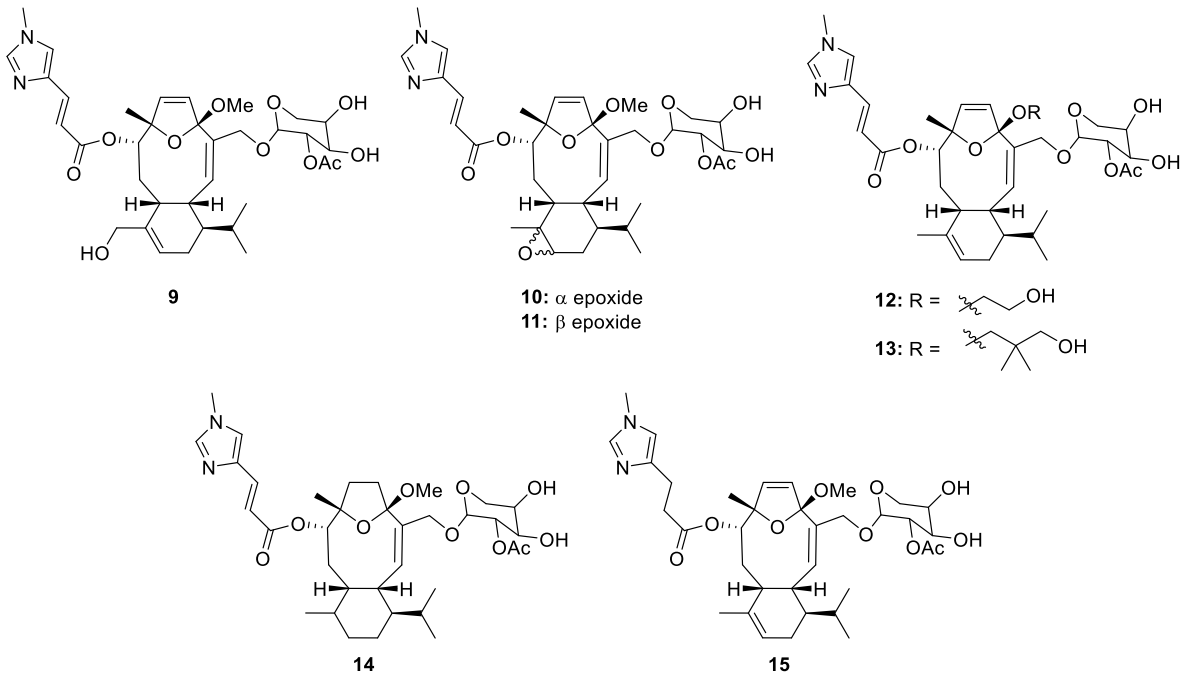


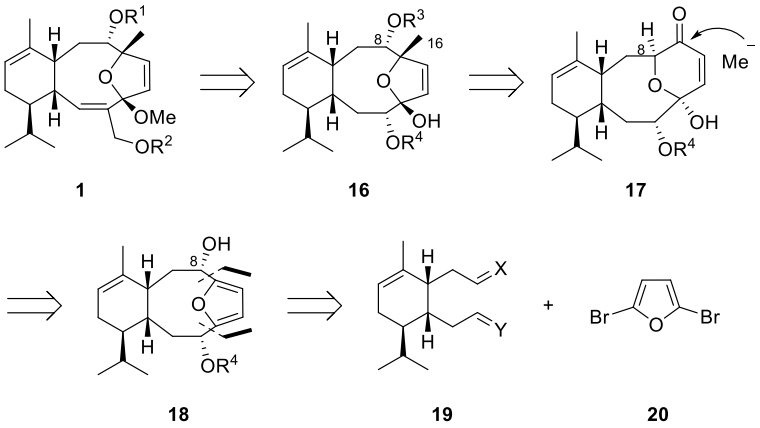
Figure 11. Eleutherobin analogues prepared by Britton *et al*.

Total syntheses of eleutherobin

Due to its promising microtubule stabilising activity as well as its novel tricyclic structure, eleutherobin attracted significant attention from synthetic chemists shortly after its isolation. Its total synthesis has been achieved by Danishefsky and Nicolaou; both groups utilised a chiral pool approach to gain access to the enantiomerically pure natural product.

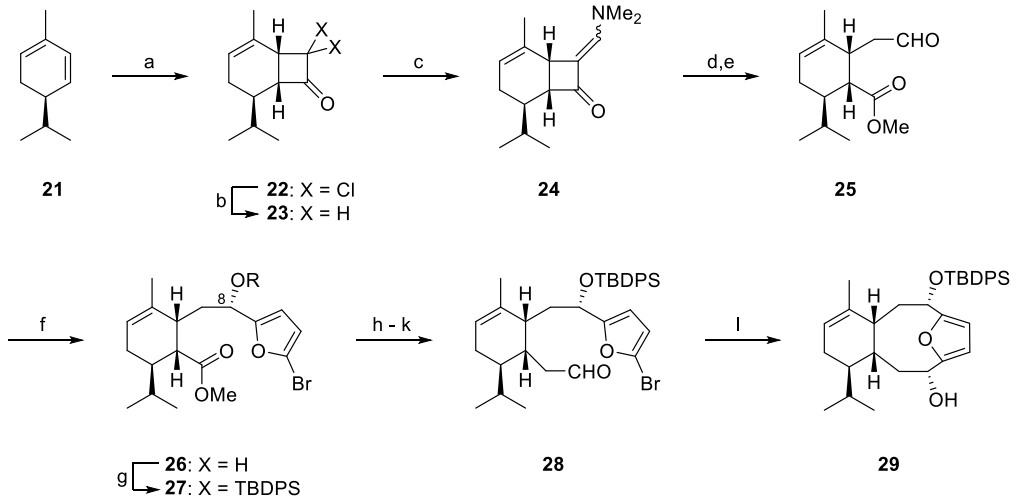
Danishefsky et al.

An outline of the strategy pursued by Danishefsky and co-workers[57,58,59] is presented in Scheme 1. Disconnecting the arabinose and urocanic ester appendages revealed simplified aglycon **16**. It was theorised that the challenging dihydrofuran sector could be accessed starting from the corresponding furan **18**, whose oxidation would lead, by virtue of the unprotected hydroxyl group on C8, to Achmatowicz reaction product **17**. Installation of the C16 methyl group would be followed by a pyranose to furanose rearrangement, potentially driven by trapping the newly revealed secondary alcohol on C8 through esterification, to reach **16**. The authors intended to reach compound **18** by a two stage addition of a nucleophile derived from 2,5-dibromofuran to cyclohexene sector **19**.



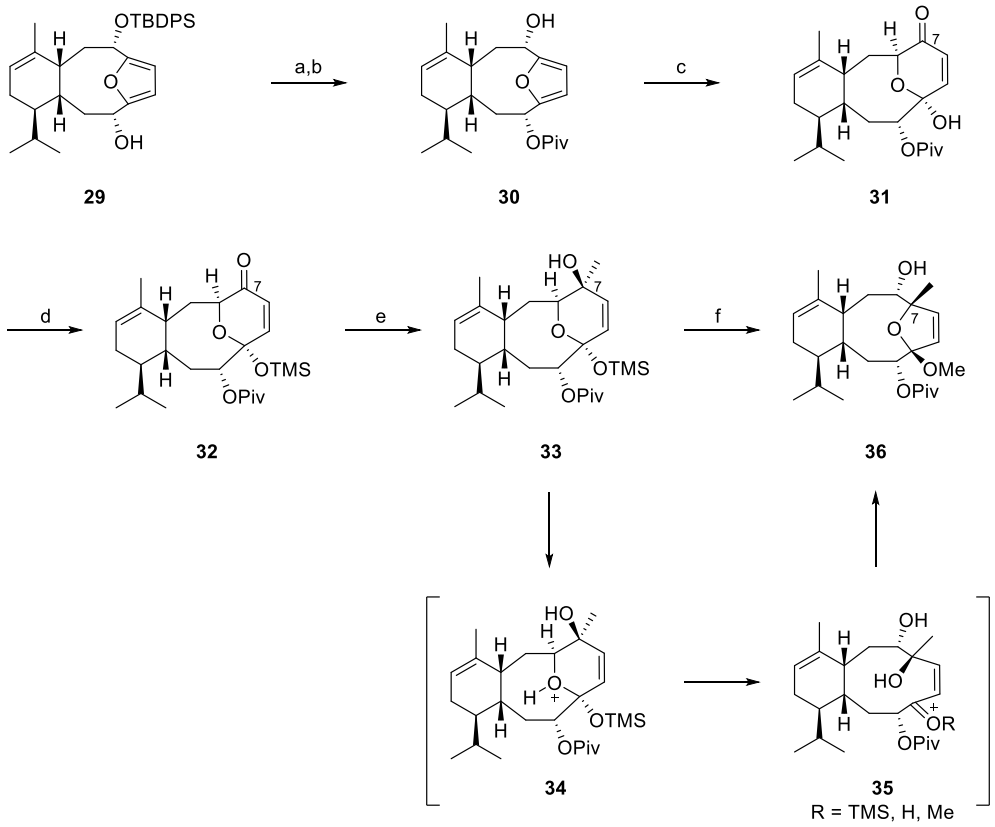
Scheme 1. Danishefsky's retrosynthetic analysis.

Commercial *R*-(−)-phellandrene **21** (Scheme 2) was thus treated with the dichloroketene generated from trichloroacetyl chloride to give ketone **22** as the major product, which was subjected to reductive dechlorination to obtain cyclobutanone **23**. Treatment of ketone **23** with Bredereck reagent led to enamine **24**, and subsequent heating with *p*-TsOH in methanol resulted in methanolysis of the cyclobutanone and concomitant formation of the dimethyl acetal from the enamine moiety; this was followed by an exchange reaction with acetone to furnish aldehyde **25**. Addition of monolithiated dibromofuran gave alcohol **26**, bearing the desired 8*S* stereochemistry, in a 57% yield b.r.s.m. The undesired 8*R* epimer formed during the reaction underwent lactonisation *via* attack on the methyl ester. Attempts were made to salvage this undesired product by inverting the 8*R* stereochemistry, but they were ultimately unsuccessful. The hydroxyl group in ester **26** was then protected as the TBDPS ether, and the ester was extended to aldehyde **28** *via* a four step sequence consisting of reduction to the alcohol, mesylation, substitution with KCN and then reduction. Attempts to achieve the cyclisation by a free radical method, by lithiation or by SmI_2 treatment to provide the desired furanocycle were all unsuccessful; the authors attribute this to the highly strained character of the desired product. Intramolecular Nozaki–Hiyama–Kishi reaction of bromo-aldehyde **28**, however, proved successful in forming the tricyclic core of the natural product in 70% yield.



Scheme 2. a) trichloroacetyl chloride, Zn, Et_2O, sonication, 0 °C, 65%; b) Zn, MeOH, NH_4Cl, 87%; c) *t*-BuOCH(NMe_2)$_2$, 60 °C, 75%; d) *p*-TsOH·H_2O, MeOH, 60 °C; e) *p*-TsOH·H_2O, acetone, 60% for two steps; f) 2,5-dibromofuran, *n*-BuLi, THF, −78 °C, 57%; g) TBDPSCl, imidazole, DMAP, 0 °C, 97%; h) DIBAL-toluene, DCM, −78 °C, >95%; i) MsCl, pyridine, DMAP, 0 °C, >95%; j) KCN, 18-crown-6, CH_3CN, 80 °C, 96%; k) DIBAL-toluene, toluene, −78 °C → 0 °C, 84%; l) $CrCl_2$, $NiCl_2$, DMF, 74%.

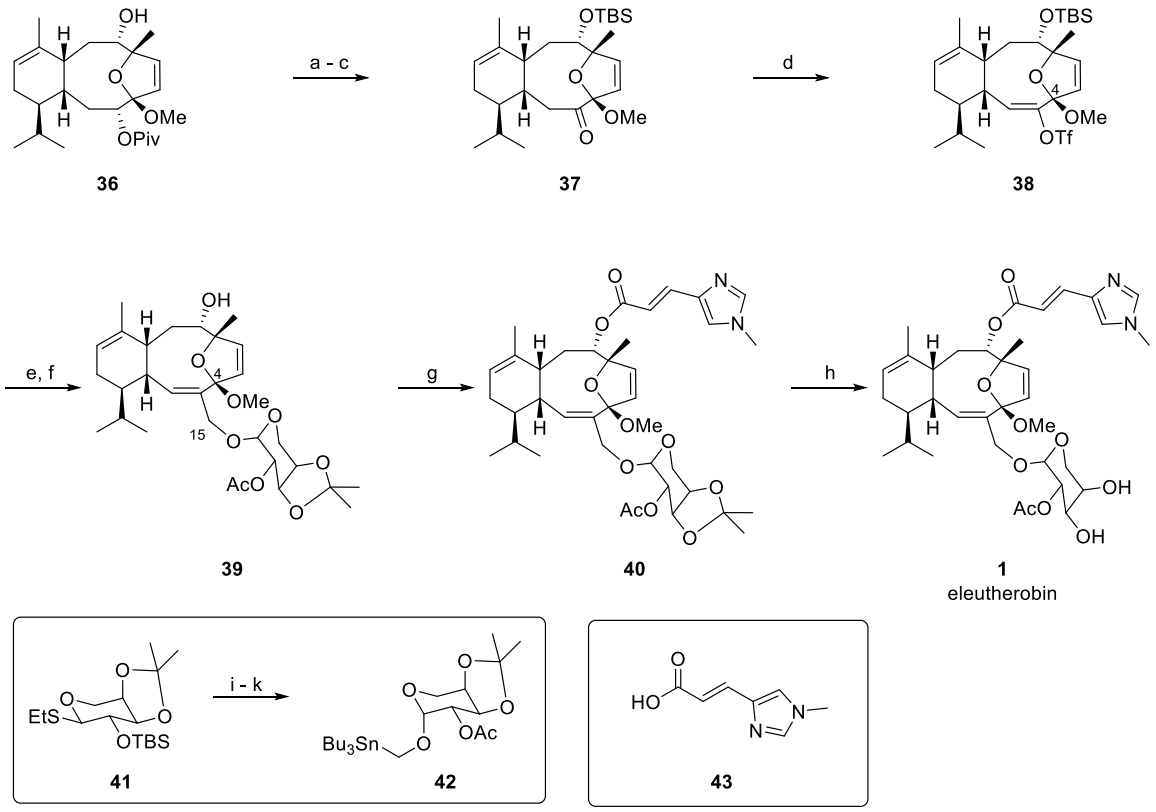
At this stage, conversion of the furan moiety to the dihydrofuran ring of eleutherobin was necessary, along with introduction of the methyl group on C7 (Scheme 3). A two-step protection-deprotection sequence revealed the C8 hydroxyl moiety, and oxidation of the furan with DMDO resulted in Achmatowicz reaction to provide hydroxypyranone **31** in 94% yield. These transformations resulted in C7 being now open to nucleophilic introduction of the necessary methyl group. This was achieved, after silylation of the acetal hydroxyl group to give ketone **32**, *via* treatment with a large excess of methyl lithium to provide alcohol **33**; attack on the unhindered side of the carbonyl provided the desired stereochemistry. Treatment with *p*-TsOH as catalyst in methanol then accomplished the key pyranose-to-furanose rearrangement giving access to dihydrofuran **36** in 90% yield.[60]



Scheme 3. a) PivCl, DMAP, Et_3N, DCM, 0 °C, 91%; b) TBAF, THF, 95%; c) DMDO/acetone, DCM, −78 °C; d) TMSOTf, 2,6-lutidine, DCM, −78 °C, 92%; e) MeLi, Et_2O, −78 °C, 86%; f) *p*-TsOH·H_2O, MeOH, 90%.

Another protection-deprotection sequence and TPAP/NMO mediated oxidation of the free alcohol gave ketone **37** (Scheme 4), which was then transformed to the enol triflate **38** *via* reaction with LiHMDS and Comins reagent. At this point the original plan called for introduction of the C15 hydroxymethyl fragment followed by glycosylation; while Stille coupling of triflate **38** with *p*-methoxybenzyl tri-*n*-butylstannane could be achieved in 55% yield, subsequent removal of the protecting group could not be accomplished without affecting the methyl acetal on C4. Additional problems arose with regards to the subsequent glycosylation reaction, as model studies resulted in unsatisfactory selectivity for the desired β-glycoside, while the presence of the acetal on C4 of the aglycon led to concerns about its potential use as a glycosylation acceptor. Danishefsky and co-workers' bold solution to these problems consisted of the direct introduction of the C15 carbon appended to the arabinose

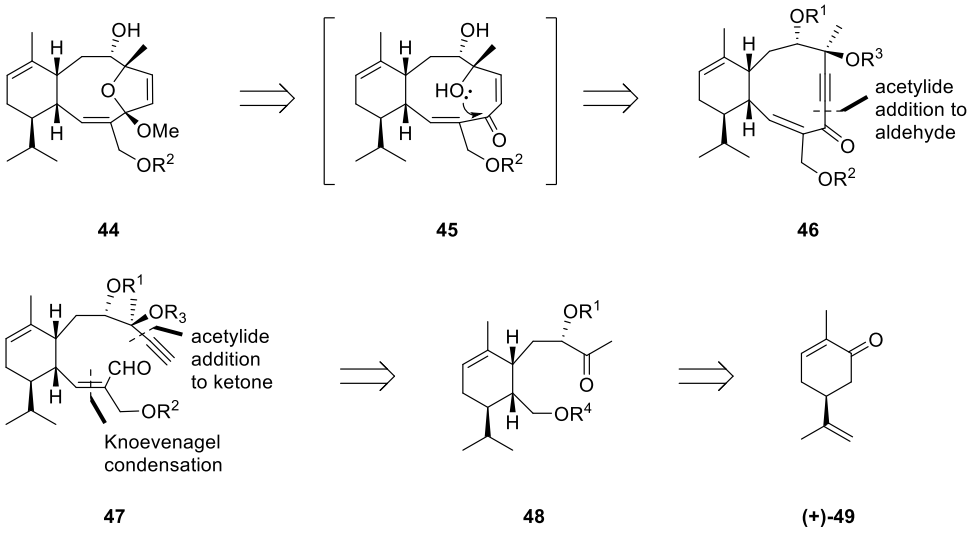
sector *via* an sp^3 Stille coupling of triflate **38** with stannane **42** to give glycoside **39** in 52% yield. Stannane **42** was prepared *via* glycosylation of tri-*n*-butylstannylmethanol with thioglycoside **41** (itself synthesised in 5 steps from D-arabinose) to give a separable 1:1 mixture of glycosides, followed by removal of the TBS protecting group and acetylation. The *N*-methyl urocanic ester was then introduced *via* a DCC/DMAP mediated coupling of alcohol **39** with acid **43**, and final deprotection of the arabinose sector with PPTS in methanol completed the synthesis.



Scheme 4. a) TBSOTf, DCM, 2,6-lutidine, 0 °C, 83%; b) DIBAL, DCM, −78 °C, 88%; c) TPAP, NMO, 4Å-MS, DCM, 87%; d) LiHMDS, THF, 0 °C → RT, then Comins reagent, −78 °C → RT, 71-80%; e) **42**, $Pd(PPh_3)_4$, LiCl, THF, 130 °C, 52%; f) TBAF, THF, 67%; g) **43**, DCC, DMAP, $CHCl_3$, 50 °C, ~80%; h) PPTS, MeOH, Δ, ~70%; i) Bu_3SnCH_2OH, MeOTf, DTBP, DCM/Et_2O, 4Å-MS, 0 °C, 93% (α:β = ~1:1); j) TBAF, THF, ~98%; k) Ac_2O, DMAP, DCM, ~99%.

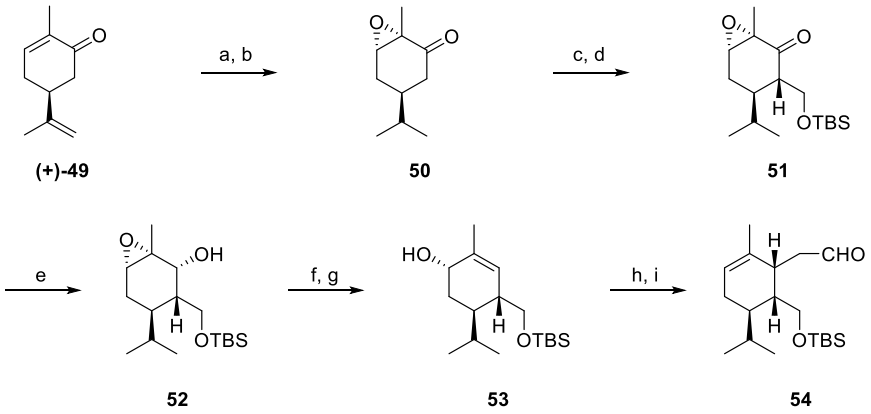
Nicolaou et al.

The retrosynthetic reasoning behind Nicolaou and co-workers' synthesis[61,62,63] is shown in Scheme 5. Disconnecting the acetal bridge on the five membered ring revealed structure **45**, which could be accessed by reduction of the triple bond in alkyne **46**. The 10-membered ring in **46** would be constructed from aldehyde **47** by intramolecular acetylide addition followed by oxidation. Further disconnections led to (+)-carvone **49** as the starting material for the synthesis.



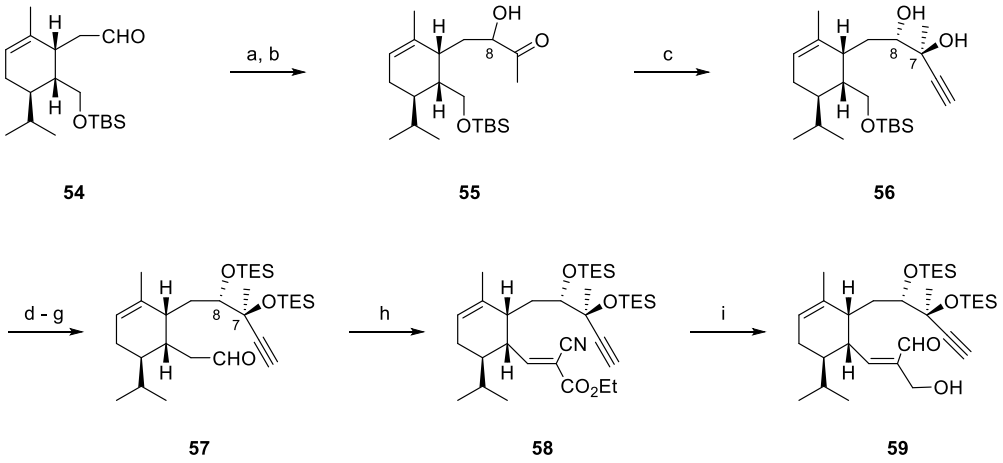
Scheme 5. Nicolaou's retrosynthetic analysis.

In practice, compound **53** was synthesised following a modified version of a procedure developed by Trost (Scheme 6).[64] (+)-Carvone was epoxidised using H_2O_2 under basic conditions, then the remaining double bond was hydrogenated to deliver epoxide **50**. Deprotonation, addition of formaldehyde, and protection of the resulting primary alcohol gave ketone **51**, which was then reduced to alcohol **52** through the use of L-selectride. This was mesylated then reduced with sodium naphthalenide to give allylic alcohol **53**. Claisen rearrangement followed by reduction of the resulting ester gave aldehyde **54**.



Scheme 6. a) H_2O_2, NaOH, MeOH, 0 °C; b) H_2, PtO_2, EtOH, 87% for two steps; c) LDA, CH_2O, THF, −78 °C → 0 °C; d) TBSCl, Et_3N, DCM, 53% for two steps; e) L-selectride, THF, −78 °C, 93%; f) MsCl, Et_3N, DCM, 0 °C; g) sodium naphthalenide, THF, 0 °C, 85% for two steps; h) $CH_3C(OEt)_3$, n-$PrCO_2H$, 170 °C, 74%; i) DIBAL, DCM, −78 °C, 97%.

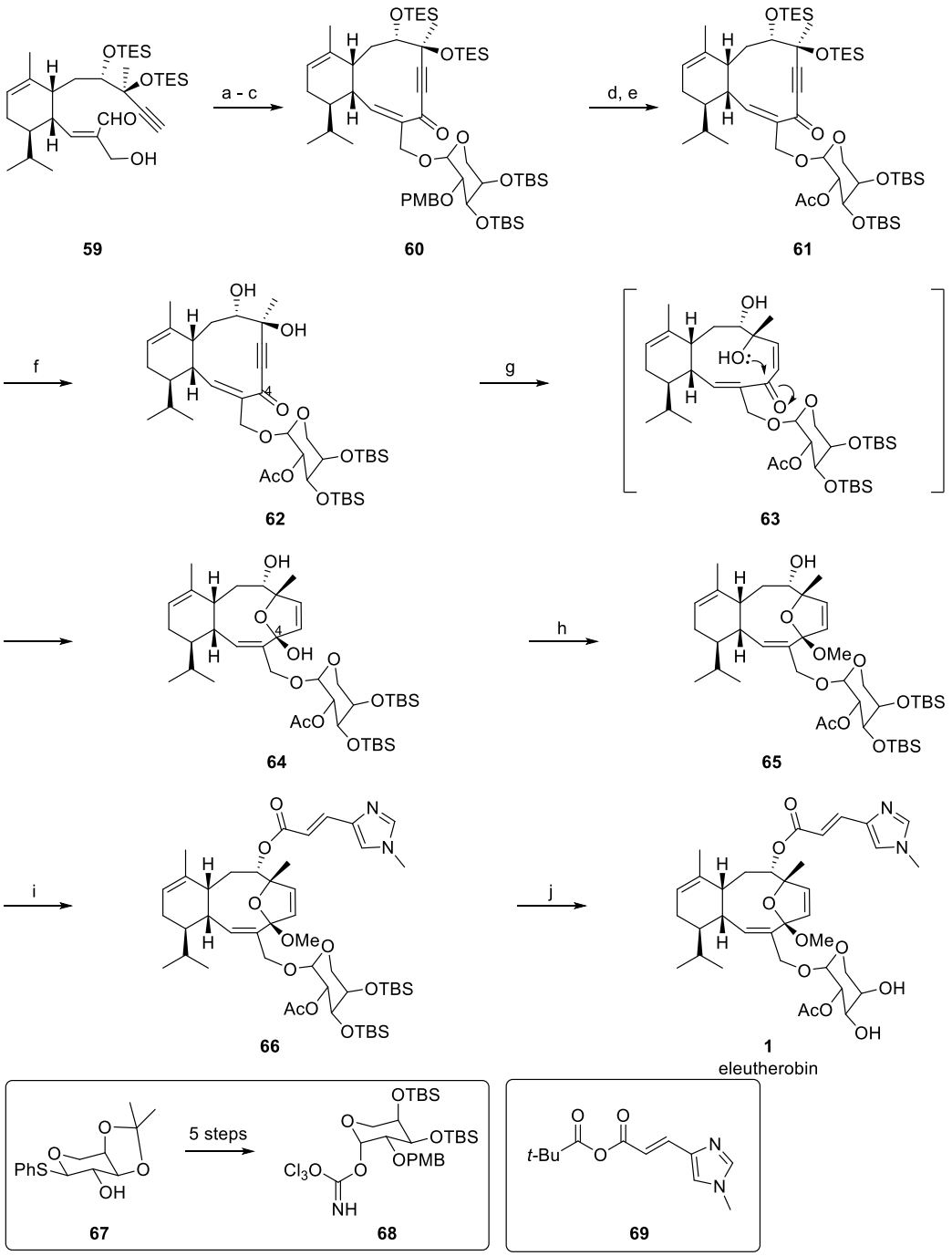
This aldehyde was then treated with 1-ethoxyvinyllithium followed by acid to give hydroxyketone **55** (Scheme 7) as a 1.25:1 mixture of C8 epimers. Addition of ethynylmagnesium bromide afforded diol **56** in 43% yield, as a separable mixture with its C7, C8 diastereomer. Deprotection of the primary alcohol with TBAF, protection of all three hydroxyl groups as TES ethers followed by selective deprotection of the primary alcohol and oxidation with TPAP/NMO led to aldehyde **57**. Knoevenagel condensation with ethyl cyanoacetate in the presence of β-alanine gave cyano ester **58**, which was then reduced *via* treatment with DIBAL to key intermediate **59**.



Scheme 7. a) Ethoxyethene, *t*-BuLi, THF, −78 °C → −40 °C; b) conc. H_2SO_4, Et_2O, 82% for two steps; c) ethynylmagnesium bromide, THF, −78 °C → RT, 76%; d) TBAF, THF, 0 °C → RT, 92%; e) TESOTf, Et_3N, DCM, 100%; f) PPTS, MeOH/DCM, 98%; g) TPAP, NMO, 4Å-MS, DCM, 98%; h) ethyl cyanoacetate, β-alanine, EtOH, 50 °C, 95%; i) DIBAL, hexanes, −78 °C → −10 °C, 90%.

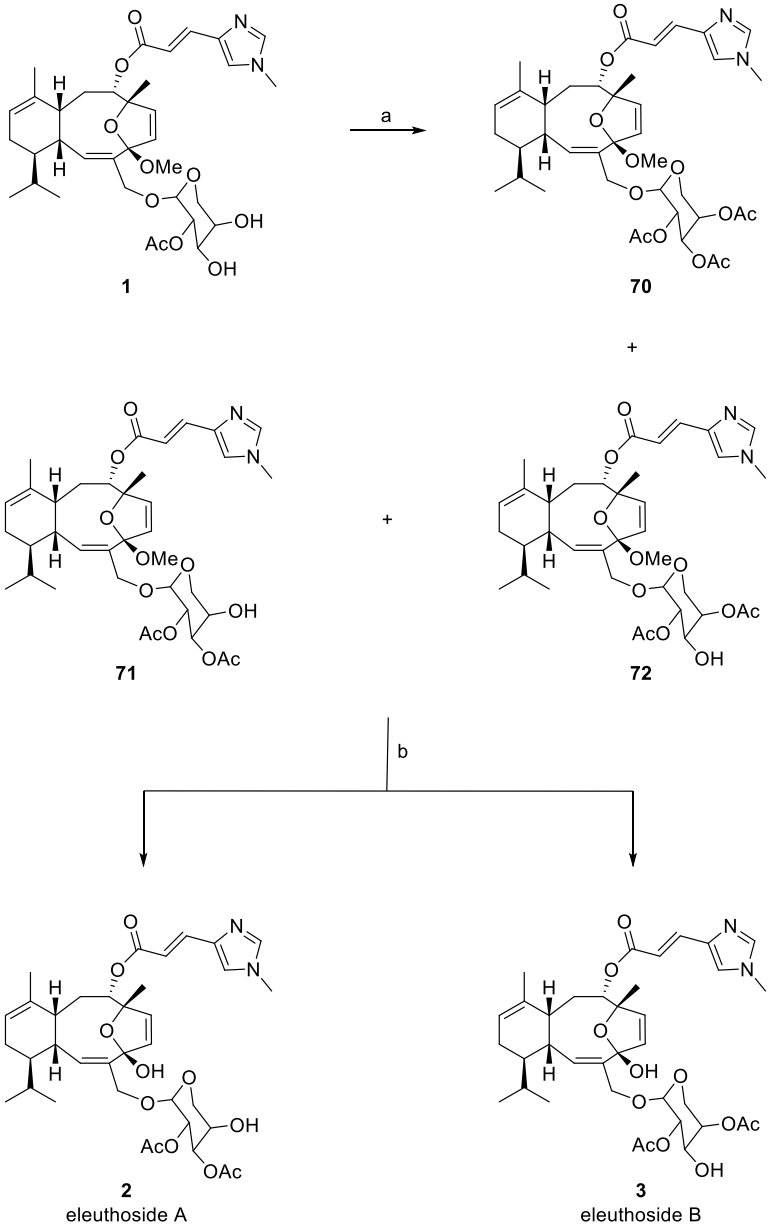
Glycosidation of alcohol **59** with donor **68** (Scheme 8) was carried out in the presence of TMSOTf; use of a dioxane-toluene mixture as the solvent was critical in achieving an 8:1 ratio of anomers in favour of the desired β-glycoside, obtained in 75% yield after purification. Trichloroacetimidate **68** was synthesised in 5 steps from known thioglycoside **67**, prepared previously by the Nicolaou group in 3 steps from arabinose tetraacetate.[65] Deprotonation by LiHMDS successfully formed the 10-membered ring by acetylide formation and attack on the aldehyde; subsequent oxidation of the resulting alcohol led to ketone **60** in 93% yield for the two steps. At this point removal of the PMB protecting group from the arabinose sector *via* use of DDQ was followed by installation of the desired acetyl group on the same hydroxyl to give acetylated derivative **61**, then selective deprotection of the two TES ethers with $Et_3N{\cdot}3HF$ provided diol **62**. It was expected that reduction of the triple bond to the *Z*-alkene would place the tertiary alcohol in a favourable position to attack the C4 carbonyl and thus form the dihydrofuran ring of eleutherobin; indeed hydrogenation in the presence of Lindlar catalyst furnished desired dihydrofuran **64**. This was treated with PPTS in methanol to form methyl acetal **65** in 76% yield over two steps. Installation of the *N*-methyl urocanic ester was achieved

via reaction with anhydride **69** in the presence of Et_3N and DMAP. Finally, removal of the TBS protecting groups completed the synthesis of the natural product.



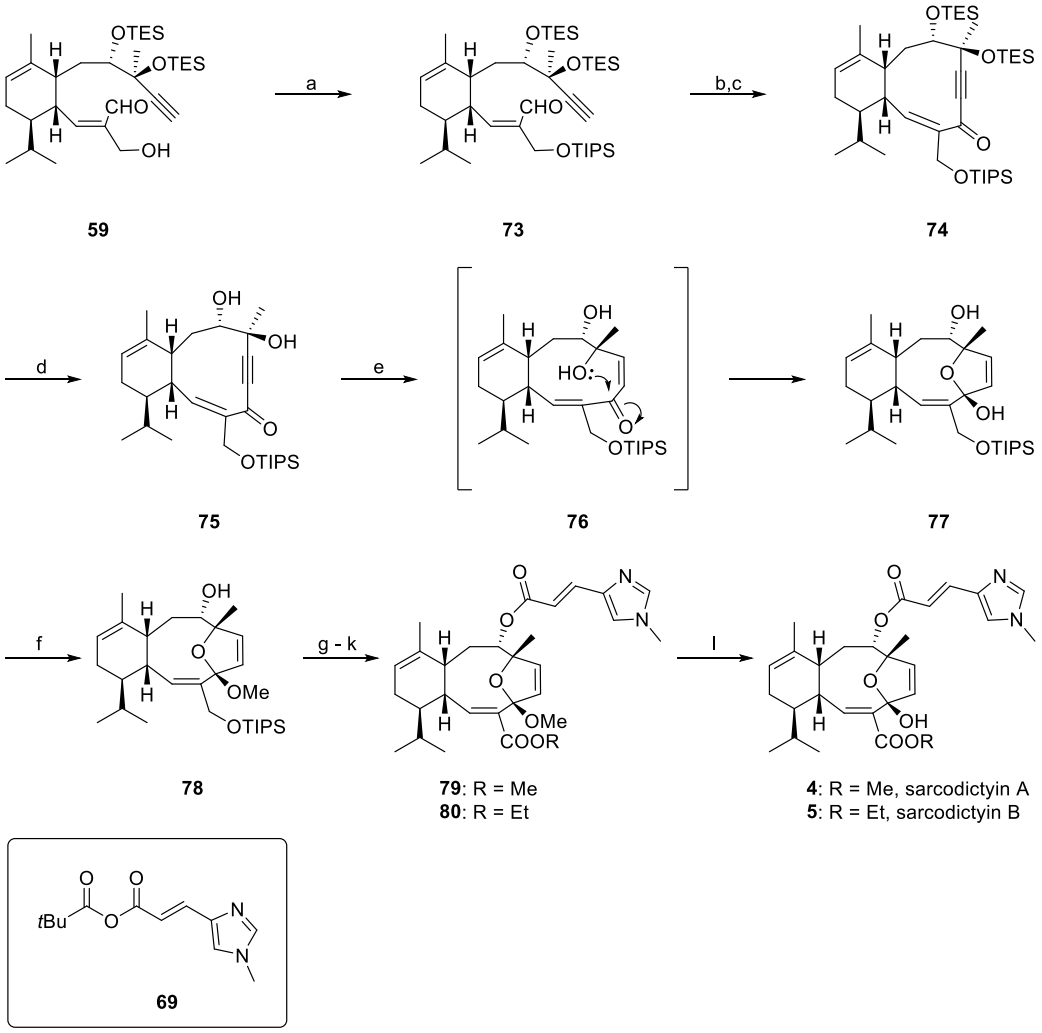
Scheme 8. a) **68**, TMSOTf, dioxane/toluene, 0 °C, 75%; b) LiHMDS, THF, −30 °C; c) DMP, $NaHCO_3$, pyridine, DCM, 0 °C, 93% for two steps; d) DDQ, DCM/H_2O, 91%; e) Ac_2O, Et_3N, DMAP, DCM, 95%; f) $Et_3N{\cdot}3HF$, THF, 81%; g) H_2, Lindlar catalyst, toluene; h) PPTS, MeOH, 76% for two steps; i) **69**, Et_3N, DMAP, DCM, 97%; j) TBAF, AcOH, THF, 96%.

In the same work,[63] eleuthosides A and B were also prepared from eleutherobin itself (Scheme 9); acetylation of eleutherobin gave an inseparable mixture of diacetates **71** and **72** (2:1 in favour of diacetate **71**, 75% yield) along with a small amount of triacetate **70**. The diacetate mixture successfully formed eleuthosides A and B upon treatment with CSA in a DCM-water mixture; the individual natural products however could not be separated, and were thus characterised as a mixture.



Scheme 9. a) Ac_2O, Et_3N, DMAP, DCM, 0 °C, 75% of **71** and **72**; b) CSA, DCM/H_2O, 80%.

Sarcodictyins A and B could also be accessed through a similar synthetic sequence starting from intermediate **59** (Scheme 10);[62] protection of the primary alcohol as the TIPS ether was followed by treatment with LiHMDS to trigger acetylide addition to the aldehyde, followed by oxidation to ketone **74** in 89% yield over the two steps. Selective deprotection of the TES ethers led to diol **75**, which was hydrogenated using [Rh(nbd)(dppb)]BF_4 as the catalyst to trigger the formation of the dihydrofuran sector. Subsequent reaction with PPTS in methanol furnished methyl acetal **78** in 80% yield over two steps. Following introduction of the *N*-methyl urocanic ester side chain, the primary hydroxyl group was deprotected and oxidised, in a two-step sequence, to the carboxylic acid. Ester formation with either diazomethane or diazoethane led to the methylated derivatives of, correspondingly, sarcodictyins A and B. Reaction with CSA in a DCM-water mixture re-established the hydroxy acetal and completed the synthesis of the natural products.

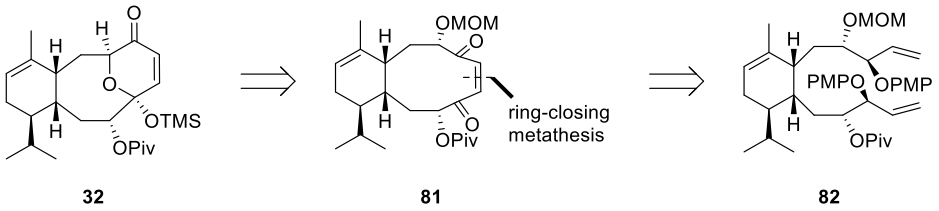


Scheme 10. a) TIPSOTf, DIPEA, DCM, −78 °C, 93%; b) LiHMDS, THF, −20 °C; c) DMP, $NaHCO_3$, pyridine, DCM, 0 °C, 89% for two steps; d) $Et_3N{\cdot}3HF$, THF, 78%; e) H_2, $[Rh(nbd)(dppb)]BF_4$, acetone; f) PPTS, MeOH, 80% for two steps; g) **69**, Et_3N, DMAP, DCM, 83%; h) TBAF, THF, 100%; i) DMP, $NaHCO_3$, DCM, 100%; j) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*-BuOH, H_2O; k) CH_2N_2, Et_2O, 88% for two steps; or $CH_3CH_2N_2$, Et_2O, 89% for two steps; l) CSA, DCM/H_2O, 80% for **4**, 86% for **5**.

Formal syntheses of eleutherobin

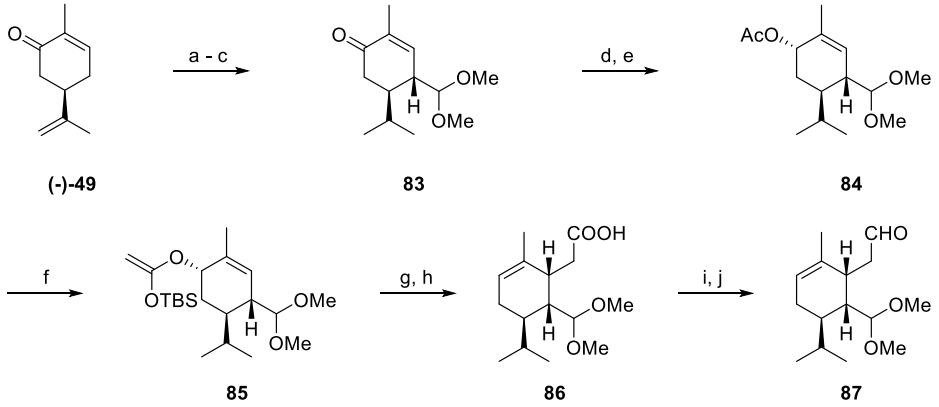
Gennari et al.

Gennari reported a synthesis of compound **32**, an advanced intermediate in Danishefsky's synthesis, by using a ring-closing metathesis reaction to form the C5-C6 double bond.[66]



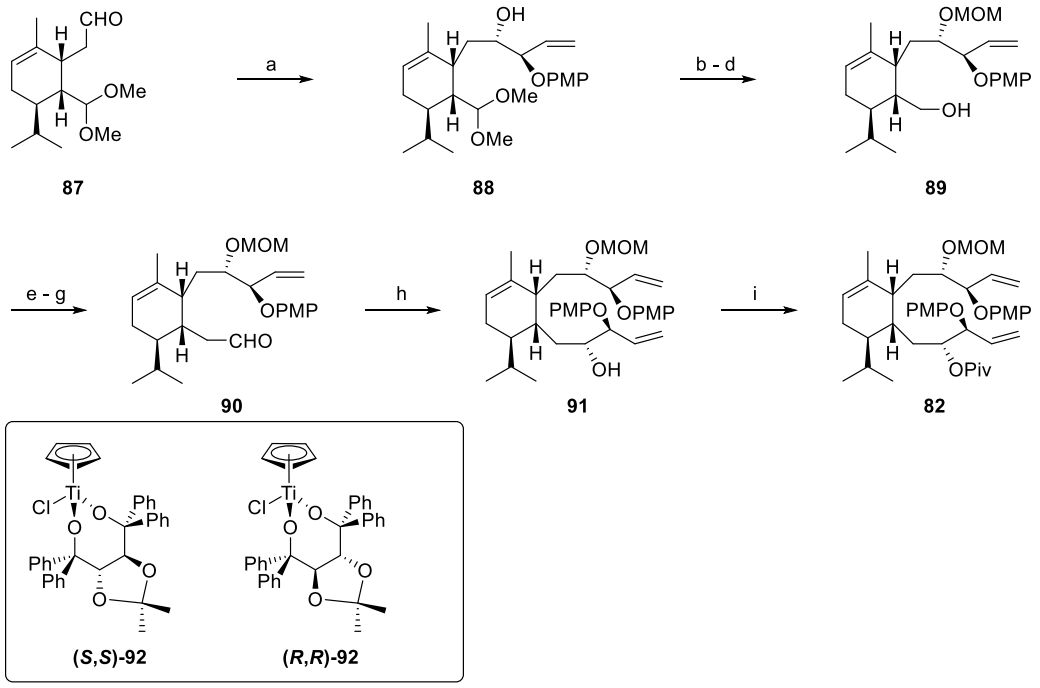
Scheme 11. Gennari's retrosynthetic analysis.

Aldehyde **87** was prepared from (−)-carvone as shown in Scheme 12:[67,68] hydrogenation of the exocyclic double bond was followed by formation of the extended silyl enol ether, which was then treated with triethyl orthoformate in the presence of $BF_3{\cdot}OEt_2$ to give acetal **83**. Reduction of the ketone and acetylation of the resulting alcohol provided acetate **84**. Deprotonation with LiHMDS and trapping of the resulting enolate with TBSCl led to silyl enol ether **85**, which upon heating to 190 °C in xylene underwent an Ireland–Claisen rearrangement to furnish, after hydrolysis of the silyl ester, acid **86** in 82-90% yield; reduction to the alcohol and oxidation led to aldehyde **87**.



Scheme 12. a) H_2, $(Ph_3P)_3RhCl$, benzene, 82%; b) MeMgBr, $FeCl_3$, TMSCl, Et_3N, DMPU, Et_2O, 100%; c) $(MeO)_3CH$, $BF_3{\cdot}OEt_2$, DCM, 30-45%; d) L-Selectride, THF, −78 °C, 70%; e) Ac_2O, Et_3N, DMAP, DCM, 95%; f) LiHMDS, TMSCl, DMPU, THF, −78 °C → RT, 100%; g) xylenes, 190 °C; h) NaOH then HCl, 82-90% for two steps; i) $LiAlH_4$, Et_2O; j) DMP, DCM, 95% for two steps.

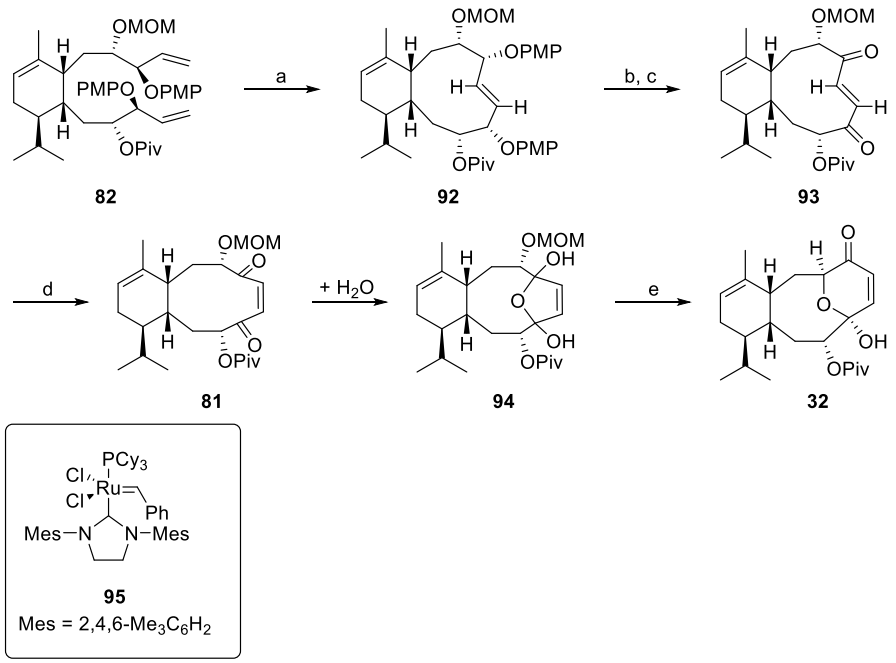
This aldehyde was subjected to a stereoselective Hufner–Duthaler oxyallylation mediated by [(*S*,*S*)-taddolCpTiCl] complex **92**. Resulting alcohol **88** was protected as the MOM ether; hydrolysis of the acetal and reduction to the alcohol gave alcohol **89**, and a 3-step sequence led to extended aldehyde **90**. Another oxyallylation followed, this time using (*R*,*R*)-**92** to give alcohol **91**, and protection of the free hydroxyl group as the pivalate ester gave RCM precursor **82**.



Scheme 13. a) *s*-BuLi, PMPOAllyl, (*S*,*S*)-**92**, THF/Et_2O, −78 °C → 0 °C, 73%; b) MOMCl, DIPEA, TBAI, DCM, 95%; c) $LiBF_4$, CH_3CN/H_2O; d) $NaBH_4$, EtOH, 75% for two steps; e) MsCl, Et_3N, DCM, 0 °C → RT, 95%; f) KCN, 18-crown-6, CH_3CN, 80 °C, 100%; g) DIBAL, toluene/hexane, -78 °C, 100%; h) *s*-BuLi, PMPOAllyl, (*R*,*R*)-**92**, THF/Et_2O, −78 °C → RT, 83%; i) PivCl, DMAP, DIPEA, DCM, 96%.

Treatment of precursor **82** with Grubbs' 2nd generation catalyst in refluxing toluene then gave RCM product **92** in 64% yield, exclusively as the *E*-isomer with regards to the newly formed double bond. The PMP groups were crucial for the success of the ring-closing metathesis reaction, as previous attempts with RCM precursors bearing different protecting groups, or the free alcohols, had proven unsuccessful.[69] The formation of the *E*-isomer was also unexpected,

as model studies of RCM reactions with precursors where one of the allylic positions lacked the alcohol moiety had provided the *Z*-isomer instead.[70,71,72] This result was inconsequential however, as removal of the PMP groups and oxidation to *E*-enedione **93** was followed by clean isomerisation to *Z*-enedione **81** in $CDCl_3$, or by addition of catalytic I_2. Furthermore, when subjected to flash chromatography, enedione **81** was converted to its hydrated form, bis-acetal **94**. Removal of the MOM protecting group led to compound **32**, accomplishing a formal synthesis of the natural product.



Scheme 14. a) **95**, toluene, 110 °C, 64%; b) CAN, CH_3CN/H_2O, 0 °C, 80%; c) DMP, DCM, 90%; d) $CDCl_3$; e) $BF_3{\cdot}OEt_2$, Me_2S, DCM, −78 °C → −20 °C, 78%.

Computational studies were carried out in order to seek an explanation for the preference for the *E*-geometry in alkene **92**;[73] it was found that intermediate *trans*-ruthenacyclobutane **97** (Figure 12) is significantly more stable than *cis*-isomer **98**, even though compound **92** is less stable than *Z*-isomer **99**. *E*-Alkene **92** is thus the kinetic product; the authors posit that the bulky PMP ethers prevent further reaction of **92** with the ruthenium-methylidene complex and therefore equilibrium with the more stable *Z*-alkene **99** cannot be established.

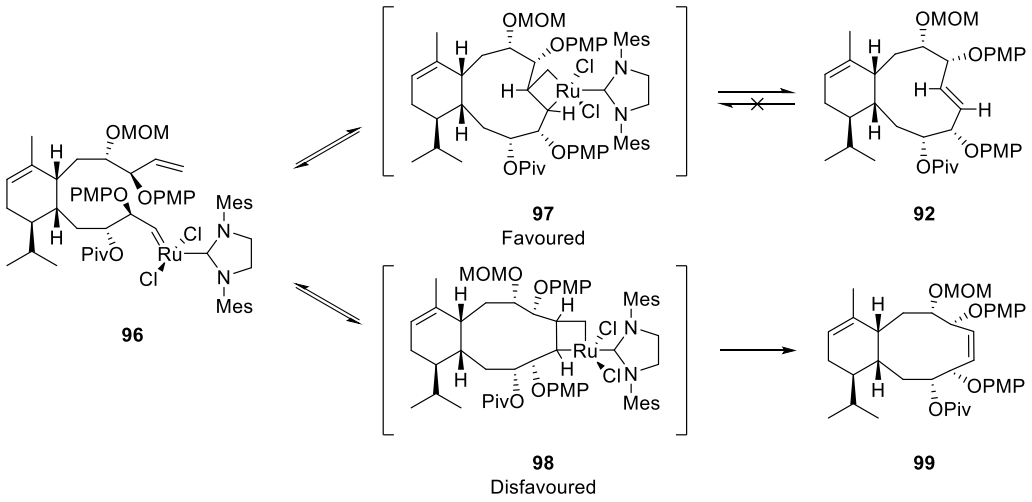
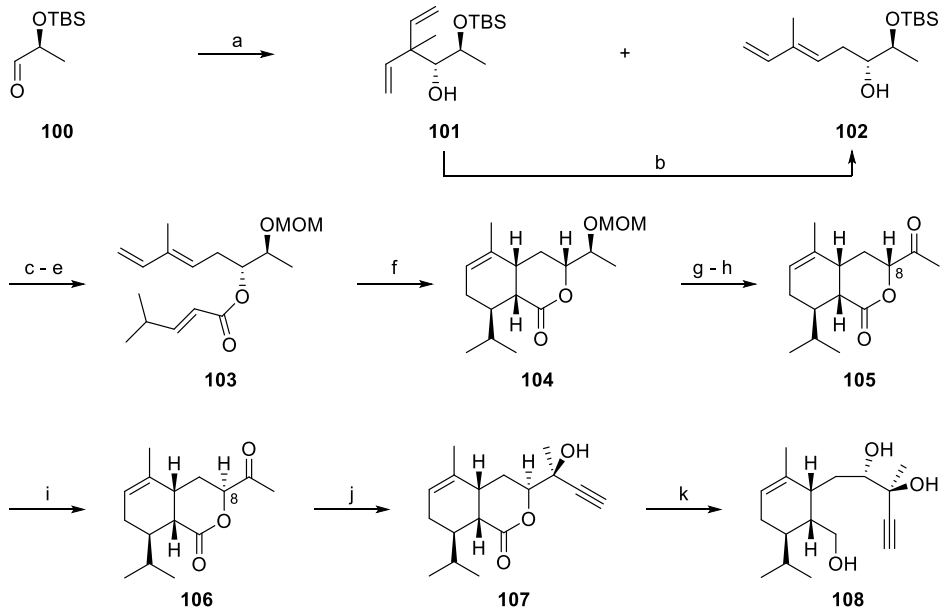


Figure 12. Mechanistic rationalisation of the RCM outcome.

Ritter and Metz

Ritter and Metz developed a novel route to compound **108** (Scheme 15), an intermediate in Nicolaou's synthesis of eleutherobin, utilising an intramolecular Diels–Alder reaction to build the cyclohexene sector of the natural product.[74] Starting from TBS protected lactaldehyde **100**, addition of the organolithium reagent derived from 3-methyl-1,4-pentadiene gave rise to a mixture of 1,4 diene **101** and 1,3 diene **102**; compound **101** could be converted to desired 1,3 diene **102** *via* treatment of the mixture with NaH and 18-crown-6 in THF. Acylation of alcohol **102** with (*E*)-4-methyl-2-pentenoic acid followed by change of the protecting group to a MOM ether led to ester **103**, which upon prolonged heating to 200 °C in toluene solution in a sealed tube underwent a Diels–Alder cycloaddition to give *endo*- adduct **104** in 75% yield. Next, epimerisation of the position corresponding to C8 of the natural product was necessary; this was achieved, after removal of the MOM protecting group and oxidation of the resulting alcohol to the ketone in **105**, by treatment with DBU in DCM to give C8 epimer **106** in 69% yield, along with 28% of starting **105**. Finally addition of ethynylmagnesium bromide to ketone **106** under chelation control mediated by $MgBr_2 \cdot OEt_2$ led to alkyne **107**, which upon reduction with $LiAlH_4$ provided compound **108**.



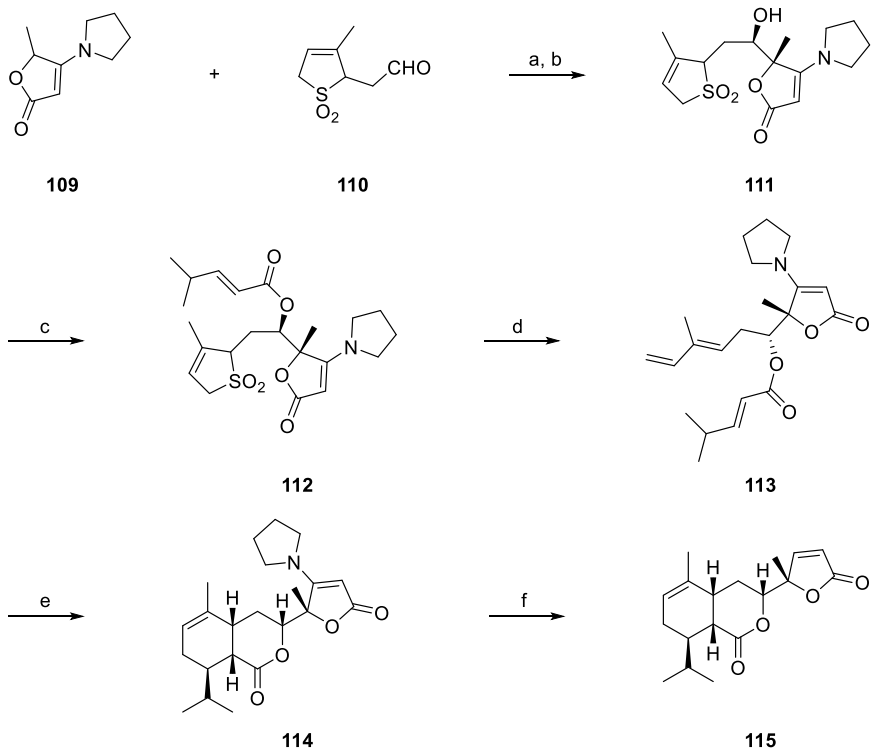
Scheme 15. a) 3-methyl-1,4-pentadiene, *n*-BuLi, THF, −78 °C → RT, 40% (**101**+**102**); b) NaH, 18-crown-6, THF, 0 °C → RT, 40%; c) (*E*)-4-methyl-2-pentenoic acid, DCC, DMAP, 0 °C → RT, 75%; d) HF, CH_3CN, 98%; e) MOMCl, DIPEA, DCM, 0 °C → RT, 98%; f) toluene, BHT, 200 °C, 75%; g) CBr_4, MeOH, reflux, 94%; h) PCC, DCM, 97%; i) DBU, DCM, 69%; j) ethynylmagnesium bromide, $MgBr_2 \cdot OEt_2$, Et_2O, −78 °C → −40 °C, 58%; k) $LiAlH_4$, Et_2O, 85%.

Other synthetic studies

Partial synthesis by Royer et al.

The group of Royer reported, as part of their studies towards a total synthesis of eleutherobin, the preparation of compound **115** (Scheme 16) *via* an intramolecular Diels–Alder reaction conceptually similar to that reported by Metz.[75,76,77] Starting material **109** was deprotonated with *t*-BuLi and reacted with aldehyde **110** in the presence of TMSCl to give *anti* aldol adduct **111**; the presence of the pyrrolidinyl substituent on furanone **109** was necessary to achieve the desired regioselectivity in the aldol reaction. Acylation of the alcohol gave ester **112**, which was then heated to reflux in toluene to accomplish cheletropic extrusion of SO_2 and reveal the diene moiety in cycloaddition precursor **113**. Treatment of this compound with $TfN[Al(Me)Cl]_2$ (*vide infra*) in refluxing DCE resulted in the formation of desired *endo*-Diels–Alder adduct **114** in 80% yield, which was then subjected to a reduction-oxidation-

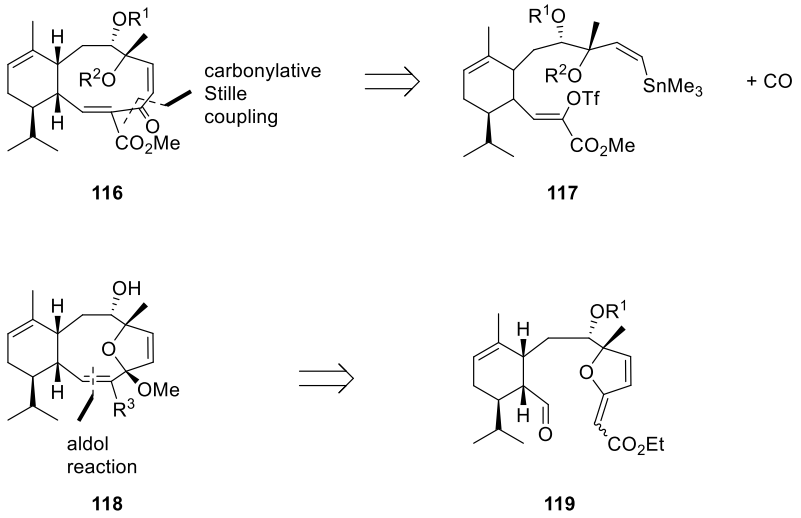
elimination sequence to furnish furanone **115**. Introduction of the C3 - C15 portion of the molecule, followed by cyclisation onto the lactone carbonyl to form the 9-membered ring, remained to provide the sarcodictyin framework; however, no further studies to that end have been published by the group.



Scheme 16. a) **109**, *t*-BuLi, TMSCl, THF, then **110**, −78 °C, 45%; b) PPTS, MeOH, DCM, 90%; c) (*E*)-4-methyl-2-pentenoic acid, DCC, DMAP, 0 °C → RT, 78%; d) hydroquinone, toluene, reflux, 87%; e) $TfN[Al(Me)Cl]_2$, DCE, reflux, 80% (85% d.e.); f) $NaBH_3CN$, AcOH; g) *m*-CPBA, $NaHCO_3$, pyridine, DCM, 79% for two steps.

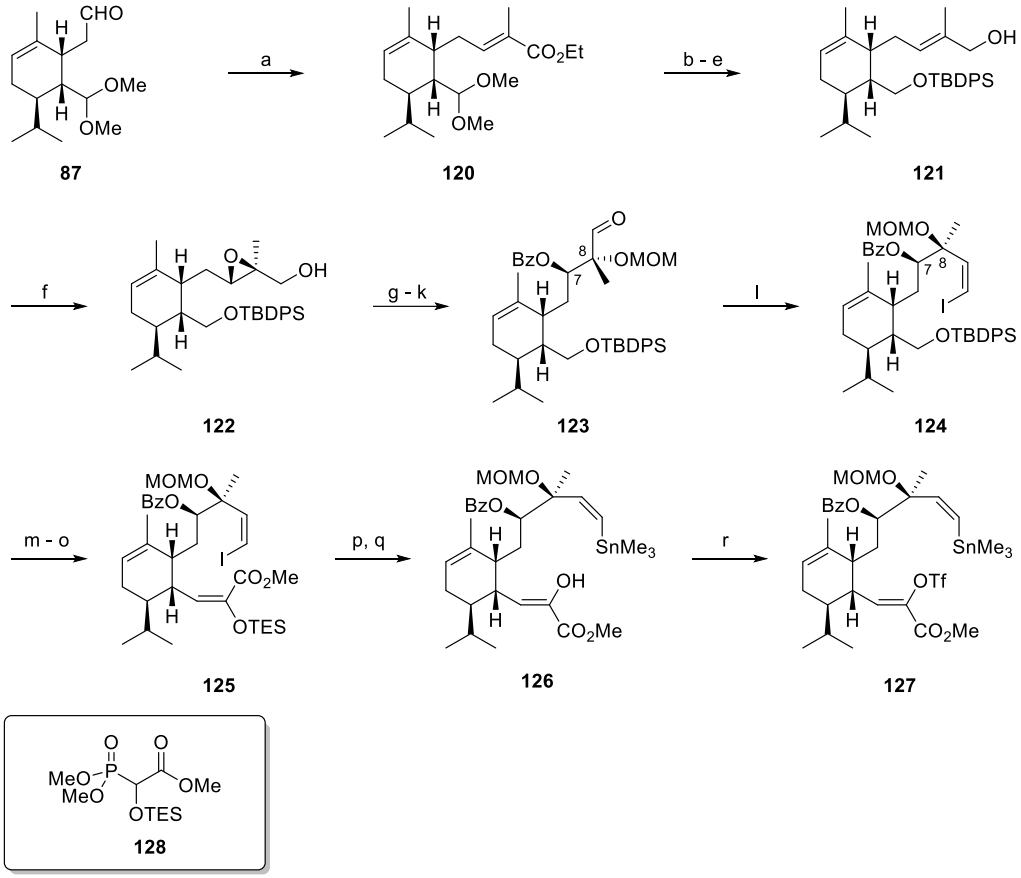
Unsuccessful approaches by the Gennari group

Prior to the aforementioned RCM-based formal synthesis, the group of Gennari investigated the approaches shown in Scheme 17; the first involved an intramolecular carbonylative Stille coupling of precursor **117** as the key step,[78] while the second one was based on the disconnection of the C2-C3 double bond *via* an aldol reaction.[67,68]



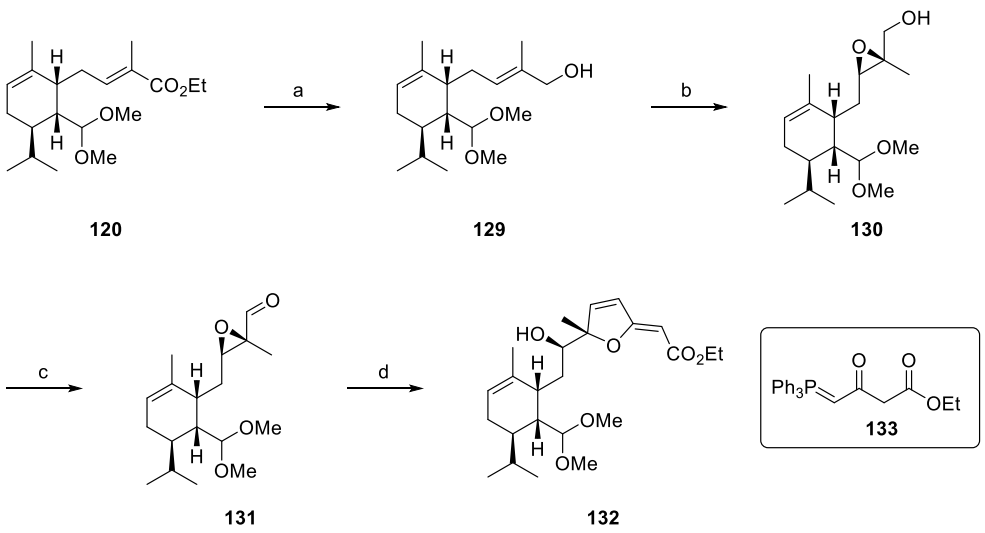
Scheme 17. Alternative disconnections investigated by the Gennari group.

To probe the carbonylative Stille coupling approach, compound **87** was converted into stannane **126** through the sequence described in Scheme 18; *E*-olefin **120** was prepared *via* a Horner–Wadsworth–Emmons coupling, and stereoselective Sharpless epoxidation of alkene **121**, followed by epoxide opening with BzOH, established the desired stereochemistry on C7 and C8 in aldehyde **123**. Installation of the vinyl stannane and enol triflate functionalities led to precursor **127**; however, the key Stille coupling proved unsuccessful.



Scheme 18. a) $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH, DME, 85%; b) AcOH, THF, H_2O, 99%; c) $NaBH_4$, EtOH, 93%; d) TBDPSCl, imidazole, DCM, 86%; e) $LiAlH_4$, Et_2O, 99%; f) TBHP, $Ti(OiPr)_4$, (+)-DET, 4Å-MS, DCM, 87%; g) $Ti(OiPr)_4$, BzOH, $CHCl_3$, 66%; h) TESCl, imidazole, DCM; i) MOMCl, DIPEA, DCM, 50 °C; j) TAS-F, DMF/H_2O, 81% for three steps; k) DMP, DCM, 99%; l) $(Ph_3PCH_2I)I$, NaHMDS, −78 °C, 61%; m) HF·pyridine, THF/pyridine, 55 °C, 97%; n) DMP, DCM, 99%; o) **128**, LiHMDS, THF, −78 °C → RT, 87%; p) HF·pyridine, THF/pyridine, 72%; q) Pd_2dba_3, $(Me_3Sn)_2$, NMP, 50 °C, 26%; r) 2-bis-trifluoromethanesulfonyl-amino pyridine, NaHMDS, THF, −78 °C, 75%.

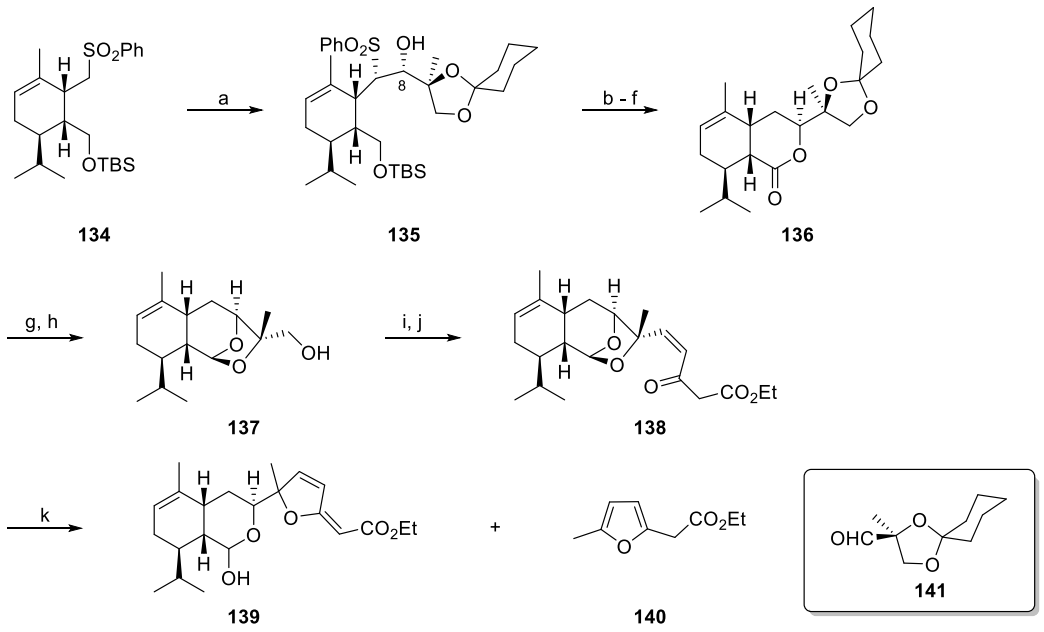
A similar sequence of reactions led to epoxide **131** (Scheme 19), which was subjected to olefination with phosphorane **133** to give dihydrofuran **132**; it was hoped that the enol ether functionality could participate in an aldol reaction with the electrophile derived from the dimethyl acetal *via* protic or Lewis acid treatment; this too, however, was unsuccessful.



Scheme 19. a) $LiAlH_4$, Et_2O, 82%; b) TBHP, $Ti(OiPr)_4$, (−)-DET, 4Å-MS, DCM, −20 °C, 65%; c) DMP, DCM, 96%; d) **133**, NaHMDS, THF, 0 °C, 44%.

Partial synthesis by the Magnus group

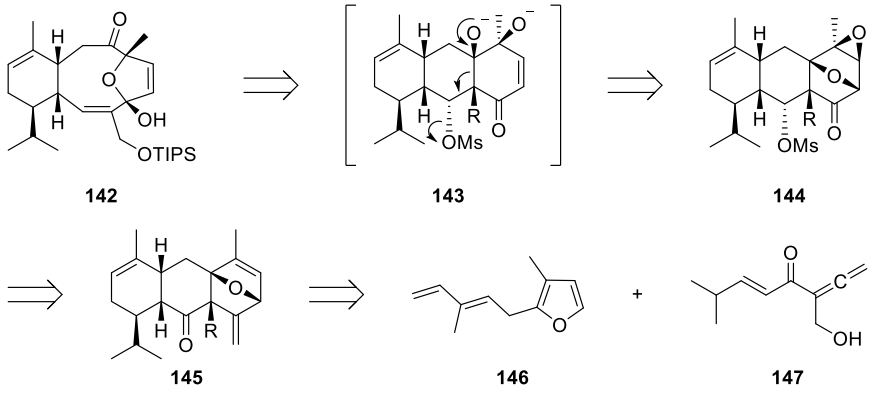
A similar approach was studied by the group of Magnus;[79] sulfone **134** (Scheme 20), prepared in 9 steps from (+)-carvone, was coupled *via* a Julia reaction with aldehyde **141**, prepared in 5 steps from 2-methyl-2-propenol, to give alcohol **135** as the minor component of a mixture of epimers; an oxidation-reduction sequence was necessary to obtain the correct stereochemistry at C8, and oxidation of the primary alcohol after deprotection led to lactone **136**. After reduction to the lactol, removal of the cyclohexyl acetal gave acetal **137**, which was extended to ester **138**. Treatment of this compound with $BF_3{\cdot}OEt_2$ in DCM led to a complex mixture, out of which compounds **139** (56% yield) and **140** (18% yield) could be isolated; the presence of furan **140** is indicative of fragmentation of compounds **138**-**139** under the reaction conditions. At that point in time the total synthesis of eleutherobin by Nicolaou *et al*. was reported, and the group did not pursue this approach further.



Scheme 20. a) EtMgBr, **141**, benzene, 64% of **135** + C8 epimer; b) DMP, DCM, 94%; c) Na/NH_3, THF, −78 °C, 92%; d) K-Selectride, THF, 0 °C, 77% e) TBAF, THF, 99%; f) TPAP, NMO, 4Å-MS, DCM, 87%; g) DIBAL, DCM, −78 °C, h) *p*-TsOH, MeOH, 70%; i) DMP, DCM, 89%; j) NaH, (4-ethoxy-2,4-dioxobutyl)triphenylphosphonium bromide, DMPU, RT → 40 °C, 84%; k) $BF_3 \cdot OEt_2$, DCM, 56% of **139** and 18% of **140.**

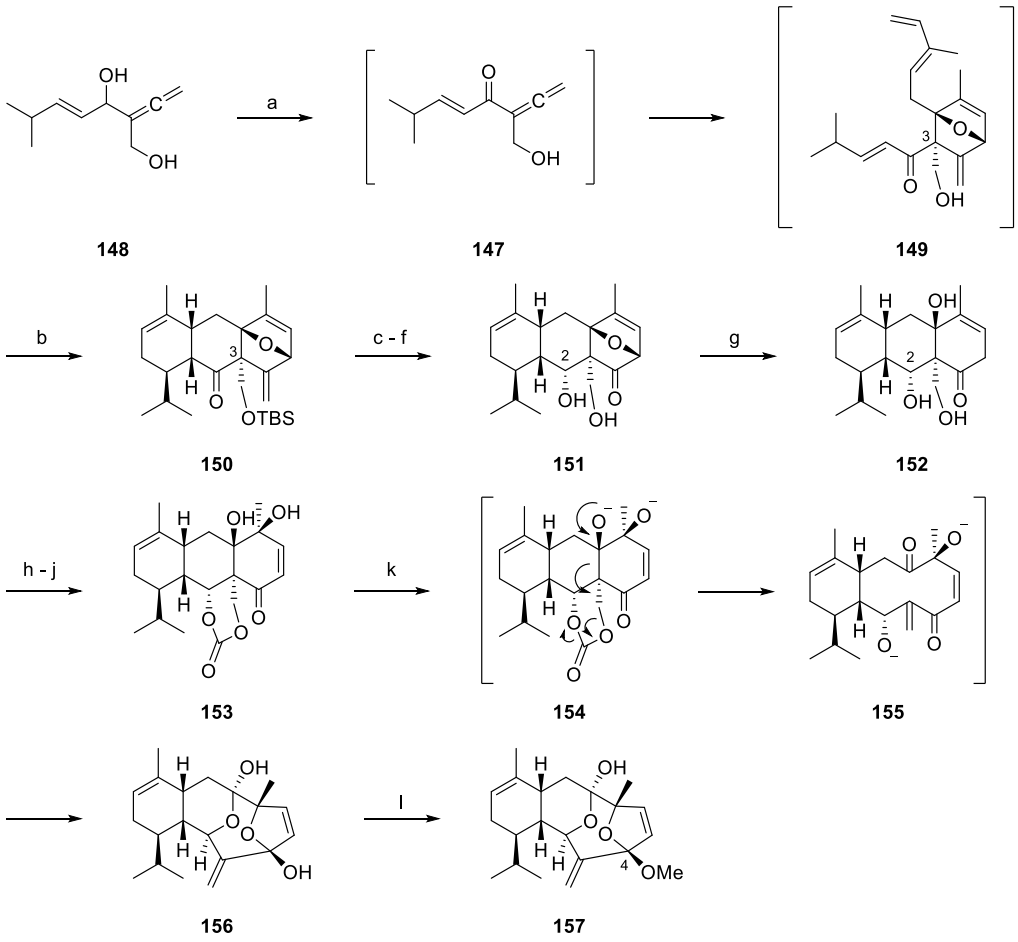
Grob fragmentation approach by Winkler et al.

Winkler's approach[80] aimed to derive the tricyclic framework of eleutherobin *via* a Grob fragmentation of dianion **143**, formed upon reduction of epoxide **144**. Precursor **145** would be prepared *via* a tandem double Diels–Alder cycloaddition between furan **146** and allene **147**.



Scheme 21. Winkler's retrosynthetic analysis.

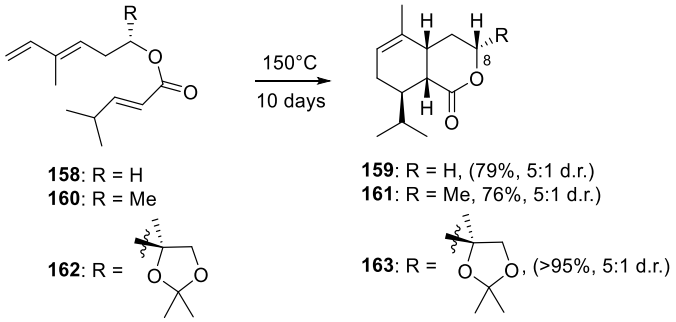
In practice, allene **148** (Scheme 22) was oxidised to bifunctional dienophile **147** and then treated with furan **146**, synthesised in 4 steps from 1-bromo-2-butyne; initial *exo*-selective cycloaddition between the furan and allene moieties was followed by a second *endo*-selective Diels–Alder reaction to furnish **150**. The *exo*-selectivity of the first cycloaddition was attributed by the authors to fast retro-Diels–Alder reaction of the *endo*- adduct, and resulted in the opposite stereochemistry on C3 to that indicated in Scheme 21; this would result in the opposite double bond geometry upon Grob fragmentation which would therefore require isomerisation. A 4-step sequence effected conversion of the exocyclic methylene group to the ketone in compound **151**; subsequent selective activation of the hydroxyl group on C2 however could not be achieved. Attempted mesylation, after silylation of the primary alcohol, was unsuccessful on both compound **151** and derivative **152**. The authors thus elected to activate both primary and secondary alcohol moieties as carbonate **153**, which provided an alternative pathway for the Grob fragmentation. This proved to be the prevailing one upon treatment of carbonate **153** with K_2CO_3 in DMF, giving acetal **156** in 68% yield. Selective formation of the C4 methyl acetal could then be achieved using MeI in the presence of Ag_2O and $CaCO_3$. Isomerisation of the exocyclic double bond to the C2-C3 alkene would be necessary to access the tricyclic eleutherobin core from this compound, though no reports on this have emerged from the group.



Scheme 22. a) $BaMnO_4$, DCM, reflux, then **146**, 50 °C; b) TBSOTf, 2,6-lutidine, DCM, 0 °C, 51% for two steps; c) DIBAL, DCM, −78 °C, 96%; d) $VO(acac)_2$, TBHP, 4Å-MS, DCM, 0 °C, 77%; e) aq. NaOH, 1,4-dioxane; f) $NaIO_4$, MeOH/H_2O, 0 °C, 66% for two steps; g) SmI_2, NiI_2, THF, −20 °C, 72%; h) $COCl_2$, pyridine, 0 °C, 79%; i) $VO(acac)_2$, TBHP, 4Å-MS, DCM, 0 °C; j) Et_3N, SiO_2, DCM, 93%; k) K_2CO_3, 4Å-MS, DMF, 75 °C, 68%; l) MeI, $CaCO_3$, Ag_2O, 76%.

IMDA studies on substituted 3,5-hexadienyl acrylates

The intramolecular Diels–Alder approaches by Metz *et al*. and Royer *et al*. have been mentioned; these were based on earlier studies by the groups of Jung[81] and independently of Kurth,[82] who reported the preparation of lactone **159**, representing the cyclohexene sector of eleutherobin, *via* an intramolecular Diels–Alder reaction of ester **158** (Scheme 23). The effects of substitution on C8 on the stereochemical outcome of the reaction were also studied.



Scheme 23. Thermal Intramolecular Diels-Alder reactions of **158** and substituted derivatives. d.r. refers to ratio of *endo:exo* adducts.

The reaction was found to require forcing conditions: heating to 150 °C for 10 days (Jung) or to 220 °C in a sealed tube for 20 h (Kurth). This is not unexpected for cycloadditions where the reacting partners are tethered through an ester linkage, and can be rationalised by invoking the preference of the ester to adopt a transoid conformation (Figure 13a) as a consequence of both steric and stereoelectronic factors.[83,84] The reaction is selective for the *endo*- adduct; to rationalise the influence of the substituent at C8, both groups suggest that the reaction proceeds *via* a boat-like transition state (Figure 13b). Jung and coworkers attribute the preference for such a transition state to poor overlap between the lone pairs of the endocyclic oxygen atom and the carbonyl group in chair-like transition states **164** and **166**. Boat-like transition state **169** is destabilised by a 1,4-flagpole-flagpole interaction, absent from transition state **168** which leads to observed product **167**.

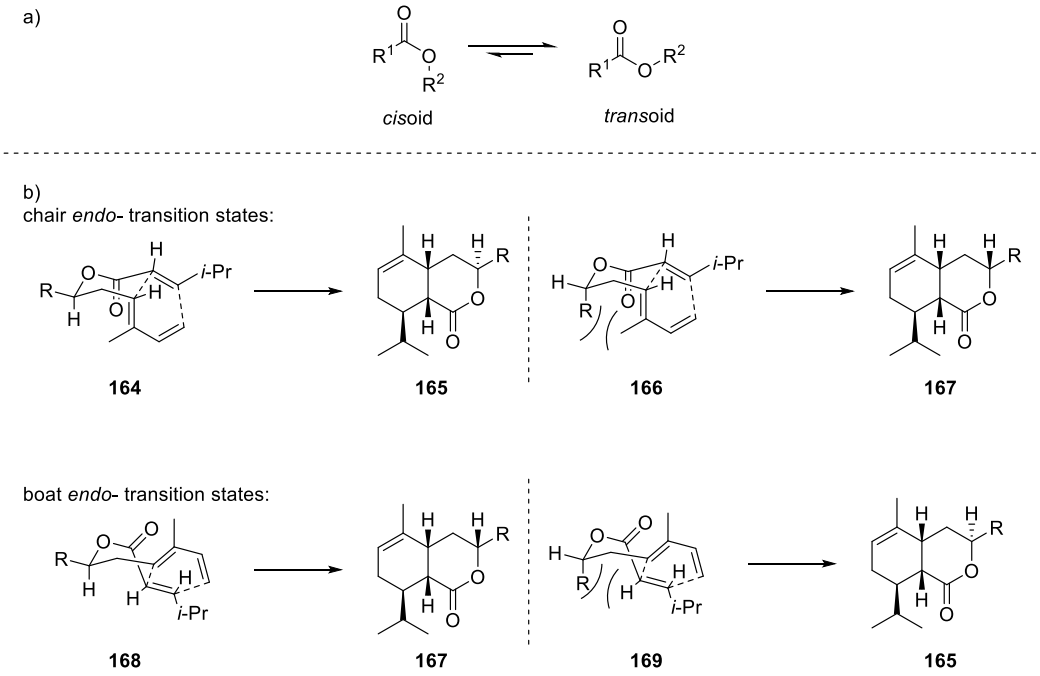
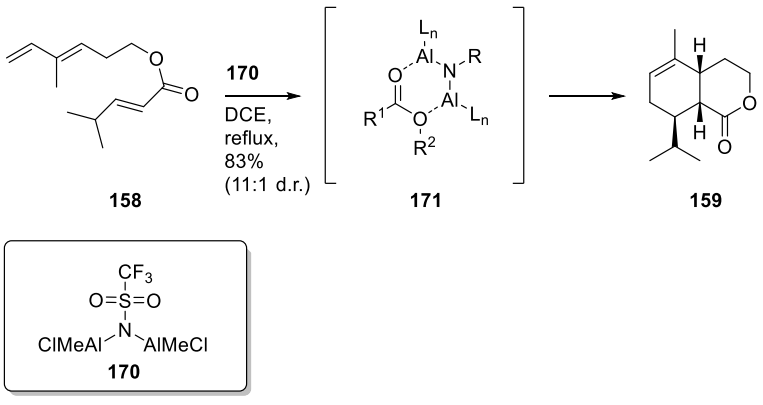


Figure 13. a) Ester conformational equilibrium;
b) Jung and coworkers' rationalisation of the IMDA stereochemical outcome.[81]

Jung and co-workers noted that attempts to promote the reaction with Lewis acids resulted in complex reaction mixtures. In a subsequent study, Taguchi *et al*. demonstrated[85] that bidentate Lewis acid **170** could successfully promote the transformation, potentially by stabilising the cisoid conformation of the ester *via* coordination to both oxygen atoms (Scheme 24).



Scheme 24. Lewis acid mediated synthesis of lactone **159**.

Project outline

Recent advances in CH oxidation methodology have led to the emergence of a new approach to the synthesis of polyhydroxylated natural products: the bare carbon framework is first accessed rapidly, as the synthetic strategy employed is unfettered by the need for complex protection-deprotection and oxidation-reduction sequences; selective CH oxidation then installs the hydroxyl groups to functionalise this framework and obtain the natural product in question, as well as differentially hydroxylated derivatives. The Baran group, who have popularised this approach, use the biosynthesis-derived terminology *cyclase phase* to refer to the former and *oxidase phase* to refer to the latter part of this process. Examples of successful application of such a strategy are the recently reported syntheses of oxidised taxanes (Figure 14).[86,87,88]

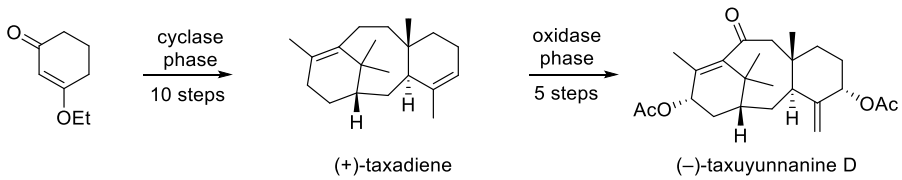


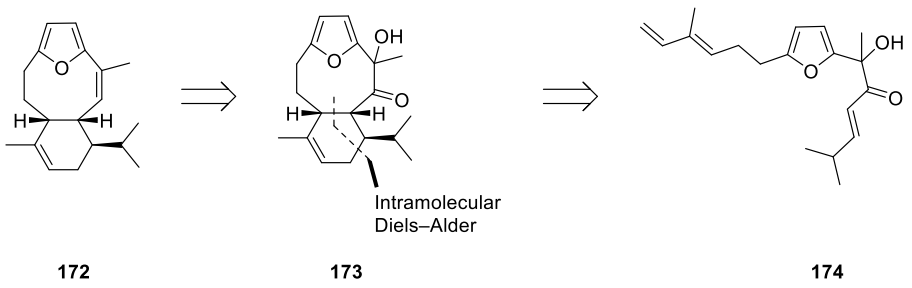
Figure 14. Application of a two-phase approach to the synthesis of taxane natural product (−)-taxuyunnanine D.

A requisite in any such synthetic effort is the availability of selective CH oxidation methods, and indeed this field has drawn considerable attention in recent years. As an alternative to "traditional" chemical reagents, biocatalytic methods hold great potential in this area.[89] Nature can effect, *via* enzymes such as cytochrome P450 monooxygenases, selective oxidation of unactivated positions in a wide range of organic molecules. It would be expected therefore that such enzymes could be modified to be used in a preparative context; while this has been demonstrated for relatively simple substrates, the application of biocatalytic methods in the synthesis of complex natural product-like molecules, for example as part of a two-phase synthetic sequence as described above, has been scarcely explored. An ongoing collaboration

between the Robertson and Wong groups aims to utilise a library of mutant P450 enzymes, developed by the Wong group, to effect late stage oxidation of complex organic compounds, both applied to the total synthesis of natural products as well as to the preparation of compound libraries for medicinal chemistry studies.

The important biological activity of eleutherobin has been emphasised earlier in this text; however, despite the aforementioned synthetic efforts, the small quantities prepared have not permitted a full evaluation of the therapeutic potential of the natural product. Furthermore, the limited medicinal chemistry studies on the compound have focused on very specific sites of the molecule (mainly on C4, C8 and C15). Therefore, there is interest in a novel synthetic route that would allow convenient access to both eleutherobin and a range of analogues for biological testing.

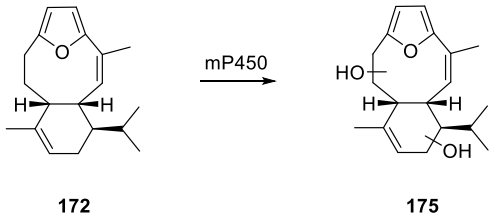
The work described in this thesis was aimed at studying the possibility of developing such a route by first designing a practical synthesis of the minimally oxidised tricyclic core of the natural product. At the outset we aimed to prepare a furanoid variant of this core by constructing the cyclohexene sector of the natural product *via* an intramolecular Diels–Alder reaction of precursor **174** (Scheme 25).



Scheme 25. Retrosynthetic analysis of minimally oxidised eleutherobin core structure **172**.

This core structure would then be subjected to late-stage oxidation using the Wong group's mP450 library; ideally this would give access to a library of differentially hydroxylated

analogues of eleutherobin (Figure 15) that could then be assayed for cytotoxic activity, and also provide valuable information on the potential use of mP450 monooxygenases in a synthetic context.



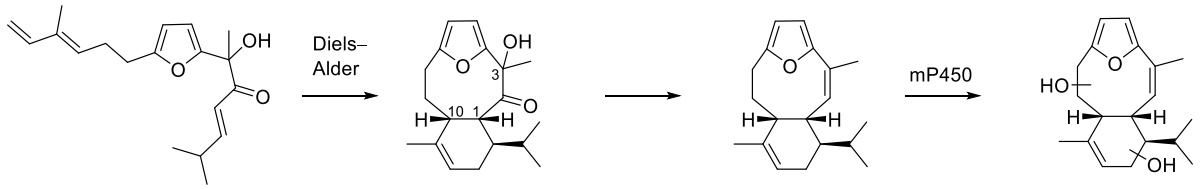
172 175

Figure 15. mP450 mediated oxidation of eleutherobin core structure **172**.

Chapter 2: IMDA approaches to the eleutherobin core structure

Aims

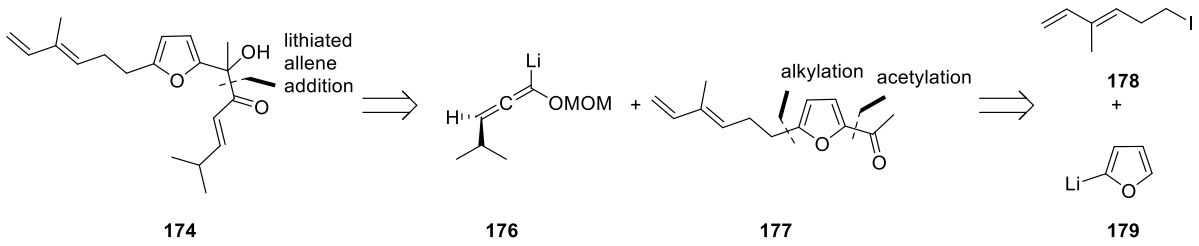
As previously described, the aim of the project was to develop a synthetic route to a furanoid variant of the tricyclic core structure of eleutherobin, which would then be subjected to mP450 mediated oxidation. It was envisaged that the six- and nine- membered rings could be constructed in one step through an intramolecular Diels–Alder reaction[90,91] of appropriately functionalised precursor **174** (Scheme 26). Such an IMDA reaction, in which the reacting partners are connected to the 2- and 5- positions of a furan tether, is unprecedented. Although it was expected that desired product **173** would be strained as a consequence of the planarity of the aromatic furan ring, the fact that Danishefsky had successfully prepared related structures in the course of his total synthesis[57,59] lent credence to the viability of the approach. *Endo*- selective cycloaddition would establish the desired relative stereochemistry at C1 and C10; the influence of the substituents on C3 was unknown at this stage.



174 **173** **172** **175**

Scheme 26. Envisaged synthesis of eleutherobin core structure **173** and mP450 oxidation.

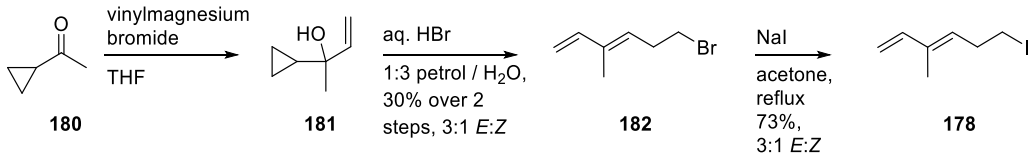
Cycloaddition precursor **174** would be prepared through the convergent approach outlined in Scheme 27: the dienophile moiety would be introduced in masked form as lithiated allene **176**, while the diene side-chain would be installed through a nucleophilic substitution on known iodide **178**.



Scheme 27. Retrosynthetic analysis of cycloaddition precursor **174**.

Preparation of the furan-tethered cycloaddition precursor

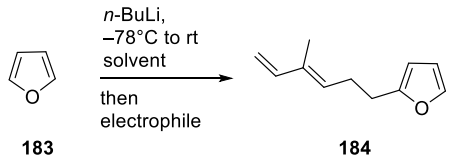
Iodide **178** was prepared according to a literature procedure.[92] Vinylmagnesium bromide addition to cyclopropyl methyl ketone gave tertiary alcohol **181** (Scheme 28), which was used directly in the next step. Treatment with aqueous HBr triggered substitution with opening of the cyclopropyl ring to deliver *E*-bromide **182**, as the major component of an inseparable 3 : 1 mixture with the *Z*- isomer (determined by comparison with literature data, 30% over two steps). Finkelstein reaction of bromide **182** furnished iodide **178**, again as an inseparable mixture of *E*- and *Z*- isomers (3 : 1 in favour of the *E*- isomer, 73% yield).



Scheme 28. Preparation of iodide **178**.

Having access to iodide **178**, nucleophilic substitution with furyllithium was next examined (Table 1). Addition of the iodide to 1.2 equiv of furyllithium in THF led to a complex reaction mixture out of which a small amount of desired product **184** could be isolated (< 10%) as an inseparable mixture of *E*- and *Z*- isomers in a 1.5 : 1.0 ratio; this deterioration of the isomeric ratio from the starting iodide suggests faster reaction of the *Z*- iodide or faster decomposition of the *E*- iodide under the strongly basic conditions. Loss of mass in the crude product

suggested possible base-mediated elimination to form a volatile triene. Use of DMPU as a cosolvent led to decomposition of the starting iodide. Changing the solvent to dimethoxyethane, or the electrophilic partner to bromide **182**, were similarly unsuccessful.

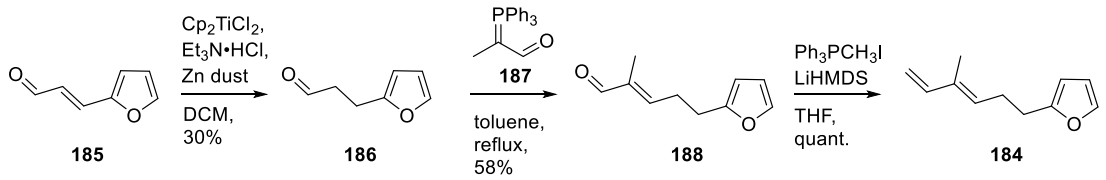


Entry	Electrophile	Solvent	Result
1	Iodide **178**	THF	< 10%
2	Iodide **178**	THF/DMPU 4:1	Decomposition
3	Bromide **182**	THF	No reaction
4	Iodide **178**	DME	Partial recovery of **178**

Table 1. Conditions attempted for the synthesis of diene **184** *via* alkylation of furan.

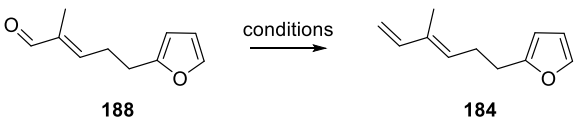
To circumvent this initial setback, the three-step sequence outlined in Scheme 29 was devised. Commercially available furylacrolein **185** was reduced to aldehyde **186** according to a procedure previously reported by our group,[93] which made use of methodology developed by Kosal and Ashfeld for the titanocene-catalysed reduction of α,β-unsaturated aldehydes with zinc dust as the stoichiometric reductant and $Et_3N{\cdot}HCl$ as the hydrogen donor.[94] The yield for this transformation was significantly lower than that previously achieved (> 90%); formation of aldehyde **186** was accompanied by generation of unidentified polar side products, necessitating purification *via* column chromatography with a considerable impact on the yield due to the compound's volatility. Interestingly, Kosal and Ashfeld report the generation of significant amounts of pinacol coupling side products in their system when non-optimal conditions were employed. This outcome was attributed to the quality of one of the reagents, though deoxygenation of the solvent *via* passage of a stream of argon, use of newly purchased Cp_2TiCl_2 and of activated Zn dust did not significantly increase the yield. As starting furylacrolein **185** is very cheap due to its use as a food additive, the low yield did not

significantly affect material throughput and therefore this issue was not investigated further. Subsequent Wittig reaction with phosphorane **187**, prepared using a modified literature procedure,[95] gave enal **188** exclusively as the desired *E*- isomer; a second Wittig reaction then provided diene **184**.



Scheme 29. Synthesis of diene **184**.

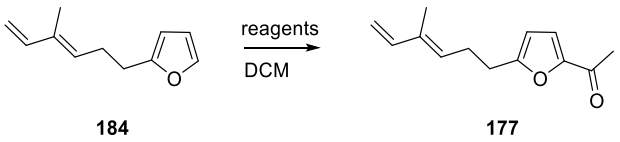
The success of the second Wittig reaction of the sequence was highly dependent on the combination of base and phosphonium halide used to generate the reactive phosphorane (Table 2): *n*-BuLi and triphenylphosphonium bromide failed to give any product, while the combination of LiHMDS and triphenylphosphonium iodide gave desired diene **184** in quantitative yield. *n*-BuLi and triphenylphosphonium iodide gave incomplete conversion after 18 h resulting in a reduced yield of 52%. Use of methodology developed by Lebel *et al*. for the formation[96] of the reactive phosphorus ylide *in situ* from $TMSCHN_2$ and triphenylphosphine with *i*-PrOH and Wilkinson's catalyst was also successful in forming diene **184** in moderate yield.



Entry	Conditions	Yield
1	*n*-BuLi, Ph_3PCH_3Br, THF	No reaction
2	LiHMDS, Ph_3PCH_3I, THF	Quantitative
3	*n*-BuLi, Ph_3PCH_3I, THF	52%
4	$RhCl(PPh_3)_3$, PPh_3, *i*-PrOH, $TMSCHN_2$	57%

Table 2. Olefination of aldehyde **188**.

To set the stage for the introduction of the enone side-chain, the acetyl group had next to be installed. Attempted Friedel–Crafts acylation (Table 3), using either $AlCl_3$ or $BF_3{\cdot}OEt_2$ as the Lewis acid and acetyl chloride or acetic anhydride as the acylating agent, proved unsuccessful. In the cases where decomposition was observed, this is believed to be due to interference from the diene moiety.

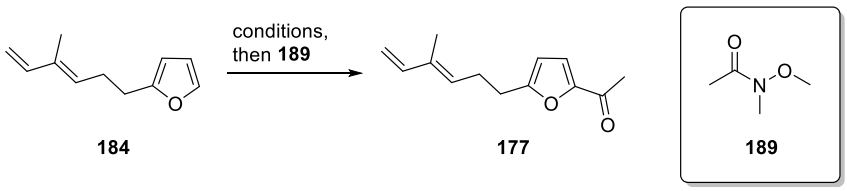


184 **177**

Entry	Lewis acid (equiv)	Acylating agent	T (°C)	Result
1	$AlCl_3$ (3)	AcCl	0	Decomposition
2	$AlCl_3$ (1.2)	AcCl	0	Decomposition
3	$AlCl_3$ (1.2)	Ac_2O	0	No reaction
4	$BF_3{\cdot}OEt_2$ (1.1)	Ac_2O	0	No reaction
5	$BF_3{\cdot}OEt_2$ (1.1)	AcCl	0	Decomposition
6	$BF_3{\cdot}OEt_2$ (1)	AcCl	−78	No reaction

Table 3. Conditions attempted for the Friedel–Crafts acetylation of furan **184**.

In contrast, deprotonation followed by addition of Weinreb amide **189** did provide the desired acetylated product, but only when *t*-BuLi was used as the base; use of *n*-BuLi, LDA, EtMgBr failed to give any product, instead returning unreacted starting material (Table 4, entries 1–4). In the case of *t*-BuLi, deprotonation had to be carried out at −78 °C, as raising the temperature to 0 °C led to no product formation (entry 5). Using a THF/DMPU mixture as the solvent was ineffective (entry 6). Increasing the amount of *t*-BuLi to 1.5 equiv raised the yield to 29%, but using 3.0 equiv did not provide any further benefit (entries 7, 8). Carrying out the reaction on a 1.5 mmol scale (as opposed to 0.12 mmol for the previous runs) resulted in a slightly improved isolated yield and a b.r.s.m. yield of 94% (entry 9).



Entry	Base (equiv)	Deprotonation T (°C)	Solvent	Yield (%)
1	*n*-BuLi (1.5)	0	THF	No reaction
2	LDA (1.0)	−78	THF	No reaction
3	EtMgBr (1.0)	−78	THF	No reaction
4	*t*-BuLi (1.0)	−78	THF	20
5	*t*-BuLi (1.0)	0	THF	No reaction
6	*t*-BuLi (1.0)	−78	THF/DMPU 1:1	No reaction
7	*t*-BuLi (1.5)	−78	THF	29
8	*t*-BuLi (3.0)	−78	THF	30
9[a]	*t*-BuLi (1.5)	−78	THF	33[b]

Table 4. Conditions screened for acetylation of furan **184**; a: reaction carried out on 1.5 mmol of **184**; b: 94% yield b.r.s.m.

The low yields (20-30%) along with the high recovery of starting material indicated that quenching of the generated furyllithium was taking place. The underlying cause is not clear; enolisation of the Weinreb amide is one possibility. It is also known that under basic conditions, Weinreb amides can undergo proton abstraction from their *O*-methyl group to give formaldehyde and the corresponding *N*-methyl acetamide[97,98,99] (Figure 16). This explanation is however offered only tentatively, as *N*-methyl acetamide was not detected in the crude reaction mixture.

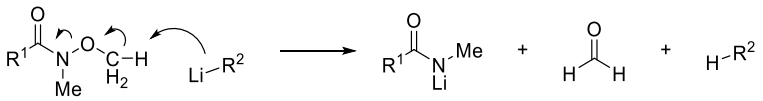
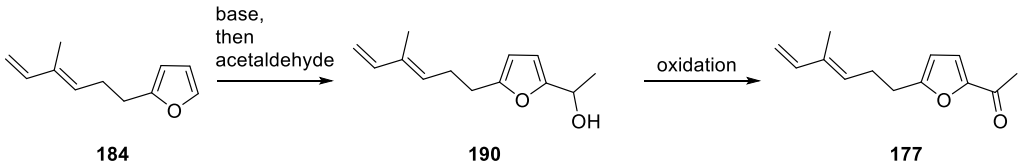


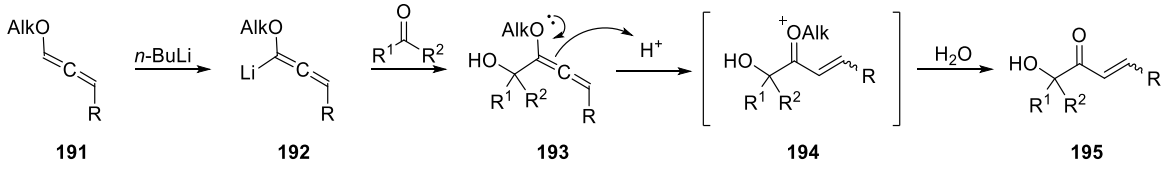
Figure 16. Pathway for the decomposition of Weinreb amides under basic conditions.

At this stage priority was given to reaching cycloaddition precursor **174** and determining the feasibility of the IMDA reaction; therefore this yield was deemed acceptable and the transformation was not optimised further. It was intended that, should this approach prove successful and further scale-up be required, ketone **177** could be accessed through a two-step sequence consisting of addition to acetaldehyde followed by oxidation (Scheme 30).



Scheme 30. Proposed alternative preparation of acetylated furan **177**.

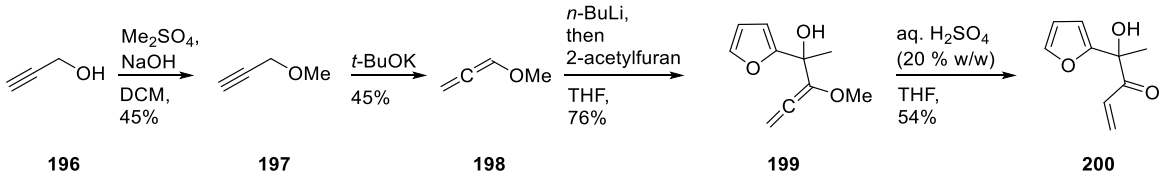
Alkoxy allenyl ethers of type **191** have been widely used as acyl anion equivalents;[100] the α-alkoxy hydrogen is sufficiently acidic that lithiated derivative **192** can be obtained by deprotonation with *n*-BuLi in THF. The resulting organolithium species can be used as a nucleophilic reagent in a wide range of reactions; addition to a ketone provides the corresponding tertiary alcohol, and the alkoxy allene functionality can then be hydrolysed with mild acid to reveal the masked enone group (Scheme 31). This reactivity formed the basis of our approach for the synthesis of the dienophilic side chain of the IMDA precursor.



Scheme 31. Use of an alkoxy allenyl ether as an acyl anion equivalent.

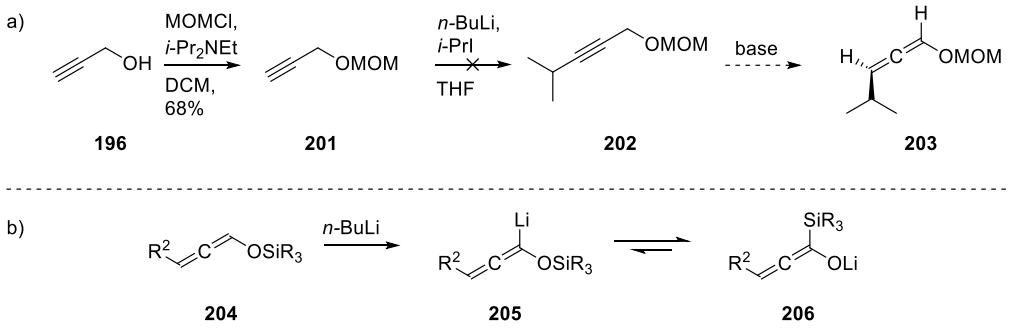
Introduction of the enone moiety was first examined on a model system, using 2-acetylfuran as a surrogate for acetylated furan **177**. Alkyne **197** was prepared by methylation of propargyl alcohol **196** with Me_2SO_4 in 45% yield, and converted to allene **198** in 45% yield by treatment

with *t*-BuOK followed by distillation (Scheme 32).[101] Allene **198** proved stable enough to be stored at −20 °C for several days, but not indefinitely: a sample stored in the freezer for 4 months was found to have completely decomposed when analysed by ^{1}H NMR spectroscopy. Deprotonation with *n*-BuLi in THF at −78 °C followed by addition of 2-acetylfuran furnished tertiary alcohol **199** in 76% yield. Acid treatment then successfully revealed the enone functionality, giving product **200** in 54% yield. Furan **200** was found to be relatively unstable to long-term storage, more so than allene derivative **199**, likely due to the electrophilic acryloyl group; samples that were stored at −20 °C for several months were found to have undergone significant decomposition.



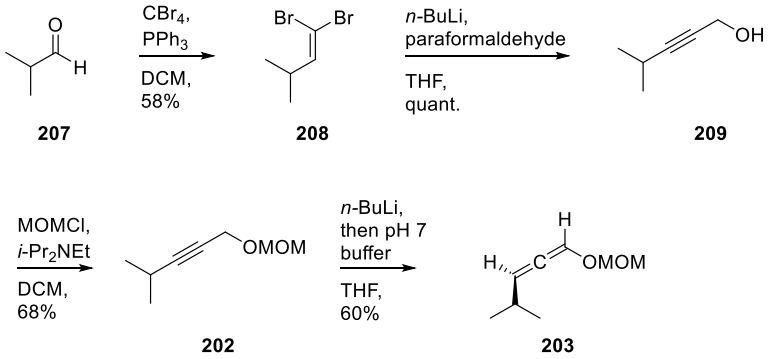
Scheme 32. Preparation of model allene **198** and subsequent addition to 2-acetylfuran.

Alkyne **202**, and by extension allene **203**, was next targeted (Scheme 33a); MOM was chosen as the protecting group to facilitate the final deprotection step, especially given the potential sensitivity of the tertiary furylic alcohol functionality to acidic conditions. Silicon based protecting groups are incompatible with this approach, as upon lithiation silyloxy allenes **204** are known to undergo Brook rearrangement to form lithium alkoxides **206** (Scheme 33b).[102] Deprotonation of protected propargylic alcohol **201**[103] in THF followed by addition of isopropyl iodide led only to recovery of starting material, even after the mixture was brought to reflux. Use of a 1 : 1 mixture of THF and DMPU as the solvent led to a complex reaction mixture.



Scheme 33. a) Attempted synthesis of allene **203**; b) Brook rearrangement of lithiated silyloxy allenes **205**.

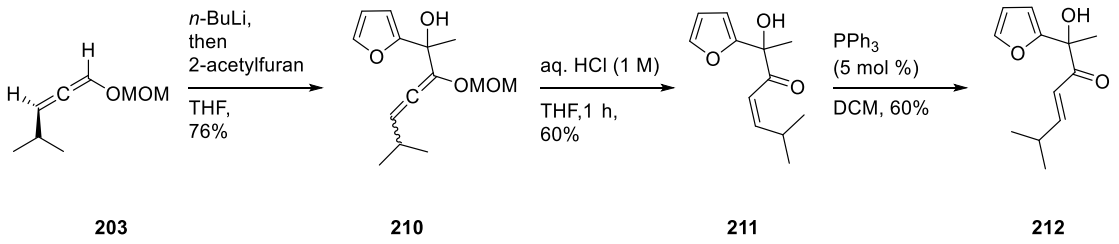
Instead, propargyl alcohol **209** was prepared by Corey–Fuchs reaction of isobutyraldehyde[104] (Scheme 34), then protected as MOM ether **202**. This alkyne was isomerised to desired allene **203** in 60% yield by treatment with *n*-BuLi and quenching the resulting organolithium with pH 7 phosphate buffer. Purification of allene **203** was not trivial, as the reaction was initially carried out in a scale that made distillation inefficient (1–2 mmol) and the product was also found, not unexpectedly, to be unstable on silica. Satisfactory results could be achieved by rapid passage of the crude mixture through basic alumina with petrol as the eluent, followed by removal of the solvent *via* distillation.



Scheme 34. Synthesis of allene **203**.

Deprotonation of allene **203** with *n*-BuLi and addition to 2-acetylfuran gave tertiary alcohol **210** in 72% yield as an inseparable (and inconsequential) mixture of diastereomers (Scheme

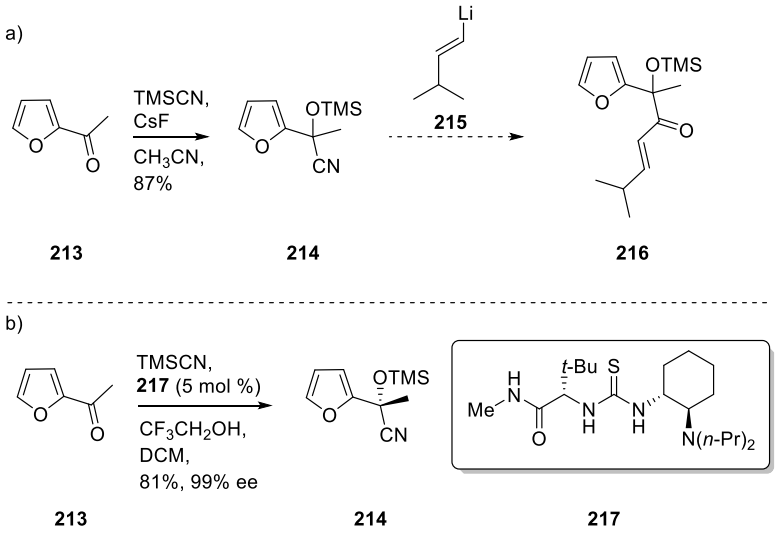
35). Treatment with 1 equiv of aqueous HCl then successfully effected hydrolysis of the allene group. It was found that *Z*- enone **211** was formed first, and was isolated as the sole product if the reaction was stopped after 1 h; upon prolonged reaction this was slowly converted to the more stable *E*- enone **212**, with complete conversion reached after 3–4 days. Increasing the concentration of acid decreased the time required for complete conversion to the *E*- isomer; however due to concerns about the stability of the products on long exposure to acid, it was elected to stop the reaction at the *Z*- enone stage, then isomerise it to the desired *E*- isomer *via* the reversible 1,4-addition of a nucleophilic species. In the event, treatment of enone **211** with 0.05 equiv of triphenylphosphine gave clean conversion to *E*- enone **212**.



203 **210** **211** **212**

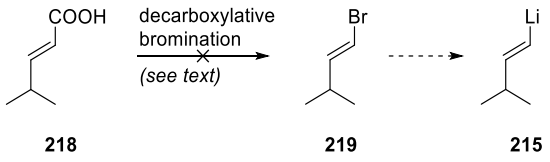
Scheme 35. Synthesis of model compound **212**.

In parallel to these studies, an alternative synthesis of the dienophilic sector was investigated. Nitrile **214** was formed in 87% yield by CsF-mediated addition of TMSCN to 2-acetylfuran (Scheme 36a). It was intended that addition of vinyllithium nucleophile **215** to the nitrile would provide enone **216**; the advantage of this approach resides in the fact that nitrile **214** may be accessed in enantiopure form through enantioelective thiourea-catalysed cyanosilylation methodology reported by Fuerst and Jacobsen[105] (Scheme 36b).



Scheme 36. a) Envisaged alternative approach for the introduction of the dienophilic side chain; b) Enantioselective preparation of nitrile **214** by Fuerst and Jacobsen.

Vinyllithium reagent **215** would be formed by lithium-halogen exchange of the corresponding vinyl halide (Scheme 37). The preparation of vinyl bromide **219** has been reported by decarboxylative bromination of acid **218** through the use of $NaNO_2$ and HBr under an oxygen atmosphere to generate bromine *in situ*;[106] attempts to replicate this transformation, however, yielded no product. Efforts to effect decarboxylative bromination with other reported conditions (DMP and TEAB in DCM,[107] or *via* Hunsdiecker reaction mediated by LiOAc and NBS in CH_3CN/H_2O[108]) proved similarly ineffective.

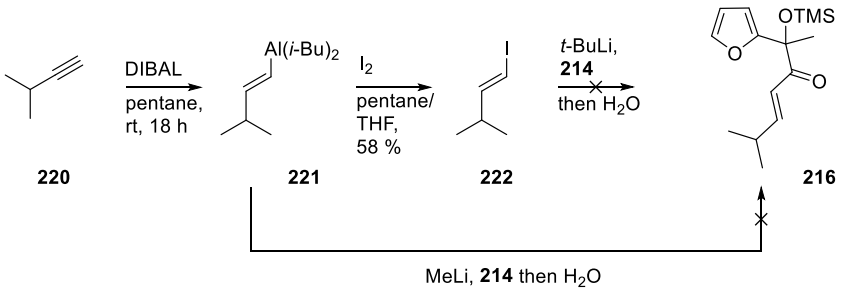


Scheme 37. Envisaged preparation of vinyllithium reagent **215**.

Wiersig *et al*. reported the preparation of iodide **222** from alkyne **220** (Scheme 38) by hydroboration with catecholborane, hydrolysis to the boronic acid and then reaction with iodine under basic conditions.[109] It was hoped that simpler synthesis of iodide **222** could be

achieved by hydroalumination of alkyne **220** and quenching the resulting vinylalane with iodine. The alkyne was dissolved in pentane and treated with DIBAL; after complete hydroalumination (18 h at RT, or 2 h at 50 °C in a pressure tube), a solution of iodine in THF/pentane was added to form desired iodide **222**. Performing the hydroalumination at RT was preferred despite the longer reaction time as the vigorous reaction upon aqueous quench proved difficult to control in a pressure tube.

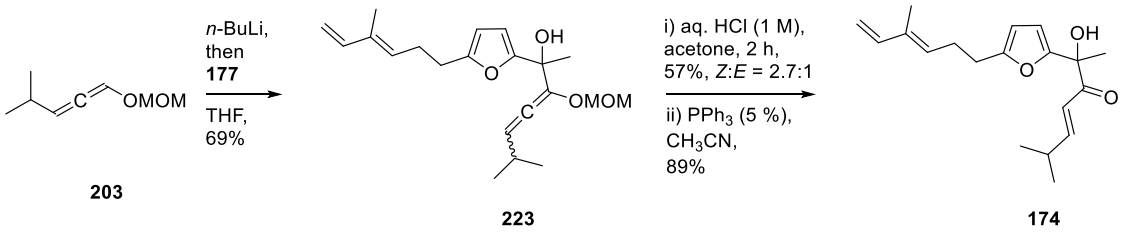
Lithium-halogen exchange of iodide **222** followed by addition to nitrile **214** formed none of the desired product; starting material was recovered instead, along with a small amount of 2-acetylfuran presumably regenerated by deprotection of the starting material. An attempt to form organolithium **215** directly from vinylalane **221**, by treatment with MeLi, then addition to nitrile **214** also returned starting material, as did an attempt to add the vinylalane formed from alkyne **220** directly to the nitrile. Given the success of the lithiated allene route, no further work was pursued on this approach.



Scheme 38. Synthesis of iodide **222** and attempted addition to nitrile **214**.

By analogy with the model studies carried out on 2-acetylfuran, allene **203** was deprotonated and added to acetylated furan derivative **177** to give alcohol **223** in 69% yield as an inseparable mixture of diastereomers (Scheme 39). Removal of the MOM protecting group with aqueous HCl gave, after 2 h of reaction time, a 2.7 : 1 mixture of the *Z*- and *E*- isomers, respectively, of the desired enone in 57% overall yield. Although the two isomers could be separated by

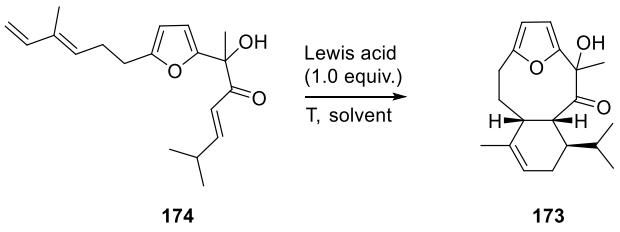
column chromatography, the mixture was subjected as before to isomerisaton by treatment with 0.1 eq of triphenylphosphine in CH_3CN, giving solely the *E*- isomer.



Scheme 39. Synthesis of cycloaddition precursor **174**.

Attempted IMDA cycloaddition

With the cycloaddition precursor now in hand, the crucial Diels–Alder reaction was attempted. Dissolving the compound in toluene and heating in a sealed tube, gradually increasing the temperature up to 190 °C, provided no product and eventually led to decomposition. A screening of various Lewis acids then followed (Table 5); $TiCl_4$ and $B(C_6F_5)_3$ led to decomposition (entries 1, 2), while $EtAlCl_2$, $Yb(OTf)_3$, $Eu(OTf)_3$ and bidentate Lewis acid $TfN[Al(Me)Cl]_2$ [85] (entries 3–6) led to recovery of starting material.



Entry	Lewis acid	T (°C)	Solvent	Result
1	$TiCl_4$	RT	DCM	Decomposition
2	$B(C_6F_5)_3$	0 °C → RT	DCM	Decomposition
3	$EtAlCl_2$	0 °C → reflux	DCM	No reaction
4	$Yb(OTf)_3$	RT → reflux	DCM	No reaction
5	$Eu(OTf)_3$	RT → reflux	DCM	No reaction
6	$TfN[Al(Me)Cl]_2$	RT → reflux	1,2-DCE	No reaction

Table 5. Conditions assayed for the IMDA of compound **174**.

The potential advantage of different solvent systems was then studied. Rideout and Breslow first demonstrated the significant acceleration imparted to Diels–Alder reactions by using water as the reaction solvent[110,111] and attributed this effect to increased hydrophobic contact between the reacting partners. In the same vein, Grieco *et al*. reported that use of 5 M $LiClO_4$ in diethyl ether as the reaction medium drastically increased the rate of [4+2] cycloadditions,[112,113] the effect being comparable in some cases with that of high pressure (*vide infra*). In our system, both solvents proved ineffective in promoting the reaction.

The application of high pressure promotes reactions with a negative volume of activation; that is, reactions in which the volume of the transition state complex is smaller than that of the reacting molecules.[114] Cycloadditions typically fall within this category (with typical volumes of activation between −20 to −40 cm^3/mol),[115] and indeed this technique has been used in natural product synthesis to effect Diels–Alder reactions that were unsuccessful by conventional means. Instruments capable of generating the pressures required (1–20 kbar) are not standard equipment in most organic laboratories, but the use of a high pressure reactor was kindly provided by the Trauner and Magauer groups at the LMU Munich. Precursor **174** was thus dissolved in DCM and subjected to 19 kbar of pressure for 18 h; even under such forcing conditions, however, no cycloaddition product was detected, with starting material being recovered instead.

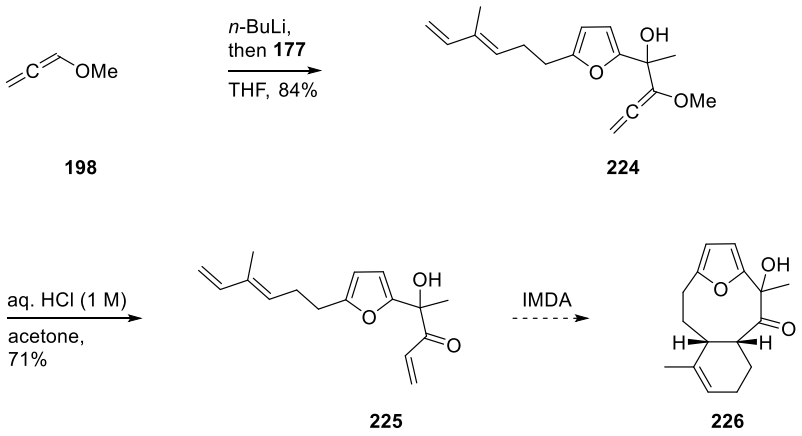
These results prompted a re-examination of the IMDA precursor **174**, with three factors identified as responsible for hindering the desired reactivity:

i. the presence of the isopropyl substituent on the dienophile is expected to deactivate the dienophile both sterically and electronically;
ii. the decomposition observed in some Lewis acid-mediated conditions could be attributed to the acid-labile tertiary furylic alcohol functionality;

iii. the rigidity of the linking furan ring is likely to lead to a strained transition state resulting in a slow reaction.

IMDA cycloaddition of a simplified precursor

To probe the negative influence of the isopropyl group, a synthesis of simplified nor-isopropyl cycloaddition precursor **225** (Scheme 40) was pursued. The primary objective was to study the effect of this substituent on the IMDA reaction, but it was appreciated that the isopropyl group could be introduced subsequently, in the event of successful cycloaddition. Preparation of compound **225** was achieved, as outlined in Scheme 40, using an analogous synthetic sequence to that used for precursor **174**. Lithiation and addition of allene **198** to furan derivative **177** gave alcohol **224** in 84% yield; this was treated with aqueous HCl in acetone to provide compound **225**. As was previously observed for enone **200**, compound **225** proved prone to degradation even when kept at −20 °C, making storage for more than a few weeks impossible. This provides some insight into the increased reactivity of the unsubstituted acryloyl moiety when contrasted with the behaviour of isopropyl-substituted compound **174**, which was stable on long-term storage.



Scheme 40. Synthesis of cycloaddition precursor **225** and envisaged IMDA reaction.

Precursor **225** did not undergo cycloaddition under the Lewis acidic conditions assayed; when $EtAlCl_2$ was used, a small amount of new product was formed, tentatively identified (based on the disappearance, in the ^1H NMR spectrum, of the enone proton peaks and appearance of new signals at the 4.8–5.2 ppm region and a singlet at 2.45 ppm) as a mixture of alcohols **227** and **228**, products of Lewis acid mediated α-ketol rearrangement (Figure 17). When $B(C_6F_5)_3$ was used instead, decomposition was observed. Heating to reflux in water provided a complex reaction mixture indicative of decomposition; however, the disappearance of the enone signals in the NMR spectrum of the crude product mixture was observed that could indicate some degree of IMDA reaction.

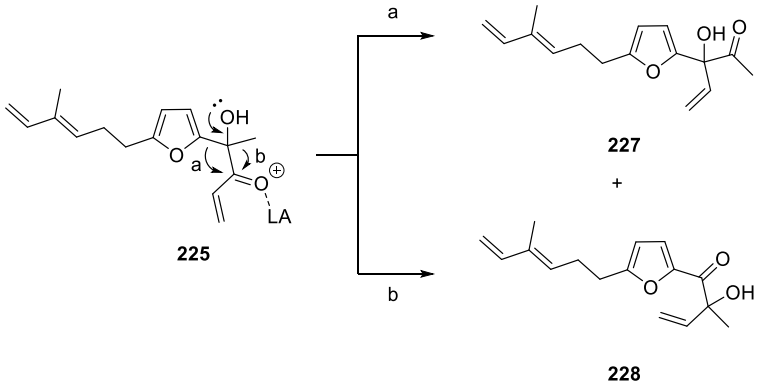
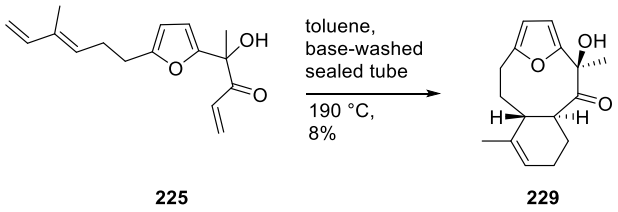


Figure 17. α-Ketol rearrangement of compound **225**.

Initial attempts to effect a thermal reaction led to decomposition of the starting material after prolonged heating. For this substrate, thermal reaction *via* microwave irradiation was attempted; heating to 130 °C in a CH_3CN/H_2O mixture or in H_2O did not effect the reaction. Attempts to employ iminium catalysis in combination with MW irradiation were also made, using L-proline benzyl ester·HCl or pyrrolidine as the amine catalyst, although it was anticipated that 1,4-addition of the amine to the enone might prevail; indeed, this did not provide any improvement and, specifically in the pyrrolidine reaction, the conjugate addition product was observed in the crude mixture.

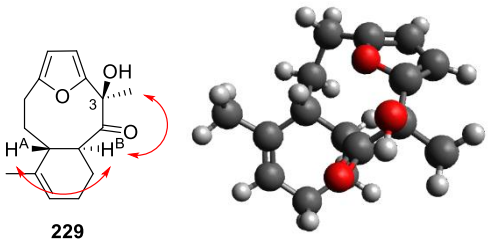
Returning to thermal reaction *via* conventional heating, it was found that by heating a toluene solution of **225** in a base-washed sealed tube to 190 °C, IMDA adduct **229** was formed in 8% yield (Scheme 41). The ^{1}H NMR spectrum of the crude reaction mixture indicated considerable competing degradation of enone **225**, potentially by polymerisation, which accounts for the low yield. Addition of 10 mol% of hydroquinone, commonly used as a radical scavenger in thermal Diels–Alder reactions, did not improve the reaction profile, nor did adding 2.0 equiv of K_2CO_3 to maintain a basic environment.



225 **229**

Scheme 41. IMDA reaction of precursor **225**.

The relative stereochemistry for adduct **229** is proposed to be that indicated in Scheme 41, corresponding to an *exo*- selective IMDA reaction (or post-cycloaddition epimerisation), based on a combination of NOE and computational studies. The observed NOE interactions indicated in Figure 3 were inconclusive as to the relative stereochemistry between H^A and H^B. DFT calculations predicted a Boltzmann-weighted average H^A-H^B dihedral angle of 46° for the *endo*- adduct and 101° for the *exo*- adduct (shown in Figure 18) – these correspond to Karplus-derived coupling constants of approximately 4 Hz and 0 Hz respectively, with the latter value being closest to the experimentally observed J = 1.5 Hz. Furthermore, the stereochemistry at the tertiary alcohol centre was inferred based on the observed NOE between the C3 methyl group and H^B.



229

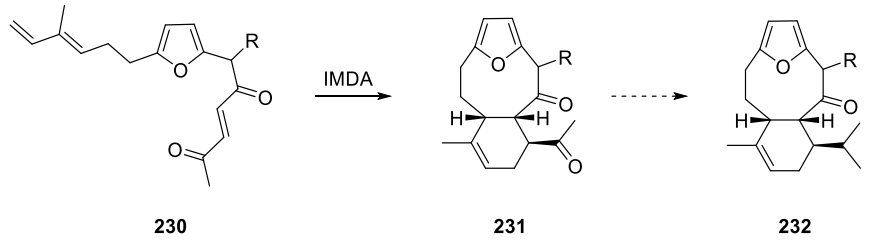
Figure 18. Indicative NOE correlations of IMDA adduct **229** and corresponding lower-energy structure. Structure was obtained from calculations on a simplified compound (CH_3/OH groups on C3 substituted by protons); the substituents were reintroduced to the final structure. This conformation accounts for ~80% of the population.

Additionally, compound **225** was subjected to high pressure conditions (19 kbar in DCM for 18 h), which resulted in complete starting material consumption but no observable product formation. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated a complex product mixture possibly indicative of polymerisation.

Studies towards the synthesis of an IMDA precursor bearing a doubly activated dienophile

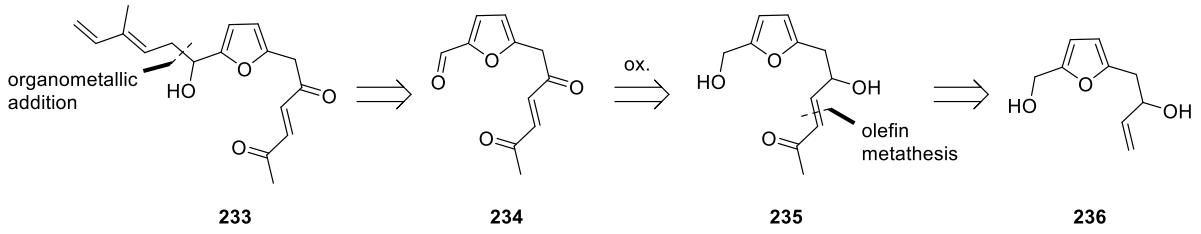
Although obtaining IMDA adduct **229** was an encouraging result, attempting to progress further along this synthetic route was deemed impractical, as i) cycloaddition precursor **225** proved far too prone to degradation, resulting in low yields of adduct **229**, and ii) subsequent introduction of the isopropyl substituent would lead to an unwieldy synthetic sequence. It was reasoned instead that in a similar vein, substituting the isopropyl group in precursor **174** with an acetyl group would result in a doubly activated dienophilic moiety, greatly favouring the desired reactivity (Scheme 42). Once adduct **231** was formed, the acetyl group could be converted into the isopropyl present in the natural product. Precedent for this transformation in related cyclohexene structures was set by Clark *et al*. who accomplished it *via* olefination followed by hydrogenation,[116] or in cases reported by Kim *et al*.[117] and by Clark *et al*.[118] where

the trisubstituted alkene interfered with the hydrogenation step, by methylmagnesium bromide addition followed by acetylation and reductive removal of the acetyl group *via* dissolving metal reduction.[119]



Scheme 42. Doubly activated cycloaddition precursor **230** and envisaged introduction of the isopropyl group after IMDA reaction.

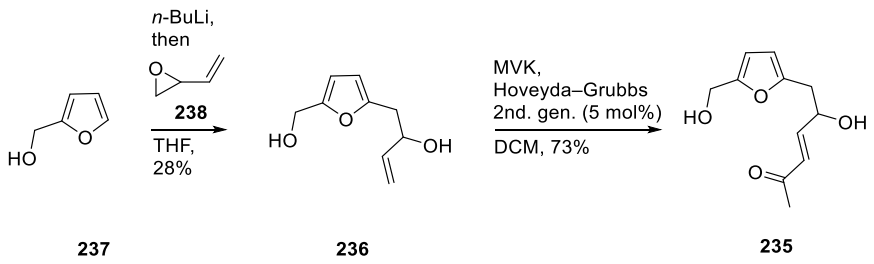
A commonly employed tactic for the synthesis of 1,4-enedione structures such as the one in **230** consists of the oxidation/hydrolysis of 2,5-disubstituted furans,[120] an approach that is however not applicable in our system. Instead it was intended that precursor **233** would be prepared by addition of lithiated 3-methyl-1,4-pentadiene to aldehyde **234** (Scheme 43), which would in turn be accessed from concomitant oxidation of the primary and the allylic alcohols in compound **235**. Finally, **235** would be derived from alcohol **236** *via* an olefin metathesis with methylvinyl ketone.



Scheme 43. Retrosynthetic analysis of cycloaddition precursor **233**.

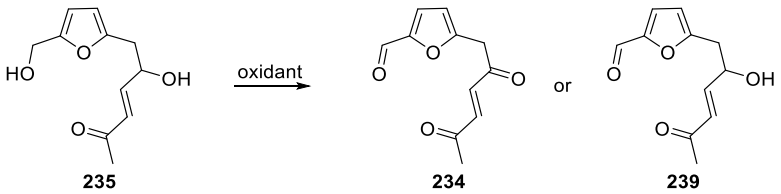
Starting from furfuryl alcohol **237**, deprotonation with *n*-BuLi and addition of propadiene oxide gave allylic alcohol **236** in 24% yield (Scheme 44). Olefin metathesis with methyl vinyl

ketone using Hoveyda–Grubbs 2nd generation catalyst proceeded readily to furnish diol **235** in 73% yield.



Scheme 44. Synthesis of diol **235**.

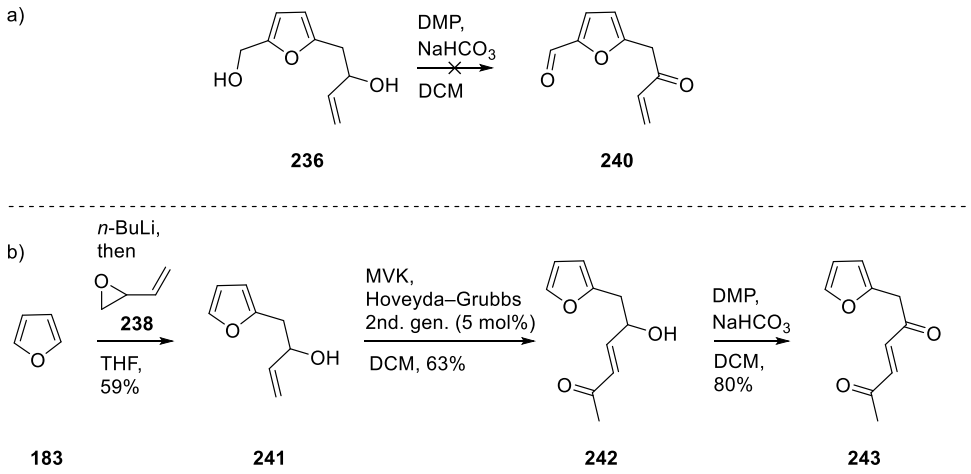
A wide range of oxidants was screened to achieve oxidation of this diol to aldehyde **234**; however, in all cases, decomposition was observed (Table 6). When MnO_2, Ag_2CO_3, or NMO/TPAP was used (entries 3, 4 and 7), stopping the reaction prematurely resulted in aldehyde **239** being detected in the crude reaction mixture (based on the appearance of the aldehyde peak at 9.57 ppm in the ^{1}H NMR spectrum); however, prolonged reaction again led to decomposition. The reason for this behaviour is not clear, as no side products were generated that could give information on the underlying process.



Entry	Oxidant	Result
1	DMP	Decomposition
2	IBX	Decomposition
3	MnO_2	**239**, then decomposition
4	Ag_2CO_3 on celite	**239**, then decomposition
5	PCC	Decomposition
6	PDC	Decomposition
7	NMO/TPAP	**239**, then decomposition
8	DMSO, $(COCl)_2$	Decomposition

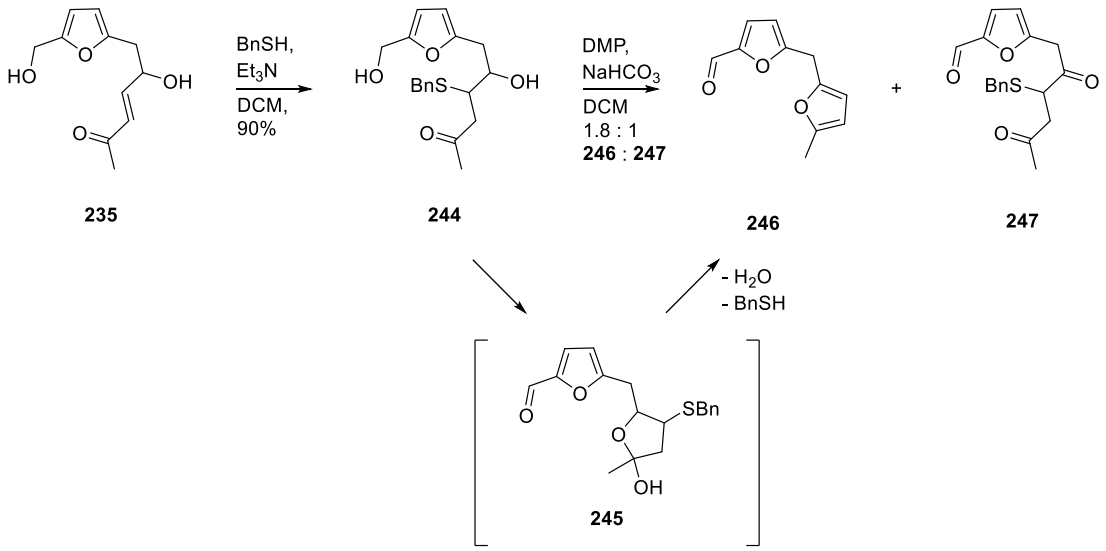
Table 6. Conditions assayed for the oxidation of diol **235**.

Model studies were carried out in an attempt to identify the functionality responsible for this instability under oxidative conditions. DMP oxidation of allylic alcohol **236** also failed to provide any product (Scheme 45a); alcohol **242** however, prepared *via* olefin metathesis of **241** with methyl vinyl ketone, could be oxidised successfully with DMP to the corresponding enedione (Scheme 45b). An attempt to form aldehyde **234** *via* a Vilsmeier–Haack formylation of enedione **243** led to decomposition of the starting material. These results point to the formyl substituent as being incompatible with the oxidation.



Scheme 45. a) Attempted oxidation of diol **236**; b) synthesis of enedione **243**.

It was next theorised that temporarily masking the α,β-unsaturated ketone system by conjugate addition of a nucleophile could allow the oxidation to take place successfully, at which point the enedione would be revealed by base-mediated elimination of the added group. In practice, treatment of **235** with benzylthiol and Et_3N in DCM formed **244** as a mixture of diastereomers in 90% yield (Scheme 46). Upon oxidation of a small sample of **244** with DMP in the presence of $NaHCO_3$, a 1.8 : 1 mixture of bis-furan **246** and desired oxidation product **247** was formed; the major product likely arises through acetal **245** *via* elimination of H_2O and benzylthiol. Subsequent treatment with DBU however led to decomposition of minor component **247**.



Scheme 46. Oxidation of modified diol **244**.

Given the success of an alternative synthetic approach investigated in parallel (see Chapter 3), no further efforts towards aldehyde **234** and consequently precursor **233** were undertaken, though the IMDA reaction of such a doubly-activated system remains an attractive approach and can form the basis for further research.

Studies towards the synthesis of a deoxygenated cycloaddition precursor

As the acid-labile tertiary furylic alcohol functionality of compound **174** was considered to contribute to the observed decomposition in the presence of some Lewis acids (Figure 19), the possibility of removing it was briefly explored.

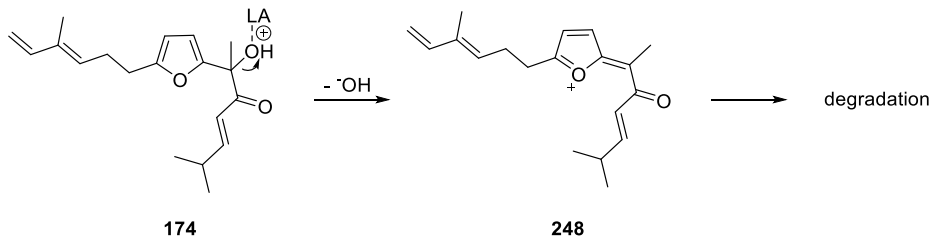
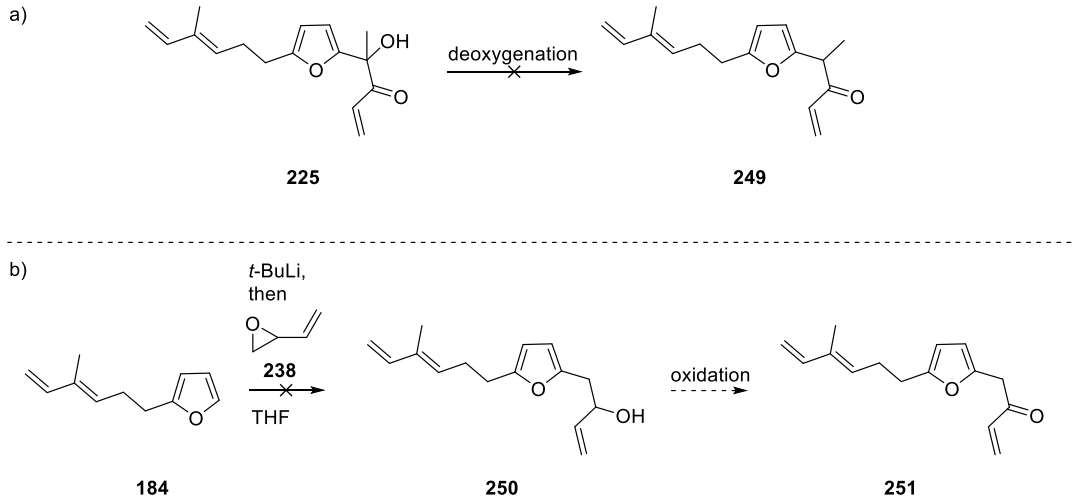


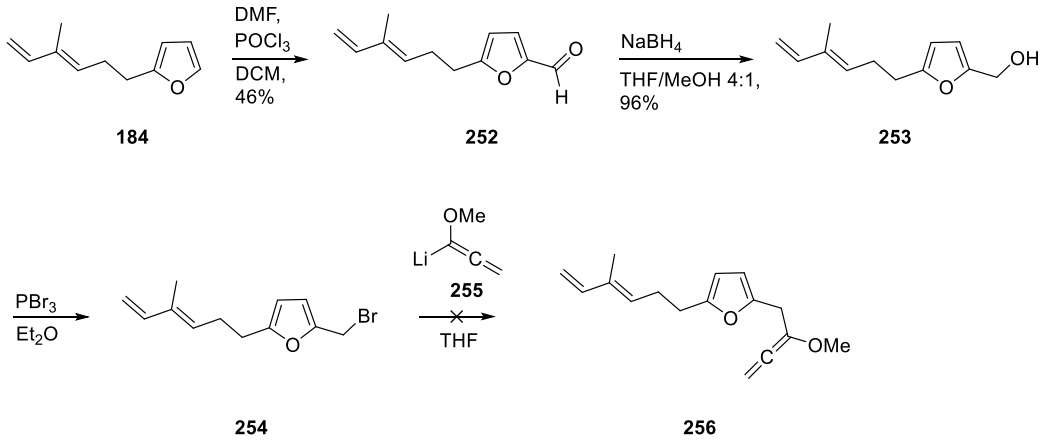
Figure 19. Lewis acid mediated decomposition of cycloaddition precursor **174**.

Initially, attempts to directly deoxygenate compound **225**, using either TFA or $BF_3{\cdot}OEt_2$ in the presence of Et_3SiH (Scheme 47a),[121,122] led to recovery of starting material and decomposition, respectively. Deprotonation of furan **184** followed by addition of butadiene oxide just led to starting material recovery (Scheme 47b).



Scheme 47. a) Attempted preparation of precursor **249** *via* deoxygenation of **225**; b) Attempted synthesis of precursor **251**.

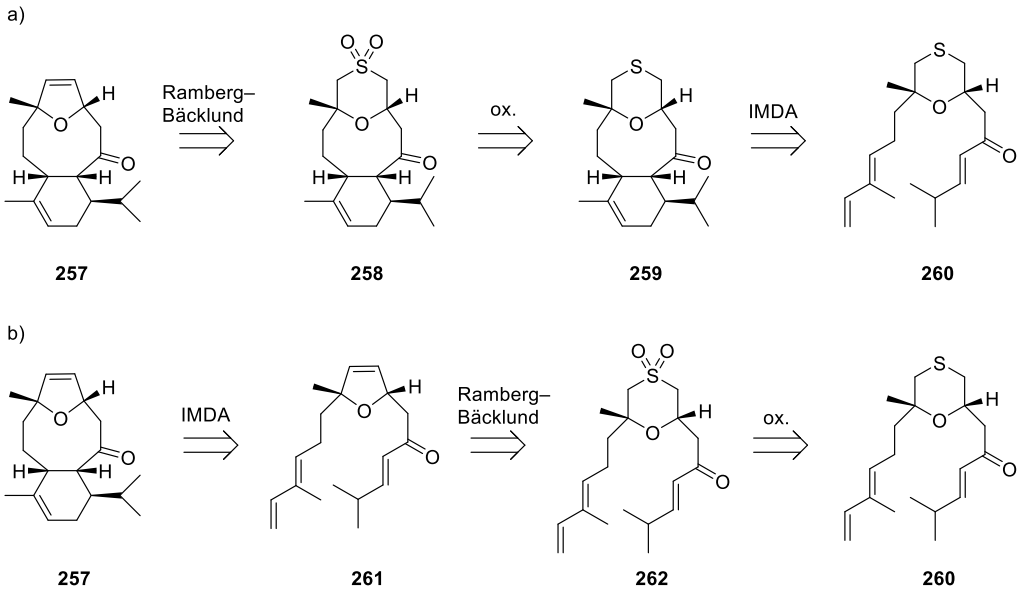
The possibility of forming allene **256** (Scheme 48) by addition of lithiated allene **255** to bromide **254** was explored. Alcohol **253** was prepared from diene **184** by Vilsmeier–Haack formylation then reduction; this was then converted into bromide **254** by treatment with PBr_3 in ether. Due to the susceptibility of primary furylic halides to displacement by water, the bromide was immediately dissolved in THF and organolithium **255** added. No desired addition product **256** was formed, and analysis of the crude reaction mixture indicated that the starting material had partially dimerised.



Scheme 48. Synthesis of bromide **254** and attempted addition of lithiated allene **255**.

IMDA studies of an oxathiane-containing cycloaddition precursor

As previously mentioned (page 59), it was theorised that the relatively rigid and planar furan tether in cycloaddition precursor **174** impeded the desired reactivity. To obviate this, it was envisaged that a heterocyclic tether could be used in which the reacting partners are connected to sp^3 carbon atoms, thereby leading to a less strained cycloaddition transition state. An oxathiane ring, as in compound **260** (Scheme 49), was chosen for this purpose, as it could be converted eventually to the dihydrofuran present in the natural product *via* a Ramberg–Bäcklund reaction; such an approach to the synthesis of a 2,5-dihydrofuran was used by Trost and Shi in their synthesis of (+)-solamin.[123] This sequence of events was preferred over the opposite, whereby the oxathiane would be converted into the dihydrofuran prior to the IMDA reaction (Scheme 49b), as the oxidation step to form the sulfone could affect the electron rich diene side chain.



Scheme 49. Retrosynthetic analysis of eleutherobin core structure **257**.

Different approaches were evaluated for the synthesis of the oxathiane ring (Figure 20). Given the placement of the carbonyl group in precursor **260**, the possibility of ring formation by intramolecular conjugate addition presented itself; tetrahydropyran derivatives have been synthesised in this manner.[124,125,126] Alternatively, incorporation of a ketone in thioether **265** could lead to an oxathiane *via* hemiacetal formation; as it was not known, however, how the hemiacetal would influence the subsequent Ramberg–Bäcklund sequence, approach A was chosen.

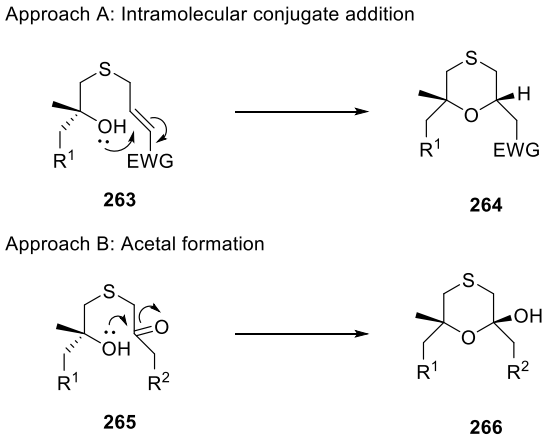
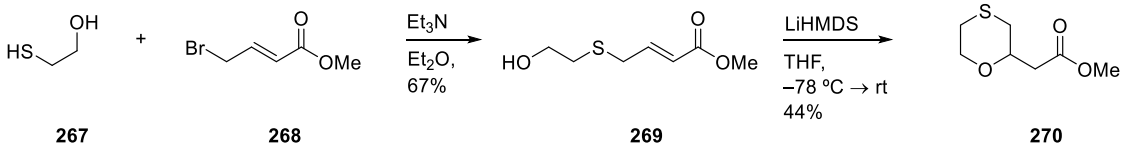


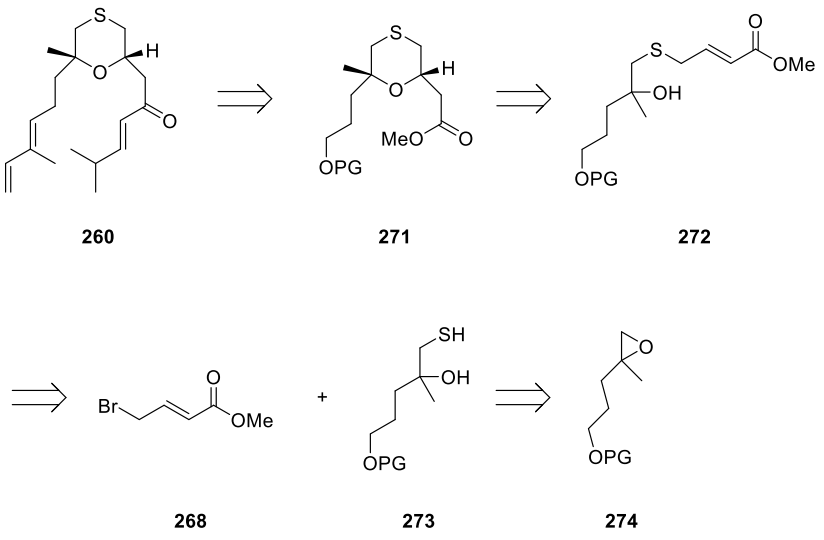
Figure 20. Approaches to the synthesis of the oxathiane ring.

To assess the feasibility of the intramolecular oxa-Michael approach, model thioether **269** was prepared from 2-mercaptoethanol and methyl bromocrotonate **268** (Scheme 50), then treatment with LiHMDS in THF successfully formed oxathiane **270** in 44% yield. Although this demonstrated that the proposed ring formation was feasible, the cyclisation diastereoselectivity remained an unknown factor.



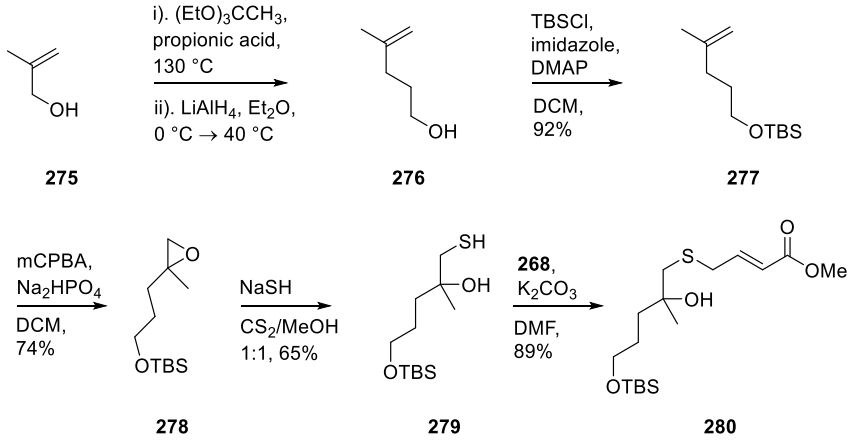
Scheme 50. Synthesis of model system **270**.

On this basis, synthesis of cycloaddition precursor **260** was planned as outlined in Scheme 51, with functionalisation of the side chains to be carried out after oxathiane formation. Thioether **272** would be prepared by etherification of methyl bromocrotonate **268** with thiol **273**, itself prepared *via* nucleophilic ring opening of epoxide **274**.



Scheme 51. Restrosynthetic analysis of IMDA precursor **260**.

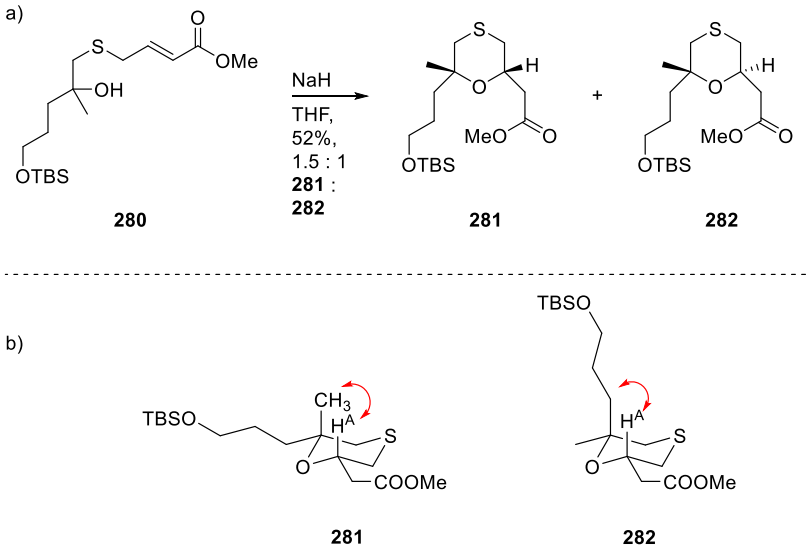
Alcohol **276**, prepared by a previous member of the group from commercial 2-methyl-2-propen-1-ol *via* a two-step sequence comprising Claisen rearrangement followed by reduction,[127,128] was protected as TBS ether **277** (Scheme 52); treatment with mCPBA in DCM then provided epoxide **278** in 74% yield. This was opened with NaSH in a 1 : 1 CS_2/MeOH mixture to give primary thiol **279**. The yield of this reaction was found to be sensitive to the water content of the NaSH used: use of the monohydrate resulted in a 49% yield for the thiol, with the corresponding primary alcohol being observed as a side product. When dried NaSH was used, the yield of the thiol increased to 65%, and the alcohol side product was not observed. Thiol **279** was coupled to methyl bromocrotonate **268** to furnish thioether **280** in 89% yield.



Scheme 52. Preparation of thioether **280**.

Oxathiane formation *via* intramolecular oxa-Michael reaction of thioether **280** was explored next. Contrary to model system **269**, LiHMDS failed to promote cyclisation of compound **280**, as did KHMDS and Et_3N. NaH however proved effective; addition of 5 mol% of imidazole was found to improve the reaction's reproducibility, giving oxathianes **281** and **282** in 52% yield as a 1.5 : 1 inseparable mixture (Scheme 53a). The imidazole has been proposed to act as a catalyst for alkoxide formation by acting as a proton shuttle between the alcohol and the insoluble base.[129] The stereochemistry of each was confirmed by the observation of NOE

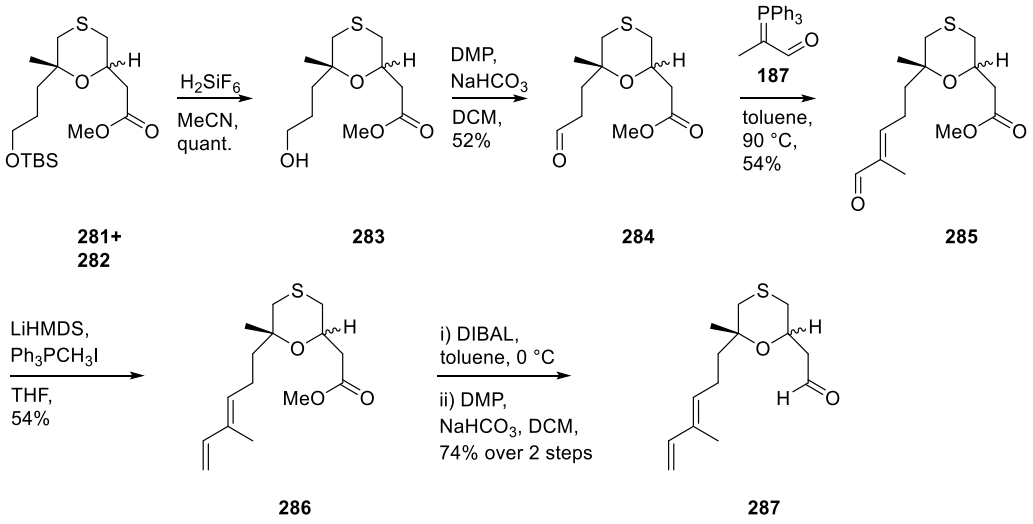
between H^A and either the methyl group in **281** or the methylene protons in the side chain of **282** (Scheme 53b).



Scheme 53. a) Oxathiane formation *via* intramolecular oxa-Michael reaction; b) Indicative NOE signals of oxathianes **281** and **282**.

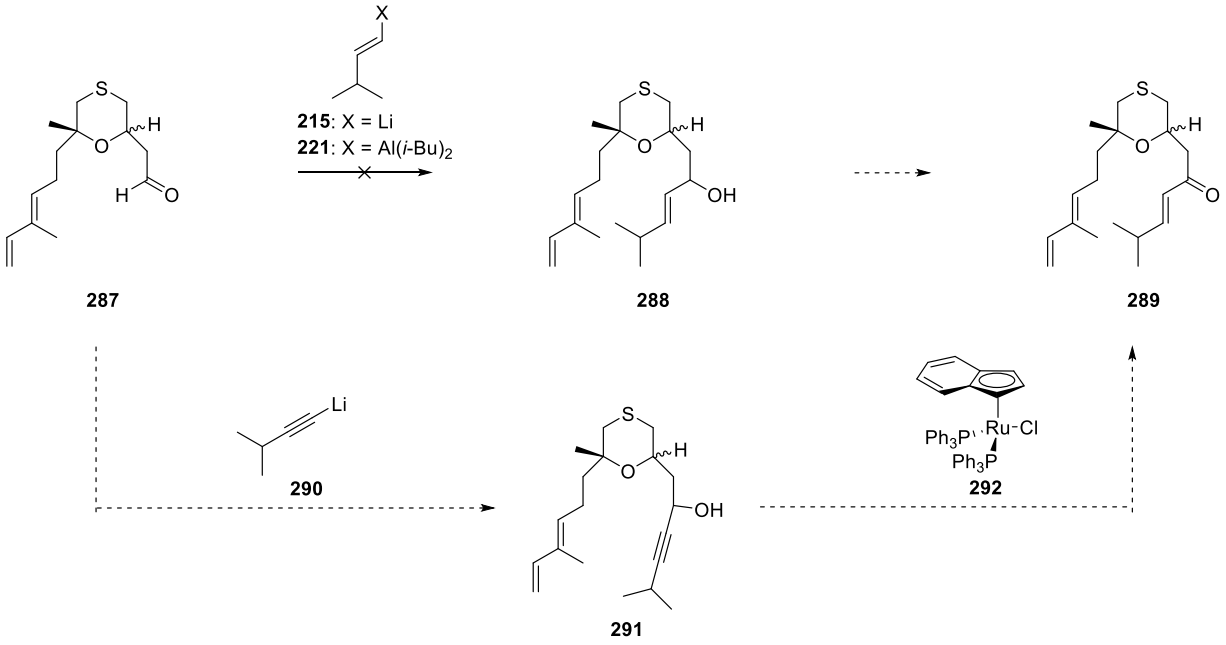
DFT calculations predicted a roughly 1 : 1 thermodynamic ratio for **281** and **282**, suggesting that the observed diastereoselectivity might indicate kinetic control. Reducing the reaction temperature to −20 °C did not improve the diastereomeric ratio of products, while further reducing it to −78 °C resulted in a drastically decreased rate. Subsequent synthetic operations were carried out on the inseparable mixture.

Deprotection of the primary alcohol with TBAF in THF only returned starting material, and H_2SiF_6 in CH_3CN was used instead (Scheme 54). The alcohol was then oxidised to aldehyde **284**, and the sequence of two Wittig reactions employed previously accomplished the formation of the diene-bearing side-chain in compound **286**. A two-step reduction-oxidation sequence then converted the ester into aldehyde **287** in 74% overall yield.



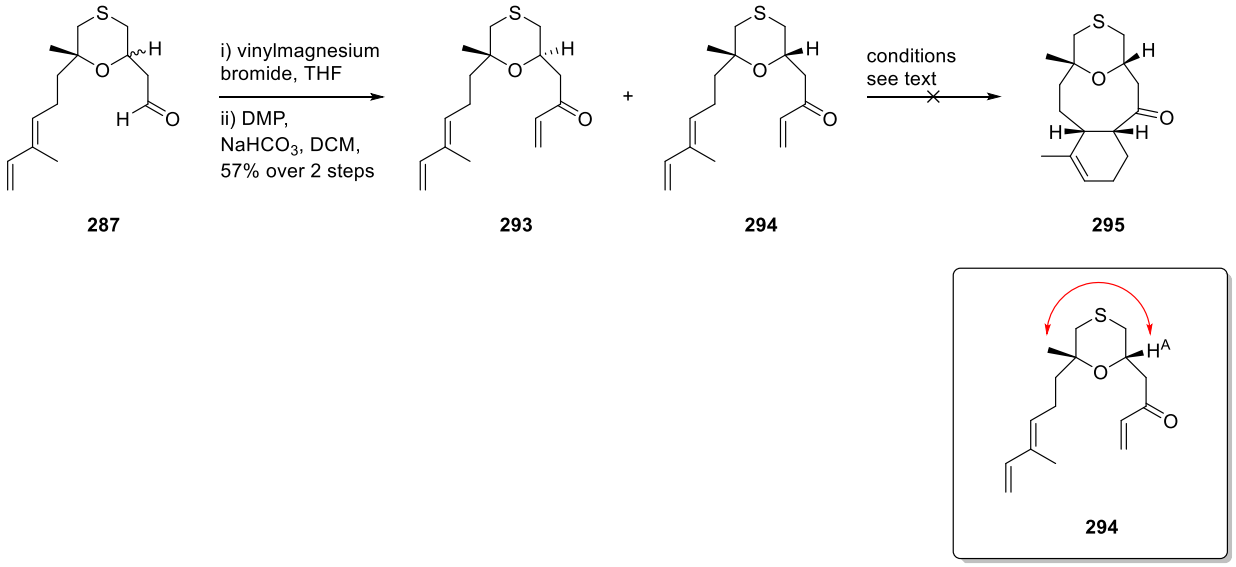
Scheme 54. Synthesis of aldehyde **287**.

Attempts to form IMDA precursor **289** by addition of vinyllithium reagent **215** (formed *via* treatment of vinyl iodide **222** with *t*-BuLi) or vinylalane **221** proved unsuccessful (Scheme 55), likely due to failed formation of the organometallic species. It was envisaged instead that **289** could be formed by alkynyl lithium addition to the aldehyde, followed by isomerisation of the resulting propargyl alcohol to the enone with ruthenium complex **292**.[130] However, given the limited quantity of aldehyde **287** available, it was decided to prioritise examination of the key cycloaddition step in a model system.



Scheme 55. Attempted introduction of the dienophilic side chain and envisaged alternative pathway.

To that end, vinylmagnesium bromide was added to aldehyde **287** and the resulting allylic alcohol was oxidised to give separable enones **293** and **294** (Scheme 56). The relative stereochemistry in *cis*-enone **294** was confirmed by the observation of NOE correlation between H^A and the methyl group. This compound was dissolved in toluene and heated to 170 °C, leading only to recovery of starting material. Addition of Et_2AlCl or $BF_3{\cdot}OEt_2$ proved ineffective in promoting the Diels–Alder reaction, possibly due to Lewis acid complexation with the sulfur atom on the oxathiane ring. Additionally, the compound was dissolved in DCM and subjected to 19 kbar of pressure for 36 h but, again, no IMDA adduct was detected. At this point, alternative approaches to furanoid eleutherobin-like compounds proved successful (see Chapter 3); given this fact and the limited quantity of compound **287** available, no further investigation was carried out on this route.



Scheme 56. Synthesis of IMDA precursor **294**, attempted cycloaddition, and key NOE correlation of the precursor.

Conclusions and future studies

The studies described in this chapter provided invaluable insight into the reactivity of the furan- and oxathiane- containing systems under examination. Synthesis of an IMDA precursor featuring a doubly-activated dienophile will be necessary in order to continue this approach, as the corresponding isopropyl-substituted compound **174** has been demonstrated to be too unreactive, while nor-isopropyl variant **225** gives an unsatisfactory yield of the IMDA adduct under forcing conditions. A potential route for the preparation of **233** through oxidation of diol **235** has been ruled out, and alternative approaches will need to be employed.

Model IMDA precursor **294** has been prepared *via* an oxa-Michael approach to oxathiane synthesis; the reason for its lack of reactivity under thermal and high-pressure conditions is not clear, and more extensive studies will be needed to assess the feasibility of both the IMDA reaction and of the subsequent Ramberg–Bäcklund reaction.

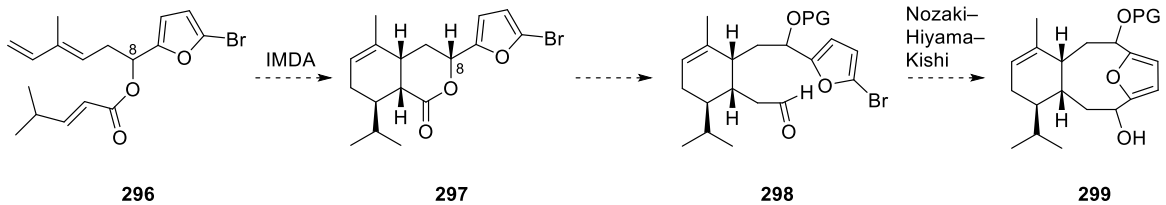
Chapter 3: Alternative approaches - A formal synthesis of eleutherobin

Aims

In view of the difficulties associated with the IMDA approach described in Chapter 2, it was reasoned that employing a temporary tether for one of the reacting partners could provide a more favourable environment for the cycloaddition; formation of the nine-membered ring would be deferred to a later stage of the synthesis.

By employing an ester linkage for this purpose, it was hoped that cycloaddition of ester **296** could provide the desired cyclohexene ring (Scheme 57). According to the studies on the IMDA reactions of ester-tethered decatrienoates undertaken by Kurth *et al*.,[82] it was anticipated that the stereochemistry on the C8 centre would be opposite to that in the natural product, thus requiring inversion at a later stage in the synthesis. It should be noted that lactone **297** was synthesised as a side product by Danishefsky *et al*.[131,59] and that attempts to invert the stereochemistry at the C8 centre, in order to reintroduce this material into their synthetic sequence, were unsuccessful; therefore, obtaining access to compound **297** would not constitute a formal synthesis of the natural product.

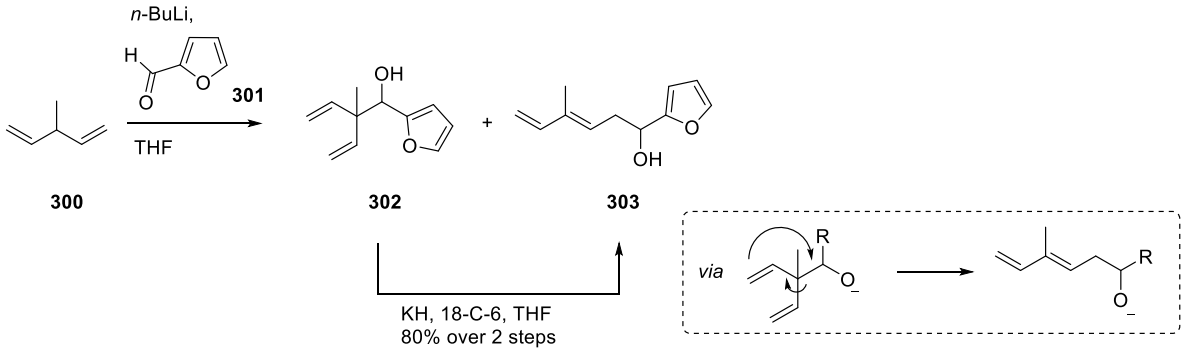
It was intended that lactone **297** would be converted into aldehyde **298**, either through mesylation of the corresponding alcohol, substitution by cyanide then reduction, or through homologation of the corresponding aldehyde. Aldehyde **298** would then be subjected to a Nozaki–Hiyama–Kishi coupling to furnish the tricyclic core of eleutherobin, following the precedent set by Danishefsky in his total synthesis.[57,59]



Scheme 57. Proposed scheme for the preparation of eleutherobin core structure **299**.

IMDA studies on ester-tethered systems

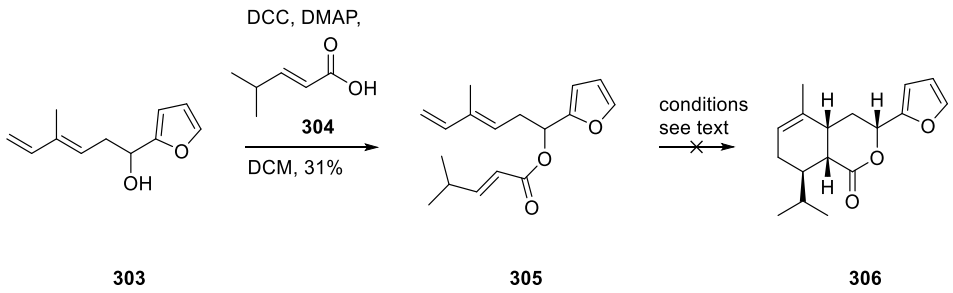
The cycloaddition was first attempted on a model system, lacking the bromine substituent on the furan ring. Addition of lithiated 3-methyl-1,4-pentadiene to furfuraldehyde provided, as expected, an equimolar mixture of the 1,3- and 1,4- dienes (Scheme 58). The two isomers could be separated *via* flash chromatography, but it is known that 1,4- dienes of this type can undergo a charge-accelerated [1,3]-sigmatropic shift, to give the corresponding 1,3- diene, upon generation of their potassium alkoxide followed by treatment with an appropriate cryptand variant.[74] Indeed, treatment of the crude mixture of compounds **302** and **303** with KH followed by addition of 18-crown-6 cleanly accomplished isomerisation to 1,3- diene **303**. Such anion-accelerated sigmatropic shift reactivity will be discussed in more detail in Chapter 4, which describes the development of related methodology.



Scheme 58. Synthesis of alcohol **303**.

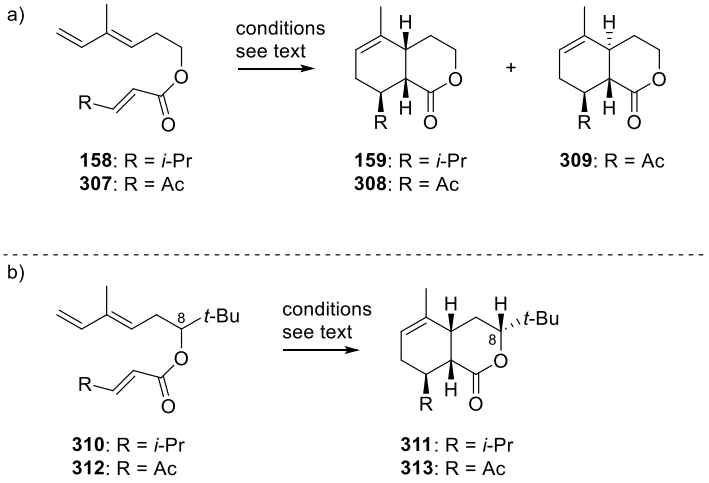
Ester **305** was then formed by DCC/DMAP mediated coupling of commercially available acid **304** with alcohol **303** (Scheme 59); Mitsunobu conditions failed to promote this transformation, resulting instead in the decomposition of the starting alcohol. IMDA reaction of ester **305** was then attempted; based on literature precedent, it was expected that cycloaddition under thermal conditions would require prolonged heating at a high temperature,[81,82] while for a Lewis acid promoted reaction the binuclear aluminium complex $TfN[Me(Al)Cl]_2$ held promise.[85] In practice, upon prolonged heating of ester **305** no

cycloaddition product was detected, with decomposition instead observed at 160 °C; evidently the temperature required for the reaction is above the sensitive furylic ester's tolerance. Similarly, treatment with $TfN[Me(Al)Cl]_2$ resulted only in decomposition of the ester; again this was attributed to the sensitivity imparted upon the ester linkage by the neighbouring furan ring. This was supported by the detection in the crude reaction mixture of acid **304**, presumably ejected from ester **305** with concurrent formation of a stabilised furylic carbocation which then decomposes.



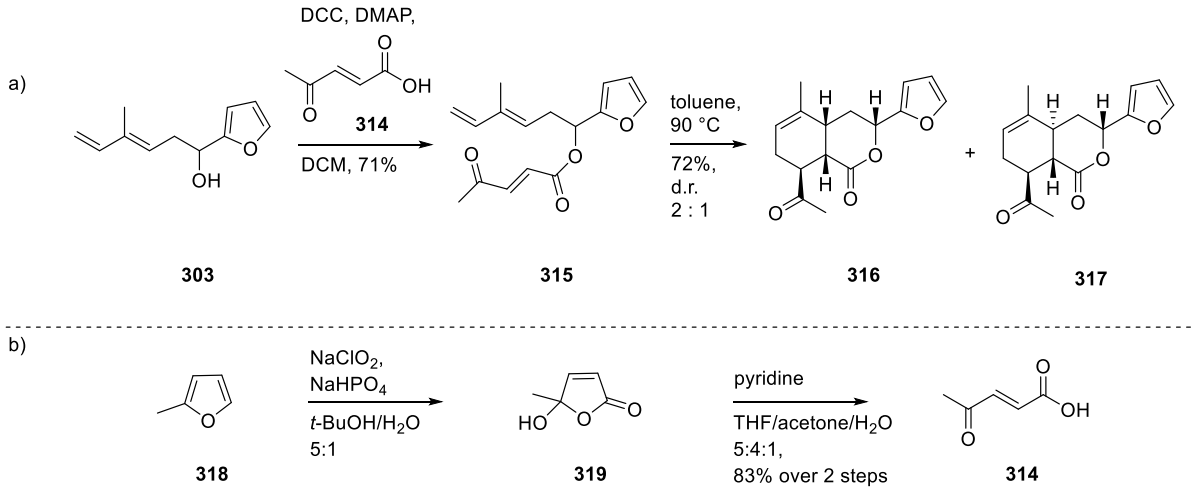
Scheme 59. Synthesis of IMDA precursor **305** and attempted cycloaddition.

It was therefore decided that the reactivity of the system would have to be improved so as to allow the IMDA reaction to take place under conditions tolerated by the precursor; to that end the idea of utilising a doubly activated dienophile again seemed appealing, especially given that Kurth *et al*. had demonstrated the large difference in reactivity between the isopropyl and acetyl substituted ester precursors in their studies (Scheme 60).[82] Specifically, compound **307** was reported to undergo cycloaddition after heating at 125 °C for 5 h to furnish *endo*- adduct **308** and *exo*- adduct **309** in a 1.5 : 1 ratio, while isopropyl-substituted precursor **158** required heating at 220 °C for 20 h to provide solely *endo*- adduct **159**. Interestingly, it was reported that introducing a *t*-butyl substituent at C8 facilitated the cycloaddition; the reaction of isopropyl-substituted precursor **310** was complete after 12 h at 200 °C, while doubly activated precursor **312** underwent the cycloaddition *in situ* after its preparation from the corresponding alcohol, and in this case furnished solely *endo*- adduct **313**.



Scheme 60. Comparison of reactivity between isopropyl and acetyl substituted dienophile carried out by Kurth *et al*. on a) C8 unsubstituted and b) C8 *t*-Bu substituted precursor.

Alcohol **303** was therefore coupled to acid **314** (synthesised in two steps from 2-methylfuran *via* oxidation followed by *Z*-to-*E* isomerisation, Scheme 61b)[132] to provide IMDA precursor **315** (Scheme 61a); this underwent cycloaddition successfully when heated to 90 °C in toluene, forming a 2 : 1 mixture of the *endo*- and *exo*- adducts.



Scheme 61. a) Synthesis of precursor **315** and subsequent IMDA; b) Synthesis of acid **314**.

Confirmation of the relative stereochemistry of the major and minor products was provided by NOE studies, the results of which are summarised in Figure 21. Specifically, NOE

interactions between H^B and H^C, H^C and H^D as well as between H^B and H^D indicated that these protons are all on the same side of the molecule in adduct **316**. In the case of minor product **317**, NOE correlations between H^A and H^C and between H^B and H^D confirmed that this product corresponds to the *exo*- adduct and that the relative stereochemistry of H^D is as shown in Figure 21b.

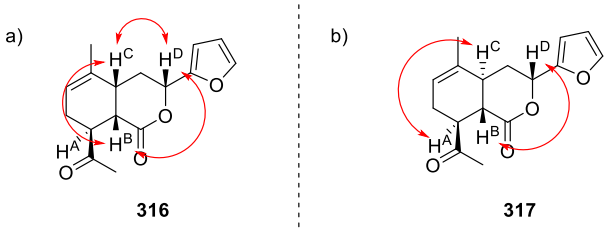
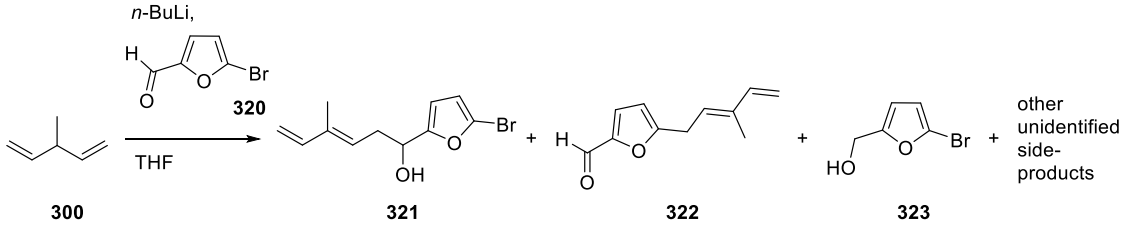


Figure 21. Indicative NOE signals of adducts **316** and **317**.

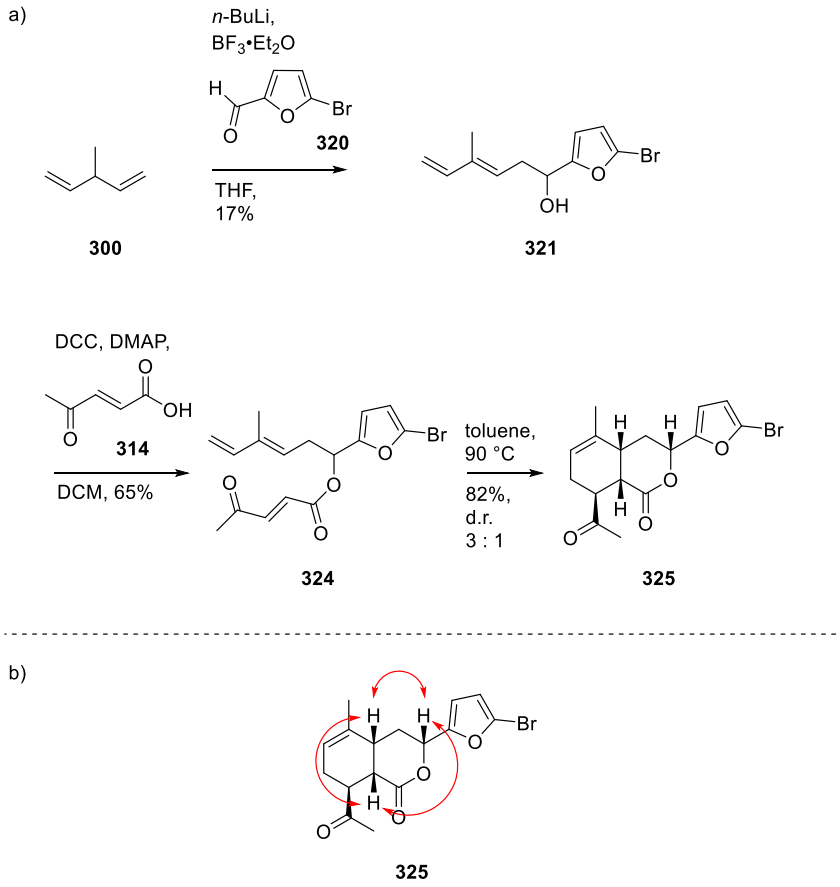
Having established the feasibility of the IMDA reaction with a doubly-activated dienophile, synthesis of the bromine-bearing adduct was then attempted. Preparation of brominated alcohol **321** *via* the method employed for the synthesis of alcohol **303** proved problematic; addition of aldehyde **320** to lithiated 3-methyl-1,4-pentadiene led to a complex mixture (Scheme 62), out of which only a trace (~ 5%) of the desired alcohol could be isolated. This outcome was attributed to lithium-halogen exchange between the organometallic species and the bromoaldehyde, with the newly formed furyllithium species undergoing further reactions; aldehyde **322** was tentatively identified as a component of the crude product mixture. Additionally, furfuryl alcohol **323**, generated *via* reduction of the starting aldehyde, was detected. Similar results were obtained in a test reaction in which *n*-BuLi was added to aldehyde **320** that resulted in a complex reaction mixture with no addition product being isolated.



Scheme 62. Organometallic addition to aldehyde **320**.

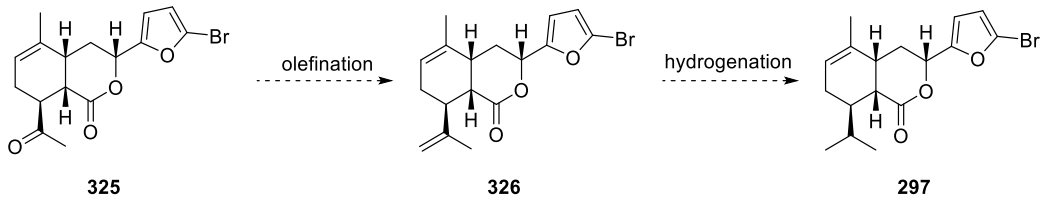
Decreasing the temperature for the organometallic addition step from RT to −78 °C, as well as employing inverse addition (adding the solution of lithiated 3-methyl-1,4-pentadiene to the aldehyde) did not improve the reaction profile. Adding $BF_3{\cdot}OEt_2$ to the aldehyde before adding the organolithium reagent, with the aim of increasing the electrophilicity of the aldehyde, provided a slightly improved yield of 17%. An attempt to add the corresponding Grignard reagent formed from treatment of the organolithium with $MgBr_2{\cdot}OEt_2$ resulted in the recovery of starting material.

Due to concerns over its stability, alcohol **321** was used immediately after purification in the coupling step with acid **314** (Scheme 63a). As with ester **315**, heating to 90 °C in toluene accomplished formation of *endo* adduct **325** as the major component of a 3 : 1 mixture of isomers. The relative stereochemistry of the major diastereomer, adduct **325**, was confirmed *via* the NOE correlations indicated in Scheme 63b.



Scheme 63. a) Synthesis of precursor **324** and subsequent IMDA reaction; b) Key NOE correlations of adduct **325**.

Conversion of the acetyl group to the isopropyl found in the natural product was next necessary. To that end olefination of the ketone was explored, with the intention that the resulting terminal alkene would then be reduced by hydrogenation (Scheme 64). The alternative strategy consisting of adding methylmagnesium bromide to the ketone, followed by deoxygenation, seemed less appealing due to potential interference of the furylic ester functionality during the deoxygenation step. Adduct **316** was used as a model system to identify optimal conditions for the olefination/hydrogenation reaction sequence.



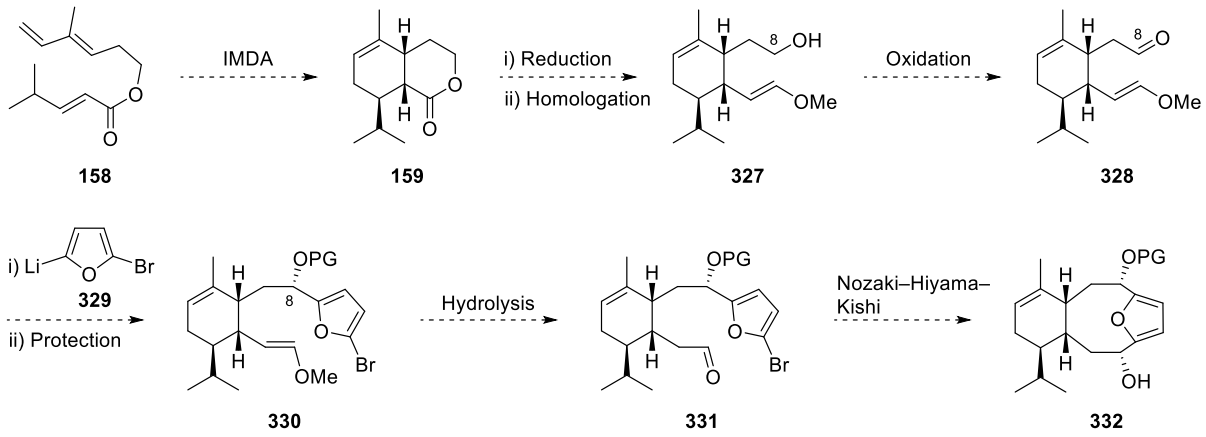
Scheme 64. Envisaged installation of the isopropyl group.

Effecting the desired olefination proved unexpectedly difficult. Wittig olefination was attempted first, with a number of different bases used to generate the reactive ylide (LiHMDS or NaDMSO with Ph_3PCH_3I, *t*-BuOK with Ph_3PCH_3Br); in all cases no product formation was observed. Olefination using Petasis reagent also provided no product, even after prolonged heating at 70 °C. Takai olefination using CH_2Br_2 in the presence of Zn, $TiCl_4$ and $PbCl_2$ in THF was also ineffective. Finally, Peterson olefination using $TMSCH_2MgCl$ also returned unreacted starting material, even when $CeCl_3$ was added to enhance the reactivity of the ketone. The reason for this lack of reactivity was not clear; Danishefsky encountered similar difficulties in the olefination of a structurally related aldehyde.[59]

Alternative synthetic sequence – Formal synthesis of eleutherobin

In view of the low yield in the synthesis of brominated alcohol **321**, the necessity for an activated dienophile to achieve the key IMDA reaction, and the unsuccessful subsequent olefination, the decision was made to re-examine the synthetic approach with the goal of introducing the bromofuran moiety at a later stage. Lactone **159**, whose preparation has been reported previously by Jung[81] and Kurth[82], as well as by Taguchi[85] utilising $TfN[Me(Al)Cl]_2$ (see page 38), seemed promising in this regard (Scheme 65). If the carbonyl group could be quickly extended by one carbon atom to a masked aldehyde, then the alcohol at C8 would be available for the installation of the bromofuran moiety. It was envisaged that this could be

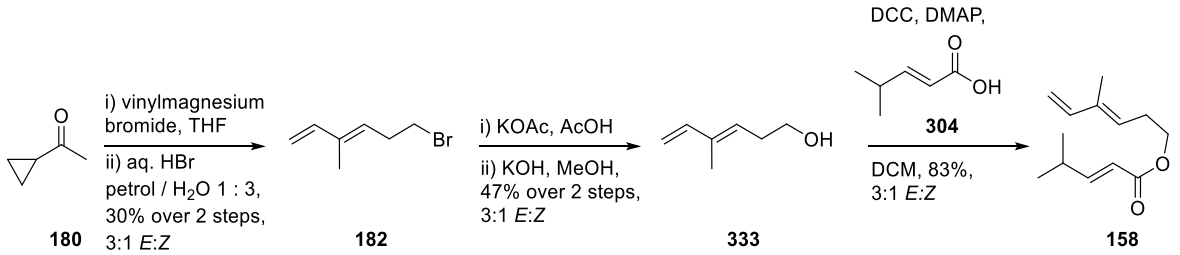
achieved by reduction to the lactol followed by homologation to enol ether **327**; after oxidation of the resulting primary alcohol, the brominated furan ring would be introduced in the form of lithiated bromofuran, following a similar step in Danishefsky's total synthesis of eleutherobin.[57,59] Although the simultaneous presence of an aldehyde and a nucleophilic enol ether within compound **328** was noted as a potential problem, there is literature precedent for the addition of organometallics to such systems.[133] Hydrolysis of the enol ether would then provide aldehyde **331**, which for PG = TBDPS would be an intermediate in Danishefsky's total synthesis, and the sequence would constitute a formal synthesis of the natural product. Following Danishefsky's precedent, intramolecular Nozaki–Hiyama–Kishi coupling would then give the desired tricyclic structure in the form of alcohol **332**.



Scheme 65. Revised scheme for the synthesis of eleutherobin core structure **332**.

For the synthesis of alcohol **333**,[134] bromide **182** was prepared as previously described in two steps from cyclopropyl methyl ketone (Scheme 66). This was then treated with KOAc in acetic acid to form the acetate which was hydrolysed to alcohol **333** *via* treatment with KOH in methanol (70% yield over the two steps). As the starting bromide **181** was obtained as a 3 : 1 mixture of the *E*- and *Z*- isomers, so was the resulting alcohol. Chromatographic separation of the acetate or the alcohol did not prove possible; the mixture was therefore used for the subsequent steps.

Ester **158** was then prepared by coupling of this mixture of alcohols with acid **304** using either Mitsunobu (DIAD/triphenylphosphine) or DCC/DMAP mediated conditions, the latter providing the better yield (83%).



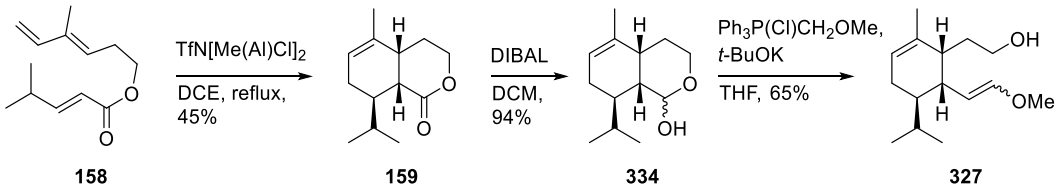
Scheme 66. Synthesis of ester **158**.

Taguchi's conditions were then applied to generate lactone **159**. $TfN[Me(Al)Cl]_2$ was generated *in situ* by treating $TfNH_2$ in DCE with 2.0 equiv of Me_2AlCl, precursor **158** was added and the mixture was heated to reflux for 3 h, resulting in the formation of *endo*- IMDA adduct **159** in 45% yield (Scheme 42), along with unreacted *Z*-**158** (25%). Interestingly, no product deriving from cycloaddition of the *Z*- ester was formed. As expected from Taguchi and coworkers' report, only the *endo* adduct was detected.

One-carbon extension of the carbonyl group was then required. Danishefsky[57,59] and Gennari[66] performed a similar transformation by mesylation of the corresponding alcohol, substitution by cyanide and reduction; this sequence would be excessively lengthy, and it was hoped that this could be achieved more rapidly by reduction to the lactol followed by Wittig homologation.

Reduction of lactone **159** with DIBAL in DCM provided lactol **334** in 94% yield (Scheme 67). Subjecting this lactone to reaction with 1.4 equiv of the ylide generated from $Ph_3P(Cl)CH_2OMe$ and *n*-BuLi resulted in recovery of the starting material; increasing the amount of ylide to 4.0 equiv gave a complex reaction mixture. Changing the base to *t*-BuOK

successfully provided the homologation product in 65% yield as a mixture of the *E*- and *Z*-isomers of the enol ether in a 3 : 1 ratio, respectively.



Scheme 67. Synthesis of enol ether **327**.

Although the homologation was successful, we were concerned about potential epimerisation at the labile position α- to the lactol centre under the basic reaction conditions. As only two enol ether products were isolated (the *E*- and *Z*- isomers of the enol ether double bond), this would mean that complete inversion of the relative stereochemistry at C1 would need to have taken place. An indication that this was not the case was given by coupling constant analysis: a value of ~5.0 Hz for the H_B-H_C pair corresponds to a 40° Karplus-derived dihedral angle, while for the H_A-H_B pair a coupling constant of ~10.0 Hz corresponds to an angle of 180°. These values are consistent with a major half-chair conformation of the unepimerised compound with the isopropyl substituent in a pseudo-equatorial position (Figure 22).

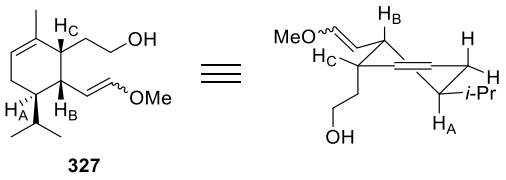
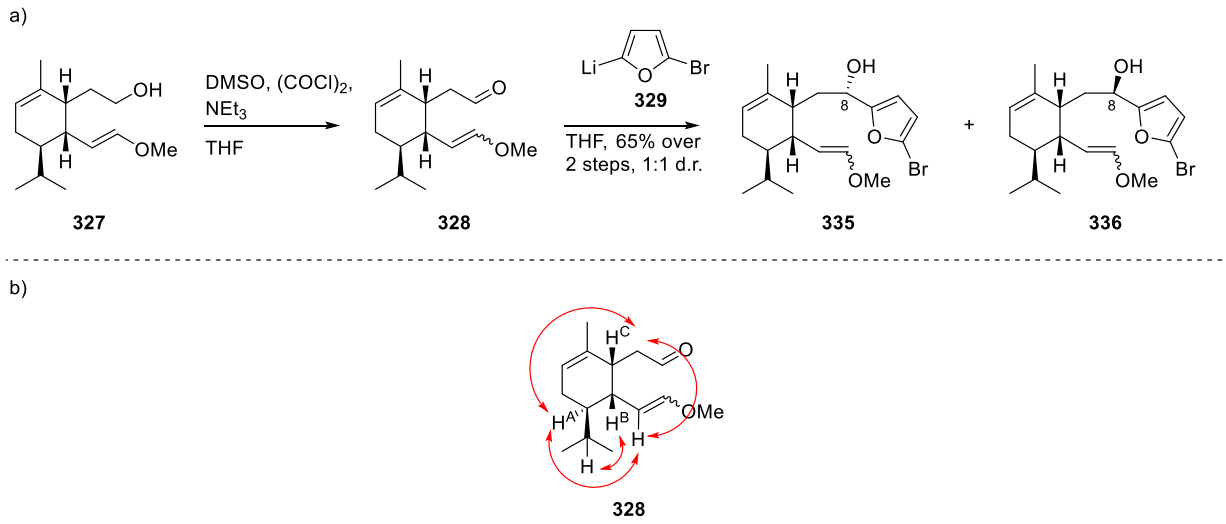


Figure 22. Half-chair conformation of enol ether **327** consistent with NMR data.

With some confidence that epimerisation was not operating during the homologation, we proceeded with the introduction of the bromofuran moiety. Precedent for the oxidation of a primary alcohol to the aldehyde in the presence of an enol ether existed in the work of the

Moeller group, who studied the use of the enol ether functionality in intramolecular anodic coupling reactions.[135,136,133] Indeed, oxidation of alcohol **327** under Swern conditions (Scheme 68a) furnished aldehyde **328**; given the instability of this compound in acidic environments, the crude product was immediately subjected to the next step, although a small sample was retained for NMR studies that gave further confirmation on the relative stereochemistry. NOE correlation of H_B with the isopropyl group, and of one the enol ether protons with H_A and with the aldehyde side chain were consistent with the stereochemistry shown in Scheme 68b, corresponding to unepimerised alcohol **327**.

Progressing the synthesis, 2,5-dibromofuran, prepared by treatment of furan in DMF with excess bromine,[137] was lithiated with *n*-BuLi then added to aldehyde **328** to give an equimolar mixture of epimeric alcohols **335** and **336**. This is consistent with the selectivity obtained in a similar addition step in Danishefsky's total synthesis of the natural product.

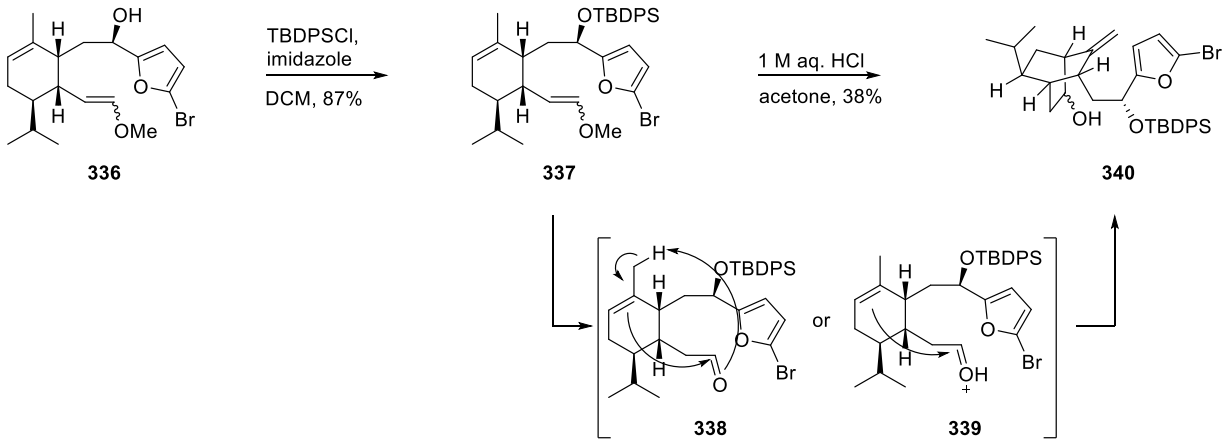


Scheme 68. a) Synthesis of enol ethers **335** and **336**; b) Key NOE correlations of aldehyde **328**.

As one of the objectives of this research venture was the investigation of the possible biological activity of different eleutherobin analogues, the generation of both epimers in this step was not considered a significant drawback; instead it was decided to advance the synthetic

route utilising both compounds in the interest of obtaining analogues bearing the β-stereochemistry at C8.

The subsequent steps were explored first on β- epimer **336**. After protection as the TBDPS ether (Scheme 69), hydrolysis of the enol ether was required in order to restore the masked aldehyde functionality in preparation for the key Nozaki–Hiyama–Kishi reaction. Although it was anticipated at the outset that the presence of the acid-labile furylic alcohol functionality may cause problems when hydrolysis of the enol ether under acidic conditions was attempted, it was expected that conditions to effect it selectively could be found; in fact, examples of such transformations have been reported.[138] In a first experiment, compound **337** was dissolved in acetone and treated with 3.0 equiv of a 1.0 M HCl aqueous solution; unexpectedly this led to the formation of alcohol **340**, the product of a formal carbonyl-ene reaction of the desired aldehyde. The presence of the alcohol group on **340** (as opposed to a methyl ether) indicates that hydrolysis of the enol ether must take place first, and is then followed by the formal ene reaction; whether this second step proceeds *via* a concerted process from aldehyde **338** or *via* a Prins reaction from oxonium ion **339** is unclear.



Scheme 69. Unexpected formation of compound **340** upon attempted hydrolysis of enol ether **337**.

In an attempt to observe intermediate aldehyde **338**, an NMR experiment was employed in which enol ether **337** was dissolved in CD_3CN and 0.1 equiv of a 1.0 M HCl aqueous solution added; however, the change of solvent greatly increased the reaction rate, such that by the time the spectrum was registered (a few minutes after addition of the acid), solely ene product **340** was observed.

Next, it was hoped that performing the reaction in the presence of a larger excess of water would sequester the intermediate aldehyde as the hydrate, thereby slowing down the undesired further reaction. However, adding a large excess of a 0.1 M HCl solution to the enol ether dissolved in either acetone or in THF provided no product; increasing the temperature to 48 °C led to a complex mixture, possibly arising from elimination of the furylic alcohol group followed by attack of the enol ether to the newly formed carbocation. Likewise, PPTS or $TsOH \cdot H_2O$ gave complex reaction mixtures.

As acidic conditions had failed, alternative reagents were explored, starting with TMSCl and NaI, a reagent combination commonly utilised for demethylation reactions.[139,140] The TMSI generated *in situ* is sufficiently Lewis acidic to react with methyl ethers to form silylated oxonium iodides **342**, which then form the silylated alcohol *via* an irreversible S_N2 process (Figure 23). Applying these conditions to enol ether **337** led to decomposition of the starting material.

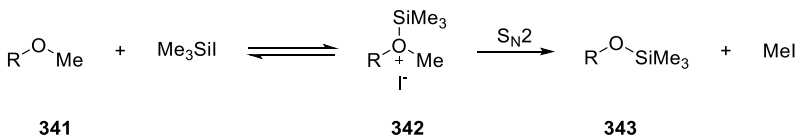
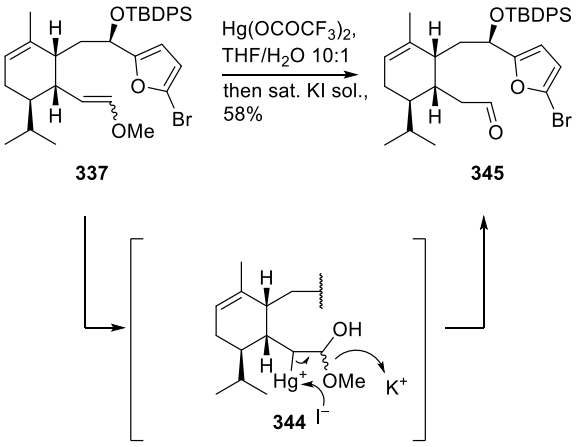


Figure 23. Mechanism for demethylation *via* TMSI.

Finally, it was hoped that the hydrolysis could be achieved *via* oxymercuration of the double bond; such an approach has been utilised for the hydrolysis of enol ethers in acid sensitive

substrates.[141,142] Reaction with $Hg(OAc)_2$ proved ineffective, as starting material was recovered; therefore, a more electrophilic mercury salt, $Hg(OCOCF_3)_2$, was investigated (Scheme 70).[143] In the event, adding $Hg(OCOCF_3)_2$ to **337** dissolved in a THF/H_2O mixture, followed by a saturated aqueous KI solution, after stirring for 30 minutes at 0 °C, provided aldehyde **345** in 58% yield. Saturated aqueous KI solution was chosen over $NaBH_4$ for the demercuration due to concerns over possible reduction of the aldehyde to the alcohol. The remaining mass was accounted for by the formation of an unidentified side product, proposed to arise from addition of the intermediate organomercurial species to the trisubstituted alkene, as evidenced from disappearance of the corresponding proton signal in the NMR spectrum. Reducing the reaction temperature and varying the reaction time led to inferior results.

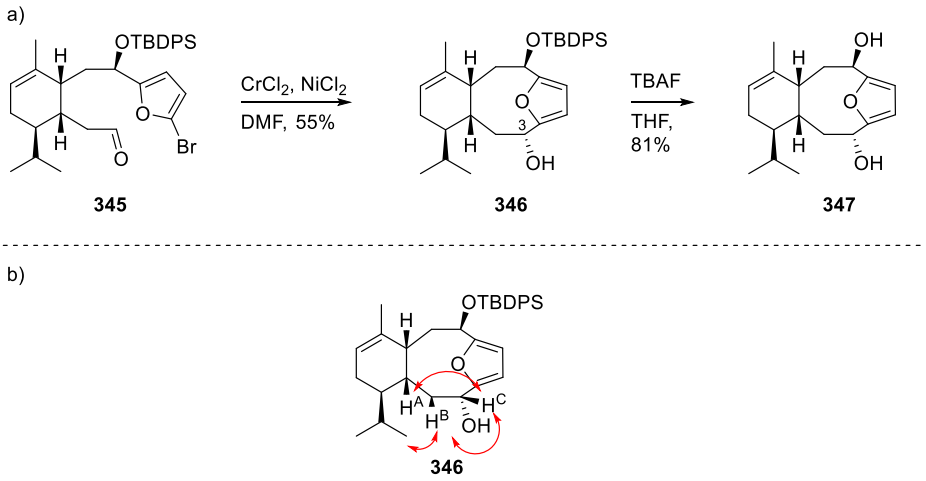


Scheme 70. Oxymercuration of enol ether **337**.

With aldehyde **345** in hand, the Nozaki–Hiyama–Kishi reaction was next attempted. Success in effecting this reaction was found to be highly dependent on the quality of the $CrCl_2$ used, as well as on careful degassing of the reaction solvent *via* a freeze-pump-thaw sequence prior to addition of the reagents; control of these factors allowed a yield of 55% to be achieved reliably (Scheme 71a). As no precedent existed for the NHK reaction with the β- C8 epimer, the stereochemistry on the newly formed centre needed to be ascertained. NMR studies (Scheme 71b) showed a clear NOE correlation between H^A and H^C; additionally, H^C displayed

an NOE correlation with only one of the two C2 protons (H^B) which, in turn, showed a correlation with one of the isopropyl methyl groups. The relative stereochemistry on C3 was therefore assigned as shown.

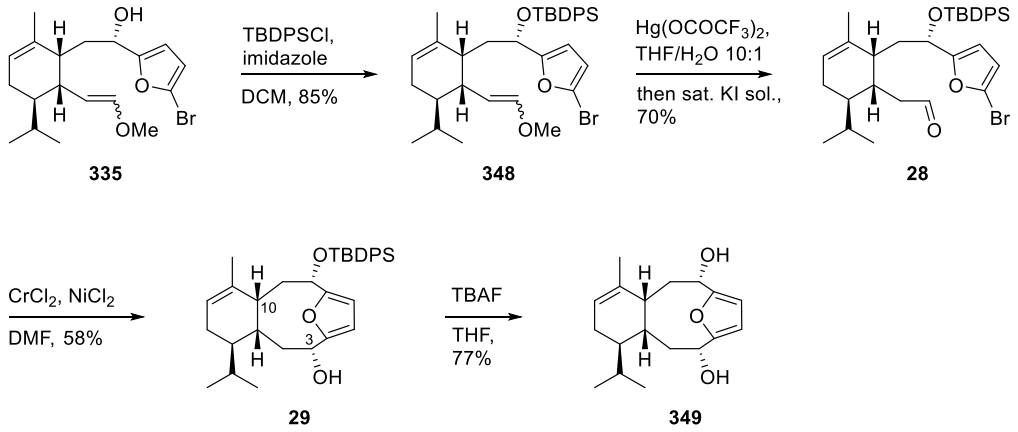
Finally, deprotection provided diol **347**. To achieve deprotection at an acceptable rate, a large excess of TBAF had to be used, giving a yield of 81% with the reaction being complete after 18 h.



Scheme 71. a) NHK reaction of aldehyde **345** and subsequent deprotection; b) Key NOE correlations of NHK reaction product **346**.

With the objective achieved for the β- C8 epimer, attention turned next to the α- epimer, corresponding to the stereochemistry found in the natural product. After protection of alcohol **335** as the TBDPS ether (Scheme 72), deprotection of the enol ether was effected, as with compound **337**, *via* oxymercuration followed by treatment with saturated KI solution. This provided aldehyde **28** in 70% yield, the spectroscopic data of which were in agreement with those reported by Danishefsky and coworkers.[59] The following NHK reaction provided the tricyclic core skeleton in alcohol **29** in 58% yield. The spectroscopic data of this compound were also in agreement with the report by Danishefsky *et al*., and the stereochemistry on C3 was assigned on this basis. Interestingly, the ^{1}H-NMR spectrum of alcohol **29** exhibited a

signal at −0.55 ppm, which was assigned to the allylic proton on C10 on the basis of COSY correlations; this is consistent with Danishefsky's data, and presumably results from shielding of the proton in question by the furan ring current. Similar spectroscopic characteristics were observed in derivatives of this compound (see Experimental Data). Finally, deprotection of **29** was found, as in the case of **346**, to require a high concentration of TBAF to proceed in an acceptable rate; use of 10 equiv of TBAF in THF furnished diol **349** in 77% yield.



Scheme 72. Synthesis of diol **349**.

Synthesis of a small library of furanoid eleutherobin analogues

Having now obtained access to a furanoid variant of the tricyclic eleuthoside core system, we became interested in examining the potential cytotoxic activity of this scaffold. As has been already alluded to in the Introduction, a number of medicinal chemistry studies on the eleuthoside scaffold have investigated variations of the dihydrofuran sector of the natural product. Specifically:

i. Nicolaou and coworkers showed that increasing the steric bulk on the acetal centre from OMe to OEt is tolerated and maintains both microtubule stabilising and cytotoxic activity; however, the propyl or trifluoroethyl acetals have significantly decreased activity.[55] Interestingly, in a separate study the same group showed that

converting the dihydrofuran ring to the tetrahydrofuran maintained the microtubule stabilising activity but reduced the cytotoxic activity in a number of cancer cell lines; this, in combination with similar results led the authors to propose that sarcodictyin derivatives may owe their cytotoxic properties not only to microtubule stabilisation, but also to the alkylating properties that derive from ionisation of the acetal centre to the corresponding oxonium ion (Figure 24)[54].

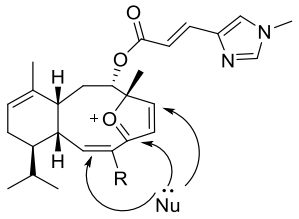


Figure 24. Proposed covalent binding action of eleuthoside natural products.

ii. As previously mentioned, Britton and coworkers studied the effects of similar modifications on eleutherobin itself, and determined that bulkier acetal groups maintain the antimitotic activity, while reduction to the tetrahydrofuran lead to a small decrease in activity.[56]

iii. Gennari and coworkers applied their ring-closing metathesis approach to the preparation of simplified macrocyclic sarcodictyin analogues which lack the ether bridge (Figure 25). Compound **350** was found to retain the microtubule stabilising activity (though it was less potent than taxol in the assay used).[70] In later studies, a wider range of analogues was prepared and compound **351** was found to possess microtubule stabilising activity comparable to that of taxol.[69,72]

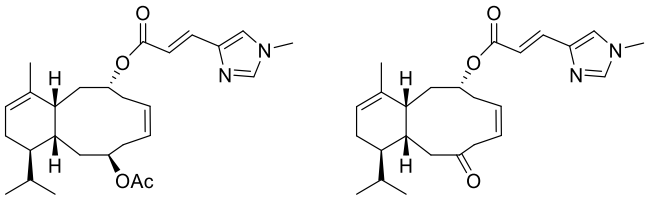
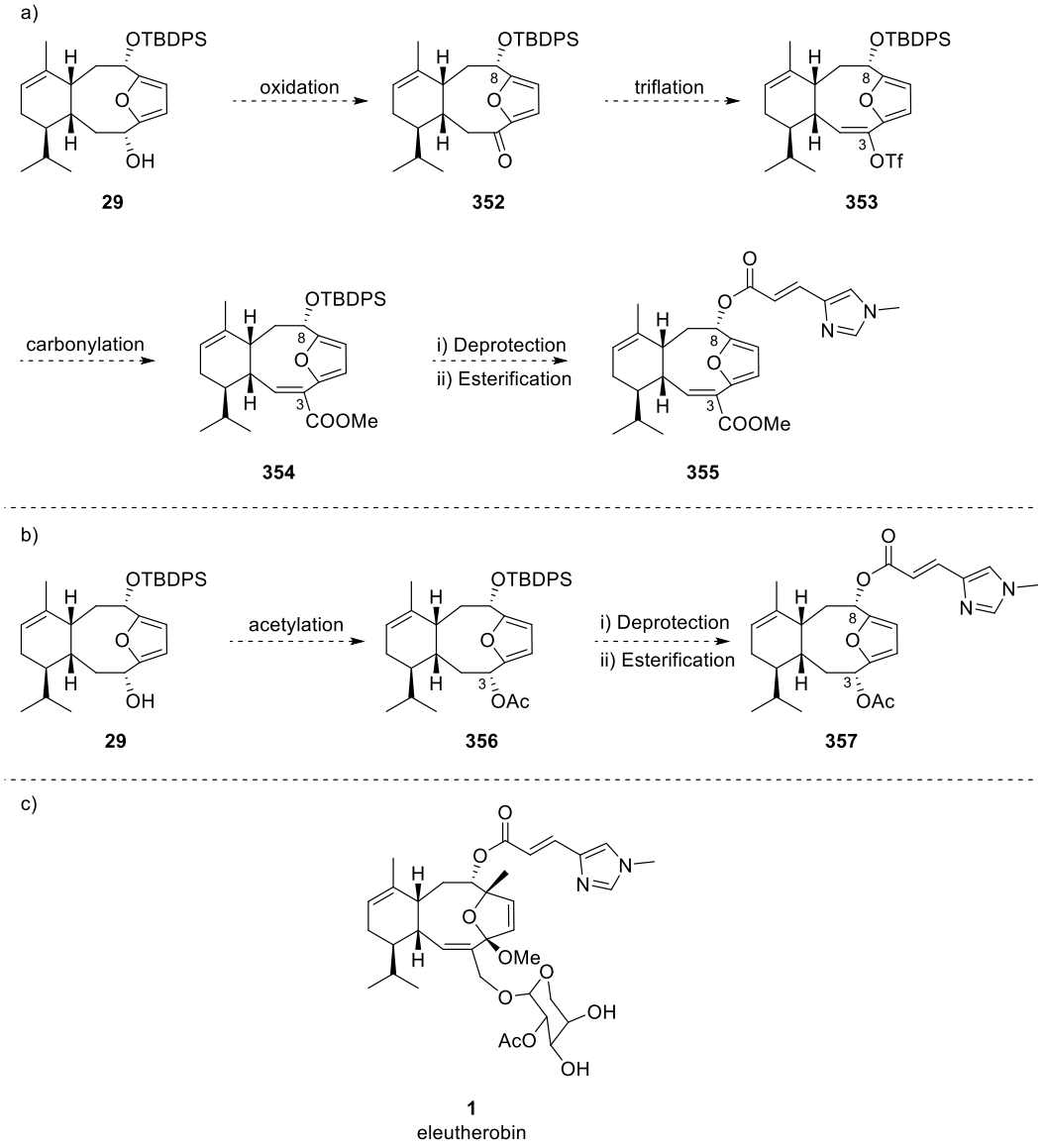


Figure 25. Examples of eleuthoside analogues prepared by Gennari and coworkers.

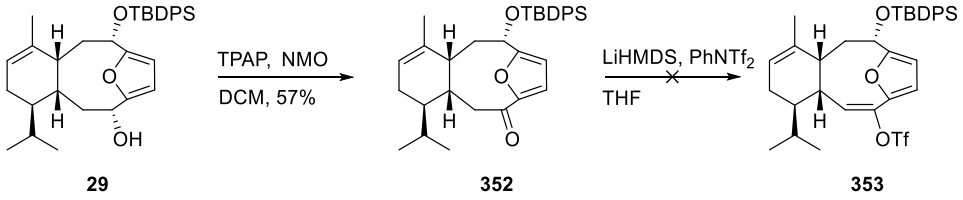
Taken together, these results demonstrate that some variation on the five-membered ring can be tolerated. Additionally, all medicinal chemistry studies on eleuthoside structures have unequivocally demonstrated that the methylurocanic side chain is essential for activity. Attempts by the Nicolaou group to substitute the methyl imidazole ring with other heterocycles led to drastically decreased activity; [54,55] however, this does not seem to account fully for the importance of the side chain, as an analogue synthesised by Britton and coworkers in which the methylimidazole ring was intact but the enone double bond was reduced also proved to be inactive.[56] No studies have been carried out that examine the alternative tethering of this side chain to a different part of the molecule.

These observations informed our design of a small library of furanoid eleuthoside derivatives to be screened for cytotoxic acitivity. First, it was intended that a close analogue of the sarcodictyin natural products, with the methylurocanic ester side chain attached at C8, would be prepared. As for the substituent at C3, two possibilities would be pursued; oxidation of the alcohol to the ketone, in preparation for formation of the triflate and carbonylative coupling en route to a furanoid analogue of sarcodictyin A (Scheme 73a). Alternatively, a simpler sequence consisting of acetylation, deprotection and esterification would lead to acetate **357** (Scheme 73b).



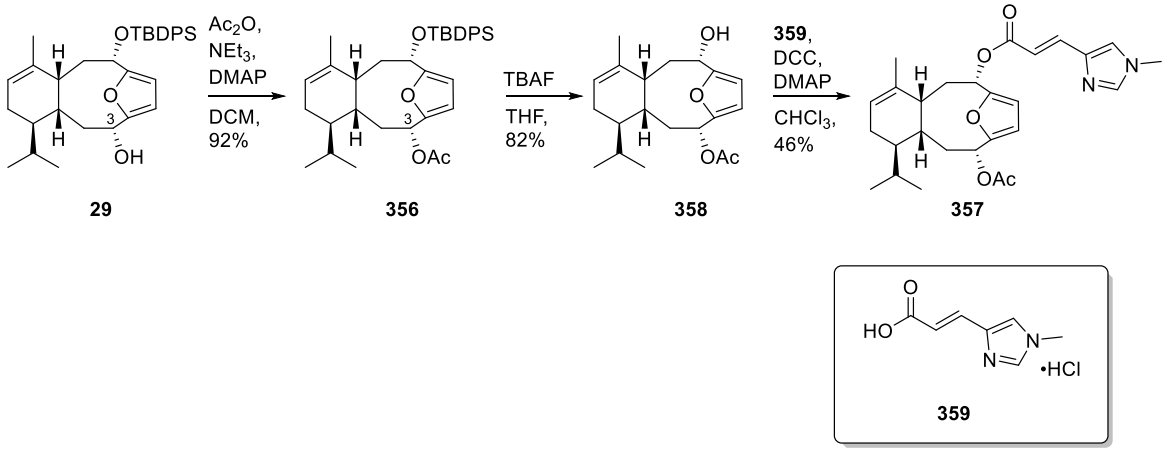
Scheme 73. Proposed synthesis of furanoid eleutherobin analogues **355** and **357**, and structure of eleutherobin for comparison.

Oxidation of alcohol **29** was carried out with TPAP/NMO to give ketone **352** in 57% yield (Scheme 74); use of DMP led to inferior results due to competing ring opening. With ketone **352** in hand, triflation was attempted. Treatment with LiHMDS/$PhNTf_2$ failed to form the triflate and it was suggested that the strained ring system prevented either α- hydrogen from adopting the conformation orthogonal to the carbonyl π- system required for deprotonation. A test experiment in which ketone **352** was successively treated with KHMDS then D_2O supported this theory, as no deuterium incorporation was detected.



Scheme 74. Synthesis of ketone **352** and proposed triflation.

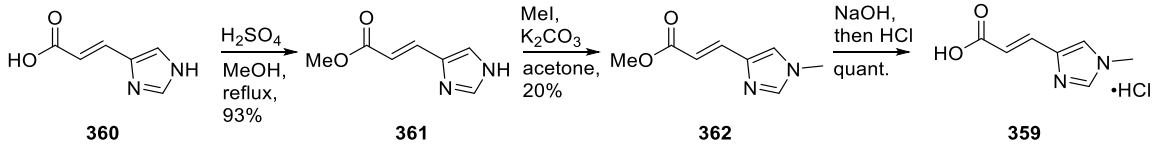
Moving on to the goal of preparing acetylated analogue **357** (Scheme 75), alcohol **29** was treated with acetic anhydride in the presence of NEt_3/DMAP to give ester **356**; in preparation for the introduction of the methyl urocanic ester side chain, the C8 alcohol group was deprotected with TBAF in THF. An attempt was also made to prepare the C3 epimer by performing a Mitsunobu reaction with acetic acid, however no product was formed even after prolonged reaction time. DCC/DMAP mediated coupling of alcohol **358** with hydrochloride salt **359** provided ester **357** in 46% yield.



Scheme 75. Synthesis of furanoid eleuthoside analogue **357**.

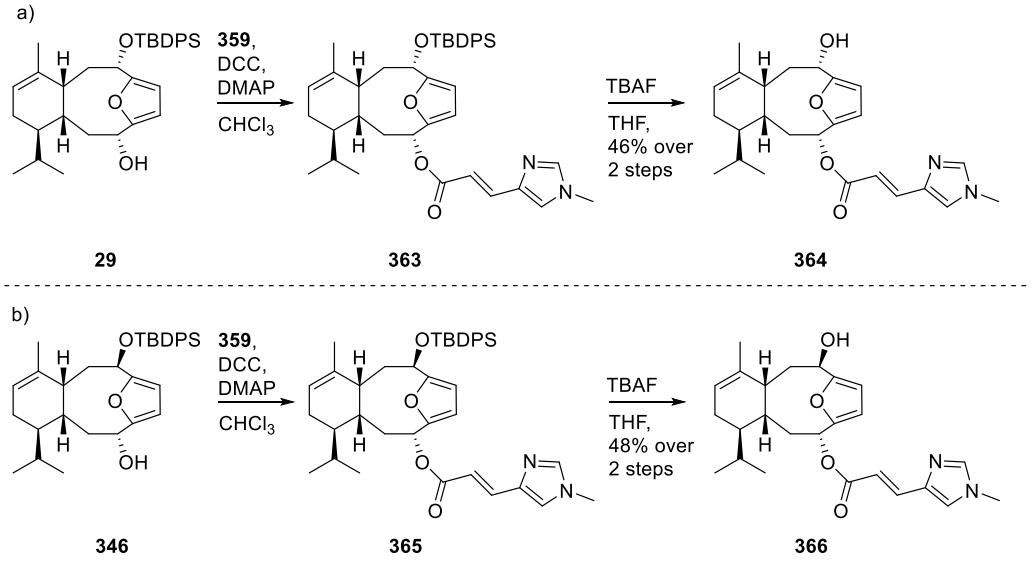
For these studies, *N*-methyl urocanic acid hydrochloride salt **359** was prepared using modified literature procedures (Scheme 76). Commercially available urocanic acid was converted into the methyl ester by heating with conc. sulfuric acid in methanol.[144] Methylation of this compound with MeI and K_2CO_3 in acetone gave a 6 : 1 mixture of the desired product along

with the vicinal methylation isomer.[145] Pleasingly it was found that pure ester **362** could be obtained by crystallisation from an ethyl acetate / pentane solvent system. The ester was then hydrolysed with NaOH;[146] upon acidic workup the hydrochloride salt was formed, as evidenced by the shift of the neighbouring proton peak to 9.06 ppm in the ^{1}H-NMR spectrum. Deprotonation to re-form the free acid was very slow upon treatment with base, and it was decided to use the hydrochloride salt for the coupling step.



Scheme 76. Preparation of hydrochloride salt **359**.

We next sought to examine the effect of moving the side chain to C3; alcohol **29** was therefore treated with hydrochloride salt **359** in the presence of DCC/DMAP to furnish ester **363** (Scheme 77). In contrast to the slow reaction of alcohol **346**, deprotection proceeded at an acceptable rate using 1.3 equiv of TBAF, being complete after 7 h to provide alcohol **364** in 46% yield over two steps. An analogous reaction sequence starting with epimer **346** furnished alcohol **366**.



Scheme 77. Synthesis of furanoid eleuthoside analogues **364** and **366**.

Lastly, it was decided that diols **347** and **349** would be screened as controls; then, should the *N*-methyl urocanic ester-bearing compounds demonstrate cytotoxic activity, it would be desirable to have an indication as to whether this is due to the same mechanism of action as eleutherobin or whether the furanoid scaffold exhibits a different effect. Diols **347** and **349**, lacking the essential methyl urocanic ester group, would be expected to be inactive, and if they were not, an alternative mechanism would be implicated.

The bioassays were carried out in the Pre-Clinical Validation Hub at the Department of Oncology, University of Oxford, by C. Towers, Dr. F. Willenbrock, and Dr. V. Macaulay. These consisted of viability assays on two cancer cell lines: MCF-7 (breast carcinoma) and H460 (lung cancer); two fluorescent stains were used: Hoechst 33342 (a blue fluorescent dye that stains nuclei) and propidium iodide (a red fluorescent dye that stains DNA and does not permeate into live cells). This allowed visualisation of the number of live and dead cells after incubation with the compound under examination; the cells were counted using a Celigo imaging cytometer and the viability estimation was calculated according to Viability = 1 – (PI/Hoechst).

The results are summarised in Table 7. As expected, diols **347** and **349** were inactive. Compound **357** exhibited good activity against both cell lines, demonstrating that the furanoid eleuthoside scaffold could be of interest in the pursuit of simplified eleutherobin analogues. Interestingly, compounds **364** and **366** also showed cytotoxic activity, albeit somewhat inferior to that of compound **357**.

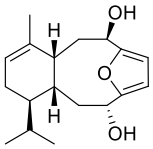
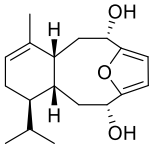
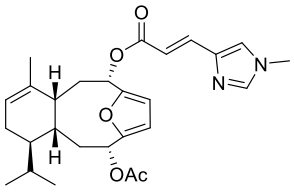
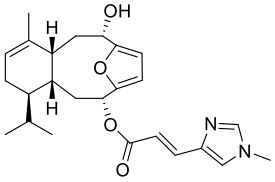
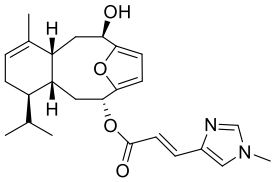
Entry	Compound	MCF7 IC_{50} (μM)	H460 IC_{50} (μM)
1	 **347**	> 50	> 50
2	 **349**	> 50	> 50
3	 **357**	6.3 ± 3.1	13.9 ± 2.3
4	 **364**	8.0 ± 2.8	22.8 ± 8.1
5	 **366**	6.7 ± 4.5	16.2 ± 2.8

Table 7. Cytotoxic activity of the eleuthoside analogues synthesised.

Conclusions and future work

A short route has been developed to aldehyde **28**, thus achieving a short formal synthesis of the natural product (9 steps to aldehyde **28**), and to its C8 epimer. Nozaki–Hiyama–Kishi reaction of these aldehydes provided access to the furanoid tricyclic eleuthoside skeleton, upon which mP450 oxidation studies were then carried out (see Chapter 5). Furthermore, this synthetic sequence was used to prepare a small library of furanoid eleuthoside analogues; these were assayed for cytotoxic activity and provided promising results. Future studies will aim to further explore the biological activity of this furanoid scaffold by modifying the structure of compound **357**.

Chapter 4: Development of methodology for the efficient synthesis of lactone 159

The efficiency of the synthetic sequence developed for the preparation of aldehyde **28** and consequently of the furanoid eleuthoside core structure was highly dependent on the ease of access to lactone **159**. The literature method for its preparation was not ideal, as it was lengthy (six steps from cyclopropyl methyl ketone) and did not provide the possibility for enantioselective preparation of the target (Figure 26). Specifically, two points in the sequence leading to **28** were identified that needed to be improved:

i. A method for the preparation of alcohol **333** in one step from commercially available reagents was desirable; furthermore, the four step method employed furnishes a 3:1 mixture of the *E*- and *Z*- isomers, an issue that needed to be rectified.

ii. The enantioselective preparation of lactone **159** has never been reported; it was hoped that an enantioselective variant of the IMDA reaction employed could be developed.

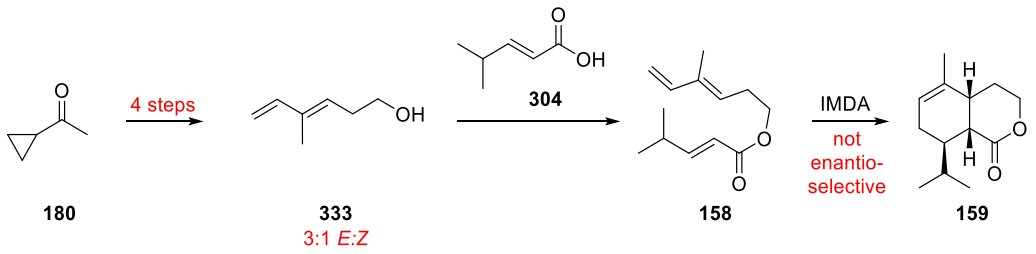


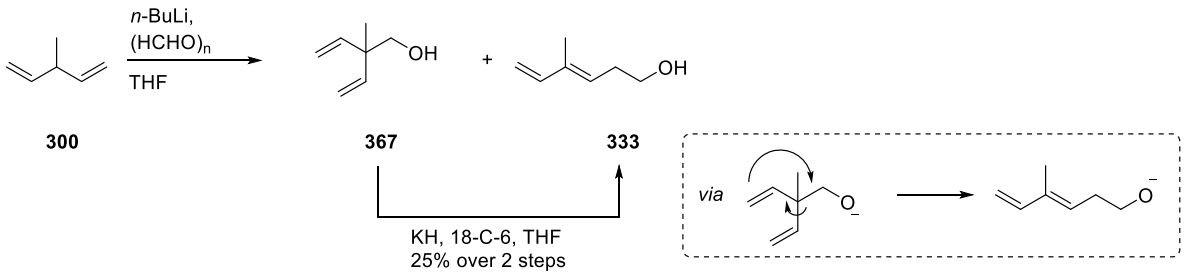
Figure 26. Outline of literature route for the preparation of lactone **159** and areas of potential improvement.

Development of methodology for the one-pot synthesis of alcohol 333

Aside from the previously described four step sequence,[92] a number of other ways have been reported in the literature for the preparation of alcohol **333**. A 1969 patent[147,148,149] describes its preparation from commercially available ocimene in two steps through ozonolysis followed

by reduction of the resulting aldehyde; ocimene is available as a mixture of isomers, therefore this process gives a mixture of *E*- and *Z*- **333**. The *E*- isomer can be prepared from (*E*)-2-methylbut-2-enal by a sequence comprising Horner–Wadsworth–Emmons reaction, deconjugation of the resulting alkene and reduction of the ester to the alcohol.[150,151,152]

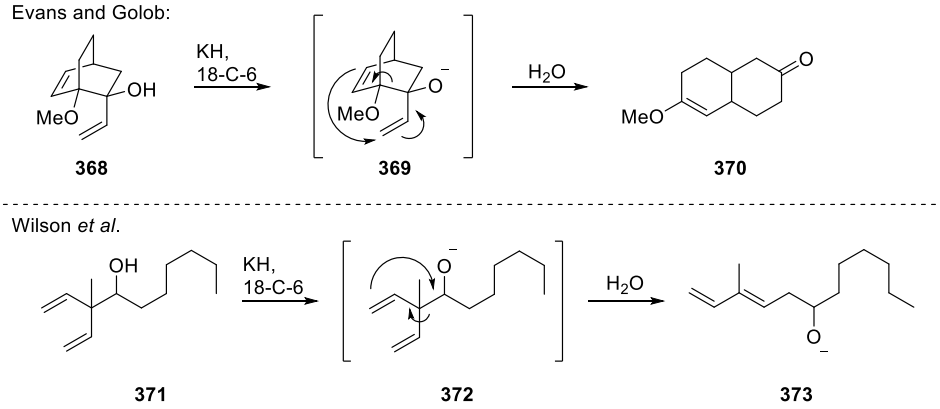
It was expected that more rapid access to this alcohol could be achieved by addition of the organolithium reagent generated from 3-methyl-1,4-pentadiene to paraformaldehyde, by analogy with the tactic employed to access furan derivative **303** (page 78); indeed this provided an equimolar mixture of 1,3-diene **333** and 1,4-diene **367** (Scheme 78). The mixture could be separated by flash chromatography, or treated with KH and 18-crown-6 to convert the 1,4-diene into the 1,3-diene *via* an anion-accelerated [1,3]-sigmatropic shift; in this manner alcohol **333** could be prepared exclusively as the *E*- isomer.



Scheme 78. Two-step synthesis of alcohol **333**.

Optimisation of this transformation, so that it could be carried out in one pot, was next studied. A brief overview of the counterion effects on the sigmatropic shifts of alkoxides is necessary at this point. In their seminal report on anion accelerated [3,3]-sigmatropic shifts,[153] Evans and Golob examined the reaction of alkoxides (Scheme 79) generated from dienol **368**, and found that generating the potassium alkoxide allowed the reaction to take place in refluxing THF; adding 18-crown-6 or changing the solvent to HMPA, so as to promote ion pair dissociation, significantly increased the reaction rate. On the other hand, the sodium alkoxide was reported to be considerably slower in undergoing the reaction, while the lithium and magnesium

bromide alkoxides did not rearrange. This paper was soon followed by a number of reports on analogous [1,3]-sigmatropic shifts: Thies and Seitz[154,155] and independently Franzus *et al.*[156] reported cases of potassium alkoxide accelerated [1,3]-sigmatropic shifts. Wilson and coworkers undertook a study of counterion, solvent and cryptand effects on the rearrangement on system **371**,[157] with the results being analogous to those obtained for the [3,3]-shifts by Evans and Golob.



Scheme 79. Seminal reports of [3,3]- and [1,3]- anion accelerated sigmatropic shifts.

The literature consensus therefore is that due to strong ion pair association, lithium alkoxides do not benefit from this rate enhancement.[158] Treatment of the mixture of the lithium alkoxides of alcohols **333** and **367** after the end of the paraformaldehyde addition with 12-crown-4 did not promote the rearrangement, even after prolonged heating to reflux.

As it was evident that the transformation would need to proceed *via* the potassium alkoxide, we decided to explore the possibility of performing an exchange reaction between the lithium alkoxide and an added potassium salt to form the reactive potassium alkoxide *in situ*. Literature precedent for such an event was scarce: Danheiser *et al*. reported[159] that the [1,3]-sigmatropic shift of the lithium alkoxides derived from vinylcyclobutanones could be effected at RT by generating the potassium alkoxide through reduction of the corresponding cyclobutanone with Li-*sec*-Bu_3BH and CH_3Li in the presence of excess EtOK. Additionally, Quirk and coworkers

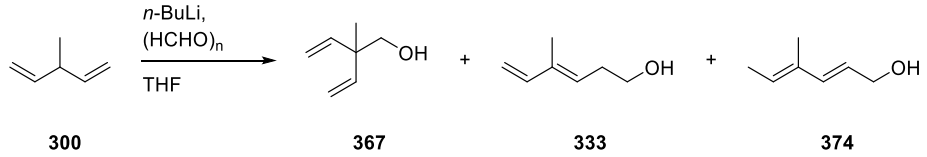
demonstrated[160] that direct addition of potassium salts to polymeric lithium alkoxide initiators promotes ethylene oxide polymerisation in a manner equivalent to using potassium alkoxide initiators; although direct counter-ion exchange is not explicitly ruled out, the authors propose a mechanism in which the added potassium alkoxide acts as a Lewis base to promote dissociation of the lithium alkoxide initiator aggregates, thus promoting polymerisation.

With this background, in a first experiment, 18-crown-6 was added to the mixture of lithium alkoxides followed by a THF solution of *t*-BuOK. Gratifyingly, the rearrangement was complete within minutes; however, it was accompanied by the formation of internal diene **374** (Table 8, entry 1), owing to the strongly basic conditions. Attempts to suppress the formation of this undesired side-product through precise control of reaction time were unsuccessful, as stopping the reaction prematurely also led to incomplete [1,3]-shift; allowing the reaction to proceed in the hope of exploiting this process for the preparation of diene **374** led to decomposition. Reducing the amount of *t*-BuOK to 0.8 equiv led to incomplete conversion, while 0.5 equiv did not promote the rearrangement at all (entries 2, 3). When solid *t*-BuOK was used, a complex reaction mixture was obtained (entry 4). Direct generation of the potassium organometallic species from 3-methyl-1,4-pentadiene followed by addition of paraformaldehyde provided an improved ratio of **333** to **367**, but addition of 18-crown-6 still resulted in the formation of internal diene **374** (entry 5).

Different potassium salts were next assayed. KHMDS gave incomplete conversion; K_2CO_3, KF and KPF_6 did not promote the rearrangement, possibly owing to their low solubility in THF (entries 6 – 9). Use of CsF in a THF/DMF solvent mixture gave no improvement, while KPF_6 in a THF/DME mixture afforded an improved **333** : **367** ratio, but generated unidentified side products, which possibly arise due to the long reaction time required (entries 10, 11).

Finally, it was found that KOTMS showed a much reduced tendency to promote the conversion of diene **333** into **374**, allowing pure **333** to be isolated after 15 min (entry 12).

Reducing the loading of KOTMS to 0.5 equiv gave only partial conversion (entry 13). In the optimised procedure, 1.0 equiv of 18-crown-6 and 2.0 equiv of KOTMS were added to the lithium alkoxide mixture, and the reaction was quenched with brine after 15 min; this provided diene **333** practically free of both **367** and **374**, in 55% yield after bulb-to-bulb distillation. Careful drying of both the crown ether (by stirring under high vacuum) and of KOTMS (by heating to 100 °C under high vacuum) was essential in order for optimal results to be achieved.



Entry	Additive (equiv)[a, b]	Time[c]	Ratio[d] **367** : **333** : **374**
1	*t*-BuOK (1.0)	5 min	trace : 83 : 17
2	*t*-BuOK (0.8)	5 min	21 : 72 : 7
3	*t*-BuOK (0.5)	20 min	50 : 50 : 0
4	*t*-BuOK (1.0)[e]	12 h	complex
5	None[f]	30 min	8 : 77 : 15
6	KHMDS (1.0)	30 min	21 : 72 : 7
7	K_2CO_3 (1.0)[e]	12 h	50 : 50 : 0
8	KF (1.0)[e]	12 h	50 : 50 : 0
9	KPF_6 (1.0)[e]	12 h	50 : 50 : 0
10	KPF_6 (1.0)[g]	12 h	9 : 91 : 0
11	CsF (1.0)[h]	12 h	19 : 62 : 19
12	KOTMS (2.0)	15 min	trace : 100 : trace
13	KOTMS (0.5)	12 h	44 : 56 : 0

Table 8. Optimisation of the one-pot synthesis of alcohol **333**. a): Added at RT after the 3-methylpentadienyl lithium had been consumed (as evidenced by the disappearance of the red colouration of the solution) and after the addition of 18-crown-6; this stage of the reaction was always performed in THF; b) added as a solution in THF except where specified; c) refers to the period following the addition of the additive up to the point at which the reaction is quenched with brine; d) determined by integration of peaks in the ^{1}H NMR spectrum of the crude product mixture; e) added as a solid; f) 3-methylpentadienyl lithium/potassium generated using Schlosser's method; g) added as a solution in THF/DME, 3 : 1; h) added as a solution in THF/DMF, 3 : 1.

The fact that a stoichiometric quantity of KOTMS is required indicates that counterion exchange from lithium alkoxides **375** and **376** to potassium alkoxides **377** and **378** is irreversible, and therefore alkoxide **378** is stable under these conditions and sequesters the potassium cation (Figure 27). Though studies exist on the aggregation state of both lithium and potassium alkoxides in solution, as well as their mixtures, the presence of the crown ether introduces another parameter making further rationalisation of the exchange phenomena difficult.

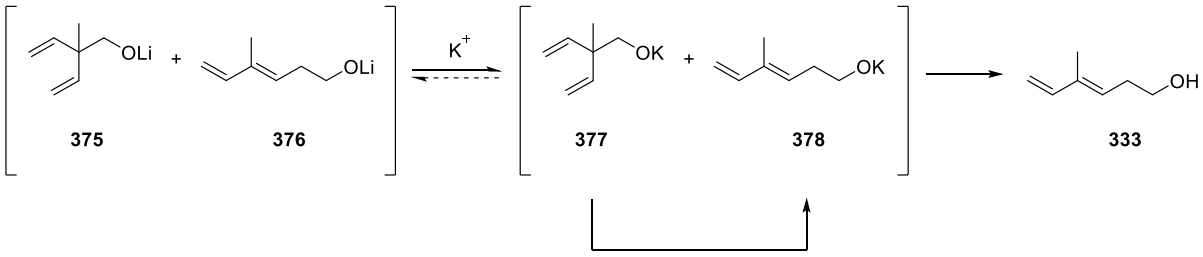
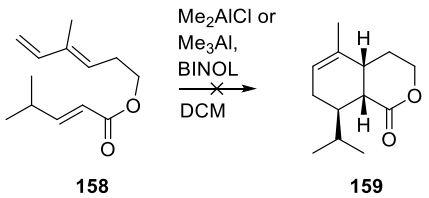


Figure 27. Proposed equilibria established upon addition of *t*-BuOK to the mixture of lithium alkoxides.

Development of an intermolecular Diels–Alder / lactonisation sequence with thioester dienophiles

Having developed a concise route to alcohol **333**, we turned our attention to seeking out a method for the enantioselective preparation of lactone **159**. The investigation of chiral versions of Taguchi's binuclear aluminium catalyst was not pursued, as it was reasoned that with both aluminium centres bound onto the same nitrogen atom, the chiral group would be placed away from the reaction centre and would be unlikely to provide a good level of stereocontrol. Instead, it was judged that a binuclear complex displaying axial chirality would be more likely to be successful. In this regard it was encouraging that the group of Taguchi has reported successful IMDA reaction of ester-tethered substrates with binuclear aluminium complexes with Br_4BIPOL[161] or BIPAM;[162] these however had not been applied successfully to the

preparation of lactone **159**, while the corresponding enantioselective transformations using enantiopure ligands were not reported. In preliminary experiments, ester **158** was treated with the complexes deriving from addition of 2.0 equiv of Me_2AlCl or Me_3Al to BINOL, but no product was detected in either case (Scheme 80).



Scheme 80. Attempted IMDA reaction with a binuclear aluminium complex.

Some other reagents that were assayed but did not promote the reaction were: $Zn(OTf)_2$; binuclear zinc complex **379**, bearing Trost's bis-prophenol ligand (Figure 28); methyl-β-cyclodextrin, in the hope that it could promote the cycloaddition by incorporating the ester within its cavity (Diels–Alder reactions promoted by cyclodextrins are known);[163,164,165] H_3PO_4, as in the event Bronsted acid catalysis was successful then chiral phosphoric acids could be assayed; and finally $InCl_3$ in aqueous medium, following methodology developed by Taguchi and coworkers.[166]

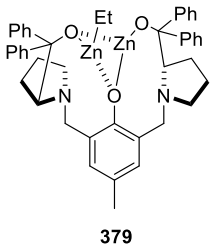
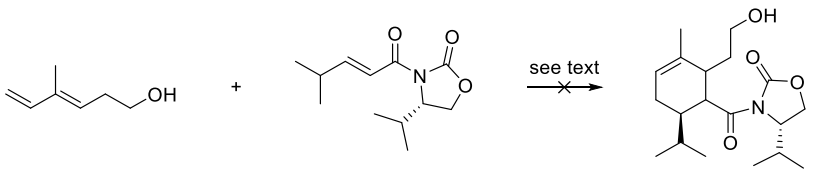


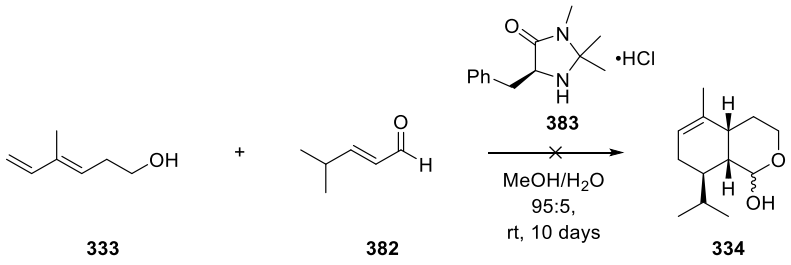
Figure 28. Structure of binuclear zinc complex **379**.

It was clear that a different approach was needed. Reasoning that the ester tether did more to hinder reactivity than to aid it, it was decided to focus on intermolecular Diels–Alder reactions instead. The use of the corresponding chiral *N*-acyloxazolidinone as the dienophile seemed appealing, as Evans auxiliaries have been employed in intermolecular Diels–Alder reactions, giving good diastereoselectivity.[167] However, treatment of a solution of imide **380**[168] and alcohol **333** with Me_2AlCl, $Cu(OTf)_2$ or $Yb(OTf)_3$ did not promote the cycloaddition (Scheme 81).



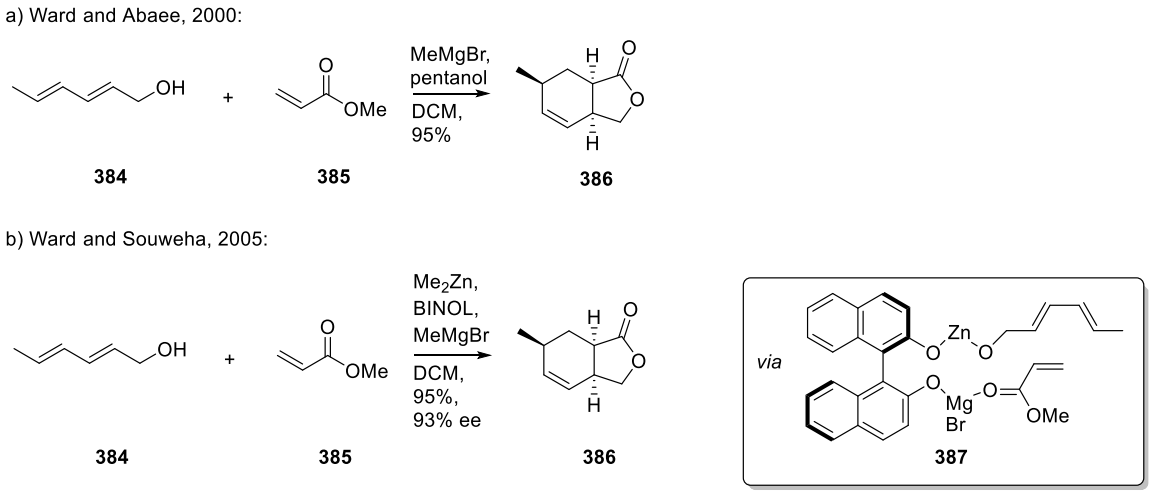
Scheme 81. Attempted intermolecular cycloaddition of alcohol **333** and imide **380**.

Next, an organocatalysed Diels–Alder reaction between aldehyde **382** and alcohol **333** was attempted using catalyst **383**, following the seminal work by MacMillan and coworkers;[169] if successful, this would have provided access to lactol **334**, shortening the overall synthetic sequence by one step. However, even after prolonged reaction times (> 10 d), no product was formed.



Scheme 82. Attempted organocatalysed cycloaddition of alcohol **333** and aldehyde **382**.

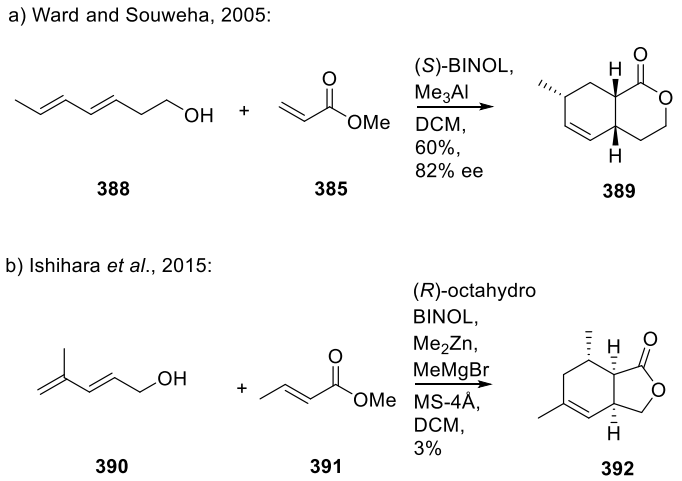
Our attention next turned to a series of studies by the group of Ward: in the first one,[170] intermolecular Diels–Alder reaction of alcohol **384** with methyl acrylate **385**, promoted by MeMgBr, was followed by esterification *in situ* to provide lactone **386** (Scheme 83a). In essence, this inverse sequence of events rectifies the decreased reactivity demonstrated by the corresponding ester-tethered DA precursor. In a subsequent study, it was found that by transiently tethering both reaction partners to enantiopure BINOL in the form of bifunctional Lewis acid complex **387**, an ee of 93% could be achieved (Scheme 83b).[171] Finally, Ishihara *et al*. recently succeeded in reducing the catalyst loading in the same reaction to 0.2 equiv through the addition of 4Å molecular sieves;[172] this serves to trap methanol formed after the lactonisation step, thus preventing it from impeding catalyst turnover.



Scheme 83. Literature precedent for the intermolecular Diels–Alder / lactonisation sequence.

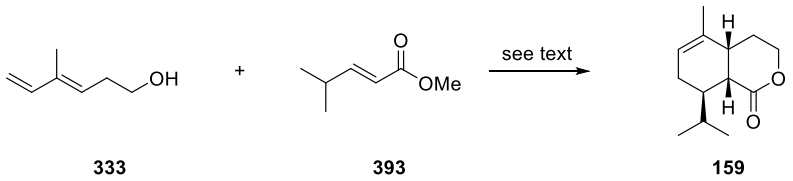
These reports were highly encouraging; however, it was suspected that significant optimisation would be needed before this approach became applicable to our system. Specifically, there were few examples on the use of homoallylic alcohol dienes;[173,174] Ward reported[171] the reaction of methyl acrylate with alcohol **388** employing a mononuclear complex formed from BINOL and Me_3Al to give adduct **389** in 60% yield and 82% ee (Scheme 84a), as the binuclear system provided inferior results in this case. Furthermore, in

Ishihara's report it was noted that introduction of a β- substituent on the dienophile, by using methyl crotonate as the reacting partner, resulted in almost complete loss of reactivity.[172]



Scheme 84. Literature precedent for the cycloaddition / lactonization sequence with a) a homoallylic alcohol; b) substituted acrylate.

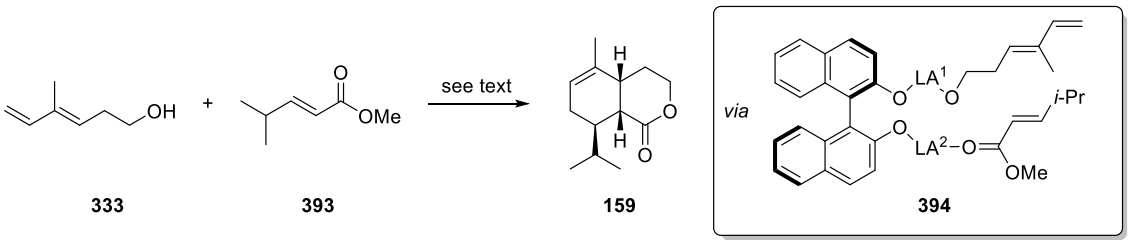
We commenced our investigation of the racemic variant of the reaction by treating a solution of alcohol **333** (1.0 equiv) and ester **393** (2.0 equiv) with Me_2AlCl, Me_3Al, or MeMgBr (Scheme 85). Only in the case of Me_2AlCl was a small amount of lactone **159** formed; heating to reflux provided a yield of 29% after 18 h, while reaction at RT required 6 d to give a yield of 41%.



Scheme 85. Cycloaddition / lactonisation sequence using alcohol **333** and ester **393**.

Moving on to BINOL-Lewis acid complexes, mononuclear complexes deriving from Me_2AlCl or Me_3Al were ineffective, in contrast to Ward's example. Binuclear complexes were generated according to Ward's procedure;[171] the results are summarised in Table 9. As can be

seen only the binuclear complex generated from 2.0 equiv of Me_2AlCl provided any product, although the reaction was very sluggish and the resulting yield low.



333 393 159 394

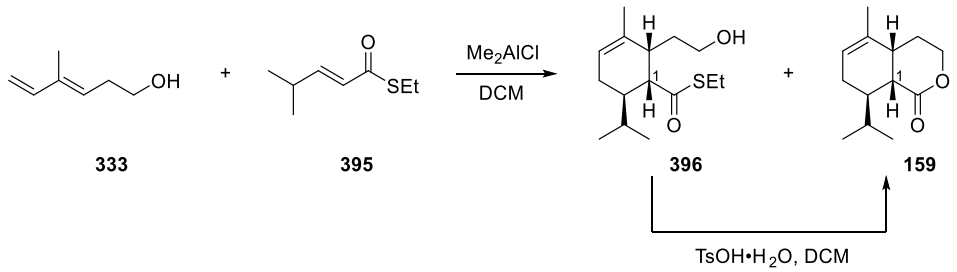
Entry	LA^1	LA^2	Temperature	Reaction time	Equiv **393**	Yield
1	Me_2AlCl	none	reflux	18 h	2	-
2	Me_3Al	none	reflux	18 h	10	-
3	Me_2AlCl	MeMgBr	reflux	18 h	2	-
4	Me_2AlCl	Me_2AlCl	reflux	36 h	2	15%
5[a]	Me_2AlCl	Me_2AlCl	reflux	18 h	2	-
6	Me_2AlCl	Me_2AlCl	reflux	18 h	5	23%
7	Me_2AlCl	Me_2AlCl	RT	18 h	2	-
8	Me_3Al	Et_2Zn	reflux	18 h	5	-

Table 9. Screening of Lewis acid / BINOL complexes for the cycloaddition of alcohol **333** with ester **393**. a): 0.2 equiv of Lewis acid / BINOL complex used.

It seemed plausible that a satisfactory yield could be obtained if the reactivity of the dienophilic partner was improved. Thioesters are known to be more reactive as acylating agents compared to the corresponding esters, an effect that is believed to arise from a lower loss of delocalisation energy due to the $p_x \rightarrow \pi^*_{C–O}$ interaction (X = O, S for an ester and thioester correspondingly).[175] It would therefore be expected that a thioester would also be a more reactive dienophile in a Diels–Alder reaction; although not completely unknown, this approach is relatively underexploited. Scattered examples exist in the literature; notably, the group of Hart has published a series of reports[176,177,178,179] on such use of thioesters in Diels–Alder reactions, emphasising their increased reactivity over the corresponding esters and disclosing the use of $Et_2AlCl{\cdot}SiO_2$ and $TiCl_4$ as Lewis acid promoters. The idea of employing

a thioester in our envisaged Diels–Alder/lactonisation sequence, therefore, seemed worth investigating.

Pleasingly, reaction of 1.0 equiv of alcohol **333** with 4.0 equiv of thioester **395** (Scheme 86) in the presence of 1.0 equiv of Me_2AlCl was complete after 36 h at RT to give an inseparable mixture of thioester Diels–Alder adduct **396** and lactone **159**, in 67% yield (after treatment of the mixture with 0.5 equiv of $TsOH{\cdot}H_2O$ to complete the lactonisation, *vide infra*). Evidently the increased rate of the cycloaddition achieved by employing the thioester as the dienophile is not accompanied by an equivalent increase in the rate of lactonisation, leading to the observed mixture of products. Decreasing the thioester loading to 2.0 equiv led to a decrease in rate, with the reaction being complete after 3 d (62% yield of **159** after lactonisation).

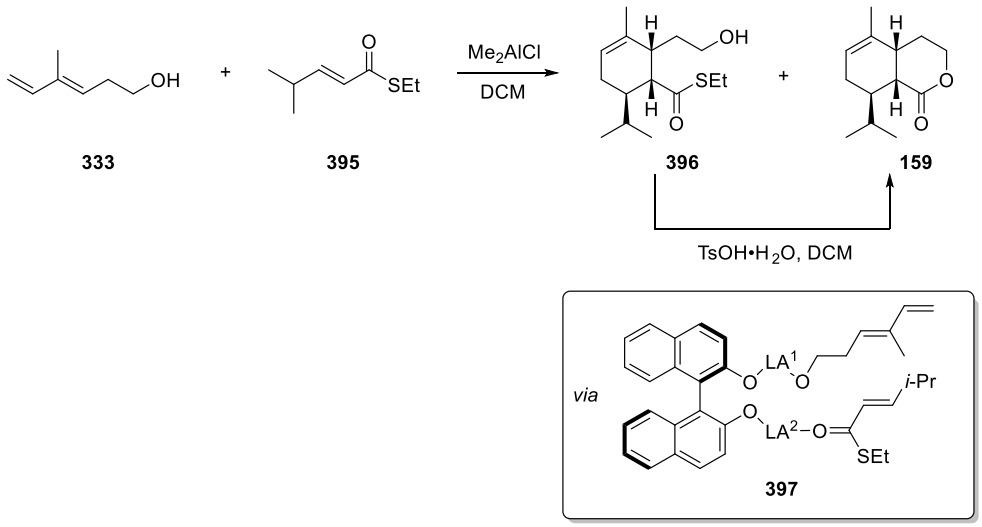


Scheme 86. Intermolecular cycloaddition between alcohol **333** and thioester **395**, and subsequent lactonisation.

Of the conditions screened for promoting lactonisation of the remaining thioester adduct **396**, use of $Cu(OAc)_2$ or CuOTf·pyridine complex provided no conversion, while $CuBr_2$ gave a mixture of products, likely arising from epimerisation at the C1 position. On the other hand, treatment with 0.5 equiv of $TsOH{\cdot}H_2O$ for 3 h in DCM promoted lactonisation to give lactone **159** cleanly.

The use of BINOL-Lewis acid complexes was then investigated. As can be seen in Table 10, the results were analogous to those obtained with ester **393**, as 2.0 equiv of Me_2AlCl were required in order to form any product (entry 5). Reducing the catalyst loading to 0.2 equiv

(entry 6) resulted in a drastically reduced reaction rate, while conducting the reaction at reflux resulted in faster conversion but decreased yield (entry 7). Changing the solvent to THF resulted in no reaction (entry 8). When enantiopure BINOL was used, the resulting lactone displayed no enantiomeric excess.

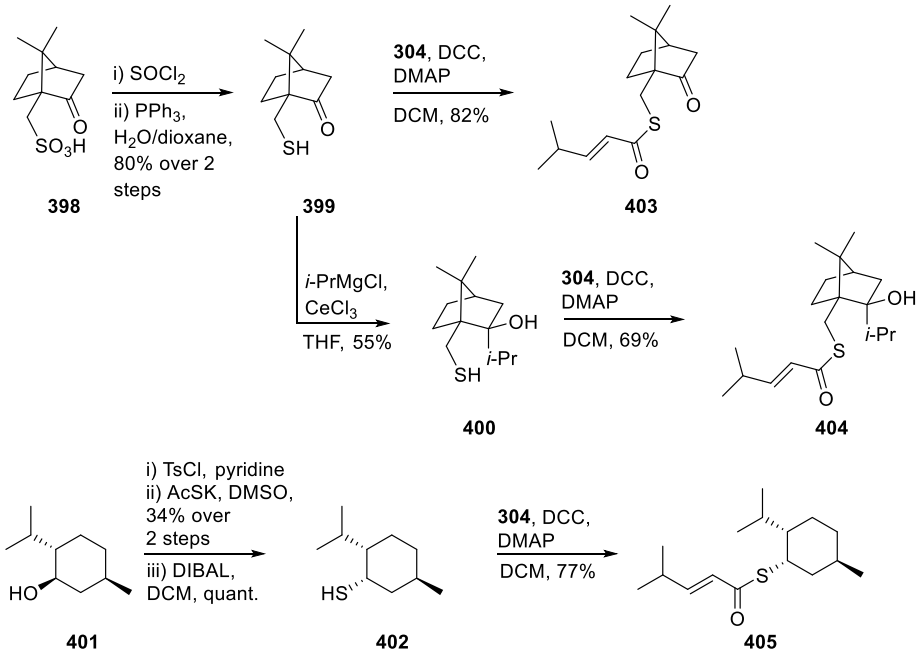


Entry	LA^1	LA^2	Temperature	Reaction time	Yield[a]
1	Me_3Al	MeMgBr	reflux	18 h	-
2	Me_3Al	Et_2Zn	RT	36 h	-
3	Me_2AlCl	MeMgBr	RT	3 d	-
4	Me_3Al	none	RT	11 d	-
5	Me_2AlCl	Me_2AlCl	RT	36 h	64%
6[b]	Me_2AlCl	Me_2AlCl	RT	11 d	12%
7	Me_2AlCl	Me_2AlCl	reflux	18 h	33%
8[c]	Me_2AlCl	Me_2AlCl	RT	36 h	-

Table 10. Screening of Lewis acid / BINOL complexes for the cycloaddition of alcohol **333** with thioester **395**. a): Refers to yield of **159** after lactonization; b): 0.2 equiv of Lewis acid / BINOL complex used; c): Reaction performed in THF.

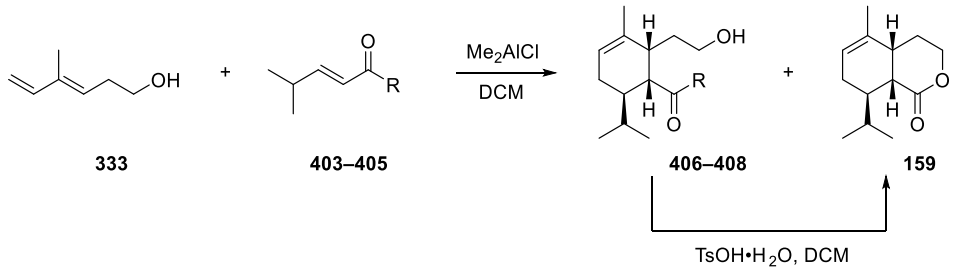
In view of these results, attention was turned to the exploration of enantiomerically pure thiols as chiral auxiliaries. Camphor thiol **399** (Scheme 87) was identified as a promising candidate which could be easily accessed from (+)-camphorsulphonic acid by formation of the sulfonyl chloride followed by reduction.[180] Derivative **400** was prepared by addition of *i*-PrMgCl to

thiol **399**, following the preparation of a similar compound by Aggarwal and coworkers.[181] Finally, to test the effect of a secondary thiol, neomenthyl thiol **402** was prepared from (−)-menthol by tosylation, substitution with thioacetate and reductive removal of the acetyl group.[182,183]



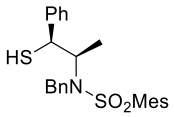
Scheme 87. Synthesis of chiral thiol auxiliaries **399**, **400** and **402** and their respective thioesters.

Results with thioester **403** were promising: reaction with 2.0 equiv of alcohol **333** and 2.0 equiv of Me_2AlCl gave a mixture of lactone **159** and adduct **406** in a 60 : 40 ratio; after treatment of this mixture with $TsOH{\cdot}H_2O$ lactone **159** was obtained in 66% yield and 72 : 28 er, determined *via* chiral GC analysis (see Experimental Section). Thioester **404** gave a 35 : 65 ratio of **159** to **407** and a poor er (53.5 : 46.5) after lactonisation. Reaction of thioester **405** was considerably slower, with the reaction being incomplete after 6 d; in this case only lactone **159** was formed (in 31% yield and 66 : 34 er).



Scheme 88. Diastereoselective intermolecular DA reactions of alcohol **333** with thioesters **403**–**405** and subsequent lactonisation. The depiction of stereochemistry around the cyclohexenyl ring in adducts **406**–**408** implies only *relative* stereochemistry with respect to the thiol component.

These results demonstrate that the use of chiral thiol auxiliaries is a viable approach to the asymmetric synthesis of lactone **159**, though further study is necessary in order to identify an auxiliary that would achieve higher diastereoselectivity. A thiol variant of the Abiko–Masamune auxiliary (Figure 29) developed by the Hulme group[184] holds promise in this regard; pursuing its synthesis was not possible in the timeframe of this work due to supply issues with required starting norephedrine, and remains as future work.



409

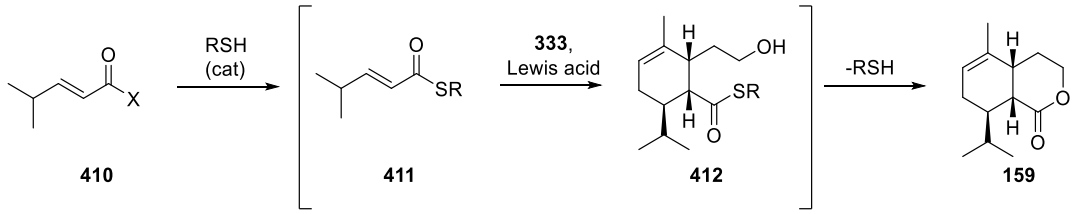
Figure 29. Thio-Abiko–Masamune auxiliary developed by the Hulme group.

Conclusions and future work

In conclusion, a novel one-pot sequence has been developed consisting of organolithium addition to formaldehyde, followed by cation exchange in-situ to effect a [1,3]-sigmatropic shift. (*E*)-4-Methylhexa-3,5-dien-1-ol **333** thus produced has been used in a novel thioester mediated intermolecular Diels–Alder reaction / lactonisation sequence to furnish lactone **159**;

use of a thioester as the dienophile overcomes the problems associated with the comparatively less reactive ester.

Furthermore, proof-of-concept level studies have demonstrated the ability of chiral thiol auxiliaries to achieve diastereoselective reaction and in this way furnish enantioenriched lactone **159**. Future studies will focus on the optimisation of the chiral thiol used. With an optimal auxiliary identified, it can be envisaged that a catalytic variant of the methodology could be developed whereby the reactive thioester is transiently formed by reaction of a thiol catalyst with an acylating agent; lactonisation after the cycloaddition would then regenerate the thiol catalyst (Scheme 89).



Scheme 89. Envisaged Diels–Alder / lactonisation cascade employing a thiol nucleophilic catalyst.

Chapter 5: mP450 oxidation studies of eleuthoside structures

Background

Cytochrome P450s are a family of monooxygenases that play a crucial role in xenobiotic metabolism and in the biosynthesis of natural products;[89] they catalyse the oxidation of organic compounds, mainly in the form of C-H hydroxylation but also through epoxidation, oxidative demethylation, and Bayer–Villiger oxidation.

In the context of xenobiotic metabolism, P450-mediated hydroxylation corresponds to so-called Phase 1 metabolism, which serves to functionalise a xenobiotic for subsequent conjugation with a charged species (such as glutathione, glucuronic acid, or glycine) in Phase 2 metabolism. If the xenobiotic is a drug, the metabolites may exhibit a different activity profile to the parent compound or may be inactive; conversely, inactive compounds (prodrugs) can be converted into the active species through Phase 1 metabolism. For example, morphine is metabolised by mammalian CYP3A4 to demethylated derivative normorphine (devoid of opioid activity) *via* hydroxylation of the *N*-methyl group followed by loss of formaldehyde (Figure 30).[185]

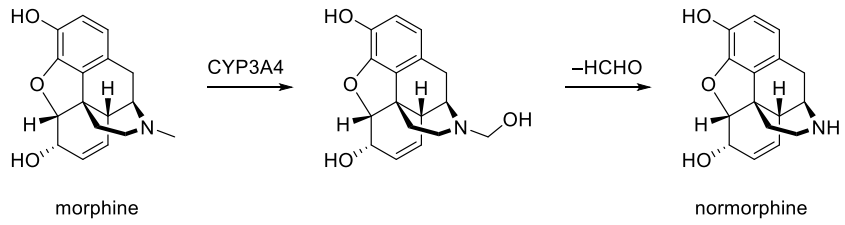


Figure 30. Cytochrome P450-mediated metabolism of morphine to normorphine.

Additionally, P450 enzymes are involved in oxidative steps in the biosynthesis of various natural products; the conversion of cholesterol to dehydroepiandrosterone (itself a precursor to other steroid hormones) proceeds *via* three P450-catalysed steps comprising oxidative side-chain cleavage, hydroxylation, and a second oxidative cleavage reaction (Figure 31a).[186,187] In

another notable example that demonstrates the enzyme's importance in the biosynthetic functionalisation of terpene skeletons, it has been shown that cytochrome P450s are responsible for the introduction of the multitude of oxygen atoms in taxol, starting from biosynthetic precursor taxadiene (Figure 31b).[188,189]

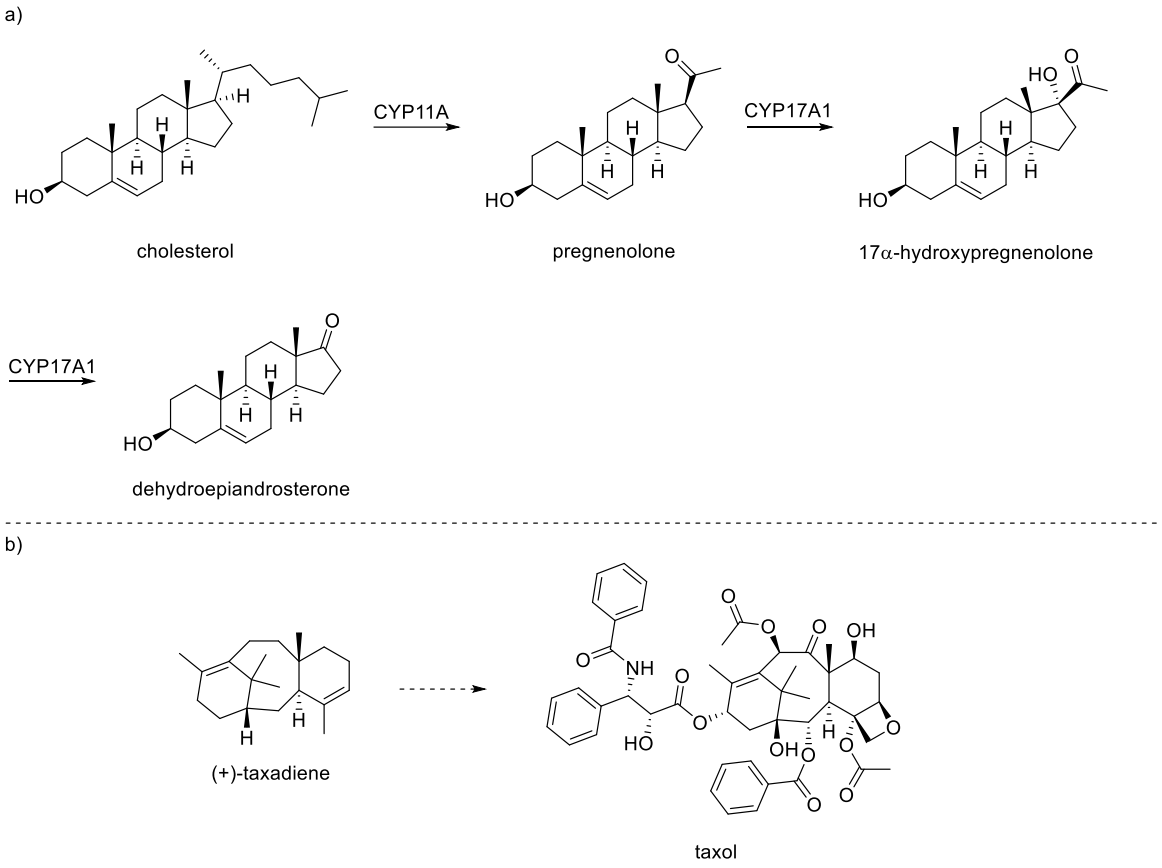


Figure 31. Examples of cytochrome P450 involvement in the biosynthesis of natural products: a) steroids; b) diterpene.

Cytochrome P450s belong in the superfamily of hemoproteins; that is, they employ an iron(III)-containing heme cofactor (specifically heme b, also known as iron-protoporphyrin IX, Figure 32), located in their active site; a cysteine thiolate and water act as the two axial ligands of the hexacoordinate Fe(III) atom. The presence of this cofactor gives the enzyme its name (pigment 450), deriving from the characteristic absorption frequency of the CO complex of its reduced form.[190,191]

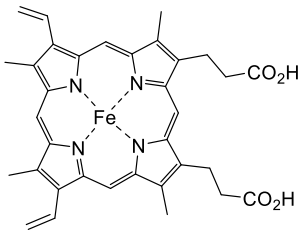


Figure 32. Structure of heme b.

The catalytic cycle of the enzyme (assuming a hydroxylation reaction) is believed to be as follows (Figure 33):[89]

- Beginning from resting state **A** (described above), ligand binding is accompanied by loss of the axial water molecule and a change of the ferric centre from a low-spin (S = 1/2) to high-spin (S = 5/2) state (**B**) which leads to an increase in the reduction potential of the species.
- As a result of this increased potential, the iron receives an electron from a molecule of NADH or NADPH, thus being reduced to the Fe(II) species (**C**). Molecular oxygen binds to this species (**D**), which receives another electron to form Fe(III) peroxo species **E**. Protonation of this species gives Compound 0 (**F**), once believed to be the active oxidising species.
- Another protonation and heterolytic bond scission with loss of water generates Compound I (**G**). This is a Fe(IV) oxo species in which a radical cation is delocalised over the porphyrin and thiolate ligands; significant evidence pointing to this being the active species was obtained recently by Rittle and Green who isolated and characterised it.[192]
- Abstraction of a hydrogen atom by Compound 1 from the substrate forms an alkyl radical and Fe(IV) hydroxide complex **H** (also known as Compound II). Radical rebound onto the iron-bound OH group forms an alcohol while regenerating the Fe(III)

centre; binding of axial water or another molecule of substrate returns the enzyme to states **A** or **B** correspondingly, closing the cycle.

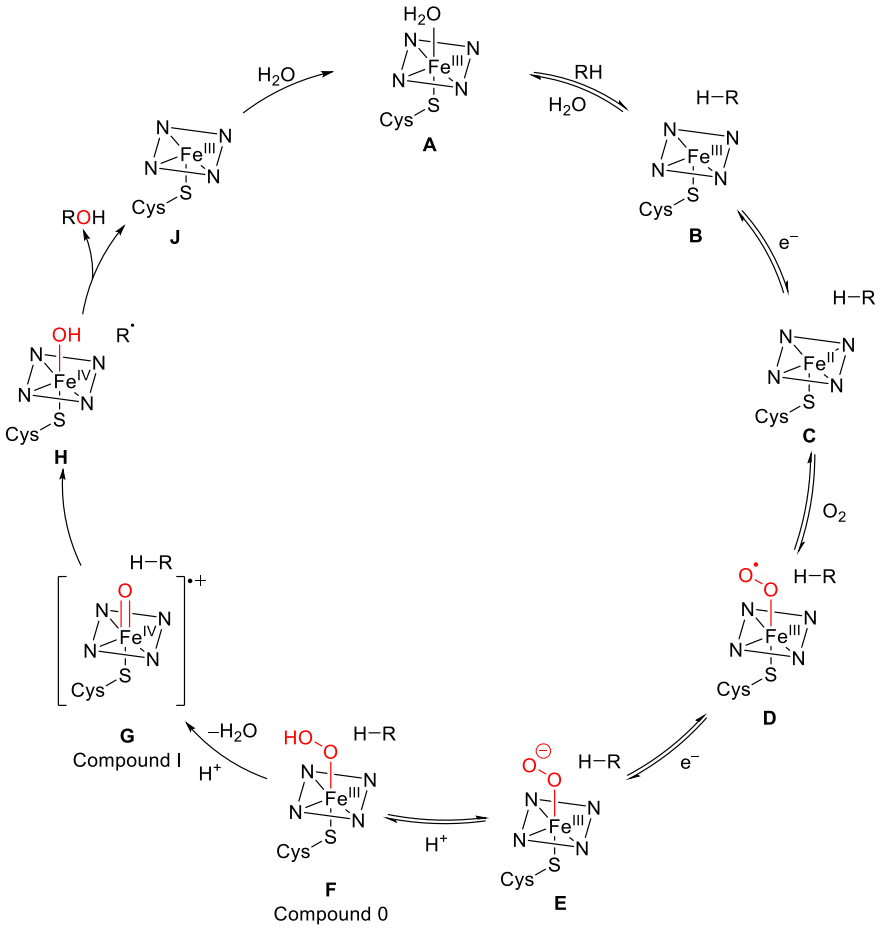


Figure 33. Cytochrome P450 catalytic cycle.

It is evident from the above that catalytic turnover requires the supply of electrons to the active site through the consumption of NADH or NADPH. Different electron transfer partners are employed to this end by the various cytochrome P450 systems.[193] Microsomal systems employ cytochrome P450 reductase, an FAD and FMN (Figure 34) containing reductase, for this purpose; mitochondrial and $P450_{CAM}$-type (bacterial) systems employ a two-protein combination consisting of a ferredoxin-type iron-sulfur protein along with an FAD-containing ferredoxin reductase, while bacterial $P450_{MEG}$-type systems are composed of a single protein bearing both a cytochrome P450 and a P450 reductase domain.

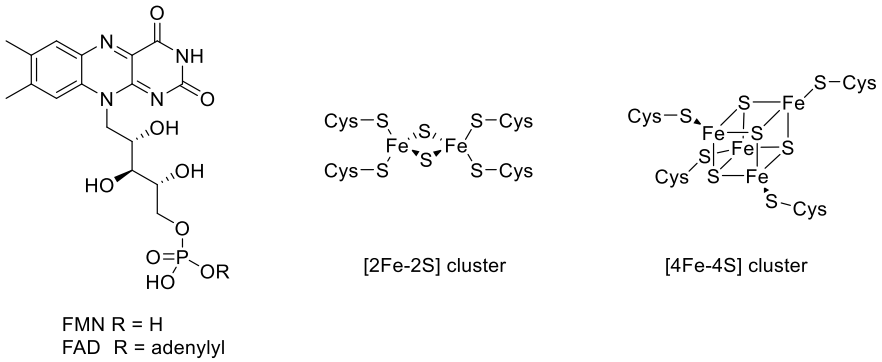
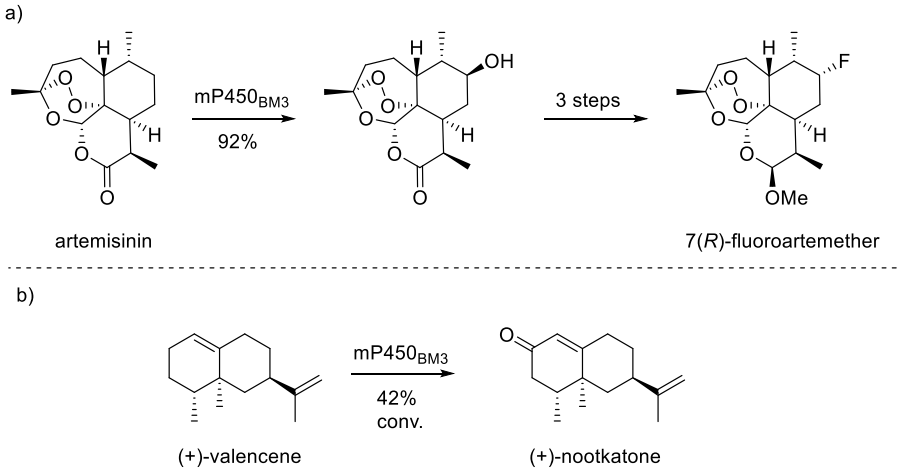


Figure 34. Structures of electron-transfer partner cofactors.

Due to their ability to hydroxylate unactivated C-H bonds, cytochrome P450s are attractive biocatalysts for application in organic synthesis. Mutant variants have been produced through both error-prone PCR and site-directed mutagenesis that demonstrate improved reactivity and wider substrate scope than wild-type enzymes. $P450_{BM3}$ (so named because it is the third P450 enzyme isolated from *Bacillus megaterium*) is a variant commonly employed[89] in such studies as it possesses a reductase domain, making it self-sufficient. Such mutant cytochrome P450 (mP450) libraries have been used in a synthetic context. An example is the mP450-mediated hydroxylation of artemisinin by Zhang *et al*.;[194] the hydroxylated derivative was then converted into 7(*R*)-fluoroartemether, thus blocking the potential site of metabolism (Scheme 90a). Another application is found in the commercially important oxidation of (+)-valencene to (+)-nootkatone developed by Wong and coworkers (Scheme 90b).[195] Applications to enantioselective hydroxylation also exist, for example, in the work of the group of Reetz.[196,197,198,199,200,201,202]



Scheme 90. Examples of synthetic applications of mP450s.

Research in the Wong group

The Wong group has developed a library of over 200 $P450_{BM3}$ mutants with a varied reactivity profile. A detailed description of the mutations introduced and their effects is beyond the scope of this short introduction; an important effect to note however is that a number of mutations were found to display a greater degree of similarity to the substrate-bound wild type structure than to the substrate-free one; this results in a *catalytically-ready* conformation, which is thought to lead to increased activity.[203,204,205]

Work in the group has also focused on the application of this library to the oxidation of various targets, especially aiming at the production of high-value oxidation products. An example is the previously mentioned oxidation of (+)-valencene to (+)-nootkatone;[195] another is the study of the metabolites produced *via* oxidation of common drugs lidocaine, naproxen, chlorzoxazone, testosterone, diclofenac and amitriptyline.[206]

As more information is gained about the selectivity profiles of the different members of this library, and given the synthetically highly attractive potential of cytochrome P450s for the oxidation of unactivated C-H bonds, an ongoing collaboration between the Robertson and

Wong groups aims to apply mP450s to more complex substrates, namely, to natural product-like structures. This aims to accomplish the following goals:

- Gain additional insight into the reactivity and selectivity profiles of the library when confronted with different structural substrate classes, so that mP450s may enter the synthetic toolbox as general oxidation catalysts alongside traditional chemical reagents.
- Generate differentially hydroxylated analogues of bioactive scaffolds, and determine their biological activity.
- Apply mP450 mediated oxidation as a late-stage functionalisation step in natural product synthesis (see concept of two-phase total synthesis, page 41).

The work described in this chapter stems from this collaboration, and involves mP450-mediated oxidation studies to generate analogues of eleutherobin. Analogous ongoing projects in this collaboration include the oxidation of taxadiene, and the application of biocatalytic late-stage oxidation to the total synthesis of trigoxyphins K and L, alvocidib and viridiol (Figure 35).

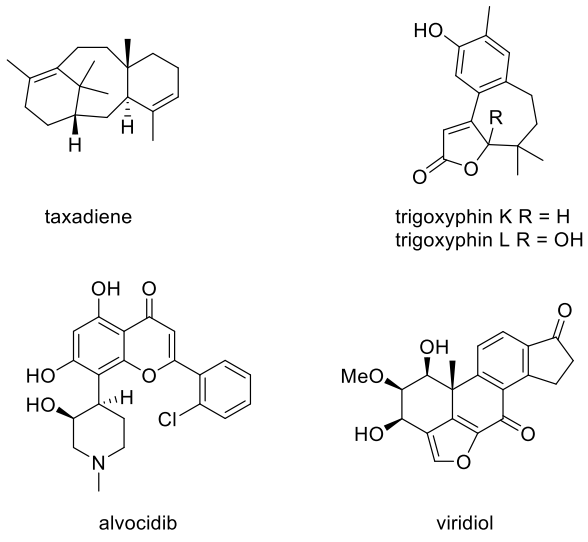


Figure 35. Natural products under study in the Robertson–Wong collaboration.

Oxidation studies of diols 347 and 349

With access to the furanoid eleuthoside skeleton achieved as described in Chapter 3, the four compounds listed in Figure 36 represented our initial panel of substrates to be subjected to mP450-mediated oxidation. Although these diols are already partially oxidised, contrary to our originally envisioned substrate **172** (see page 45), it was expected that they would provide valuable insight into the behaviour of this scaffold upon mP450-mediated oxidation.

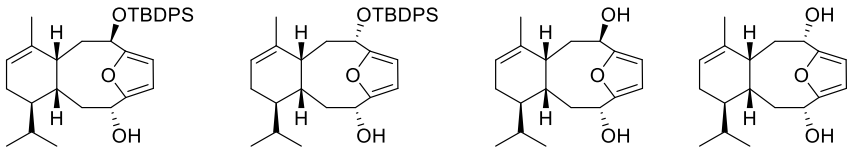
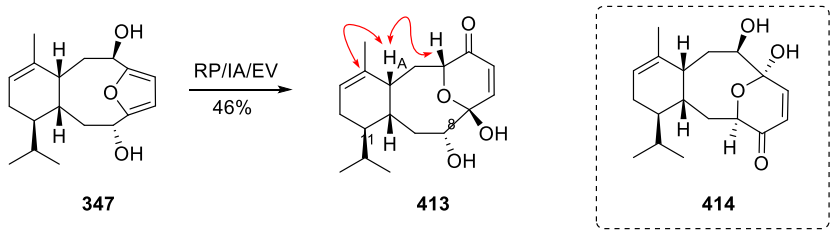


Figure 36. Initial panel of furanoid eleuthoside structures to be screened.

A first experiment consisted of screening protected diol **346** against a standard 24 mutant panel; in all reactions no conversion was observed, no doubt due to the very large protecting group precluding access to the enzyme's active site. In view of this result oxidation of epimeric diol **29** was not attempted. We next turned our attention to diol **347**; analysis of the reactions was hindered as conditions to observe this compound upon GC analysis with a flame ionisation detector could not be identified, either because of non-volatility or due to decomposition. Instead an HPLC/UV-vis method was employed, coupled with TLC analysis to identify potential non-UV active products. Upon screening against the 24 mutant panel, one metabolite was formed, with variant RP/IA/EV providing full conversion. Scale-up of the reaction (0.012 mmol scale) with this enzyme resulted in a significantly reduced reaction rate, and therefore extension of the reaction time to 3 d (from the typical 24 h) was necessary to reach satisfactory conversion (66%) and obtain the single product in 46% yield after chromatographic purification. This product was found to be hydroxypyrone **413** (Scheme 91), the result of an Achmatowicz reaction. This structure is proposed over alternative **414** due to clear HMBC

correlation between H_A and C8 as well as H_A and C11; the out-out relationship of the bridgehead substituents was inferred based on the same stereochemistry being observed in a related hydroxypyrone eleuthoside derivative synthesised by Danishefsky.[59]



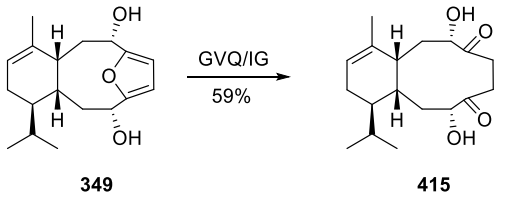
347 413 414

Scheme 91. mP450 mediated oxidation of diol **347** and key HMBC correlations of hydroxypyrone **413**.

Although this was not an unexpected outcome given the strained and electron-rich nature of the furan ring, it should be noted that only a few biocatalytic Achmatowicz reactions have been reported to date; a number of laccase catalysed examples were reported in 2013 by Asta *et al.*,[207] and a method employing a combination of a glucose oxidase and a chloroperoxidase was reported in 2014 by Deska and coworkers.[208]

We next turned to oxidation of diol **349**, expecting to observe analogous reactivity. However, upon screening against the standard panel of mutants, no products were formed. In previous cases it was found by the Wong group that varying the amount of methyl-β-cyclodextrin present in the reaction media (added to solubilise non-polar substrates) could improve conversion; repeating the screening in the absence of methyl-β-cyclodextrin led to formation of a UV-vis inactive product. Scale-up with GVQ/IG led to this being isolated (in 59% yield) and identified as diketone **415**, the product of formal hydrolysis of the furan ring in **349** (Scheme 92). It was not clear whether this was formed *via* direct hydrolysis or by oxidation to the 1,4-enedione followed by reduction of the double bond; such oxidation-reduction sequences have been observed by the Wong group in the past, though never for a furan. The fact that different degrees of conversion were observed with different mutants supports the

theory that this is an enzyme-mediated process and not a simple hydrolysis of the strained furan in the aqueous reaction media.

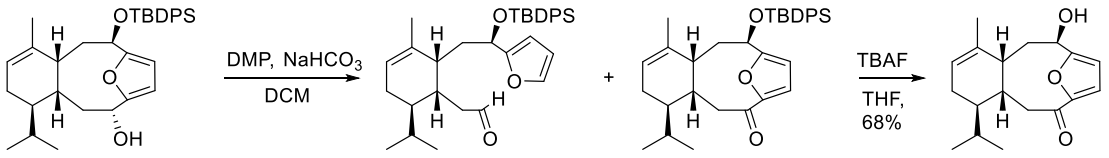


349 **415**

Scheme 92. Hydrolysis of diol **349** observed upon attempted mP450 oxidation.

Oxidation of a derivative bearing an electron-deficient furan

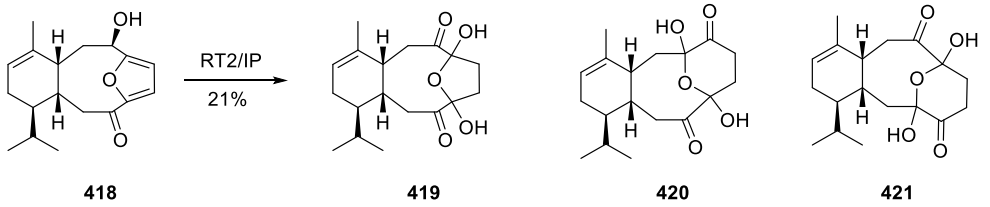
As it was evident that the electron rich furan ring dominated the compound's reactivity towards mP450 oxidation, it was next envisaged that oxidation of one of the alcohol groups next to the furan to the corresponding ketone would deactivate it, potentially directing oxidation to other parts of the molecule. Upon DMP oxidation of alcohol **346**, desired ketone **417** was formed in 23% yield along with aldehyde **416** (in 29% yield), resulting from ring opening of the strained starting material (Scheme 93). Swern conditions or MnO_2 resulted in the formation of solely aldehyde **416**, while use of TPAP/NMO gave ketone **417** along with a significant amount of unidentified side products. Deprotection of ketone **417** with TBAF then gave ketol **418**.



346 **416** 23% **417** 29% **418**

Scheme 93. Synthesis of ketol **418**.

Screening of compound **418** provided one major product, which after scale-up with RT2/IP was identified as a bis-acetal arising from hydrolysis of the furan ring with concomitant oxidation of the alcohol group, and trapping of water (Scheme 94). The spectroscopic data did not allow discrimination between the three structures proposed. It is possible that due to the strained nature of the ring system, the carbonyl group cannot adopt a coplanar conformation with the furan ring and therefore does not deactivate it electronically.



Scheme 94. mP450 mediated oxidation of ketol **418**.

Oxidation of lactone 159

To probe mP450 mediated oxidation of the cyclohexene portion of the eleuthoside scaffold without interference from the furan ring, it was decided to investigate oxidation of lactone **159**. Screening against the standard panel of mutants provided six distinct products; indicative GC traces are shown in Figure 37. The structures of the metabolites were determined after scale-up and isolation (*vide infra*). As can be seen, good selectivity could be achieved between formation of primary allylic alcohol **422** and secondary allylic alcohol **423**. Additionally, a number of mutants achieved oxidation on the isopropyl group to give tertiary alcohol **425**, with RL/YF/KSK19, for example, providing good selectivity for this product. The two final metabolites identified were aldehyde **424**, arising from further oxidation of alcohol **422**, and tertiary alcohol **426**. KSK19/IG formed **424** as a minor product along with alcohol **422** and a small amount of alcohol **425**; tertiary alcohol **426** was formed, again along with primary alcohol **422**, using RT2/AP/AM. A sixth unidentified metabolite was formed as a minor product with some variants (for example, with RP and with RT2/F81W).

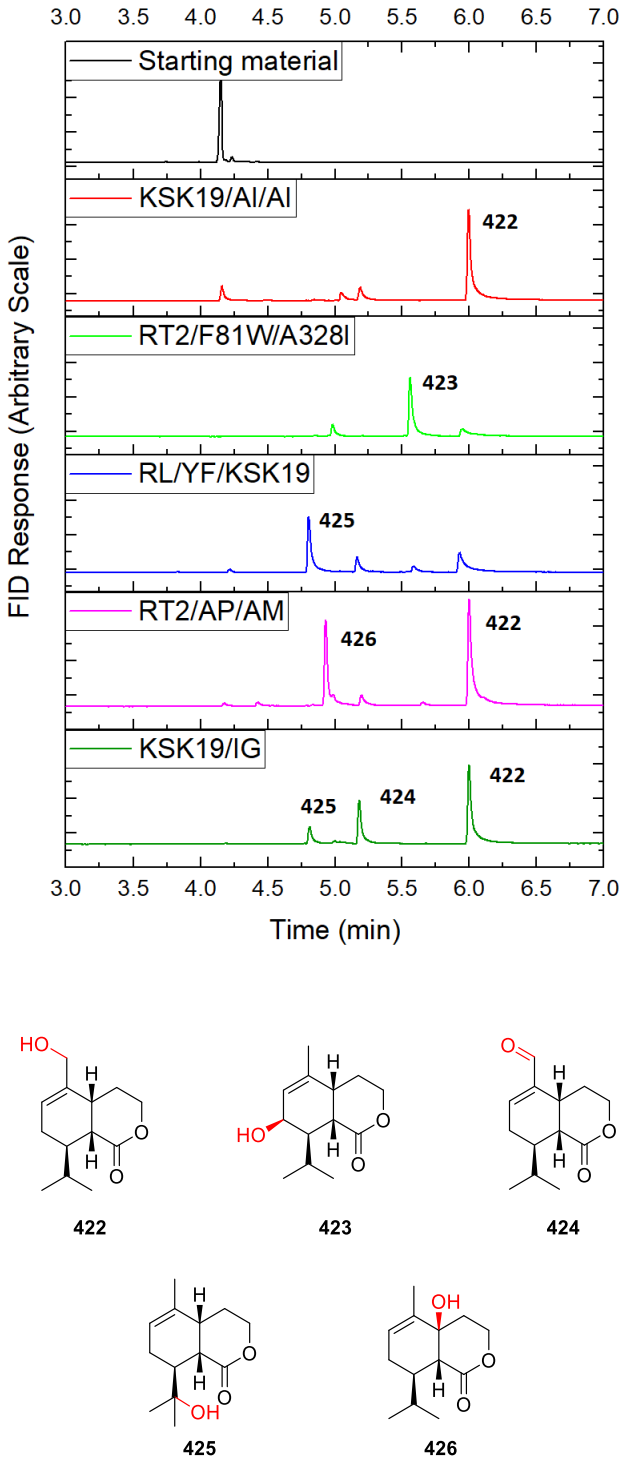
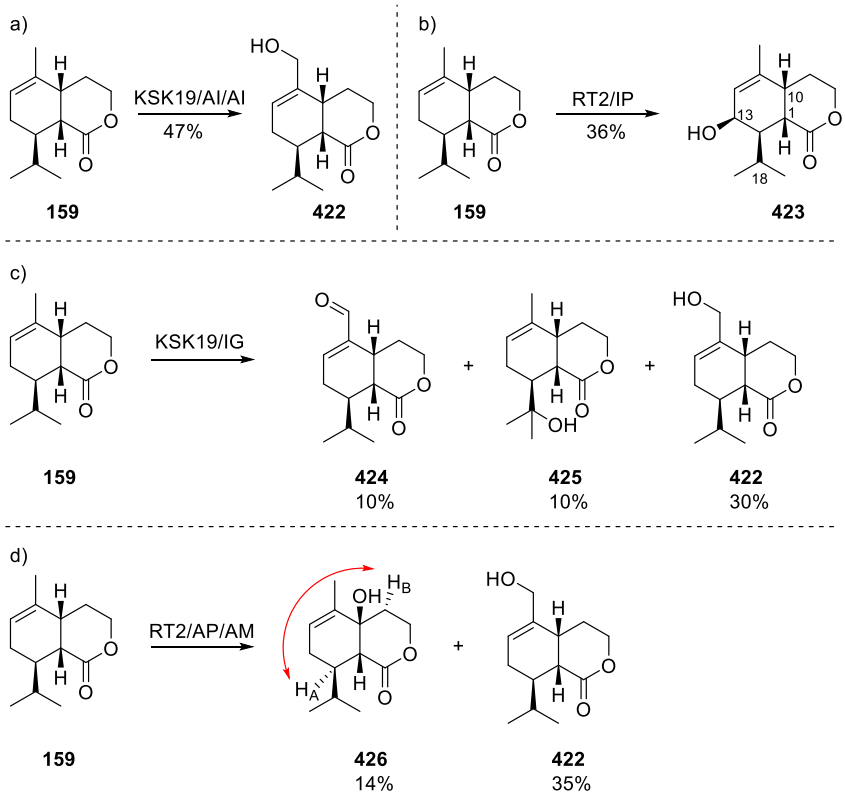


Figure 37. GC traces of selected runs showing the selectivity achieved between different hydroxylated products. (See Experimental Section for full screening data).

For the isolation of these metabolites, preparative reactions were carried out on a 0.04 – 0.1 mmol scale (Scheme 95). Reaction with KSK19/AI/AI furnished alcohol **422** with complete

conversion and in 47% isolated yield. Mutant RT2/IP provided secondary alcohol **423** in 36% yield (along with primary alcohol **422**, not isolated); the stereochemistry of the newly formed centre was assigned based on lack of NOE correlation between H13 and H1, H10, or H18. KSK19/IG allowed the isolation of aldehyde **424** and tertiary alcohol **425**, each in 10% isolated yield. Finally, RT2/AP/AM displayed a much lower activity in the preparative scale reaction compared to the screening run, likely due to problems during large-scale expression of the enzyme; however, use of a prolonged reaction time (10 d) allowed isolation of tertiary alcohol **426** in 14% yield. Confirmation of stereochemistry was provided by the NOE correlation observed between H_A and H_B.



Scheme 95. Preparative scale oxidations of lactone **159**.

Conclusions and future work

The results obtained from these studies demonstrate that the strained nature of the furanoid eleuthoside scaffold is incompatible with mP450-mediated oxidation. Preliminary experiments with lactone **159**, however, are encouraging for the oxidation of eleuthoside substrates lacking the furan ring. In view of these data, future studies will focus on the bioenzymatic oxidation of structures such as compound **427** (Figure 38); specifically, it is envisaged that in this substrate, allylic oxidation on C7 would lead to the acetal present in the natural products while allylic oxidation on C15 would introduce the hydroxyl present in eleutherobin, thus allowing a biocatalytic total synthesis of the natural product. Additional sites of oxidation will then provide differentially hydroxylated analogues.

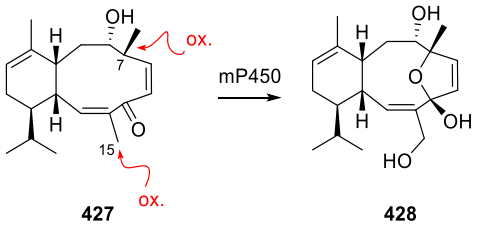


Figure 38. Envisaged precursor for the mP450 mediated generation of the eleuthoside skeleton.

Chapter 6: Flow anodic oxidation of furfuryl alcohols and subsequent Achmatowicz reaction

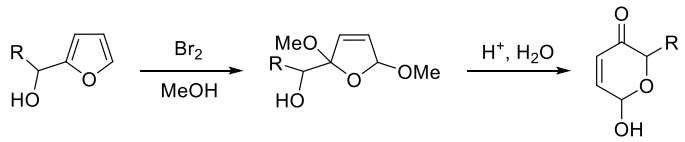
Background and aims

The application of electrochemistry to organic synthesis holds great potential, both in the pursuit of sustainable chemical transformations in view of its inherent atom economy, as well as in the synthesis of complex molecules by virtue of the selectivity afforded through precise control of the applied potential. Applications of electrochemical synthetic methodology to the synthesis of natural products are relatively scarce; Moeller and coworkers' synthesis of alliacol A[209] is one notable example. The topic has recently been reviewed.[210]

This under-utilisation of synthetic electrochemistry can be ascribed to the low familiarity of many practitioners of organic synthesis with the technique, as well as to a perceived need for specialised equipment. The development of a number of enabling technologies in recent years has the potential to address these issues and facilitate adoption of electrochemical techniques in organic synthesis research. Foremost amongst these is flow chemistry; it has been demonstrated that when performing an electrolysis reaction in flow mode, use of a short inter-electrode distance in the flow cell allows the reaction to be carried out in the absence of supporting electrolyte,[211,212,213] facilitating analysis and product isolation. Additionally, an increasing number of examples have arisen where synthetically useful electrochemical transformations are performed under a constant-current regime, simplifying the equipment required. In these cases a commercial power supply is commonly employed, though there are reports where the power source is a battery,[214,215] a mobile phone charger,[216] or photovoltaic cells.[217,218]

The Achmatowicz reaction consists of the oxidative conversion of a furfuryl alcohol to the corresponding hydroxypyrone (Scheme 96); this and analogous oxidative rearrangements of

furans have been widely utilised in natural product synthesis. In the original report, bromine in methanol was used to form dimethoxy dihydrofuran derivatives **430** which, upon acid treatment, rearranged to hydroxypyrones **431**.[219] Since then, a number of methods to effect this transformation have emerged, including: pyridinium chlorochromate,[220] *N*-bromosuccinimide,[221] peroxy acids,[222,223] dimethyldioxirane,[224] *t*-butyl hydroperoxide / vanadyl acetonylacetonate,[225] singlet oxygen followed by hydrolysis,[226] and more recently biocatalytic methods.[207,208]



429 **430** **431**

Scheme 96. Synthesis of hydroxypyrones **431** by Achmatowicz.

Interestingly, the generation of 2,5-dimethoxy dihydrofurans **430** *via* anodic oxidation (but not the subsequent acid-mediated rearrangement to hydroxypyrones) had been reported almost 20 years before the publication of Achmatowicz's study.[227,228] The mechanism of the anodic oxidation of furans in methanol is depicted in Figure 39:[229] radical cation **433**, formed by one-electron oxidation of the furan at the anode, is attacked by a molecule of solvent to give, after deprotonation, radical **434**. Another one-electron oxidation forms cation **435**, which leads to product **436** after capture of another molecule of solvent and deprotonation. At the cathode, methanol is reduced to form methoxide and hydrogen gas. 2,5-Dimethoxy dihydrofurans generated *via* anodic oxidation have been employed in Achmatowicz reactions by Shono *et al*.[230] and by Torii *et al*.;[231] to date, however, this remains an underexplored way of effecting the reaction.

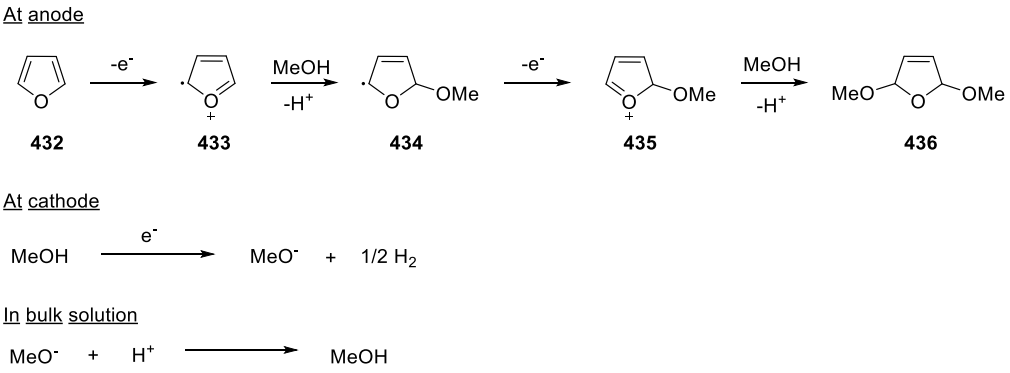


Figure 39. Mechanism for the anodic oxidation of furan in methanol.

Aiming at the long-term objective of electrochemical dimethoxylation of the furanoid eleuthoside scaffold, we wished to develop a flow method for the anodic oxidation of furfuryl alcohol derivatives under a constant current regime, employing a power supply as the source of electricity. As the dimethoxylated derivatives formed were expected to undergo rearrangement under acidic conditions, this would also provide a useful alternative method for accessing substituted hydroxypyrones.

Construction of the flow cell

The work described in this chapter stems from a short placement in the Institute of Microelectronics of Barcelona, where the electrochemical flow cell used for the development of the anodic oxidation methodology was constructed under the supervision of Dr. Javier del Campo. A starting point was identified in work by Atobe *et al*., who reported the preparation of a flow cell for the anodic oxidation of furan to 2,5-dimethoxy dihydrofuran;[232] most importantly, this informed our choice of optimal electrode materials.

The cell is built from two electrode holders (Figure 40a, d) composed of polyether ether ketone (PEEK), a plastic characterised by excellent chemical and mechanical resistance properties. These were carved out of a slab of PEEK using a Roland MDX-40 desktop milling machine;

the high mechanical resistance of PEEK made laser cutting, a considerably faster technique, impossible. Each holder features a socket within which the electrode is embedded using Araldite® epoxy resin. Three ports were drilled in this socket to accommodate three spring-loaded pins for electrical connection (e); on the opposite side of the cell a straight socket was carved to facilitate cable connection (f). The top holder is also equipped with threaded ports acting as fluidic inlet and outlet (g, h); finally, the two parts are held together using 10 M2 screws.

Following the study by Atobe *et al*., glassy carbon was chosen as the anode material and platinum as the cathode (b, c). After attachment to their respective holders, these were polished flush to a mirror finish.

Between the cells is placed a gasket which delineates the channel the solution flows through (i). The shape employed was chosen to maximise utilisation of electrode surface; the suitability of its microfluidic properties (that is, lack of bubble formation) was verified by visual inspection of a prototype using PMMA holders (rapidly prepared *via* laser cutting and transparent to allow inspection). The gaskets were cut from sheets of the material employed using a Roland GX-24 CAMM cutter plotter. Gaskets of different thickness (25–100 μm) and material composition (PEEK, PTFE, FEP, Kapton) were employed.

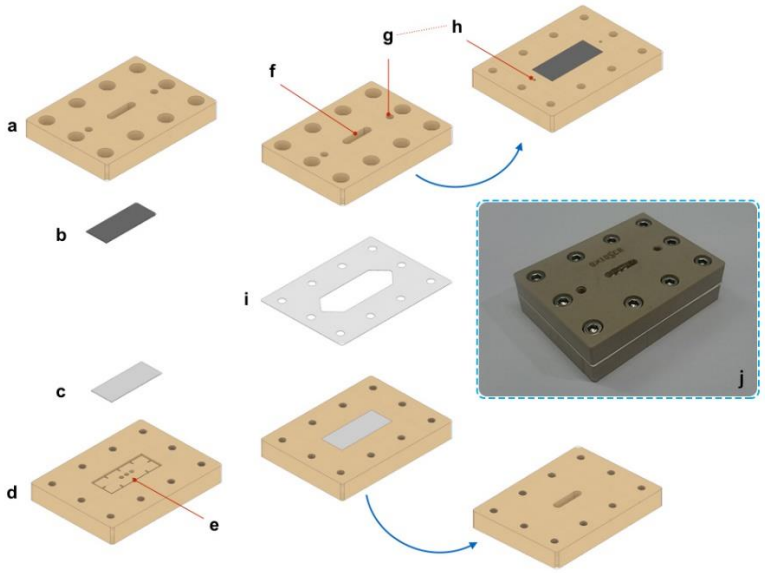
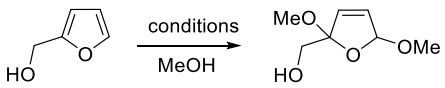


Figure 40. Outline (a–i) and photo (j) of the flow cell; see text for description.

Anodic oxidation of furfuryl alcohols in flow

With the flow cell in hand, anodic oxidation of a 20 mM methanol solution of furfuryl alcohol was attempted, using a Keithley 2200-72-1 programmable power supply as the power source. Conversion was determined by GC analysis of the electrolysis mixture. Initial runs in the absence of supporting electrolyte gave inconsistent results, with solution conductivity often being too low, preventing useful current densities from being reached. In the report by Atobe *et al*. no supporting electrolyte was necessary due to the short interelectrode distance, however in our case using a 25 μm thin gasket did not provide any improvement. Pleasingly, it was found that adding a trace (1–2 crystals) of $NaClO_4$ to the substrate solution considerably increased conductivity, restoring reproducibility between subsequent runs. As can be seen in Table 11, increasing the current density (calculated as the current supplied divided by the electrode area) to 5.8 mA/cm^2 allowed a conversion of 78% to be achieved; further increases did not provide a benefit. A flow rate of 165 μL/min was deemed optimal; decreasing it to 118 μL/min provided only a small improvement in conversion.



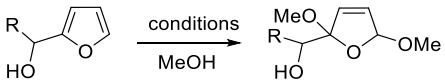
237 **437**

Entry	Potential (V)	Current density (mA/cm^2)	Flow (μL/min)	Conversion (%)
1	2.6	2.9	330	22
2	3.4	8.0	330	65
3	2.7	5.8	330	46
4	3.3	5.8	165	78
5	3.9	5.8	118	80
6	4.1	6.8	165	79

Table 11. Optimisation of anodic dimethoxylation of furfuryl alcohol.

Having identified optimal conditions for the electrolysis, a substrate screen was initiated to test the method's tolerance for common chemical functionalities. The examples in Table 12 show that alkyl chains, alkene and alkyne groups (entries 1–3) are tolerated. Phenyl groups, as in furan derivative **441** (entry 4), do not interfere with complete consumption of starting material; however, in the case of substrate **441** significant decomposition occurred (proposed to proceed as indicated in Figure 41 due to the presence of benzaldehyde in the crude reaction mixture), leading to a low isolated yield. Siting the phenyl ring further away from the furan, that is, as a benzyl substituent (entry 5), was sufficient to restore the desired reactivity.

Finally, it was decided to explore the possibility of capturing the generated radical carbocation with a pendant alcohol; such intramolecular reactions of electrochemically generated carbocations have been reported.[233,234,235,236,237,238,239,240] Alcohol **443** was employed for this purpose (entry 6); electrolysis provided a nearly equimolar mixture of dimethoxylated product **450** and spirocycle **449**. GC analysis was found to be misleading in this case, as compound **450** was converted into spirocycle **449** upon vapourisation. The same was true when **450** was left to stand in a $CDCl_3$ solution, in which case clean conversion to **449** was observed.



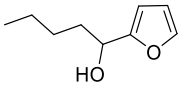
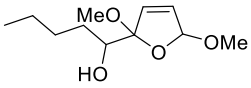
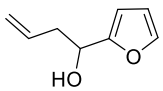
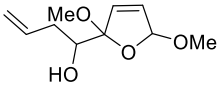
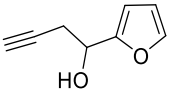
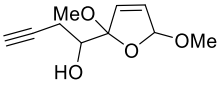
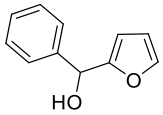
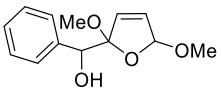
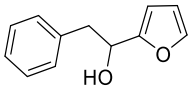
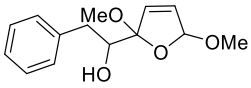
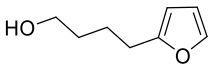
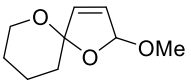
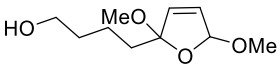
Entry	Substrate	Product	Conversion (%)	Isolated yield (%)
1	 **438**	 **444**	82	66
2	 **439**	 **445**	84	71
3	 **440**	 **446**	79	54
4	 **441**	 **447**	100	24
5	 **442**	 **448**	100	57
6	 **443**	 **449** +  **450**	100	29 + 23

Table 12. Investigation of scope of flow anodic dimethoxylation.

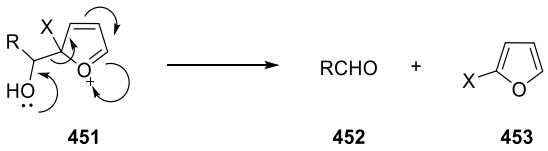
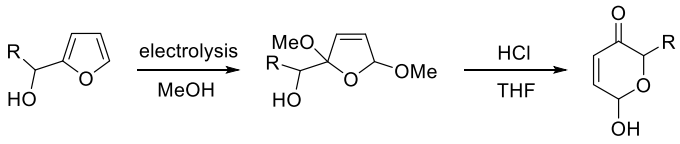


Figure 41. Proposed mechanism for the decomposition of furfuryl alcohol under the electrolysis conditions. X = MeO- or radical.

Although electrochemical synthetic methods can be considered "green" by virtue of their reagentless nature, it is important to bear in mind that generation of the electricity utilised does have an environmental impact; therefore, the current efficiency (defined as the fraction of the supplied current that is consumed to drive the transformation) of such a process is an important factor. In our process this was found to be 50–60% depending on the substrate, a significant improvement over the <10% efficiency reported by Atobe *et al*.; loss of efficiency is attributed to oxidation of the solvent to formaldehyde or formic acid.

Achmatowicz reaction *via* anodic oxidation

As anticipated, when the crude electrolysis mixtures of **438**–**442** were treated with aqueous HCl (after evaporation of solvent and redissolution in THF) hydroxypyrones **454**–**458** were formed in good to moderate yields (Table **13**), with the exception of **457** due to the aforementioned decomposition observed in the electrolysis step.



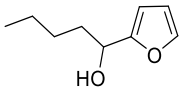
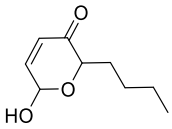
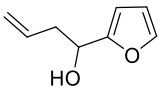
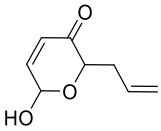
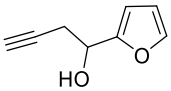
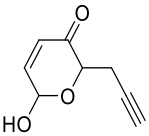
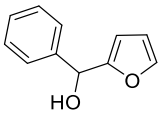
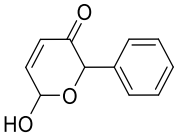
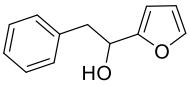
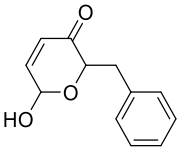
Entry	Substrate	Product	Isolated yield (%)
1	 **438**	 **454**	62
2	 **439**	 **455**	69
3	 **440**	 **456**	31
4	 **441**	 **457**	17
5	 **442**	 **458**	32

Table 13. Acid mediated rearrangement of electrochemically generated dihydro-dimethoxyfurans.

The ease with which derivatives **444**–**448** rearranged under acidic conditions led us to consider the possibility of incorporating an acidic treatment step in the flow process to obtain the hydroxypyrone derivative directly. An attractive possibility presented itself in the work of Shono,[230] who effected this rearrangement in batch mode by stirring alkyl dimethoxy dihydrofurans with acidic Dowex 50 ion exchange resin. However, passage of the electrolysis mixture of furan **438**, after addition of water, through a short column of Dowex 50W-X8 led

to a complex mixture of products, a result that was not improved by varying the amount of Dowex or the contact time. It is possible that, in contrast to the batch example, strongly acidic sulfonic resins are not suited for effecting this transformation in flow, and alternatives will need to be investigated in future studies.

Conclusions and future studies

In conclusion, an electrochemical flow cell has been constructed and used for the anodic oxidation of furfuryl alcohols in flow; the dimethoxylated derivatives thus formed can give hydroxypyrones, products of a formal Achmatowicz reaction of the starting alcohols, in synthetically useful isolated yields. An example with a pendant alcohol demonstrates that intramolecular capture of the formed radical cation is possible and can be useful for the synthesis of spirocyclic structures. Future studies will also aim to translate the final acid treatment step into a flow modality so that it can be performed in series after the electrolysis.

Experimental Section

General Experimental

All reactions were carried out under an atmosphere of dry argon in oven-dried glassware unless otherwise stated. Solvents were either used as commercially supplied or as purified by standard techniques. Tetrahydrofuran was freshly distilled over Na and benzophenone prior to use. DCM, DMF and DME were obtained from an MBraun 5 solvent purification system. 18-crown-6 was dried by stirring under high vacuum. TMSOK was dried by heating to 100 °C under high vacuum. $CeCl_3$ was dried by heating under high vacuum, first at 90 °C then at 140 °C. All other reagents were used as obtained from the supplier unless otherwise stated. Petrol refers to the fraction of light petroleum ether boiling at 30–40 °C. Ether refers to diethyl ether. Brine refers to a saturated aqueous solution of NaCl.

Thin-layer chromatography was performed on Merck DC-Alufolien 60 F254 0.2 mm pre-coated plates with reaction progress visualised using basic $KMnO_4$ dip, acidic anisaldehyde dip, or ultraviolet light. Retention factors (R_f) are quoted with the solvent system in parentheses. Column chromatography was performed on Merck Geduran® 60 SiO_2 (40–63 μm) and the solvent system is recorded in parentheses.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Bruker AVIII600 (600/150 MHz), Bruker AVII500 (500/125 MHz), Bruker AVIII400 (400/100 MHz), Bruker AV400 (400/100 MHz), or Bruker DPX-200 (200/50 MHz). Proton and carbon chemical shifts (δ_H, δ_C) are quoted in ppm with residual protiated solvent as the internal standard and referenced to tetramethylsilane unless otherwise stated. Assignments were made on the basis of chemical shifts, coupling constants, COSY, NOESY, HSQC, and HMBC data, and by comparison with spectra of related compounds. Coupling constants are rounded to the nearest 0.5 Hz. For known compounds, ^1H (and where available, ^{13}C) spectroscopic data were found to be in good agreement with the literature. The *E*- or *Z*- geometry of trisubstituted alkenes was determined,

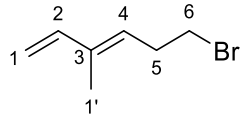
for known compounds, by comparison with literature data, and in subsequent compounds assumed to remain the same. For novel compounds, it was inferred from the stereochemistry of precursors, and from comparison of spectroscopic data with that of known compounds. Atom numbering reflects NMR peak assignments and does not necessarily correspond to IUPAC nomenclature.

Low resolution mass spectra were recorded on a Micromass LCT Premier spectrometer (ES) with values reported in Daltons. High resolution mass spectra were recorded by the Mass Spectrometry service of the Chemistry Research Laboratory, University of Oxford, using a Bruker microTOF Spectrometer. High resolution values are calculated to 4 decimal places from the chemical formula with all found values being within a tolerance of 5 ppm. Gas chromatographic analysis was performed on a Thermo Finnigan TRACE gas chromatograph equipped with a flame ionisation detector (FID) and an AS3000 autosampler on a DB-1 capillary GC column (30 m × 0.25 mm i.d. × 0.25 μm film thickness). The injector temperature was 280 °C and the FID was at 250 °C. Chiral GC measurements were conducted on an HP6890 (H_2 as vector gas) or HP6850 (H_2 as vector gas) with a Lipodex® E column.

Infrared spectra were recorded on a Bruker Tensor 27 Fourier transform spectrometer as a thin film on a diamond ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and identified as strong (s), medium (m), or weak (w) as a measure of peak intensity. Melting points were recorded on a Griffin melting point apparatus. Specific rotations were determined using a Perkin-Elmer 241 polarimeter at a wavelength 589 nm and at 25 °C, and are quoted in units of 10^{-1} deg cm^2 g^{-1}; concentrations (*c*) are expressed in g/100 mL.

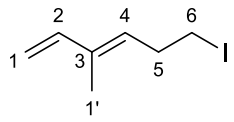
Data for Chapter 2

(*E*)-6-Bromo-3-methylhexa-1,3-diene (182)[92]



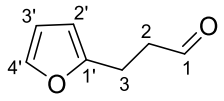
To a solution of cyclopropyl methyl ketone (1.0 g, 1.20 mL, 11.9 mmol) in THF (12 mL) was added vinylmagnesium bromide (13.1 mL, 1.0 M solution in THF, 13.1 mmol) at −10 °C. The reaction mixture was allowed to warm to RT and stirred for 1 h, then quenched with satd. aq. NH_4Cl solution (15 mL) and extracted with ether (3 × 15 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The obtained crude 2-cyclopropylbut-3-en-2-ol (1.19 g) was dissolved in petrol / water (1:3, 5 mL), and aqueous HBr 48% (7.1 mL, 63.0 mmol) was added at 0 °C over 5 min. After 1 h, water (15 mL) was added to the reaction mixture, which was then extracted with petrol (3 × 15 mL). The combined organic layers were washed with satd. aq. $NaHCO_3$ solution (30 mL) then brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by flash chromatography (petrol) gave the title compound as a mixture of the *E*- and *Z*- isomers (3:1 *E*:*Z*, 547 mg, 30% over two steps; isomer ratio determined by integration of the C(2)H signal in the ^{1}H NMR spectrum). R_f 0.69 (petrol); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.77 (3H, s, C(1')H_3), 2.67 – 2.82 (2H, m, C(5)H_2), 3.34 – 3.45 (2H, m, C(6)H_2), 5.03 (1H, d, *J* = 10.5 Hz, C(1)H), 5.18 (1H, d, *J* = 17.0 Hz, C(1)H), 5.48 (1H, t, *J* = 7.0 Hz, C(4)H), 6.38 (1H, dd, *J* = 17.0, 10.5 Hz, C(2)H). *Diagnostic signals for minor isomer:* ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.85 (3H, br s, C(1')H_3), 5.28 (1H, d, *J* = 17.5 Hz, C(1)H), 5.38 (1H, t, *J* = 7.5 Hz, C(4)H), 6.72 (1H, ddd, *J* = 17.5, 11.0, 1.0 Hz, C(2)H).

(*E*)-6-Iodo-3-methylhexa-1,3-diene (178)[92]



To a stirred solution of bromide **182** (3:1 *E*:*Z*, 547 mg, 3.13 mmol) in acetone (13 mL) was added NaI (1.41 g, 9.39 mmol), and the reaction mixture was heated to reflux for 1 h. After cooling to RT, aq. $Na_2S_2O_3$ solution (1.0 M, 5.0 mL) was added and the reaction mixture was extracted with DCM (3 × 15 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was filtered through a pad of silica gel using DCM as the eluent to give the title compound as a mixture of the *E*- and *Z*- isomers (3:1 *E*:*Z*, 502 mg, 73%; isomer ratio determined by integration of the C(2)H signal in the ^{1}H NMR spectrum). ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.76 (3H, s, C(1')H_3), 2.70 – 2.82 (2H, m, C(5)H_2), 3.10 – 3.22 (2H, m, C(6)H_2), 5.04 (1H, d, *J* = 10.5 Hz) and 5.18 (1H, d, *J* = 17.5 Hz, C(1)H_2), 5.44 (1H, t, *J* = 7.0 Hz, C(4)H), 6.38 (1H, dd, *J* = 17.5, 10.5 Hz, C(2)H). *Diagnostic signals for minor isomer:* ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.83 (3H, br s, C(1')H_3), 5.28 (1H, d, *J* = 17.5 Hz, C(1)H), 5.34 (1H, t, *J* = 8.0 Hz, C(4)H), 6.70 (1H, ddd, *J* = 17.5, 11.0, 1.0 Hz, C(2)H).

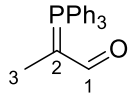
3-(Furan-2-yl)propanal (186)[93]



Zinc dust (2.00 g, 30.6 mmol) was added to a stirred solution of Cp_2TiCl_2 (152 mg, 0.61 mmol) and NEt_3·HCl (8.46 g, 61.4 mmol) in degassed DCM (240 mL) at RT. When the mixture changed in colour from dark red to yellow (after 5 min) 3-(2-furyl)acrolein (1.50 g, 12.3 mmol) was added and stirring was continued for 1 h. The reaction was then quenched with satd. aq.

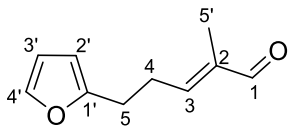
NH_4Cl solution (100 mL), filtered through celite, the layers separated and the aqueous layer extracted with DCM (3 × 150 mL). The combined organic layers were then washed with brine (200 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 9:1) to give the title compound as a yellow oil (461 mg, 30%). R_f 0.29 (petrol / ether, 8:2); ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 2.81 (2H, t, *J* = 7.0 Hz, C(2)H_2), 2.99 (2H, t, *J* = 7.0 Hz, C(3)H_2), 6.03 (1H, dd, *J* = 3.0, 1.0 Hz, C(2')H), 6.29 (1H, dd, *J* = 3.0, 2.0 Hz, C(3')H), 7.31 (1H, d, *J* = 2.0, 1.0 Hz, C(4')H), 9.83 (1H, t, *J* = 1.5 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 20.6 (C(3)), 41.8 (C(2)), 105.4 (C(2')), 110.2 (C(3')), 141.2 (C(4')), 153.8 (C(1')), 200.9 (C(1)).

2-(Triphenylphosphoranylidene)propanal (187)[95]



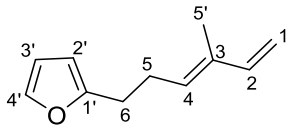
To a stirred suspension of NaH (60% dispersion in mineral oil, 324 mg, 8.1 mmol) in THF (8 mL) was added ethyltriphenylphosphonium bromide (1.0 g, 2.7 mmol). The mixture was stirred for 18 h at RT, then ethyl formate (540 μL, 6.6 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 2 h then at RT for 2 h. It was then quenched with HCl (1.0 M aqueous solution, 8 mL), and NaOH (1.0 M aqueous solution) was added until pH = 8. The mixture was then extracted with DCM (3 × 10 mL), the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to give the crude title compound as an off-white solid (740 mg, 86%) which was used in the next reaction with no further purification. ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 1.87 (3H, d, *J* = 13.5 Hz, C(3)H_3), 7.40 – 7.78 (15H, m, PPh_3), 8.06 (1H, d, *J* = 5.0 Hz, C(1)H).

(*E*)-5-(Furan-2-yl)-2-methylpent-2-enal (188)



A mixture of aldehyde **186** (510 mg, 4.11 mmol) and phosphorane **187** (3.15 g, 9.86 mmol) in toluene (20 mL) was heated to 80 °C for 18 h. The solvent was then removed *in vacuo*, the resulting residue triturated with ether (30 mL) and filtered through celite. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography (petrol / ether, 9:1) to give the *title compound* as a yellow oil (392 mg, 58%). *E*- stereochemistry was inferred based on literature precedent for Wittig reactions with phosphorane **187**.[95] R_f 0.31 (petrol / ether, 8:2); ν_{max} (thin film) 2923m, 2824m, 2715m, 1683s, 1645m, 1507m, 1150m, 1008m, 733m; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.72 (3H, s, C(5')H_3), 2.70 (2H, q, *J* = 7.5 Hz, C(4)H_2), 2.84 (2H, t, *J* = 7.5 Hz, C(5)H_2), 6.02 (1H, d, *J* = 3.0 Hz, C(2')H), 6.29 (1H, dd, *J* = 3.0, 2.0 Hz, C(3')H), 6.49 (1H, td, *J* = 7.5, 1.0 Hz, C(3)H), 7.31 – 7.33 (1H, m, C(4')H), 9.39 (1H, s, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 9.1 (C(5')), 26.6 (C(5)), 27.4 (C(4)), 105.6 (C(2')), 110.2 (C(3')), 140.0 (C(2)), 141.3 (C(4')), 152.5 (C(3)), 154.2 (C(1')), 195.1 (C(1)); HRMS (ESI^+) found 187.0733, $C_{10}H_{12}NaO_2$ $[MNa]^+$ requires 187.0730.

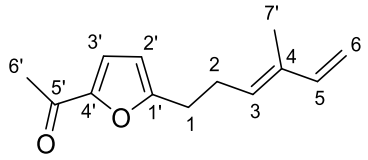
(*E*)-2-(4-Methylhexa-3,5-dien-1-yl)furan (184)



LiHMDS (1.0 M solution in THF, 2.30 mL, 2.30 mmol) was added to a suspension of methyltriphenylphosphonium iodide (1.01 g, 2.48 mmol) in THF (10 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 30 min, then cooled to −78 °C and a solution of aldehyde **188** in THF (3 mL) added dropwise. The reaction mixture was stirred for 5 min at

−78 °C then warmed to RT. After 3 h water (15 mL) was added and the reaction mixture was extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol) to give the *title compound* as a yellow oil (264 mg, quantitative). R_f 0.73 (petrol / ether, 8:2); ν_{max} (thin film) 2920m, 2855w, 1607m, 1597m, 1507m, 1438m, 1150m, 1078m, 1011m, 990s, 895s, 798m, 728s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.74 (3H, s, C(5')H_3), 2.50 (2H, q, *J* = 7.5 Hz, C(5)H_2), 2.73 (2H, t, *J* = 7.5 Hz, C(6)H_2), 4.96 (1H, d, *J* = 10.5 Hz, C(1)H), 5.11 (1H, d, *J* = 17.5 Hz, C(1)H), 5.52 (1H, t, *J* = 7.5 Hz, C(4)H), 6.01 (1H, d, *J* = 3.0 Hz, C(2')H), 6.29 (1H, dd, *J* = 3.0, 2.0 Hz, C(3')H), 6.38 (1H, dd, *J* = 17.5, 10.5 Hz, C(2)H), 7.32 (1H, d, *J* = 2.0 Hz, C(4')H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.6 (C(5')), 26.8 (C(5)), 27.8 (C(6)), 105.0 (C(2')), 110.1 (C(3')), 110.9 (C(1)), 131.4 (C(4)), 134.8 (C(3)), 140.9 (C(4')), 141.3 (C(2)), 155.6 (C(1')); HRMS (ESI$^+$) found 162.1049, $C_{11}H_{14}O$ $[MH]^+$ requires 162.1045.

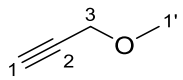
(*E*)-1-[5-(4-Methylhexa-3,5-dien-1-yl)furan-2-yl]ethan-1-one (177)



Diene **184** (241 mg, 1.49 mmol) was dissolved in THF (8mL). To this solution was added dropwise at −78 °C, *t*-BuLi (1.7 M solution in pentane, 1.3 mL, 2.24 mmol) and the reaction mixture was stirred at the same temperature for 2 h. After this period, *N*-methoxy-*N*-methylacetamide (307 mg, 2.98 mmol) was added as a solution in THF (1 mL), and the reaction mixture was stirred at RT for 18 h. The reaction was then quenched with brine (10 mL), extracted with ether (3 × 10 mL), the organic layers combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol

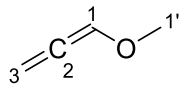
→ petrol / ether 85:15) to give the *title compound* as a yellow oil (101 mg, 33%, 94% b.r.s.m.). R_f 0.11 (petrol / ether, 9:1); ν_{max} (thin film) 2924br, 2251w, 1671s, 1515s, 1433s, 909s, 732s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.73 (3H, s, C(7')H_3), 2.44 (3H, s, C(6')H_3), 2.55 (2H, q, *J* = 7.5 Hz, C(2)H_2), 2.80 (2H, t, *J* = 7.5 Hz, C(1)H_2), 4.97 (1H, d, *J* = 10.5 Hz, C(6)H), 5.12 (1H, d, *J* = 17.5 Hz, C(6)H), 5.48 (1H, t, *J* = 7.5 Hz, C(3)H), 6.18 (1H, d, *J* = 3.5 Hz, C(2')H), 6.35 (1H, dd, *J* = 17.5, 10.5 Hz, C(5)H), 7.11 (1H, d, *J* = 3.5 Hz, C(3')H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.7 (C(7')), 25.7 (C(6')), 26.4 (C(2)), 28.2 (C(1)), 108.5 (C(2')), 111.4 (C(6)), 119.1 (C(3')), 130.4 (C(3)), 135.4 (C(4)), 141.1 (C(5)), 151.6 (C(1')), 161.1 (C(4')), 186.2 (C(5')); HRMS (ESI$^+$) found 205.1220, $C_{13}H_{17}O_2$ $[MH]^+$ requires 205.1223.

3-Methoxyprop-1-yne (197)[103]



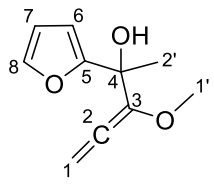
To a mixture of prop-2-yn-1-ol (20 g, 21 mL, 357 mmol) and water (25 mL) was added NaOH aqueous solution (25 M, 40 mL, 536 mmol). The temperature of the reaction mixture was kept below 50 °C while dimethyl sulphate (20 mL, 214 mmol) was added dropwise; the reaction mixture was then heated to 60 °C for 2 h, then placed in a separatory funnel and the layers separated. The organic layer was distilled (62 °C at 760 mmHg) to give the title compound, which was then passed through a plug of $MgSO_4$ to remove traces of water (colourless oil, 6.7 g, 45%). ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 2.45 (1H, t, *J* = 2.5 Hz, C(1)H), 3.40 (3H, s, C(1')H_3), 4.11 (2H, d, *J* = 2.5 Hz, C(3)H_2); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 57.4 (C(1')), 59.4 (C(3)), 74.4 (C(1)), 79.4 (C(2)).

1-Methoxypropa-1,2-diene (198)[101]



*t*BuOK (3.2 g, 28.6 mmol) was added to 3-methoxy-propyne **197** (2 g, 28.6 mmol) and the mixture was heated to reflux. After 2 h the reflux condenser was swapped for a distillation head and the product distilled (52°C at 760 mmHg) to give the pure title compound as a colourless oil (900 mg, 45%). ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 3.42 (3H, s, C(1')H_3), 5.49 (2H, *J* = 6.0 Hz, C(3)H_2), 6.78 (1H, t, *J* = 6.0 Hz, C(1)H).

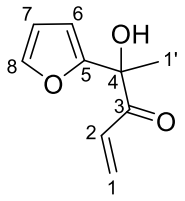
2-(Furan-2-yl)-3-methoxypenta-3,4-dien-2-ol (199)



To a solution of allene **198** (200 mg, 2.86 mmol) in THF (2 mL) and at −78°C was added *n*-BuLi (2.5M solution in hexane, 1.3 mL, 3.15 mmol). The reaction mixture was stirred at the same temperature for 30 min, then 2-acetylfuran (314 mg, 2.86 mmol) was added as a solution in THF (1 mL). After 3 h the reaction was quenched with phosphate buffer (pH 7, 5 mL), extracted with ether (3 × 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 8:2) to give the *title compound* as a yellow oil (390 mg, 76%). R_f 0.43 (petrol / ethyl acetate, 8:2); ν_{max} (thin film) 3440br, 2957m, 2937m, 1957w, 1462m, 1343m, 1157s, 1011s, 908s, 733s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.65 (3H, s, C(2')H_3), 3.45 (3H, s, C(1')H_3), 5.62 (2H, s, C(1)H_2), 6.27 (1H, dd, *J* = 3.5, 1.0 Hz, C(6)H), 6.31 (1H, dd, *J* = 3.5, 2.0 Hz, C(7)H), 7.35 (1H, dd, *J* = 2.0, 1.0 Hz, C(8)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 24.9 (C(2')), 56.7

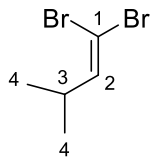
(C(1')H_3), 70.7 (C(4)), 93.6 (C(1)H_2), 105.7 (C(6)H), 110.0 (C(7)H), 137.4 (C(3)), 141.7 (C(8)H), 157.3 (C(5)), 196.1 (C(2)); HRMS (ESI^+) found 203.0678, $C_{10}H_{12}NaO_3$ $[MNa]^+$ requires 203.0679.

4-(Furan-2-yl)-4-hydroxypent-1-en-3-one (200)



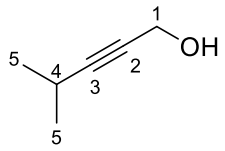
To allene **199** (50 mg, 0.3 mmol) dissolved in THF (1 mL) was added H_2SO_4 (20% w/w aqueous solution, 130 μL, 0.3 mmol) and the reaction mixture was stirred for 15 min at RT. Water (3 mL) was then added, the mixture extracted with ether (3 × 10 mL), and the combined organic layers washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 8:2) to give the *title compound* as a yellow oil (27 mg, 54%). R_f 0.43 (petrol / ethyl acetate, 8:2); ν_{max} (thin film) 3460br, 2986w, 2937w, 1698s, 1612m, 1404m, 1359m, 1157m, 1110m, 1040s, 1014s, 985m, 743s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.73 (3H, s, C(1')H_3), 4.58 (1H, br s, C(4)OH), 5.81 (1H, dd, *J* = 9.5, 2.5 Hz, C(1)H), 6.38 (1H, dd, *J* = 3.5, 2.0 Hz, C(7)H), 6.43 (1H, dd, *J* = 3.5, 1.0 Hz, C(6)H), 6.52 (1H, dd, *J* = 17.0, 2.5 Hz, C(1)H), 6.58 (1H, dd, *J* = 17.0, 9.5 Hz, C(2)H), 7.40 (1H, dd, *J* = 2.0, 1.0 Hz, C(8)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 22.9 (C(1')), 75.5 (C(4)), 108.0 (C(6)), 110.7 (C(7)), 129.0 (C(2)), 131.6 (C(1)), 143.1 (C(8)), 153.7 (C(5)), 197.6 (C(3)); HRMS (ESI^+) found 189.0522, $C_9H_{10}NaO_3$ $[MNa]^+$ requires 189.0522.

1,1-Dibromo-3-methylbut-1-ene (208)[104]



To a cooled (0 °C) solution of isobutyraldehyde (3.8 mL, 3.0 g, 41.7 mmol) and triphenylphosphine (43.7 g, 167.0 mmol) in DCM (100 mL) was added CBr_4 (27.8 g, 83.4 mmol) in small portions. After stirring at 0 °C for 10 min, the reaction mixture was washed with satd. aq. $NaHCO_3$ solution (100 mL) then water (100 mL), dried over $MgSO_4$ and concentrated. Ether / pentane (1:1, 300mL) was added, and the mixture filtered through celite. The filtrate was concentrated *in vacuo* and then distilled under vacuum (65°C at 32 mmHg) to give the title compound as a colourless oil (5.5 g, 58%). ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 1.03 (6H, d, J = 6.5 Hz, C(4)H_3), 2.41 – 2.76 (1H, m, C(3)H), 6.22 (1H, d, J = 9.0 Hz, C(2)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 21.2 (C(4)), 33.1 (C(3)), 86.9 (C(1)), 145.1 (C(2)).

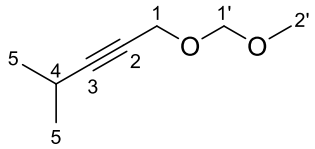
4-Methylpent-2-yn-1-ol (209)[104]



To a solution of dibromide **208** (3.7 g, 16.6 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M solution in hexane, 13.3 mL, 33.2 mmol) dropwise at −78°C. The reaction mixture was stirred at the same temperature for 1 h, then a suspension of paraformaldehyde (1 g, 33.2 mmol) in THF (20 mL) was added *via* cannula. The reaction mixture was stirred for 10 min at −78°C and for 30 min at RT. The reaction was then quenched with brine (50 mL), extracted with ether (3 × 50 mL), and the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 9:1) to give

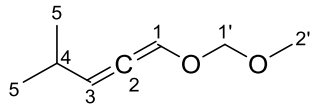
the title compound as a colourless oil (2.7 g, quantitative). R_f 0.27 (petrol / ethyl acetate, 9:1); ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 1.15 (6H, d, *J* = 7.0 Hz, C(5)H_3), 2.48 – 2.65 (1H, m, C(4)H), 4.23 (2H, s, C(1)H_2), 5.29 (1H, s, C(1)H_2O*H*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 20.4 (C(4)), 22.8 (C(5)), 51.2 (C(1)), 77.5 (C(2)), 91.8 (C(3)).

1-(Methoxymethoxy)-4-methylpent-2-yne (202)



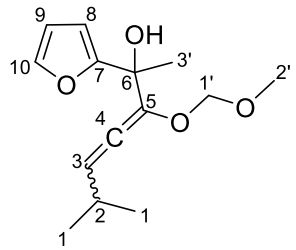
To a solution of alkyne **209** (1.5 g, 15.3 mmol) and *N*,*N*-Diisopropylethylamine (8 mL, 45.9 mmol) in DCM (100 mL) at −10 °C was added dropwise chloromethyl methylether (2.4 mL, 30.6 mmol). The reaction mixture was then allowed to warm to RT and stirred for 18 h. Water was then added (100 mL), the layers separated and the aqueous layer extracted with DCM (3 × 80 mL). The combined organic layers were then washed with HCl (5% aqueous solution, 150 mL), satd. aq. $NaHCO_3$ solution (150 mL), water (150 mL) and brine (150 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude proudct was purified by flash chromatography (petrol / ether, 9:1) to give the *title compound* as a colourless oil (1.6 g, 74%). R_f 0.80 (petrol / ethyl acetate, 7:3); ν_{max} (thin film) 2970m, 2934m, 2886m, 1465m, 1376m, 1362m, 1320m, 1185s, 1101s, 1038s, 990s, 922s; δ_H (400 MHz, $CDCl_3$) 1.16 (6H, d, *J* = 7.0 Hz, C(5)H_3), 2.49 – 2.65 (1H, m, C(4)H), 3.37 (3H, s, C(2')H3), 4.19 (2H, d, *J* = 2.0 Hz, C(1)H_2), 4.69 (2H, s, C(1')H_2); δ_C (100 MHz, $CDCl_3$) 20.5 (C(4)), 22.8 (C(5)), 54.7 (C(1)), 55.4 (C(2')), 74.4 (C(2)), 92.4 (C(3)), 94.6 (C(1')); HRMS failed due to sample evaporating in the vacuum lock before introduction into the Mass Spectrometer.

1-(Methoxymethoxy)-4-methylpenta-1,2-diene (203)



Alkyne **202** (300 mg, 2.1 mmol) was dissolved in THF (4 mL), then *n*-BuLi (2.5 M solution in hexanes, 1.3 mL, 3.2 mmol) was added dropwise at −78 °C. The reaction mixture was stirred at the same temperature for 2 h, then quenched by addition of phosphate buffer (pH 7, 5 mL), extracted with petrol (3 × 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The crude mixture was purified by column chromatography on basic alumina (petrol) to give the title compound, after removal of the petrol by distillation, as a yellow oil (180 mg, 60%). R_f 0.63 (petrol / ethyl acetate, 9:1); ν_{max} (thin film) 2960s, 2932s, 2871m, 2825m, 1959m, 1466m, 1423m, 1153s, 1023s, 924s; ^{1}H NMR δ_H (400MHz, C_6D_6) 0.94 (3H, d, *J* = 7.0 Hz, C(5)H_3), 0.96 (3H, d, *J* = 7.0 Hz, C(5)H_3), 2.09 – 2.29 (1H, m, C(4)H), 3.16 (3H, s, C(2')H_3), 4.62 (1H, d, *J* = 6.0 Hz, C(1')H_2), 4.68 (1H, d, *J* = 6.0 Hz, C(1')H_2), 5.72 (1H, t, *J* = 5.5 Hz, C(3)H), 6.64 (1H, dd, *J* = 5.5, 2.5 Hz, C(1)H); ^{13}C NMR δ_C (100MHz, C_6D_6) 21.9 and 21.9 (C(5)), 30.1 (C(4)), 55.6 (C(2')), 94.8 (C(1')), 113.1 (C(3)), 119.6 (C(1)), 192.3 (C(2)); HRMS (FI^+) found 142.0995, $C_8H_{14}O_2$ $[M]^+$ requires 142.0994.

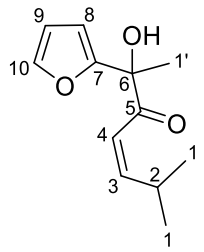
2-(Furan-2-yl)-3-(methoxymethoxy)-6-methylhepta-3,4-dien-2-ol (210)



Allene **203** (500 mg, 3.5 mmol) was dissolved in THF (4 mL). *n*BuLi (2.5 M in hexane, 1.25 mL, 3.15 mmol) was then added dropwise at −78 °C, the reaction mixture stirred for 30 min at this temperature, then for 30 min at 0 °C. After being cooled again to −78 °C, 2-acetylfuran

(129 mg, 1.17 mmol) dissolved in THF (2 mL) was added dropwise. After 3 h at −78 °C, the reaction was quenched with phosphate buffer (pH 7, 5 mL) and extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 8:2) to give the *title compound* as a yellow oil (212 mg, 72%). R_f 0.19 (petrol / ether, 8:2); ν_{max} (thin film) 3448br, 2961m, 2871m, 1964m, 1421m, 1365m, 1321m, 1154s, 1054s, 733s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$, major isomer) 1.02 – 1.06 (6H, m, C(1)H_3), 1.68 (3H, s, C(3')H_3), 2.33 – 2.45 (1H, m, C(2)H), 3.31 (3H, s, C(2')H_3), 4.79 – 4.86 (2H, m, C(1')H_2), 6.03 (1H, d, *J* = 5.5 Hz, C(3)H), 6.28 – 6.36 (2H, m, C(8)H, C(9)H), 7.36 (1H, dd, *J* = 2.0, 1.0 Hz, C(10)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$, major isomer) 21.6 and 21.8 (C(1)), 25.0 (C(3')), 30.1 (C(2)), 56.1 (C(2')), 70.9 (C(6)), 94.3 (C(1')), 105.6 and 110.1 (C(8), C(9)), 116.8 (C(3)), 133.5 (C(5)), 141.6 (C(10)), 157.6 (C(7)), 186.0 (C(4)); HRMS (ESI$^+$) found 275.1252, $C_{14}H_{20}NaO_4$ $[MNa]^+$ requires 275.1254.

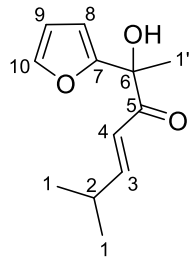
(*Z*)-2-(Furan-2-yl)-2-hydroxy-6-methylhept-4-en-3-one (211)



Allene **210** (10 mg, 0.04 mmol) was dissolved in acetone (500 μL) and HCl was added (1.0 M aqueous solution, 40 μL). After 1 h the reaction mixture was diluted with water (3 mL) and extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 9:1) to give the *title compound* as a yellow oil (5 mg, 60%). R_f 0.35 (petrol / ether, 7:3); ν_{max} (thin film) 3451br, 2966m, 1688s, 1621s, 1362m,

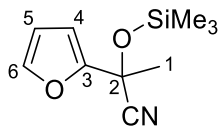
1104s, 1047s, 1013s, 740s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* = 7.0 Hz, C(1)H_3), 1.04 (3H, d, *J* = 7.0 Hz, C(1)H_3), 1.71 (3H, s, C(1')H_3), 2.38 – 2.53 (1H, m, C(2)H), 4.72 (1H, br s, C(6)OH), 6.07 (1H, d, *J* = 11.5 Hz, C(4)H), 6.08 (1H, dd, *J* = 11.5, 8.0 Hz, C(3)H), 6.37 (1H, dd, *J* = 3.5, 2.0 Hz, C(9)H), 6.39 (1H, dd, *J* = 3.5, 1.0 Hz, C(8)H), 7.39 (1H, dd, *J* = 2.0, 1.0 Hz, C(10)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 22.1 and 22.2 (C(1)), 23.3 (C(1')), 28.4 (C(2)), 75.6 (C(6)), 107.7 (C(8)), 110.6 (C(9)), 118.5 (C(4)), 142.9 (C(10)), 154.5 (C(7)), 160.2 (C(3)), 198.8 (C(5)); HRMS (ESI$^+$) found 231.0990, $C_{12}H_{16}NaO_3$ $[MNa]^+$ requires 231.0992.

(*E*)-2-(Furan-2-yl)-2-hydroxy-6-methylhept-4-en-3-one (212)



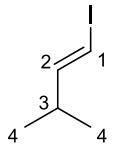
Enone **211** (5.0 mg, 0.024 mmol) was dissolved in DCM (500 μL) and triphenylphosphine (0.3 mg, 0.0012 mmol) was added. After 2 h the solvent was removed *in vacuo* and the crude product purified by flash chromatography (petrol / ether, 9:1) to give the *title compound* as a yellow oil (3.0 mg, 60%). R_f 0.55 (petrol / ether, 7:3); ν_{max} (thin film) 3449br, 2965s, 2934m, 2872m, 1692s, 1626s, 1107m, 1058s, 743s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* = 5.5 Hz, C(1)H_3), 1.05 (3H, d, *J* = 5.5 Hz, C(1)H_3), 1.72 (3H, s, C(1')H_3), 2.37 – 2.51 (1H, m, C(2)H), 4.69 (1H, s, C(6)OH), 6.21 (1H, dd, *J* = 15.5, 1.0 Hz, C(4)H), 6.37 – 6.42 (2H, m, C(8)H, C(9)H), 7.11 (1H, dd, *J* = 15.5, 7.0 Hz, C(3)H), 7.40 (1H, d, *J* = 1.0 Hz, C(10)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 21.1 (2 signals) (C(1)), 23.2 (C(1')), 31.5 (C(2)), 75.3 (C(6)), 107.8 and 110.6 (C(8), C(9)), 119.6 (C(4)), 142.9 (C(10)), 154.2 (C(7)), 157.7 (C(3)), 197.8 (C(5)); HRMS (ESI$^+$) found 231.0993, $C_{12}H_{16}NaO_3$ $[MNa]^+$ requires 231.0992.

2-(Furan-2-yl)-2-[(trimethylsilyl)oxy]propanenitrile (214)[241]



To a stirred solution of 2-acetyl furan (275 mg, 2.5 mmol) and CsF (38 mg, 0.25 mmol) in CH_3CN (2.5 mL) was added TMSCN (465 μL, 3.75 mmol) dropwise, and the reaction mixture was stirred at RT for 1 h. The reaction mixture was then extracted with petrol (3 × 5 mL), the combined organic layers washed with brine (20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by flash chromatography (petrol → petrol / ethyl acetate, 9:1) to give the title product as a colourless oil (454 mg, 87%). R_f 0.77 (petrol / ethyl acetate, 7:3); ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 0.10 (9H, s, $Si(CH_3)_3$), 1.94 (3H, s, $C(1)H_3$), 6.40 (1H, dd, J = 3.5, 2.0 Hz, C(5)H), 6.51 (1H, dd, J = 3.5, 1.0 Hz, C(4)H), 7.45 (1H, dd, J = 2.0, 1.0 Hz, C(6)H).

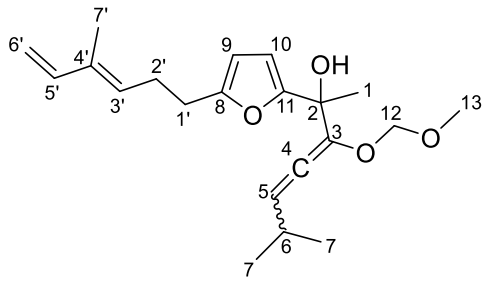
(*E*)-1-Iodo-3-methylbut-1-ene (215)[109]



3-methylbut-1-yne (800 μL, 533 mg, 8 mmol) was dissolved in pentane (2 mL). To this solution was added DIBAL (1.0 M solution in hexane, 8.0 mL, 8.0 mmol) and the reaction mixture was stirred for 18 h at RT. Iodine was then added (2.03 g, 8.0 mmol) as a solution in THF (6 mL) dropwise at −78 °C. The reaction mixture was warmed to RT and stirred for 1 h, then quenched by slowly adding water (15 mL) at 0 °C. The mixture was then extracted with pentane (3 × 15 mL), the organic layers combined and washed first with H_2SO_4 (0.1 M aqueous solution, 20 mL) then satd. aq. $Na_2S_2O_3$ solution (20 mL), dried over $MgSO_4$ and the solvent

evaporated to give the title product as a yellow oil (910 mg, 58%). R_f 0.83 (petrol); ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 1.01 (6H, d, *J* = 7.0 Hz, C(4)H_3), 2.28 – 2.37 (1H, m, C(3)H), 5.97 (1H, dd, *J* = 14.5, 1.0 Hz, C(1)H), 6.51 (1H, dd, *J* = 14.5, 7.0 Hz, C(2)H); ^{13}C NMR δ_C (100 MHz, C_6D_6) 21.4 (C(4)), 35.2 (C(3)), 73.4 (C(1)), 153.0 (C(2)).

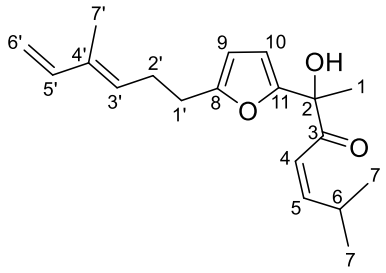
(*E*)-3-(Methoxymethoxy)-6-methyl-2-[5-(4-methylhexa-3,5-dien-1-yl)furan-2-yl]hepta-3,4-dien-2-ol (223)



Allene **203** (208 mg, 1.41 mmol) was dissolved in THF (2 mL) and *n*-BuLi (2.5 M in hexanes, 530 μL, 1.33 mmol) was added dropwise at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then for 30 min at 0 °C, then brought again to −78 °C and ketone **177** (100 mg, 0.49 mmol) added as a solution in THF (1 mL). The reaction mixture was stirred for 4 h at −78 °C, then quenched with phosphate buffer (pH 7, 5 mL), extracted with ether (3 × 10 mL), the organic layers combined, washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 9:1 → 8:2) to give the *title compound* as a yellow oil (117 mg, 69%, mixture of diastereomers). R_f 0.16 (petrol / ether, 8:2); ν_{max} (thin film) 3461br, 2961s, 2935m, 2871m, 1690m, 1465m, 1364m, 1152s, 1055s, 1031s, 910m, 787m, 732m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$, major component) 1.05 (6H, d, *J* = 7.0 Hz, C(7)H_3), 1.64 (3H, s, C(1)H_3), 1.73 (3H, s, C(7')H_3), 2.35 – 2.42 (1H, m, C(6)H), 2.42 – 2.50 (2H, m, C(2')H_2), 2.68 (2H, t, *J* = 7.5 Hz, C(1')H_2), 3.30 (3H, s, C(13)H_3), 4.78 – 4.88 (2H, m, C(12)H_2), 4.94 (1H, d, *J* = 10.5 Hz, C(6')H), 5.10 (1H, d, *J* = 17.5 Hz, C(6')H), 5.50 (1H, t, *J* = 7.0 Hz, C(3')H), 5.91 – 5.94 (1H, m, C(9)H or

C(10)H), 6.02 (1H, d, *J* = 5.5 Hz, C(5)H), 6.17 (1H, t, *J* = 3.5 Hz, C(9)H or C(10)H), 6.36 (1H, dd, *J* = 17.5, 10.5 Hz, C(5')H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$, major component) 11.6 (C(7')), 21.6 and 21.7 (C(7)), 25.1 (C(1)), 26.7 (C(2')), 27.9 (C(1')), 30.1 (C(6)), 56.1 (C(13)), 71.0 (C(2)), 94.3 (C(12)), 105.6 and 106.1 (C(9), C(10)), 110.9 (C(6')), 116.5 (C(5)), 131.5 (C(3')), 133.5 (C(3)), 134.7 (C(4')), 141.3 (C(5')), 154.7 and 155.9 (C(8), C(11)), 186.2 (C(4)); HRMS (ESI$^+$) found 369.2026, $C_{21}H_{30}O_4Na$ $[MNa]^+$ requires 369.2036.

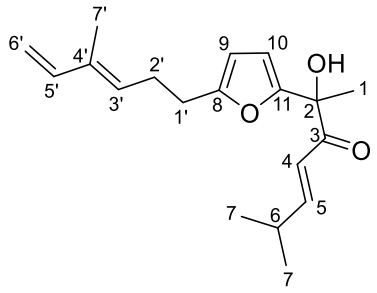
(*Z*)-2-Hydroxy-6-methyl-2-{5-[(*E*)-4-methylhexa-3,5-dien-1-yl]furan-2-yl}hept-4-en-3-one



Allene **223** (50 mg, 0.14 mmol) was dissolved in acetone (2.5 mL) and HCl (1.0 M aqueous solution, 150 mL, 0.14 mmol) was added. After 2 h the solvent was removed *in vacuo*, water (5 mL) was added, and the mixture was extracted with ether (3 × 10 mL), the combined organic layers washed with satd. aq. $NaHCO_3$ solution (20 mL), brine (20 mL), then dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 95:5) to give the *title compound* (18 mg, 42%) as a yellow oil, along with the *E*- isomer (6 mg, 15%). R_f 0.47 (petrol / ether, 7:3); ν_{max} (thin film) 3450br, 2964s, 2934m, 2868m, 1688s, 1610s, 1362s, 1103s, 1047s, 1018s, 790s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.01 (3H, d, *J* = 6.0 Hz, C(7)H_3), 1.02 (3H, d, *J* = 6.0 Hz, C(7)H_3), 1.67 (3H, s, C(1)H_3), 1.70 (3H, s, C(7')H_3), 2.44 (2H, q, *J* = 7.5 Hz, C(2')H_2), 2.67 (2H, t, *J* = 7.5 Hz, C(1')H_2), 3.51 – 3.62 (1H, m, C(6)H), 4.67 (1H, s br, C(2)OH), 4.95 (1H, d, *J* = 10.5 Hz, C(6')H), 5.09 (1H, d, *J* = 17.5 Hz, C(6')H), 5.46 (1H, t, *J* = 7.5 Hz, C(3')), 5.97 (1H, d, *J* = 3.5 Hz, C(9)H or C(10)H),

6.06 (2H, AB q, *J* = 11.5 Hz, C(4)H, C(5)H), 6.28 (1H, d, *J* = 3.5 Hz, C(9)H or C(10)H), 6.34 (1H, q, *J* = 17.5, 10.5 Hz, C(5')); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.7 (C(7')), 22.0, 22.2 (C(7)), 23.1 (C(1)), 26.7 (C(2')), 27.8 (C(1')), 28.3 (C(6)), 75.5 (C(2)), 106.1 and 108.4 (C(9), C(10)), 111.0 (C(6')), 118.6 (C(4)), 131.3 (C(3'), 134.8 (C(4')), 141.3 (C(5')), 152.6 and 156.2 (C(8), C(11)), 159.7 (C(5)), 199.1 (C(3)); HRMS (ESI$^+$) found 325.17648, $C_{19}H_{26}O_3Na$ $[MNa]^+$ requires 325.17742.

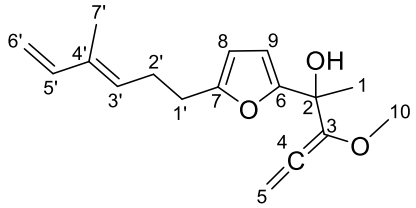
(*E*)-2-Hydroxy-6-methyl-2-{5-[(*E*)-4-methylhexa-3,5-dien-1-yl]furan-2-yl}hept-4-en-3-one (174)



The mixture of (*Z*)- and (*E*)- enones obtained from the previous step (24 mg, 0.08 mmol, 2.7:1 *Z*:*E*) was dissolved in CH_3CN (1 mL) and to this solution was added triphenylphosphine (2.0 mg, 0.01 mmol). After 2 h the solvent was removed *in vacuo*, water (5 mL) was added and the mixture extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by column chromatography (petrol / ether, 98:2 → 95:5) to give the *title compound* as a yellow oil (20 mg, 89%). R_f 0.41 (petrol / ether, 7:3); ν_{max} (thin film) 3451br, 2963s, 2929s, 2870m, 2360s, 2341s, 1771m, 1690s, 1626s, 1103s, 1059s, 1020s, 988m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.03 (3H, d, *J* = 7.0 Hz, C(7)H_3), 1.04 (3H, d, *J* = 7.0 Hz, C(7)H_3), 1.69 (3H, s, C(1)H_3), 1.70 (3H, s, C(7')H_3), 2.39 – 2.48 (3H, m, C(2')H_2 and C(6)H), 2.68 (2H, t, *J* = 7.5 Hz, C(1')H_2), 4.95 (1H, d, *J* = 10.5 Hz, C(6')H), 5.09 (1H, d, *J* = 17.5 Hz, C(6')H), 5.46 (1H, t, *J*

= 7.0 Hz, C(3')H), 5.97 (1H, d, *J* = 3.0 Hz, C(9)H or C(10)H), 6.21 (1H, dd, *J* = 15.5, 1.5 Hz, C(4)H), 6.29 (1H, d, *J* = 3.0 Hz, C(9)H or C(10)H), 6.34 (1H, dd, *J* = 17.5, 10.5 Hz, C(5')H), 7.10 (1H, dd, *J* = 15.5, 7.0 Hz, C(5)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.7 (C(7')), 21.1, 21.2 (C(7)), 23.2 (C(1)), 26.7 (C(2')), 27.8 (C(1')), 31.4 (C(6)), 75.3 (C(2)), 106.2 and 108.4 (C(9), C(10)), 111.0 (C(6')), 119.7 (C(4)), 131.2 (C(3')), 134.9 (C(4')), 141.2 (C(5')), 152.4 and 156.2 (C(8), C(11)), 157.3 (C(5)), 198.1 (C(3)); HRMS (ESI$^+$) found 325.1764, $C_{19}H_{26}O_3Na$ $[MNa]^+$ requires 325.1774.

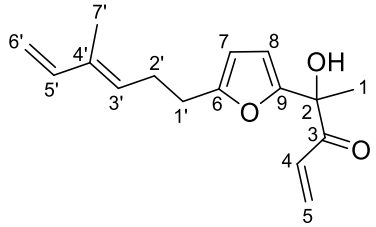
(*E*)-3-Methoxy-2-[5-(4-methylhexa-3,5-dien-1-yl)furan-2-yl]penta-3,4-dien-2-ol (224)



Allene **198** (55 mg, 0.78 mmol) was dissolved in THF (1 mL) and *n*-BuLi (2.5 M in hexanes, 356 μL, 0.89 mmol) was added dropwise at −78 °C. The reaction mixture was stirred for 30 min at the same temperature, then ketone **177** (160 mg, 0.78 mmol) was added as a solution in THF (1 mL). The reaction mixture was stirred for 2 h at −78 °C, then quenched with phosphate buffer (pH 7, 5 mL), extracted with ether (3 × 10 mL), the organic layers combined, washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude *title compound* (yellow oil, 180 mg, 84%) was used in the next step with no further purification. R_f 0.11 (petrol / ether, 9:1); ν_{max} (thin film) 3459br, 2936m, 1956w, 1461m, 1445m, 1195s, 1127s, 1092s, 991s, 892s, 783s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.66 (3H, s, C(1)H_3), 1.72 (3H, s, C(7')H_3), 2.41 – 2.51 (2H, m, C(2')H_2), 2.69 (2H, t, *J* = 7.5 Hz, C(1')H_2), 2.82 (1H, s, C(2)OH), 3.47 (3H, s, C(10)H_3), 4.95 (1H, d, *J* = 10.5 Hz, C(6')H), 5.10 (1H, d, *J* = 17.5 Hz, C(6')H), 5.51 (1H, t, *J* = 7.0 Hz, C(3')H), 5.61 (2H, s, C(5)H_2), 5.92 (1H, d, *J* = 3.0 Hz) and 6.15 (1H, d, *J* = 3.0 Hz, C(8)H and C(9)H), 6.36 (1H, dd, *J* = 17.5, 10.5 Hz,

C(5')H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.6 (C(7')), 24.8 (C(1)), 26.8 (C(2')), 27.9 (C(1')), 56.7 (C(10)), 70.7 (C(2)), 93.4 (C(5)), 105.6 and 106.3 (C(8), C(9)), 110.9 (C(6')), 131.5 (C(3')), 134.7 (C(4')), 137.6 (C(3)), 141.3 (C(5')), 154.9 and 155.5 (C(6), C(7)), 196.4 (C(4)); HRMS (ESI^+) found 297.1458, $C_{17}H_{22}O_3Na$ $[MNa]^+$ requires 297.1461.

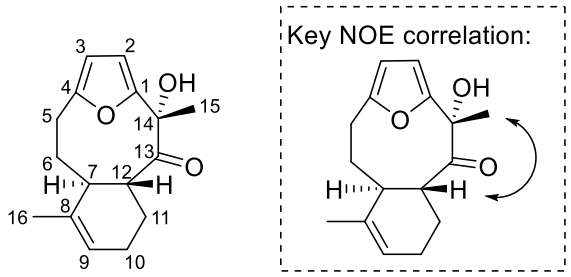
(*E*)-4-Hydroxy-4-(5-[4-methylhexa-3,5-dien-1-yl)furan-2-yl]pent-1-en-3-one (225)



Allene **224** (124 mg, 0.45 mmol) was dissolved in acetone (12 mL) and HCl (1.0 M aqueous solution, 450 mL, 0.45 mmol) was added. After 1 h satd. aq. $NaHCO_3$ solution (10 mL) was added, the acetone was removed *in vacuo*, and the reaction mixture was extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 95:5 → 8:2) to give the *title compound* as a yellow oil (83 mg, 71%). R_f 0.20 (petrol / ether, 9:1); ν_{max} (thin film) 3464br, 2936m, 2360w, 2341w, 1698s, 1612m, 1403m, 1107s, 1041s, 987m, 792m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.70 (6H, s, C(7')H_3 and C(1)H_3), 2.40 – 2.49 (2H, m, C(2')H_2), 2.68 (2H, t, *J* = 7.5 Hz, C(1')H_2), 4.51 (1H, s, C(2)OH), 4.95 (1H, d, *J* = 11.0 Hz, C(6')H), 5.09 (1H, d, *J* = 17.5 Hz, C(6')H), 5.46 (1H, t, *J* = 7.5 Hz, C(3')H), 5.79 (1H, dd, *J* = 9.5, 2.5 Hz, C(5)H), 5.98 (1H, d, *J* = 3.0 Hz) and 6.31 (1H, d, *J* = 3.0 Hz, C(7)H, C(8)H), 6.34 (1H, dd, *J* = 17.5, 11.0 Hz, C(5')H), 6.51 (1H, dd, *J* = 17.0, 2.5 Hz, C(5)H), 6.57 (1H, dd, *J* = 17.0, 9.5 Hz, C(4)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.7 (C(7')), 22.8 (C(1)), 26.7 (C(2')), 27.8 (C(1')), 75.4 (C(2)), 106.3 and 108.8 (C(7), C(8)), 111.0 (C(6')), 129.1 (C(4)), 131.2 and 131.3 (C(5), C(3')), 134.9 (C(4')), 141.2 (C(5')), 151.9

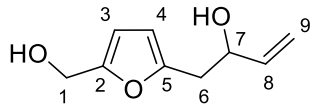
and 156.5 (C(6), C(9)), 197.9 (C(3)); HRMS (ESI$^+$) found 261.1484, $C_{16}H_{21}O_3$ [MH]$^+$ requires 261.1485.

(4a*R,6*S**,12a*S**)-6-Hydroxy-1,6-dimethyl-4,4a,6,11,12,12a-hexahydro-7,10-epoxybenzo[10]annulen-5(3H)-one (226)**



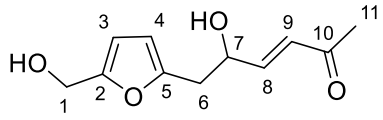
IMDA precursor **225** (25 mg, 0.10 mmol) was dissolved in toluene (10 mL) in a previously base washed pressure tube. The reaction mixture was heated to 190 °C for 12 h, then the solvent was removed *in vacuo* and the crude product purified by flash chromatography (petrol / ether, 9:1 → 8:2) to give the *title compound* as a yellow oil (2.0 mg, 8%). R_f 0.23 (petrol / ether, 7:3); ν_{max} (thin film)/cm^{-1} 3472br, 2921s, 2855m, 1715s, 1540m, 1445m, 1238s, 1106s, 1011m, 791m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.07 – 1.13 (1H, m, C(6)H), 1.16 (1H, app. td, *J* = 6.5, 1.5 Hz, C(12)H), 1.39 – 1.43 (1H, m, C(11)H), 1.46 – 1.51 (1H, m, C(11)H), 1.54 (3H, s, C(15)H_3), 1.75 (3H, s, C(16)H_3), 1.77 – 1.78 (1H, m, C(10)H), 2.06 – 2.08 (1H, m, C(10)H), 2.11 (1H, app. dt, *J* = 14.5, 3.5 Hz, C(6)H), 2.26 – 2.30 (1H, m, C(7)H), 2.66 (1H, ddd, *J* = 14.5, 12.0, 4.0 Hz, C(5)H), 2.76 (1H, ddd, *J* = 14.5, 4.0, 3.5 Hz, C(5)H), 4.10 (1H, s, C(14)OH), 5.62 – 5.65 (1H, m, C(9)H), 6.14 (1H, d, *J* = 3.0 Hz, C(3)H), 6.52 (1H, d, *J* = 3.0 Hz, C(2)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 22.1 (C(10)), 22.2 (C(15)), 23.0 (C(16)), 25.2 (C(11)), 29.0 (C(5)), 40.0 (C(6)), 43.9 (C(7)), 47.5 (C(12)), 76.1 (C(14)), 108.2 (C(3)), 114.9 (C(2)), 123.3 (C(9)), 135.9 (C(8)), 155.8 and 163.0 (C(1), C(4)), 215.3 (C(13)); HRMS (ESI$^+$) found 283.1298, $C_{16}H_{20}O_3Na$ [MNa]$^+$ requires 283.1305.

1-[5-(Hydroxymethyl)furan-2-yl]but-3-en-2-ol (236)



Furfuryl alcohol (130 μL, 1.50 mmol) was dissolved in THF (5 mL), and *n*-BuLi (2.5 M solution in hexanes, 1.20 mL, 3.00 mmol) was added dropwise at −78 °C. After 10 min at this temperature, the reaction mixture was warmed to 0 °C and allowed to stir for 1 h, at which point it was cooled down to −78 °C and 3,4-epoxy-1-butene (250μL, 3 mmol) was added. The reaction mixture was stirred at RT for 18 h; brine (10 mL) was then added, the layers separated and the aqueous layer extracted with ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 1:1 → 2:8) to give the title compound as a colourless oil (60 mg, 24%). R_f 0.09 (petrol / ether, 2:8); ν_{max} (thin film)/cm^{-1} 3334br, 2921w, 2871w, 1561m, 1423m, 1009s, 927m, 791m; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.39 (2H, br s, C(7)HO*H*, C(1)H_2O*H*), 2.80 (1H, dd, *J* = 15.0, 8.0 Hz, C(6)H), 2.89 (1H, dd, *J* = 15.0, 4.5 Hz, C(6)H), 4.35 – 4.47 (1H, m, C(7)H), 4.54 (2H, s, C(1)H_2), 5.15 (1H, d, *J* = 10.5 Hz, C(9)H), 5.29 (1H, d, *J* = 17.0 Hz, C(9)H), 5.91 (1H, ddd, *J* = 17.5, 10.5, 6.0 Hz, C(8)H), 6.06 (1H, d, *J* = 3.0 Hz) and 6.20 (1H, d, *J* = 3.0 Hz, C(3)H, C(4)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 36.2 (C(6)), 57.3 (C(1)), 71.3 (C(7)), 108.0 and 108.7 (C(3), C(4)), 115.3 (C(9)), 139.7 (C(8)), 152.3 and 153.0 (C(2), C(5)); HRMS (ESI$^+$) found 191.0679, $C_9H_{12}O_3Na$ $[MNa]^+$ requires 191.0679.

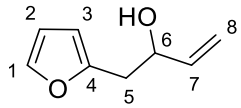
(*E*)-5-Hydroxy-6-(5-(hydroxymethyl)furan-2-yl)hex-3-en-2-one (235)



Furan **236** (44 mg, 0.26 mmol) was dissolved in DCM (3 mL), previously degassed by bubbling Ar through the solvent. Methyl vinyl ketone (110 μL, 1.31 mmol) and then Hoveyda–

Grubbs 2nd generation catalyst (8.2 mg, 0.013 mmol) were added and the reaction mixture was stirred at RT for 18 h. The solvent was then removed *in vacuo* and the crude residue was purified by flash chromatography (petrol / ether, 2:8 → ether) to give the *title compound* as a brown viscous oil (40 mg, 73%). R_f 0.09 (ether); ν_{max} (thin film)/cm^{-1} 3375br, 2923w, 1673s, 1637s, 1362s, 1260s, 1010s, 980s, 795s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s, C(11)H_3), 2.88 (1H, dd, *J* = 15.0, 8.0 Hz, C(6)H), 2.99 (1H, dd, *J* = 15.0, 5.0 Hz, C(6)H), 4.57 (2H, s, C(1)H_2), 4.61 – 4.69 (1H, m, C(7)H), 6.11 (1H, d, *J* = 3.0 Hz) and 6.23 (1H, d, *J* = 3.0 Hz, C(3)H, C(4)H), 6.32 (1H, dd, *J* = 16.0, 1.5 Hz, C(9)H), 6.80 (1H, dd, *J* = 16.0, 4.5 Hz, C(8)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 27.5 (C(11)), 35.7 (C(6)), 57.2 (C(1)), 69.5 (C(7)), 108.5 and 108.8 (C(3), C(4)), 129.4 (C(9)), 147.4 (C(8)), 151.2 and 153.3 (C(2), C(5)), 198.8 (C(10)); HRMS (ESI$^+$) found 233.0785, $C_{11}H_{14}O_4Na$ [MNa]$^+$ requires 233.0784.

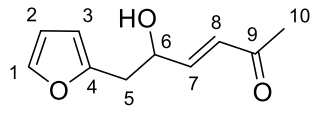
1-(Furan-2-yl)but-3-en-2-ol (241)[242]



Furan (550 μL, 7.50 mmol) was dissolved in THF (10 mL) and *n*-BuLi (2.5 M solution in hexanes, 3.0 mL, 7.50 mmol) was added dropwise at −78 °C. After 10 min at this temperature, the reaction mixture was warmed to 0 °C and left to stir for 1 h, then cooled down to −78 °C and 3,4-epoxy-1-butene (125 μL, 1.50 mmol) added. The reaction mixture was then stirred at RT for 18 h. Brine (10 mL) was then added, the layers separated and the aqueous layer extracted with ether (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 8:2) to give the title compound as a colourless oil (121 mg, 59%). R_f 0.43 (petrol / ether, 7:3); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.77 – 2.97 (2H, m, C(5)H_2), 4.36 – 4.48 (1H, m, C(6)H), 5.15 (1H, d, *J* = 10.5 Hz, C(8)H), 5.29 (1H, d, *J* = 17.0 Hz, C(8)H), 5.92 (1H, ddd, *J*

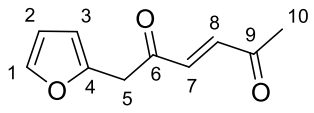
= 17.0, 10.5, 6.0 Hz, C(7)H), 6.13 (1H, dd, *J* = 3.0, 1.0 Hz) and 6.32 (1H, dd, *J* = 3.0, 2.0 Hz, C(2)H, C(3)H), 7.35 (1H, dd, *J* = 2.0, 1.0 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 36.1 (C(5)), 71.4 (C(6)), 107.2 and 110.26 (C(2), C(3)), 115.19 (C(8)), 139.7 (C(7)), 141.6 and 152.0 (C(1), C(4)).

(*E*)-6-(Furan-2-yl)-5-hydroxyhex-3-en-2-one (242)



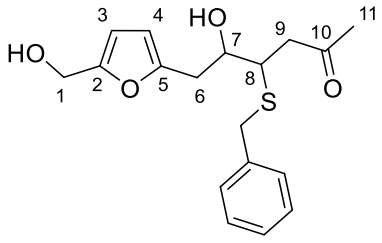
Alkene **241** (101 mg, 0.73 mmol) and methyl vinyl ketone (300 μL, 3.65 mmol) were dissolved in degassed DCM (10 mL) and Hoveyda–Grubbs 2nd generation catalyst (25.0 mg, 0.04 mmol) was added to the solution. The reaction mixture was stirred at RT for 18 h, then the solvent was removed *in vacuo* and the crude residue purified by flash chromatography (petrol / ether, 7:3 → 1:1) to give the *title compound* as a brown oil (83 mg, 63%). R_f 0.14 (petrol / ether, 7:3); ν_{max} (thin film)/cm^{-1} 3404br, 1673s, 1630s, 1361s, 1257s, 1010s, 983s, 734s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, C(10)H_3), 2.90 (1H, dd, *J* = 15.0, 7.5 Hz, C(5)H), 3.00 (1H, d, *J* = 15.0 Hz, C(5)H), 4.63 (1H, br s, C(6)H), 6.16 (1H, d, *J* = 3.0 Hz, C(3)H), 6.25 – 6.37 (2H, m, C(2)H, C(8)H), 6.79 (1H, dd, *J* = 16.0, 4.5 Hz, C(7)H), 7.36 (1H, br s, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 27.5 (C(10)), 35.6 (C(5)), 69.7 (C(6)), 107.8 (C(3)), 110.4 (C(2)), 129.5 (C(8)), 142.0 (C(1)), 147.1 (C(7)) , 150.9 (C(4)), 198.4 (C(9)); HRMS (Ammonia CI$^+$) found 181.0859, $C_{10}H_{12}O_3$ $[MH]^+$ requires 181.0859.

(*E*)-1-(Furan-2-yl)hex-3-ene-2,5-dione (243)



To a solution of furan **242** (15 mg, 0.08 mmol) in DCM (5 mL) was added $NaHCO_3$ (70 mg, 0.83 mmol) followed by DMP (68 mg, 0.16 mmol). After 30 min satd. aq. $Na_2S_2O_3$ solution (5 mL) was added followed by satd. aq. $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was of sufficient purity to be used in the next step without further purification (yellow oil, 12 mg, 80%). R_f 0.30 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 1683s, 1361m, 1013m, 979m, 743m; ^1H NMR δ_H (400 MHz, $CDCl_3$) 2.36 (1H, s, C(10)H_3), 3.96 (3H, s, C(5)H_2), 6.25 (1H, dd, *J* = 3.0, 1.0 Hz, C(3)H), 6.37 (1H, dd, *J* = 3.0, 2.0 Hz, C(2)H), 6.91 (2H, AB q, *J* = 16.0 Hz, C(7)H, C(8)H), 7.39 (1H, dd, *J* = 2.0, 1.0 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, CDCl3) 28.4 (C(10)), 41.3 (C(5)), 108.9 and 110.8 (C(2), C(3)), 135.6 and 137.9 (C(7), C(8)), 142.6 and 146.8 (C(1), C(4)), 195.0 and 198.0 (C(6), C(9)); HRMS (ESI^+) found 179.0701, $C_{10}H_{11}O_3$ $[MH]^+$requires 179.0703.

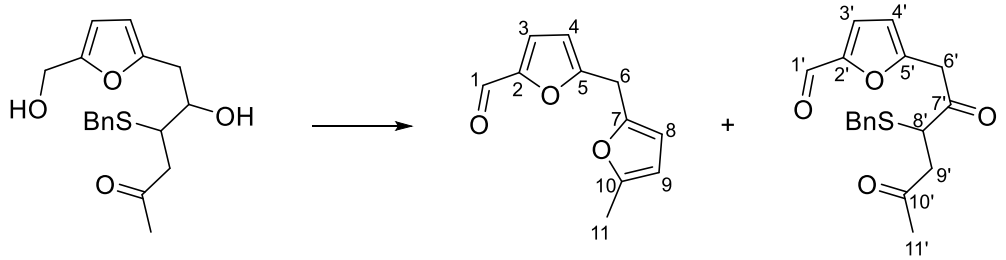
4-(Benzylthio)-5-hydroxy-6-[5-(hydroxymethyl)furan-2-yl]hexan-2-one (244)



Enone **235** (25 mg, 0.12 mmol) and benzyl thiol (15 μL, 0.12 mmol) were dissolved in DCM and triethylamine (17 μL, 0.12 mmol) was added. After 1 h the solvent was removed *in vacuo*

and the crude residue purified by flash chromatography (petrol / ether, 1:1) to give the *title compound* as a colourless oil (36 mg, mixture of diastereomers, 90%). R_f 0.33 (petrol / ether, 3:7); ν_{max} (thin film)/cm^{-1} 3402br, 2923m, 1710s, 1454m, 1362m, 1013s, 732s, 703s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$, major component) 2.12 (3H, s, C(11)H_3), 2.71 – 2.95 (4H, m, C(6)H_2 and C(9)H_2), 3.15 (1H, ddd, *J* = 7.5, 6.0, 3.5 Hz, C(8)H), 3.81 (2H, s, -SC*H*$_2$Ph), 3.92 (1H, br s, C(7)H), 4.54 (2H, s, C(1)H_2), 6.00 (1H, d, *J* = 3.0 Hz) and 6.19 (1H, d, *J* = 3.0 Hz, C(3)H, C(4)H), 7.22 – 7.35 (5H, m, -SCH$_2$*Ph*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$, major component) 30.6 (C(11)), 33.4 (C(9)), 37.1 (-S*C*H$_2$Ph), 45.7 C(8)), 46.9 (C(6)), 57.4 (C(7)), 72.0 C(1)), 108.0 and 108.7 (C(3), C(4)), 127.2, 128.6, 129.0 and 138.2 (-SCH$_2$*Ph*), 152.4 and 153.1 (C(2), C(5)), 207.0 (C(10); HRMS (ESI$^+$) found 357.1130, $C_{18}H_{22}O_4NaS$ [MNa]$^+$ requires 357.1131.

Procedure for the attempted oxidation of diol 244



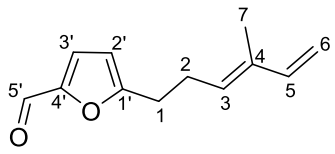
Diol **244** (10 mg, 0.03 mmol) was dissolved in DCM (2 mL), and to this solution was added $NaHCO_3$ (50 mg, 0.60 mmol) followed by DMP (38 mg, 0.09 mmol). After stirring at RT for 30 min, another equiv of DMP was added (13 mg, 0.03 mmol) and the reaction was stirred at RT for a further 1 h, at which point complete consumption of starting material was observed by TLC. The mixture was then diluted with DCM (10 mL), satd. aq. $Na_2S_2O_3$ solution added (10 mL) followed by satd. aq. $NaHCO_3$ solution (10 mL), the layers separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine

(20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol/ether, 1:1) to give aldehyde **245** (colourless oil, 3.0 mg, 53%) along with aldehyde **246** (colourless oil, 3.0 mg, 30%).

Data for **5-[(5-methylfuran-2-yl)methyl]furan-2-carbaldehyde (245)**: R_f 0.47 (petrol / ether = 1:1); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, C(11)H_3), 4.06 (2H, s, C(6)H_2), 5.91 (1H, dd, *J* = 3.0, 1.0 Hz) and 6.05 (1H, d, *J* = 3.0 Hz, C(8)H, C(9)H), 6.30 (1H, d, *J* = 3.5 Hz, C(4)H), 7.19 (1H, d, *J* = 3.5 Hz, C(3)H), 9.57 (1H, s, C(1)H).

Data for **5-[3-(benzylthio)-2,5-dioxohexyl]furan-2-carbaldehyde (246)**: R_f 0.11 (petrol / ether = 1:1); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.12 (3H, s, C(11')H_3), 2.73 (1H, dd, *J* = 18.5, 4.0 Hz, C(9')H), 3.28 (1H, dd, *J* = 18.5, 10.0 Hz, C(9')H), 3.63 (1H, d, *J* = 13.0 Hz, C(6')H), 3.71 (1H, d, *J* = 13.0 Hz, C(6')H), 3.80 (1H, dd, *J* = 10.0, 4.0 Hz, C(8')H), 3.99 (1H, d, *J* = 17.5 Hz, -SC*H*$_2$Ph), 4.18 (1H, d, *J* = 17.5 Hz, -SC*H*$_2$Ph), 6.47 (1H, d, *J* = 3.5 Hz, C(4')H), 7.22 (1H, d, *J* = 3.5 Hz, C(3')H), 7.31 – 7.39 (5H, m, -SCH$_2$*Ph*), 9.59 (1H, s, C(1')H).

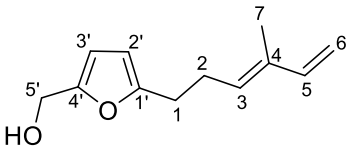
(*E*)-5-(4-Methylhexa-3,5-dien-1-yl)furan-2-carbaldehyde (252)



$POCl_3$ (29 μL, 0.31 mmol) and DMF (24 μL, 0.31 mmol) were dissolved in dry DCM (0.5 mL) at 0 °C and stirred at the same temperature for 30 min, then diene **184** (23 mg, 0.31 mmol) was added as a solution in DCM (0.5 mL) and the reaction mixture was stirred at RT for 18 h. Satd. aq. $NaHCO_3$ solution (2 mL) was then added, and the reaction mixture extracted with DCM (3 × 5 mL), the organic layers washed with brine (5 mL) and the solvent removed *in vacuo*. Purification by flash chromatography (petrol / ether, 95:5 → 8:2) gave the *title compound* as a yellow oil (27mg, 46%). R_f 0.19 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1}

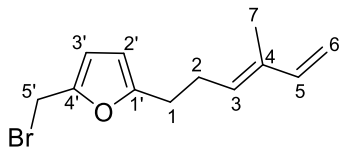
2922w, 2820w, 1676s, 1518s, 1024m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.73 (3H, s, C(7)H_3), 2.56 (2H, dt, *J* = 7.5, 7.0 Hz, (C(2)H_2)), 2.83 (2H, t, *J* = 7.5 Hz, C(1)H_2), 4.97 (1H, d, *J* = 10.5 Hz, C(6)H), 5.12 (1H, d, *J* = 17.5 Hz, C(6)H), 5.46 (1H, t, *J* = 7.0 Hz, C(3)H), 6.25 (1H, d, *J* = 3.5 Hz, C(2')H), 6.35 (1H, dd, *J* = 17.5, 10.5 Hz, (C(5)H), 7.18 (1H, d, *J* = 3.5 Hz, C(3')), 9.54 (1H, s, C(5')H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.7 (C(7)), 26.2 (C(2)), 28.2 (C(1)), 109.0 (C(2')), 111.6 (C(6)), 130.1 (C(3)), 135.6 (C(4)), 141.0 (C(5)), 151.9 (C(1')), 163.0 (C(4')), 177.0 (C(5')); HRMS not obtained due to decomposition.

(*E*)-[5-(4-Methylhexa-3,5-dien-1-yl)furan-2-yl]methanol (253)



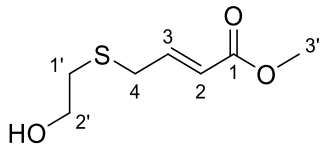
Aldehyde **252** (50 mg, 0.25 mmol) was dissolved in THF / MeOH (4:1, 5 mL), then $NaBH_4$ (15 mg, 0.40 mmol) was added. After 1 h the solvent was evaporated and the reaction mixture diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layers were washed with brine (15 mL) and the solvent removed *in vacuo* to give the *title compound* as a colourless oil (48 mg, 96%), of sufficient purity to be used in the next step with no further purification. R_f 0.25 (petrol / ether, 7:3); ν_{max} (thin film)/cm^{-1} 3352br, 2949s, 1561m, 1442m, 1013s, 787s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.73 (3H, s, C(7)H_3), 2.49 (2H, dt, *J* = 7.5, 7.0 Hz, C(2)H_2), 2.71 (2H, t, *J* = 7.5 Hz, C(1)H_2), 4.57 (2H, s, C(5')H_2), 4.96 (1H, d, *J* = 11.0 Hz, C(6)H), 5.11 (1H, d, *J* = 17.5 Hz, C(6)H), 5.51 (1H, t, *J* = 7.0 Hz, C(3)H), 5.95 (1H, d, *J* = 3.0 Hz) and 6.19 (1H, d, *J* = 3.0 Hz, C(2')H, C(3')H), 6.37 (1H, dd, *J* = 17.5, 11.0 Hz, (C(5)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.6 (C(7)), 26.7 (C(2)), 27.9 (C(1)), 57.6 (C(5')), 105.8 and 108.6 (C(2'), C(3')), 111.0 (C(6)), 131.3 (C(3)), 134.9 (C(4)), 141.3 (C(5)), 152.3 and 155.9 (C(1'), C(4')); HRMS (ESI$^+$) found 215.1042, $C_{12}H_{16}O_2Na$ [MNa]$^+$ requires 215.1043.

(*E*)-2-(Bromomethyl)-5-(4-methylhexa-3,5-dien-1-yl)furan (254)



Alcohol **253** (10 mg, 0.06 mmol) was dissolved in ether (1 mL), then PBr_3 (6 μL, 0.07 mmol) was added at 0 °C, and the reaction mixture stirred at RT for 3 h. Aqueous NaOH solution (40% w/w, 1 mL) was then added and the reaction mixture extracted with ether (3 × 5 mL), the organic layers washed with brine (5 mL) and the solvent removed *in vacuo* to give the *title compound* as a colourless oil (8 mg, 52%) which was used immediately in the next step. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.73 (3H, s, C(7)H_3), 2.50 (2H, dt, *J* = 7.5, 7.0 Hz, (C(2)H_2), 2.71 (2H, t, *J* = 7.5 Hz, C(1)H_2), 4.51 (2H, s, C(5')H_2), 4.96 (1H, d, *J* = 10.5 Hz, C(6)H), 5.11 (1H, d, *J* = 17.5 Hz, C(6)H), 5.49 (1H, t, *J* = 7.0 Hz, C(3)H), 5.96 (1H, d, *J* = 3.0 Hz) and 6.29 (1H, d, *J* = 3.0 Hz, C(2')H, C(3')H), 6.37 (1H, dd, *J* = 17.5, 10.5 Hz, C(5)H).

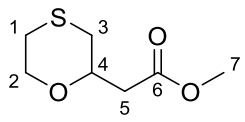
Methyl (*E*)-4-[(2-hydroxyethyl)thio]but-2-enoate (269)



To a solution of mercaptoethanol (300 μL, 4.28 mmol) and triethylamine (595 μL, 4.28 mmol) in ether (25 mL) was added a solution of methyl 4-bromocrotonate (503 μL, 4.28 mmol) in ether (25 mL) and the reaction mixture was stirred for 18 h at RT. It was then filtered through celite, washed with satd. aq. NH_4Cl solution (50 mL) and brine (50 mL) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 7:3 → 6:4) to give the *title compound* as a yellow oil (517 mg, 69%). R_f 0.45 (petrol / ether, 7:3); ν_{max} (thin film)/cm^{-1} 3415br, 2952w, 1715s, 1651m, 1436m, 1321m, 1274m, 1204m,

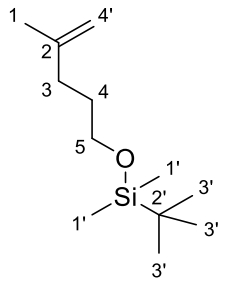
1148m, 1039m, 978m; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.67 (2H, t, *J* = 6.0 Hz, C(1')H_2), 3.26 (2H, dd, *J* = 7.5, 1.5 Hz, C(4)H_2), 3.73 (2H, t, *J* = 6.0 Hz, C(2')H_2), 3.75 (3H, s, C(3')H_3), 5.89 (1H, dt, *J* = 15.5, 1.5 Hz, C(2)H), 6.89 (1H, dt, *J* = 15.5, 7.5 Hz, C(3)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 32.3 (C(4)), 33.8 (C(1')), 51.6 (C(3')), 60.5 (C(2')), 122.6 (C(2)), 143.5 (C(3)), 166.4 (C(1)); HRMS (ESI$^+$) found 199.0396, $C_7H_{12}O_3NaS$ $[MNa]^+$ requires 199.0399.

Methyl 2-(1,4-oxathian-2-yl)acetate (270)



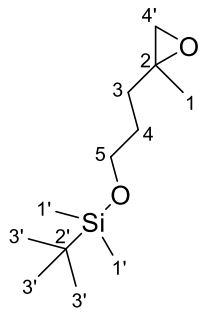
To a stirred solution of thioether **269** (100 mg, 0.55 mmol) in THF (10 mL) at −78 °C was added LiHMDS (1.0 M solution in THF, 850 mL, 0.85 mmol), and the reaction mixture was stirred at RT for 18 h. Brine (10 mL) was then added and the mixture was extracted with ether (3 × 10 mL). The organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 7:3) to give the *title compound* as a yellow oil (44 mg, 44%). R_f 0.49 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 2952w, 1735s, 1436m, 1311m, 1246m, 1208m, 1148s, 1091s, 843m; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.27 (1H, app. dq, *J* = 13.5, 2.0 Hz, C(1)H), 2.43 (1H, d, *J* = 13.5 Hz, C(3)H), 2.46 (1H, dd, *J* = 15.0, 5.5 Hz, C(5)H), 2.58 (1H, dd, *J* = 15.0, 7.5 Hz, C(5)H), 2.68 (1H, dd, *J* = 13.5, 10.5 Hz, C(3)H), 2.88 (1H, ddd, *J* = 13.5, 12.0, 3.5 Hz, C(1)H), 3.71 (3H, s, C(7)H_3), 3.80 (1H, app. td, *J* = 12.0, 2.0 Hz, C(2)H), 4.05 (1H, dddd, *J* = 10.5, 7.5, 5.5, 2.0 Hz, C(4)H), 4.21 (1H, app. dt, *J* = 12.0, 2.0 Hz, C(2)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 26.2 (C(1)), 30.9 (C(3)), 41.1 (C(5)), 51.8 (C(7)), 69.2 (C(2)), 74.4 (C(4)), 171.0 (C(6)); HRMS (ESI$^+$) found 199.0397, $C_7H_{12}O_3NaS$ $[MNa]^+$ requires 199.0399.

tert-Butyldimethyl[(4-methylpent-4-en-1-yl)oxy]silane (277)[243]



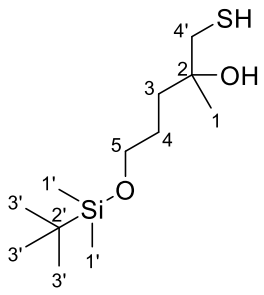
4-methylpent-4-en-1-ol (2.50 g, 25.0 mmol)[127,128] was dissolved in DCM (50 mL), and to this solution was added TBSCl (4.53 g, 30.0 mmol), imidazole (2.55 g, 37.5 mmol) and DMAP (155 mg, 1.25 mmol) and the reaction mixture was stirred at RT for 18 h. It was then filtered through a plug of silica using hexane / ethyl acetate (99:1, 100 mL) as the eluent, and the solvent evaporated to give the title compound as a colourless oil (4.94 g, 92%), of sufficient purity to be used in the next step with no further purification. R_f 0.71 (petrol / ether, 7:3); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.65 – 1.70 (2H, m, $C(4)H_2$), 1.73 (3H, s, $C(1)H_3$), 2.06 (2H, t, J = 7.5 Hz, $C(3)H_2$), 3.62 (2H, t, J = 6.5 Hz, $C(5)H_2$), 4.69 (1H, br s, $C(4')H_2$), 4.71 (1H, br s, $C(4')H_2$).

***tert*-Butyldimethyl[3-(2-methyloxiran-2-yl)propoxy]silane (278)**[244]



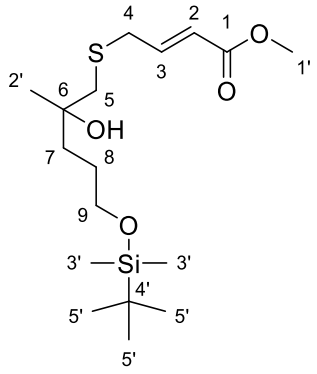
Alkene **277** (1.0 g, 4.7 mmol) was dissolved in DCM (24 mL), then Na_2HPO_4 (1.7 g, 11.7 mmol) and mCPBA (1.7 g, 9.8 mmol) were added at 0 °C and the reaction mixture stirred at the same temperature for 1.5 h. satd. aq. $NaHCO_3$ solution (25 mL) was then added, the layers separated and the aqueous layer extracted with DCM (2 × 25 mL). The combined organic layers were then washed with NaOH aqueous solution (10% w/w, 15 mL), brine (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 9:1) to give the title compound as a colourless oil (799 mg, 74%). R_f 0.44 (petrol / ether, 9:1); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.32 (3H, s, $C(1)H_3$), 1.59 – 1.64 (4H, m, $C(3)H_2$, $C(4)H_2$), 2.58 (1H, d, *J* = 5.0 Hz, C(4')H), 2.62 (1H, d, *J* = 5.0 Hz, C(4')H), 3.57 – 3.66 (2H, m, $C(5)H_2$); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) −5.4 (C(1')), 18.3 (C(2')), 20.9 (C(1)), 25.9 (C(3')), 28.5 and 33.1 (C(3), C(4)), 53.8 (C(4)), 56.9 (C(2)), 62.8 (C(5)).

5-[(*tert*-Butyldimethylsilyl)oxy]-1-mercapto-2-methylpentan-2-ol (279)



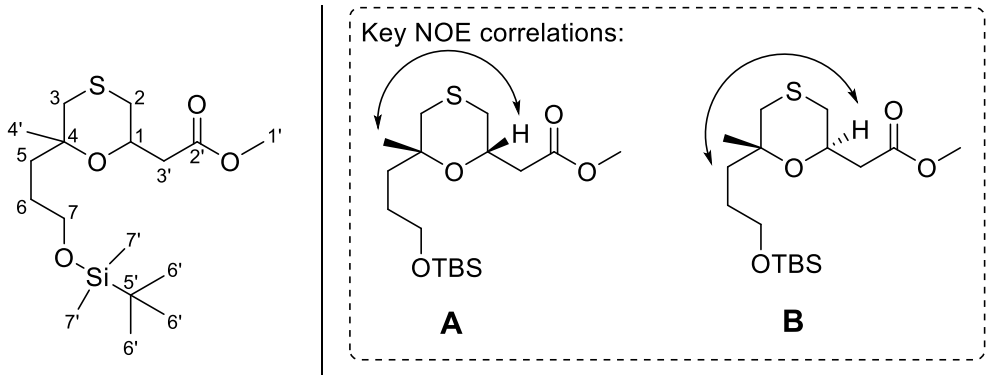
A solution of epoxide **278** (524 mg, 2.28 mmol) in CS_2 (10 mL) was added slowly to a solution of NaSH (844 mg, 15.0 mmol) in MeOH (10 mL) at RT and the reaction mixture was stirred at the same temperature for 18 h. HCl (1.0 M aqueous solution) was then added until pH ≈ 7, and the mixture extracted with ether (3 × 20 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 8:2) to give the *title compound* as a yellow oil (455 mg, 76%). R_f 0.44 (petrol / ether, 9:1); ν_{max} (thin film)/cm^{-1} 3416br, 2953s, 2930s, 2857s, 1255s, 1097s, 836s, 776s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 0.11 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.24 (3H, s, $C(1)H_3$), 1.58 – 1.64 (4H, m, $C(3)H_2$, $C(4)H_2$), 2.59 – 2.68 (2H, m, $C(4')H_2$), 3.66 (2H, t, J = 5.5 Hz, $C(5)H_2$); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) −5.4 (C(1')), 18.3 (C(2')), 25.5 (C(1)), 25.9 (C(3')), 27.3 (C(3) or C(4)), 36.7 (C(4')), 37.1 (C(3) or C(4)), 63.6 (C(5)), 71.1 (C(2)); HRMS (ESI^+) found 265.1648, $C_{12}H_{29}O_2SSi$ $[MH]^+$ requires 265.1652.

Methyl (*E*)-4-({5-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-2-methylpentyl}thio)but-2-enoate (280)



To thiol **279** (903 mg, 3.42 mmol) and K_2CO_3 (566 mg, 4.10 mmol) in DMF (10 mL) was added methyl 4-bromocrotonate (568 μL, 4.10 mmol). The reaction mixture was stirred for 18 h at RT, then water (10 mL) and DCM (10 mL) were added, the layers separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were washed with water (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 7:3) to give the *title compound* as a yellow oil (1.11 g, 89%). R_f 0.09 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 3460br, 2953s, 2930s, 2857s, 2360s, 2341s, 1727s, 1222s, 1097s, 836s; ^{1}H NMR δ_H (600 MHz, $CDCl_3$) 0.07 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.24 (3H, s, C(2')H_3), 1.52 – 1.75 (4H, m, C(7)H_2, C(8)H_2), 2.59 (2H, d, *J* = 5.0 Hz, C(5)H_2), 3.30 (2H, dt, *J* = 7.5, 1.5 Hz, C(4)H_2), 3.65 (2H, t, *J* = 5.5 Hz, C(9)H_2), 3.76 (3H, s, C(1')H_3), 5.89 (1H, dt, *J* = 15.5, 1.5 Hz, C(2)H), 6.90 (1H, dt, *J* = 15.5, 7.5 Hz, C(3)H); ^{13}C NMR δ_C (150 MHz, $CDCl_3$) −5.4 (C(3')), 18.3 (C(4')), 25.9 (C(5')), 26.5 (C(2')), 27.2 (C(7) or C(8)), 34.5 (C(4)), 38.2 (C(7) or C(8)), 43.7 (C(5)), 51.6 (C(1')), 63.6 (C(9)), 72.1 (C(6)), 122.6 (C(2)), 143.9 (C(3)), 166.4 (C(1)); HRMS (ESI^+) found 385.1835, $C_{17}H_{34}O_4NaSSi$ $[MNa]^+$ requires 385.1839.

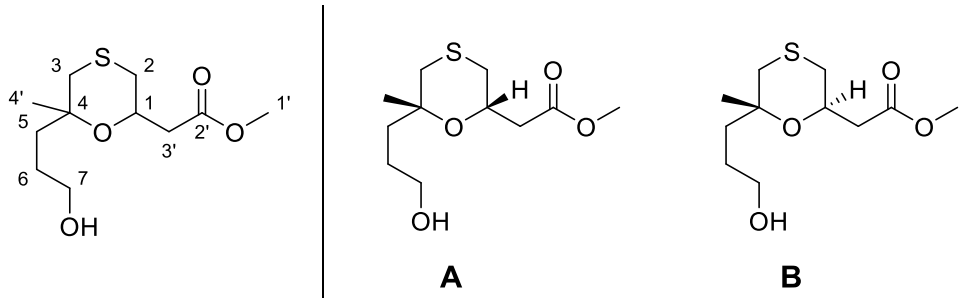
Methyl 2-(6-{3-[(*tert*-butyldimethylsilyl)oxy]propyl}-6-methyl-1,4-oxathian-2-yl)acetate (281, 282)



To a solution of thioether **280** (452 mg, 1.25 mmol) in THF (50 mL) was added NaH (60% w/w dispersion in mineral oil, 100 mg, 2.5 mmol) and the reaction mixture stirred for 18 h at RT. Brine (50 mL) was then added, the mixture extracted with petrol (3 × 50 mL), the organic layers combined, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 95:5) to give the *title compound* as a yellow oil (mixture of diastereomers, 1.5:1 A:B, 235 mg, 52%; isomer ratio determined by integration of the C(1)H signal in the ^{1}H NMR spectrum). R_f 0.61 (petrol / ether, 6:4); ν_{max} (thin film)/cm^{-1} 2953s, 2929s, 2857s, 1742s, 1255s, 1095s, 835s, 714s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 0.05 (3.6H, s, C(7')H_3, A), 0.07 (2.4H, s, C(7')H_3, B), 0.89 (5.4H, s, C(6')H_3, A), 0.91 (3.6H, s, C(6')H_3, B), 1.17 (1.2H, s, C(4')H_3, B), 1.41 (1.8H, s, C(4')H_3, A), 1.42 – 1.66 (3H, m, C(5)H_2, C(6)H_2), 2.14 (0.6H, dd, *J* = 13.5, 1.5 Hz, C(3)H, A), 2.24 (0.4H, dd, *J* = 13.5, 1.5 Hz, C(3)H, B), 2.32 – 2.50 (5H, m, C(3')H_2, C(2)H_2, and C(5)H_2 or C(6)H_2), 2.72 (0.6H, d, *J* = 13.5 Hz, C(3)H, A), 2.73 (0.4H, d, *J* = 13.5 Hz, C(3)H, B), 3.51 – 3.67 (2H, m, C(7)H_2), 3.68 (3H, s, C(1')H_3), 4.20 (0.4H, dddd, *J* = 10.5, 7.5, 6.0, 2.5 Hz, C(1)H, B), 4.27 (0.6H, dddd, *J* = 11.0, 7.5, 5.5, 2.0 Hz, C(1)H, A); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) −5.3 (C(7')), 18.3 (C(5')), 19.1 (C(4'), A), 26.0 (C(6')), 26.3 and 26.5 (C(5) or C(6)), 27.8 (C(4'), B), 28.9 (C(5) or C(6)), 30.7 and 31.0 (C(2) or C(3')), 35.5 (C(3), A), 36.1 (C(3), B), 40.1 (C(5) or

C(6)), 41.6 and 41.8 (C(2) or C(3')), 51.6 (C(1')), 63.4 and 63.5 (C(7)), 67.0 (C(1), B), 67.3 (C(1), A), 73.1 (C(4)), 171.0 and 171.2 (C(2')); HRMS (ESI^+) found 363.2018, $C_{17}H_{35}O_4SSi$ $[MH]^+$ requires 363.2020.

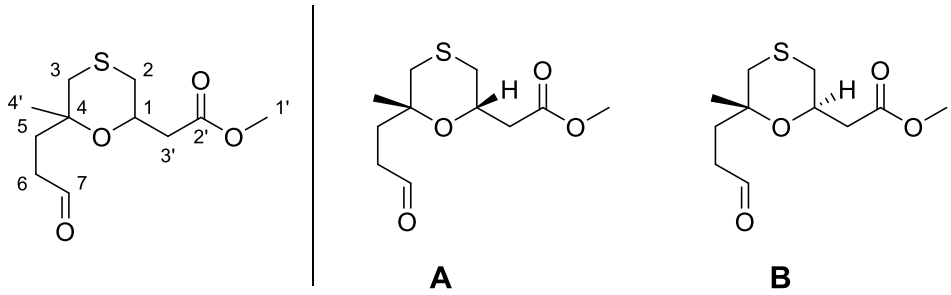
Methyl 2-[6-(3-hydroxypropyl)-6-methyl-1,4-oxathian-2-yl]acetate (283)



To a solution of oxathianes **281** and **282** (100 mg, 0.28 mmol) in MeCN (5 mL) in a polypropylene vial, was added H_2SiF_6 (25% w/w in H_2O, 132 μL, 0.28 mmol). After 2 h satd. aq. NH_4Cl solution was added (10 mL) and the reaction mixture extracted with ether (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude *title compound* (yellow oil, mixture of diastereomers, 1.5:1 A:B, 70 mg, quantitative; isomer ratio determined by integration of the C(4')H signal in the ^1H NMR spectrum) was used in the next step without further purification. R_f 0.09 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3424br, 2951, 2922s, 2364m, 2343m, 1737s, 1438s, 1418m, 1375s, 1263s, 1206s, 1151s, 1061s, 1015s; ^1H NMR δ_H (500 MHz, $CDCl_3$) 1.18 (1.2H, s, C(4')H_3, B), 1.35 – 1.43 (0.4H, m, C(5)H, B), 1.45 (1.8H, s, C(4')H_3, A), 1.49 – 1.73 (3.2H, m, C(5)H_2, A and C(6)H_2), 2.14 (0.6H, dd, *J* = 13.5, 1.5 Hz, C(3)H, A), 2.24 (0.4H, dd, *J* = 13.5, 1.5 Hz, C(3)H, B), 2.31 – 2.54 (4H, m, (C(2)H_2 and C(3')H_2), 2.58 – 2.69 (0.4H, m, C(5)H, B), 2.76 (1H, d, *J* = 13.5 Hz, C(3)H), 3.63 (1.2H, t, *J* = 6.0 Hz, C(7)H_2, A), 3.69 (3H, s, C(1')H_3), 3.70 – 3.80 (0.8H, m, C(7)H_2, B) 4.24 – 4.33 (1H, m, C(1)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 19.1 (C(4'), A), 26.0 and 26.5 (C(5), C(6)), 27.6 (C(4'), B), 28.7 (C(5), B), 30.7

and 30.9 (C(3') or C(2)), 35.5 (C(3), A), 36.3 (C(3), B), 39.9 (C(5) and C(6)), 41.5 (C(3') or C(2)), 51.7 and 51.8 (C(1')), 63.0 and 63.1 (C(7)), 66.9 and 67.6 (C(1)), 73.0 and 73.4 (C(4)), 171.1 and 171.5 (C(2')); HRMS (ESI$^+$) found 271.0974, $C_{11}H_{20}O_4NaS$ $[MNa]^+$ requires 271.0975.

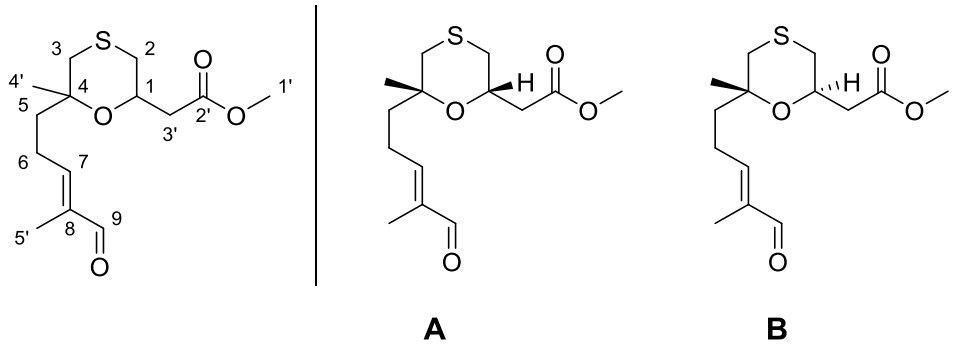
Methyl 2-[6-methyl-6-(3-oxopropyl)-1,4-oxathian-2-yl]acetate (284)



To a solution of alcohol **283** (45 mg, 0.18 mmol) and $NaHCO_3$ (150 mg, 1.8 mmol) in DCM (2 mL) was added Dess–Martin periodinane (85 mg, 0.20 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, then satd. aq. $Na_2S_2O_3$ solution was added (2 mL), followed by satd. aq. $NaHCO_3$ solution (2 mL) and the mixture stirred for 30 min. It was then extracted with DCM (3 × 5 mL), the organic layers combined, washed with brine (5 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 7:3) to give the *title compound* as a yellow oil (mixture of diastereomers, 1.5:1 A:B, 23 mg, 52%; isomer ratio determined by integration of the C(1)H signal in the ^{1}H NMR spectrum). R_f 0.22 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 2953s, 2917s, 1736s, 1725s, 1437s, 1375s, 1314s, 1263s, 1208s, 1152s, 1038s, 1014s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.15 (1.2H, s, C(4')H_3, B), 1.44 (1.8H, s, C(4')H_3, A), 1.51 – 1.58 (0.4H, m, C(5)H, B), 1.70 – 1.96 (1.2H, m, C(5)H_2, A), 2.14 (0.6H, dd, *J* = 13.5, 1.5 Hz, C(3)H, A), 2.26 (0.4H, dd, *J* = 13.5, 2.0 Hz, C(3)H, B), 2.30 – 2.67 (6H, m, C(3')H_2, C(2)H_2, C(6)H_2), 2.75 (0.6H, d, *J* = 13.5 Hz, C(3)H, A), 2.78 (0.4H, d, *J* = 13.5 Hz, C(3)H, B), 3.01 (0.4H, ddd,

J = 15.0, 10.5, 5.0 Hz, C(5)H, B), 3.69 (3H, s, C(1')H_3), 4.15 (0.4H, dddd, *J* = 10.5, 8.5, 4.5, 2.0 Hz, C(1)H, B), 4.25 (0.6H, dddd, *J* = 11.0, 7.5, 5.5, 2.0 Hz, C(1)H, A), 9.72 (0.6H, t, *J* = 2.0 Hz, (C(7)H, A), 9.87 (0.4H, t, *J* = 1.5 Hz, C(7)H, B); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 19.3 (C(4'), A), 24.5 (C(5), B), 27.6 (C(4'), B), 30.6 and 30.8 (C(3'), C(2) or C(6)), 35.3 (C(3), A), 35.9 (C(5), A), 36.3 (C(3), B), 37.7, 38.1, 41.3 and 41.4 (C(3'), C(2) or C(6)), 51.7 (C(1')), 67.2 (C(1), B), 67.6 (C(1), A), 72.4 and 72.5 (C(4)), 171.0 (C(2')), 202.3 (C(7)); HRMS (ESI$^+$) found 269.0819, $C_{11}H_{18}O_4NaS$ $[MNa]^+$ requires 269.0818.

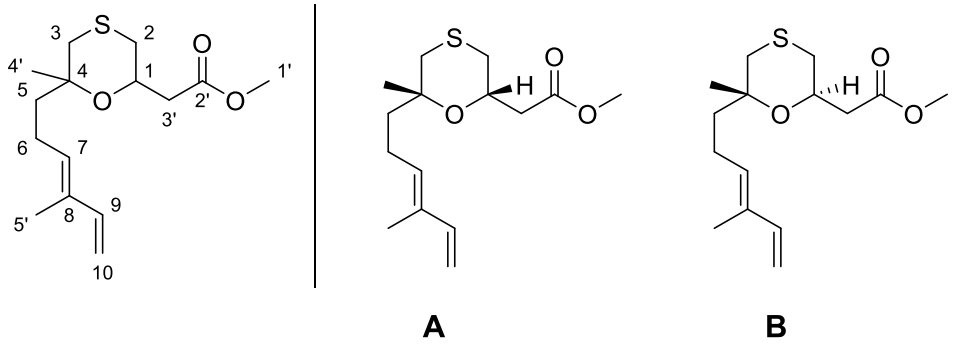
Methyl (*E*)-2-[6-methyl-6-(4-methyl-5-oxopent-3-en-1-yl)-1,4-oxathian-2-yl]acetate (285)



To a solution of aldehyde **284** (471 mg, 1.91 mmol) in toluene (8 mL) was added phosphorane **187** (1.80 g, 5.66 mmol) and the reaction mixture was heated to 90 °C for 48 h. The solvent was then removed *in vacu*o and the crude residue purified by flash chromatography (petrol / ether , 9:1 → 6:4) to give the title compound as a yellow oil (mixture of diastereomers, 1.5:1 A:B, 403 mg, 74%; isomer ratio determined by integration of the C(1)H signal in the ^{1}H NMR spectrum). *E*- stereochemistry was inferred based on literature precedent for Wittig reactions with phosphorane **187**.[95] R_f 0.35 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 2952m, 2910m, 2818m, 2361m, 2342m, 1738s, 1684s, 1437m, 1206m, 1149m, 1067m, 1014m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.23 (1.2H, s, C(4')H_3, B), 1.48 (1.8H, s, C(4')H_3, A), 1.64 (2H, dt, *J* 9.5,

6.5 Hz, C(5)H_2), 1.75 (1.8H, s, C(5')H_3, A), 1.80 (1.2H, s, C(5')H_3, B), 2.15 (0.6H, dd, *J* = 13.5, 1.5 Hz, C(3)H, A), 2.26 (0.4H, dd, *J* = 13.5, 1.5 Hz, C(3)H, B), 2.34 – 2.54 (6H, m, C(3')H_2, C(2)H_2 and C(6)H_2), 2.75 (0.6H, d, *J* = 13.5 Hz, C(3)H, A), 2.78 (0.4H, d, *J* = 13.5 Hz, C(3)H, B) , 3.68 (1.8H, s, C(1')H_3, A), 3.69 (1.2H, s, C(1')H_3, B), 4.22 (0.4H, dddd, *J* 10.5, 7.5, 5.0, 2.0 Hz, C(1)H, B), 4.29 (0.6H, dddd, *J* 10.5, 7.5, 5.5, 2.0 Hz, C(1)H, A), 6.50 (0.6H, td, *J* 7.5, 1.5 Hz, C(7)H, A), 6.57 (0.4H, td, *J* 7.5, 1.5 Hz, C(7)H, B), 9.39 (0.6H, s, C(9)H, A), 9.43 (0.4H, s, C(9)H, B); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 9.1 (C(5')), 19.2 (C(4'), A), 22.5 and 22.9 (C(3'), C(2) or C(6)), 27.8 (C(4'), B), 30.7 and 30.9 (C(3'), C(2) or C(6)), 35.4 (C(3), A), 36.3 (C(3), B), 41.5 (C(3'), C(2) or C(6)), 42.0 (C(5)), 51.7 (C(1')), 67.3 (C(1), B), 67.5 (C(1), A), 72.8 and 72.9 (C(4)), 139.1 and 139.5 (C(8)), 154.6 (C(7), B), 154.8 (C(7), A), 171.0 (C(2')), 195.3 (C(9)); HRMS (ESI^+) found 309.1130, $C_{14}H_{22}O_4NaS$ $[MNa]^+$ requires 309.1131.

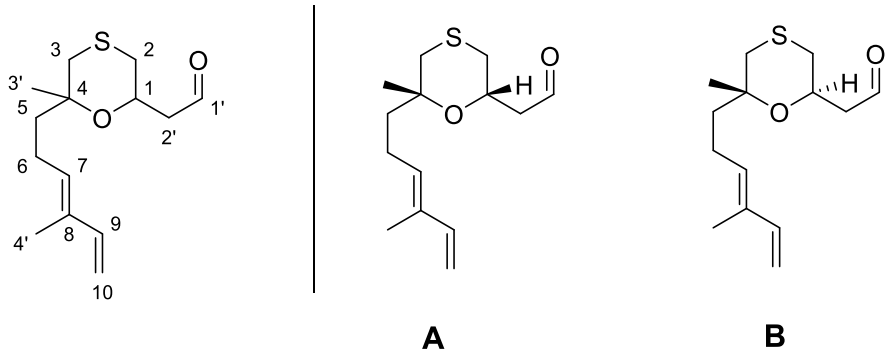
Methyl (*E*)-2-[6-methyl-6-(4-methylhexa-3,5-dien-1-yl)-1,4-oxathian-2-yl]acetate (286)



To methyltriphenylphosphonium iodide (853 mg, 2.10 mmol) in THF (5 mL) was added, at 0 °C, LiHMDS (1.0 M solution in THF, 1.90 mL, 1.90 mmol), and the reaction mixture was stirred for 30 min at RT. It was then cooled down to −78 °C and aldehyde **285** (200 mg, 0.70 mmol) was added as a solution in THF (5 mL). After 3 h brine was added (10 mL) and the layers separated. The aqueous layer was extracted with ether (3 × 10 mL), the organic layers

combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 8:2) to give the *title compound* as a yellow oil (mixture of diastereomers, 1.5:1 A:B, 108 mg, 54%; isomer ratio determined by integration of the C(1)H signal in the ^{1}H NMR spectrum). R_f 0.58 (petrol / ether, 6:4); ν_{max} (thin film)/cm^{-1} 2975m, 2951m, 2916m, 2359w, 2340w, 1740s, 1437m, 1374m, 1313m, 1205m, 1148m, 1082m, 1066m, 1014m, 993m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.21 (1.2H, s, C(4')H_3, B), 1.44 (1.8H, s, C(4')H_3, A), 1.46 – 1.55 (2H, m, C(5)H_2), 1.74 (1.8H, s, C(5')H_3, A), 1.78 (1.2H, s, C(5')H_3, B), 2.08 – 2.29 (2H, m, C(6)H_2), 2.14 (0.6H, dd, *J* = 13.5, 2.0 Hz, C(3)H, A), 2.25 (0.4H, dd, *J* = 13.5, 2.0 Hz, C(3)H, B), 2.32 – 2.54 (4H, m, C(3')H_2, C(2)H_2), 2.72 (0.6H, d, *J* = 13.5 Hz, C(3)H, A), 2.75 (0.4H, d, *J* = 13.5 Hz, C(3)H, B), 3.69 (3H, s, C(1')H_3), 4.23 (0.4H, dddd, *J* = 10.5, 7.5, 5.5, 2.5 Hz, C(1)H, B), 4.28 (0.6H, dddd, *J* = 10.5, 7.5, 5.5, 2.0, C(1)H, A), 4.93 (0.6H, d, *J* = 10.5 Hz, C(10)H, A), 4.95 (0.4H, d, *J* = 10.5 Hz, C(10)H, B), 5.07 (0.6H, d, *J* = 17.5 Hz, C(10)H, A), 5.11 (0.4H, d, *J* = 17.5 Hz, C(10)H, B), 5.47 (0.6H, t, *J* = 7.5 Hz, C(7)H, A), 5.54 (0.4H, t, *J* = 7.5 Hz, C(7)H, B), 6.36 (0.6H, dd, *J* = 17.5, 10.5 Hz, C(9)H, A), 6.39 (0.4H, dd, *J* = 17.5, 10.5 Hz, C(9)H, B); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.5 and 11.6 (C(5')), 19.1 (C(4'), A), 21.7 and 21.9 (C(6)), 27.7 (C(4'), B), 30.7 and 31.0 (C(3') or C(2)), 32.4 (C(5)), 35.4 (C(3), A), 36.1 (C(3), B), 41.6 and 41.7 (C(3') or C(2)), 43.3 (C(5)), 51.6 and 51.7 (C(1')), 67.2 (C(1), B), 67.4 (C(1), A), 73.0 and 73.1 (C(4)), 110.5 and 110.6 (C(10)), 132.8 (C(7), B), 132.9 (C(7), A), 134.0 and 134.1 (C(8)), 141.5 (C(9)), 171.0 and 171.2 (C(2')); HRMS (ESI$^+$) found 285.1520, $C_{15}H_{25}O_3S$ $[MH]^+$ requires 285.2519.

(*E*)-2-[6-Methyl-6-(4-methylhexa-3,5-dien-1-yl)-1,4-oxathian-2-yl]acetaldehyde (287)

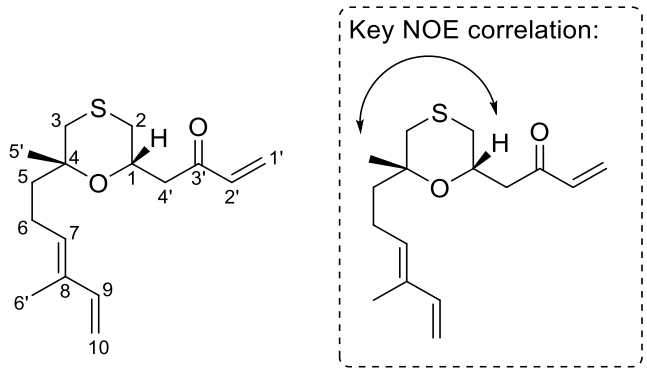


A **B**

To a solution of ester **286** (65 mg, 0.23 mmol) in toluene (6 mL) was added DIBAL (1.0 M solution in hexanes, 230 μL, 0.23 mmol) at −78 °C. After 2 h at the same temperature, satd. aq. Rochelle salt solution was added (5 mL), the mixture warmed to RT and stirred for 15 min. The layers were then separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude residue obtained was dissolved in dry DCM (10 mL), and to this solution was added $NaHCO_3$ (193 mg, 2.3 mmol) and DMP (68 mg, 0.16 mmol). After 15 min, satd. aq. $Na_2S_2O_3$ solution was added (10 mL), followed by satd. aq. $NaHCO_3$ solution (10 mL). The mixture was stirred for 15 min, the layers separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 9:1) to give the *title compound* as a yellow oil (mixture of diastereomers, 1.5:1 A:B, 44 mg, 75 % over two steps; isomer ratio determined by integration of the C(1)H signal in the ^{1}H NMR spectrum). R_f 0.35 (petrol / ether, 6:4); ν_{max} (thin film)/cm^{-1} 2980s, 2972s, 2890s, 1727m, 1382s, 1260s, 1082s, 863m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.21 (1.2H, s, C(3')H_3, B), 1.47 (1.8H, s, C(3')H_3, A), 1.50-1.61 (2H, m, C(5)H_2), 1.73 (1.8H, s, C(4')H_3, A), 1.77 (1.2H, s, C(4')H_3, B), 2.07 - 2.24 (2H, m, C(6)H_2), 2.16 (0.6H, dd, *J* = 13.5, 2.0 Hz, C(3)H, A), 2.27 (0.4H, dd, *J* = 13.5, 2.0 Hz, C(3)H, B), 2.31 – 2.37 (1H, m, C(2)H), 2.40 – 2.62 (3H, m, C(2')H_2 and C(2)H), 2.75 (0.6H, d, *J* = 13.5 Hz,

C(3)H, A), 2.76 (0.4H, d, *J* = 13.5 Hz, C(3)H, B), 4.33 (0.4H, dddd, *J* = 10.5, 8.0, 4.5, 2.0 Hz, C(1)H, B), 4.40 (0.6H, dddd, *J* = 10.5, 8.5, 4.5, 2.0 Hz, C(1)H, A), 4.93 (1H, d, *J* = 10.5 Hz, C(10)H), 4.95 (1H, d, *J* = 10.5 Hz, C(10)H), 5.09 (1H, d, *J* = 17.5 Hz, C(10)H), 5.11 (1H, d, *J* = 17.5 Hz, C(10)H), 5.46 (0.6H, t, *J* = 7.5 Hz, C(7)H, A), 5.53 (0.4H, t, *J* = 7.5 Hz, C(7)H, B), 6.35 (0.6H, dd, *J* = 17.5, 10.5 Hz, C(9)H, A), 6.38 (0.4H, dd, *J* = 17.5, 10.5 Hz, B), 9.74 (0.6H, dd, *J* = 2.5, 1.5 Hz, C(1')H, A), 9.77 (0.4H, dd, *J* = 2.5, 1.5 Hz, C(1')H, B); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.6 and 11.7 (C(4')), 19.3 (C(3'), A), 22.0 (C(6)), 27.7 (C(3'), B), 30.9 and 31.2 (C(2)), 32.4 (C(5), B), 35.4 (C(3), A), 36.0 (C(3), B), 43.3 (C(5), A), 49.8 and 50.0 (C(2')), 66.0 (C(1), B), 66.3 (C(1), A), 73.2 (C(4)), 110.6 and 110.8 (C(10)), 132.4 (C(7), B), 132.7 (C(7), A), 134.1 and 134.2 (C(8)), 141.4 (C(9)), 200.4 and 200.6 (C(1')); HRMS (EI^+) found 254.1348, $C_{14}H_{22}O_2S$ $[MH]^+$ requires 254.1340.

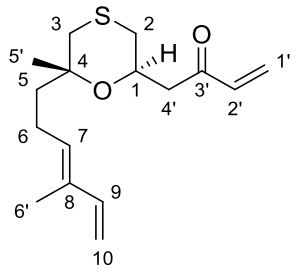
1-{(2*S,6*R**)-6-Methyl-6-[(*E*)-4-methylhexa-3,5-dien-1-yl]-1,4-oxathian-2-yl}but-3-en-2-one (294)**



To a solution of aldehyde **287** in THF (4 mL) was added, at −78 °C, vinylmagnesium bromide (1.0 M solution in THF, 190 μL, 0.19 mmol). The reaction mixture was stirred at −78 °C for 4 h, then brine (4 mL) was added, the layers separated and the aqueous layer extracted with ether (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ (10 mL) and the solvent removed *in vacuo*. The crude residue was dissolved in DCM (5 mL) and to the solution was

added $NaHCO_3$ (84 mg, 1.00 mmol) and DMP (55 mg, 0.13 mmol). After 30 min, satd. aq. $Na_2S_2O_3$ solution was added (5 mL), followed by satd. aq. $NaHCO_3$ solution (10 mL). The mixture was stirred for 15 min, the layers separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 9:1) to give the *title compound* as a yellow oil (11 mg, 34% over two steps) along with the C4 epimer (*vide infra*). R_f 0.27 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2923s, 1700s, 1682s, 1352m, 1313m, 1078s, 1058s; ^1H NMR δ_H (500 MHz, $CDCl_3$) 1.43 (3H, s, C(5')H_3), 1.45 – 1.55 (2H, m, C(5)H_2), 1.72 (3H, s, C(6')H_3), 2.05 – 2.26 (2H, m, C(6)H_2), 2.14 (1H, dd, *J* = 13.5, 2.0 Hz, C(3)H), 2.36 – 2.60 (3H, m, C(4')H, C(2)H_2), 2.73 (1H, d, *J* = 13.5 Hz, C(3)H), 2.84 (1H, dd, *J* = 15.5, 7.5 Hz, C(4')H), 4.35 (1H, dddd, *J* = 10.0, 7.5, 5.0, 2.5 Hz, C(1)H), 4.93 (1H, d, *J* = 11.0 Hz, C(10)H), 5.08 (1H, d, *J* = 17.5 Hz, C(10)H), 5.45 (1H, t, *J* = 7.5 Hz, C(7)H), 5.85 (1H, dd, *J* = 10.5, 1.0 Hz, C(1')H), 6.23 (1H, dd, *J* = 17.5, 1.0 Hz, C(1')H), 6.31 – 6.41 (2H, m, C(2')H and C(9)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.6 (C(6')), 19.1 (C(5')), 22.0 (C(6)), 31.3 (C(2)), 35.5 (C(3)), 43.4 (C(5)), 46.2 (C(4')), 67.5 (C(1)), 73.1 (C(4)), 110.5 (C(10)), 128.6 (C(1')), 132.9 (C(7)), 134.0 (C(8)), 137.0 (C(2')), 141.4 (C(9)), 198.4 (C(3')); HRMS (ESI^+) found 303.1390, $C_{16}H_{24}O_2NaS$ $[MNa]^+$ requires 303.1389.

1-{(2*R,6*R**)-6-Methyl-6-[(*E*)-4-methylhexa-3,5-dien-1-yl]-1,4-oxathian-2-yl}but-3-en-2-one (293)**



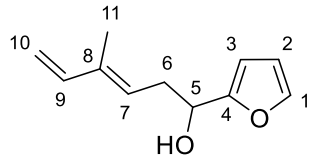
See preparation of oxathiane **294**; *title compound* isolated by flash chromatography (petrol / ether, 9:1) of crude residue (yellow oil, 8 mg, 23% over two steps). R_f 0.23 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2977s, 1728s, 1261m, 1080s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.19 (3H, s, C(5')H_3), 1.50 – 1.63 (2H, m, C(5)H), 1.77 (3H, s, C(6')H_3), 2.01 – 2.17 (2H, m, C(6)H_2), 2.23 – 2.30 (1H, m, C(3)H), 2.38 – 2.51 (3H, m, C(2)H_2, C(5)H), 2.52 – 2.61 (1H, m, C(4')H), 2.74 (1H, dd, *J* = 13.5, 9.5 Hz, C(3)H), 2.86 (1H, dd, *J* = 15.5, 6.5 Hz, C(4')H), 4.23 – 4.37 (1H, m, C(1)H), 4.93 (1H, d, *J* = 10.0 Hz, C(10)H), 5.09 (1H, d, *J* = 17.5 Hz, C(10)H), 5.53 (t, *J* = 7.5 Hz, C(7)H), 5.86 (1H, dd, *J* = 10.5, 1.0 Hz, C(1')H), 6.23 (1H, dd, *J* = 17.5, 1.0 Hz, C(1')H), 6.30 – 6.43 (2H, m, C(2')H and C(9)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 11.6 (C(6')), 22.0 (C(6)), 27.7 (C(5')), 31.1 (C(2)), 32.4 (C(5)), 36.1 (C(3)), 46.3 (C(4')), 67.0 (C(1)), 73.1 (C(4)), 110.7 (C(10)), 128.2 (C(1')), 132.8 (C(7)), 134.1 (C(8)), 137.0 (C(2')), 141.5 (C(9)), 200.4 (C(3')); HRMS (ESI$^+$) found 303.1389, $C_{16}H_{24}O_2NaS$ [MNa]$^+$ requires 303.1389.

Conformational analysis of IMDA adduct 226 (performed by Prof. J. Robertson)

For the endo- and exo- diastereomer of **226**, calculations were performed on an analogue with the CH_3/OH substituents on C3 (eleuthoside numbering) substituted by protons. Conformers were obtained in Spartan 14 following a Monte Carlo search (MMFF). Each conformer was then submitted for an equilibrium geometry calculation (B3LYP/6-31G*) (gas phase), and the conformers and their corresponding HCCH dihedral angles were Boltzmann-weighted from the enthalpy values, and a predicted average coupling constant obtained from a standard Karplus relationship.

Data for Chapter 3

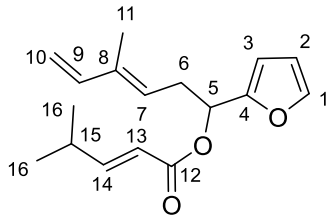
(*E*)-1-(Furan-2-yl)-4-methylhexa-3,5-dien-1-ol (303)



3-methyl-1,4-pentadiene (488 μL, 4.0 mmol) was dissolved in THF (8 mL), *n*-BuLi (2.5 M in hexanes, 1.90 mL, 4.8 mmol) was added at −78 °C, and the reaction mixture was stirred at the same temperature for 20 min; it was then allowed to warm to RT over the course of 1.5 h. The reaction mixture was then cooled to −78 °C and 2-furaldehyde (330 μL, 4.0 mmol) was added as a solution in THF (2 mL). After 1.5 h brine was added (15 mL) and the layers separated, the aqueous layer extracted with ether (3 × 15 mL), the organic layers combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was redissolved in THF (50 mL), and KH was added (60% dispersion in mineral oil, 270 mg, 4.0 mmol) followed by 18-crown-6 (1.06 g, 4.0 mmol). After 30 min the reaction mixture was diluted with ether (50 mL) and water was added (50 mL); the layers were separated and the organic layer washed with water (2 × 25 mL). The solvent was then removed *in vacuo* and the crude residue purified by flash chromatography (petrol / ether, 7:3 → 6:4) to give the *title compound* as an orange oil (631 mg, 89% over two steps). *E*- stereochemistry was inferred based on literature precedent for alkylations with 3-methylpentadienyllithium.[74] R_f 0.35 (petrol / ether, 6:4); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.77 (3H, d, *J* = 1.0 Hz, C(11)H_3), 2.73 (2H, app. t, *J* = 7.0 Hz, C(6)H_2), 4.74 (1H, dd, *J* = 11.5, 7.0 Hz, C(5)H), 4.98 (1H, d, *J* = 10.5 Hz, C(10)H), 5.13 (1H, d, *J* = 17.5 Hz, C(10)H), 5.50 (1H, app. t, *J* = 7.0 Hz, C(7)H), 6.24 (1H, d, *J* = 3.0 Hz, C(3)H), 6.33 (1H, dd, *J* = 3.0, 2.0 Hz, C(2)H), 6.37 (1H, dd, *J* = 17.5, 10.5 Hz, C(9)H), 7.38 (1H, dd, *J* = 2.0, 1.0 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.8 (C(11)), 34.6 (C(6)), 67.3 (C(5)), 106.1 and

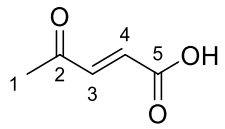
110.1 (C(2), C(3)), 111.5 (C(10)), 127.1 (C(7)), 136.9 (C(8)), 141.1 (C(9)), 141.9 (C(1)), 156.1 (C(4)); HRMS (ESI$^+$) found 179.1068, $C_{11}H_{15}O_2$ $[MH]^+$ requires 179.1067.

(*E*)-1-(Furan-2-yl)-4-methylhexa-3,5-dien-1-yl (*E*)-4-methylpent-2-enoate (305)



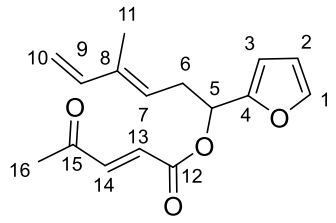
Alcohol **303** (25 mg, 0.14 mmol) was dissolved in DCM (1 mL) and to the solution was added 4-methyl-2-pentenoic acid (15 μL, 0.13 mmol), DCC (29 mg, 0.14 mmol) and DMAP (2 mg, 0.013 mmol). The reaction mixture was stirred for 18 h at RT, then filtered through celite, washed with water (5 mL) and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 9:1→7:3) to give the *title compound* as a yellow oil (11 mg, 31%). R_f 0.63 (petrol / ether, 6:4); ν_{max} (thin film)/cm^{-1} 2981m, 2855m, 1713w, 1383w, 1262w, 1164w, 907s, 731s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.06 (6H, d, *J* = 7.0 Hz, C(16)H_3), 1.76 (3H, s, C(11)H_3), 2.32 – 2.56 (1H, m, C(15)H), 2.75 – 2.95 (2H, m, C(6)H_2), 4.96 (1H, d, *J* = 10.5 Hz, C(10)H), 5.12 (1H, d, *J* = 17.5 Hz, C(10)H), 5.39 (1H, t, *J* = 7.5 Hz, C(7)H), 5.78 (1H, dd, *J* = 15.5, 1.5 Hz, C(13)H), 5.93 (1H, t, *J* = 7.0 Hz, C(5)H), 6.33 (1H, dd, *J* = 17.5, 10.5 Hz, C(9)H), 6.34 (2H, br s, (C(2)H and C(3)H), 6.98 (1H, dd, *J* = 15.5, 6.5 Hz, C(14)H), 7.40 (1H, t, *J* = 1.5 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.8 (C(11)), 21.1 (C(16)), 29.4 (C(15)), 31.0 (C(6)), 67.88 (C(5)), 108.7 and 110.2 (C(2), C(3)), 111.6 (C(10)), 118.3 (C(13)), 126.1 (C(7)), 136.8 (C(8)), 141.0 (C(9)), 142.5 (C(1)), 152.3 (C(4)), 156.3 (C(14)), 166.1 (C(12)); HRMS (ESI$^+$) found 297.1462, $C_{17}H_{22}O_3Na$ $[MNa]^+$ requires 297.1461.

(*E*)-4-Oxopent-2-enoic acid (314)[132]



2-methyl furan (2.0 mL, 22.2 mmol) was dissolved in a *t*-BuOH/water mixture (5:1 v/v, 100 mL), and $NaClO_2$ (6.0 g, 66.6 mmol) and $NaHPO_4$ (9.2 g, 66.6 mmol) were added. The mixture was stirred for 2 h, then the solvent was removed *in vacuo*. DCM (100 mL) and brine (100 mL) were added, the layers separated and the aqueous layer extracted with DCM (3 × 75 mL). The combined organic layers were dried over $MgSO_4$, and the solvent removed *in vacuo* to give the crude 5-hydroxy-5-methylfuran-2(5*H*)-one. One third of the crude residue (700 mg, 6.14 mmol) was dissolved in a THF/acetone/water mixture (5:4:1 v/v, 2 mL) and pyridine was added (5 μL, 0.06 mmol). After 2 h the solvent was removed *in vacuo* to give the title compound as a white solid (696 mg, 83% over two steps). ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.40 (3H, s, C(1)H_3), 6.66 (1H, d, *J* = 16.0 Hz, C(4)H), 7.10 (1H, d, *J* = 16.0 Hz, C(3)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 28.2 (C(1)), 130.7 (C(4)), 141.5 (C(3)), 170.3 (C(5)), 197.6 (C(2)).

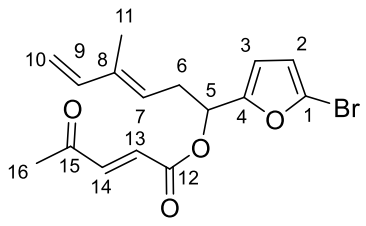
(*E*)-1-(Furan-2-yl)-4-methylhexa-3,5-dien-1-yl (*E*)-4-oxopent-2-enoate (315)



Alcohol **303** (94 mg, 0.53 mmol) was dissolved in DCM (7 mL). To the solution was added acid **314** (66 mg, 0.58 mmol), DCC (119 mg, 0.58 mmol) and DMAP (13 mg, 0.11 mmol), and the reaction mixture was stirred for 2 h at RT. It was then filtered through celite and the

solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 8:2) to give the *title compound* as a yellow oil (103 mg, 71%). R_f 0.29 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2926w, 1724s, 1703s, 1687s, 1289s, 1256s, 1172s, 981s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.77 (3H, s, C(11)H_3), 2.35 (3H, s, C(16)H_3), 2.78 – 2.95 (2H, m, C(6)H_2), 4.98 (1H, d, *J* = 10.5 Hz, C(10)H), 5.14 (1H, d, *J* = 17.5 Hz, C(10)H), 5.38 (1H, t, *J* = 7.5 Hz, C(7)H), 5.97 (1H, t, *J* = 7.0 Hz, C(5)H), 6.32 (1H, dd, *J* = 17.5, 10.5 Hz, C(9)H), 6.35 - 6.39 (2H, m, C(2)H, C(3)H), 6.65 (1H, d, *J* = 16.0 Hz) and 7.02 (1H, d, *J* = 16.0 Hz, C(13)H, C(14)H), 7.41 (1H, d, *J* = 1.5 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.9 (C11)), 28.1 (C(16)), 31.4 (C(6)), 69.2 (C(5)), 109.3 and 110.4 (C(2), (C(3)), 112.0 (C(10)), 125.5 (C(7)), 131.3 and 140.0 (C(13), C(14)), 137.2 (C(8)), 140.8 (C(9)), 142.8 (C(1)), 151.3 (C(4)), 164.6 (C(12)), 197.5 (C(15)); HRMS (ESI$^+$) found 275.1279, $C_{16}H_{19}O_4$ [MH]$^+$ requires 275.1278.

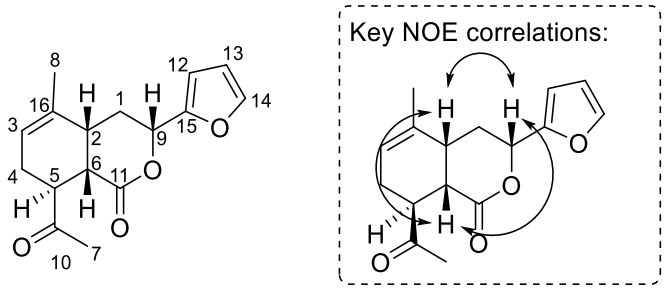
(*E*)-1-(5-Bromofuran-2-yl)-4-methylhexa-3,5-dien-1-yl (*E*)-4-oxopent-2-enoate (324)



3-methyl-1,4-pentadiene (370 μL, 3.0 mmol) was dissolved in THF (1.8 mL), *n*-BuLi (2.5 M in hexanes, 1.2 mL, 3 mmol) was added at −78 °C, and the reaction mixture was stirred at the same temperature for 20 min; it was then allowed to warm to RT over the course of 1.5 h. The reaction mixture was then cooled to −78 °C, and an aliquot (580 μL, 0.58 mmol) was added to a solution of 5-bromofuran-2-carbaldehyde (100 μL, 0.58 mmol) and $BF_3{\cdot}OEt_2$ (72 μL, 0.58 mmol) in THF (3 mL). The reaction mixture was allowed to warm to RT; after 3.5 h brine was added (10 mL) and the layers separated, the aqueous layer extracted with ether (3 × 15 mL),

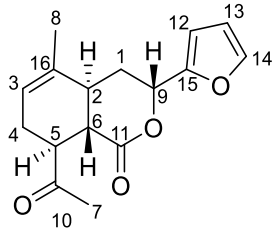
the organic layers combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 8:2 → 6:4) to give alcohol **321** as an orange oil (26 mg, 17%). This alcohol (26 mg, 0.10 mmol) was dissolved in DCM (2 mL); to the solution was added (*E*)-4-oxopent-2-enoic acid (17 mg, 0.15 mmol), DCC (31 mg, 0.15 mmol) and DMAP (2 mg, 0.02 mmol), and the reaction mixture was stirred for 1 h at RT. It was then filtered through celite and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 9:1) to give the *title compound* as a yellow oil (23 mg, 65%). *E*- stereochemistry of the trisubstituted alkene was inferred based on literature precedent for alkylations with 3-methylpentadienyllithium.[74] R_f 0.31 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2961m, 1780s, 1721s, 1686s, 1287s, 1256s, 1172s, 991s; ^1H NMR δ_H (400 MHz, $CDCl_3$) 1.77 (3H, d, *J* = 1.5 Hz, C(11)H_3), 2.36 (3H, s, C(16)H_3), 2.77 – 2.93 (2H, m, C(6)H_2), 4.99 (1H, d, *J* = 10.5 Hz, C(10)H), 5.15 (1H, d, *J* = 17.5 Hz, C(10)H), 5.35 (1H, t, *J* = 7.5 Hz, C(7)H), 5.88 (1H, t, *J* = 7.0 Hz, C(5)H), 6.27 (1H, d, *J* = 3.5 Hz) and 6.35 (1H, d, *J* = 3.5 Hz, C(2)H, C(3)H), 6.32 (1H, dd, *J* = 17.5, 10.5 Hz, C(9)H), 6.64 (1H, d, *J* = 16.0 Hz) and 7.02 (1H, d, *J* = 16.0 Hz, C(13)H, C(14)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 12.0 (C11)), 28.1 (C(16)), 31.2 (C(6)), 68.9 (C(5)), 112.1 (2 signals) (C(2), C(3)), 112.2 (C(10)), 122.5 (C(1)), 125.0 (C(7)), 131.1 and 140.5 (C(13), C(14)), 137.5 (C(8)), 140.7 (C(9)), 153.2 (C(4)), 164.5 (C(12)), 197.4 (C(15)); HRMS (ESI^+) found 375.0204, 377.0183, $C_{16}H_{17}O_4{}^{79}BrNa$ $[MNa]^+$ requires 375.0202, $C_{16}H_{17}O_4{}^{81}BrNa$ $[MNa]^+$ requires 377.0182.

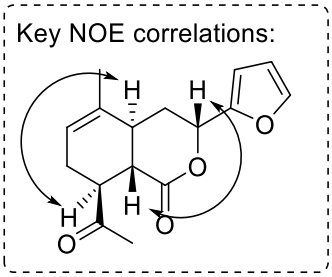
(3*S,4a*S**,8*R**,8a*R**)-8-Acetyl-3-(furan-2-yl)-5-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (316)**



Ester **315** (50 mg, 0.18 mmol) was dissolved in toluene (20 mL) in a pressure tube, and the solution was heated to 90 °C for 18 h. The solvent was then removed *in vacuo* to give the *title compound* as the major component of a mixture of diastereomers (36 mg, 72%, 2:1 d.r.). Flash chromatography (petrol / ether, 9:1 → 7:3) afforded pure *title compound* (colourless oil, 20 mg, 40%), as well as the *exo*-adduct **317** (colourless oil, 8 mg, 16%). R_f 0.26 (petrol / ether = 3:7); ν_{max} (thin film)/cm^{-1} 2919w, 1733s, 1705s, 1358m, 1173s, 1156s, 1010m, 693m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.65 (3H, d, *J* = 1.5 Hz, C(8)H_3), 1.77 (1H, app. dt, *J* = 14.0, 12.0 Hz, C(1)H), 2.21 (3H, s, C(7)H_3), 2.40 – 2.47 (1H, m, C(4)H), 2.53 (1H, ddd, *J* = 14.0, 8.0, 2.0 Hz, C(1)H), 2.56 – 2.63 (1H, m, C(4)H), 2.94 – 3.04 (1H, m, C(2)H), 3.25 (1H, app. dt, *J* = 6.0, 3.5 Hz, C(5)H), 3.47 (1H, ddd, *J* = 9.5, 3.5, 1.5 Hz, C(6)H), 5.39 (1H, dd, *J* = 12.0, 2.0 Hz, C(9)H), 5.47 (1H, br s, C(3)H), 6.38 (1H, dd, *J* = 3.5, 2.0 Hz, C(13)H), 6.42 (1H, d, *J* = 3.5 Hz, C(12)H), 7.43 (1H, dd, *J* = 2.0, 1.0 Hz, C(14)); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 21.0 (C(8)), 23.9 (C(4)), 27.4 (C(7)), 32.5 (C(1)), 32.7 (C(2)), 38.3 (C(6)), 46.1 (C(5)), 71.7 (C(9)), 108.5 (C(12)), 110.4 (C(13)), 119.4 (C(3)), 135.2 (C(16)), 143.0 (C(14)), 150.8 (C(15)), 172.9 (C(11)), 209.3 (C(10)); HRMS (ESI$^+$) found 297.1098, $C_{16}H_{18}O_4Na$ [MNa]$^+$ requires 297.1097.

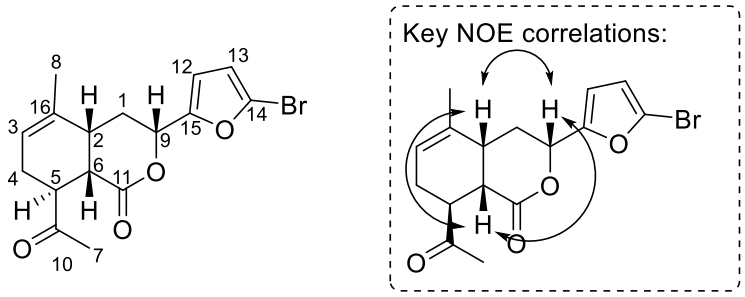
(3*R,4a*S**,8*S**,8a*S**)-8-Acetyl-3-(furan-2-yl)-5-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (317)**





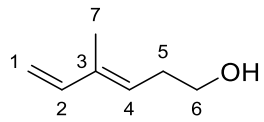
See preparation of lactone **316**. R_f 0.29 (petrol / ether = 3:7); ν_{max} (thin film)/cm^{-1} 2920m, 1740s, 1711s, 1174s, 1013m, 746m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.72 (3H, s, C(8)H_3), 1.94 – 2.05 (2H, m, C(1)H, C(4)H), 2.31 – 2.35 (1H, m, C(4)H), 2.37 (3H, s, C(7)H_3), 2.47 – 2.58 (1H, m, C(2)H), 2.68 (1H, app. dt, *J* = 13.5, 9.0 Hz, C(1)H), 2.94 (1H, app. td, *J* = 11.0, 5.5 Hz, C(5)H), 3.00 (1H, dd, *J* = 12.0, 11.0 Hz, C(6)H), 5.44 – 5.51 (2H, m, C(3)H, C(9)H), 6.39 (1H, dd, *J* = 3.5, 2.0 Hz, C(13)H), 6.45 (1H, d, *J* = 3.5 Hz, C(12)H), 7.45 (1H, d, *J* = 2.0 Hz, C(14)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 20.0 (C(8)), 28.3 (C(4)), 30.2 and 30.2 (C(1), C(7)), 35.7 (C(2)), 43.4 (C(6)), 45.9 (C(5)), 70.8 (C(9)), 109.4 (C(12)), 110.5 (C(13)), 120.9 (C(3)), 133.7 (C(16)), 143.3 (C(14)), 150.6 (C(15)), 173.5 (C(11)), 211.4 (C(10)); HRMS (ESI$^+$) found 275.1277, $C_{16}H_{18}O_4$ $[MH]^+$ requires 275.1278.

(3*R,4a*R**,8*S**,8a*S**)-8-Acetyl-3-(5-bromofuran-2-yl)-5-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (325)**



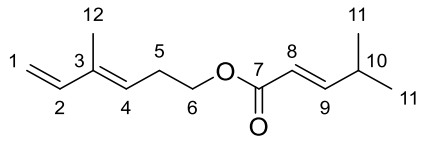
Ester **324** (11 mg, 0.03 mmol) was dissolved in toluene (3 mL) in a pressure tube. A few pieces of copper wire were added and the mixture was heated to 90 °C for 18 h. The solvent was then removed *in vacuo* to give the title compound as the major component of a mixture of diastereomers (9 mg, 82%, 3:1 d.r. ; isomer ratio determined by integration of the C(9)H signal in the ^{1}H NMR spectrum). Flash chromatography (petrol / ether, 8:2) afforded pure *title compound* (colourless oil, 3 mg, 27%). R_f 0.12 (petrol / ether, 6:4); ν_{max} (thin film)/cm^{-1} 2921w, 1777s, 1735s, 1355m, 1124s, 1156s, 1012m, 794w; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.65 (3H, d, *J* = 1.5 Hz, C(8)H_3), 1.75 (1H, dt, *J* = 14.0, 12.0 Hz, C(1)H), 2.21 (3H, s, C(7)H_3), 2.41 – 2.48 (1H, m, C(4)H), 2.53 (1H, ddd, *J* = 14.0, 8.0, 2.0 Hz, C(1)H), 2.55 – 2.63 (1H, m, C(4)H), 2.95 – 3.05 (1H, m, C(2)H), 3.25 (1H, dt, *J* = 6.5, 3.5 Hz, C(5)H), 3.45 (1H, ddd, *J* = 9.5, 3.5, 1.5 Hz, C(6)H), 5.33 (1H, dd, *J* = 12.0, 2.0 Hz, C(9)H), 5.47 (1H, br s, C(3)H), 6.31 (1H, d, *J* = 3.5 Hz) and 6.39 (1H, d, *J* = 3.5 Hz, C(12)H, C(13)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 21.0 C(8)), 23.9 C(4)), 27.4 (C(7)), 32.4 (C(1)), 32.6 (C(2)), 38.3 (C(6)), 46.1 (C(5)), 71.4 (C(9)), 111.2 and 112.2 (C(12), C(13)), 119.5 (C(3)), 122.8 (C(14)), 135.1 (C(16)), 152.7 (C(15)), 172.7 (C(11)), 209.2 (C(10)); HRMS (ESI$^+$) found 375.0203, 377.0182, $C_{16}H_{17}{}^{79}BrO_4Na$ $[MNa]^+$ requires 375.0202, $C_{16}H_{17}{}^{81}BrO_4Na$ $[MNa]^+$ requires 377.0182. *Diagnostic signals for minor isomer*: ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.72 (3H, br s, C(8)H_3), 2.37 (3H, s, C(7)H_3), 5.42 (1H, dd, *J* = 10.0, 7.0 Hz, C(9)H).

(*E*)-4-Methylhexa-3,5-dien-1-ol (333)[134]



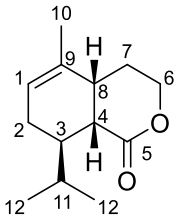
Bromide **182** (23.8 g, 136 mmol) was dissolved in acetic acid (120 mL), KOAc (42.6 g) was added, and the mixture heated to 120 °C for 18 h. Water (100 mL) was then added and the mixture extracted with ether (3 × 200 mL). The combined organic layers were washed with satd. aq. $NaHCO_3$ solution (3 × 300 mL) then brine (200 mL), dried over $MgSO_4$ and the solvent removed in vacuo to give 4-methylhexa-3,5-dien-1-yl acetate (3:1 *E*:*Z*, 18.8 g). This was dissolved in MeOH (110 mL), KOH was added (18.5 g, 330 mmol), and the mixture was heated to 70 °C for 2 h. Water (100 mL) was then added and the mixture extracted with ether (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified *via* bulb-to-bulb distillation (110°C at 20 mmHg) to give the title compound as a colourless oil (3:1 *E*:*Z*, 7.2 g, 47% over two steps; isomer ratio determined by integration of the C(2)H signal in the ^{1}H NMR spectrum). R_f 0.45 (petrol / ether, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.77 (3H, s, C(7)H_3), 1.96 (1H, br s, C(6)H_2O*H*), 2.42 (2H, app. q, *J* = 7.0 Hz, C(5)H_2), 3.66 (2H, t, *J* = 6.5 Hz, C(6)H_2), 4.97 (1H, d, *J* = 10.5 Hz, C(1)H), 5.12 (1H, d, *J* = 17.5 Hz, C(1)H), 5.49 (1H, t, *J* = 7.5 Hz, C(4)H), 6.38 (1H, dd, *J* = 17.5, 10.5 Hz, C(2)H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 11.8 (C(7)), 31.7 (C(5)), 62.1 (C(6)), 111.3 (C(1)), 128.2 (C(4)), 136.5 (C(3)), 141.1 (C(2)). *Diagnostic signals for minor isomer*: ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.86 (3H, s, C(7)H_3), 5.26 (1H, d, *J* = 17.5 Hz, C(1)H), 5.41 (1H, t, *J* = 8.0 Hz, C(4)H), 6.79 (1H, dd, *J* = 17.5, 11.0 Hz, C(2)H).

(*E*)-4-Methylhexa-3,5-dien-1-yl (*E*)-4-methylpent-2-enoate (158)[81]



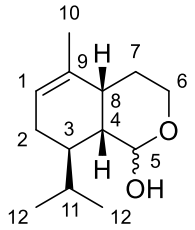
Alcohol **333** (10.1 g, 90.2 mmol) and (*E*)-4-methylpent-2-enoic acid (15.4 g, 136 mmol) were dissolved in DCM (400 mL), then DCC (28.0 g, 136 mmol) was added in portions followed by DMAP (2.2 g, 18.0 mmol). After stirring for 18 h at RT the reaction mixture was filtered through celite, washed with satd. aq. $NaHCO_3$ solution (300 mL) then brine (300 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 95:5) to give the title compound as a yellow oil (3:1 *E*:*Z*, 15.6 g, 83%; isomer ratio determined by integration of the C(2)H signal in the ^{1}H NMR spectrum). R_f 0.74 (petrol / ether, = 1:1); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.07 (6H, d, *J* = 7.0 Hz, C(11)H_3), 1.77 (3H, s, C(12)H_3), 2.41 – 2.58 (3H, m, C(5)H_2 and C(10)H), 4.16 (2H, t, *J* = 7.5 Hz, C(6)H_2), 4.98 (1H, d, *J* = 10.5 Hz, C(1)H), 5.14 (1H, d, *J* = 17.5 Hz, C(1)H), 5.49 (1H, t, *J* = 7.5 Hz, C(4)H), 5.77 (1H, dd, *J* = 15.5, 1.5 Hz, C(8)H), 6.38 (1H, dd, *J* = 17.5, 10.5 Hz, C(2)H), 6.95 (1H, dd, *J* = 15.5, 6.5 Hz, C(9)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.8 (C(12)), 21.2 C(11)), 27.8 C(5)), 30.9 C(10)), 63.4 C(6)), 111.5 (C(1)), 118.4 (C(8)), 127.4 C(4)), 136.4 C(3)), 141.0 (C(2)), 155.7 C(9)), 167.0 C(7)). *Diagnostic signals for minor isomer*: ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.84 (3H, s, C(12)H_3), 5.25 (1H, d, *J* = 17.5 Hz, C(1)H), 5.39 (1H, t, *J* = 8.0 Hz, C(4)H), 6.77 (1H, ddd, *J* = 17.5, 11.0, 1.0 Hz, C(2)H).

(4a*R,8*R**,8a*R**)-8-Isopropyl-5-methyl-3,4,4a,7,8,8a-hexahydro-1H-isochromen-1-one (159)**[85]



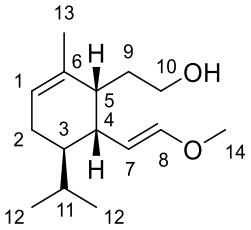
$TfNH_2$ (4.20 g, 28.2 mmol) was dissolved in DCE (250 mL), then Me_2AlCl (1.0 M solution in hexanes, 56.6 mL, 56.6 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at RT for 1 h. Ester **158** (5.35 g, 25.7 mmol) was then added as a solution in DCE (10 mL) and the reaction mixture was heated to reflux for 4 h. The reaction was quenched with HCl (1.0 M aqueous solution, 200 mL), the layers were separated and the aqueous layer extracted with ether (3 × 200 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 8:2) to give the title compound as a brown oil (2.38 g, 45%) as well as unreacted starting (*Z*)-4-Methylhexa-3,5-dien-1-yl (*E*)-4-methylpent-2-enoate (1.32 g, 25%). R_f 0.11 (petrol / ether, 8:2); ^{1}H NMR δ_H (400 MHz, C_6D_6) 0.75 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.86 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.17 – 1.22 (2H, m, C(7)H_2), 1.30 (3H, br s, C(10)H_3), 1.41 – 1.52 (1H, m, C(11)H), 1.77 – 1.87 (1H, m, C(2)H), 1.90 – 1.98 (1H, m, C(8)H), 2.10 (1H, dtd, *J* = 9.0, 5.0, 3.5 Hz, C(3)H), 2.17 – 2.28 (1H, m, C(2)H), 2.50 (1H, ddd, *J* = 6.5, 4.5, 1.5 Hz, C(4)H), 3.57 (1H, dddd, *J* = 11.5, 5.5, 4.5, 1.0 Hz, C(6)H), 3.67 (1H, ddd, *J* = 11.5, 7.5, 5.0 Hz, C(6)H), 5.25 (1H, br s, C(1)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 20.4 and 20.5 (C(10), C(12)), 21.0 (C(12)), 24.6 (C(2)), 26.1 (C(7)), 27.1 (C(11)), 33.1 (C(8)), 39.5 (C(3)), 43.1 (C(4)), 65.6 (C(6)), 124.0 (C(1)), 132.5 (C(9)), 172.6 (C(5)).

(4a*R,8*R**,8a*R**)-8-Isopropyl-5-methyl-3,4,4a,7,8,8a-hexahydro-1H-isochromen-1-ol (334)**



Lactone **159** (2.38 g, 11.4 mmol) was dissolved in DCM (150 mL) and DIBAL (1.0 M solution in cyclohexane, 13.7 mL, 13.7 mmol) was added dropwise at −78 °C. The reaction mixture was stirred at the same temperature for 3 h, then satd. aq. Rochelle salt solution was added (150 mL), the layers separated and the aqueous layer extracted with DCM (3 × 150 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to give the *title compound* as a yellow oil, of sufficient purity to be used directly in the next step (2.25 g, 94%). R_f 0.33 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3379br, 2958s, 1464m, 1438m, 1387m, 1368m, 1114m, 1071m, 1030s, 1000m; ^{1}H NMR δ_H (400 MHz, C_6D_6) 0.73 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.84 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.38 – 1.52 (2H, m, C(7)H_2), 1.56 (3H, d, *J* = 2.0 Hz, C(10)H_3), 1.62 – 1.80 (3H, m), 1.80 – 1.90 (1H, m) and 1.91 – 2.02 (2H, m, C(2)H_2, C(3)H, C(4)H, C(11)H), 2.46 – 2.57 (1H, m, C(8)H), 3.48 (1H, ddd, *J* = 11.0, 4.5, 3.5 Hz, C(6)H), 3.99 (1H, app. td, *J* = 11.0, 3.5 Hz, C(6)H), 5.23 (1H, d, *J* = 2.0 Hz, C(5)H), 5.32 (1H, br s, C(1)H); ^{13}C NMR δ_C (100 MHz, C_6D_6) 15.4 (C(12)), 20.8 (C(12)), 21.1 (C(10)), 24.3 (C(2)), 26.3 (C(11)), 27.5 (C(7)), 33.4 (C(8)), 34.1 (C(3)), 40.3 (C(4)), 59.1 (C(6)), 92.0 (C(5)), 121.4 (C(1)), 135.7 (C(9)); HRMS (ESI^+) found 233.1514, $C_{13}H_{22}O_2Na$ $[MNa]^+$ requires 233.1512.

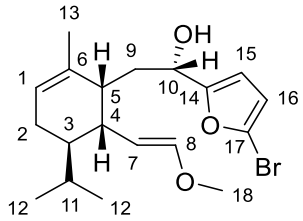
2-{(1*R,5*R**,6*R**)-5-Isopropyl-6-[(*E*)-2-methoxyvinyl]-2-methylcyclohex-2-en-1-yl}ethan-1-ol (327)**



(Methoxymethyl)triphenylphosphonium chloride (18.1 g, 52.4 mmol) was dissolved in THF (200 mL) and *t*-BuOK was added (1.0 M solution in THF, 47.6 mL, 47.6 mmol) at −78 °C. The mixture was stirred at the same temperature for 30 min, then lactol **334** (5.0 g, 23.8 mmol) was added as a solution in THF (20 mL), and the mixture allowed to warm to RT and stirred for 18 h. Brine (200 mL) was then added, the layers separated and the aqueous layer extracted with ether (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 9:1 → 8:2) to give the *title compound* along with the *Z*- isomer as a colourless oil (3:1 *E*:*Z*, 3.66 g, 65%; isomer ratio determined by integration of the C(7)H signal in the ^{1}H NMR spectrum). R_f 0.25 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3351br, 2957s, 2931s, 2891s, 1651s, 1466m, 1450m, 1208s, 1145m, 1115m, 1033m, 1020m, 939m, 773m; ^{1}H NMR δ_H (400 MHz, C_6D_6, major isomer) 0.73 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.91 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.36 – 1.46 (1H, m, C(3)H), 1.60 – 1.66 (2H, m, C(9)H_2), 1.68 (3H, s, C(13)H_3), 1.75 – 1.89 (2H, m, C(2)H, C(11)H), 1.90 – 2.00 (2H, m, C(2)H, C(5)H), 2.10 (app. td, *J* = 10.0, 4.5 Hz, C(4)H), 3.18 (3H, s, C(14)H_3), 3.45-3.57 (2H, m, C(10)H_2), 4.67 (1H, *J* = 12.5, 10.0 Hz , C(7)H), 5.35 (1H, br s, C(1)H), 6.25 (d, *J* = 12.5 Hz, C(8)H); ^{13}C NMR δ_C (100 MHz, C_6D_6) 16.5 (C(12)), 21.3 (C(12)), 22.8 (C(13)), 24.6 (C(2)), 28.1 (C(11)), 33.7 (C(9)), 39.8 (C(4)), 40.3 (C(3)), 41.3 (C(5)), 55.5 (C(14)), 62.4 (C(10)), 104.5 (C(7)), 121.4 (C(1)), 136.9 (C(6)), 147.8 (C(8)); HRMS (ESI$^+$) found 239.2007, $C_{15}H_{27}O_2$ [MH]$^+$

requires 239.2006. *Diagnostic signals for minor isomer:* ^{1}H NMR δ_H (400 MHz, C_6D_6) 4.33 (1H, dd, *J* = 10.0, 6.5 Hz, C(7)H), 5.65 (1H, d, *J* = 6.5 Hz, C(8)H).

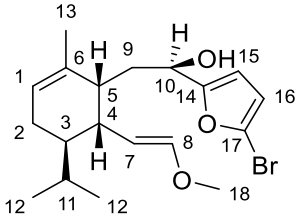
(*S)-1-(5-Bromofuran-2-yl)-2-{(1*R**,5*R**,6*R**)-5-isopropyl-6-[(*E*)-2-methoxyvinyl]-2-methylcyclohex-2-en-1-yl}ethan-1-ol (335)**



Alcohol **327** (3.66 g, 15.4 mmol) and DMSO (1.4 mL, 20.0 mmol) were dissolved in THF (120 mL). The mixture was cooled to −78 °C and oxalyl chloride was added (1.6 mL, 18.5 mmol). After stirring for 20 min at −78 °C, NEt_3 (6.4 mL, 46.1 mmol) was added and the reaction mixture was allowed to warm to RT. After 30 min ether was added (100 mL) and the mixture filtered through celite. The solvent was removed *in vacuo* to give the crude aldehyde, which was used immediately in the next step. Dibromofuran (5.0 mL, 50.0 mmol) was dissolved in THF (40 mL) and cooled to −78 °C, then *n*-BuLi was added (2.5 M solution in hexanes, 18.8 mL, 46.9 mmol). The mixture was stirred at the same temperature for 10 min, then added to the previously prepared aldehyde dissolved in THF (100 mL), at −78 °C. The reaction mixture was allowed to warm to RT and stirred for 18 h, then brine (100 mL) was added, the layers separated and the aqueous layer extacted with ether (2 × 100 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, the solvent removed *in vacuo* and the crude residue purified by flash chromatography (petrol / ether, 9:1 → 8:2) to give the *title compound* as a colourless oil (3:1 *E*:*Z*, 2.30 g, 39% over two steps; *E*:*Z* isomer ratio determined by integration of the C(7)H signal in the ^{1}H NMR spectrum), as well as its C10 epimer **336** (3:1 *E*:*Z*, 2.20 g, 37% over two steps; *E*:*Z* isomer ratio determined by

integration of the C(7)H signal in the ^{1}H NMR spectrum). R_f 0.44 (petrol / ether, 7:3); ν_{max} (thin film)/cm^{-1} 3421br, 2955s, 1652s, 1505m, 1450m, 1207s, 1125s, 1010m, 939m, 784s; ^{1}H NMR δ_H (400 MHz, C_6D_6) 0.75 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.92 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.30 – 1.40 (1H, m, C(3)H), 1.71 (3H, d, *J* = 2.0 Hz, C(13)H_3), 1.74 – 1.89 (4H, m, C(2)H, C(9)H_2, C(11)H), 1.91 – 2.03 (1H, m, C(2)H), 2.15 – 2.27 (2H, m, C(4)H, C(5)H), 3.18 (3H, s, C(18)H_3), 4.57 (1H, dd, *J* = 9.0, 4.5 Hz, C(10)H), 4.66 (1H, dd, *J* = 12.5, 10.0 Hz, C(7)H), 5.35 (1H, br s, C(1)H), 5.82 (1H, d, *J* = 3.5 Hz) and 5.90 (1H, d, *J* = 3.5 Hz, C(15)H, C(16)H), 6.27 (1H, d, *J* = 12.5 Hz, C(8)H); ^{13}C NMR δ_C (100 MHz, C_6D_6) 17.0 (C(12)), 21.2 (C(12)), 22.4 (C(13)), 24.5 (C(2)), 28.0 (C(11)), 36.4 (C(9)), 39.3 and 39.9 (C(4), C(5)), 40.7 (C(3)), 55.5 (C(18)), 66.9 (C(10)), 104.1 (C(7)), 108.2 and 112.1 (C(15), C(16)), 121.0 (C(17)), 121.6 (C(1)), 136.5 (C(6)), 147.9 (C(8)), 160.6 (C(14)); HRMS (Ammonia CI) found 400.1476, 400.1482, $C_{19}H_{31}{}^{79}BrNO_3$ $[MNH_4]^+$ requires 400.1482, $C_{19}H_{31}{}^{81}BrNO_3$ $[MNH_4]^+$ requires 402.1461. *Diagnostic signals for Z- enol ether isomer:* ^{1}H NMR δ_H (400 MHz, C_6D_6) 4.32 (1H, dd, *J* = 10.5, 6.5 Hz, C(7)H), 5.61 (1H, d, *J* = 6.5 Hz, C(8)H).

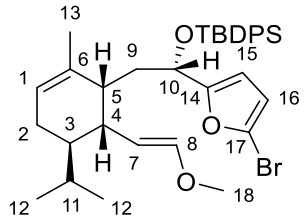
(*R)-1-(5-Bromofuran-2-yl)-2-{(1*R**,5*R**,6*R**)-5-isopropyl-6-[(*E*)-2-methoxyvinyl]-2-methylcyclohex-2-en-1-yl}ethan-1-ol (336)**



See preparation of enol ether **335**. R_f 0.23 (petrol / ether, 7:3); ν_{max} (thin film)/cm^{-1} 3397br, 2955s, 1651s, 1504m, 1451m, 1208s, 1124s, 1055s, 940s, 785s; ^{1}H NMR δ_H (400 MHz, C_6D_6) 0.68 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.84 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.32 – 1.41 (1H, m, C(3)H), 1.63 (3H, d, *J* = 1.5 Hz, C(13)H_3), 1.68 – 1.80 (2H, m, C(2)H, C(11)H), 1.83 – 1.99

(4H, m, C(2)H, C(5)H, C(9)H_2), 2.00 – 2.09 (1H, m, C(4)H), 3.17 (3H, s, C(18)H_3), 4.57 – 4.75 (2H, m, C(7)H, C(10)H), 5.31 (1H, br s, C(1)H), 5.86 (1H, d, *J* = 3.5 Hz) and 5.91 (1H, d, *J* = 3.5 Hz, C(15)H, C(16)H), 6.23 (1H, d, *J* = 12.5 Hz, C(8)H); ^{13}C NMR δ_C (100 MHz, C_6D_6) 16.1 (C(12)), 21.2 (C(12)), 22.7 (C(13)), 24.4 (C(2)), 28.0 (C(11)), 37.1 (C(9)), 39.6 (C(3)), 40.1 (C(4)), 41.4 (C(5)), 55.6 (C(18)), 67.7 (C(10)), 104.3 (C(7)), 109.3 and 112.1 (C(15)), C(16)), 121.1 (C(14)), 121.9 (C(1)), 136.7 (C(6)), 148.0 (C(8)), 159.8 (C(14)); HRMS (ESI$^+$) found 405.1036, 407.1015, $C_{19}H_{27}{}^{79}BrO_3Na$ $[MNa]^+$ requires 405.1036, $C_{19}H_{27}{}^{81}BrO_3Na$ $[MNa]^+$ requires 407.1015. *Diagnostic signals for Z- enol ether isomer:* ^{1}H NMR δ_H (400 MHz, C_6D_6) 4.31 (1H, dd, *J* = 10.0, 6.5 Hz, C(7)H), 5.61 (1H, d, *J* = 6.5 Hz, C(8)H).

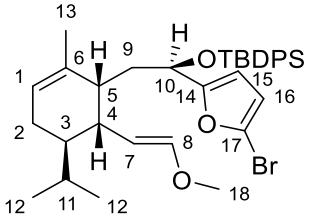
((*S)-1-(5-Bromofuran-2-yl)-2-{(1*R**,5*R**,6*R**)-5-isopropyl-6-[(*E*)-2-methoxyvinyl]-2-methylcyclohex-2-en-1-yl}ethoxy)(*tert*-butyl)diphenylsilane (348)**



Enol ether **335** (56 mg, 0.15 mmol), TBDPSCl (156 μL, 0.60 mmol) and imidazole (82 mg, 1.20 mmol) were dissolved in DCM (7 mL) and stirred for 18 h at RT. The reaction mixture was then diluted with DCM (10 mL), washed with water (10 mL) then brine (10mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 95:05) to give the *title compound* as a colourless oil (3:1 *E*:*Z*, 79 mg, 85%; *E*:*Z* isomer ratio determined by integration of the C(7)H signal in the ^{1}H NMR spectrum). R_f 0.89 (petrol / ether, 9:1); ν_{max} (thin film)/cm^{-1} 2955m, 2931m, 1651m, 1463m, 1111s, 701s; ^{1}H NMR δ_H (400 MHz, C_6D_6) 0.67 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.84 (3H, d, *J*

= 7.0 Hz, C(12)H_3), 1.16 (9H, s, SiC(CH_3)$_3$), 1.30 – 1.40 (1H, m, C(3)H), 1.66 – 1.81 (3H, m, C(2)H_2, C(11)H), 1.83 (3H, s, C(13)H_3), 1.98 – 2.07 (2H, m, C(4)H, C(9)H), 2.17 – 2.31 (2H, m, C(6)H, C(9)H), 3.05 (3H, s, C(18)H_3), 4.41 (1H, dd, *J* = 12.5, 10.5 Hz, C(7)H), 4.95 (1H, dd, *J* = 8.5, 4.0 Hz, C(10)H), 5.36 (1H, br s, C(1)H), 5.41 (1H, d, *J* = 3.0 Hz) and 5.65 (1H, d, *J* = 3.0 Hz, C(15)H, C(16)H), 6.17 (1H, d, *J* = 12.5 Hz, C(8)H), 7.17 – 7.31 (6H, m), 7.64 – 7.68 (2H, m) and 7.78 – 7.87 (2H, m, $SiPh_2$); ^{13}C NMR δ_C (100 MHz, C_6D_6) 15.4 (C(12)), 19.7 (Si*C*(CH_3)$_3$), 21.4 (C(12)), 22.8 (C(13)), 24.3 (C(2)), 27.1 (SiC(*C*H_3)$_3$), 27.8 (C(11)), 38.0 (C(9)), 38.7 (C(3)), 40.6 (C(4)), 41.7 (C(5)), 55.1 (C(18)), 69.3 (C(10)), 103.7 (C(7)), 110.1 and 111.8 (C(15), C(16)), 121.1 (C(17)), 121.5 (C(1)), 129.7, 130.0, 133.7, 133.9, 135.9 and 136.4 ($SiPh_2$), 136.5 (C(6)), 147.5 (C(8)), 158.6 (C(14)), 2 signals obscured by residual solvent peak; HRMS (ESI$^+$) found 643.2212, 645.2190, $C_{35}H_{45}O_3{}^{79}BrNaSi$ $[MNa]^+$ requires 643.2214, $C_{35}H_{45}O_3{}^{81}BrNaSi$ $[MNa]^+$ requires 645.2193. *Diagnostic signals for Z- enol ether isomer:* ^{1}H NMR δ_H (400 MHz, C_6D_6) 4.19 (1H, dd, *J* = 10.5, 6.5 Hz, C(7)H), 5.60 (1H, d, *J* = 6.5 Hz, C(8)H).

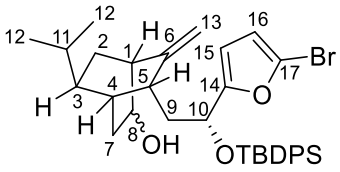
((*R)-1-(5-Bromofuran-2-yl)-2-{(1*R**,5*R**,6*R**)-5-isopropyl-6-[(*E*)-2-methoxyvinyl]-2-methylcyclohex-2-en-1-yl}ethoxy)(*tert*-butyl)diphenylsilane (337)**



Enol ether **336** (62 mg, 0.16 mmol), TBDPSCl (167 µL, 0.64 mmol) and imidazole (87 mg, 1.28 mmol) were dissolved in DCM (7 mL) and stirred for 18 h at RT. The reaction mixture was then diluted with DCM (10 mL), washed with water (10 mL) then brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash

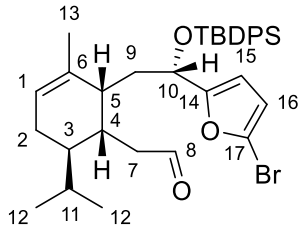
chromatography (petrol / ether, 95:05) to give the *title compound* as a colourless oil (86 mg, 87%; *E*:*Z* isomer ratio determined by integration of the C(7)H signal in the ^{1}H NMR spectrum); R_f 0.89 (petrol / ether, 9:1); ν_{max} (thin film)/cm^{-1} 2956m, 2932m, 1650m, 1428m, 1112s, 703s; ^{1}H NMR δ_H (500 MHz, C_6D_6) 0.66 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.78 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.14 (9H, s, SiC(CH_3)$_3$), 1.22 – 1.29 (1H, m, C(3)H), 1.54 – 1.60 (1H, m, C(11)H), 1.62 (3H, s, C(13)H_3), 1.68 – 1.76 (2H, m, C(2)H, C(5)H), 1.87 – 2.00 (2H, m, C(2)H, C(4)H), 2.10 – 2.21 (1H, m, C(9)H), 2.30 – 2.39 (1H, m, C(9)H), 3.04 (3H, s, C(18)H_3), 4.45 (1H, dd, *J* = 12.5, 10.5 Hz, C(7)H), 4.99 (1H, dd, *J* = 10.5, 5.5 Hz, C(10)H), 5.28 (1H, br s, C(1)H), 5.66 (1H, d, *J* = 3.0 Hz) and 5.80 (1H, d, *J* = 3.0 Hz, C(15)H, C(16)H), 6.11 (1H, d, *J* = 12.5 Hz, C(8)H), 7.17 – 7.27 (6H, m), 7.63 – 7.70 (2H, m) and 7.77 – 7.85 (2H, m, $SiPh_2$); ^{13}C NMR δ_C (125 MHz, C_6D_6) 16.9 (C(12)), 19.6 (Si*C*(CH_3)$_3$), 21.1 (C(12)), 22.2 (C(13)), 24.4 (C(2)), 27.1 (SiC(*C*H_3)$_3$), 27.8 (C(11)), , 37.6 (C(9)), 39.5 C(4)), 40.5 (C(3), C(5)), 55.4 (C(18)), 69.0 (C(10)), 104.2 (C(7)), 111.0 and 111.8 (C(15), C(16)), 121.4 (C(17)), 121.6 (C(1)), 129.9, 130.1, 134.0, 134.3, 136.2 and 136.4 ($SiPh_2$), 147.9 (C(8)), 158.2 (C(14)), C(6) not seen, 2 signals obscured by residual solvent peak; HRMS (ESI$^+$) found 643.2214, 645.2192, $C_{35}H_{45}{}^{79}BrNaO_3Si$ [MNa]$^+$ requires 643.2214, $C_{35}H_{45}{}^{81}BrNaO_3Si$ [MNa]$^+$ requires 645.2193. *Diagnostic signals for Z- enol ether isomer:* ^{1}H NMR δ_H (400 MHz, C_6D_6) 5.41 (1H, d, *J* = 6.5 Hz, C(8)H).

(1*S,4*R**,5*R**,8*R**)-5-{(*R**)-2-(5-Bromofuran-2-yl)-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-8-isopropyl-6-methylenebicyclo[2.2.2]octan-2-ol (340)**



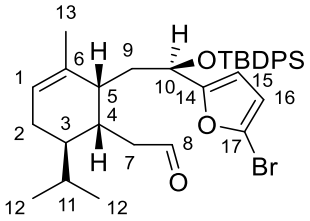
Enol ether **337** (5.6 mg, 0.01 mmol) was dissolved in acetone (1 mL) and HCl was added (1.0 M aqueous solution, 30 μL, 0.03 mmol). The reaction mixture was stirred at RT for 3 h, then satd. aq. $NaHCO_3$ solution (5 mL) was added and the mixture extracted with ether (3 × 10 mL). The combined organic layers are washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* column chromatography (petrol / ether, 9:1 → 7:3) to give the *title product* as a yellow oil (2.3 mg, 38%). R_f 0.09 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 3402br, 2956m, 1447m, 1111m, 703m; ^{1}H NMR δ_H (500 MHz, C_6D_6) 0.67 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.72 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.99 (1H, ddd, *J* = 13.5, 7.0, 2.5 Hz, C(2)H), 1.02 – 1.11 (1H, m, C(3)H), 1.14 (9H, s, SiC(CH_3)$_3$), 1.31 – 1.48 (4H, m, C(2)H, C(4)H, C(7)H, C(11)), 1.54 – 1.63 (1H, m, C(7)H), 1.93 – 1.99 (1H, m, C(1)H), 2.11 (1H, app. dt, *J* = 13.5, 7.0 Hz, C(9)H), 2.27 – 2.32 (1H, m, C(5)H), 2.36 (1H, ddd, *J* = 13.5, 7.0, 5.0 Hz, C(9)H), 3.60 – 3.70 (1H, m, C(8)H), 4.75 – 4.78 (2H, m, C(13)H_2), 4.80 (1H, t, *J* = 7.0 Hz, C(10)H), 5.58 (1H, d, *J* = 3.0 Hz) and 5.74 (1H, d, *J* = 3.0 Hz, C(15)H, C(16)H), 7.18 – 7.25 (6H, m), 7.61 – 7.68 (2H, m), 7.77 – 7.84 (2H, m, $SiPh_2$); ^{13}C NMR δ_C (125 MHz, C_6D_6) 19.6 (Si*C*(CH_3)$_3$), 21.1 (C(12)), 21.8 (C(12)), 27.1 (SiC(*C*H_3)$_3$), 30.4 (C(2)), 30.5 (C(11)), 31.3 (C(3)), 33.5 (C(4)), 34.0 (C(5)) , 35.3 (C(7)), 40.6 (C(9)), 46.7 (C(1)), 68.6 (C(8)), 69.3 (C(10)), 109.5 (C(13)), 110.4 and 111.9 (C(15), C(16)), 121.3 (C(17)) 129.9, 130.2, 133.9, 134.0, 136.2 and 136.4 (Si*Ph*$_2$), 152.3 (C(6)), 158.5 (C(14)), 2 unresolved; HRMS (ESI$^+$) found 629.2057, 631.2037, $C_{34}H_{43}{}^{79}BrNaO_3Si$ [MNa]$^+$ requires 629.2057, $C_{34}H_{43}{}^{81}BrNaO_3Si$ [MNa]$^+$ requires 631.2037.

2-((1*R,2*R**,6*R**)-2-{(*S**)-2-(5-Bromofuran-2-yl)-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-6-isopropyl-3-methylcyclohex-3-en-1-yl)acetaldehyde (28)**[59]



Enol ether **348** (36 mg, 0.06 mmol) was dissolved in THF/H_2O (10:1, 3 mL), and $Hg(OCOCF_3)_2$ (25 mg, 0.06 mmol) was added at 0 °C. The reaction mixture was stirred at the same temperature for 30 min, then satd. aq. KCl solution was added (3 mL) and the mixture stirred at RT for 18 h. The layers were then separated and the aqueous layer extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (15 mL) then dried over $MgSO_4$ and the solvent removed *in vacuo*; the crude residue was purified *via* flash chromatography (petrol / ether, 95:5) to give the title compound as an orange oil (25 mg, 70%). R_f 0.65 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2959s, 1724s, 1427m, 1111s; ^1H NMR δ_H (500 MHz, $CDCl_3$) 0.71 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.80 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.03 (9H, s, SiC(CH_3)$_3$), 1.21 – 1.29 (1H, m, C(3)H), 1.44 (3H, s, C(13)H_3), 1.53 – 1.61 (1H, m, C(11)H), 1.75 – 2.02 (5H, m, C(2)H_2, C(5)H, C(9)H_2), 2.12 – 2.18 (1H, m, C(4)H), 2.24 (1H, ddd, *J* = 16.5, 7.0, 1.5 Hz, C(7)H), 2.32 (1H, ddd, *J* = 16.5, 7.0, 2.5 Hz, C(7)H), 4.62 (1H, dd, *J* = 9.0, 5.5 Hz, C(10)H), 5.21 (1H, s, C(1)H), 5.74 (1H, d, *J* = 3.0 Hz, C(15)H), 6.04 (1H, d, *J* = 3.0 Hz, C(16)H), 7.29 – 7.34 (2H, m, $SiPh_2$), 7.36 – 7.50 (6H, m, $SiPh_2$), 7.65 – 7.70 (2H, m, $SiPh_2$), 9.56 (1H, app. t, *J* = 2.0 Hz, C(8)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 17.3 (C12)), 19.2 (Si*C*(CH_3)$_3$), 20.8 (C(12)), 22.7 (C13)), 24.0 (C(2)), 26.9 (SiC(*C*H_3)$_3$), 27.4 (C(11)), 34.4 (C(4)), 36.3 (C(5)), 37.5 (C(9)), 38.9 (C(3)), 43.7 (C(7)), 68.6 (C(10)), 110.7 (C(15)), 111.6 (C(16)), 120.8 (C(17)), 121.0 (C(1)), 127.3, 127.6, 129.4, 129.8, 133.3, 133.4, 135.6 and 135.9 ($SiPh_2$), 136.4 (C(6)), 157.2 (C(14)), 202.7 (C(8)); HRMS (ESI^+) found 629.2055, $C_{34}H_{43}O_3{}^{79}BrNaSi$ $[MNa]^+$ requires 629.2057.

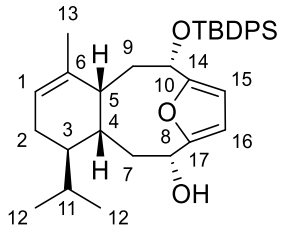
2-((1*R,2*R**,6*R**)-2-{(*R**)-2-(5-Bromofuran-2-yl)-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-6-isopropyl-3-methylcyclohex-3-en-1-yl)acetaldehyde (345)**



Enol ether **337** (338 mg, 0.54 mmol) was dissolved in THF/H_2O (10:1, 24 mL), and $Hg(OCOCF_3)_2$ (232 mg, 0.54 mmol) was added at 0 °C. The reaction mixture was stirred at the same temperature for 30 min, then satd. aq. KCl solution was added (3 mL) and the mixture stirred at RT for 18 h. The layers were then separated and the aqueous layer extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (15 mL) then dried over $MgSO_4$ and the solvent removed *in vacuo*; the crude residue was purified *via* flash chromatography (petrol / ether, 95:5) to give the *title compound* as an orange oil (191 mg, 58%); R_f 0.69 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2959s, 1725s, 1112s, 1057s, 703s; ^1H NMR δ_H (500 MHz, C_6D_6) 0.59 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.67 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.99 – 1.07 (1H, m, C(3)H), 1.13 (9H, s, SiC(CH_3)$_3$), 1.27 – 1.35 (1H, m, C(11)H), 1.50 (3H, s, C(13)H_3), 1.51 – 1.56 (1H, m, C(7)H), 1.59 – 1.67 (1H, m, C(2)H), 1.74 – 1.94 (4H, m, C(2)H, C(5)H, C(7)H, C(9)H), 2.01 – 2.11 (1H, m, C(4)H), 2.21 – 2.31 (1H, m, C(9)H), 4.75 (1H, dd, *J* = 10.0, 5.5 Hz, C(10)H), 5.13 (1H, br s, C(1)H), 5.79 (1H, d, *J* = 3.0 Hz, C(15)H), 5.82 (1H, d, *J* = 3.0 Hz, C(16)H), 7.16 – 7.27 (6H, m), 7.59 – 7.66 (2H, m, $SiPh_2$), 7.74 – 7.84 (2H, m, $SiPh_2$), 9.20 (1H, dd, *J* = 3.0, 2.0 Hz, C(8)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 18.6 (C(12)), 19.5 (Si*C*(CH_3)$_3$), 20.8 (C(12)), 22.2 (C(13)), 24.0 (C(2)), 27.2 (SiC(*C*H_3)$_3$), 27.4 (C(11)), 32.6 (C(4)), 35.7 (C(5)), 37.1 (C(9)), 39.7 (C(3)), 43.0 (C(7)), 68.1 (C(10)), 111.1 (C(15)), 112.0 (C(16)), 121.4 (C(1)), 121.5 (C(17)), 130.1, 130.3, 133.7, 134.0 ($SiPh_2$), 135.4 (C(6)), 136.2 and 136.4 ($SiPh_2$), 157.9 (C(14)), 201.2 (C(8)), 2 unresolved;

HRMS (ESI$^+$) found 629.2056 and 631.2035, $C_{34}H_{43}O_3{}^{79}BrNaSi$ $[MNa]^+$ requires 629.2057, $C_{34}H_{43}O_3{}^{81}BrNaSi$ $[MNa]^+$ requires 631.2037.

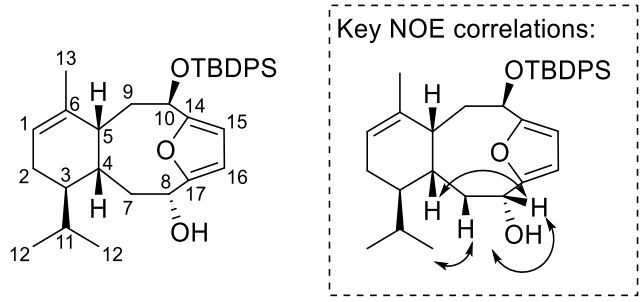
(4*R,4a*R**,6*R**,11*S**,12a*R**)-11-[(*tert*-Butyldiphenylsilyl)oxy]-4-isopropyl-1-methyl-3,4,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulen-6-ol (29)**[59]



A solution of aldehyde **28** (660 mg, 1.08 mmol) in DMF (75 mL) was degassed *via* three cycles of a freeze-pump-thaw sequence, then $CrCl_2$ (1.34 g, 10.8 mmol) and $NiCl_2$ (141 mg, 1.08 mmol) were added in one portion at −20°C. The reaction mixture was stirred for 18 h at RT, then water (75 mL) was added, the layers separated and the aqueous layer extracted with ether (3 × 75 mL). The combined organic layers were washed with water (2 × 50 mL) then brine (75 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 95:5 → 8:2) to give the title compound as a white solid (334 mg, 58%); m.p. 45°C; R_f 0.17 (Petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 3334br, 2958s, 1428m, 1065s, 702s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) −0.55 (1H, br s, C(5)H), 0.73 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.90 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.10 (12H, s, C(13)H_3, SiC(CH_3)$_3$), 1.20 – 1.29 (1H, m, C(4)H), 1.33 – 1.42 (1H, m, C(3)H), 1.43 – 1.50 (1H, m, C(9)H), 1.61 – 1.73 (1H, m, C(2)H), 1.81 – 1.89 (1H, m, C(2)H), 1.92 – 1.95 (1H, m, C(8)O*H*), 2.01 – 2.07 (1H, m, C(11)H), 2.12 (1H, dt, *J* = 13.0, 3.5 Hz, C(7)H), 2.41 (1H, app. q, *J* = 13.0 Hz, C(7)H), 2.58 (1H, ddd, *J* = 12.5, 10.0, 2.5 Hz, C(9)H), 4.48 (1H, ddd, *J* = 10.0, 6.0, 3.5 Hz, C(8)H), 4.62 (1H, dd, *J* = 10.0, 5.5 Hz, C(10)H), 5.04 (1H, br s, C(1)H), 5.98 (1H, d, *J* = 3.0 Hz), 6.07 (1H, d, *J* = 3.0 Hz, C(15)H, C(16)H), 7.35 – 7.46 (6H, m, $SiPh_2$), 7.68 – 7.80

(4H, m, $SiPh_2$); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 15.1 (C(12)), 19.2 ($SiC(CH_3)_3$), 21.5 (C(12)), 22.1 (C(13)), 24.9 (C(2)), 26.9 ($SiC(CH_3)_3$), 27.0 (C(11)), 36.9 (C(5)), 37.4 (C(7)), 38.5 (C(3)), 39.8 (C(4)), 43.4 (C(9)), 68.3 (C(8)), 70.6 (C(10)), 110.8 and 116.6 (C(15), C(16)), 118.5 (C(1)), 127.5, 127.6, 129.6, 129.7, 133.8, 133.9, 135.8 and 136.0 ($SiPh_2$), 139.2 (C(6)), 159.7 and 160.6 (C(14), C(17)); HRMS (ESI^+) found 551.2951, $C_{34}H_{44}O_3NaSi$ $[MNa]^+$ requires 551.2952.

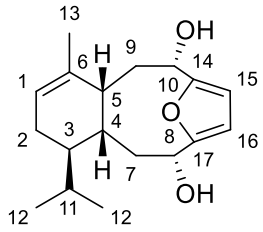
(4*R,4a*R**,6*R**,11*R**,12a*R**)-11-[(*tert*-Butyldiphenylsilyl)oxy]-4-isopropyl-1-methyl-3,4,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulen-6-ol (346)**



A solution of aldehyde **345** (660 mg, 1.08 mmol) in DMF (75 mL) was degassed *via* three cycles of a freeze-pump-thaw sequence, then $CrCl_2$ (1.34 g, 10.8 mmol) and $NiCl_2$ (141 mg, 1.08 mmol) were added in one portion at −20°C. The reaction mixture was stirred for 18 h at RT, then water (75 mL) was added, the layers separated and the aqueous layer extracted with ether (3 × 75 mL). The combined organic layers were washed with water (2 × 50 mL) then brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 95:5 → 8:2) to give the *title compound* as a white solid (316 mg, 55%); m.p. 55 °C; R_f 0.08 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 3335br, 2959m, 1107s, 701s; ^1H NMR δ_H (500 MHz, C_6D_6) 0.52 – 0.57 (1H, m, C(5)H), 0.68 (3H, d, *J* = 7.0 Hz, $C(12)H_3$), 0.80 (3H, d, *J* = 7.0 Hz, $C(12)H_3$), 0.94 – 1.03 (1H, m, C(4)H), 1.14 – 1.20 (1H, m, C(3)H), 1.22 (9H, s, $SiC(CH_3)_3$), 1.53 (1H, ddd, *J* = 14.5, 4.0, 1.5 Hz,

C(9)H), 1.63 – 1.74 (1H, m, C(2)H), 1.75 – 1.82 (1H, m, C(11)H), 1.85 (3H, s, C(13)H_3), 1.87 – 1.92 (2H, m, C(2)H, C(7)H), 2.06 (1H, dt, *J* = 13.0, 10.5 Hz, C(7)H), 2.19 – 2.27 (1H, m, C(9)H), 4.19 (1H, dd, *J* = 10.5, 4.5 Hz, C(8)H), 5.24 (1H, br s, C(1)H), 5.32 (1H, dt, *J* = 5.0, 1.5 Hz, C(10)H), 5.89 (1H, d, *J* = 3.0 Hz, C(16)H), 6.43 (1H, dd, *J* = 3.0, 1.5 Hz, C(15)H), 7.17 – 7.24 (6H, m, $SiPh_2$), 7.73 – 7.80 (2H, m, $SiPh_2$), 7.80 – 7.88 (2H, m, $SiPh_2$); ^{13}C NMR δ_C (125 MHz, C_6D_6) 16.6 (C(12)), 19.6 (Si*C*$(CH_3)_3$), 21.5 (C(12)), 23.3 (C(13)), 25.3 (C(2)), 27.3 (SiC(*C*$H_3)_3$), 27.9 (C(11)), 36.0 C(5)), 38.5 (C(4), C(7)), 40.2 (C(3)), 43.7 (C(9)), 67.5 (C(8)), 73.2 (C(10)), 112.3 (C(16)), 113.0 (C(15)), 119.9 (C(1)), 125.7, 125.9, 128.6, 129.3, 130.3, 133.9 and 136.3 ($SiPh_2$), 139.6 C(6)), 159.8 and 163.3 (C(14), C(17)), 1 signal obscured by residual solvent peak; HRMS (ESI^+) found 551.2953, $C_{34}H_{44}O_3NaSi$ $[MNa]^+$ requires 551.2952.

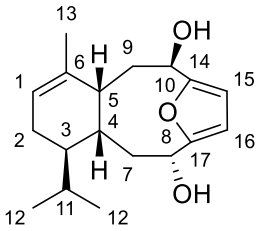
(1*R,4a*R**,6*S**,11*R**,12a*R**)-1-Isopropyl-4-methyl-1,2,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulene-6,11-diol (349)**



To a solution of alcohol **29** (50 mg, 0.094 mmol) in THF (3 mL) was added TBAF (1.0 M solution in THF, 1.0 mL, 1.0 mmol) and the reaction mixture was stirred for 18 h at RT. Phosphate buffer (pH 7, 5 mL) was then added followed by ether (5 mL), the layers were separated and the aqueous layer extracted with ether (2 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 8:2 → 5:5) to give the title compound as a white solid (21 mg, 77%). m.p. 120 °C; R_f 0.09 (Petrol / ether, 5:5); ν_{max} (thin film)/cm^{-1} 3324br, 2959s, 1456m, 1026s, 734m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) −0.31 (1H,

br s, C(5)H), 0.74 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.88 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.24 – 1.31 (1H, m, C(4)H), 1.31 – 1.40 (1H, m, C(3)H), 1.45 (3H, s, C(13)H_3), 1.65 – 1.75 (2H, m, C(2)H, C(9)H), 1.85 – 1.93 (1H, m, C(2)H), 1.96 – 2.04 (1H, m, C(11)H), 2.09 – 2.15 (1H, m, C(7)H), 2.29 – 2.44 (2H, m, C(7)H, C(9)H), 4.54 (1H, dd, *J* = 10.0, 3.5 Hz, C(8)H), 4.75 (1H, dd, *J* = 10.0, 5.5 Hz, C(10)H), 5.14 (1H, br s, C(1)H), 6.20 (1H, dd, *J* = 3.0, 1.0 Hz), 6.47 (1H, d, *J* = 3.0 Hz, C(15)H, C(16)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 15.2 (C(12)), 21.4 (C(12)), 22.5 (C(13)), 24.9 (C(2)), 27.1 (C(11)), 37.1 (C(5)), 37.5 (C(7)), 38.7 (C(3)), 39.6 (C(4)), 43.3 (C(9)), 68.1 (C(8)), 69.7 (C(10)), 111.1 and 116.9 (C(15), C(16)), 119.1 (C(1)), 138.7 (C(6)), 160.2 and 160.4 (C(14), C(17)); HRMS (ESI$^+$) found 313.1775, $C_{18}H_{26}O_3Na$ $[MNa]^+$ requires 313.1774.

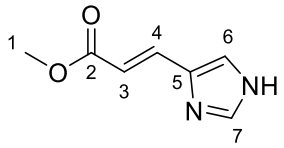
(1*R,4a*R**,6*R**,11*R**,12a*R**)-1-Isopropyl-4-methyl-1,2,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulene-6,11-diol (347)**



To a solution of alcohol **346** (25 mg, 0.047 mmol) in THF (1.5 mL) was added TBAF (1.0 M solution in THF, 500 μL, 0.5 mmol) and the reaction mixture was stirred for 18 h at RT. Phosphate buffer (pH 7, 3 mL) was then added followed by ether (3 mL), the layers separated and the aqueous layer extracted with ether (2 × 3 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 8:2 → 5:5) to give the title compound as a white solid (11 mg, 81%). m.p. 85°C; R_f 0.33 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3364br, 2958s, 1196m, 1094s, 1069s, 1006s, 787s; ^{1}H NMR δ_H (500 MHz, C_6D_6)

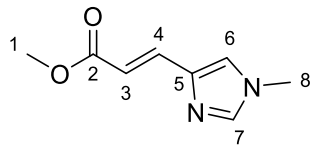
0.22 (1H, s, C(5)H), 0.67 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.81 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.04 – 1.12 (1H, m, C(4)H), 1.20 – 1.33 (2H, m, C(3)H, C(9)H), 1.65 – 1.68 (1H, m, C(2)H), 1.70 (3H, s, C(13)H_3), 1.79 – 1.92 (2H, m, C(2)H, C(11)H), 1.95 (1H, app. dt, *J* = 13.5, 4.0 Hz, C(7)H), 2.13 – 2.24 (1H, m, C(7)H), 2.32 (1H, ddd, *J* = 14.5, 5.0, 4.0 Hz, C(9)H), 4.19 (1H, dd, *J* = 10.5, 4.0 Hz, C(8)H), 4.85 (1H, d, *J* = 5.0 Hz, C(10)H), 5.22 (1H, br s, C(1)H), 5.87 (1H, d, *J* = 3.0 Hz), 6.31 (1H, dd, *J* = 3.0, 1.5 Hz, C(15)H, C(16)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 16.6 (C(12)), 22.2 (C(12)), 23.7 (C(13)), 25.9 (C(2)), 28.3 (C(11)), 36.8 (C(5)), 38.9 (C(7)), 39.6 (C(4)), 40.4 (C(3)), 44.6 (C(9)), 68.1 (C(8)), 71.9 (C(10)), 112.4, 113.0 (C(15), C(16)), 120.4 (C(1)), 140.3 (C(6)), 160.3, 164.0 (C(14), C(17)); HRMS (Ammonia CI) found 308.2220, $C_{18}H_{30}NO_3$ $[MNH_4]^+$ requires 308.2220.

Methyl (*E*)-3-(1*H*-imidazol-4-yl)acrylate (361)[245]



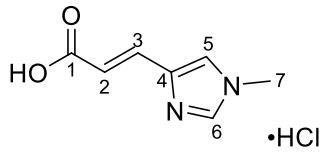
Urocanic acid (1.38 g, 10 mmol) was suspended in MeOH (25 mL) and conc. sulfuric acid (1.0 mL) was added dropwise. The mixture was heated to reflux for 18 h, then conc. NH_4OH was added (2.5 mL) at 0 °C and the solvent removed *in vacuo*. Water (100 mL) and ethyl acetate (100 mL) were then added, the layers separated and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to give the title compound as a white solid (1.42 g, 93%). ^{1}H NMR δ_H (200 MHz, $(CD_3)_2CO$) 3.79 (3H, s, C(1)H_3), 6.55 (1H, d, *J* = 15.5 Hz, C(3)H), 7.60 (1H, s, C(6)H), 7.68 (1H, d, *J* = 15.5 Hz, C(4)H), 7.84 (1H, s, C(7)H).

Methyl (*E*)-3-(1-methyl-1*H*-imidazol-4-yl)acrylate (362)[246]



Methyl ester **361** (750 mg, 4.93 mmol) was dissolved in acetone (8 mL), then K_2CO_3 (680 mg, 4.93 mmol) was added, followed by dropwise addition of methyl iodide (300 μL, 4.79 mmol). The reaction mixture was stirred at RT for 18 h, then filtered through celite and the solvent removed *in vacuo*. The residue was redissolved in DCM (20 mL) and washed with water (2 × 20 mL). The solvent was removed *in vacuo* and the crude product purified by flash chromatography (DCM / MeOH, 98:2 → 9:1) to give the title product as the major component of a 6:1 mixture with the proximal methylation product (330 mg). Recrystallisation from ethyl acetate / pentane afforded pure title compound as a white solid (162 mg, 20%). R_f 0.52 (DCM / MeOH, 9:1); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.71 (3H, s, C(8)H_3), 3.78 (3H, s, C(1)H_3), 6.55 (1H, d, *J* = 15.5 Hz, C(3)H), 7.08 (1H, s, C(6)H), 7.46 (1H, s, C(7)H), 7.56 (1H, d, *J* = 15.5 Hz, C(4)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 33.6 (C(8)), 51.5 (C(1)), 115.6 (C(3)), 122.5 (C(6)), 136.2 C(4)), 138.5 (C(5)), 139.1 (C(7)), 168.1 C(2)).

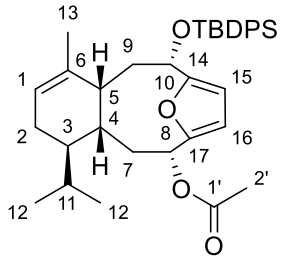
(*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)acrylic acid hydrochloride salt (359)[146]



Ester **362** (157 mg, 0.95 mmol) was dissolved in a 1 : 1 THF/water mixture, and NaOH was added (76.4 mg, 2.01 mmol). The mixture was stirred for 32 h at RT, then HCl aqueous solution (1.0 M, 2 mL, 2.00 mmol) was added and the solvent evaporated to give the *title compound* as a 59% w/w mixture with NaCl (white solid, 302 mg, max. 179 mg of **359**

assuming quantitative conversion). ν_{max} (thin film)/cm^{-1} 3426br, 3078m, 2920w, 2775w, 2456w, 1670s, 1636s, 1209m, 1181m; ^{1}H NMR δ_H (400 MHz, CD_3OD) 3.97 (3H, s, C(7)H_3), 6.57 (1H, d, *J* = 16.0 Hz, C(2)H), 7.53 (1H, d, *J* = 16.0 Hz, C(3)H), 7.92 (1H, s, C(5)H), 9.03 (1H, s, C(6)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 36.6 (C(7)), 123.5 (C(2)), 125.4 (C(5)), 129.4 (C(3)), 131.1 (C(4)), 138.9 (C(6)), 168.5 (C(1)); HRMS (ESI$^+$) found 153.0658, $C_7H_9N_2O_2$ $[MH]^+$ requires 153.0659.

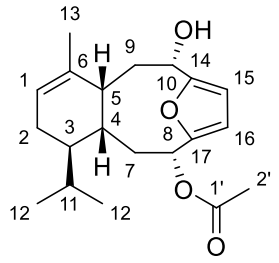
(4*R,4a*R**,6*R**,11*S**,12a*R**)-11-[(*tert*-Butyldiphenylsilyl)oxy]-4-isopropyl-1-methyl-3,4,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulen-6-yl acetate (356)**



Alcohol **29** (40 mg, 0.076 mmol) and DMAP (5.2 mg, 0.043 mmol) were dissolved in DCM (4 mL), then NEt_3 (6 μL, 0.043 mmol) and acetic anhydride (24 μL, 0.254 mmol) were added and the reaction mixture stirred at RT for 18 h. It was then diluted with DCM (10 mL), phosphate buffer was added (pH = 7, 10 mL), the layers separated and the aqueous layer extracted with DCM (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography (petrol / ether, 9:1) to give the *title compound* as a colourless oil (40 mg, 92%). R_f 0.58 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2959s, 1739s, 1240s, 1070s, 703s; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) −0.53 (1H, s, C(5)H), 0.74 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.92 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.12 (12H, s, C(13)H_3, SiC(CH_3)$_3$), 1.25 – 1.36 (1H, m, C(4)H), 1.37 – 1.45 (1H, m, C(3)H), 1.46 – 1.55 (1H, m, C(9)H), 1.62 – 1.80 (1H, m, C(2)H), 1.82 – 1.92 (1H, m, C(2)H), 1.94 – 2.12 (2H, m, C(7)H, C(11)H), 2.14 (3H, s, C(2')H_3), 2.55 (1H, app. q, *J* = 12.0 Hz, C(7)H),

2.62 (1H, ddd, *J* = 12.5, 10.0, 2.0 Hz, C(9)H), 4.63 (1H, dd, *J* = 10.0, 5.5 Hz, C(10)H), 5.05 (1H, br s, C(1)H), 5.48 (1H, dd, *J* = 11.0, 4.0 Hz, C(8)H), 6.00 (1H, d, *J* = 3.0 Hz) and 6.22 (1H, d, *J* = 3.0 Hz, C(15)H, C(16)H), 7.34 – 7.51 (6H, m, $SiPh_2$), 7.68 – 7.83 (4H, m, $SiPh_2$); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 14.9 (C(12)), 19.2 (C(Si*C*(CH_3)), 21.3 and 21.4 (C(12), C(2')), 22.0 (C(13)), 24.9 (C(2)), 26.9 (C(SiC(*C*H_3)), 27.1 (C(11)), 33.0 (C(7)), 38.4 (C(3)), 39.8 (C(4)), 43.4 (C(9)), 69.7 (C(8)), 70.5 (C(10)), 113.1 and 116.7 (C(15), C(16)), 118.5 (C(1)), 127.5, 127.6, 129.7, 129.7, 133.7, 133.8, 135.8 and 135.9 ($SiPh_2$), 139.0 (C(6)), 156.4 and 161.2 (C(14), C(17)), 170.5 (C(1')); HRMS (ESI^+) found 593.3056, $C_{36}H_{46}O_4NaSi$ $[MNa]^+$ requires 593.3058.

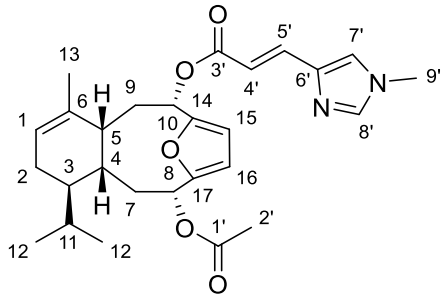
(4*R,4a*R**,6*R**,11*S**,12a*R**)-11-Hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulen-6-yl acetate (358)**



Ester **356** (50 mg, 0.088 mmol) was dissolved in THF (1 mL), then TBAF was added (1.0 M solution in THF, 440 μL, 0.400 mmol). After 2 h, phosphate buffer was added (pH = 7, 10 mL) followed by ether (10 mL), the layers were separated and the aqueous layers extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo*, and the crude residue purified by flash chromatography (petrol / ether, 9:1 → 6:4) to give the title compound as a colourless oil (24 mg, 82%). R_f 0.29 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3401br, 2959s, 1738s, 1240s, 1017m; ^1H NMR δ_H (500 MHz, $CDCl_3$) −0.30 (1H, s, C(5)H), 0.74 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.88 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.28 – 1.34 (1H, m, C(4)H), 1.35 – 1.42 (1H, m, C(3)H), 1.46 (3H, s, C(13)H_3),

1.65 – 1.77 (2H, m, C(2)H, C(9)H), 1.85 – 1.93 (1H, m, C(2)H), 1.94 – 2.00 (1H, m, C(11)H), 2.05 (1H, app. dt, *J* = 13.5, 4.0 Hz, C(7)H), 2.11 (3H, s, C(2')H_3), 2.37 – 2.52 (2H, m, C(7)H, C(9)H), 4.76 (1H, dd, *J* = 10.0, 5.5 Hz, C(10)H), 5.15 (1H, br s, C(1)H), 5.50 (1H, dd, *J* = 11.0, 4.0 Hz, C(8)H), 6.33 (1H, d, *J* = 3.0 Hz) and 6.48 (1H, d, *J* = 3.0 Hz, C(15)H, C(16)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 15.1 (C(12)), 21.3 and 21.4 (C(12), C(2')), 22.5 (C(13)), 24.9 (C(2)), 27.9 (C(11)), 33.3 (C(7)), 37.2 (C(5)), 38.7 (C(3)), 39.6 (C(4)), 43.4 (C(9)), 69.5 and 69.6 (C(8), C(10)), 113.5 and 117.0 (C(15), C(16)), 119.1 (C(1)), 138.6 (C(6)), 157.0 and 160.7 (C(14), C(16)), 170.5 (C(1')); HRMS (ESI$^+$) found 355.1882, $C_{20}H_{28}O_4Na$ $[MNa]^+$ requires 355.1880.

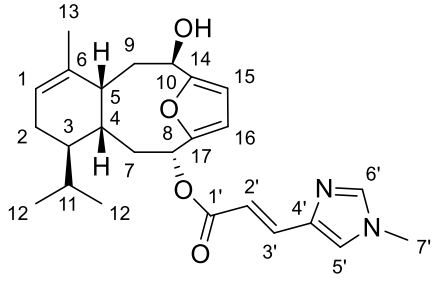
(1*R,4a*R**,6*S**,11*R**,12a*R**)-11-Acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulen-6-yl (*E*)-3-(1-methyl-1*H*-imidazol-4-yl)acrylate (357)**



Alcohol **358** (12 mg, 0.036 mmol), hydrochloride salt **359** (59% w/w, 37 mg, 0.115 mmol) and DCC (41 mg, 0.198 mmol) were dissolved in $CHCl_3$ (3 mL), and DMAP (40 mg, 0.324 mmol) was added. After 18 h, satd. aq. $NaHCO_3$ solution was added (10 mL), the layers separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (DCM / MeOH, 98:2 → 96:4) to give the *title compound* as a white solid (7.8 mg, 46%). R_f 0.25 (DCM / MeOH, 96:4);

ν_{max} (thin film)/cm^{-1} 2958m, 1736s, 1704s, 1638s, 1242s, 1154s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) −0.19 (1H, s, C(5)H), 0.75 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.88 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.29 – 1.36 (1H, m, C(4)H), 1.36 – 1.46 (1H, m, C(3)H), 1.52 (3H, s, C(13)H_3), 1.69 – 1.79 (2H, m, C(2)H, C(9)H), 1.87 – 1.94 (1H, m, C(2)H), 1.94 – 2.01 (1H, m, C(11)H), 2.07 (1H, app. dt, *J* = 13.5, 4.0 Hz, C(7)H), 2.11 (3H, s, C(2')H_3), 2.50 (1H, app. dt, *J* = 13.5, 11.0 Hz, C(7)H), 2.60 (1H, ddd, *J* = 13.0, 10.5, 3.0 Hz, C(9)H), 3.71 (3H, s, C(9')H_3), 5.16 (1H, br s, C(1)H), 5.53 (1H, dd, *J* = 11.0, 4.0 Hz, C(8)H), 5.76 (1H, dd, *J* = 10.5, 5.5 Hz, C(10)H), 6.37 (1H, d, *J* = 3.0 Hz, C(15)H or C(16)H), 6.56 (1H, d, *J* = 15.5 Hz, C(4')H), 6.64 (1H, d, *J* = 3.0 Hz, C(15)H or C(16)H), 7.09 (1H, s, C(7')H), 7.46 (1H, s, C(8')H), 7.60 (1H, d, *J* = 15.5 Hz, C(5')H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 15.3 (C(12)), 21.2 and 21.4 (C(12), C(2')), 22.5 (C(13)), 24.9 (C(2)), 27.2 (C(11)), 33.3 (C(7)), 33.6 (C(9')), 37.0 (C(5)), 38.8 (C(3)), 39.0 (C(9)), 39.5 (C(4)), 69.4 (C(8)), 70.0 (C(10)), 113.7 (C(15) or C(16)), 115.6 (C(4')), 118.8 (C(15) or C(16)), 119.2 (C(1)), 122.5 (C(7')), 136.7 (C(5')), 138.4 (C(6)), 138.5 (C(8')), 139.2 (C(6')), 157.4 and 157.8 (C(14), C(17)), 166.9 (C(1')), 170.5 (C(3')); HRMS (ESI$^+$) found 467.2538, $C_{27}H_{35}O_5N_2$ $[MH]^+$ requires 467.2541.

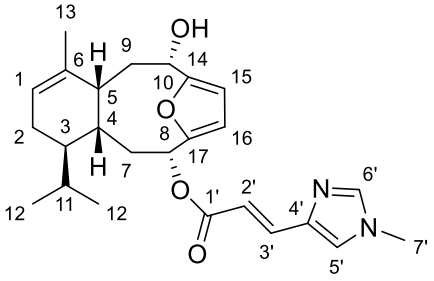
(4*R,4a*R**,6*R**,11*R**,12a*R**)-11-Hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulen-6-yl (*E*)-3-(1-methyl-1*H*-imidazol-4-yl)acrylate (364)**



Alcohol **346** (20 mg, 0.038 mmol), hydrochloride salt **359** (59% w/w, 39 mg, 0.122 mmol) and DCC (43 mg, 0.209 mmol) were dissolved in $CHCl_3$ (3 mL), and DMAP (42 mg, 0.342 mmol) was added. After 18 h, satd. aq. $NaHCO_3$ solution was added (10 mL), the layers separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. Half of the crude ester obtained was dissolved in THF (1.6 mL) and TBAF was added (1.0 M solution in THF, 400 μL, 0.40 mmol). The reaction mixture was stirred at RT for 5 h, then brine was added (10 mL) followed by ethyl acetate (10 mL), the layers separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, the solvent evaporated *in vacuo* and the crude residue purified by flash chromatography (DCM / MeOH, 98:2 → 96:4) to give the *title compound* as a white solid (7.7 mg, 48% over two steps). R_f 0.21 (DCM / MeOH, 96:4); ν_{max} (thin film)/cm^{-1} 3248br, 2960m, 1702s, 1640s, 1272s, 1158s, 733m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 0.25 (1H, br s, C(5)H), 0.75 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.86 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.20 – 1.27 (1H, m, C(4)H), 1.33 – 1.43 (1H, m, C(3)H), 1.50 (1H, dd, *J* = 14.5, 4.0 Hz, C(9)H), 1.58 (3H, d, *J* = 2.0 Hz, C(13)H_3), 1.65 – 1.81 (1H, m, C(2)H), 1.86 – 1.98 (2H, m, C(2)H, C(11)H), 2.04 (1H, app. dt, *J* = 13.5, 4.0 Hz, C(7)H), 2.38 (1H, app. dt, *J* = 13.5, 11.0 Hz, C(7)H), 2.60 (1H, app. dt, *J* = 15.0, 4.0 Hz, C(9)H), 3.70 (3H, s, C(13)H_3), 5.19 (1H, br s, C(1)H), 5.31 (1H,

d, *J* = 4.5 Hz, C(10)H), 5.61 (1H, dd, *J* = 11.0, 4.0 Hz, C(8)H), 6.41 (1H, d, *J* = 3.0 Hz) and 6.45 (1H, dd, *J* = 3.0, 1.5 Hz, C(15)H, C(16)H), 6.55 (1H, d, *J* = 15.5 Hz, C(2')H), 7.07 (1H, s, C(5')H), 7.45 (1H, s, C(6')H), 7.58 (1H, d, *J* = 15.5 Hz, (C(3')H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 15.9 C(12)), 21.4 (C(12)), 22.8 (C(13)), 24.9 (C(2)), 27.5 (C(11)), 33.6 (C(7')), 33.8 (C(7)), 36.1 (C(5)), 38.8 (C(4)), 39.4 (C(3)), 43.7 (C(9)), 68.7 (C(8)), 71.3 (C(10)), 112.0 and 114.3 (C(15), C(16)), 116.0 (C(2')), 120.0 (C(1)), 122.4 (C(5')), 136.5 (C(3')), 138.6 and 138.8 (C(6), C(4')), 139.2 (C(6')), 155.8 and 163.7 (C(14), C(17)), 167.0 (C(1')); HRMS (ESI$^+$) found 425.2438, $C_{25}H_{33}N_2O_4$ $[MH]^+$ requires 425.2435.

(4*R,4a*R**,6*R**,11*S**,12a*R**)-11-Hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,11,12,12a-octahydro-7,10-epoxybenzo[10]annulen-6-yl (*E*)-3-(1-methyl-1*H*-imidazol-4-yl)acrylate (366)**



Alcohol **29** (20 mg, 0.038 mmol), hydrochloride salt **359** (59% w/w, 39 mg, 0.122 mmol) and DCC (43 mg, 0.209 mmol) were dissolved in $CHCl_3$ (3 mL), and DMAP (42 mg, 0.342 mmol) was added. After 18 h, satd. aq. $NaHCO_3$ solution was added (10 mL), the layers separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. Half of the crude ester obtained was dissolved in THF (200 μL) and TBAF was added (1.0 M solution in THF, 25 μL, 0.025 mmol). The reaction mixture was stirred at RT for 7 h, then brine was added (10 mL) followed by ethyl acetate (10 mL), the layers separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were

dried over $MgSO_4$, the solvent evaporated *in vacuo* and the crude residue purified by flash chromatography (DCM / MeOH, 98:2 → 96:4) to give the *title compound* as a white solid (7.4 mg, 46% over two steps). R_f 0.20 (DCM / MeOH, 96:4); ν_{max} (thin film)/cm^{-1} 3237br, 2925m, 1707m, 1636s, 1152s; ^1H NMR δ_H (500 MHz, $CDCl_3$) −0.27 (1H, s, C(5)H), 0.75 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.88 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.27 – 1.45 (2H, m, C(3)H, C(4)H), 1.47 (3H, s, C(13)H_3), 1.66 – 1.79 (2H, m, C(2)H, C(9)H), 1.86 – 1.94 (1H, m, C(2)H), 1.95 – 2.03 (1H, m, C(11)H), 2.12 (1H, app. dt, *J* = 13.5, 4.0 Hz, C(7)H), 2.44 (1H, ddd, *J* = 12.5, 10.0, 2.5 Hz, C(9)H), 2.54 (1H, app dt, *J* = 13.5, 11.0 Hz, C(7)H), 3.71 (3H, s, C(7')H_3), 4.77 (1H, dd, *J* = 10.0, 5.5 Hz, C(10)H), 5.16 (1H, br s, C(1)H), 5.63 (1H, dd, *J* = 11.0, 4.0 Hz, C(8)H), 6.36 (1H, d, *J* = 3.0 Hz) and 6.49 (1H, d, *J* = 3.0 Hz, C(15)H, C(16)H), 6.56 (1H, d, *J* = 15.5 Hz, C(2')H), 7.09 (1H, s, C(5')H), 7.46 (1H, s, C(6')H), 7.60 (1H, d, *J* = 15.5 Hz, C(3')H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 15.2 (C(12)), 21.4 (C(12)), 22.5 (C(13)), 25.0 (C(2)), 27.2 (C(11)), 33.4 (C(7)), 33.6 (C(7')), 37.3 (C(5)), 38.7 and 39.7 (C(3), C(4)), 43.4 (C(9)), 69.2 (C(8)), 69.7 (C(10)), 113.3 (C(15) or C(16)), 115.9 (C(2')), 117.0 (C(15) or (C(16)), 119.1 (C(1)), 122.5 (C(5')), 136.6 (C(3')), 138.6 and 138.7 (C(6), C(4')), 139.2 (C(6')), 157.5 and 160.6 (C(14), C(17)), 166.9 (C(1')); HRMS (ESI^+) found 425.2429, $C_{25}H_{33}N_2O_4$ $[MH]^+$ requires 425.2435.

Experimental protocol for cell viability assays (Performed by Dr V. Macaulay, Dr. F. Willenbrock, C. Towers)

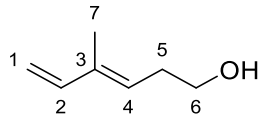
All established cell lines were cultured in Dulbecco's Modified Eagle's (DMEM) or Roswell Park Memorial Institute (RPMI) media under standard conditions. All were validated using Short Tandem Repeat (STR) analysis and tested regularly for mycoplasma. Primary T cells were activated using phytohaemagglutinin and then cultured in RPMI containing interleukin-2 for up to 2 weeks. Assays were performed in 96-well plates in medium containing DMSO up to 0.5%. Compounds were provided as 10mM solutions in DMSO and were used at a maximum concentration of 50μM.

On Day 1, cells were seeded at 10 - 20% confluence in 96-well dish. On Day 2, compounds were applied at 8 different concentrations, 1 – 50 μM. Vehicle control was 0.5% DMSO. On day 5, Hoechst 33342 (4 μM) and propidium iodide (0.5 μM) were added directly to cells in the medium. Whole well analysis was performed using a Celigo imaging cytometer at $\lambda_{ex/em}$ of 377/470 nm and 540/630 nm. Normalised data was plotted against log[compound] and fitted to the equation:

$$y = 100/(1 + 10^{(m(\log IC50 - x))})$$

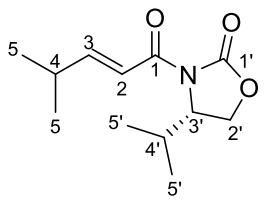
Data for Chapter 4

One-pot preparation of (*E*)-4-methylhexa-3,5-dien-1-ol (333)



To 3-methyl-1,4-pentadiene (2.0 mL, 16.5 mmol) dissolved in THF (45 mL) was added, at −78 °C, *n*-BuLi (2.5 M solution in hexanes, 6.0 mL, 15 mmol). The reaction mixture was allowed to warm to RT over 40 min, then cooled again to −78 °C and paraformaldehyde (675 mg, 22.5 mmol) added as a suspension in THF (5 mL). The mixture was then allowed to warm to RT. Once reaction was complete, judged by disappearance of the red colouration of the organometallic species, 18-crown-6 was added (3.96 g, 15.0 mmol) followed by KOTMS (4.27 g, 30.0 mmol) as a solution in THF (5 mL). After stirring at RT for 15 min, brine (10 mL) was added, the layers separated and the aqueous layer extracted with ether (2 × 15 mL). The combined organic layers were washed with water (15 mL) then brine (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* bulb-to-bulb distillation (110°C at 20 mmHg) to give the title compound as a colourless oil (921 mg, 55%).

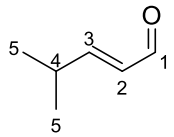
(*S*,*E*)-4-Isopropyl-3-(4-methylpent-2-enoyl)oxazolidin-2-one (380)[168]



(*E*)-4-methylpent-2-enoic acid (500 mg, 4.4 mmol) and NEt_3 (1.5 mL, 11.0 mmol) were dissolved in THF (20 mL). Pivaloyl chloride (515 μL, 4.2 mmol) was added at 0 °C and the mixture stirred for 2 h. LiCl (175 mg, 4.2 mmol) was then added followed by (*S*)-4-isopropyl-2-oxazolidinone (509 mg, 4.0 mmol). The mixture was allowed to warm to RT and stirred for

18 h. Satd. aq. NH_4Cl solution (20 mL) was then added, the mixture extracted with ether (3 × 30 mL), the combined organic layers washed with satd. aq. $NaHCO_3$ solution (50 mL), water (50 mL) then brine (50 mL), dried over $MgSO_4$ and the solvent removed in vacuo. The crude residue was purified by flash chromatography (petrol / ether, 9:1 → 7:3) to give the title compound as a colourless oil (500 mg, 51%). R_f 0.37 (petrol / ether, 7:3); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* = 7.0 Hz), 0.86 (3H, d, *J* = 7.0 Hz), 1.03 (3H, d, *J* = 6.5 Hz) and 1.03 (3H, d, *J* = 6.5 Hz, C(5)H_3, C(5')H_3), 2.28 – 2.41 (1H, m, C(4)H), 2.48 (1H, octd, *J* = 7.0, 1.0 Hz, C(4')H), 3.64 – 3.75 (1H, m), 4.11 – 4.27 (1H, m) and 4.39 – 4.47 (1H, m, C(2')H_2, C(3')H), 7.04 (1H, dd, *J* = 15.5, 6.5 Hz, C(3)H), 7.16 (1H, dd, *J* = 15.5, 1.0 Hz, C(2)H).

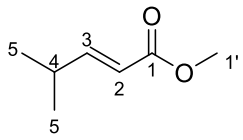
(*E*)-4-Methylpent-2-enal (382)[247]



Isobutyraldehyde (500 mg, 7.0 mmol) was added to a solution of ethynylmagnesium bromide solution in THF (0.5 M, 21 mL, 10.5 mmol) at 0 °C. The reaction mixture was stirred at RT for 18 h, then satd. aq. NH_4Cl solution was added (20 mL), the layers separated and the aqueous layer extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. The resulting crude alcohol, crotonic acid (146 mg, 1.7 mmol), CuCl (20 mg, 0.2 mmol), and (*i*-PrO)$_4$Ti (60 μL, 0.2 mmol) were dissolved in 1,2-dichlorobenzene (2 mL) and the mixture heated to 150 °C for 4 h. DCM (20 mL) and water (20 mL) was then added, the layers separated and the aqueous layer extracted with DCM (2 × 20 mL). The combined organic layers were washed with satd. aq. NH_4Cl solution (40 mL) and brine (40 mL), then dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether,

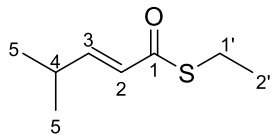
9:1) to give the title compound as a yellow oil (270 mg, 39% over two steps). R_f 0.37 (petrol / ether, 8:2); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.12 (6H, d, *J* = 7.0 Hz, C(5)H_3), 2.54 – 2.69 (1H, m, C(4)H), 6.08 (1H, ddd, *J* = 15.5, 8.0, 1.5 Hz, C(2)H), 6.82 (1H, dd, *J* = 15.5, 6.5 Hz, C(3)H), 9.52 (1H, d, *J* = 8.0 Hz, C(1)H).

Methyl (*E*)-4-methylpent-2-enoate (393)[248]



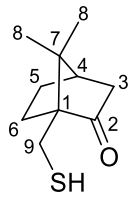
(*E*)-4-methylpent-2-enoic acid (1.0 g, 8.8 mmol) was dissolved in MeOH (5 mL) and conc. H_2SO_4 added (100 μL, 1.8 mmol). The mixture was heated to 70 °C for 7 h, then satd. aq. $NaHCO_3$ solution (10 mL) added and the mixture extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL) then dried over $MgSO_4$ and the solvent removed *in vacuo* to give the title product as a colourless oil (1.04g, 93%). ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.06 (6H, d, *J* = 7.0 Hz, C(5)H_3), 2.35 – 2.56 (1H, m, C(4)H), 3.73 (3H, s, C(1')H_3), 5.78 (1H, d, *J* = 15.5 Hz, C(2)H), 6.96 (1H, ddd, *J* = 15.5, 6.5, 1.0 Hz, C(3)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 21.2 (C(5)), 30.9 (C(4)), 51.4 (C(1')), 118.2 (C(2)), 155.8 (C(3)), 167.5 (C(1)).

_S_-Ethyl (_E_)-4-methylpent-2-enethioate (395)[249]



(*E*)-4-methylpent-2-enoic acid (1.00 g, 8.8 mmol), ethanethiol (850 μL, 11.4 mmol), and DMAP (107 mg, 0.88 mmol) were dissolved in DCM (35 mL); the mixture was cooled to 0 °C and DCC was added (1.92 g, 9.3 mmol). The mixture was then stirred at RT for 18 h, before being filtered through celite and washed with satd. aq. $NaHCO_3$ solution (20 mL) then brine (20 mL). The organic layer was then dried over $MgSO_4$ and the solvent removed *in vacuo* to give the title compound as a yellow oil (1.13 g, 82%). ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.08 (6H, d, *J* = 7.0 Hz, C(5)H_3), 1.28 (3H, t, *J* = 7.5 Hz, C(2')H_3), 2.40 – 2.53 (1H, m, C(4)H), 2.95 (2H, q, *J* = 7.5 Hz, C(1')H_2), 6.06 (1H, dd, *J* = 15.5, 1.5 Hz, C(2)H), 6.87 (1H, dd, *J* = 15.5, 6.5 Hz, C(3)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 14.8 (C(2')), 21.2 (C(5)), 23.1 (C(1')), 30.9 (C(4)), 126.0 (C(2)), 151.3 (C(3)), 190.5 (C(1)).

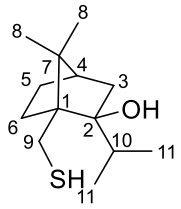
(1*S*,4*R*)-1-(Mercaptomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (399)[180]



$SOCl_2$ (2.2 mL, 30.1 mmol) was added dropwise to (1*S*,4*R*)-(+)-camphorsulfonic acid (2.0 g, 8.6 mmol). The mixture was purged with Ar for 5 min, then heated to 80 °C for 2 h. After cooling to RT, water (10 mL) was added, and the mixture extracted with ether (3 × 30 mL). The combined organic layers were washed with satd. aq. $NaHCO_3$ solution (50 mL) then brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting sulfonyl chloride was dissolved in an 1 : 4 water / dioxane mixture (35 mL), and triphenylphosphine (9.0 g, 34.5

mmol) was added. The mixture was heated to 105 °C for 2 h, then cooled to RT, extracted with petrol (3 × 30 mL), the combined organic layers washed with water (50 mL) then brine (50 mL), dried over MgSO4 and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 9:1) to give the title compound as a white solid (1.02 g, 80% over two steps). R_f 0.40 (petrol / ether, 9:1); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.92 (3H, s, C(8)H_3), 1.03 (3H, s, C(8)H_3), 1.34 – 1.47 (1H, m, CH_2), 1.58 (1H, br s, C(9)H_2S*H*), 1.67 – 1.77 (1H, m, CH_2), 1.83 – 2.06 (3H, m, CH_2), 2.09 (1H, t, *J* = 4.5 Hz, C(4)H), 2.33 – 2.41 (2H, m, C(9)H, CH_2), 2.88 (1H, dd, *J* = 14.0, 6.5 Hz, C(9)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 19.8 and 20.3 (C(8)), 21.4 (C(9)), 26.6, 27.1 and 43.3 (CH_2), 43.7 (C(4)), 47.9 and 60.7 (C(1), C(7)), C(2) not seen.

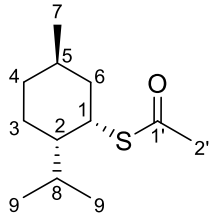
(1*S*,2*S*,4*R*)-2-Isopropyl-1-(mercaptomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (400)



Prepared following a literature procedure for a similar compound.[181] $CeCl_3$ (750 mg, 3.0 mmol) was suspended in THF (2.0 mL) and the mixture was sonicated for 30 min, then stirred for 15 min. The mixture was cooled to –78 °C, then *i*-PrMgCl (2.0 M solution in THF, 1.5 mL, 3.0 mmol) was added dropwise; the mixture was stirred for 2 h at –78 °C then a solution of camphor thiol (175 mg, 0.95 mmol) in THF (2.0 mL) was added. The reaction mixture was allowed to warm to RT then stirred for 18 h, quenched with hydrochloric acid (1.0 M, 2.0 mL) and extracted with petrol (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4), and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 19:1) to give the *title compound* as a

colourless oil (120 mg, 55%). $[\alpha]_D$ = –1.7 (*c* = 1.0, $CHCl_3$); R_f 0.29 (petrol / ether, 9:1); ν_{max} (thin film)/cm^{-1} 3504br, 2949s, 1456m, 1386m, 1029m, 984m; ^1H NMR δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* = 6.5 Hz, C(11)H_3), 0.97 (3H, s, C(8)H_3), 0.98 (3H, d, *J* = 6.5 Hz, C(11)H_3), 1.00 – 1.08 (1H, m, CH_2), 1.22 (3H, s, C(8)H_3), 1.39 (1H, dd, *J* = 8.5, 7.5 Hz, C(9)S*H*), 1.43 (1H, ddd, *J* = 12.5, 10.0, 2.5 Hz, CH_2), 1.44 (1H, d, *J* = 13.0 Hz, CH_2), 1.64 (1H, t, *J* = 4.5 Hz, C(4)H), 1.70 – 1.89 (3H, m, C(10)H, CH_2 × 2), 1.94 (1H, ddd, *J* = 13.0, 4.5, 3.0 Hz, CH_2), 2.02 (1H, s, C(2)O*H*), 2.83 (1H, dd, *J* = 14.5, 8.5 Hz) and 2.93 (1H, dd, *J* = 14.5, 7.5 Hz, C(9)H_2); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 18.1 and 18.4 (C(11)), 22.2 and 22.3 (C(8)), 23.1 (C(9)), 27.2 (CH_2), 27.4 (CH_2), 37.3 (C(10)), 45.3 (C(4)), 47.8 (CH_2), 51.6 and 54.5 (C(1), C(7)), 84.1 (C(2)); HRMS (ESI^-) found 227.1472, $C_{13}H_{23}OS$ $[M-H]^-$ requires 227.1475.

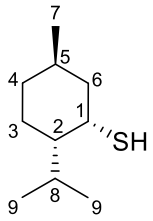
_S_-[(1_S_,2_S_,5_R_)-2-Isopropyl-5-methylcyclohexyl] ethanethioate[182]



To (−)-Menthol (3.1 g, 20 mmol) dissolved in pyridine (25 mL), was added TsCl (4.6 g, 24 mmol) and the mixture was stirred at RT for 18 h. Water (35 mL) was then added, and the precipitate formed was filtered and dried under high vacuum. Half of this tosylate (1.76 g) was suspended in DMSO (11 mL) and potassium thioacetate was added (1.94 g, 17.03 mmol). The mixture was heated to 60 °C for 36 h; it was then cooled to RT, diluted with water (50 mL), and extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 9:1) to give the title compound as a colourless oil (726 mg, 34% over two steps). R_f 0.92 (petrol / ether, 1:1); ^1H NMR δ_H (400 MHz, $CDCl_3$)

0.84 (3H, d, *J* = 6.5 Hz), 0.87 (3H, d, *J* = 6.5 Hz) and 0.89 (3h, d, *J* = 6.5 Hz, C(7)H_3, C(9)H_3), 0.91 – 0.95 (2H, m, CH_2), 1.08 – 1.17 (1H, m, CH_2), 1.28 – 1.49 (2H, m, CH, CH_2), 1.56 – 1.76 (2H, m, CH, CH_2), 1.79 – 1.88 (2H, m, CH_2), 2.33 (3H, s, C(2')H_3), 4.08 (1H, s, C(1)H).

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexane-1-thiol (402)[183]

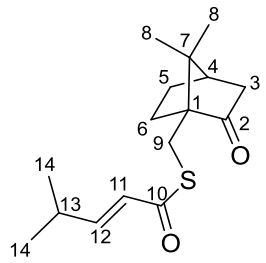


S-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl] ethanethioate (726 mg, 3.4 mmol) was dissolved in DCM (30 mL), cooled to 0 °C, and DIBAL (1.0 M solution in cyclohexane, 10.4 mL, 10.4 mmol) added dropwise. After stirring for 6 h at this temperature, satd. aq. NH_4Cl solution (30 mL) was added, followed by water (60 mL) and acq. HCl solution (1.0 M, 30 mL). The layers were separated and the aqueous layer extracted with DCM (3 × 50 mL); the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and the solvent removed *in vacuo* to give the title compound as a yellow oil (580 mg, quantitative). ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.79 – 0.86 (1H, m, C(4)H), 0.87 (3H, d, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 6.5 Hz) and 0.92 (3H, d, *J* = 6.5 Hz, C(7)H_3, C(9)H_3), 0.99 – 1.09 (1H, m, C(2)H), 1.23 (1H, d, *J* = 7.0 Hz, C(1)HS*H*), 1.25 – 1.43 (2H, m, C(3)H, C(6)H), 1.45 – 1.55 (1H, m, C(8)H), 1.64 – 1.76 (2H, m, C(3)H, C(4)H), 1.76 – 1.83 (1H, m, C(5)H), 1.83 – 1.90 (1H, m, C(6)H), 3.48 – 3.54 (1H, m, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 20.4, 20.9 and 22.2 (C(7), (C(9)), 24.2 (C(3)), 26.0 (C(5)), 30.3 (C(8)), 35.3 (C(4)), 40.2 (C(1)), 44.0 (C(6)), 48.2 (C(2)).

General procedure for the preparation of thioesters 403–405

To a solution of the thiol (x mmol) and 4-methyl-2-pentenoic acid (1.2x mmol) in dichloromethane (5.0x mL) was added DCC (1.3x mmol) and DMAP (0.1x mmol). The reaction mixture was stirred for 18 h at RT, filtered through celite, and washed with satd. aq. $NaHCO_3$ solution then brine. The organic portion was then dried (MgSO4), the solvent was removed *in vacuo*, and the crude residue was purified by flash chromatography.

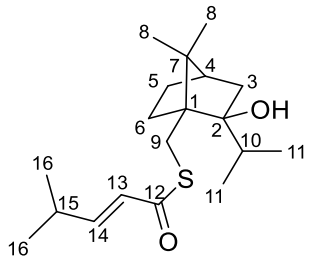
***S*-{[(1*S*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methyl} (*E*)-4-methylpent-2-enethioate (403)**



Obtained as a colourless oil (462 mg, 82%) following flash chromatography (petrol / ether, 9:1). $[\alpha]_D$ = –53.7 (*c* = 1.00, $CHCl_3$); R_f 0.39 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2961m, 1742s, 1670m, 1629m, 1038m, 777m; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.92 (3H, s, C(8)H_3), 1.06 (6H, d, *J* = 7.0 Hz, C(14)H_3), 1.07 (3H, s, C(8)H_3), 1.35 (1H, ddd, *J* = 12.5, 9.5, 3.5 Hz) and 1.53 (1H, ddd, *J* = 14.0, 9.5, 4.5 Hz, CH_2), 1.84 (1H, td, *J* = 13.5, 3.5 Hz), 1.87 (1H, d, *J* = 18.5 Hz) and 1.92 – 2.02 (1H, m, CH_2), 2.09 (1H, t, *J* = 4.5 Hz, C(4)H), 2.38 (1H, ddd, *J* = 18.5, 4.5, 3.0 Hz, CH_2), 2.44 (1H, octd, *J* = 7.0, 1.5 Hz, C(13)H), 2.98 (1H, d, *J* = 14.0 Hz) and 3.23 (1H, d, *J* = 14.0 Hz, C(9)H), 6.06 (1H, dd, *J* = 15.5, 1.5 Hz, C(11)H), 6.88 (1H, dd, *J* = 15.5, 6.5 Hz, C(12)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 19.8 and 20.2 (C(8)), 21.3 (2 signals) (C(14)), 24.6 (C(9)), 26.7 (CH_2), 26.8 (CH_2), 31.1 (C(13)), 43.1 (CH_2), 43.8 (C(4)),

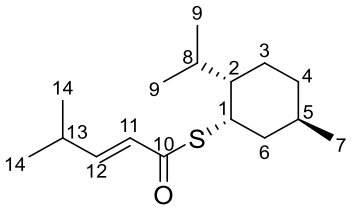
48.0 and 60.8 (C(1), C(7)), 125.9 (C(11)), 151.6 (C(12)), 190.7 (C(10)), 217.4 (C(2)); HRMS (ESI^+) found 281.1569, $C_{16}H_{25}O_2S$ $[MH]^+$ requires 281.1570.

_S_-{[(1_S_,2_S_,4_R_)-2-Hydroxy-2-isopropyl-7,7-dimethylbicyclo[2.2.1]heptan-1-yl]methyl} (_E_)-4-methylpent-2-enethioate (404)



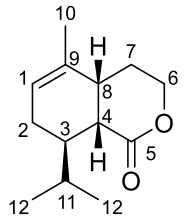
Obtained as a colourless oil (180 mg, 69%) following flash chromatography (petrol / ether, 19:1). $[\alpha]_D$ = –1.6 (*c* = 0.45, $CHCl_3$); R_f 0.49 (petrol / ether, 7:3); ν_{max} (thin film)/cm^{-1} 3525br, 2961s, 1662s, 1628s, 1038s, 749m; ^1H NMR δ_H (500 MHz, $CDCl_3$) 0.94 (3H, s, C(8)H_3), 0.96 (3H, d, *J* = 6.5 Hz, C(11)H_3), 1.03 – 1.13 (1H, m, CH_2), 1.07 (6H, d, *J* = 6.5 Hz) and 1.09 (3H, d, *J* = 6.5 Hz, C(11)H_3, C(16)H_3), 1.20 (3H, s, C(11)H_3), 1.43 – 1.49 (1H, m, CH_2), 1.46 (1H, d, *J* = 13.0 Hz, CH_2), 1.62 (1H, t, *J* = 4.5 Hz, C(4)H), 1.65 – 1.78 (2H, m, CH_2), 1.81 (1H, sept, *J* = 6.5 Hz, C(10)H), 1.95 (1H, ddd, *J* = 13.0, 4.5, 2.5 Hz, CH_2), 2.44 (1H, octd, *J* = 6.5, 1.5 Hz, C(15)H), 3.17 (1H, d, *J* = 14.5 Hz) and 3.48 (1H, d, *J* = 14.5 Hz, C(9)H_2), 6.07 (1H, dd, *J* = 15.5, 1.5 Hz, C(13)H), 6.87 (1H, dd, *J* = 15.5, 6.5 Hz, C(14)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 18.2, 18.6, 21.3 (2 signals), 22.0 and 22.4 (C(8), C(11), C(16)), 26.5 (CH_2), 27.2 (C(9)), 27.4 (CH_2), 31.1 (C(15)), 37.3 (C(10)), 45.1 (C(4)), 47.6 (CH_2), 51.7 and 54.8 (C(1), C(7)), 83.8 (C(2)), 126.0 (C(13)), 151.1 (C(14)), 190.9 (C(12)); HRMS (ESI^+) found 347.2014, $C_{19}H_{32}NaO_2S$ $[MH]^+$ requires 347.2015.

_S_-[(1_R_,2_S_,5_R_)-2-Isopropyl-5-methylcyclohexyl] (_E_)-4-methylpent-2-enethioate (405)



Obtained as a colourless oil (207 mg, 77%) following flash chromatography (petrol / ether, 19:1). $[\alpha]_D$ = +64.7 (*c* = 1.00, $CHCl_3$); R_f 0.84 (petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2956m, 1673s, 1630m, 1036s, 776s; ^1H NMR δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* = 6.5 Hz), 0.86 (3H, d, *J* = 6.5 Hz) and 0.89 (3H, d, *J* = 6.5 Hz (C(7)H_3, C(9)H_3), 0.92 – 1.03 (2H, m, CH_2), 1.07 (6H, d, *J* = 7.0 Hz, C(14)H_3), 1.15 (1H, ddt, *J* = 11.5, 9.5, 3.5 Hz, C(2)H), 1.35 (1H, ddd, *J* = 13.5, 12.0, 3.5 Hz, C(6)H), 1.39 – 1.49 (1H, m, C(8)H), 1.59 – 1.70 (1H, m, C(5)H), 1.70 – 1.76 (1H, m, CH_2), 1.85 (2H, app. dq, *J* = 13.5, 3.0 Hz, C(6)H, CH_2), 2.44 (1H, octd, *J* = 7.0, 1.5 Hz, C(13)H), 4.18 (1H, qd, *J* = 3.5, 2.0 Hz, C(1)H), 6.05 (1H, dd, *J* = 15.5, 1.5 Hz, C(11)H), 6.86 (1H, dd, *J* = 15.5, 6.5 Hz, C(12)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 20.9, 21.1, 21.4 and 22.3 (C(7), C(9), C(14)), 28.0 (CH_2), 28.3 (C(5)), 30.7 (C(8)), 31.1 (C(13)), 35.2 (CH_2), 42.2 (C(6)), 44.9 (C(1)), 47.9 (C(2)), 126.6 (C(11)), 150.9 (C(12)), 190.0 (C(10)); HRMS (ESI^+) found 269.1934, $C_{16}H_{29}OS$ $[MH]^+$ requires 269.1939.

Preparation of (4a*R,8*R**,8a*R**)-8-isopropyl-5-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (159) *via* intermolecular Diels–Alder reaction**



To a solution of alcohol **333** (28.0 mg, 0.25 mmol) and thioester **395** (160 mg, 1.01 mmol) in DCM (2.0 mL) was added a solution of Me_2AlCl (1.0 M solution in hexanes, 250 μL, 0.25 mmol). The reaction mixture was stirred at RT for 48 h, diluted with DCM (5.0 mL), satd. aq. Rochelle salt solution (10 mL) was added, and the resulting mixture was stirred for 10 min. The layers were separated, the aqueous layer extracted with DCM (3 × 10 mL), the combined organic layers washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting mixture of adduct **396** and lactone **159** was dissolved in DCM (2.0 mL) and $TsOH·H_2O$ (24.0 mg, 0.125 mmol) was added. Stirring was continued for 3 h at RT, then the mixture was diluted with DCM (5.0 mL), satd. aq. $NaHCO_3$ solution (10 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were washed with brine (10 mL) then dried ($MgSO_4$). The solvent was removed *in vacuo* and the so-formed residue was purified by flash chromatography (petrol / ether, 9:1 → 1:1) to give lactone **159** as a pale yellow oil (35.0 mg, 67%). *Diagnostic signals for adduct **396***: ^{1}H NMR δ_H (400 MHz, C_6D_6) 2.59 – 2.79 (2H, m, SCH_2), 2.86 (1H, dd, *J* = 11.0, 4.5 Hz, C*H*), 3.40 – 3.48 (2H, m, CH_2OH).

Diastereoselective Diels–Alder reactions with thioesters 403–405

Reactions were run according to the procedure with *S*-ethyl thioester **395** but with an excess of alcohol **333** (2.0 equiv) and Me_2AlCl (2.0 equiv) with respect to the thioester **403**–**405**. The enantiomeric ratio of the resulting lactone **159** was determined by chiral GC [Lipodex® E column; flow: 3.6 mL/min; 10 min at 50 °C, then +2 °C min^{-1} to 170 °C, hold for 10 min, then +10 °C min^{-1} to 220 °C, hold for 10 min; major enantiomer, t_R = 67.6 min; minor enantiomer, t_R = 68.3 min]. From the reaction with thioester **403**, lactone **159** was found to be enriched in the (+)-enantiomer (er = 72 : 28); $[\alpha]_D$ = +3.7 (*c* = 0.9, $CHCl_3$).

Data for Chapter 5

Enzymes and Molecular Biology

The $P450_{BM3}$ enzymes were produced in *Escherichia coli* BL21 (DE3) and purified by addition of $(NH_4)_2SO_4$ to a concentration of 40% w/v and centrifugation at 37,500g for 10 min at 4 °C; the residue was discarded and $(NH_4)_2SO_4$ was added to a concentration of 60% w/v. The solution was submitted to centrifugation at 37,500g for 10 min at 4 °C, the supernatant was discarded and the residue was resuspended in phosphate buffer. The enzymes were stored as stock solutions at –20 °C and thawed at RT before use.

General procedure for screening of compounds

Compounds were screened using an NADPH regeneration system in 200 mM phosphate buffer (pH 7.5), at a total volume of 0.5 mL, contained in 24 well plates. The substrate was added as a 100 mM stock solution in methanol (final concentration 2 mM), and the mutant $P450_{BM3}$ enzyme was added as a 10 μM stock solution in phosphate buffer (pH 7.5, final concentration 2 μM). The NADPH regeneration system consisted of glucose dehydrogenase, added as a 2 U/μL stock solution in 200 mM phosphate buffer (pH 7.5, final concentration 40 U/mL), glucose, added as a 1.0 M stock solution in 200 mM phosphate buffer (pH 7.5, final concentration 100 mM), and $NADP^+$, added as a 4.0 mM stock solution in 200 mM phosphate buffer (pH 7.5, final concentration 8 μM). The reactions were shaken at RT for 16 h, extracted with 300 μL of ethyl acetate and, following centrifugation at 14,300 g for 2 minutes, the organic phase was analysed by GC.

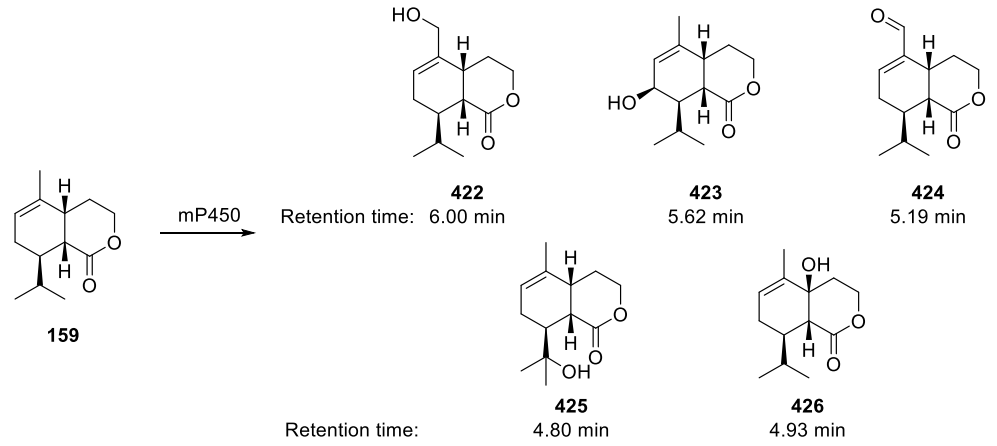
P450$_{BM3}$ variants and the mutations in each

Enzyme	Mutations
A328V	A328V
AP	A330P
EV/VI/LI	E267V/V302I/L353I
F87A	F87A
F87A/I401P	F87A/I401P
F87A/T88A/I401P	F87A/T88A/I401P
FS/IP	F87S/I401P
GVQ	A74G/F87V/L188Q
IP/QP	I401P/Q403P
KSK19	F87A/H171L/Q307H/N319Y
KSK19/A82M	F87A/A82M/H171L/Q307H/N319Y
KSK19/A82M/E267F	F87A/A82M/H171L/E267F/Q307H/N319Y
KSK19/AI	F87A/H171L/Q307H/N319Y/A328I
KSK19/AI/IA	F87A/ H171L/I263A/Q307H/N319Y/A328I
KSK19/AI/Y51V	F87A/ H171L/I263A/Q307H/N319Y/A328I
KSK19/AI/Y51L	F87A/ H171L/I263A/Q307H/N319Y/A328I
KSK19/AI/F87V	F87V/H171L/Q307H/N319Y/A328I
KSK19/AI/AI	F87A/H171L/A184I/Q307H/N319Y/A328I
KSK19/AI/V78I	V78I/F87A/H171L/Q307H/N319Y/A328I
KSK19/I263A	V78I/F87A/H171L/Q307H/N319Y/A328I
KSK19/IA/QP	F87A/H171L/I263A/Q307H/N319Y/Q403P
KSK19/QP	F87A/H171L/Q307H/N319Y/Q403P
KSK19/QP/F87V	F87V/H171L/Q307H/N319Y/Q403P
KSK48	R179H/L233V/S270I/Q307H/N319Y
KT2	A191T/N239H/I259V/A276T/L353I
KT2/A82G	A82G/A191T/N239H/I259V/A276T/L353I
KT2/A328V	A191T/N239H/I259V/A276T/A328V/L353I
KT2/E267L	A191T/N239H/I259V/E267L/A276T/L353I
KT2/F87I	F87I/A191T/N239H/I259V/A276T/L353I
KSK19/T88A	T88A/A191T/N239H/I259V/A276T/L353I
QP	Q403P
QP/A82M	A82M/Q403P
RLYF	R47L/Y51F
RLYF/KSK19	R47L/Y51F/F87A/H171L/Q307H/N319Y
RLYF/KSK19/AI	R47L/Y51F/F87A/H171L/Q307H/N319Y/A328I
RP	R47L/Y51F/I401P
RP/A82M	R47L/Y51F/A82M/I401P
RP/AM/A328I	R47L/Y51F/A82M/A328I/I401P
RP/AM/IA	R47L/Y51F/A82M/I263A/I401P
RP/AP	R47L/Y51F/A330P/I401P
RP/AP/AM	R47L/Y51F/A82M/A330P/I401P
RP/AP/PV	R47L/Y51F/P329V/A330P/I401P
RP/E267I	R47L/Y51F/E267I/I401P
RP/E267M	R47L/Y51F/E267M/I401P
RP/EV	R47L/Y51F/E267V/I401P
RP/FA	R47L/Y51F//F87A/I401P
RP/F87A/A328I	R47L/Y51F//F87A/A328I/I401P
RP/F87A/A328P	R47L/Y51F//F87A/A328P/I401P
RP/FV	R47L/Y51F/F87V/I401P
RP/FV/EV	R47L/Y51F/F87V/E267V/I401P

Enzyme	Mutations
RP/FV/EV/F81W	R47L/Y51F/F81W/F87V/E267V/I401P
RP/FV/EV/L188Q	R47L/Y51F/F87V/L188Q/E267V/I401P
RP/FV/EV/V78F	R47L/Y51F/F87V/L188Q/E267V/I401P
RP/F81W	R47L/Y51F/I401P/ F81W
RP/H171L	R47L/Y51F/H171L/I401P
RP/H171L/IG	R47L/Y51F/I263G/H171L/I401P
RP/IA	R47L/Y51F/I263A/I401P
RP/IA/EV	R47L/Y51F/I263A/E267F/I401P
RQA	R47L/Y51F/A82M/I263A/Q403P
RT2	R47L/Y51F/A191T/N239H/I259V/A276T/L353I
RT2/A330W	R47L/Y51F/A191T/N239H/I259V/A276T/A330W/L353I
RT2/A330W/A82F	R47L/Y51F/A82F/A191T/N239H/I259V/A276T/A330W/L353I
RT2/A330W/A82M	R47L/Y51F/A82M/A191T/N239H/I259V/A276T/A330W/L353I
RT2/A330W/I263A	R47L/Y51F/I263A/A191T/N239H/I259V/A276T/A330W/L353I
RT2/AP	R47L/Y51F/A191T/N239H/I259V/A276T/A330P/L353I
RT2/AP/A184I	R47L/Y51F/A184I/A191T/N239H/I259V/A276T/A330P/L353I
RT2/AP/A82F	R47L/Y51F/A82F/A191T/N239H/I259V/A276T/A330P/L353I
RT2/AP/A82L	R47L/Y51F/A82L/A191T/N239H/I259V/A276T/A330P/L353I
RT2/AP/AM	R47L/Y51F/A82M/A191T/N239H/I259V/A276T/A330P/L353I
RT2/AP/AM/AI	R47L/Y51F/A82M/A184I/A191T/N239H/I259V/A276T/A330P/L353I
RT2/AP/E267F	R47L/Y51F/A191T/N239H/I259V/E267F/A276T/A330P/L353I
RT2/AP/E267L	R47L/Y51F/A191T/N239H/I259V/E267L/A276T/A330P/L353I
RT2/AP/F81W	R47L/Y51F/F81W/A191T/N239H/I259V/A276T/A330P/L353I
RT2/AP/I401M	R47L/Y51F/A191T/N239H/I259V/A276T/A330P/L353I/I401M
RT2/AP/I401M/A82G	R47L/Y51F/A82G/A191T/N239H/I259V/A276T/A330P/L353I/I401M
RT2/AP/K440L	R47L/Y51F/A191T/N239H/I259V/A276T/A330P/L353I/K440L
RT2/AP/PV	R47L/Y51F/A191T/N239H/I259V/A276T/P329V/A330P/L353I
RT2/AP/V78I	R47L/Y51F/V78I/A191T/N239H/I259V/A276T/A330P/L353I
RT2/F81W	R47L/Y51F/F81W/A191T/N239H/I259V/A276T/L353I
RT2/F81W/A82M	R47L/Y51F/F81W/A82M/A191T/N239H/I259V/A276T/L353I
RT2/F81W/A328I	R47L/Y51F/F81W/A191T/N239H/I259V/A276T/A328I/L353I
RT2/IP	R47L/Y51F/A191T/N239H/I259V/A276T/L353I/I401P
RT2/IP/A184I	R47L/Y51F/A184I/A191T/N239H/I259V/A276T/L353I/I401P
RT2/IP/E267V	R47L/Y51F/A191T/N239H/I259V/E267V/A276T/L353I/I401P
RT2/IP/V78I	R47L/Y51F/V78I/A191T/N239H/I259V/A276T/L353I/I401P
RT2/V78F	R47L/Y51F/V78F/A191T/N239H/I259V/A276T/L353I
RT2/V78F/A330W	R47L/Y51F/V78F/A191T/N239H/I259V/A276T/A330W/L353I
T88M/IP	T88M/I401P
WT	WT

Screening data for lactone 159

Conversion was determined by GC analysis (DB-1 capillary GC column, flow rate 1.50 mL min^{-1}; 2 min at 180 °C, then +15 °C min^{-1} up to 300°C, hold for 2 min)

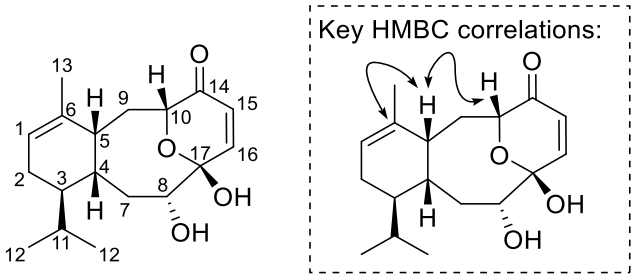


			Conversion to metabolite					
Entry	**Mutant**	**Conversion**	**422**	**423**	**424**	**425**	**426**	**Unkn[a]**
1	RL/YF/KSK19/AI	89%	57%	-	6%	25%	-	-
2	KSK19/A82M	100%	-	-	-	-	-	-
3	KSK19/AI/Y51L	61%	47%	-	7%	15%	-	-
4	KSK19/AI/AI	90%	75%	-	10%	-	5%	-
5	R19/F87I	0%	-	-	-	-	-	-
6	KSK19/I263A	100%	-	-	-	-	-	-
7	RP	84%	30%	40%	-	-	-	14%
8	RP/EV	0%	-	-	-	-	-	-
9	RT2/F81W	100%	38%	53%	-	-	-	9%
10	RP/FV/EV	55%	47%	-	8%	-	-	-
11	KSK19/AI/F87V	95%	81%	9%	5%	-	-	-
12	RP/FV/EV/L437LV	28%	28%	-	-	-	-	-
13	KSK19/IG	100%	63%	-	26%	11%	-	-
14	RT2/AP/I401M	87%	56%	-	-	-	30%	-
15	RT2/AP/AM	100%	64%	-	-	-	36%	-
16	RT2/IP	100%	39%	52%	-	-	-	9%
17	RT2/AP	69%	50%	-	-	-	19%	-
18	RT2/AP/A184I	100%	71%	-	-	-	29%	-
19	RT2/AP/V78I	0%	-	-	-	-	-	-
20	RT2	95%	39%	47%	-	-	-	9%
21	RP/IA/EV	35%	35%	-	-	-	-	-
22	WT	0%	-	-	-	-	-	-
23	RP/AP	0%	-	-	-	-	-	-
24	RP/FV	100%	-	-	-	-	-	-
25	A330P	57%	41%	-	-	-	16%	-
26	RP/HL/IA/EV	22%	18%	-	-	4%	-	-
27	RT2/AP/AI/S72A	30%	19%	-	-	-	5%	6%

			Conversion to metabolite					
Entry	**Mutant**	**Conversion**	**422**	**423**	**424**	**425**	**426**	**Unkn[a]**
28	RP/H171L/I263G	100%	100%	-	-	-	-	-
29	GVQ/IG	94%	70%	-	18%	6%	-	-
30	GVQ	90%	29%	13%	6%	42%	-	-
31	RT2/A330W	100%	43%	45%	-	-	-	12%
32	F87A	98%	26%	14%	11%	47%	-	-
33	RL/YF/KSK19	98%	32%	6%	13%	47%	-	-
34	RP/AM/IA	53%	18%	16%	-	-	9%	8%
35	RP/HL/IG/EV	76%	68%	-	6%	2%	-	-
36	RL/YF	57%	23%	27%	-	-	-	7%
37	KSK19/A82M/E267F	47%	33%	4%	2%	8%	-	-
38	RP/H171L	100%	22%	64%	-	-	-	14%
39	RP/E267G	0%	-	-	-	-	-	-
40	KSK48	30%	10%	16%	-	-	-	4%
41	KSK19/QP/F87V	100%	39%	8%	11%	41%	-	-
42	RT2/AP/VI/AI	59%	32%	-	-	-	20%	7%
43	RP/FV/EV/L188Q	28%	24%	-	4%	-	-	-
44	RP/FV/EV/V78F	64%	64%	-	-	-	-	-
45	RT2/F81W/A328I	100%	19%	70%	-	-	-	11%
46	RP/E267M	7%	-	7%	-	-	-	-
47	KSK19/AI/IA	93%	78%	-	15%	-	-	-
48	RT2/S72W/A330W	100%	25%	61%	-	-	-	14%

a: Unkn = Unidentified metabolite, retention time 4.99 min.

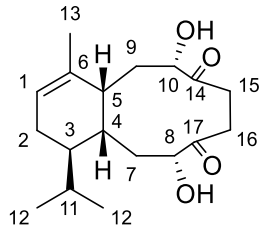
(1*R,4a*R**,6*R**,10*R**,11*R**,12a*R**)-10,11-Dihydroxy-1-isopropyl-4-methyl-2,4a,5,6,10,11,12,12a-octahydro-6,10-epoxybenzo[10]annulen-7(1*H*)-one (413)**



To a solution of furan **347** (0.12 mL of a 100 mM solution in methanol, 0.012 mmol), glucose (0.6 mL of a 1.0 M solution in water, 0.60 mmol), GDH (60 μL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (60 μL of a 4.0 mM solution in water, 0.24 μmol), and methyl-β-cyclodextrin (300 μL of a 200 mM solution in water, 60 μmol) in 200 mM phosphate buffer (pH 7.5, 4.26 mL) was added $P450_{BM3}$ mutant RP/IA/EV (600 μL of a 20 μM solution in phosphate buffer, pH 7.5, 0.012 μmol). The solution was stirred open to air for 72 h. It was then centrifuged at 9,500 g, and extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 8:2 → 6:4) to afford the *title compound* as a colourless oil (1.7 mg, 46%). R_f 0.11 (Petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3403br, 2958s, 1690s, 1087s; ^{1}H NMR δ_H (500 MHz, C_6D_6) 0.61 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.74 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.97 – 1.04 (1H, m, C(3)H), 1.19 (1H, ddd, *J* = 15.5, 12.0, 9.5 Hz, C(7)H), 1.39 – 1.44 (1H, m, C(9)H), 1.51 (3H, s, C(13)H_3), 1.52 – 1.65 (3H, m, C(2)H, C(4)H, C(9)H), 1.65 – 1.72 (1H, m, C(2)H), 1.72 – 1.78 (1H, m, C(11)H), 1.93 (1H, dd, *J* = 15.5, 4.5 Hz, C(7)H), 2.47 (1H, br s, C(5)H), 3.58 (1H, d, *J* = 9.5 Hz, C(8)H), 4.28 (1H, dd, *J* = 11.5, 8.0 Hz, C(10)H), 5.24 (1H, br s, C(1)H), 5.86 (1H, d, *J* = 10.5 Hz, C(15)H), 6.47 (1H, d, *J* = 10.5 Hz, C(16)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 14.7 (C(12)), 21.5 (C(12)), 22.0 (C(13)), 24.1 (C(2)), 26.3 (C(11)), 32.3 (C(9)), 32.4 (C(7)), 34.7 (C(5)), 37.9 (C(3)), 38.5 (C(4)), 76.0 (C(8)), 77.8 (C(10)), 96.8 (C(17)), 121.3

(C(1)), 127.5 (C(15)), 135.7 (C(6)), 144.8 (C(16)), 194.3 (C(14)); HRMS (ESI^+) found 305.1757, $C_{18}H_{25}O_4$ $[MH]^+$ requires 305.1758.

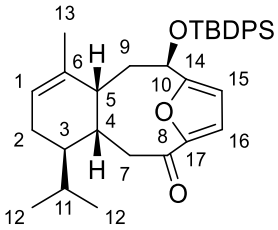
(1*R,4a*R**,6*S**,11*R**,12a*R**)-6,11-Dihydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,8,9,11,12,12a-decahydrobenzo[10]annulene-7,10-dione (415)**



To a solution of furan **349** (0.26 mL of a 70 mM solution in methanol, 0.019 mmol), glucose (1.3 mL of a 1.0 M solution in water, 1.30 mmol), GDH (130 μL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), and $NADP^+$ monosodium salt (130 μL of a 4.0 mM solution in water, 0.52 μmol) in 200 mM phosphate buffer (pH 7.5, 9.88 mL) was added $P450_{BM3}$ mutant GVQ/IG (1.3 mL of a 20 μM solution in phosphate buffer, pH 7.5, 0.026 μmol). The solution was stirred open to air for 24 h. It was then centrifuged at 9,500 g, and extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 2:8) to afford the *title compound* as a colourless oil (3.4 mg, 59%). R_f 0.24 (petrol / ether, 2:8); ν_{max} (thin film)/cm^{-1} 3414br, 2958m, 1707m, 1067m; ^1H NMR δ_H (500 MHz, $CDCl_3$) 0.78 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.89 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.20 – 1.25 (1H, m, C(7)H), 1.32 – 1.40 (1H, m, C(3)H), 1.45 – 1.49 (1H, m, C(7)H), 1.73 – 1.76 (2H, m, C(9)H), 1.77 (3H, s, C(13)H_3), 1.79 – 1.85 (2H, m, C(2)H, C(11)H), 1.86 – 1.98 (2H, m, C(2)H, C(4)H), 2.03 – 2.11 (1H, m, C(5)H), 2.86 – 3.03 (2H, m) and 3.04 – 3.15 (2H, m, C(15)H_2, C(16)H_2), 4.23 (1H, app. t, *J* = 7.5 Hz, C(8)H), 4.29 (1H, app. t, *J* = 8.5 Hz, C(10)H), 5.31 (1H, br s, C(1)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 14.7 (C(12)), 21.0 (C(12)), 22.5

(C(13)), 24.5 (C(2)), 26.7 (C(11)), 32.7 (C(7)), 33.8 and 33.9 (C(15), C(16)), 36.3 (C(5)), 37.1 (C(3)), 38.1 (C(4), C(9)), 72.8 (C(8)), 78.5 (C(10)), 120.5 (C(1)), 137.1 (C(6)), 210.7 and 212.2 (C(14), C(17)); HRMS (ESI$^+$) found 331.1879, $C_{18}H_{28}O_4Na$ $[MNa]^+$ requires 331.1880.

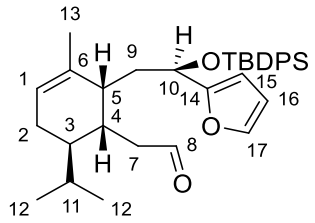
(4*R,4a*R**,11*R**,12a*R**)-11-[(*tert*-Butyldiphenylsilyl)oxy]-4-isopropyl-1-methyl-3,4a,5,11,12,12a-hexahydro-7,10-epoxybenzo[10]annulen-6(4*H*)-one (417)**



Alcohol **417** (57 mg, 0.11 mmol) was dissolved in DCM (5 mL). $NaHCO_3$ was added (92 mg, 1.10 mmol) followed by DMP (59 mg, 0.14 mmol), and the mixture stirred at RT for 1 h. satd. aq. $NaHCO_3$ solution was then added (5 mL) followed by satd. aq. $Na_2S_2O_3$ solution (5 mL), the layers separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 98:2 → 95:5) to give the title compound as a colourless oil (13.5 mg, 23%) as well as aldehyde **416** as a colourless oil (15.4 mg, 29%). R_f 0.57 (Petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2960m, 1689s, 1108s, 703s; ^{1}H NMR δ_H (400 MHz, C_6D_6) 0.23 (1H, br s, C(5)H), 0.67 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.75 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.18 (9H, s, SiC(CH_3)$_3$), 1.28 – 1.36 (1H, m, C(3)H), 1.52 (1H, dd, *J* = 15.0, 3.5 Hz, C(9)H), 1.57 – 1.80 (4H, m, C(2)H_2, C(4)H, C(11)H), 1.83 (3H, s, C(13)H_3), 2.33 (1H, ddd, *J* = 15.0, 5.5, 3.0 Hz, C(9)H), 2.39 (1H, dd, *J* = 12.0, 4.0 Hz, C(7)H), 2.94 (1H, t, *J* = 12.0 Hz, C(7)H), 5.12 (1H, br s, C(1)H), 5.20 (1H, d, *J* = 5.5 Hz, C(10)H), 6.29 (1H, dd, *J* = 3.5, 1.0 Hz, C(15)H), 6.61 (1H, d, *J* = 3.5 Hz, C(16)H), 7.17 – 7.22 (6H, m, $SiPh_2$), 7.66 – 7.74 (2H, m, $SiPh_2$), 7.74 – 7.80 (2H, m, $SiPh_2$); ^{13}C NMR δ_C (125

MHz, C_6D_6) 14.8 (C(12)), 19.5 (Si*C*$(CH_3)_3$), 21.5 (C(12)), 23.2 (C(13)), 25.3 (C(2)), 27.3 (SiC(*C*$H_3)_3$), 27.6 C(11)), 38.9 (C(3), C(5))), 43.7 (C(4)), 45.0 (C(7)), 45.7 (C(9)), 70.5 (C(10)), 114.8 (C(15)), 118.0 (C(16)), 119.4 (C(1)), 130.4, 130.5, 133.3, 133.6, 136.2 and 136.3 ($SiPh_2$), 140.2 (C(17)), 156.6 (C(6)), 168.8 (C(14)), 190.0 (C(8)), 2 signals obscured by residual solvent peak; HRMS (ESI^+) found 527.2977, $C_{34}H_{43}O_3Si$ $[MH]^+$ requires 527.2976.

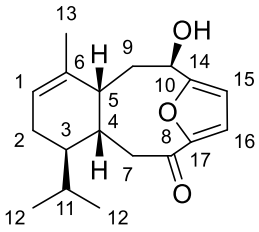
2-((1*R,2*R**,6*R**)-2-{(*R**)-2-[(*tert*-Butyldiphenylsilyl)oxy]-2-(furan-2-yl)ethyl}-6-isopropyl-3-methylcyclohex-3-en-1-yl)acetaldehyde (416)**



See preparation of ketone **417**; R_f 0.71 (Petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 2960m, 1725s, 1150s, 703s; ^1H NMR δ_H (500 MHz, C_6D_6) 0.60 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.66 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.00 – 1.06 (1H, m, C(3)H), 1.15 (9H, s, SiC$(CH_3)_3$) 1.26 – 1.36 (1H, m, C(11)H), 1.50 (3H, s, C(13)H_3), 1.51 – 1.55 (1H, m, C(7)H), 1.60 – 1.71 (1H, m, C(2)H), 1.72 – 1.98 (4H, m, C(2)H, C(5)H, C(7)H, C(9)H), 2.06 – 2.16 (1H, m, C(4)H), 2.41 (1H, ddd, *J* = 14.0, 10.5, 3.5 Hz, C(9)H), 4.85 (1H, dd, *J* = 10.5, 5.0 Hz, C(10)H), 5.14 (1H, br s, C(1)H), 5.99 (1H, dd, *J* = 3.0, 2.0 Hz, C(16)H), 6.03 (1H, dd, *J* = 3.0, 1.0 Hz, C(15)H), 7.05 (1H, dd, *J* = 2.0, 1.0 Hz, C(17)H), 7.15 – 7.23 (6H, m, $SiPh_2$), 7.60 – 7.65 (2H, m, $SiPh_2$), 7.79 – 7.87 (2H, m, $SiPh_2$), 9.22 (1H, dd, *J* = 3.0, 1.5 Hz, C(8)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 19.1 (C(12)), 19.6 (Si*C*$(CH_3)_3$), 20.7 (C(12)), 22.0 (C(13)), 24.0 (C(2)), 27.2 (SiC(*C*$H_3)_3$), 27.4 (C(11)), 32.2 (C(4)), 35.4 (C(5)), 37.1 (C(9)), 39.9 (C(3)), 42.8 (C(7)), 68.1 (C(10)), 108.4 (C(15)), 110.4 (C(16)), 121.2 (C(1)), 130.0, 130.3, 133.9 and 134.3 ($SiPh_2$), 135.4 (C(14)), 136.3 and 136.5 ($SiPh_2$), 141.9 (C(1)), 155.7 (C(6)), 201.2 (C(8)), 2 signals obscured by

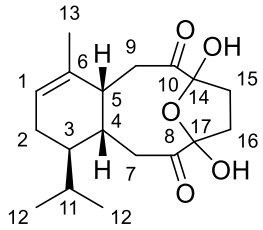
residual solvent peak; HRMS (ESI$^+$) found 551.2952, $C_{34}H_{44}O_3NaSi$ $[MNa]^+$ requires 551.2952.

(4*R,4a*R**,11*R**,12a*R**)-11-Hydroxy-4-isopropyl-1-methyl-3,4a,5,11,12,12a-hexahydro-7,10-epoxybenzo[10]annulen-6(4*H*)-one (418)**



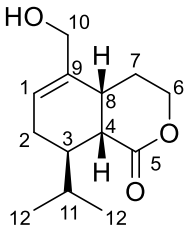
Ketone **417** (13.5 mg, 0.026 mmol) was dissolved in THF (2 mL) and TBAF was added (1.0 M solution in THF, 500 μL, 0.5 mmol). After 3 h ether (10 mL) and brine (5 mL) were added, the layers separated and the aqueous layer extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo*, and the crude product purified by column chromatography to give the *title compound* as a colourless oil (5.1 mg, 68%). R_f 0.09 (Petrol / ether, 8:2); ν_{max} (thin film)/cm^{-1} 3440br, 2960m, 1666s, 1492m, 1103m, 1008m; ^{1}H NMR δ_H (500 MHz, C_6D_6) 0.05 (1H, s, C(5)H), 0.69 (3H, d, *J* = 7.0 Hz, C(12)H_3), 0.80 (3H, d, *J* = 7.0 Hz, C(12)H_3), 1.18 (1H, ddd, *J* = 15.0, 4.0, 1.5 Hz, C(9)H), 1.33 – 1.44 (1H, m, C(3)H), 1.60 (3H, s, C(13)H_3), 1.63 – 1.72 (2H, m, C(2)H, C(11)H), 1.72 – 1.87 (2H, m, C(2)H, C(4)H), 2.39 (1H, ddd, *J* = 15.0, 5.0, 3.0 Hz, C(9)H), 2.44 (1H, dd, *J* = 12.0, 4.0 Hz, C(7)H), 3.01 (1H, t, *J* = 12.0 Hz, C(7)H), 4.62 (1H, br s, C(10)H), 5.10 (1H, s, C(1)H), 6.21 (1H, dd, *J* = 3.5, 1.0 Hz, C(15)H), 6.63 (1H, d, *J* = 3.5 Hz, C(16)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 14.7 (C(12)), 21.6 (C(12)), 22.9 (C(13)), 25.3 (C(2)), 27.6 (C(11)), 38.9 and 39.0 (C(3), C(5)), 43.7 (C(4)), 45.0 (C(7)), 45.3 (C(9)), 70.8 (C(10)), 114.2 (C(15)), 118.1 (C(16)), 119.5 (C(1)), 140.0 (C(17)), 156.8 (C(6)), 168.9 (C(14)), 190.0 (C(8)); HRMS (ESI$^+$) found 289.1798, $C_{18}H_{25}O_3$ $[MH]^+$ requires 289.1798.

(1*R,4a*R**,12a*R**)-7,10-Dihydroxy-1-isopropyl-4-methyl-1,2,4a,5,7,8,9,10,12,12a-decahydro-7,10-epoxybenzo[10]annulene-6,11-dione (419)**



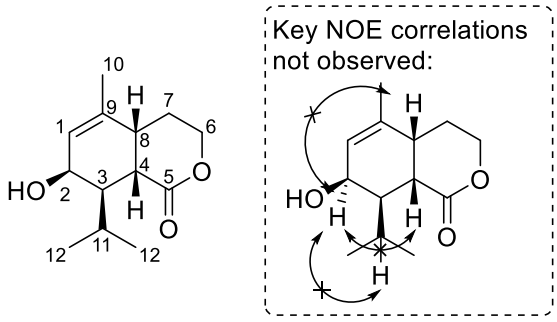
To a solution of furan **418** (0.22 mL of a 70 mM solution in methanol, 0.016 mmol), glucose (1.1 mL of a 1.0 M solution in water, 1.10 mmol), GDH (110 μL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), and $NADP^+$ monosodium salt (110 μL of a 4.0 mM solution in water, 0.44 μmol) in 200 mM phosphate buffer (pH 7.5, 8.80 mL) was added $P450_{BM3}$ mutant RT2/IP (660 μL of a 33.4 μM solution in phosphate buffer, pH 7.5, 0.022 μmol). The solution was stirred open to air for 24 h. It was then centrifuged at 9,500 g, and extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 1:1) to afford the *title compound* (tentative structure, see pg. 129) as a colourless oil (1.1 mg, 21%). R_f 0.13 (Petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3452br, 2958s, 1714s, 1141s; ^1H NMR δ_H (500 MHz, C_6D_6) 0.56 (3H, d, J = 7.0 Hz, C(12)H_3), 0.71 (3H, d, J = 7.0 Hz, C(12)H_3), 1.42 – 1.56 (3H, m, C(3)H, C(11)H and C(15)H or C(16)H), 1.60 (3H, s, C(13)H), 1.66 – 1.75 (3H, m, C(2)H, C(4)H and C(15)H or C(16)H), 1.83 – 1.91 (2H, m, C(5)H and C(15)H or C(16)H), 1.95 – 2.07 (2H, m, C(2)H and C(15)H or C(16)H), 2.38 – 2.45 (2H, m) and 2.54 – 2.66 (2H, m, C(7)H_2, C(9)H_2), 5.36 (1H, br s, C(1)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 14.1 (C(12)), 21.3 (C(12)), 22.0 (C(13)), 24.8 and 26.2 (C(15), C(16)), 27.12 (C(11)), 29.2 (C(2)), 33.8 and 34.0 (C(7), C(9)), 34.4 (C(3)), 35.3 (C(4)), 36.5 (C(5)), 77.6 and 78.4 (C(14), C(17)), 122.4 (C(1)), 135.7 (C(6)), 205.0 and 205.2 (C(8), C(10)); HRMS (ESI^+) found 345.1672, $C_{18}H_{26}O_5Na$ $[MNa]^+$ requires 345.1673.

(4a*R,8*R**,8a*R**)-5-(Hydroxymethyl)-8-isopropyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (422)**



To a solution of lactone **159** (0.60 mL of a 70 mM solution in methanol, 0.043 mmol), glucose (3.0 mL of a 1.0 M solution in water, 3.00 mmol), GDH (300 μL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), and $NADP^+$ monosodium salt (300 μL of a 4.0 mM solution in water, 1.20 μmol) in 200 mM phosphate buffer (pH 7.5, 24.63 mL) was added $P450_{BM3}$ mutant KS/K19/AI/AI (870 μL of a 68.9 μM solution in phosphate buffer, pH 7.5, 0.060 μmol). The solution was stirred open to air for 24 h. It was then centrifuged at 9,500 g, and extracted with ethyl acetate (4 × 25 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 1:1 → 2:8) to afford the *title compound* as a colourless oil (4.5 mg, 47%). R_f 0.11 (Petrol / ether, 2:8); ν_{max} (thin film)/cm^{-1} 3410br, 2959m, 1720s, 1284m, 1154m; ^{1}H NMR δ_H (500 MHz, C_6D_6) 0.74 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.86 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.28 – 1.38 (2H, m, C(7)H), 1.46 – 1.55 (1H, m, C(11)H), 1.74 – 1.87 (1H, m, C(2)H), 2.05 – 2.13 (1H, m, C(3)H), 2.14 – 2.23 (1H, m, C(2)H), 2.30 – 2.36 (1H, m, C(8)H), 2.49 (1H, ddd, *J* = 6.5, 5.0, 1.5 Hz, C(4)H), 3.52 (1H, d, *J* = 12.5 Hz, C(10)H), 3.56 – 3.65 (2H, m, (C(6)H, C(10)H), 3.70 (1H, ddd, *J* = 11.0, 8.0, 4.5 Hz, C(6)H), 5.38 (1H, br s, C(1)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 20.2 and 21.0 (C(12)), 24.3 (C(2)), 26.1 (C(7)), 27.2 (C(11)), 30.0 (C(8)), 39.3 (C(3)), 42.7 (C(4)), 64.9 (C(10)), 66.0 (C(6)), 125.0 (C(1)), 137.1 (C(9)), 172.3 (C(5)); HRMS (ESI^-) found 223.1338, $C_{13}H_{19}O_3$ $[M-H]^-$ requires 223.1340.

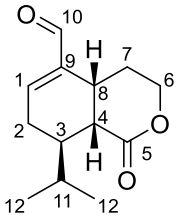
(4a*R,7*R**,8*R**,8a*S**)-7-Hydroxy-8-isopropyl-5-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (423)**



To a solution of lactone **159** (0.60 mL of a 70 mM solution in methanol, 0.043 mmol), glucose (3.0 mL of a 1.0 M solution in water, 3.00 mmol), GDH (300 μL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), and $NADP^+$ monosodium salt (300 μL of a 4.0 mM solution in water, 1.20 μmol) in 200 mM phosphate buffer (pH 7.5, 23.70 mL) was added $P450_{BM3}$ mutant RT2/IP (2.1 mL of a 28.2 μM solution in phosphate buffer, pH 7.5, 0.059 μmol). The solution was stirred open to air for 24 h. It was then centrifuged at 9,500 g, and extracted with ethyl acetate (4 × 25 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (petrol / ether, 1:1 → 4:6) to afford the *title compound* as a colourless oil (3.5 mg, 36%). R_f 0.29 (petrol / ether, 2:8); ν_{max} (thin film)/cm^{-1} 3438br, 2917m, 1721s, 1388m, 1255m, 1077s; ^1H NMR δ_H (500 MHz, C_6D_6) 0.91 (3H, d, J = 6.5 Hz, C(12)H_3), 0.96 – 1.04 (1H, m) and 1.10 – 1.18 (1H, m, C(7)H_2) 1.20 (3H, d, J = 6.5 Hz, C(12)H_3), 1.25 (3H, s, C(10)H_3), 1.81 – 1.90 (1H, m, C(8)H), 1.91 – 2.01 (1H, m, C(11), 2.01 – 2.07 (1H, m, C(3)H), 2.69 (1H, app. t, J = 6.5 Hz, C(4)H), 3.50 (1H, ddd, J = 11.5, 7.5, 4.0 Hz, C(6)H), 3.66 (1H, ddd, J = 11.5, 7.5, 4.0 Hz, C(6)H), 4.26 (1H, br s, C(2)H), 5.34 (1H, br s, C(1)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 20.4 (C(10)), 22.1 and 22.2 (C(12)), 25.8 (C(7)), 27.2 (C(11)), 35.2 (C(8)), 41.5 (C(4)), 44.6 (C(3)), 65.7 (C(6)), 66.4 (C(2)), 135.3 (C(9)), 172.5 (C(5)), one signal

obscured by residual solvent peak; HRMS (ESI$^+$) found 247.1304, $C_{13}H_{20}O_3Na$ [MNa]$^+$ requires 247.1305.

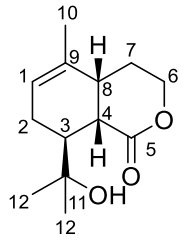
(4a*R,8*R**,8a*R**)-8-Isopropyl-1-oxo-3,4,4a,7,8,8a-hexahydro-1*H*-isochromene-5-carbaldehyde (424)**



To a solution of lactone **159** (1.40 mL of a 70 mM solution in methanol, 0.100 mmol), glucose (7.0 mL of a 1.0 M solution in water, 7.00 mmol), GDH (700 μL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), and NADP$^+$ monosodium salt (700 μL of a 4.0 mM solution in water, 2.80 μmol) in 200 mM phosphate buffer (pH 7.5, 57.60 mL) was added $P450_{BM3}$ mutant KS/K19/IG (2.60 mL of a 54.1 μM solution in phosphate buffer, pH 7.5, 0.141 μmol). The solution was stirred open to air for 24 h. It was then centrifuged at 9,500 g, and extracted with ethyl acetate (4 × 50 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 6:4 → 2:8) to afford the *title compound* as a colourless oil (2.2 mg, 10%) along with alcohol **425** (2.3 mg, 10%) and alcohol **422** (6.7 mg, 30%). R_f 0.59 (petrol / ether, 2:8); ν_{max} (thin film)/cm^{-1} 2960m, 1728s, 1682s, 1181m, 1159m; ^{1}H NMR δ_H (500 MHz, C_6D_6) 0.58 (3H, d, *J* = 6.5 Hz, C(12)H_3), 0.69 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.09 – 1.20 (1H, m, C(11)H), 1.51 – 1.62 (1H, m, C(7)H), 1.71 – 1.80 (2H, m, C(2)H, C(7)H), 1.90 – 1.98 (1H, m, C(3)H), 2.13 – 2.22 (1H, m, C(2)H), 2.32 (1H, ddd, *J* = 7.0, 5.0, 1.5 Hz, C(4)H), 2.55 – 2.64 (1H, m, C(8)H), 3.50 (1H, ddd, *J* = 11.5, 8.0, 4.0 Hz, C(6)H), 3.57 (1H, ddd, *J* = 11.5, 6.5, 4.0 Hz, C(6)H), 5.88 (1H, br s, C(1)H), 9.02 (1H, s, C(10)H); ^{13}C NMR δ_C (125

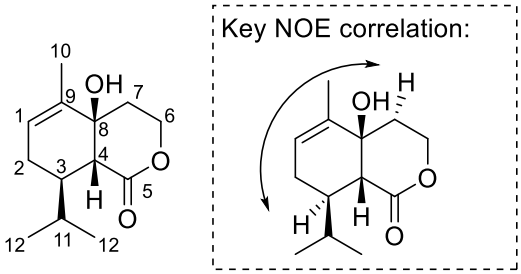
MHz, C_6D_6) 19.9 and 20.8 (C(12)), 25.8 (C(2)), 26.7 (C(7)), 27.1 (C(11)), 27.9 (C(8)), 38.6 (C(3)), 41.2 (C(4)), 65.8 (C(6)), 141.6 (C(9)), 151.1 (C(1)), 171.7 (C(5)), 192.3 (C(10)); HRMS (EI^+) found 222.1256, $C_{13}H_{18}O_3$ $[M]^+$ requires 222.1256.

(4a*R,8*S**,8a*S**)-8-(2-Hydroxypropan-2-yl)-5-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (425)**



See preparation of aldehyde **424**. R_f 0.46 (petrol / ether, 2:8); ν_{max} (thin film)/cm^{-1} 3434br, 2916m, 1760s, 1269m, 1073m, 1042m; ^1H NMR δ_H (500 MHz, C_6D_6) 0.74 (3H, s) and 1.05 (3H, s, C(10)H_3), 1.28 – 1.55 (4H, m, C(2)H_2, C(7)H_2), 1.56 (3H, s, C(10)H_3), 1.75 (1H, ddd, *J* = 14.0, 11.5, 5.0 Hz, C(3)H), 2.05 (1H, dd, *J* = 14.0, 5.0 Hz, C(4)H), 2.16 (1H, br s, C(11)OH), 2.40 – 2.49 (1H, m, C(8)H), 3.59 – 3.80 (2H, m, C(6)H_2), 5.02 (1H, br s, C(1)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 21.1 (C(12)), 22.1 (C(10)), 25.9 (C(7)), 27.6 (C(12)), 34.5 (C(2)), 35.4 (C(8)), 42.3 (C(3)), 45.8 (C(4)), 61.7 (C(6)), 84.6 (C(11)), 120.2 (C(1)), 138.4 (C(9)), 176.0 (C(5)); HRMS (ESI^+) found 225.1486, $C_{13}H_{21}O_3$ $[MH]^+$ requires 225.1485.

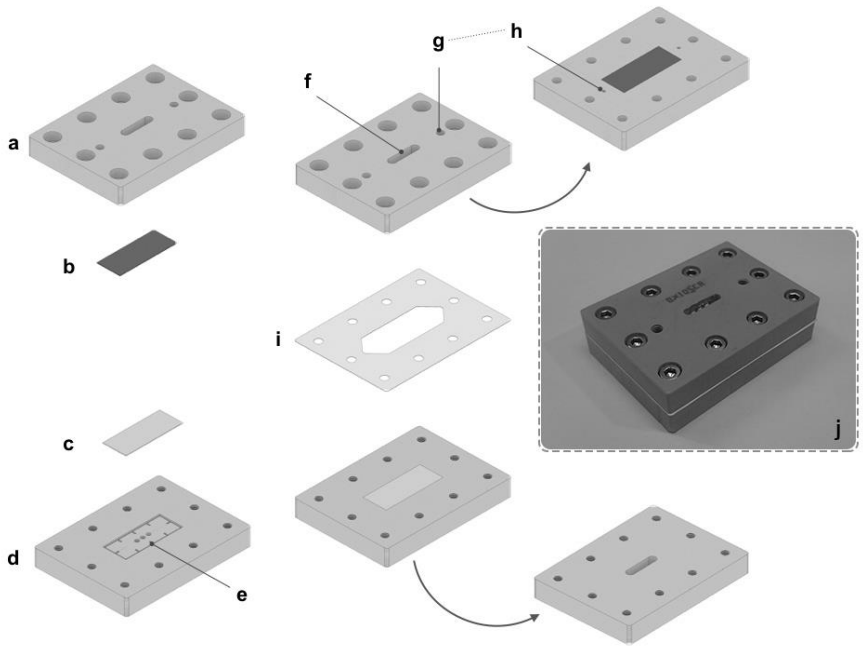
(4a*S, 8*R**, 8a*R**)-4a-Hydroxy-8-isopropyl-5-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (426)**



To a solution of lactone **159** (0.80 mL of a 70 mM solution in methanol, 0.058 mmol), glucose (4.0 mL of a 1.0 M solution in water, 4.00 mmol), GDH (400 μL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), and $NADP^+$ monosodium salt (400 μL of a 4.0 mM solution in water, 1.00 μmol) in 200 mM phosphate buffer (pH 7.5, 28.90 mL) was added $P450_{BM3}$ mutant RT2/AP/AM (5.50 mL of a 14.6 μM solution in phosphate buffer, pH 7.5, 0.080 μmol). The solution was stirred open to air for 10 d. It was then centrifuged at 9,500 g, and extracted with ethyl acetate (4 × 30 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 5:5 → 2:8) to afford the *title compound* as a colourless oil (1.8 mg, 14%) along with alcohol **422** (4.5 mg, 35%). R_f 0.48 (petrol / ether, 2:8); ν_{max} (thin film)/cm^{-1} 3420br, 2959m, 1714s, 1265m, 1120m; ^1H NMR δ_H (500 MHz, C_6D_6) 0.79 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.00 (3H, d, *J* = 6.5 Hz, C(12)H_3), 1.28 – 1.36 (1H, m, C(7)H_2), 1.40 – 1.42 (1H, m, C(7)H_2), 1.43 (3H, s, C(10)H_3), 1.62 – 1.72 (2H, m, C(2)H_2), 1.73 – 1.81 (1H, m, C(3)H), 1.84 – 1.93 (1H, m, C(11)H), 2.35 (1H, dd, *J* = 10.0, 1.5 Hz, C(4)H), 3.72 (1H, ddd, *J* = 11.0, 5.5, 3.5 Hz, C(6)H), 4.12 (1H, app. td, *J* = 11.0, 4.5 Hz, C(6)H), 5.10 (1H, br s, C(1)H); ^{13}C NMR δ_C (125 MHz, C_6D_6) 16.5 (C(10)), 17.1 and 21.2 (C(12)), 24.6 (C(2)), 28.7 (C(11)), 31.5 (C(7)), 41.3 (C(3)), 53.7 (C(4)), 64.9 (C(6)), 72.4 (C(8)), 124.0 (C(1)), 136.2 (C(9)), 171.2 (C(5)); HRMS (ESI^+) found 225.1487, $C_{13}H_{21}O_3$ $[MH]^+$ requires 225.1485.

Data for Chapter 6

Cell design and construction

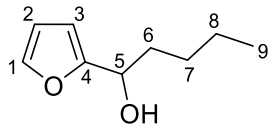


The electrochemical cell was designed using Vectorworks 2015 (Nemetschek/Techlimits, ES), and made using a Roland MDX-40 desktop milling machine (Roland DG, ES) using VCarvePro 7.5 CAM software (Vectric, UK). The cell, depicted above, consisted of two PEEK main pieces. The top part (a) holds the carbon anode (b) in a socket akin to the one that hosts the platinum cathode (c) in the bottom part (d). This socket (e) features a series of grooves to facilitate the adhesion of the electrodes to the PEEK using Araldite®. Following the attachment of the electrodes into the sockets, the electrodes were polished flush into the PEEK parts using diamond polishing suspensions down to 50 nm in a metallographic grinder. Both electrodes were polished to mirror finish.

Electrical connection to the electrodes was made using three spring-loaded-pins (Preci-dip, CH) with a standard pitch separation of 2.54 mm, and hidden in a straight socket (f) to facilitate the attachment of a cable. The top part also presents fluidic threaded ports (g) to match M660 1/16” super flangeless fittings (Upchurch Scientific, USA). Solutions were driven in and out

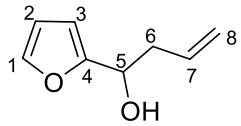
the cell through 1/16” outer diameter PTFE tubing (Cole Parmer, ES). Inside the cell, the inlet and outlet are 1mm in diameter (h). Suitable gaskets (i) were made in thin sheets (25-100 μm) of different materials including PEEK, PTFE, FEP, and Kapton, using a Roland GX-24 CAMM cutter plotter (Roland DG, ES). The cell is held together by 10 M2 screws.

1-(Furan-2-yl)pentan-1-ol (438)[250]



To 2-furaldehyde (1.5 g, 15.6 mmol) dissolved in THF (25 ml) was added, at −78 °C, a solution of *n*-BuLi (2.5 M in hexanes, 6.3 mL, 15.6 mmol), and the reaction mixture was allowed to warm to RT and stirred for 18 h. Brine (30 mL) was then added, the layers separated and the aqueous layer extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 8:2) to give the title compound as a yellow oil (2.3 g, 96 %). R_f 0.66 (petrol / ether, 6:4); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* = 7.0 Hz, C(9)H_3), 1.24 – 1.47 (4H, m, C(7)H_2, C(8)H_2), 1.77 – 1.93 (2H, m, C(6)H_2), 4.66 (1H, t, *J* = 7.0 Hz, C(5)H), 6.22(1H, d, *J* = 3.0 Hz, C(3)H), 6.32 (1H, dd, *J* = 3.0, 2.0 Hz, C(2)H), 7.33 – 7.39 (1H, m, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 14.0 (C(9)), 22.4 and 27.7 (C(7), C(8)), 35.2 (C(6)), 67.7 (C(5)), 105.7 and 110.0 (C(2), C(3)), 141.8 (C(1)), 156.9 (C(4)).

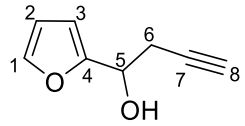
1-(Furan-2-yl)but-3-en-1-ol (439)[251]



To 2-furaldehyde (1.5 g, 15.6 mmol) dissolved in THF (25 mL) was added, at −78 °C, a solution of allylmagnesium bromide (2.0 M solution in hexanes, 9.4 mL, 18.8 mmol), and the reaction mixture was allowed to warm to RT and stirred for 18 h. Brine (30 mL) was then added, the layers separated and the aqueous layer extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to give the title compound as a yellow oil (1.9 g, 88%). R_f 0.54 (petrol / ether, 6:4); ^{1}H NMR δ_H (400

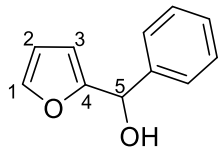
MHz, $CDCl_3$) 2.55 – 2.67 (2H, m, C(6)H_2), 4.72 (1H, br s, (C(5)H), 5.08 – 5.20 (2H, m, C(8)H_2), 5.72 – 5.87 (1H, m, C(7)H), 6.20 – 6.27 (1H, m) and 6.27 – 6.36 (1H, m, C(2)H, C(3)H), 7.32 – 7.38 (1H, m, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 39.9 (C(6)), 66.8 (C(5)), 106.0 and 110.0 (C(2), C(3)), 118.3 (C(8)), 133.7 (C(7)), 141.8 (C(1)), 156.0 (C4)).

1-(Furan-2-yl)but-3-yn-1-ol (440)[252]



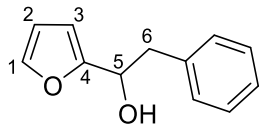
To a solution of 2-furaldehyde (930 μL, 11.2 mmol) and propargyl bromide (80 % in toluene, 2.5 mL, 22.4 mmol) in THF (15 mL) was added Zn dust (3.6 g, 56 mmol), followed by dropwise addition of a satd. aq. NH_4Cl solution (10 mL) at 0°C; the reaction mixture was then allowed to warm to RT and stirred for 18 h. The mixture was filtered through celite, and the filtrate washed with satd. aq. NH_4Cl solution (20 mL) followed by brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 8:2) to give the title compound as a yellow oil (1.2 g, 78 %). R_f 0.53 (petrol / ether, 1:1); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.07 (1H, t, *J* = 2.5 Hz, C(8)H), 2.68 (1H, br s, C(5)HO*H*), 2.76 (2H, dd, *J* = 6.0, 2.5 Hz, C(6)H_2), 4.86 (1H, dd, *J* = 12.0, 6.0 Hz, C(5)H), 6.29 – 6.38 (2H, m, C(2)H, C(3)H), 7.38 (1H, dd, *J* = 1.5, 1.0 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 25.9 (C(6)), 66.0 (C(5)), 71.0 (C(8)), 79.9 (C(7)), 106.6 and 110.2 (C(2), C(3)), 142.2 (C(1)), 154.6 (C(4)).

Furan-2-yl(phenyl)methanol (441)[253]



To a solution of furan (1.1 mL, 15 mmol) in THF (10 mL) was added a solution of *n*-BuLi (2.5 M in hexanes, 6.0 mL, 15 mmol) at 0 °C. After stirring for 2 h at this temperature benzaldehyde (1.7 mL, 16.5 mmol) was added and the reaction mixture allowed to warm to RT and stirred for 18 h. Brine (20 mL) was then added, the layers separated and the aqueous layer extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 8:2) to give the title compound as a yellow oil (2.6 g, quantitative). R_f 0.39 (petrol / ether, 7:3); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.63 (1H, br s, C(5)HO*H*), 5.69 (1H, d, *J* = 4.0 Hz, C(5)H), 6.01 (1H, d, *J* = 3.5 Hz, C(3)H), 6.21 (1H, dd, *J* = 3.5, 2.0 Hz, C(2)H), 7.20 – 7.35 (6H, m, C(1)H, C(5)H*Ph*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 70.0 (C(5)), 107.3 (C(3)), 110.1 (C(2)), 126.5, 128.0 and 128.4 (C(5)*Ph*), 140.8 and 142.4 (C(1), C(5)*Ph*), 155.9 (C(4)).

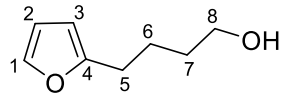
1-(Furan-2-yl)-2-phenylethan-1-ol (442)[254]



To a solution of furan (2.1 mL, 28.5 mmol) in THF (10 mL) was added a solution of *n*-BuLi (2.5 M, in hexanes, 6.0 mL, 15.0 mmol) at 0 °C. After stirring for 2 h at this temperature phenylacetaldehyde (1.9 mL, 16.5 mmol) was added and the reaction mixture allowed to warm to RT and stirred for 18 h. Brine (20 mL) was then added, the layers separated and the aqueous layer extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$

and the solvent removed *in vacuo*. The crude residue was purified *via* flash chromatography (petrol / ether, 8:2) to give the title compound as a yellow oil (2.2 g, 78 %). R_f 0.39 (petrol / ether, 7:3); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.16 (1H, d, *J* = 4.5 Hz, C(5)HO*H*), 3.08 (1H, dd, *J* = 13.5, 8.0 Hz, C(6)H), 3.16 (1H, dd, *J* = 13.5, 5.5 Hz, C(6)H), 4.81 – 4.92 (1H, m, C(5)H), 6.18 (1H, d, *J* = 3.5 Hz, C(3)H), 6.30 (1H, dd, *J* = 3.5, 2.0 Hz, C(2)H), 7.13 – 7.30 (5H, m, C(6)H$_2$*Ph*), 7.37 (1H, dd, *J* = 2.0, 1.0 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 42.1 (C(6)), 68.7 (C(5)), 106.3 (C(3)), 110.1 (C(2)), 126.6, 128.4, 129.4, 137.3 and 141.9 (C(1), C(6)*Ph*), 155.7 (C(4)).

4-(Furan-2-yl)butan-1-ol (443)[255]



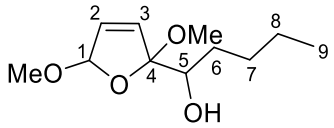
Furan (1.0 mL, 13.8 mmol) was dissolved in THF (10 mL) and a solution of *n*-BuLi (2.5 M in hexanes, 5.5 mL, 13.8 mmol) was added at −78 °C. The reaction mixture was allowed to warm to 0 °C and stirred for 2h, then cooled back to −78 °C and *tert*-butyl(4-iodobutoxy)dimethylsilane (2.35 g, 7.5 mmol) was added as a solution in THF (5 mL). The reaction mixture was allowed to warm to RT then stirred for 18 h. Brine (20 mL) was then added, the layers separated and the aqueous layer further extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was then dissolved in THF (20 mL) and TBAF was added (1.0 M solution in THF, 7.6 mL, 7.6 mmol). After 1 h, brine (20 mL) was added, the layers separated and the aqueous layer extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo*, and the crude residue purified *via* flash chromatography (petrol / ether, 8:2 → 7:3) to give the title compound as a yellow oil (649 mg, 61% over two steps). R_f 0.14 (petrol / ether, 8:2); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.52 – 1.85

(4H, m, C(6)H_2, C(7)H_2), 2.66 (2H, t, *J* = 7.5 Hz, C(5)H_2), 3.66 (2H, t, *J* = 6.5 Hz, C(8)H_2), 5.99 (1H, dd, *J* = 3.0, 1.0 Hz, C(3)H), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz, C(2)H), 7.30 (1H, dd, *J* = 2.0, 1.0 Hz, C(1)H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 24.2 and 27.6 (C(6), C(7)), 32.1 (C(5)), 62.5 (C(8)), 104.8 and 110.0 (C(2), C(3)), 140.7 (C(1)), 156.0 (C(4)).

General procedure for the anodic oxidation of alcohols 439–443

A 20 mM solution of the alcohol in MeOH, with added a trace of $NaClO_4$ (two crystals for 100 mL stock solution) was flowed through the cell (165 μL/min) while a constant current of 14.6 mA was applied using a Keithley 2200-72-1 programmable power supply; the electrolysis mixture was collected and the solvent removed *in vacuo*. Isolated yields refer to the yield of product after purification *via* flash chromatography.

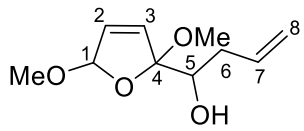
1-(2,5-Dimethoxy-2,5-dihydrofuran-2-yl)pentan-1-ol (444)



Obtained as a colourless oil (mixture of 4 isomers, 66%) following flash chromatography (petrol / ether, 1:1). R_f 0.32 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3490br, 2955m, 2932m, 1372m, 1120m, 1099m, 1018s, 977m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 0.87 – 0.96 (12H, m), 1.20 – 1.45 (16H, m) and 1.52 – 1.76 (8H, m, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 2.16 (1H, br s), 2.23 (1H, br s), 2.31 (1H, br s) and 2.62 (1H, br s, C(5)HO*H*), 3.17 (3H, s), 3.17 (3H, s), 3.23 (3H, s), 3.24 (3H, s), 3.51 (3H, s), 3.53 (3H, s), 3.54 (3H, s) and 3.54 (3H, s, OCH_3), 3.58 – 3.63 (3H, m) and 3.65 – 3.70 (1H, m, C(5)H), 5.46 (1H, br s), 5.50 (1H, br s) and 5.72 – 5.75 (2H, m, C(1)H), 5.93 (1H, dd, *J* = 6.0, 1.0 Hz), 5.96 – 6.00 (3H, m), 6.10 – 6.14 (3H, m) and 6.15 (1H, dd, *J* = 6.0, 1.0 Hz, C(2)H, C(3)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 14.0, 22.7, 22.7,

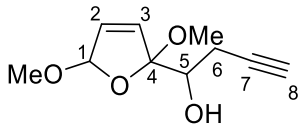
22.7, 28.3, 28.4, 28.5, 28.6, 30.4, 30.7, 31.0 and 31.1 (C(6), C(7), C(8), C(9)), 50.0, 50.1, 50.4, 50.5, 56.3, 56.5, 56.5 and 56.5 (OCH_3), 74.2, 74.3, 75.2 and 75.4 (C(5)), 107.3 (2 signals), 108.0 and 108.3 (C(1)), 115.0, 115.2, 116.7 and 117.5 (C(4)), 130.6, 130.7, 130.9, 131.8, 132.0, 132.1, 132.5 and 132.6 (C(2), C(3)); HRMS (ESI^+) found 239.1255, $C_{11}H_{20}O_4Na$ $[MNa]^+$ requires 239.1254.

1-(2,5-Dimethoxy-2,5-dihydrofuran-2-yl)but-3-en-1-ol (445)



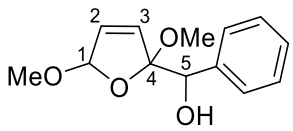
Obtained as a colourless oil (mixture of 4 isomers, 71%) following flash chromatography (petrol / ether, 1:1). R_f 0.32 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3493br, 2936w, 2835w, 1195w, 1100m, 1021s, 979m; ^1H NMR δ_H (500 MHz, $CDCl_3$) 2.04 – 2.58 (8H, m, C(6)H_2), 3.18 (3H, s), 3.18 (3H, s), 3.24 (3H, s), 3.25 (3H, s), 3.52 (3H, s), 3.53 (6H, s) and 3.55 (3H, s, OCH_3), 3.65 – 3.75 (3H, m) and 3.75 – 3.81 (1H, m, C(5)H), 5.07 – 5.18 (8H, m, C(8)H_2), 5.47 (1H, br s), 5.51 (1H, br s), 5.74 (1H, br s) and 5.75 (1H, br s, C(1)H), 5.84 – 6.02 (8H, m), 6.12 – 6.15 (3H, m) and 6.17 (1H, dd, J = 6.0, 1.0 Hz, C(2)H, C(3)H, C(7)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 35.5, 35.9 and 36.0 (C(6)), 50.0, 50.1, 50.4, 50.5, 56.4, 56.5 and 56.5 (OCH_3), 73.5, 73.9, 74.4 and 74.7 (C(5)), 107.4, 108.0 and 108.4 (C(1)), 114.6, 114.7, 116.3, 116.8, 116.9, 117.0 and 117.1 (C(4), C(8)), 130.6, 130.6, 130.9, 131.8, 132.1, 132.4, 132.6, 132.7, 135.3, 135.3, 135.5 and 135.7 (C(2), C(3), C(7)); HRMS (ESI^+) found 223.0943, $C_{10}H_{16}O_4Na$ $[MNa]^+$ requires 223.0941.

1-(2,5-Dimethoxy-2,5-dihydrofuran-2-yl)but-3-yn-1-ol (446)



Obtained as a colourless oil (mixture of 4 isomers, 54%) following flash chromatography (petrol / ether, 1:1). R_f 0.22 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3472br, 3285w, 2939w, 2836w, 1373w, 1096m, 1021s, 976m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 2.02 – 2.06 (4H, m, C(8)H), 2.27 – 2.53 (6H, m), 2.59 – 2.62 (2H, m), 2.63 – 2.66 (1H, m), 2.67 – 2.70 (1H, m), 2.72 (1H, t, *J* = 3.0 Hz) and 2.84 (1H, d, *J* = 3.0 Hz, C(5)HO*H*, C(6)H_2), 3.16 (3H, s), 3.17 (3H, s), 3.22 (3H, s), 3.23 (3H, s), 3.53 (9H, s) and 3.53 (3H, s, OCH_3), 3.76 – 3.88 (3H, m) and 3.92 (1H, dt, *J* = 9.0, 4.0 Hz, C(5)H), 5.49 (1H, t, *J* = 1.0 Hz), 5.51 (1H, t, *J* = 1.0 Hz) and 5.73 – 5.74 (2H, m, C(1)H), 5.99 (1H, dd, *J* = 6.0, 1.5 Hz), 6.00 (1H, dd, *J* = 6.0, 1.0 Hz), 6.04 (1H, dd, *J* = 6.0, 1.0 Hz), 6.08 (1H, dd, *J* = 6.0, 1.0 Hz), 6.13 – 6.16 (3H, m) and 6.17 (1H, dd, *J* = 6.0, 1.0 Hz, C(2)H, C(3)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 21.4, 21.6, 21.7 and 21.8 (C(6)), 50.1, 50.5, 50.5, 56.4, 56.5 (2 signals), and 56.6 (OCH_3), 69.5, 69.8, 69.9 and 70.2 (C(8)), 72.3, 73.1, 73.5 and 73.9 (C(5)), 81.2, 81.3, 81.5 and 81.9 (C(7)), 107.4, 107.4, 107.9 and 108.4 (C(1)), 113.9, 114.0, 115.7 and 116.0 (C(4)), 130.3, 130.4, 130.8, 131.5, 132.4, 132.7, 132.8 and 132.8 (C(2), C(3)); HRMS (ESI$^+$) found 221.0786, $C_{10}H_{14}O_4Na$ $[MNa]^+$ requires 221.0784.

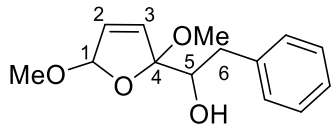
(2,5-Dimethoxy-2,5-dihydrofuran-2-yl)(phenyl)methanol (447)



Obtained as a colourless oil (mixture of 2 isomers, 24%) following flash chromatography (petrol / ether, 1:1). R_f 0.51 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3501br, 2938w, 2907w,

2835w, 1127m, 1098m, 1021s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 2.93 (1H, d, *J* = 2.5 Hz, C(5)HO*H*), 3.12 (3H, s, OCH_3), 3.24 (1H, d, *J* = 1.5 Hz, C(5)HO*H*), 3.29 (3H, s), 3.49 (3H, s) and 3.62 (3H, s, OCH_3), 4.74 (1H, br s, C(5)H), 4.86 (1H, d, *J* = 2.0 Hz, C(5)H), 4.98 (1H, t, *J* = 1.0 Hz, (C(1)H), 5.73 (1H, dd, *J* = 6.0, 1.0 Hz, C(2)H or C(3)H), 5.78 (1H, t, *J* = 1.0 Hz, (C(1)H), 5.85 (1H, dd, *J* = 6.0, 1.0 Hz), 5.96 (1H, dd, *J* = 6.0, 1.0 Hz) and 6.16 (1H, dd, *J* = 6.0, 1.0 Hz, C(2)H, C(3)H), 7.27 – 7.49 (10H, m, C(5)H*Ph*); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 50.4, 50.7, 56.4 and 57.0 (OCH_3), 75.8 and 77.9 (C(5)), 107.4 and 108.4 (C(1)), 114.8 and 117.6 C(4)), 127.0, 127.5, 127.6, 127.6, 127.7 and 128.6 (C(5)H*Ph*), 130.1, 130.5, 132.4 and 132.7 (C(2), C(3)), 138.3 and 138.9 (C(5)H*Ph*); HRMS (Methane CI^+) found 205.0850, $C_{12}H_{13}O_3$ $[M-CH_3O^-]^+$ requires 205.0859.

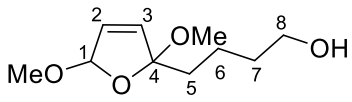
1-(2,5-Dimethoxy-2,5-dihydrofuran-2-yl)-2-phenylethan-1-ol (448)



Obtained as a colourless oil (mixture of 4 isomers, 57%) following flash chromatography (petrol / ether, 1:1). R_f 0.38 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3486br, 2937w, 2834w, 1454w, 1372w, 1097m, 1021s, 977m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 2.17 (1H, d, *J* = 4.0 Hz), 2.26 (1H, d, *J* = 2.0 Hz), 2.34 (1H, d, *J* = 6.0 Hz), 2.51 – 2.70 (5H, m), 2.86 (1H, dd, *J* = 14.0, 3.0 Hz), 3.06 (1H, dd, *J* = 14.0, 2.5 Hz) and 3.13 (2H, dd, *J* = 14.5, 2.5 Hz, C(5)HO*H*, C(6)H), 3.21 (3H, s), 3.23 (3H, s), 3.28 (6H, s), 3.52 (3H, s), 3.53 (3H, s), 3.55 (3H, s) and 3.56 (3H, s, OCH_3), 3.87 (2H, dt, *J* = 10.5, 2.5 Hz), 3.92 (1H, ddd, *J* = 10.0, 6.0, 2.5 Hz) and 3.99 (1H, dt, *J* = 10.0, 3.0 Hz, C(5)H), 5.49 (1H, t, *J* = 1.0 Hz), 5.55 (1H, t, *J* = 1.0 Hz), 5.76 (1H, t, *J* = 1.0 Hz) and 5.78 (1H, t, *J* = 1.0 Hz, C(1)H), 5.97 – 6.04 (4H, m), 6.15 – 6.18 (3H, m) and 6.19 (1H, dd, *J* = 6.0, 1.0 Hz, C(2)H, C(3)H), 7.20 – 7.34 (20H, m, C(5)H*Ph*); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 37.2, 37.6 and 37.8 (C(6)), 50.1, 50.2, 50.5, 50.6, 56.3, 56.4 and

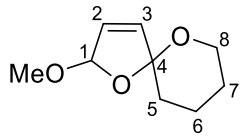
56.5 (2 signals) (OCH_3), 75.2, 75.6, 76.1 and 76.4 (C(5)), 107.4 (2 signals), 107.9 and 108.4 (C(1)), 114.7 (2 signals), 116.3 and 117.0 (C(4)), 126.0, 126.2, 126.2, 128.2, 128.3, 128.3, 129.2, 129.3, 129.4, 130.6, 130.7, 130.9, 131.7, 132.2, 132.4, 132.7, 132.8, 138.8, 139.0, 139.2 and 139.4 (C(2), C(3), C(6)*Ph*); HRMS (ESI^+) found 273.1099, $C_{14}H_{18}O_4Na$ $[MNa]^+$ requires 273.1097.

4-(2,5-Dimethoxy-2,5-dihydrofuran-2-yl)butan-1-ol (450)



Obtained as a colourless oil (mixture of 2 isomers, 23%) following flash chromatography (petrol / ether, 1:1). R_f 0.07 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3430br, 2941m, 2873m, 1373m, 1118m, 1100m, 1070s, 991m, 975m; ^1H NMR δ_H (500 MHz, $CDCl_3$, major isomer) 1.31 – 1.45 (2H, m, C(6)H_2), 1.55 – 1.65 (2H, m, C(7)H_2), 1.79 – 1.87 (2H, m, C(5)H_2), 3.20 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 3.65 (2H, t, J = 5.5 Hz, C(8)H_2), 5.47 (1H, br s, C(1)H), 5.89 (1H, dd, J = 6.0, 1.0 Hz) and 6.03 (1H, dd, J = 6.0, 1.0 Hz, C(2)H, C(3)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$, major isomer) 20.2 (C(6)), 32.7 (C(7)), 38.6 (C(5)), 50.3 (OCH_3), 56.2 (OCH_3), 62.8 (C(8)), 107.1 (C(1)), 114.2 (C(4)), 130.9 and 133.1 (C(2), C(3)); HRMS (ESI^+) found 225.1099, $C_{10}H_{18}O_4Na$ $[MNa]^+$ requires 225.1097.

2-Methoxy-1,6-dioxaspiro[4.5]dec-3-ene (449)

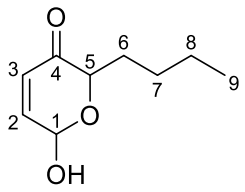


Obtained as a colourless oil (mixture of 2 isomers, 29%) following flash chromatography (petrol / ether, 1:1). R_f 0.44 (petrol / ether, 1:1). ν_{max} (thin film)/cm^{-1} 3657w, 2981s, 2887m, 1382m, 1150m, 1073m, 955m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 1.57 – 1.86 (10H, m) and 1.89 – 2.00 (2H, m, C(5)H_2, C(6)H_2, C(7)H_2), 3.40 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 3.75 – 3.83 (2H, m) and 3.99 – 4.07 (2H, m, C(8)$_2$), 5.70 (1H, t, *J* = 1.0 Hz) and 5.86 (1H, t, *J* = 1.0 Hz, C(1)H), 5.95 (1H, dd, *J* = 6.0, 1.0 Hz), 5.97 (1H, dd, *J* = 6.0, 1.0 Hz), 6.05 (1H, dd, *J* = 6.0, 1.0 Hz) and 6.06 (1H, dd, *J* = 6.0, 1.0 Hz, C(2)H, C(3)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 19.4, 19.5, 24.8, 24.9, 34.0 and 34.7 (C(5), C(6), C(7)), 53.4 and 54.1 (OCH_3), 63.3 and 63.5 (C(8)), 107.1 and 108.2 (C(1)), 108.4 and 109.7 (C(4)), 129.2, 129.8, 135.9 and 136.0 (C(2), C(3)); HRMS (ESI$^+$) found 193.0838, $C_9H_{14}O_3Na$ [MNa]$^+$ requires 193.0835.

General procedure for Achmatowicz rearrangement

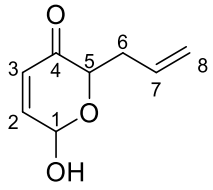
The crude electrolysis mixture was concentrated *in vacuo*, then redissolved in THF (1 mL), and 1.0 M aq. HCl solution was added (1 mL). After stirring for 2 h satd. aq. $NaHCO_3$ solution (2 mL) was added, the layers separated and the aqueous layer extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*.

2-Butyl-6-hydroxy-2*H*-pyran-3(6*H*)-one (454)[256]



Obtained as a colourless oil (mixture of 2 isomers, 62%) following flash chromatography (petrol / ether, 1:1). R_f 0.31 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3404br, 2929m, 2861m, 1690s, 1088m, 1031s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) *major isomer:* 0.92 (3H, t, *J* = 7.0 Hz, C(9)H_3), 1.31 – 1.46 (4H, m), 1.66 – 1.75 (1H, m) and 1.91 – 2.01 (1H, m, C(6)H_2, C(7)H_2, C(8)H_2), 4.57 (1H, dd, *J* = 8.0, 4.0 Hz, C(5)H), 5.66 (1H, br s, C(1)H), 6.11 (1H, d, *J* = 10.5 Hz, C(3)H), 6.90 (1H, dd, *J* = 10.5, 3.5 Hz, C(2)H); *minor isomer*: 0.92 (3H, t, *J* = 7.0 Hz, C(9)H_3), 1.32 – 1.48 (4H, m), 1.76 – 1.84 (1H, m) and 1.91 – 2.01 (1H, m, C(6)H_2, C(7)H_2, C(8)H_2), 4.08 (1H, ddd, *J* = 8.5, 4.0, 1.0 Hz, C(5)H), 5.66 (1H, br s, C(1)H), 6.15 (1H, dd, *J* = 10.5, 1.5 Hz, C(3)H), 6.93 (1H, dd, *J* = 10.5, 1.5 Hz, C(2)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) *major isomer:* 13.9 (C(9)), 22.5, 27.1 and 29.3 (C(6), C(7), C(8)), 74.2 (C(5)), 87.7 (C(1)), 127.7 (C(3)), 144.1 (C(2)), 196.6 (C(4)); *minor isomer*: 13.9 (C(9)), 22.5, 27.3 and 30.4 (C(6), C(7), C(8)), 79.0 (C(5)), 90.9 (C(1)), 128.8 (C(3)), 147.5 (C(2)), 196.2 (C(4)); HRMS (ESI$^+$) found 185.1174, $C_{10}H_{17}O_3$ $[M-OH+CH_3OH]^+$ requires 185.1172.

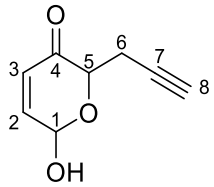
2-Allyl-6-hydroxy-2*H*-pyran-3(6*H*)-one (455)[257]



Obtained as a colourless oil (mixture of 2 isomers, 69%) following flash chromatography (petrol / ether, 1:1). R_f 0.31 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3401br, 2926m, 1691s,

1090m, 1029s, 920m; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) *major isomer:* 2.50 (1H, ddd, *J* = 15.0, 8.0, 7.0 Hz) and 2.68 – 2.78 (1H, m, C(6)H_2), 3.26 (1H, br s, C(1)HO*H*), 4.68 (1H, dd, *J* = 8.0, 4.0 Hz, C(5)H), 5.09 – 5.21 (2H, m, C(8)H_2), 5.67 (1H, br s, C(1)H), 5.79 – 5.91 (1H, m, C(7)H), 6.12 (1H, d, *J* = 10.0 Hz, C(3)H), 6.91 (1H, dd, *J* = 10.0, 3.5 Hz, C(2)H); *minor isomer*: 2.57 (1H, ddd, *J* = 15.0, 8.5, 7.0 Hz) and 2.68 – 2.78 (1H, m, C(6)H_2), 3.47 – 3.56 (1H, br s, C(1)HO*H*), 4.18 (1H, ddd, *J* = 8.5, 4.0, 1.0 Hz, C(5)H), 5.09 – 5.21 (2H, m, C(8)H_2), 5.67 (1H, br s, C(1)H), 5.79 – 5.91 (1H, m, C(7)H), 6.17 (1H, dd, *J* = 10.5, 1.5 Hz, C(3)H), 6.95 (1H, dd, *J* = 10.5, 1.5 Hz, C(2)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) *major isomer:* 34.0 (C(6)), 73.6 (C(5)), 87.7 (C(1)), 117.8 (C(8)), 127.6 (C(3)), 133.6 (C(7)), 144.3 (C(2)), 195.7 (C(4)); *minor isomer*: 35.1 (C(6)), 78.4 (C(5)), 90.8 (C(1)), 118.0 (C(8)), 128.6 (C(3)), 133.5 (C(7)), 147.6 (C(2)), 195.3 (C(4)); HRMS (ESI$^-$) found 153.0557, $C_8H_9O_3$ $[M-H]^-$ requires 153.0557.

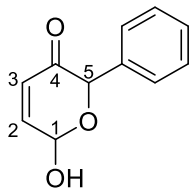
6-Hydroxy-2-(prop-2-yn-1-yl)-2*H*-pyran-3(6*H*)-one (456)



Obtained as a colourless oil (mixture of 2 isomers, 31%) following flash chromatography (petrol / ether, 1:1). R_f 0.29 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3412br, 3285m, 1693s, 1028s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) *major isomer:* 2.03 (1H, t, *J* = 2.5 Hz, C(8)H), 2.68 (1H, ddd, *J* = 17.5, 7.5, 2.5 Hz) and 2.89 (1H, dd, *J* = 17.5, 3.5 Hz, C(6)H_2), 3.11 (1H, d, *J* = 5.0 Hz, C(1)HO*H*), 4.77 (1H, dd, *J* = 7.5, 3.5 Hz, C(5)H), 5.71 – 5.78 (1H, m, C(1)H), 6.16 (1H, d, *J* = 10.5 Hz, C(3)H), 6.95 (1H, dd, *J* = 10.5, 3.5 Hz, C(2)H); *minor isomer*: 2.09 (1H, t, *J* = 2.5 Hz, C(8)H), 2.76 (1H, ddd, *J* = 17.5, 8.0, 2.5 Hz) and 2.89 (1H, dd, *J* = 17.5, 3.5 Hz, C(6)H_2), 3.41 (1H, d, *J* = 7.5 Hz, C(1)HO*H*), 4.32 (1H, ddd, *J* = 8.0, 3.5, 1.0 Hz, C(5)H), 5.71

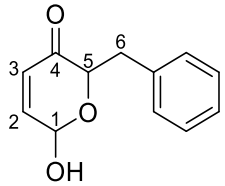
– 5.74 (1H, m, C(1)H), 6.20 (1H, dd, *J* = 10.5, 1.5 Hz, C(3)H), 6.98 (1H, dd, *J* = 10.5, 1.5 Hz, C(2)H); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) *major isomer:* 20.2 (C(6)), 69.9 (C(8)), 72.5 (C(5)), 80.0 (C(7)), 88.0 (C(1)), 127.4 (C(3)), 144.5 (C(2)), 194.1 (C(4)); *minor isomer*: 21.8 (C(6)), 70.5 (C(8)), 80.1 (C(7)), 90.4 (C(1)), 128.2 (C(3)), 147.5 (C(2)), 193.7 (C(4)), one signal obscured by residual solvent peak; HRMS (ESI$^-$) found 151.0400, $C_8H_7O_3$ $[M-H]^-$ requires 151.0401.

6-Hydroxy-2-phenyl-2*H*-pyran-3(6*H*)-one (457)[257]



Obtained as a colourless oil (mixture of 2 isomers, 17%) following flash chromatography (petrol / ether, 1:1). R_f 0.16 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3400br, 1692s, 1223m, 1091m, 1075m, 1027s, 699s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) *major isomer:* 3.20 (1H, d, *J* = 5.0 Hz, C(1)HO*H*), 5.61 (1H, s, C(5)H), 5.77 (1H, dd, *J* = 5.0, 3.5 Hz, C(1)H), 6.24 (1H, dd, *J* = 10.5, 1.0 Hz, C(3)H), 6.99 (1H, dd, *J* = 10.5, 3.5 Hz, C(2)H), 7.32 – 7.44 (5H, m, C(5)H*Ph*); *minor isomer*: 3.36 (1H, d, *J* = 7.0 Hz, C(1)HO*H*), 5.13 (1H, d, *J* = 1.5 Hz, C(5)H), 5.83 (1H, dd, *J* = 7.0, 1.5 Hz, C(1)H), 6.30 (1H, dd, *J* = 10.5, 1.5 Hz, C(3)H), 7.04 (1H, dd, *J* = 10.5, 1.5 Hz, C(2)H), 7.32 – 7.44 (5H, m, C(5)H*Ph*); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) *major isomer:* 88.1 (C(1)), 127.9 (2 signals) (C(5)*Ph*, C(3)), 128.5, 128.6 and 135.2 (C(5)*Ph*), 144.6 (C(2)), 194.4 (C(4)), one signal obscured by residual solvent peak; *minor isomer*: 81.1 (C(5)) , 91.5 (C(1)), 127.8, 128.5, 128.7, 129.4 and 135.4 (C(5)*Ph*, C(3)), 148.0 (C(2)), 194.0 (C(4)); HRMS (ESI$^-$) found 189.0556, $C_{11}H_9O_3$ $[M-H]^-$ requires 189.0557.

2-Benzyl-6-hydroxy-2*H*-pyran-3(6*H*)-one (458)[258]



Obtained as a colourless oil (mixture of 2 isomers, 32%) following flash chromatography (petrol / ether, 1:1). R_f 0.25 (petrol / ether, 1:1); ν_{max} (thin film)/cm^{-1} 3393br, 1692s, 1029s; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) *major isomer:* 2.87 (1H, d, *J* = 4.5 Hz, C(1)HO*H*), 2.91 (1H, dd, *J* = 14.5, 9.0 Hz) and 3.40 (1H, dd, *J* = 14.5, 3.5 Hz, C(6)H_2), 4.86 (1H, dd, *J* = 9.0, 3.5 Hz, C(5)H), 5.61 (1H, br s, C(1)H), 6.13 (1H, d, *J* = 10.0 Hz, C(3)H), 6.88 (1H, dd, *J* = 10.0, 3.5 Hz, C(2)H), 7.19 – 7.37 (5H, m, C(6)H_2*Ph*); *minor isomer*: 3.00 (1H, dd, *J* = 14.5, 9.5 Hz, C(6)H), 3.12 (1H, d, *J* = 6.5 Hz, C(1)HO*H*), 3.38 (1H, dd, *J* = 14.5, 3.5 Hz, C(6)H), 4.33 (1H, ddd, *J* = 9.5, 3.5, 1.0 Hz, C(5)H), 5.58 (1H, br s, C(1)H), 6.19 (1H, dd, *J* = 10.5, 1.5 Hz, C(3)H), 6.93 (1H, dd, *J* = 10.5, 1.5 Hz, C(2)H), 7.19 – 7.37 (5H, m, C(6)H_2*Ph*); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) *major isomer:* 35.7 (C(6)), 74.9 (C(5)), 87.7 (C(1)), 126.5, 127.6, 128.3, 129.4 and 137.7 (C(6)*Ph*, C(3)), 144.2 (C(2)), 195.5 (C(4)); *minor isomer*: 36.7 (C(6)), 79.8 (C(5)), 90.8 (C(1)), 126.6, 128.4, 128.6, 129.5 and 137.7 (C(6)*Ph*, C(3)), 147.6 (C(2)), 195.1 (C(4)); HRMS (ESI$^-$) found 203.0714, $C_{12}H_{11}O_3$ $[M-H]^-$ requires 203.0714.

References

(1) Nelson, M. L.; Dinardo, A.; Hochberg, J.; Armelagos, G. J. *Am. J. Phys. Anthropol.* **2010**, *143* (1), 151.

(2) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75* (3), 311.

(3) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1* (2), 74.

(4) Van Hattum, H.; Waldmann, H. *J. Am. Chem. Soc.* **2014**, *136* (34), 11853.

(5) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016**, *79* (3), 629.

(6) Tomasz, M. *Chem. Biol.* **1995**, *2* (9), 575.

(7) Pommier, Y. *ACS Chem. Biol.* **2013**, *8* (1), 82.

(8) Tacar, O.; Sriamornsak, P.; Dass, C. R. *J. Pharm. Pharmacol.* **2013**, *65* (2), 157.

(9) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4* (4), 253.

(10) Nogales, E. *Annu. Rev. Biochem.* **2000**, *69* (1), 277.

(11) Mitchison, T.; Kirschner, M. *Nature* **1984**, *312* (5991), 237.

(12) Rodionov, V. I.; Borisy, G. G. *Science* **1997**, *275* (5297), 215.

(13) Akhmanova, A.; Steinmetz, M. O. *Nat. Rev. Mol. Cell Biol.* **2008**, *9* (4), 309.

(14) Nogales, E.; Wolf, S. G.; Khan, I. A.; Ludueña, R. F.; Downing, K. H. *Nature* **1995**, *375* (6530), 424.

(15) Nogales, E.; Wolf, S. G.; Downing, K. H. *Nature* **1998**, *391* (6663), 199.

(16) Löwe, J.; Li, H.; Downing, K. .; Nogales, E. *J. Mol. Biol.* **2001**, *313* (5), 1045.

(17) Nogales, E.; Whittaker, M.; Milligan, R. A.; Downing, K. H. *Cell* **1999**, *96* (1), 79.

(18) Mitchison, T. J. *Annu. Rev. Cell Biol.* **1988**, *4* (1), 527.

(19) Jordan, M. A.; Wendell, K.; Gardiner, S.; Derry, W. B.; Copp, H.; Wilson, L. *Cancer Res.* **1996**, *56* (4), 816.

(20) Johnson, I. S.; Armstrong, J. G.; Gorman, M.; Burnett, J. P. *Cancer Res.* **1963**, *23* (77), 1390.

(21) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N. Y. Acad. Sci.* **1958**, *76* (3), 882.

(22) Bai, R. L.; Pettit, G. R.; Hamel, E. *J. Biol. Chem.* **1990**, *265* (28), 17141.

(23) Towle, M. J.; Salvato, K. A.; Budrow, J.; Wels, B. F.; Kuznetsov, G.; Aalfs, K. K.; Welsh, S.; Zheng, W.; Seletsky, B. M.; Palme, M. H.; Habgood, G. J.; Singer, L. A.; DiPietro, L. V.; Wang, Y.; Chen, J. J.; Quincy, D. A.; Davis, A.; Yoshimatsu, K.; Kishi, Y.; Yu, M. J.; Littlefield, B. A. *Cancer Res.* **2001**, *61* (3), 1013.

(24) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109* (22), 6883.

(25) Hartung, E. F. *Ann. Rheum. Dis.* **1954**, *13* (3), 190.

(26) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93* (9), 2325.

(27) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277* (5698), 665.

(28) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55* (11), 2325.

(29) Goodin, S.; Kane, M. P.; Rubin, E. H. *J. Clin. Oncol.* **2004**, *22* (10), 2015.

(30) Holton, R. a; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, *116* (4), 1597.

(31) Holton, R. a; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, *116* (4), 1599.

(32) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367* (6464), 630.

(33) Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110* (17), 5917.

(34) Nogales, E. *Annu. Rev. Biophys. Biomol. Struct.* **2001**, *30*, 397.

(35) Field, J. J.; Díaz, J. F.; Miller, J. H. *Chem. Biol.* **2013**, *20* (3), 301.

(36) Giannakakou, P.; Sackett, D. L.; Kang, Y. K.; Zhan, Z.; Buters, J. T.; Fojo, T.; Poruchynsky, M. S. *J. Biol. Chem.* **1997**, *272* (27), 17118.

(37) Giannakakou, P.; Gussio, R.; Nogales, E.; Downing, K. H.; Zaharevitz, D.; Bollbuck, B.; Poy, G.; Sackett, D.; Nicolaou, K. C.; Fojo, T. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97* (6), 2904.

(38) Rao, S.; Horwitz, S. B.; Ringel, I. *JNCI J. Natl. Cancer Inst.* **1992**, *84* (10), 785.

(39) Rao, S.; Krauss, N. E.; Heerding, J. M.; Swindell, C. S.; Ringel, I.; Orr, G. A.; Horwitz, S. B. *J. Biol. Chem.* **1994**, *269* (5), 3132.

(40) Rao, S.; Orr, G. A.; Chaudhary, A. G.; Kingston, D. G.; Horwitz, S. B. *J. Biol. Chem.* **1995**, *270* (35), 20235.

(41) Rao, S.; He, L.; Chakravarty, S.; Ojima, I.; Orr, G. A.; Horwitz, S. B. *J. Biol. Chem.* **1999**, *274* (53), 37990.

(42) Fenical, W. H.; Jensen, P. R.; Lindel, T. U.S. Pat. 5473057, 1995.

(43) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119* (37), 8744.

(44) Long, B. H.; Carboni, J. M.; Wasserman, A. J.; Cornell, L. A.; Casazza, A. M.; Jensen, P. R.; Lindel, T.; Fenical, W.; Fairchild, C. R. *Cancer Res.* **1998**, *58* (6), 1111.

(45) Ketzinel, S.; Rudi, A.; Schleyer, M.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **1996**, *59* (9), 873.

(46) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70* (8), 2019.

(47) D'Anbrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1988**, *71* (5), 964.

(48) Ciomei, M.; Albanese, C.; Pastori, W.; Grandi, M.; Pietra, F.; D'Ambrosio, M.; Guerriero, A.; Battistini, C. *Proc. Am. Ass. Canc. Res.* **1997**, *38* (5), (Abstract 30).

(49) Lin, Y.; Bewley, C. A.; Faulkner, D. J. *Tetrahedron* **1993**, *49* (36), 7977.

(50) Ellis, J. M.; Crimmins, M. T. *Chem. Rev.* **2008**, *108* (12), 5278.

(51) Stierle, D. B.; Carte, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102* (15), 5088.

(52) Britton, R.; Roberge, M.; Berisch, H.; Andersen, R. J. *Tetrahedron Lett.* **2001**, *42* (16), 2953.

(53) Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S.; He, L.; Horwitz, S. B.; Kuduk, S. D.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96* (8), 4256.

(54) Nicolaou, K. C.; Kim, S.; Pfefferkorn, J.; Xu, J.; Ohshima, T.; Hosokawa, S.; Vourloumis, D.; Li, T. *Angew. Chem. Int. Ed.* **1998**, *37* (10), 1418.

(55) Nicolaou, K. C.; Winssinger, N.; Vourloumis, D.; Ohshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J.-Y.; Li, T. *J. Am. Chem. Soc.* **1998**, *120* (42), 10814.

(56) Britton, R.; de Silva, E. D.; Bigg, C. M.; McHardy, L. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2001**, *123* (35), 8632.

(57) Chen, X.-T.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37* (1–2), 185.

(58) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37* (6), 789.

(59) Chen, X.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121* (28), 6563.

(60) Bhattacharya, S. K.; Chen, X.-T.; Gutteridge, C. E.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40* (17), 3313.

(61) Nicolaou, K. C.; Xu, J.-Y.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119* (46), 11353.

(62) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120* (34), 8661.

(63) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120* (34), 8674.

(64) Trost, B. M.; Tasker, A. S.; Ruther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113* (2), 670.

(65) Nicolaou, K. C.; Trujillo, J. I.; Chibale, K. *Tetrahedron* **1997**, *53* (26), 8751.

(66) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Angew. Chem. Int. Ed.* **2005**, *44* (4), 588.

(67) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40* (1), 153.

(68) Ceccarelli, S. M.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, *57* (40), 8531.

(69) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayón, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44* (43), 7913.

(70) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Monti, D.; Gennari, C. *Tetrahedron Lett.* **2001**, *42* (52), 9187.

(71) Beumer, R.; Bayón, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron* **2003**, *59* (44), 8803.

(72) Beumer, R.; Bayón, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron* **2003**, *59* (44), 8803.

(73) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem. Eur. J.* **2006**, *12* (1), 51.

(74) Ritter, N.; Metz, P. *Synlett* **2003**, No. 15, 2422.

(75) Samaritani, S.; Bruyère, H.; Ballereau, S.; Royer, J. *Comptes Rendus Chim.* **2005**, *8* (5), 841.

(76) Bruyère, H.; Samaritani, S.; Ballereau, S.; Tomas, A.; Royer, J. *Synlett* **2005**, No. 9, 1421.

(77) Bruyère, H.; Dos Reis, C.; Samaritani, S.; Ballereau, S.; Royer, J. *Synthesis* **2006**, *2006* (10), 1673.

(78) Ceccarelli, S. M.; Piarulli, U.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2001**, *42* (42), 7421.

(79) Carter, R.; Hodgetts, K.; McKenna, J.; Magnus, P.; Wren, S. *Tetrahedron* **2000**, *56* (26), 4367.

(80) Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5* (10), 1805.

(81) Jung, M. E.; Huang, A.; Johnson, T. W. *Org. Lett.* **2000**, *2* (13), 1835.

(82) Kim, P.; Nantz, M. H.; Kurth, M. J.; Olmstead, M. M. *Org. Lett.* **2000**, *2* (13), 1831.

(83) Nakanishi, H.; Fujita, H.; Yamamoto, O. *Bull. Chem. Soc. Jpn.* **1978**, *51* (1), 214.

(84) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109* (20), 5935.

(85) Saito, A.; Ito, H.; Taguchi, T. *Org. Lett.* **2002**, *4* (26), 4619.

(86) Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2011**, *4* (1), 21.

(87) Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136* (13), 4909.

(88) Yuan, C.; Jin, Y.; Wilde, N. C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2016**, *55* (29), 8280.

(89) Whitehouse, C. J. C.; Bell, S. G.; Wong, L.-L. *Chem. Soc. Rev.* **2012**, *41* (3), 1218.

(90) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

(91) Heravi, M. M.; Vavsari, V. F. *RSC Adv.* **2015**, *5* (63), 50890.

(92) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, *102* (15), 5085.

(93) Naud, S.; Macnaughton, S. J.; Dyson, B. S.; Woollaston, D. J.; Dallimore, J. W. P.; Robertson, J. *Org. Biomol. Chem.* **2012**, *10* (17), 3506.

(94) Kosal, A. D.; Ashfeld, B. L. *Org. Lett.* **2010**, *12* (1), 44.

(95) Kiyooka, S.; Hena, M. A. *J. Org. Chem.* **1999**, *64* (15), 5511.

(96) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem. Int. Ed.* **2001**, *40* (15), 2887.

(97) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31* (44), 6269.

(98) Seong, M. R.; Kim, J. N.; Kim, H. R.; Ryu, E. K. *Synth. Commun.* **1998**, *28* (1), 139.

(99) Labeeuw, O.; Blanc, D.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Eur. J. Org. Chem.* **2004**, *2004* (11), 2352.

(100) Seebach, D. *Angew. Chem. Int. Ed.* **1969**, *8* (9), 639.

(101) Chengebroyen, J.; Linke, M.; Robitzer, M.; Sirlin, C.; Pfeffer, M. *J. Organomet. Chem.* **2003**, *687* (2), 313.

(102) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102* (22), 6900.

(103) Mames, A.; Stecko, S.; Mikołajczyk, P.; Soluch, M.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **2010**, 7580.

(104) Aoyagi, S.; Wang, T. C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115* (24), 11393.

(105) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127* (25), 8964.

(106) Telvekar, V. N.; Takale, B. S. *Tetrahedron Lett.* **2011**, *52* (18), 2394.

(107) Telvekar, V. N.; Arote, N. D.; Herlekar, O. P. *Synlett* **2005**, No. 16, 2495.

(108) Chowdhury, S.; Roy, S. *J. Org. Chem.* **1997**, *62* (1), 199.

(109) Wiersig, J. R.; Waespe-Sarcevic, N.; Djerassi, C. *J. Org. Chem.* **1979**, *44* (19), 3374.

(110) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102* (26), 7816.

(111) Pirrung, M. C. *Chem. Eur. J.* **2006**, *12* (5), 1312.

(112) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112* (11), 4595.

(113) Kumar, A. *Chem. Rev.* **2001**, *101* (1), 1.

(114) Hugelshofer, C.; Magauer, T. *Synthesis* **2014**, *46* (10), 1279.

(115) Asano, T.; Le Noble, W. J. *Chem. Rev.* **1978**, *78* (4), 407.

(116) Clark, J. S.; Berger, R.; Hayes, S. T.; Senn, H. M.; Farrugia, L. J.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *J. Org. Chem.* **2013**, *78* (2), 673.

(117) Kim, H.; Lee, H.; Kim, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2006**, *128* (49), 15851.

(118) Clark, J. S.; Berger, R.; Hayes, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem. Int. Ed.* **2010**, *49* (51), 9867.

(119) Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, *i* (10 ml), 1501.

(120) Foote, C. S.; Wuesthoff, M. T.; Wexler, S.; Burstain, I. G.; Denny, R.; Schenck, G. O.; Schulte-Elte, K.-H. *Tetrahedron* **1967**, *23* (6), 2583.

(121) Kursanov, D. N.; Parnes, Z. N.; Bassova, G. I.; Loim, N. M.; Zdanovich, V. I. *Tetrahedron* **1967**, *23* (5), 2235.

(122) Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, *17* (34), 2955.

(123) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116* (16), 7459.

(124) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, *51* (10), 967.

(125) Hiebel, M.-A.; Pelotier, B.; Lhoste, P.; Piva, O. *Synlett* **2008**, *2008* (8), 1202.

(126) Hiebel, M.-A.; Pelotier, B.; Piva, O. *Tetrahedron Lett.* **2010**, *51* (38), 5091.

(127) Anthony Wu DPhil Thesis, University of Oxford, 2012.

(128) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A. J. *Tetrahedron* **2005**, *61* (2), 353.

(129) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, No. 16, 1574.

(130) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130* (36), 11970.

(131) Chen, X.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37* (1–2), 185.

(132) Annangudi, S. P.; Sun, M.; Salomon, R. G. *Synlett* **2005**, No. 9, 1468.

(133) Frey, D. A.; Krishna Reddy, S. H.; Moeller, K. D. *J. Org. Chem.* **1999**, *64* (8), 2805.

(134) Mori, K.; Ohki, M.; Sato, A.; Matsui, M. *Tetrahedron* **1972**, *28* (14), 3739.

(135) Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114* (3), 1033.

(136) Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59* (9), 2381.

(137) Keegstra, M. A.; Klomp, A. J. A.; Brandsma, L. *Synth. Commun.* **1990**, *20* (21), 3371.

(138) Fu, J.; Tjandra, M.; Becker, C.; Bednarczyk, D.; Capparelli, M.; Elling, R.; Hanna, I.; Fujimoto, R.; Furegati, M.; Karur, S.; Kasprzyk, T.; Knapp, M.; Leung, K.; Li, X.; Lu, P.; Mergo, W.; Miault, C.; Ng, S.; Parker, D.; Peng, Y.; Roggo, S.; Rivkin, A.; Simmons, R. L.; Wang, M.; Wiedmann, B.; Weiss, A. H.; Xiao, L.; Xie, L.; Xu, W.; Yifru, A.; Yang, S.; Zhou, B.; Sweeney, Z. K. *J. Med. Chem.* **2014**, *57* (20), 8503.

(139) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42* (23), 3761.

(140) Kosarych, Z.; Cohen, T. *Tetrahedron Lett.* **1980**, *21* (41), 3959.

(141) Corey, E. J.; Goto, G. *Tetrahedron Lett.* **1980**, *21* (36), 3463.

(142) Bettelli, E.; Cherubini, P.; D'Andrea, P.; Passacantilli, P.; Piancatelli, G. *Tetrahedron* **1998**, *54* (22), 6011.

(143) Fan, C.-A.; Tu, Y.-Q.; Song, Z.-L.; Zhang, E.; Shi, L.; Wang, M.; Wang, B.; Zhang, S.-Y. *Org. Lett.* **2004**, *6* (25), 4691.

(144) Shih, N.-Y.; Lupo, A. T.; Aslanian, R.; Orlando, S.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Clark, M. A.; Tozzi, S. *J. Med. Chem.* **1995**, *38* (10), 1593.

(145) Mawlawi, H.; Monje, M. C.; Lattes, A.; Rivère, M. *J. Heterocycl. Chem.* **1992**, *29* (6), 1621.

(146) Valeev, F. A.; Salikhov, S. M.; Krasnoslobodtseva, O. Y.; Sharipov, B. T.; Spirikhin, L. V.; Tolstikov, G. A. *Chem. Nat. Compd.* **2007**, *43* (2), 143.

(147) Bertele, E.; Schudel, P. ZA 19690115, 1969.

(148) Taillefumier, C.; Chapleur, Y.; Bayeul, D.; Aubry, A. *J. Chem. Soc., Chem. Commun.* **1995**, No. 9, 937.

(149) Taillefumier, C.; Chapleur, Y. *Can. J. Chem.* **2000**, *78* (6), 708.

(150) Buss, A. D.; Hirst, G. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1987**, No. 24, 1836.

(151) Auerbach, J.; Weinreb, S. M. *J. Org. Chem.* **1975**, *40* (22), 3311.

(152) Shing, T. K. M.; Ying, T. *Tetrahedron* **1990**, *46* (6), 2187.

(153) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97* (16), 4765.

(154) Thies, R. W.; Seitz, E. P. *J. Chem. Soc., Chem. Commun.* **1976**, No. 21, 846.

(155) Thies, R. W.; Seitz, E. P. *J. Org. Chem.* **1978**, *43* (6), 1050.

(156) Franzus, B.; Scheinbaum, M. L.; Waters, D. L.; Bowlin, H. B. *J. Am. Chem. Soc.* **1976**, *98* (5), 1241.

(157) Wilson, S. R.; Mao, D. T.; Jernberg, K. M.; Ezmirly, S. T. *Tetrahedron Lett.* **1977**, *18*

(30), 2559.

(158) Gajewski, J. J.; Gee, K. R. *J. Am. Chem. Soc.* **1991**, *113* (3), 967.

(159) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37* (23), 3943.

(160) Quirk, R. P.; Kim, J.; Kausch, C.; Chun, M. *Polym. Int.* **1996**, *39* (1), 3.

(161) Saito, A.; Yanai, H.; Sakamoto, W.; Takahashi, K.; Taguchi, T. *J. Fluor. Chem.* **2005**, *126* (5), 709.

(162) Saito, A.; Sakamoto, W.; Yanai, H.; Taguchi, T. *Tetrahedron Lett.* **2006**, *47* (25), 4181.

(163) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102* (26), 7816.

(164) Sternbach, D. D.; Rossana, D. M. *J. Am. Chem. Soc.* **1982**, *104* (21), 5853.

(165) Schneider, H.-J.; Sangwan, N. K. *J. Chem. Soc., Chem. Commun.* **1986**, No. 24, 1787.

(166) Yanai, H.; Ogura, H.; Taguchi, T. *Org. Biomol. Chem.* **2009**, *7* (18), 3657.

(167) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110* (4), 1238.

(168) Armstrong, A.; Convine, N.; Popkin, M. *Synlett* **2006**, *2006* (10), 1589.

(169) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122* (17), 4243.

(170) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2* (24), 3937.

(171) Ward, D. E.; Souweha, M. S. *Org. Lett.* **2005**, *7* (16), 3533.

(172) Ishihara, J.; Nakadachi, S.; Watanabe, Y.; Hatakeyama, S. *J. Org. Chem.* **2015**, *80* (4), 2037.

(173) Souweha, M. S.; Enright, G. D.; Fallis, A. G. *Org. Lett.* **2007**, *9* (25), 5163.

(174) Souweha, M. S.; Arab, A.; ApSimon, M.; Fallis, A. G. *Org. Lett.* **2007**, *9* (4), 615.

(175) Yang, W.; Drueckhammer, D. G. *J. Am. Chem. Soc.* **2001**, *123* (44), 11004.

(176) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58* (15), 3840.

(177) Hart, D. J.; Wu, W.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1995**, *117* (36), 9369.

(178) Hart, D. J.; Li, J.; Wu, W.; Kozikowski, A. P. *J. Org. Chem.* **1997**, *62* (15), 5023.

(179) Byeon, C.-H.; Chen, C.-Y.; Ellis, D. A.; Hart, D. J.; Li, J. *Synlett* **1998**, *1998* (6), 596.

(180) Knoppe, S.; Kothalawala, N.; Jupally, V. R.; Dass, A.; Bürgi, T. *Chem. Commun.* **2012**, *48* (38), 4630.

(181) Aggarwal, V. K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonquerna, S. J.; Ford, G. D.; Hynd, G.; Jones, E.; Jones, R. V. H.; Jubault, P.; Palmer, M. J.; Ratcliffe, P. D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, No. 20, 2604.

(182) Banach, A.; Ścianowski, J.; Ozimek, P. *Phosphorus Sulfur Silicon Relat. Elem.* **2014**, *189* (2), 274.

(183) Hsu, J.-L.; Fang, J.-M. *J. Org. Chem.* **2001**, *66* (25), 8573.

(184) Fanjul, S.; Hulme, A. N.; White, J. W. *Org. Lett.* **2006**, *8* (19), 4219.

(185) Projean, D.; Morin, P.-E.; Tu, T. M.; Ducharme, J. *Xenobiotica* **2003**, *33* (8), 841.

(186) Waterman, M. R.; Keeney, D. S. *Horm. Res.* **1992**, *38* (5–6), 217.

(187) Hanukoglu, I. *J. Steroid Biochem. Mol. Biol.* **1992**, *43* (8), 779.

(188) Kaspera, R.; Croteau, R. *Phytochem. Rev.* **2006**, *5* (2–3), 433.

(189) Zhao, Y.-J.; Cheng, Q.-Q.; Su, P.; Chen, X.; Wang, X.-J.; Gao, W.; Huang, L.-Q. *Appl. Microbiol. Biotechnol.* **2014**, *98* (6), 2371.

(190) Omura, T.; Sato, R. *J. Biol. Chem.* **1964**, *239* (7), 2370.

(191) Omura, T.; Sato, R. *J. Biol. Chem.* **1964**, *239* (7), 2379.

(192) Rittle, J.; Green, M. T. *Science* **2010**, *330* (6006), 933.

(193) Hanukoglu, I. In *Advances in Molecular and Cell Biology*; 1996; pp 29–56.

(194) Zhang, K.; Shafer, B. M.; Demars, M. D.; Stern, H. A.; Fasan, R. *J. Am. Chem. Soc.* **2012**, *134* (45), 18695.

(195) Sowden, R. J.; Yasmin, S.; Rees, N. H.; Bell, S. G.; Wong, L.-L. *Org. Biomol. Chem.* **2005**, *3* (1), 57.

(196) Agudo, R.; Roiban, G.-D.; Reetz, M. T. *ChemBioChem* **2012**, *13* (10), 1465.

(197) Roiban, G.-D.; Agudo, R.; Reetz, M. T. *Tetrahedron* **2013**, *69* (26), 5306.

(198) Roiban, G.-D.; Agudo, R.; Ilie, A.; Lonsdale, R.; Reetz, M. T. *Chem. Commun.* **2014**, *50* (92), 14310.

(199) Roiban, G.-D.; Agudo, R.; Reetz, M. T. *Angew. Chem. Int. Ed.* **2014**, *53* (33), 8659.

(200) Ilie, A.; Agudo, R.; Roiban, G.-D.; Reetz, M. T. *Tetrahedron* **2015**, *71* (3), 470.

(201) Agudo, R.; Roiban, G.-D.; Lonsdale, R.; Ilie, A.; Reetz, M. T. *J. Org. Chem.* **2015**, *80* (2), 950.

(202) Li, A.; Ilie, A.; Sun, Z.; Lonsdale, R.; Xu, J.-H.; Reetz, M. T. *Angew. Chem. Int. Ed.* **2016**, *55* (39), 12026.

(203) Whitehouse, C. J. C.; Bell, S. G.; Yang, W.; Yorke, J. A.; Blanford, C. F.; Strong, A. J. F.; Morse, E. J.; Bartlam, M.; Rao, Z.; Wong, L.-L. *ChemBioChem* **2009**, *10* (10), 1654.

(204) Whitehouse, C. J. C.; Yang, W.; Yorke, J. A.; Rowlatt, B. C.; Strong, A. J. F.;

Blanford, C. F.; Bell, S. G.; Bartlam, M.; Wong, L.-L.; Rao, Z. *ChemBioChem* **2010**, *11* (18), 2549.

(205) Whitehouse, C. J. C.; Yang, W.; Yorke, J. A.; Tufton, H. G.; Ogilvie, L. C. I.; Bell, S. G.; Zhou, W.; Bartlam, M.; Rao, Z.; Wong, L.-L. *Dalt. Trans.* **2011**, *40* (40), 10383.

(206) Ren, X.; Yorke, J. A.; Taylor, E.; Zhang, T.; Zhou, W.; Wong, L. L. *Chem. Eur. J.* **2015**, *21* (42), 15039.

(207) Asta, C.; Schmidt, D.; Conrad, J.; Förster-Fromme, B.; Tolasch, T.; Beifuss, U. *RSC Adv.* **2013**, *3* (42), 19259.

(208) Thiel, D.; Doknić, D.; Deska, J. *Nat. Commun.* **2014**, *5*, 5278.

(209) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126* (29), 9106.

(210) Horn, E. J.; Rosen, B. R.; Baran, P. S. *ACS Cent. Sci.* **2016**, *2* (5), 302.

(211) Paddon, C. A.; Pritchard, G. J.; Thiemann, T.; Marken, F. *Electrochem. commun.* **2002**, *4* (10), 825.

(212) Horcajada, R.; Okajima, M.; Suga, S.; Yoshida, J. *Chem. Commun.* **2005**, *36* (10), 1303.

(213) Amemiya, F.; Horii, D.; Fuchigami, T.; Atobe, M. *J. Electrochem. Soc.* **2008**, *155* (11), E162.

(214) Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37* (46), 8317.

(215) Finney, E. E.; Ogawa, K. A.; Boydston, A. J. *J. Am. Chem. Soc.* **2012**, *134* (30), 12374.

(216) Frankowski, K. J.; Liu, R.; Milligan, G. L.; Moeller, K. D.; Aubé, J. *Angew. Chem. Int. Ed.* **2015**, *54* (36), 10555.

(217) Nguyen, B. H.; Redden, A.; Moeller, K. D. *Green Chem.* **2014**, *16* (1), 69.

(218) Nguyen, B. H.; Perkins, R. J.; Smith, J. A.; Moeller, K. D. *Beilstein J. Org. Chem.* **2015**, *11*, 280.

(219) Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27* (10), 1973.

(220) Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron Lett.* **1977**, *18* (25), 2199.

(221) Couladouros, E. A.; Georgiadis, M. P. *J. Org. Chem.* **1986**, *51* (14), 2725.

(222) Lefebvre, Y. *Tetrahedron Lett.* **1972**, *13* (2), 133.

(223) Dominguez, C.; G. Csa´ky, A.; Plumet', J. *Tetrahedron Lett.* **1990**, *31* (52), 7669.

(224) Adger, B. M.; Barrett, C.; Brennan, J.; McKervey, M. A.; Murray, R. W. *J. Chem. Soc., Chem. Commun.* **1991**, No. 21, 1553.

(225) Ho, T.-L.; Sapp, S. G. *Synth. Commun.* **1983**, *13* (3), 207.

(226) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1983**, *5* (12), 666.

(227) Clauson-Kaas, N.; Limborg, F.; Dietrich, P.; Stenhagen, E.; Östling, S. *Acta Chem. Scand.* **1952**, *6*, 545.

(228) Nedenskov, P.; Elming, N.; Nielsen, J. T.; Clauson-Kaas, N. *Acta Chem. Scand.* **1955**, *9*, 17.

(229) Weinberg, N. L.; Weinberg, H. R. *Chem. Rev.* **1968**, *68* (4), 449.

(230) Shono, T.; Matsumura, Y. *Tetrahedron Lett.* **1976**, *17* (17), 1363.

(231) Torii, S.; Tanaka, H.; Anoda, T.; Simizu, Y. *Chem. Lett.* **1976**, *5* (5), 495.

(232) Horii, D.; Atobe, M.; Fuchigami, T.; Marken, F. *Electrochem. commun.* **2005**, *7* (1), 35.

(233) Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122* (23), 5636.

(234) Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3* (17), 2685.

(235) Duan, S.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124* (32), 9368.

(236) Xu, H.-C.; Moeller, K. D. *Org. Lett.* **2010**, *12* (8), 1720.

(237) Xu, G.; Moeller, K. D. *Org. Lett.* **2010**, *12* (11), 2590.

(238) Smith, J. A.; Moeller, K. D. *Org. Lett.* **2013**, *15* (22), 5818.

(239) Redden, A.; Perkins, R. J.; Moeller, K. D. *Angew. Chem. Int. Ed.* **2013**, *52* (49), 12865.

(240) Okimoto, M.; Ohashi, K.; Yamamori, H.; Nishikawa, S.; Hoshi, M.; Yoshida, T. *Synthesis* **2012**, *44* (9), 1315.

(241) Kim, S. S.; Rajagopal, G.; Song, D. H. *J. Organomet. Chem.* **2004**, *689* (10), 1734.

(242) Tsubuki, M.; Kamata, T.; Okita, H.; Arai, M.; Shigihara, A.; Honda, T. *Chem. Commun.* **1999**, No. 22, 2263.

(243) Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133* (38), 14892.

(244) Steinreiber, A.; Osprian, I.; Mayer, S. F.; Orru, R. V. A.; Faber, K. **2000**.

(245) Agelis, G.; Kelaidonis, K.; Resvani, A.; Kalavrizioti, D.; Androutsou, M.-E.; Plotas, P.; Vlahakos, D.; Koukoulitsa, C.; Tselios, T.; Mavromoustakos, T.; Matsoukas, J. *Molecules* **2013**, *18* (7), 7510.

(246) Sharipov, B. T.; Pershin, A. A.; Salikhov, S. M.; Valeev, F. A. *Russ. J. Org. Chem.* **2016**, *52* (5), 721.

(247) Boeckman, Jr., R. K.; Clark, T. J.; Shook, B. C. *Helv. Chim. Acta* **2002**, *85* (12), 4532.

(248) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129* (2), 276.

(249) Maciá Ruiz, B.; Geurts, K.; Fernández-Ibáñez, M. Á.; ter Horst, B.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2007**, *9* (24), 5123.

(250) Kazancioglu, E. A.; Kazancioglu, M. Z.; Fistikci, M.; Secen, H.; Altundas, R. *Org. Lett.* **2013**, *15* (18), 4790.

(251) Freitas, J. C. R.; de Oliveira, C. K.; Cunha, E. C.; Malvestiti, I.; Alves, S.; Longo, R. L.; Menezes, P. H. *Tetrahedron Lett.* **2013**, *54* (12), 1558.

(252) Cahill, S.; O'Brien, M. *Tetrahedron Lett.* **2006**, *47* (22), 3665.

(253) Moore, P. W.; Mirzayans, P. M.; Williams, C. M. *Chem. Eur. J.* **2015**, *21* (9), 3567.

(254) Das, M.; O'Shea, D. F. *J. Org. Chem.* **2014**, *79* (12), 5595.

(255) Noutsias, D.; Alexopoulou, I.; Montagnon, T.; Vassilikogiannakis, G. *Green Chem.* **2012**, *14* (3), 601.

(256) Hodgson, R.; Majid, T.; Nelson, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, No. 12, 1444.

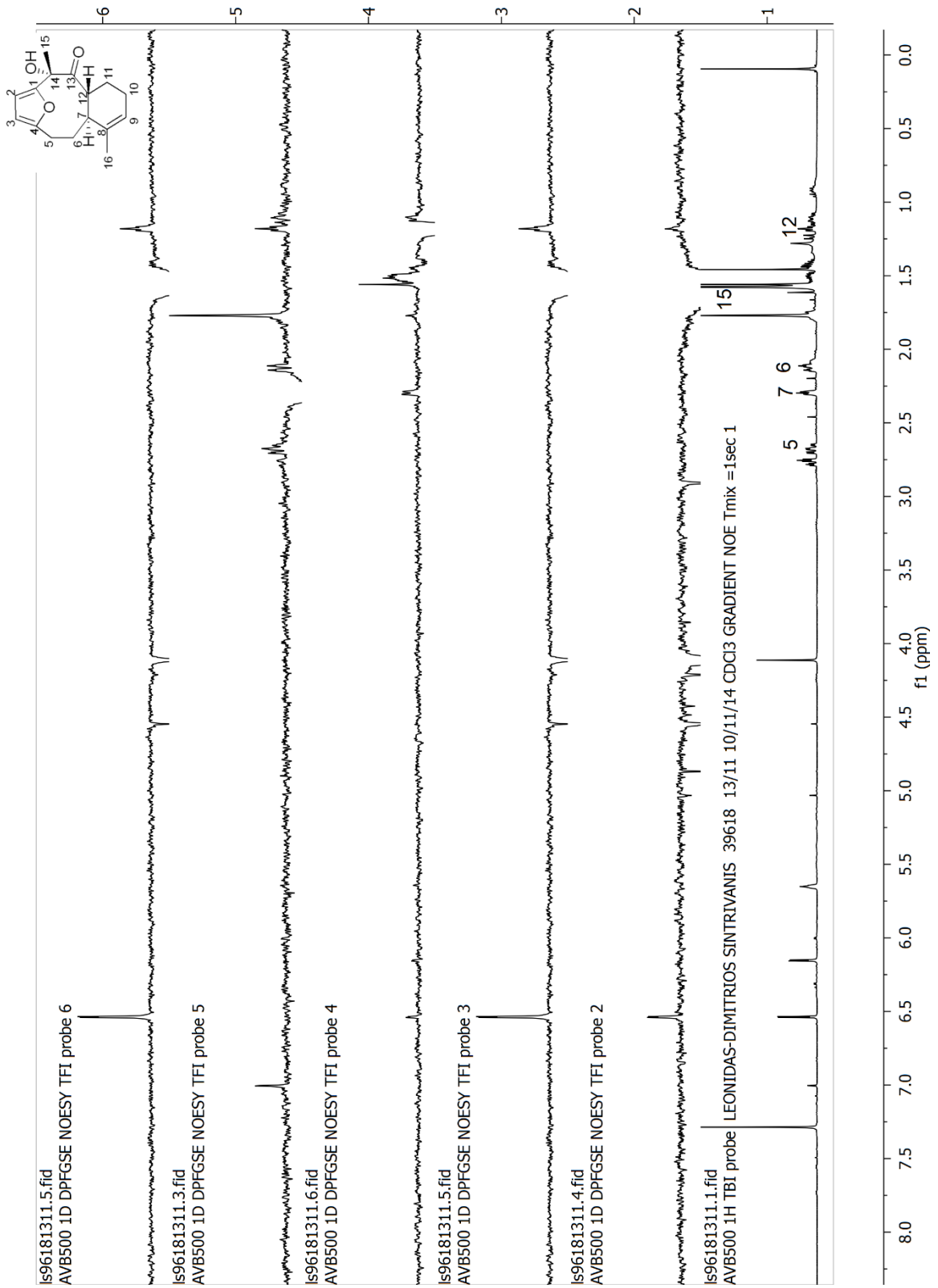
(257) Li, Z.; Tong, R. *J. Org. Chem.* **2016**, *81* (11), 4847.

(258) Witten, M. R.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2014**, *53* (23), 5912.

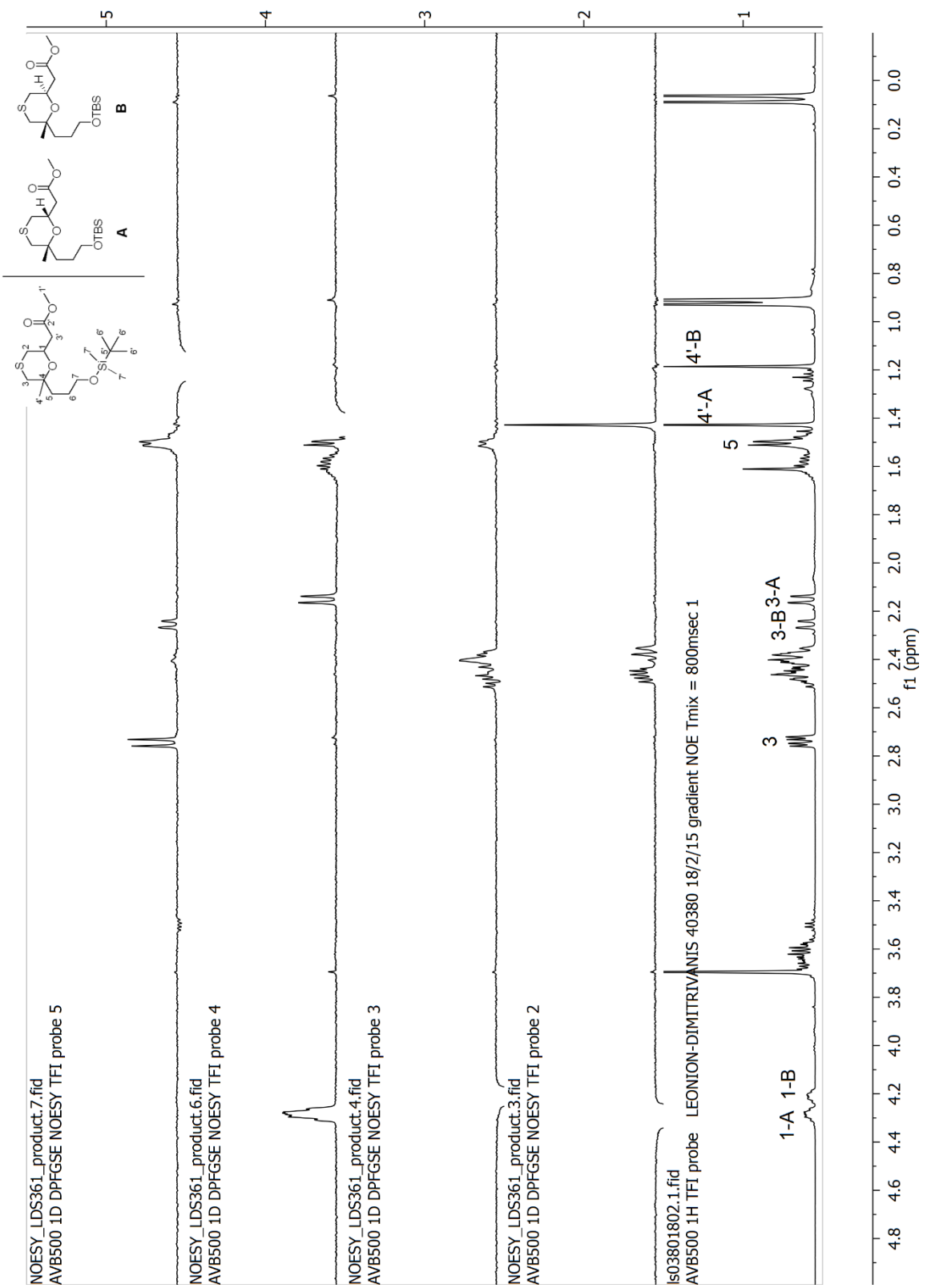
Appendices

The numbering system used in the following appendices reflects that used in the Experimental Section, and not the eleuthoside numbering system.

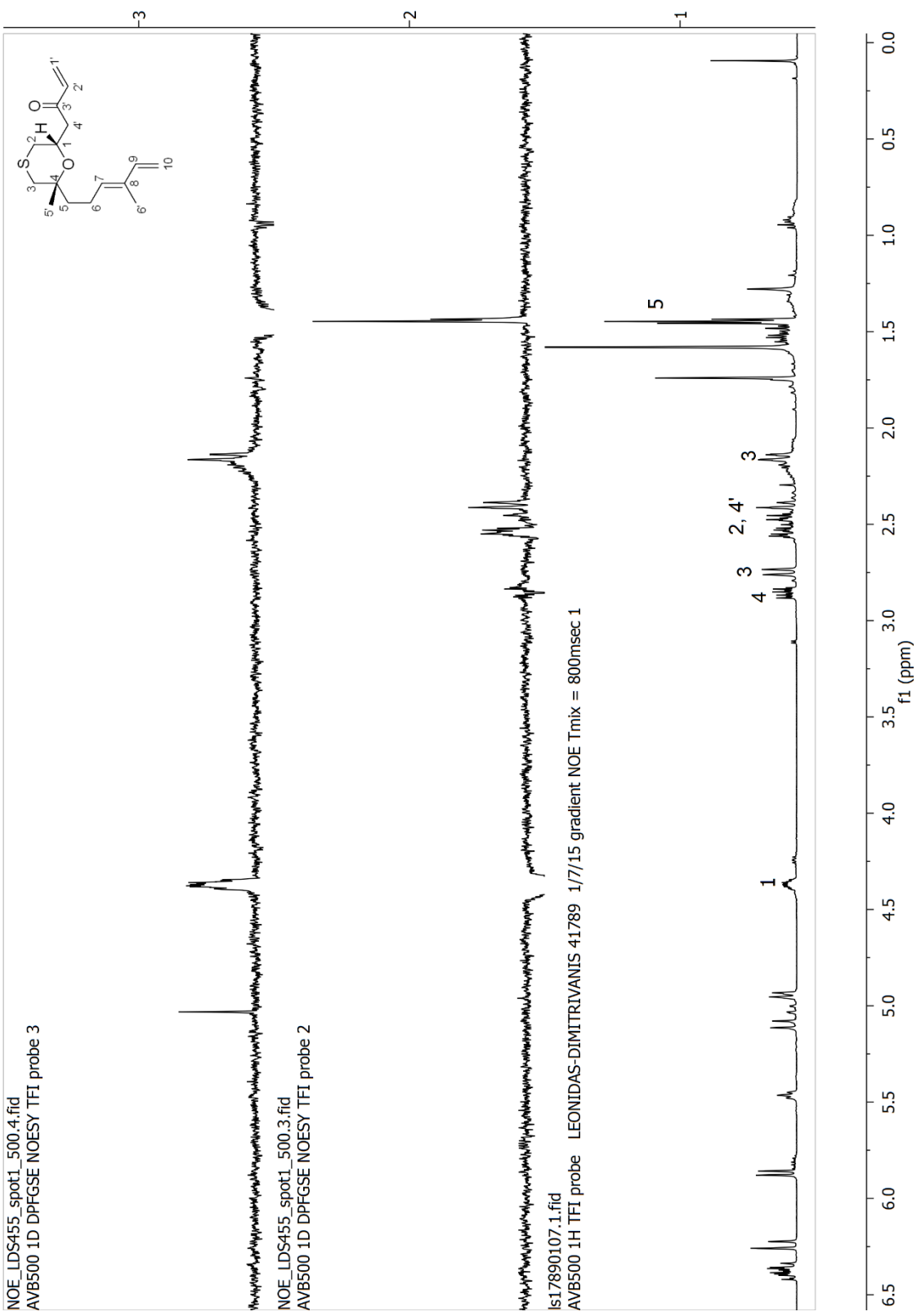
Appendix 1: NOE spectra of compound 229



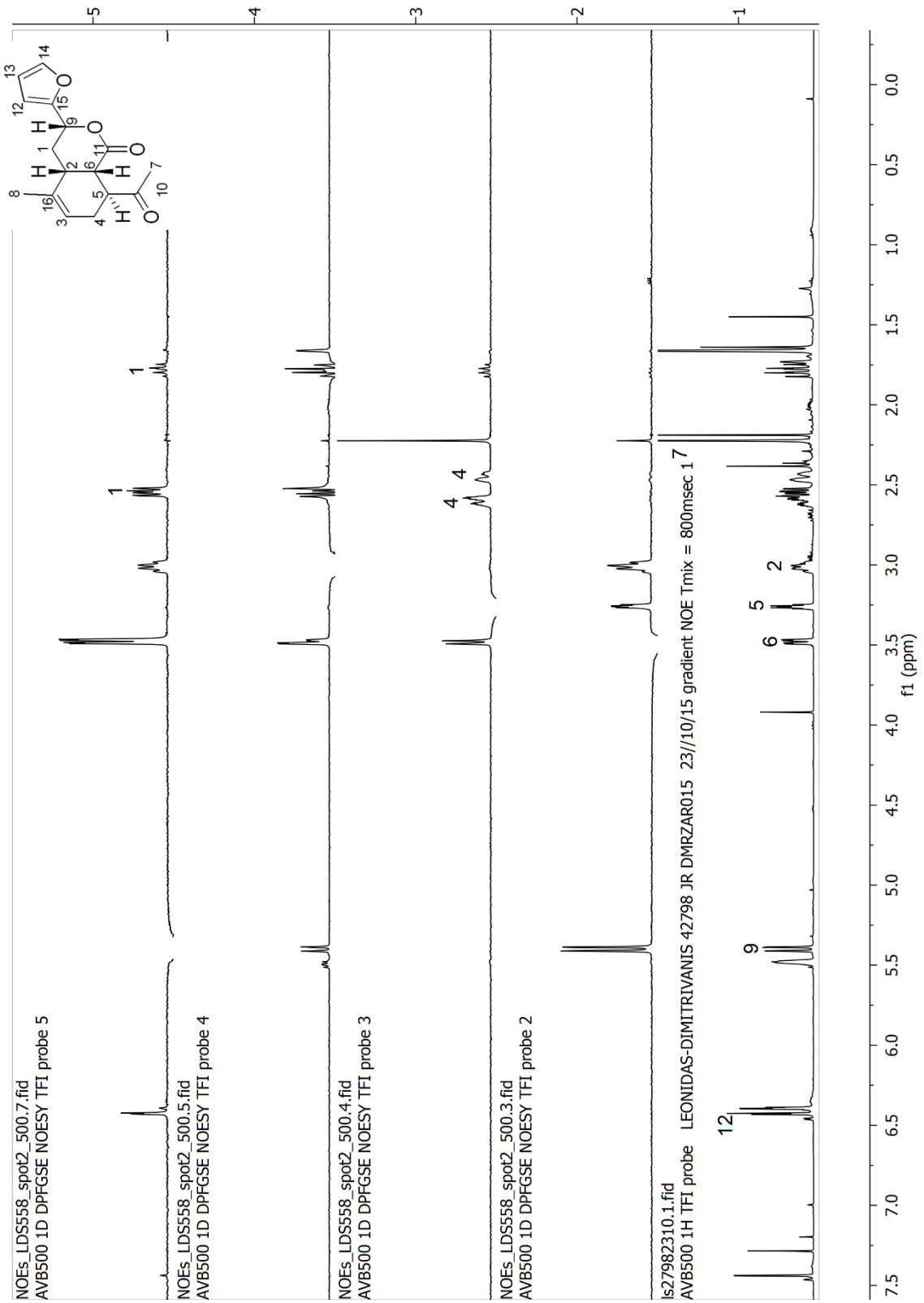
Appendix 2: NOE spectra of compounds 281 and 282



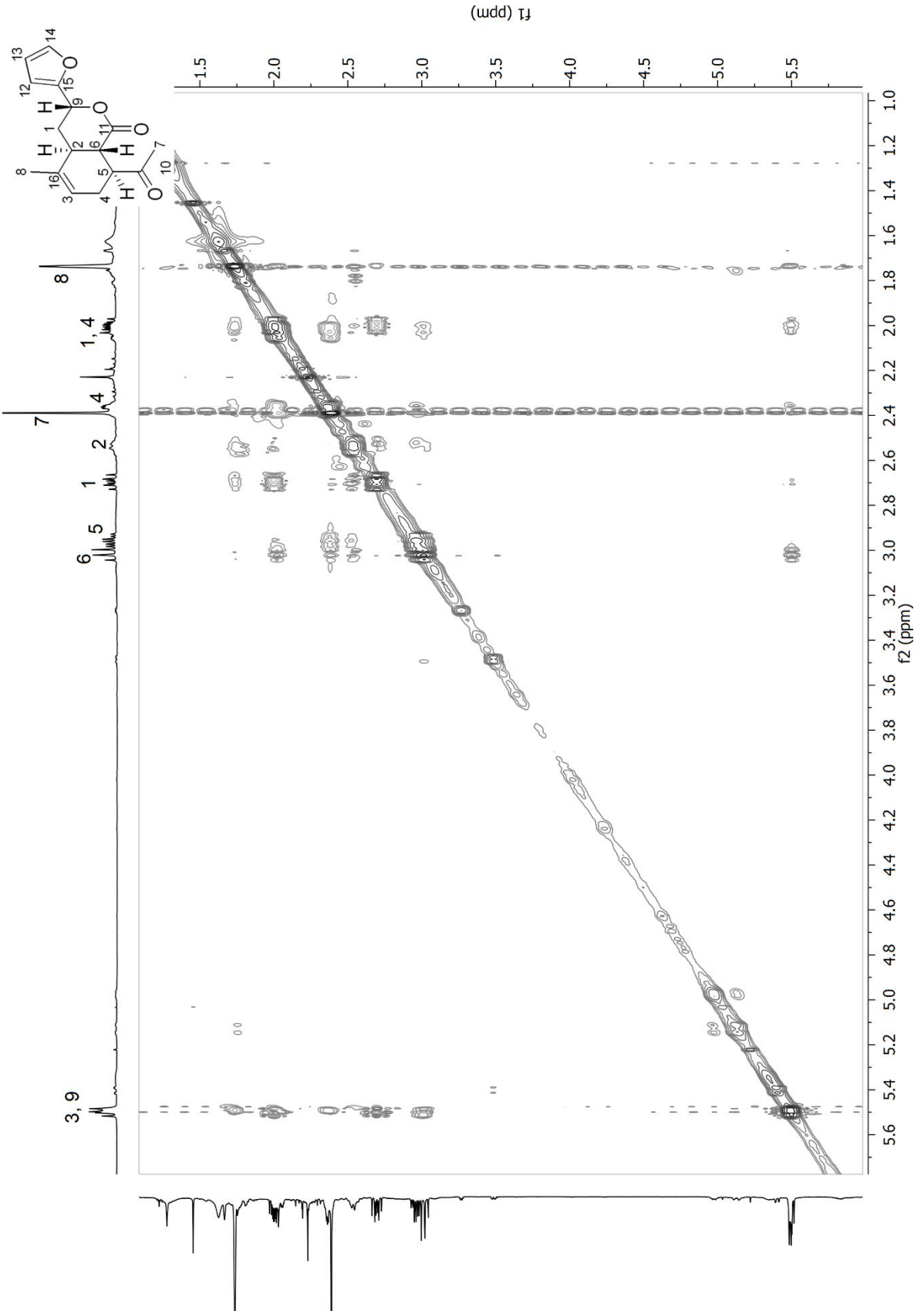
Appendix 3: NOE spectra of compound 294



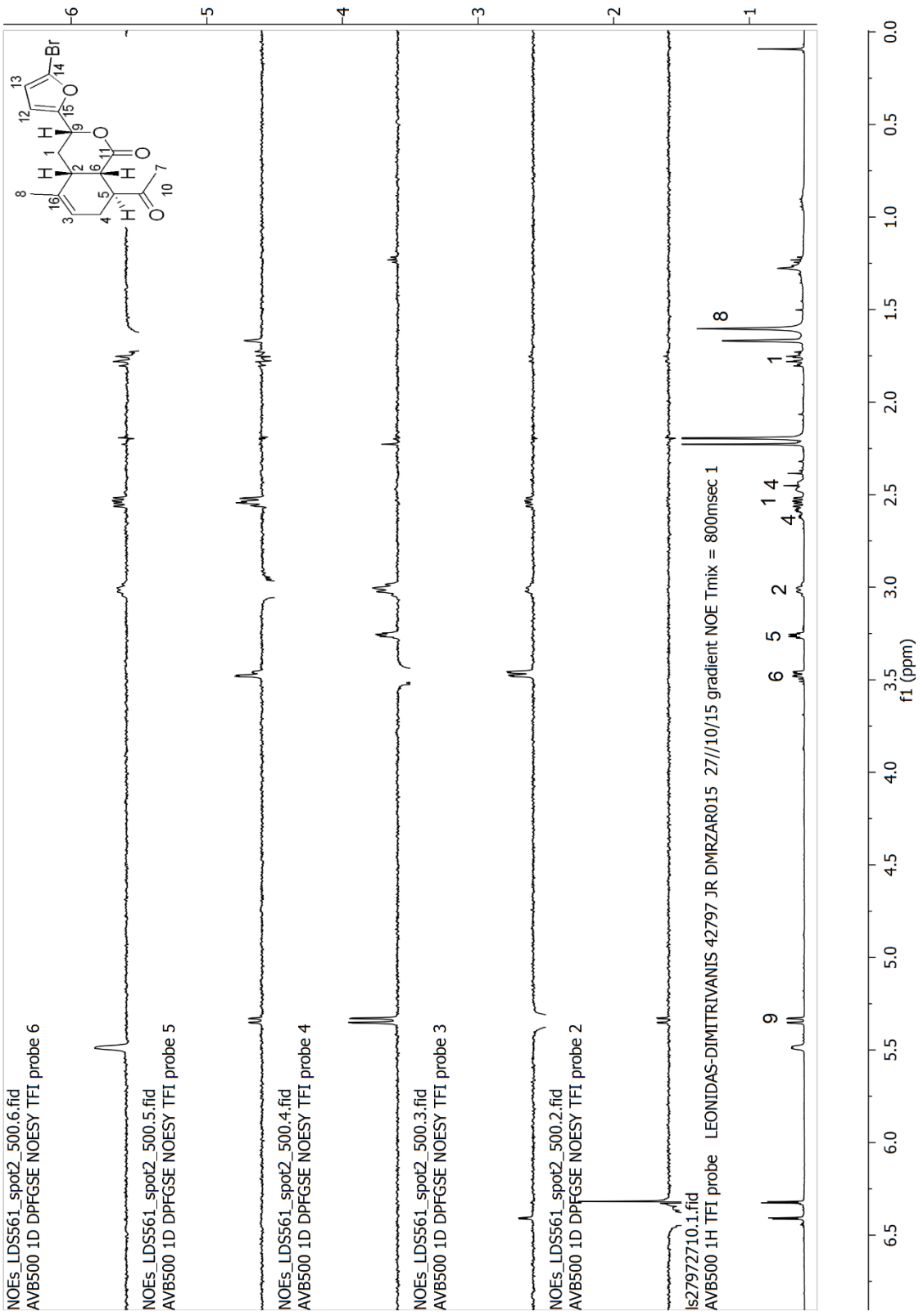
Appendix 4: NOE spectra of compound 316



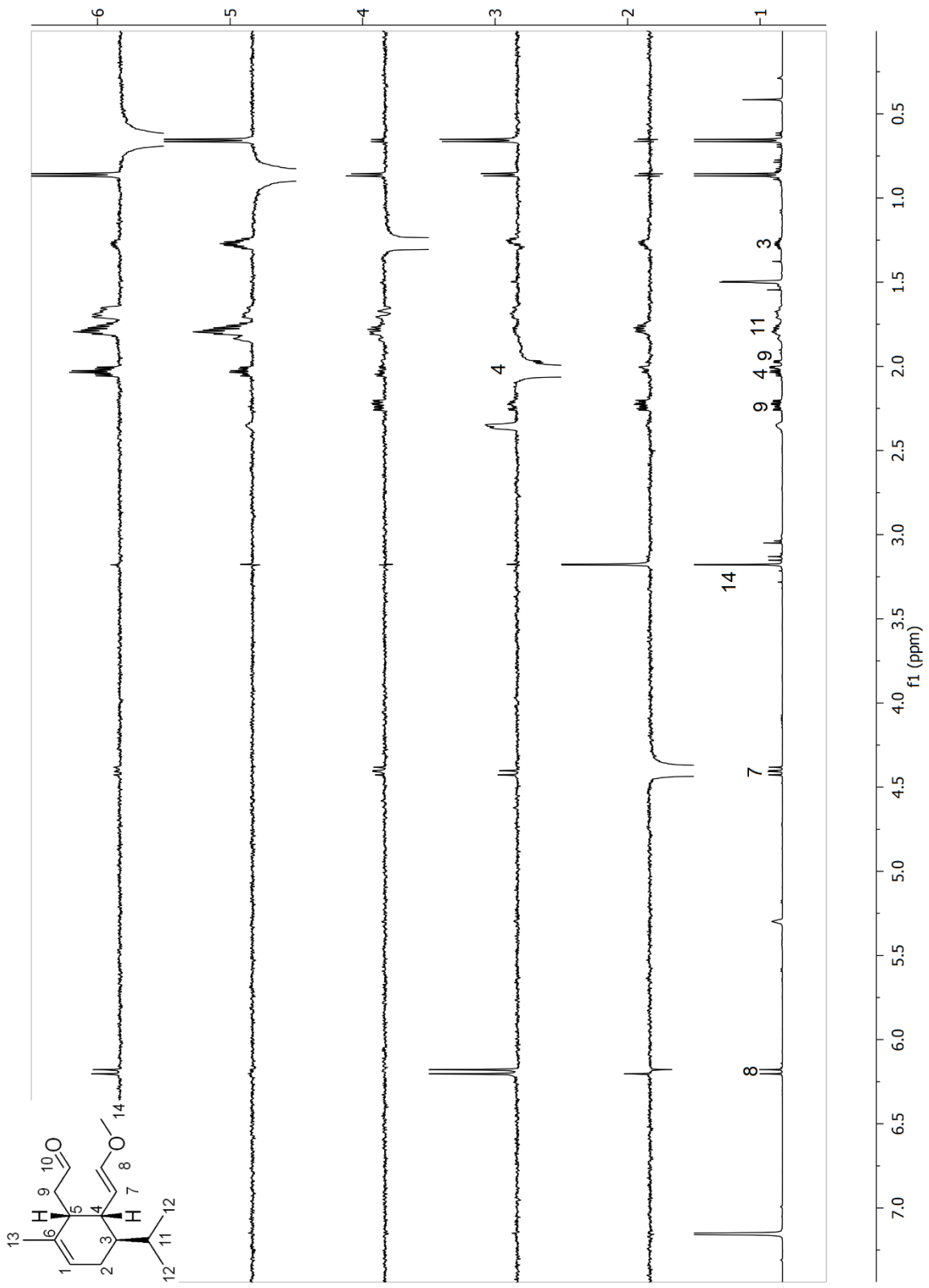
Appendix 5: 2D-NOE spectrum of compound 317



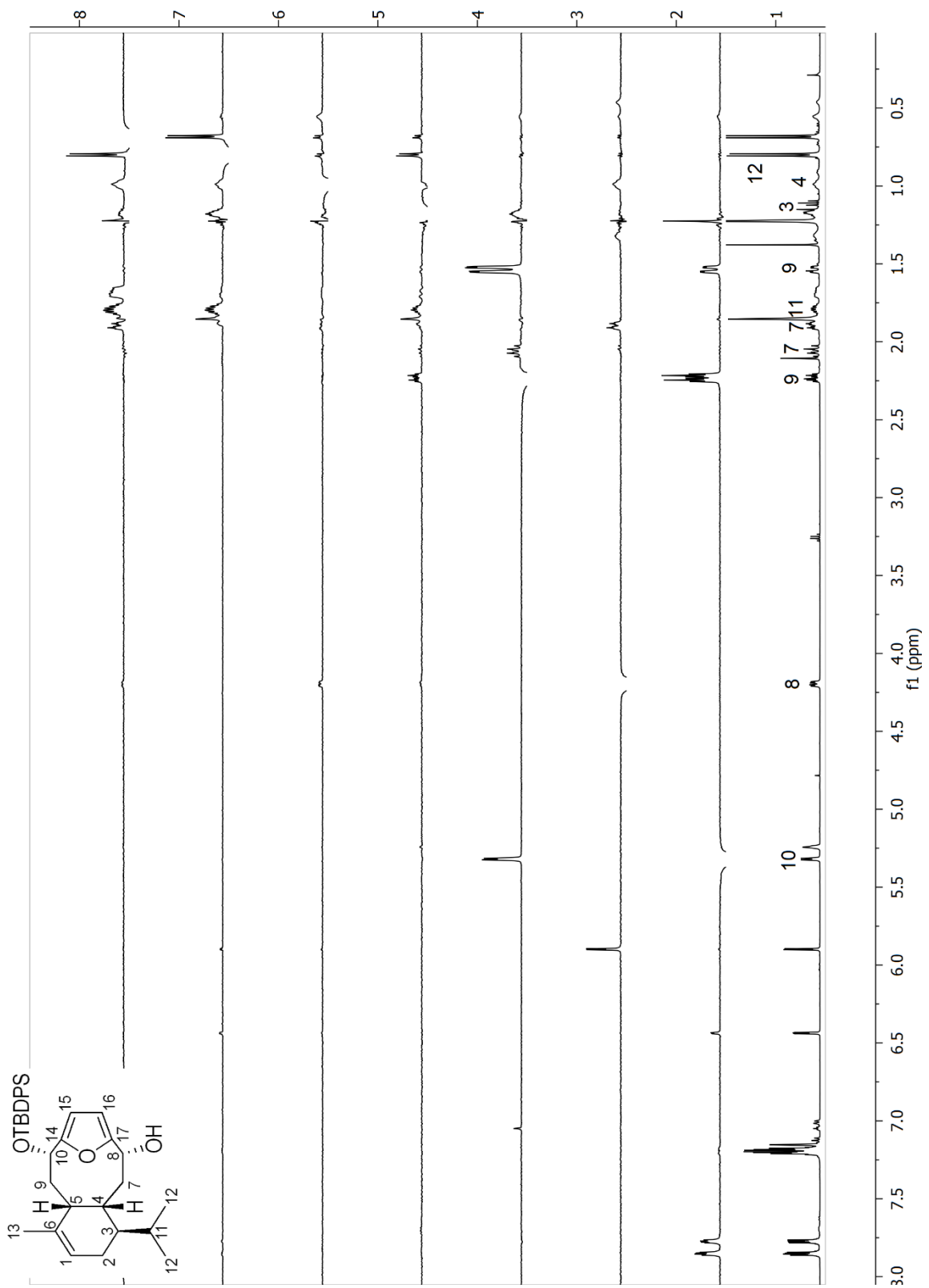
Appendix 6: NOE spectra of compound 325



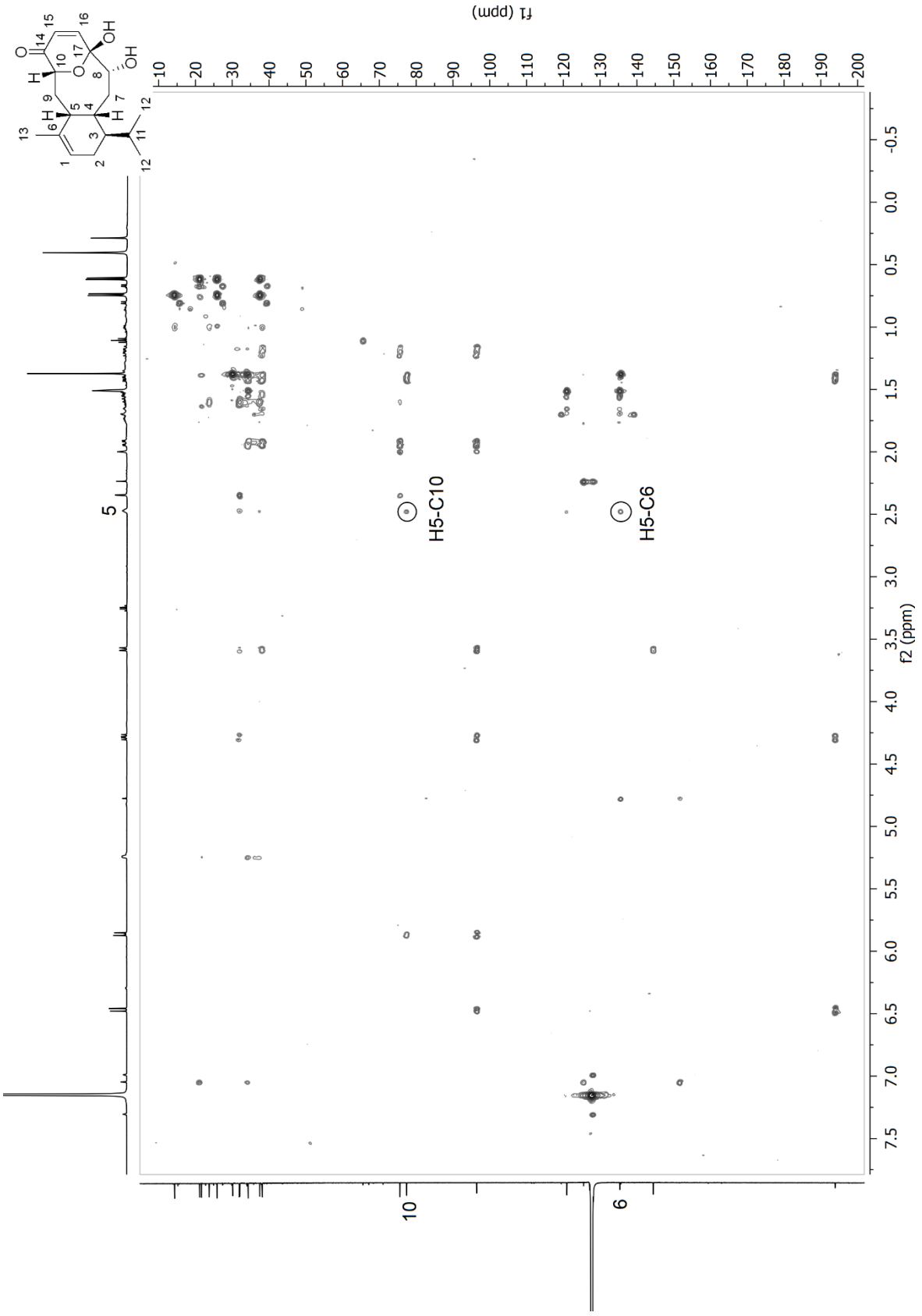
Appendix 7: NOE spectra of compound 328



Appendix 8: NOE spectra of compound 346

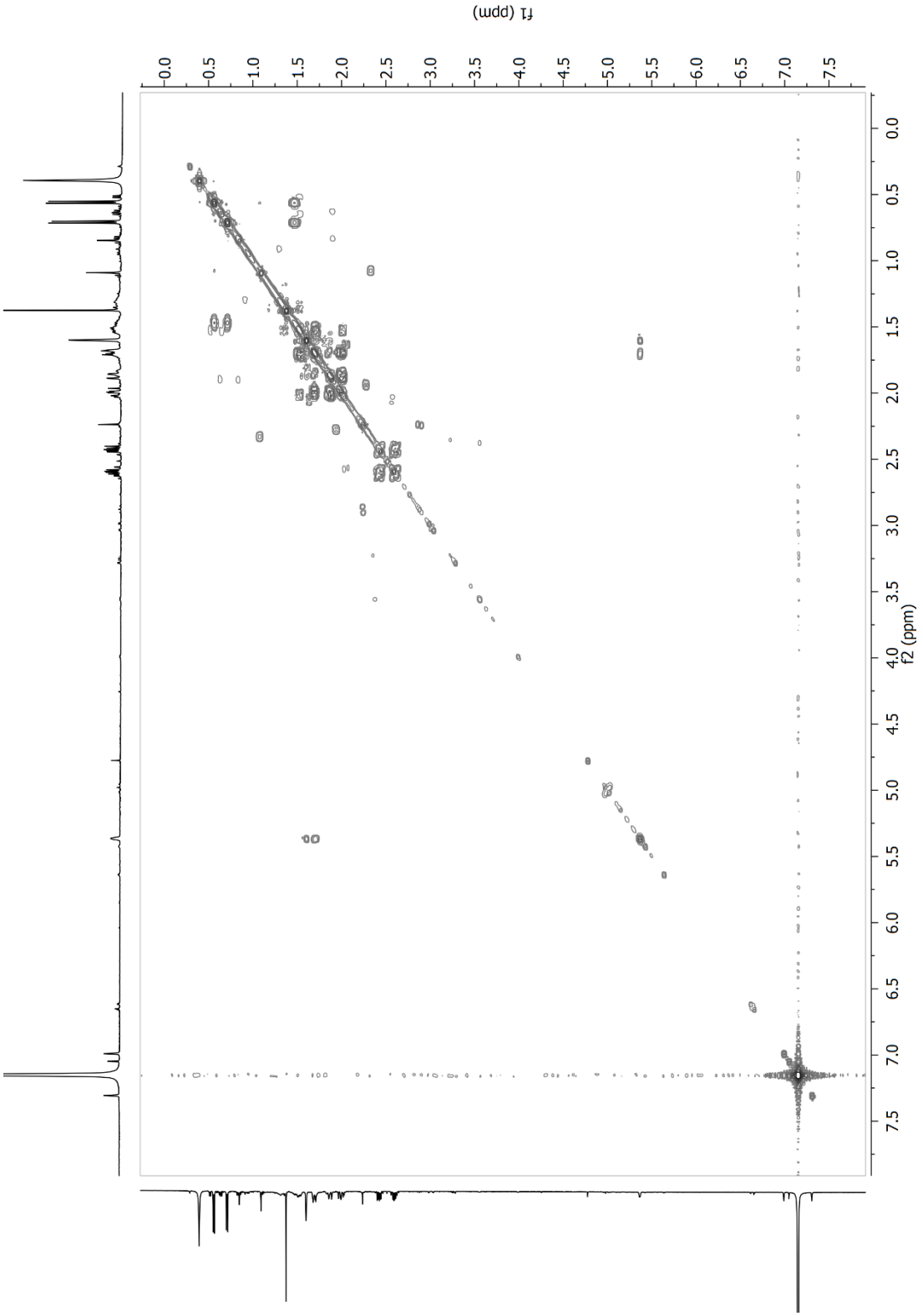


Appendix 9: HMBC spectrum of compound 413

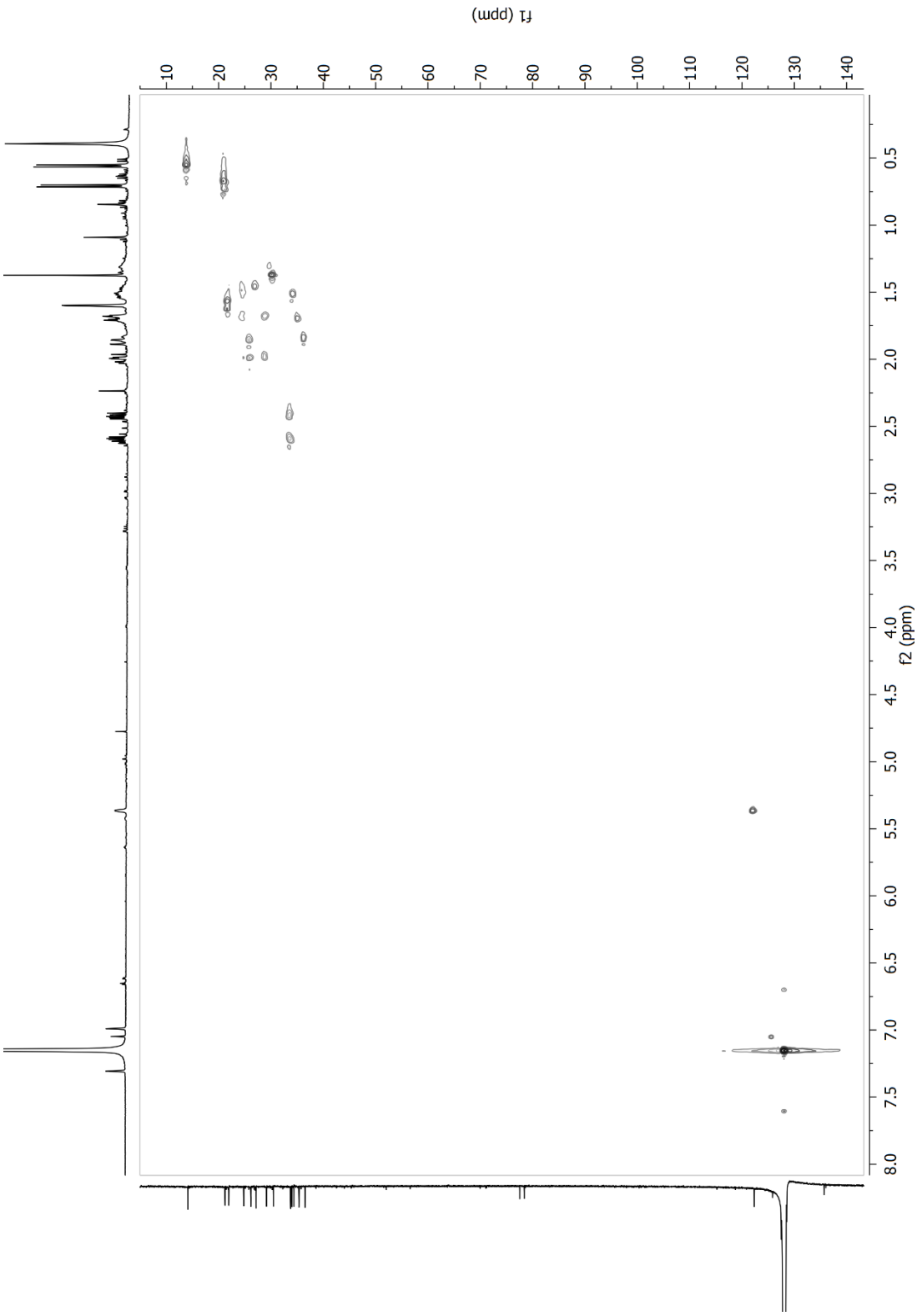


Appendix 10: COSY, HSQC, and HMBC spectra of the product of mP450 oxidation of ketol 418

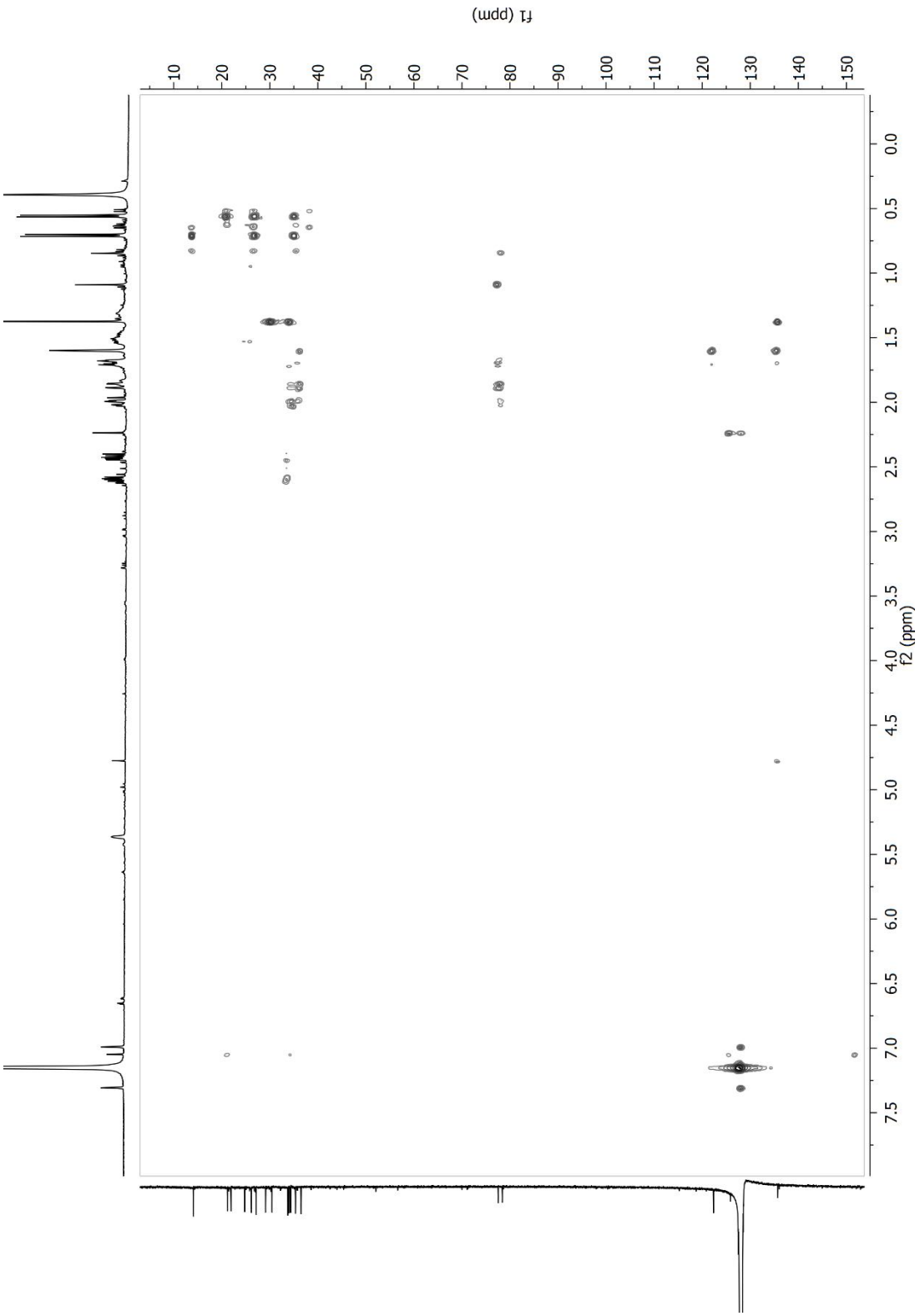
COSY



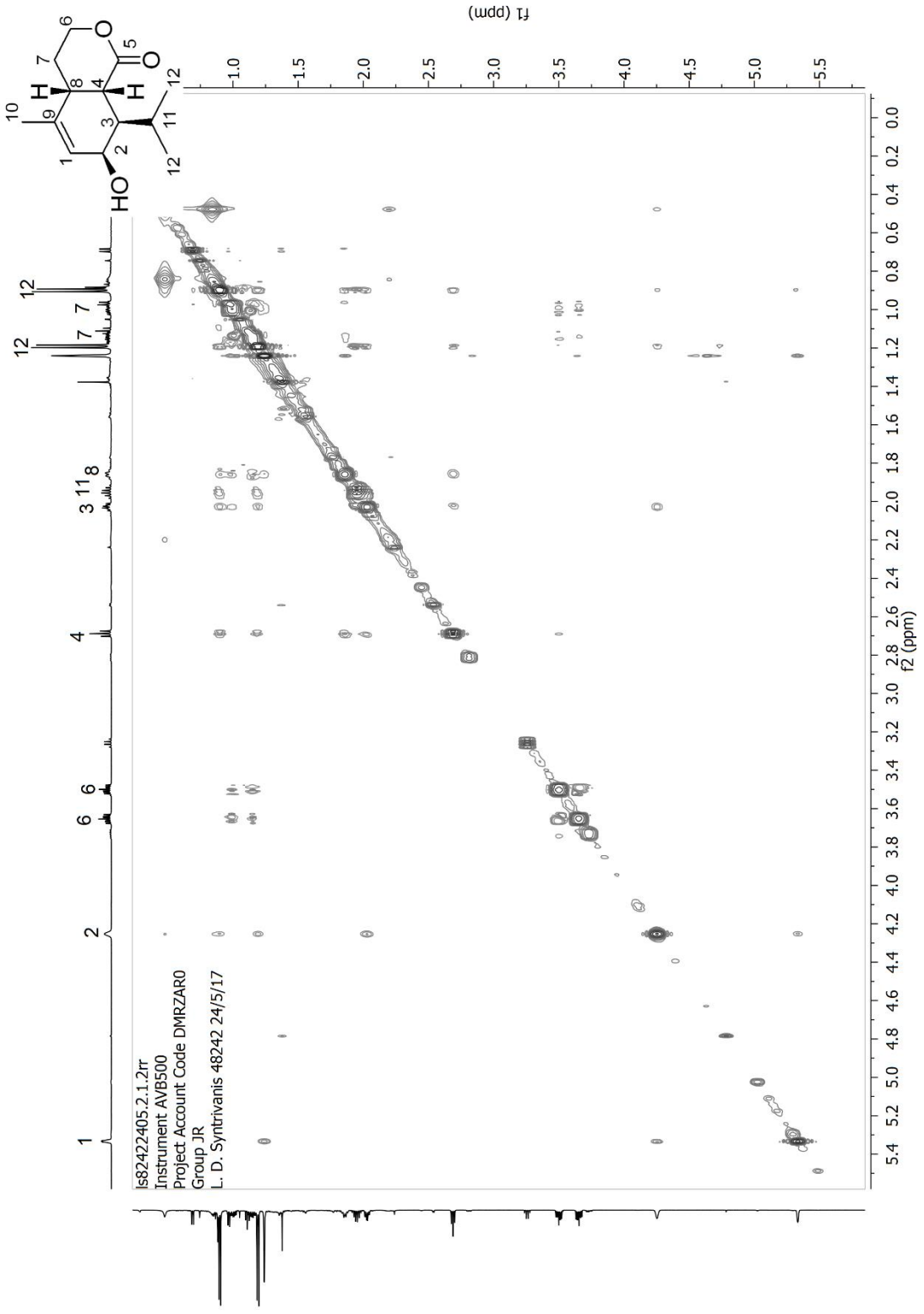
HSQC


f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0

HMBC



Appendix 11: 2D-NOE spectrum of compound 423



Appendix 12: 2D-NOE spectrum of compound 426

