Fused ring systems in natural product synthesis

Robert Rodger

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

School of Chemistry

University of Sydney

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Abstract

On the instigation of A/Prof C. S. P. McErlean I investigated the rapid synthesis of fused ring compounds by a key polyene cyclisation.

Chapter 1 sets the scene by highlighting deficiencies in literature syntheses of selected fused-ring compounds, where synthetic strategies are often suboptimal. In particular, the scarcity of reported syntheses involving a *direct* cyclisation method is noted.

Chapter 2 discusses the taiwaniaquinoids and previous synthetic approaches including McErlean group efforts which delivered the non-natural stereochemistry. A method to produce the desired *trans* stereochemistry of (±)-taiwaniaquinone G was developed. Attempts to apply this methodology to a divergent synthesis of the taiwaniaquinoids are detailed.

Chapter 3 extends this strategy to the attempted synthesis of compounds with a greater number of rings: the dasyscyphins, pelorol, atomarianone B and disidein. The successful partial cyclisation and subsequent full cyclisation of two farnesylarenes was reported. Larger architectures remain an elusive goal.

Chapter 4 discusses efforts in the synthesis of a different class of fused-ring compounds: the marine polycyclic ethers. The application of newer methodologies to the synthesis of the polycyclic ethers is described, however this did not lead to a viable strategy to these compounds.

Author attribution statement

This thesis contains published material from Rodger, R.T.; Graham, M.S.; McErlean, C.S.P.; Hyperconjomer stereocontrol of cationic polyene cyclisations. *Org. Biomol. Chem.* **2019**, 17 (37), 8551–8560 throughout sections 2.1 and 2.2. All synthetic work was carried out by me, except for some intermediates in sections 2.2 and 3.2 provided by Dr Marlowe Graham. All computational work was performed by A/Prof McErlean.

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

A/Prof Christopher S. P. McErlean

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All calculations performed in sections 2.1, 2.2 and 3.1 were conducted by A/Prof Christopher S. P. McErlean. Intermediates in sections 2.2 and 3.2 were synthesised and provided by Dr Marlowe Graham. All 200 and 300 MHz NMR spectra were acquired by me; some higher resolution NMR spectra were obtained by technical staff at the University of Sydney NMR Facility. All mass spectra were acquired by technical staff at the University of Sydney Mass Spectrometry Facility.

Statement of Originality

This is to certify that the content of this thesis is my own work, carried out between March 2016 and October 2021 at the School of Chemistry of the University of Sydney, under the supervision of A/Prof Christopher S. P. McErlean, for the fulfilment of the requirements of a Doctor of Philosophy. This thesis has not been submitted for any degree or any other purpose.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Robert T. Rodger

Dedication

First of all I'd like to thank A/Prof McErlean for his guidance over the past 6 years. Chris has an unmatched passion for chemistry and it has been an absolute pleasure to work for him.

Thanks to all my friends in the McErlean group and in the School of Chemistry who have made it such a great place to work.

Mostly I need to thank my mum for her constant support, especially over the past two years. I couldn't have made it this far without her.

Contents

Abbreviations

Å ..... angstrom(s)

Ac ..... acetyl

AIBN ..... azabisisobutyronitrile

APCI ..... atmospheric pressure chemical ionisation

APPI ..... atmospheric pressure photoionisation

aq. ..... aqueous

BDSB ..... bromodiethylsulfonium bromopentachloroantimonate

BINOL ..... 1,1′-bi-2-naphthol

bpy ..... 2,2′-bipyridine

br ..... broad

***n*-Bu** ..... primary butyl

°C ..... degrees Celsius

calcd. ..... calculated

CAN ..... ceric ammonium nitrate

CBS ..... Corey-Bakshi-Shibata reduction

CDSC ..... chlorodiethylsulfonium hexachloroantimonate

CFL ..... compact fluorescent lamp

CoA ..... coenzyme A

COD ..... cyclooctadiene

cm^{-1} ..... reciprocal centimetres (wavenumber(s))

CTAB ..... cetyl trimethylammonium bromide

CuAAC ..... copper-catalysed azide-alkyne condensation

d ..... doublet

δ ..... chemical shift in parts per million downfield from trimethylsilane.

DBDMH ..... dibromodimethylhydantoin

DBU ..... 1,8-diazabicyclo[5.4.0]undec-7-ene

DCA 9,10-dicyanoanthracene

DCC ..... *N,N*-dicyclohexylcarbodiimide

DCE ..... dichloroethane

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL ..... diisobutylaluminium hydride

DMAP 4-dimethylaminopyridine

DMAPP ..... dimethylallyl pyrophosphate

DMDO ..... dimethyldioxirane

DMF ..... *N,N*-dimethylformamide

DMN 1,5-dimethoxynaphthalene

DMSO ..... dimethylsulfoxide

dppf ..... diphenylphosphinoferrocene

dr ..... diastereomeric ratio

ee ..... enantiomeric excess

EI ..... electron ionisation

ESI ..... electrospray ionisation

Et ..... ethyl

g ..... gram(s)

HMBC ..... heteronuclear multiple bond correlation

HMDS ..... hexamethyldisilazane; hexamethyldisilazide

HMPA ..... hexamethylphosphoramide

HPLC ..... high performance liquid chromatography

HRMS ..... high resolution mass spectrometry

HSQC ..... heteronuclear single quantum coherence

Hz ..... hertz

IBX ..... iodoxybenzoic acid

IC_{50} ..... half maximal inhibitory concentration

IDSI ..... "iododiethylsulfonium iodopentachloroantimonate", named by analogy to BDSB and CDSC.

IR ..... infrared

J ..... joule(s)

J ..... spin coupling constant

k ..... kilo

λ ..... wavelength

L ..... litre(s)

LBA ..... Lewis-assisted Brønsted acid

LDA ..... lithium diisopropylamide

LED ..... light emitting diode

lit. ..... literature value

LUMO ..... lowest unoccupied molecular orbital

m ..... milli; multiplet

M ..... molar (mol/L)

M$^+$ ..... parent molecular ion

mCPBA ..... *meta*-chloroperbenzoic acid

Me ..... methyl

MHz ..... megahertz

MIC ..... minimum inhibitory concentration

μ ..... micro

mol ..... mole(s)

MOM ..... methoxymethyl

m.p. ..... melting point

Ms ..... methanesulfonyl (mesyl)

MS ..... mass spectrometry

m/z ..... mass-to-charge ratio

NBS ..... *N*-bromosuccinimide

NCS ..... *N*-chlorosuccinimide

NIS ..... *N*-iodosuccinimide

NHC ..... *N*-heterocyclic carbene

NMI ..... *N*-methylimidazole

NMM ..... *N*-methylmorpholine

NMO ..... *N*-methylmorpholine *N*-oxide

NMR ..... nuclear magnetic resonance

NOESY ..... nuclear Overhauser effect spectroscopy

Ph ..... phenyl

PIFA ..... phenyliodine bis(trifluoroacetate)

ppm ..... parts per million

PPTS ..... pyridinium *para*-toluenesulfonate

ppy 2-phenylpyridinium

***i*-Pr** ..... isopropyl

q ..... quartet

s ..... singlet

SHIP ..... Src homology 2-containing inositol 5-phosphatase

T ..... temperature

TBADT ..... tetrabutylammonium decatungstate

TBAF ..... tetra-*n*-butylammonium fluoride

TBCO 2,4,4,6-tetrabromo-2,5-cyclohexadienone

TBDPS ..... *tert*-butyldiphenylsilyl

TBHP ..... *tert*-butylhydroperoxide

TBS ..... *tert*-butyldimethylsilyl

***t*-Bu** ..... *tert*-butyl

TCPT ..... 2,4,6-trichlorophenyl triazolyl catalyst (**157**)

TEMPO ..... (2,2,6,6-tetramethylpiperidin-1-yl)oxyl

Tf ..... trifluoromethylsulfonyl (triflyl)

TFA ..... trifluoroacetic acid

TFSI ..... bis(trifluoromethane)sulfonimide

THF ..... tetrahydrofuran

TIPS ..... triisopropylsilyl

TMEDA ..... *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

TMS ..... trimethylsilyl

Ts ..... *para*-toluenesulfonyl (tosyl)

UV ..... ultraviolet light

Chapter 1

Introduction

1.1 Total synthesis

"What is the point of total synthesis?" is a question that every chemist in the field has been asked at one time or another. There are multiple answers and justifications to this question. The bulk of this work, which explores the generation of polycyclic natural products through the acid-catalysed cyclisation of terpenoid precursors covers the issues below.

Our project begins with studies on the synthesis of taiwaniaquinoids, compounds found in *Taiwania cryptomerioides*, a now endangered tree. This is due in part to overlogging and in part to its slow growth and strict habitat needs, meaning it is found in only small regions in Taiwan and Southeast Asia. It is legally protected in these countries.[1] The study of the plants' chemical constituents is further complicated by the low concentration of the taiwaniaquinoids: in one example, 12 kilograms of tree bark was extracted to give approximately 10 mg of each of a number of compounds.[2] Some of the taiwaniaquinoid family have been found to possess potent biological properties and are worthy of further biological research. Total synthesis is the only way to acquire useful amounts of these compounds. This justification for the continued development of total synthesis is a recurring theme in the literature.

The story behind paclitaxel (Taxol; **2**) is a similar one. Paclitaxel is a potent anticancer natural product from *Taxus brevifolia* (Pacific yew), another endangered species.[3]

Paclitaxel was obtained from the bark of the yew tree, a process that killed the tree. In addition, an entire tree contains a mere 300 mg of the natural product, enough for a single medicinal dose. Taxol's potent bioactivity, difficulties in sourcing it and its intriguing and complicated chemical structure led to intense focus from the synthetic community: at one point in the early 90s, at least 30 research groups were working on its synthesis.[4] While many groups such as Nicolaou's focused on the total synthesis from simple starting materials,[3] such a complex molecule necessarily requires too many steps for commercial production. Other groups including Holton's instead worked on semisynthesis starting from 10-deacetylbaccatin (**1**),[5] which is abundant in the leaves of the more common *Taxus baccata* (European yew). This route has formed the basis of the vast bulk of commercial supply of Taxol.

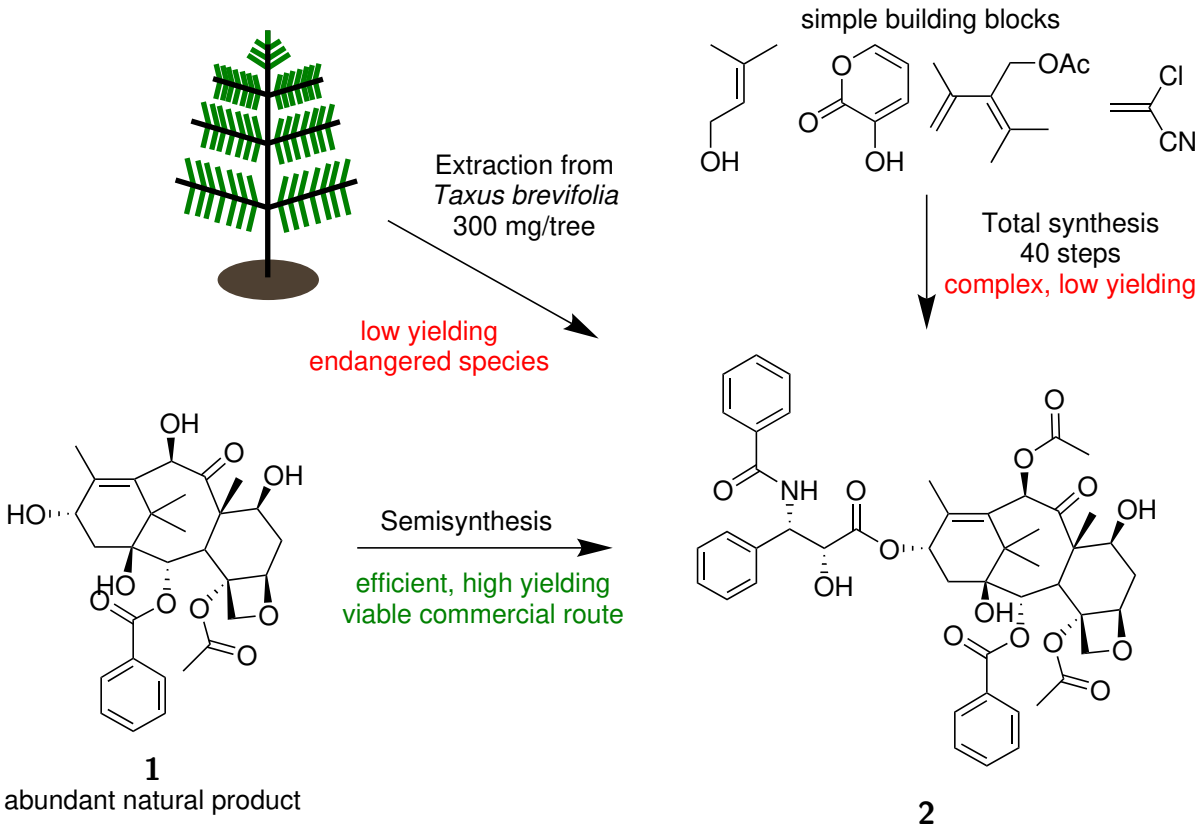


Figure 1: Sources of Taxol.

The scarcity of useful or intriguing natural products in biomass is a problem limited not only to paclitaxel and the taiwaniaquinoids. The isolation literature is full of reports where obscene amounts of material—sometimes up to tonnes—is processed and extracted to give milligram or microgram amounts of a particular compound or a number of compounds.[6] This is best exemplified by the polycyclic ether natural products, which are nevertheless potent toxins at even nanomolar concentrations and can cause billions of

dollars in economic damage. The extraction of these materials and indeed more abundant compounds can be labour-intensive and less effective than chemical synthesis. This detracts from biological approaches such as fermentation or bacterial expression.

In at least one case, fermentation and extraction to obtain medicinally relevant compounds are outright unfeasible: thienamycin (**3**), a highly potent carbapenem antibiotic. High concentrations of thienamycin in an aqueous solution leave it prone to dimerisation, meaning it can only be produced in dilute solution.[7] Ed Paul, head engineer at Merck remarked:

> *"To produce 40 000 kg of imipenem per year, we would have to run the thienamycin fermentation in Lake Erie and pump to Lake Ontario for the workup!"*[7]

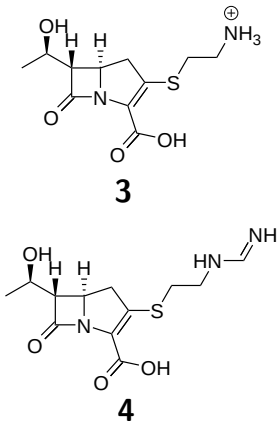
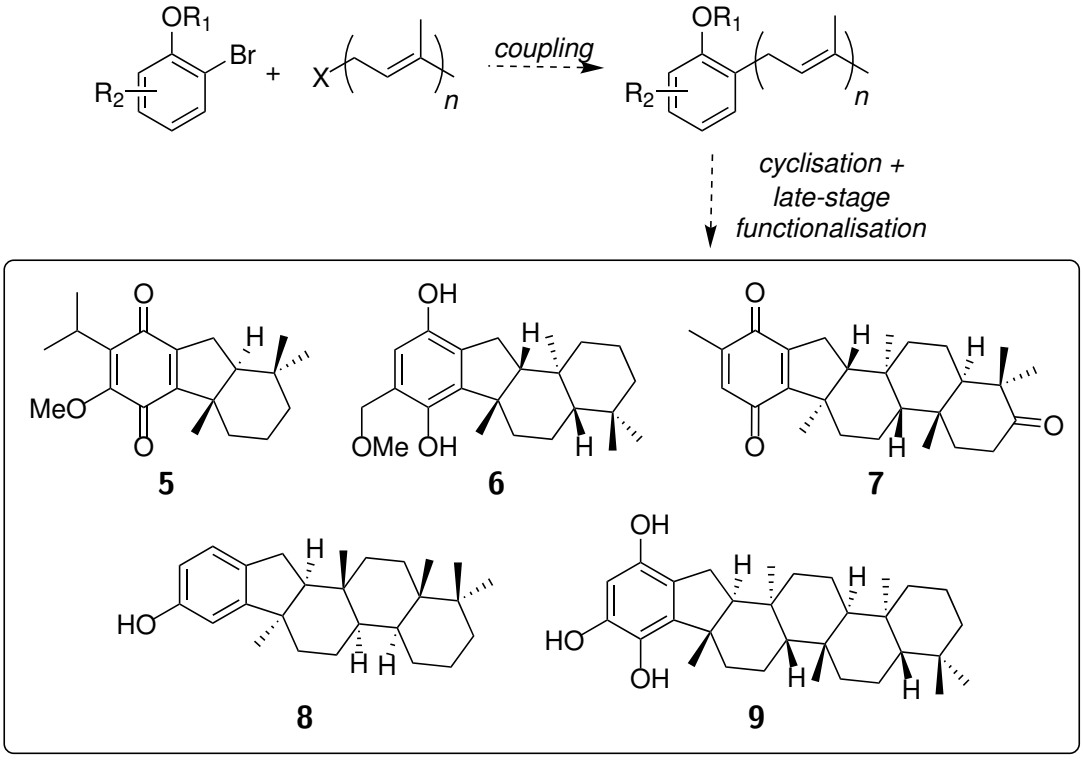


Figure 2: Lake Erie and Lake Ontario have capacities well over 100 km^3. Fermentation to produce thienamycin (**3**) would have made imipenem (**4**) production unfeasible.[7] Adapted from Google Maps.

This led again to chemical synthesis being the preferred method of production, with Merck researchers producing six total syntheses of thienamycin with the aim to scale to production volumes.[7] Subsequent work developed imipenem (**4**) as a derivative that does not dimerise in aqueous solution, allowing for it to be far more valuable as a drug. This derivative is also produced via chemical synthesis. Therefore, total synthesis is a route to access biologically promising molecules that are otherwise inaccessible.

The production of analogues is a key use of total synthesis via divergent total synthesis. In the current project we will take a relatively simple aromatic ring and couple it to a

polyprenyl chain of the desired length, in which each isoprene unit will form the backbone of another carbocyclic ring. Cyclisation will give the carbon framework of a particular natural product (Scheme 1). We have chosen the natural products as exemplars with known characterisation data and often some (albeit minimal) biological screening data. However, in principle we should be able to take a variety of suitably nucleophilic aromatics and a polyprenol of any length to develop libraries of compounds for biological screening. This approach has already been utilised on similar molecules, in particular with Andersen's investigation of SHIP-1 inhibiting pelorol analogues produced via an epoxide-mediated cationic cyclisation,[8] as well as Snyder's work on peyssonol derivatives produced by a bromonium-mediated cyclisation.[9] [10] Such approaches to taiwaniaquinoid analogues by direct cyclisation have not yet been reported, but laborious work on some analogues has shown great promise. Access to natural product analogues is another powerful justification for continued interest in total synthesis.



Scheme 1: Coupling of a suitable aryl bromide and a polyprenoid chain, followed by cationic cyclisation should lead to these products in short order.

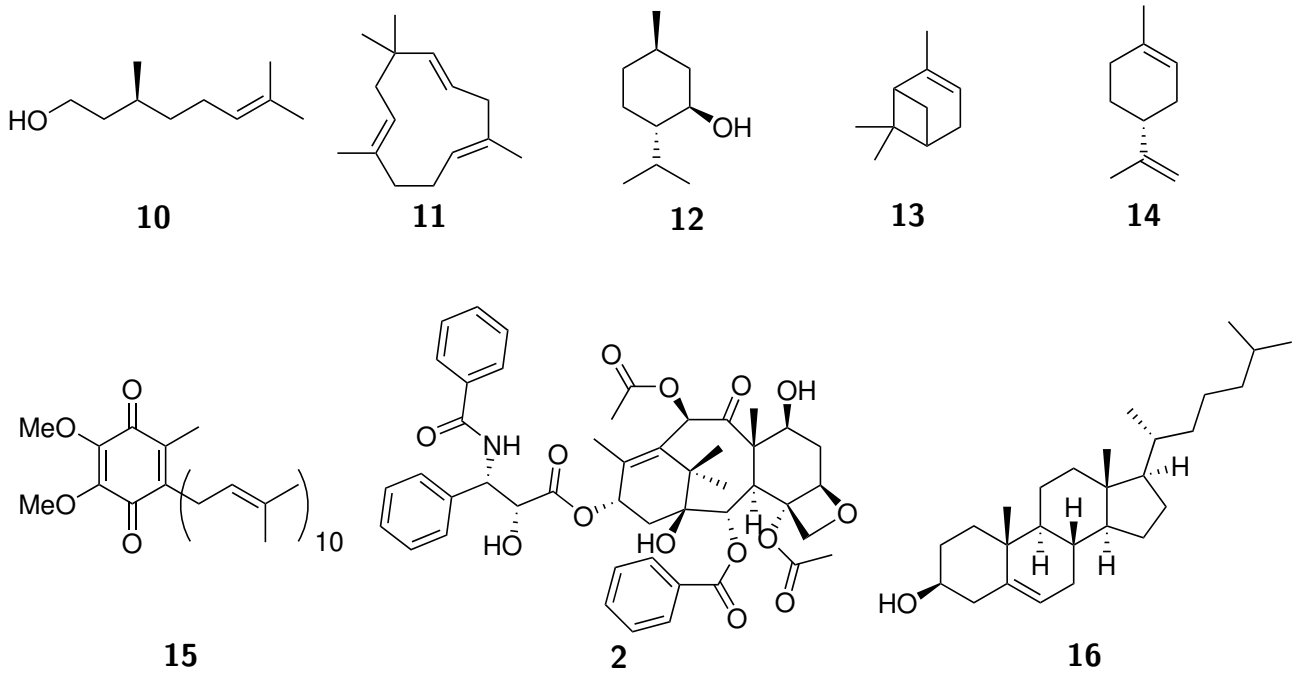
Perhaps the most common justification for engaging in total synthesis is to explore the scope of an existing reaction. Total synthesis has long served as a testing ground for synthetic methodologies. While the 6,6,6-cyclisations are well studied, taiwaniaquinoids possess a 6,5,6 framework. To the best of our knowledge, direct cyclisations of polyenes onto aromatics to access this framework have not been previously reported. We aim

to investigate several aspects of acid-catalysed polyene cyclisation: control over the diastereoselectivity of the BC ring junction as in taiwaniaquinone G (**5**) and dasyscyphin B (**6**); chain length, as in the cyclisation towards disidein (**7**) with five isoprene units; the stereochemistry of the more distal rings as in cyclisations towards atomarianone B (**9**); and the stability of various functionalities in these cyclisations, especially in the context of dasyscyphin B. Some of the compounds described in this thesis have been made before, albeit in extremely inefficient ways. We expect that our cationic polyene cyclisation strategy will deliver the chosen natural products much more directly.

The taiwaniaquinoids make an ideal target for a total synthesis project. They are found in scarce abundance in an endangered plant. They possess useful biological activity and analogue development through inefficient means has led to the identification of potent compounds. Most importantly for us, the taiwaniaquinoids possess an unusual 6,5,6-fused, stereochemically diverse polycyclic system, which presents an intriguing opportunity for reaction development.

1.2 Terpenoids

Terpenoids are the largest family of natural products, with over 22 000 compounds with applications ranging from maintaining biological function (e.g. cholesterol, **16**; ubiquinone, **15**; Figure 3), solvents (e.g. turpentine, **13**; limonene, **14**) and scents and flavourings (e.g. limonene; menthol, **12**). Even rubber can be considered a terpenoid, being derived from polymers of isoprene. The terpenoids vary from simple linear chains (e.g. citronellol; **10**), relatively simple 6-member monocycles like limonene (**14**), all the way to complex, highly functionalised products like paclitaxel (**2**). What unites all of these is their biosynthetic origin as oligomers of isoprene (Table 1), followed by rearrangement, cyclisation and functionalisation to give the many various architectures. The 'isoprene rule' was derived from early studies which discovered that many terpenoids could pyrolyse to give isoprene.[12] This was formulated into the isoprene rule by Wallach, who stated that all terpenoids came from head-to-tail oligomerisation of isoprene, and was helpful in determining the structures of many terpenoids before the advent of the advanced characterisation techniques we now employ. Later work led to Ruzicka's 'biogenetic isoprene rule',[13] the recognition that biosynthesis begins with the head-to-tail



10 **11** **12** **13** **14**

15 **2** **16**

Figure 3: Representative terpenoid natural products: citronellol (**10**), humulene (**11**), menthol (**12**), α-pinene (**13**), limonene (**14**), ubiquinone (**15**), paclitaxel (**2**), cholesterol (**16**).

Table 1: Nomenclature of terpenes. Adapted from ref. 11.

Family	# carbons	# isoprene units	polyprenoid	example
hemiterpenes	C_5	1	DMAPP	n/a
monoterpenes	C_{10}	2	geraniol	limonene
sesquiterpenes	C_{15}	3	farnesol	humulene
diterpenes	C_{20}	4	geranylgeraniol	retinol
triterpenes	C_{30}	6	squalene	cholesterol
tetraterpenes	C_{40}	8	phytoene	β-carotene

condensation of an 'active' isoprene unit, which could then be followed by rearrangement, such as in abietic acid where three isoprene units are attached head-to-tail, with a fourth attached in the opposite direction (Figure 4).[13]

Today, we know that the route to these terpenoids begins with the mevalonate pathway (Scheme 2).[11] Two units of acetyl-CoA (**18**) are condensed to form acetoacetyl-CoA (**19**), then condensation with a third unit gives 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA; **20**). Reduction of the thioester to the alcohol gives mevalonic acid (**21**), which is then phosphorylated twice to 5-pyrophosphomevalonate (**22**). A concerted decarboxylative

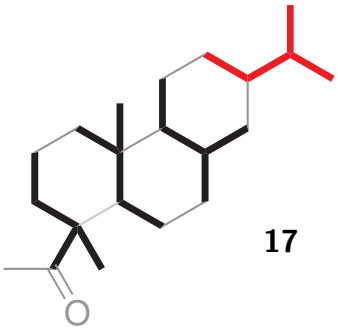
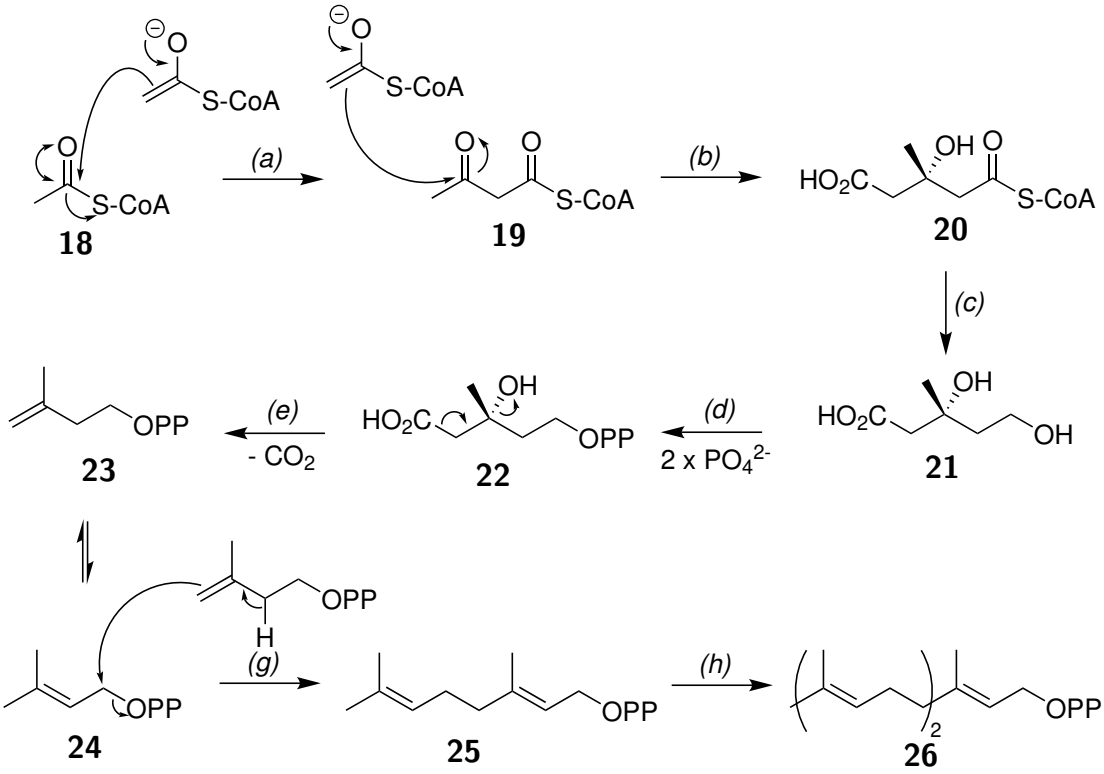


Figure 4: Abietic acid (**17**) shown with the constituent isoprene units bolded and unusual tail-tail disconnection highlighted in red.[13]

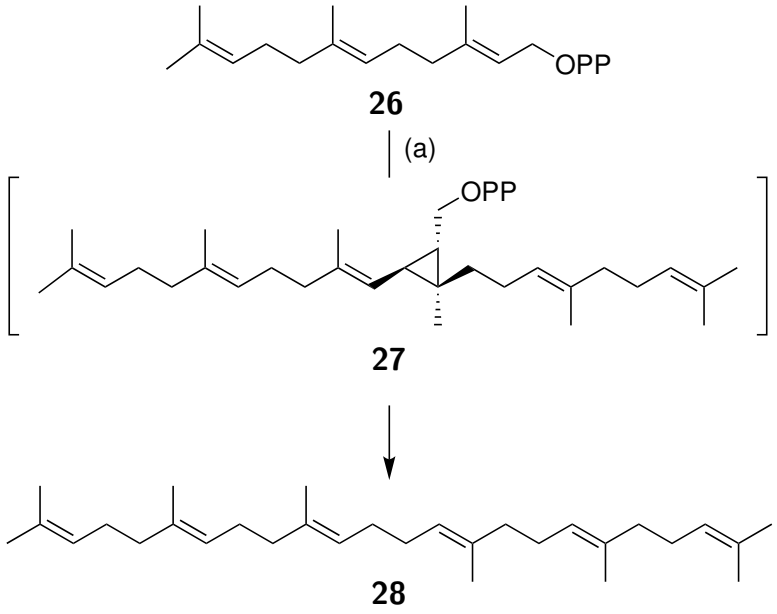
elimination gives isopentenyl pyrophosphate (IPP; **23**), the active monomer used in chain elongation.



Scheme 2: Biosynthesis of isopentenyl pyrophosphate (IPP) and the polyprenyl pyrophosphates:[11] (a) acetyl-CoA acetyltransferase; (b) HMG-CoA synthase; (c) HMG reductase; (d) Mevalonate kinase, phosphomevalonate kinase; (e) pyrophosphomevalonate decarboxylase.

From here, a molecule of IPP can be isomerised to dimethylallyl pyrophosphate (DMAPP), which can then be chain extended to geranyl pyrophosphate (**25**) and, in turn, longer compounds like farnesyl pyrophosphate (**26**), by condensing with IPP through the action of prenyl transferases. These polyprenols are then rearranged, cyclised and functionalised by further enzymes to produce all terpenoids. Squalene (**28**), for example, is produced by the tail-to-tail condensation of two molecules of farnesyl pyrophosphate (**26**) by squalene

synthase (Scheme 3). Squalene is then cyclised and enzymatically transformed into all the natural steroids.



Scheme 3: Two equivalents of farnesyl pyrophosphate (**26**) condense to form squalene (**28**) via presqualene pyrophosphate (**27**) under the action of squalene synthase. Adapted from ref. 12.

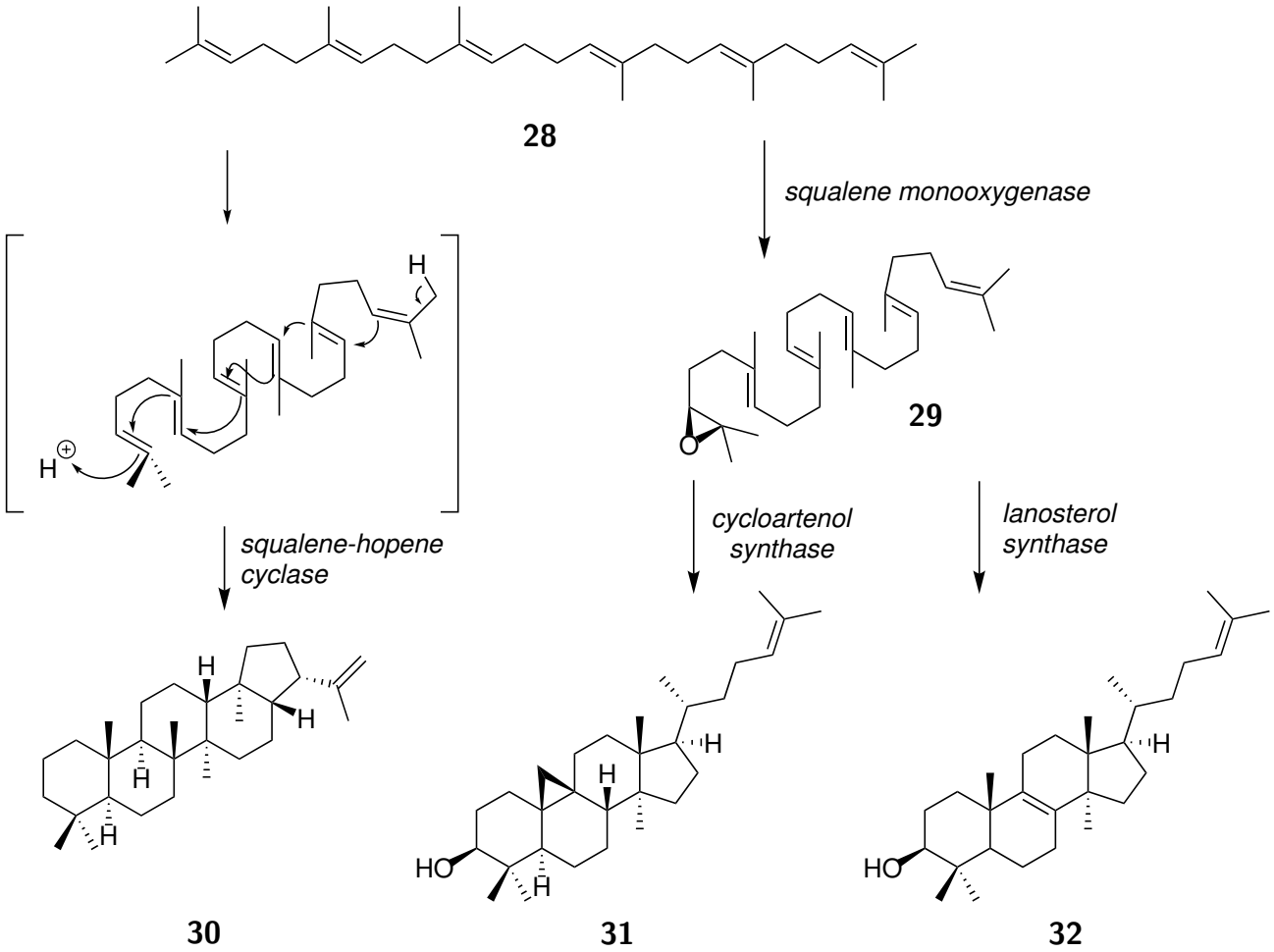
1.3 Polyene cyclisations

The most important chemical modification that linear polyprenol compounds undergo is cyclisation. From straight-chain precursors, biology produces myriad stereochemically rich compounds: most notably, steroids that are found in all life forms and many secondary metabolites used for plant defence and signalling. Humans have found many uses for this diverse family of chemicals.

The biosynthesis of steroids is likely the most well-studied of these cyclisation pathways (Scheme 4).[11] Two molecules of farnesyl pyrophosphate (**26**) obtained via the mevalonate pathway are condensed, producing squalene (**28**). In prokaryotes, squalene is directly converted to hopene (**30**) by the enzyme squalene-hopene cyclase. In eukaryotes, squalene is epoxidised by squalene monooxygenase and then protonation of epoxide **29** initiates polyene cyclisation. This is done by cycloartenol synthase in plants, producing cycloartenol (**31**); in animals and fungi, lanosterol synthase produces lanosterol (**32**). Enzymatic modification of these substrates provides the wide variety of steroids found in

nature.

Given the direct nature and atom economy of this reaction, synthetic chemists have developed its use in the laboratory to provide an expedient chemical synthesis of natural products and analogues that are medicinally relevant.[12] While these biomimetic methodologies are generally not able to achieve the same exquisite stereoselectivity as biosynthesis under enzymatic control, they hold the advantage of being having a far wider scope. In particular, biosynthetic polyene cyclisation cascades must be initiated by a proton or ring-opening of an epoxide. Synthetic chemists may employ these tactics or use more exotic electrophiles, including bromonium ions and mercury(II) salts.

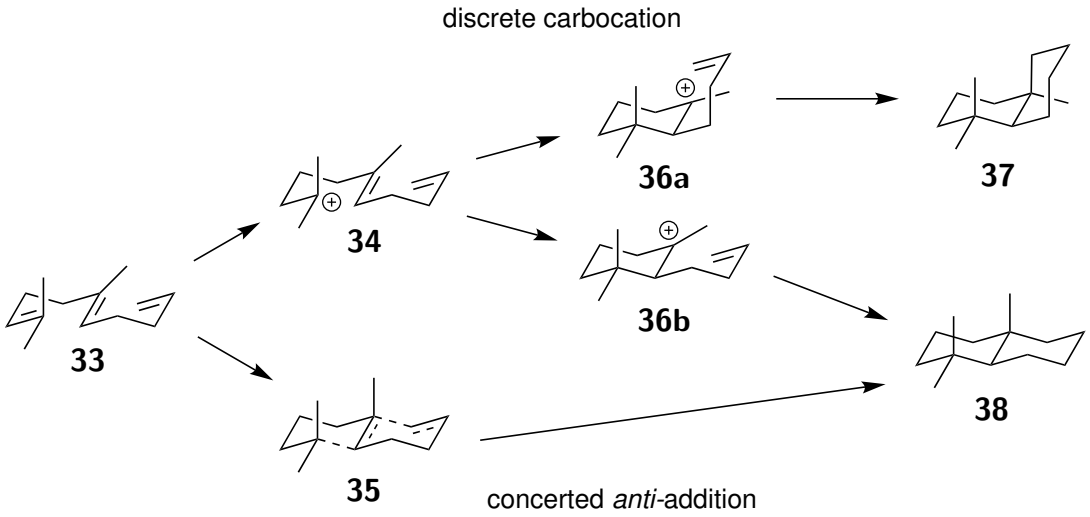


Scheme 4: Steroid biosynthesis to hopene, cycloartenol and lanosterol. Adapted from ref. 12.

1.3.1 Acid-initiated polyene cyclisation

Investigation of the acid-initiated cyclisation of dienes and polyenes dates back to the 1950s.[12] The discovery of the biogenetic isoprene rule and the recognition that 1,5-dienes could cyclise led to fervent discussion of the mechanism of these cyclisations. Two likely courses can be taken. The reaction could proceed through a series of discrete carbocations or a concerted, charge delocalised transition state.[12] [14]

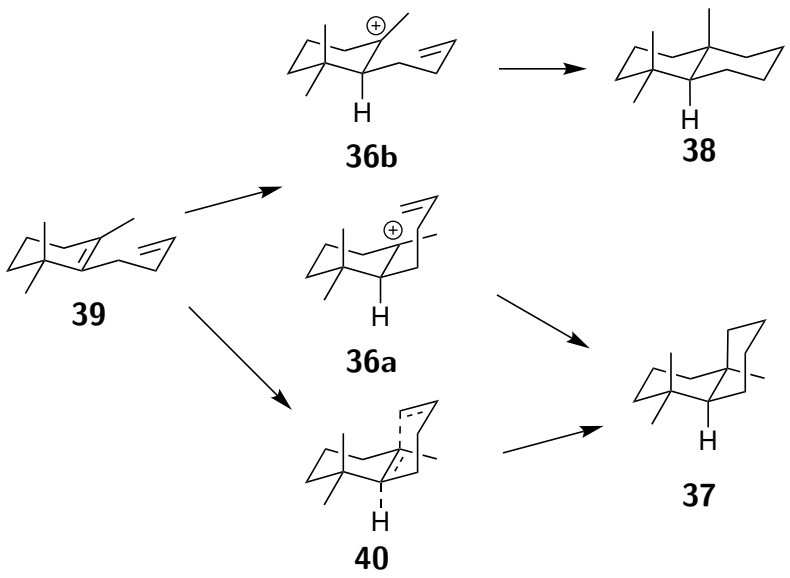
The reaction pathway has important ramifications the for stereochemistry of the cyclised product.[12] [14] Take, for example, the cyclisation of triene **33** (Scheme 5). Protonation of the alkene may lead first to carbocation **34**, then attack by the proximal alkene leads to either conformation **36a** or **36b**. Intermediate **36a** will lead to the *cis*-decalin **37**, while **36b** will lead to the *trans*-decalin **38**. If the reaction occurs via a concerted transition state **35**, *anti*-addition enforces the stereospecific generation of *trans*-decalin **38**.



Scheme 5: Cyclisation of cyclohexene **33** gives both diastereomers **37** and **38** if proceeding through a discrete mechanism but only *trans* diastereomer **38** through a concerted mechanism.[12] [14]

Similarly, consider cyclohexene **39** (Scheme 6). If the reaction occurs using a discrete carbocation, again both diastereomers **36a** and **36b** are possible, leading to the *cis* isomer **37** and *trans* isomer **38**, respectively.[12] [14] Concerted *anti*-addition will instead go through transition state **40** and stereospecifically generate the *cis* isomer **37**.

The mechanism that is more likely was the subject of much debate. Robinson was sure that concerted *anti*-addition was preferred.[12]

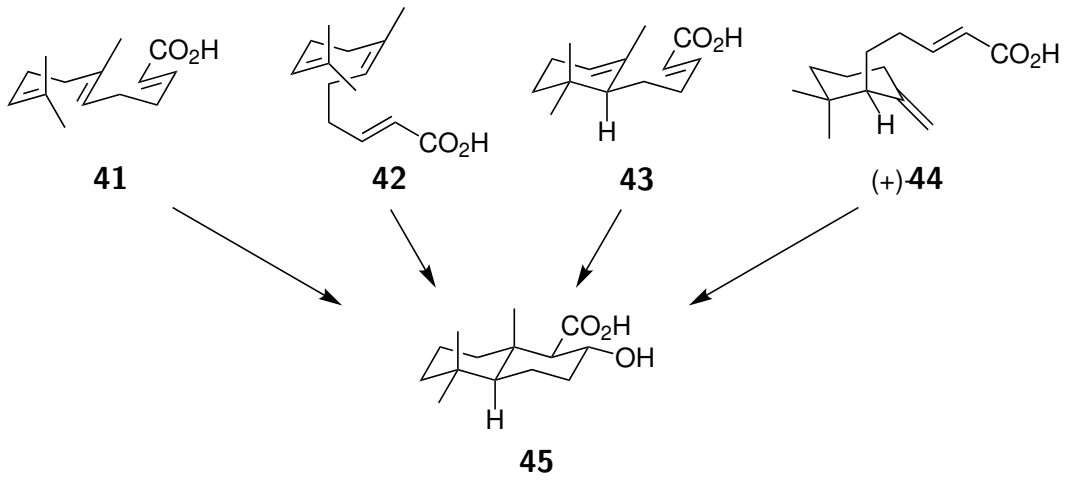


Scheme 6: Cyclisation of **39** gives both diastereomers **37** and **38** through a discrete mechanism but only *cis* diastereomer **37** through a concerted mechanism.

> *"I would like to give a warning, from a theoretical point of view, about all the carbonium ion mechanisms. They are all probably concerted reactions with a beginning and an end, and the reason you write down your carbonium mechanisms in the way you do is chiefly because in writing down on paper you are bound to write something first and then something else afterwards, and the human mind is not quick and clever as the enzyme."* – Sir Robert Robinson [12]

This situation was complicated by the results put forward by Eschenmoser (Scheme 7).[15] Treatment of apofarnesic acid (**41**) with a formic acid/sulfuric acid mixture gave decalin **45** as a single diastereomer, most consistent with the concerted mechanism. Partially cyclised cyclohexene **42** should produce the *cis*-decalin, but *trans*-decalin **45** was the only product. The (*Z*)-alkene **43** should not undergo concerted *anti*-addition, but again decalin **45** was seen. Perhaps the best evidence in support of the discrete cationic mechanism is that enantiopure compound (+)-**44** gave the *racemate* of decalin **45**. Certainly in this latter cyclisation, a discrete carbocation must be invoked, resulting in racemisation of the substrate.

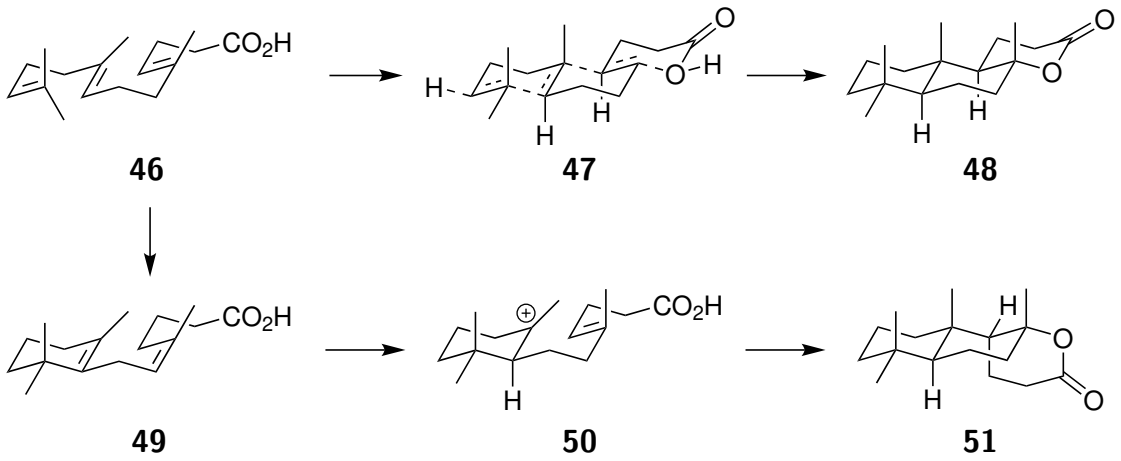
We see both mechanisms occurring in the cyclisation of farnesylacetic acid (**46**) by Stork (Scheme 8).[15] Farnesylacetic acid produced ambreinolide (**48**) as a single diastereomer upon treatment with tin(IV) bromide, but the treatment of cyclohexene **49** under the same conditions gives the *trans*-decalin compound isoambreinolide (**51**). Cyclohexene **49** would be invoked as a likely intermediate in the cyclisation of acid **46** in a discrete



Scheme 7: Eschenmoser's cyclisations of apofarnesic acid (**41**) and isomers to decalin **45**.[15]

carbocationic mechanism, but cyclisation of cyclohexene **49** by a concerted mechanism should produce the *cis*-decalin compound. Thus cyclisation of farnesylacetic acid occurs by the concerted transition state **47**, but cyclohexene **49** must be cyclised via the discrete carbocation **50**.[12]

From the results discussed above, it is clear that the identity of the substrate is critical to determining the mechanism by which these cyclisations occur.

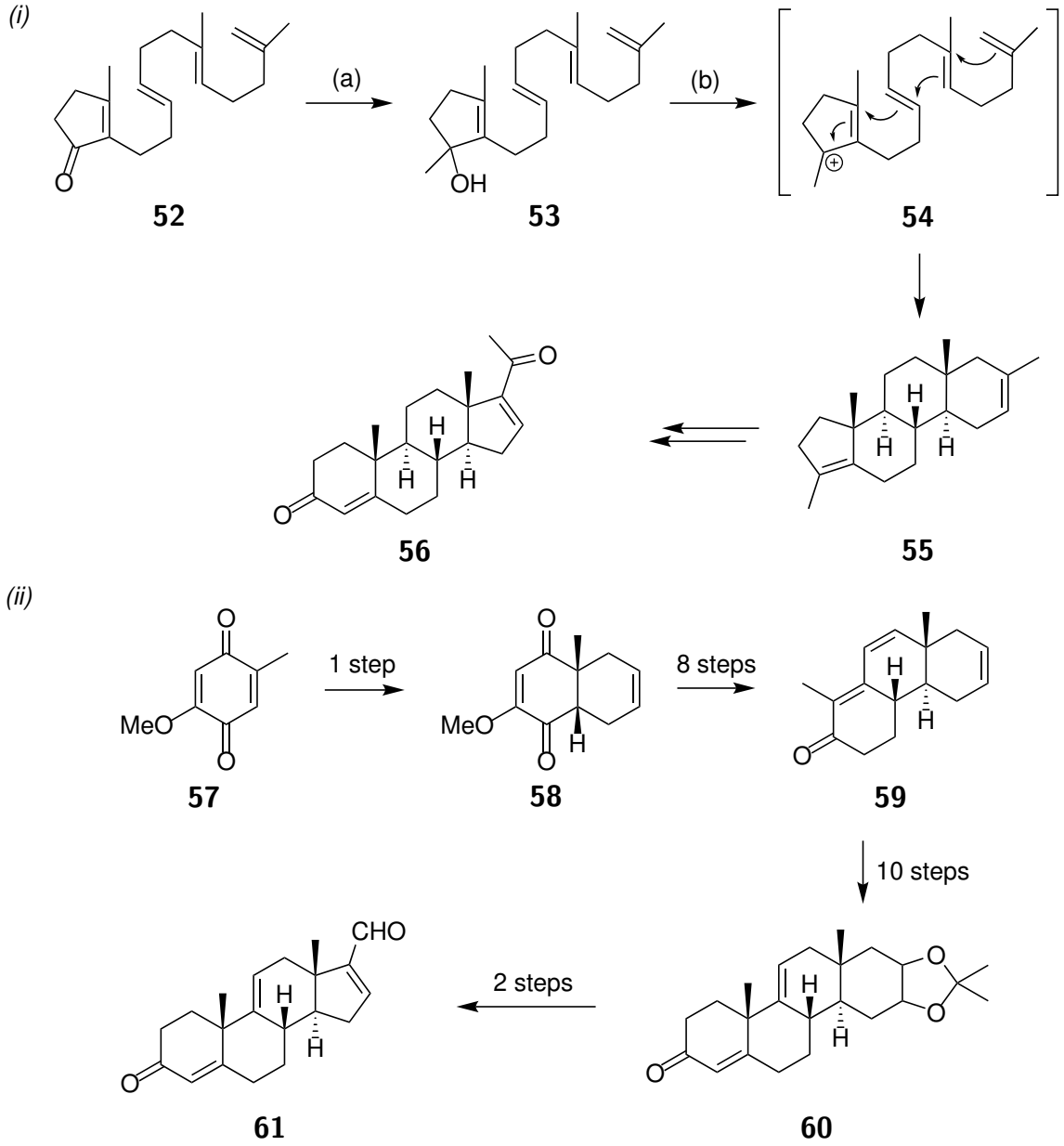


Scheme 8: Stork's polyene cyclisation to ambreinolide (**48**) and isoambreinolide (**51**).[15]

Acid-catalysed polyene cyclisation is a useful tool in total synthesis. The stereoselective generation of so many carbon-carbon bonds is incredibly useful.

Johnson devised the first biomimetic synthesis of the steroid framework in 1968 with a total synthesis of *dl*-dehydroprogesterone (Scheme 9).[16] Cyclopentenone **52** was produced in 6 steps, with the subsequent addition of methyllithium producing a tertiary

allyl carbinol **53**. This alcohol was readily eliminated in the presence of trifluoroacetic acid in dichloromethane, forming carbocation **54** that initiated the polyene cyclisation to form compound **55** in 30% yield. It should be noted that this modest yield represents the elimination of an alcohol and the formation of 3 rings with 3 new carbon-carbon bonds in a highly diastereoselective manner. From here, expansion of the cyclopentene A ring and contraction of the cyclohexene D ring gave *dl*-dehydroprogesterone (**56**) in a relatively efficient manner.

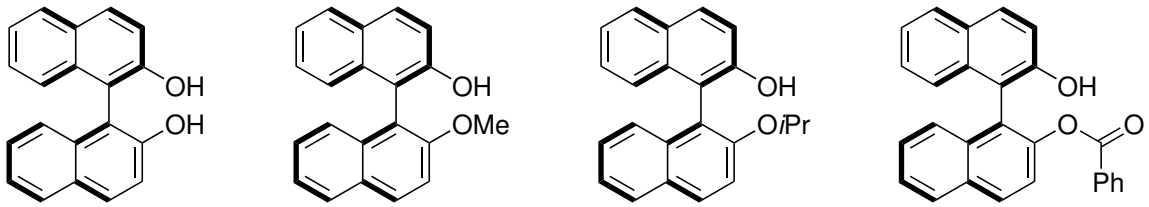


Scheme 9: (*i*) Johnson's 1968 synthesis of *dl*-16,17-dehydroprogesterone (**56**).[16] (a) MeLi (b) CF_3CO_2H. (*ii*) Abridged synthesis of cholesterol by Woodward from starting material **57** to intermediate **61**.[17] Eight steps were needed to generate the A-ring and twelve to make the D-ring with the desired stereochemistry. Polyene cyclisation is far quicker.

That work should be compared to the laborious syntheses of cholesterol performed by the

groups of Woodward (Scheme 9*ii*)[17] and Robinson[18] in the previous decade, in which each new ring was synthesised independently, with careful (albeit brilliant) use of strategy to control the stereochemistry at each new ring junction. Polyene cyclisation allowed for the same framework to be built up far more quickly: while Woodward's synthesis of cholesterol took 35 steps and Robinson's took 68, Johnson's synthesis of the similar steroid progesterone took only 18 operations. A single reaction step produces four rings with the desired stereochemistry and all of this without much of the carbon-carbon bond producing chemistry we enjoy today.

Attempts have been made to render this acid catalysed polyene cyclisation process enantioselective using chiral Lewis-assisted Brønsted acids (LBA), pioneered by Ishihara and Yamamoto.[19] The first generation of these acids began with the simple monoethers of (*R*)-BINOL (**62**) shown in Figure 5, complexed to tin(IV) chloride. The complexed tin(IV) increases the acidity of the BINOL, which provides a sterically demanding environment for delivery of a proton from a single face of the alkene.

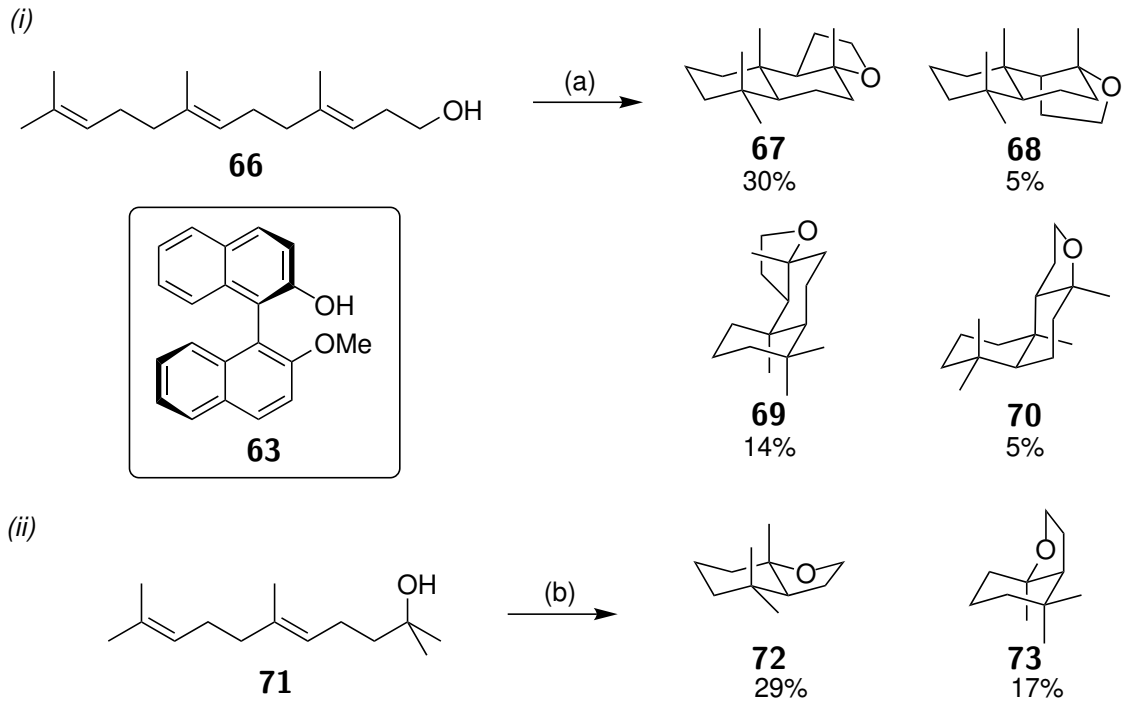


62 **63** **64** **65**

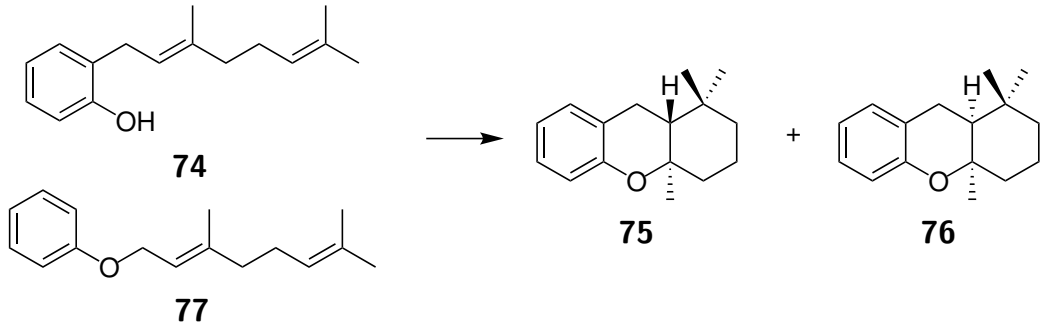
Figure 5: Ishihara and Yamamoto's chiral Lewis-assisted Brønsted acid catalysts derived from (*R*)-BINOL (**62**).[19]

The first target for these chiral LBAs was (–)-ambrox (**67**; Scheme 10*i*).[19] Treatment of homofarnesol (**66**) with tin(IV) chloride and ligand **63** suffered from poor diastereoselectivity and enantioselectivity: a 54% yield of a mixture of diastereomers was obtained, with ambrox being obtained in only 42% ee. The same reaction performed with geranylacetone derived tertiary alcohol **71** led to good diastereoselectivity in 49% ee (Scheme 10*ii*).

Ishihara and Yamamoto extended this methodology to the benzopyrans **75** and **76** (Scheme 11).[19] In the cyclisation of 2-geranylphenol (**74**), excellent yields and good diastereoselectivities were seen, but again enantioselectivity was only modest. The diastereoselectivity was probably impacted by hyperconjugative factors, which will later be seen to hamper our efforts in the synthesis of the taiwaniaquinoids.



Scheme 10: (*i*) Chiral cyclisation to produce (–)-ambrox (**67**). (a) **63**, $SnCl_4$, CH_2Cl_2, –78 °C, 3 days. (*ii*) Cyclisation of tertiary alcohol **71** (b) **63**, $SnCl_4$, CH_2Cl_2, –78 °C, 1 day.



Scheme 11: Enantioselective cyclisation of polyene **74** or **77**. Conditions: Table 2

Table 2: Enantioselective cyclisation of polyene **74**.[19] Conditions: 1 eq. (*R*)-LBA, CH_2Cl_2, –78 °C, 1 day. [a] No isolated yield reported. [b] (*Z*)-alkene used. [c] Alternative substrate **77** used.

Catalyst	**75**		**76**	
	Yield	ee	Yield	ee
(*R*)-**62**·$SnCl_4$[a]	84%	36%	16%	32%
(*R*)-**63**·$SnCl_4$	>62%	50%	>18%	34%
(*R*)-**65**·$SnCl_4$	87%	54%	5%	–
(*R*)-**62**·$SnCl_4$[b]	0%	–	33%	18%
(*R*)-**65**·$SnCl_4$[c]	79%	69%	<2%	–

Ishihara and Yamamoto pursued a second generation of BINOL-based LBA catalysts for polyene cyclisations.[20] These catalysts are available in six steps from BINOL and feature a five-member chelate between the scaffold (e.g. **78**) and tin(IV) chloride. Higher yields and enantioselectivities were seen with these catalysts, with Ishihara and Yamamoto showing their success with a few short total syntheses of polycyclic natural products.

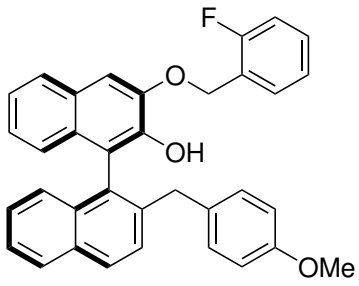
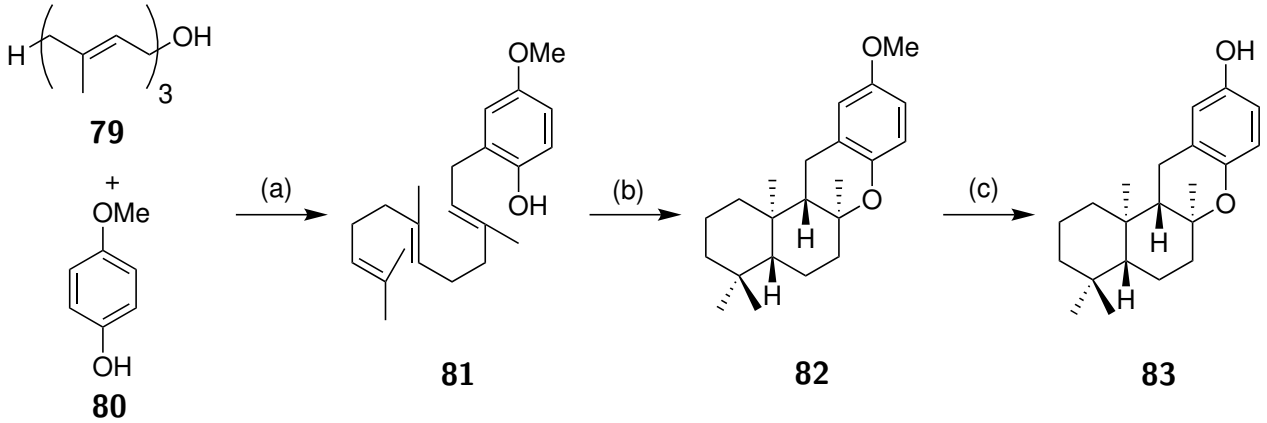


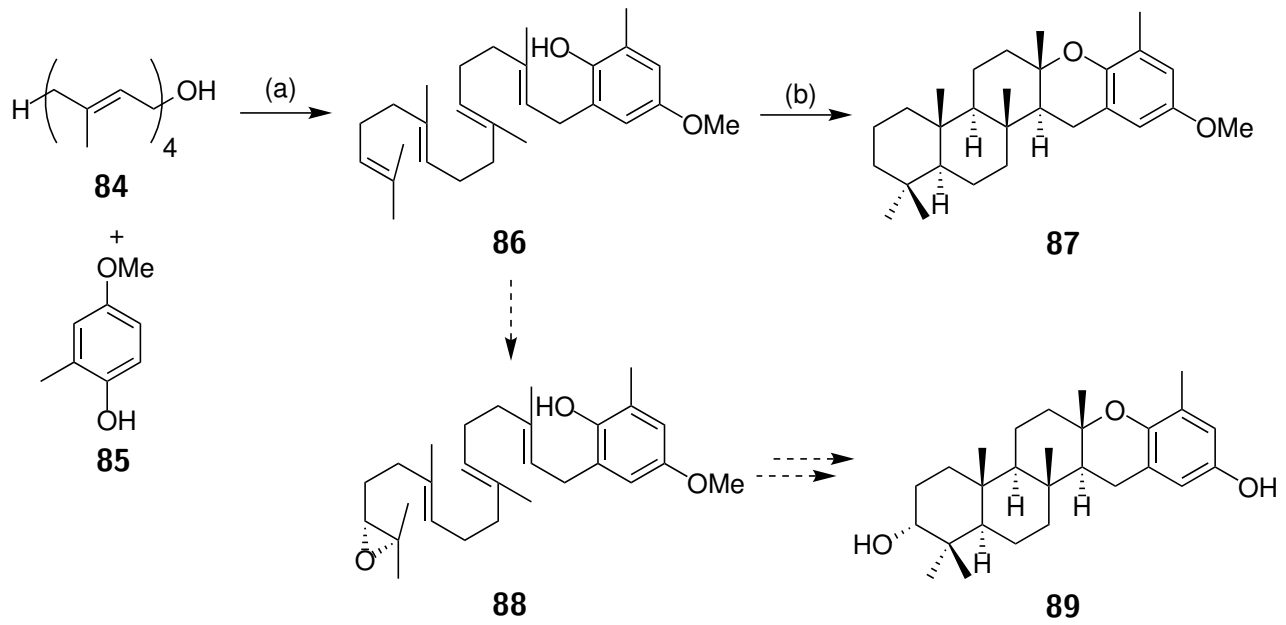
Figure 6: Second generation LBA catalyst scaffold **78**.[20]

(–)-Chromazonarol (**83**) was produced in a mere three steps (Scheme 12).[20] Direct Friedel-Crafts alkylation of 4-methoxyphenol (**80**) with farnesol (**79**) using boron trifluoride etherate in dioxane gave a modest yield of the coupled product. Cyclisation using (*R*)-**78**·$SnCl_4$ then provided the fully cyclised compound **82** in a single step, with good enantioselectivity and decent diastereoselectivity. However, using the opposite enantiomer (*S*)-**78**·$SnCl_4$ gave a lower yield with a nearly 1:1 mixture of diastereomers and only 40% ee. From here, removal of the methyl ether gave (–)-chromazonarol in total 10% yield.[20] This is astonishing: from the linear polyene farnesol and an arene, a complex natural product with four rings and four stereocentres is produced in only three steps. Moreover, this was all done with over 90% ee.



Scheme 12: Ishihara and Yamamoto's synthesis of (–)-chromazonarol.[20] (a) BF_3·OEt_2, dioxane, 20 h, 25%. (b) **78**, $SnCl_4$, PhMe, –78 °C, 2 d; then TFA, $SnCl_4$, *i*$PrNO_2$, –78 °C, 1 d. 40%, 69% dr, 88% ee. (c) $B(C_6F_5)_3$, Et_3SiH, hexane, 1 d; then Bu_4NF, THF, 0 °C, 0.5 h 97%.

Ishihara and Yamamoto also produced pentacyclic compound **87** in only 2 steps (Scheme 13).[20] Coupling 4-methoxy-2-methylphenol (**85**) with geranylgeraniol, this time using scandium(III) triflate in toluene, gave the desired polyene **86** in modest yield. Treating with (*R*)-**78**·$SnCl_4$ gave the desired compound (–)-**87** in a 1:1 mixture with an undescribed diastereomer, again in high ee but poor yield. This 22% yield still represents the formation of four rings and six stereogenic centres.



Scheme 13: Synthesis of (–)-deoxytaondiol methyl ether (**87**).[20] Conditions: (a) $Sc(OTf)_3$, PhMe, rt, 39%. (b) (*R*)-**78**, $SnCl_4$, PhMe, –78 °C, 2 d. 22%, 48% dr, 90% ee.

We should also note that compound (–)-**87** is an analogue of the natural product taondiol (**89**). These complexes perform *direct* cyclisation which does not install an oxygen at the sp^3 carbon, but (–)-taondiol could be produced quite simply by intercepting intermediate **86**. Installation of a chiral epoxide (**88**), then epoxide-opening cationic cyclisation and ether cleavage would generate the natural product (–)-**89** in 4 steps. To our knowledge, no synthesis of compound (–)-**89** in this manner has been reported. Ironically, before the advent of this chiral acid approach, the only reported method of producing compounds like (–)-**87** was to initiate cyclisation via a chiral epoxide, followed by deoxygenation. We will discuss this approach later.

The enantioselectivity in these transformations is proposed to arise as shown in Figure 7.[20] As the catalyst approaches the terminal isoprenyl group, the R_1 benzyl substituent of the catalyst clashes with the rest of the polyprenyl chain (R_3) in conformation **90b**. Coordination from the opposite face, as in conformation **90a** minimises steric

hindrance, then the acidic proton is delivered from inside this cavity, generating preferentially the desired enantiomer.

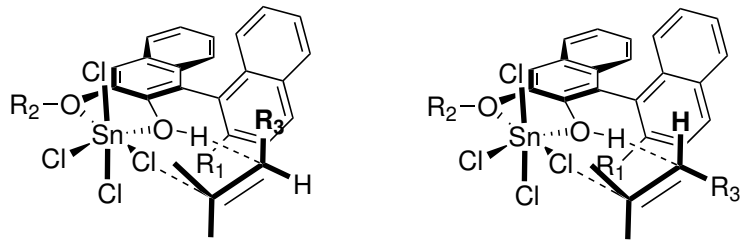


Figure 7: Proposed transition state geometry for the second generation LBAs.[20]

Corey investigated LBAs along similar lines. *o,o′*-Dichloro-BINOL (**91**) was complexed with antimony pentachloride and reacted with a series of homogeranylarenes and homofarnesylarenes.[21] Good to excellent yields were seen across the board, while ee rarely strayed below 90%. High catalyst loadings were needed (50–100 mol%). The BINOL scaffold was easily recoverable by basic extraction and regardless, was easily obtained from BINOL. However, the high loading of toxic antimony pentachloride is undesirable.

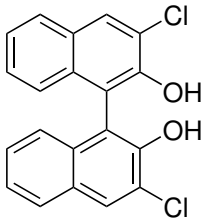


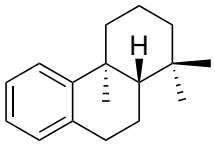
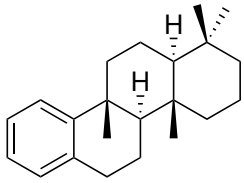
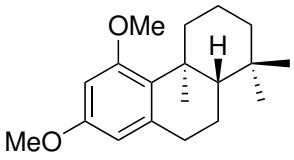
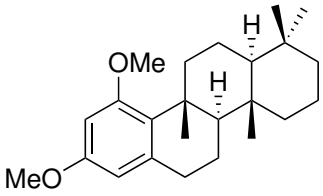
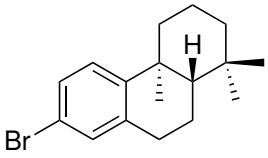
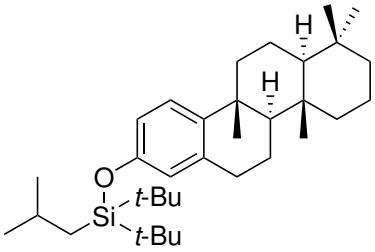
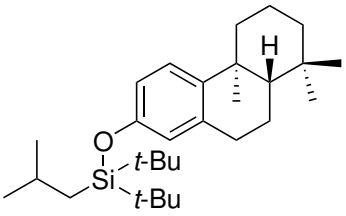
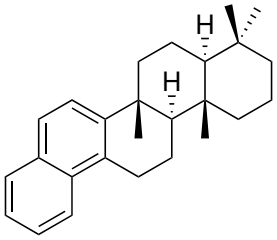
Figure 8: *o,o′*-Dichloro-BINOL (**91**).

An interesting case of polyene cyclisation is seen in Luo's cyclisation initiated by photoredox catalysis.[22] Eosin Y was used as a photocatalyst to oxidise the distal alkene, forming a radical cation that can undergo cyclisation. Although the reaction was initiated by a one-electron process, the cyclisation itself probably proceeded via the normal cationic two-electron pathway.

It is apparent that acid catalysed cyclisation of polyenes is a direct approach to carbocyclic frameworks. Oxygenation or halogenation of activated C–H groups in these cyclised compounds is likely to be useful for adding synthetic handles to an unfunctionalised system. This may be useful in analogue generation via diverted total synthesis.

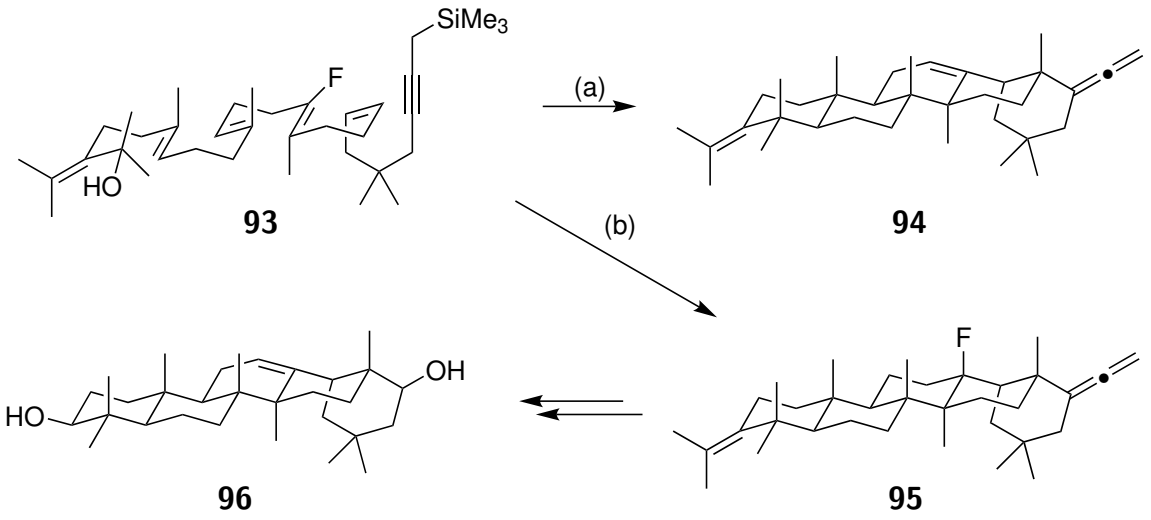
However, it is pertinent to note that there are issues with acid-catalysed polyene cyclisations. For one, strong acids and forcing conditions are often required. In later

Table 3: Corey's enantioselective polyene cyclisation.[21]

#	Substrate	Yield	ee	#	Substrate	Yield	ee
92a		80%	91%	**92e**		70%	90%
92b		85%	87%	**92f**		76%	84%
92c		82%	90%	**92g**		74%	90%
92d		89%	92%	**92h**		78%	86%

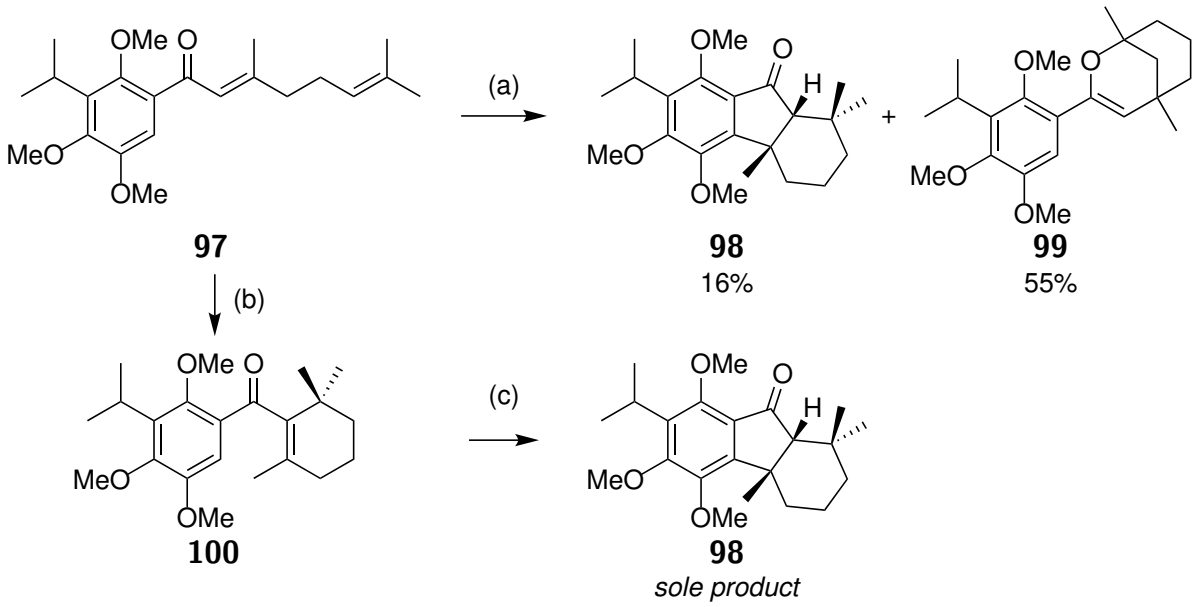
examples, we will see polyenes reacted in 95% sulfuric acid or catalytic boron trifluoride etherate at 100 °C. This necessarily limits the substrate scope, with elimination of labile leaving groups being a primary concern. A judicious choice of acid can help; for example, in Johnson's cyclisation of monofluorinated polyene **93**, tin(IV) chloride led to elimination of fluoride during cyclisation, producing alkene **94**.[23] Instead, treatment with trifluoroacetic acid gave instead the alkyl fluoride **95** (Scheme 14). Early elimination of the fluoride thwarted Johnson's endgame and only alkyl fluoride **95** was able to produce the final product, sophoradiol (**96**).

Cationic rearrangements are also possible under these reaction conditions. Large amounts of an undesired side product are often seen, such as in Chiu's synthesis of taiwaniaquinol D (Scheme 15).[24] This happened at a relatively late stage of Chiu's synthesis and the side products could not be recycled to provide useful intermediates. Ensuring that the carbocation reacts expectedly, before any rearrangement can occur, is important. When Chiu treated polyene **97** with trimethylsilyl trifluoromethanesulfonate, a mixture of



Scheme 14: Johnson's polyene cyclisation towards sophoradiol (**96**).[23] (a) $SnCl_4$, CH_2Cl_2, –78 °C, 10 min, 50%. (b) TFA, CH_2Cl_2, –78 °C, 15 min, 31%.

desired compound **98** and *O*-cyclised compound **99** was observed.[24] Treating polyene **97** instead with tin(IV) chloride first generated only the monocyclised compound **100** which was subsequently reacted with triflic acid to furnish the fully cyclised compound **98**.



Scheme 15: Polyene cyclisation can lead to significant amounts of rearrangement products.[24] (a) TMSOTf, $MeNO_2$, Δ, 1 h. *(note: unoptimised conditions)* (b) $SnCl_4$, $MeNO_2$, rt, 89%. (c) TfOH, $MeNO_2$, 71%.

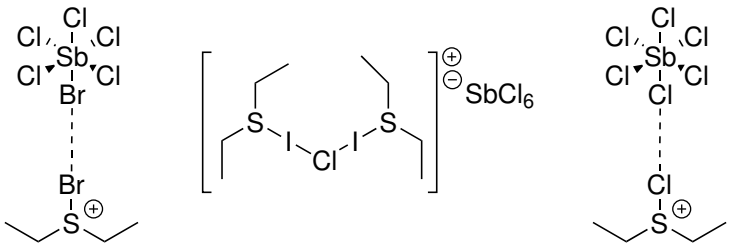
The proton is not the only electrophile that can react with alkenes. Other electrophiles can similarly generate the desired carbocation which can undergo attack by a polyene in the same manner.

1.3.2 Halonium-mediated polyene cyclisation

A number of groups, including the McErlean group, have sought to initiate a cationic polyene cyclisation by electrophilic attack by a halonium source such as *N*-bromosuccinimide. Electrophilic bromine sources such as *N*-bromosuccinimide typically do not perform this reaction by themselves, thus requiring new strategies and reagents.[25]

Antimony compounds

Snyder's group developed bromodiethylsulfonium bromopentachloroantimonate (BDSB; **101**) as a highly electrophilic bromonium source to be used in these π-cationic cyclisations.[26] The reagent is prepared by mixing bromine, diethylsulfide and antimony pentachloride leading to the precipitation of an orange complex which is stable for years at –20 °C and at least a week at room temperature in a sealed vial.



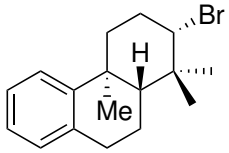
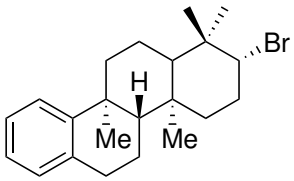
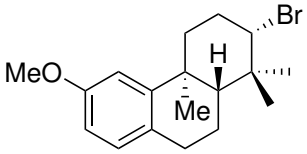
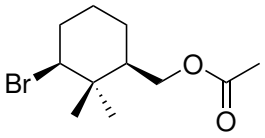
101 **102** **103**

Figure 9: Snyder's antimony-based halonium sources:[9] BDSB (**101**), IDSI (**102**), CDSC (**103**).[9]

Snyder compared the yields obtained from a number of similar protocols and found that BDSB gave superior yields in every case shown (Table 4).[26] Importantly, it was more general than any of the other protocols tested and could be used on 5 millimole scale with only a modest reduction in yield and a slight increase in diastereoselectivity. In general, BDSB is able to perform much of the same chemistry as *N*-bromosuccinimide, including electrophilic aromatic substitution, but appears to be particularly reactive with alkenes, leading to fewer side products and rapid reaction times.

Snyder suggested that the antimony counterion is especially effective at sequestering bromide compared to other sulfur-bromonium complexes, forming a tight ion pair that makes BDSB a superior bromonium source.[26] Further, an acidic byproduct is produced during the course of these reactions (likely protonated diethyl sulfide) which further

Table 4: A selection of reactions comparing BDSB and other bromination protocols.[26]

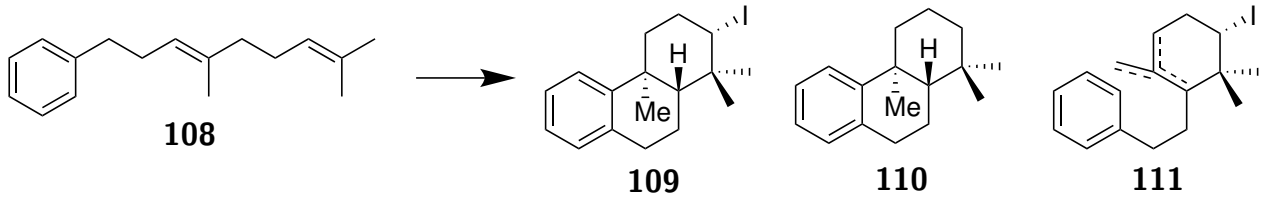
#	Product	Yield			
		BDSB $MeNO_2$	$Br_2/AgBF_4$ $MeNO_2$	TBCO MeCN	NBS/Ph_3P CH_2Cl_2
104		75%	9%	27%	13%
105		58%	<5%	14%	<5%
106		76%	11%	27%	20%
107		80%	22%	<5%	<5%

promotes cyclisation: this avoids a common problem with other protocols where partially cyclised products often predominate and complete cyclisation only takes place after treating with additional acid, commonly chlorosulfonic or methanesulfonic acid.

Importantly though, while it is itself a stable odorless solid, preparation of BDSB requires the use of diethylsulfide, which has a foul odor and antimony pentachloride, which hydrolyses to hydrogen chloride in air and has the toxic and environmentally damaging properties of all antimony compounds.[26] Stoichiometric amounts of BDSB must be used.

Snyder's group has also developed the similar IDSI (**102**) and CDSC (**103**) to generate the corresponding iodinated and chlorinated compounds.[9] These are produced in the same way as BDSB, replacing bromine with iodine and chlorine respectively. While CDSC has the same structure as BDSB, IDSI is in fact a chlorine-linked dimer. IDSI is far less stable than BDSB: it must be stored below –20 °C and will degrade within 30 min at 25 °C. However it will typically engage in the same reactions with similarly high yields and diastereoselectivity. These reagents compared favourably to previous protocols, as partially cyclised compounds and non-halogenated compounds were prominent

byproducts in the other protocols.



108 **109** **110** **111**

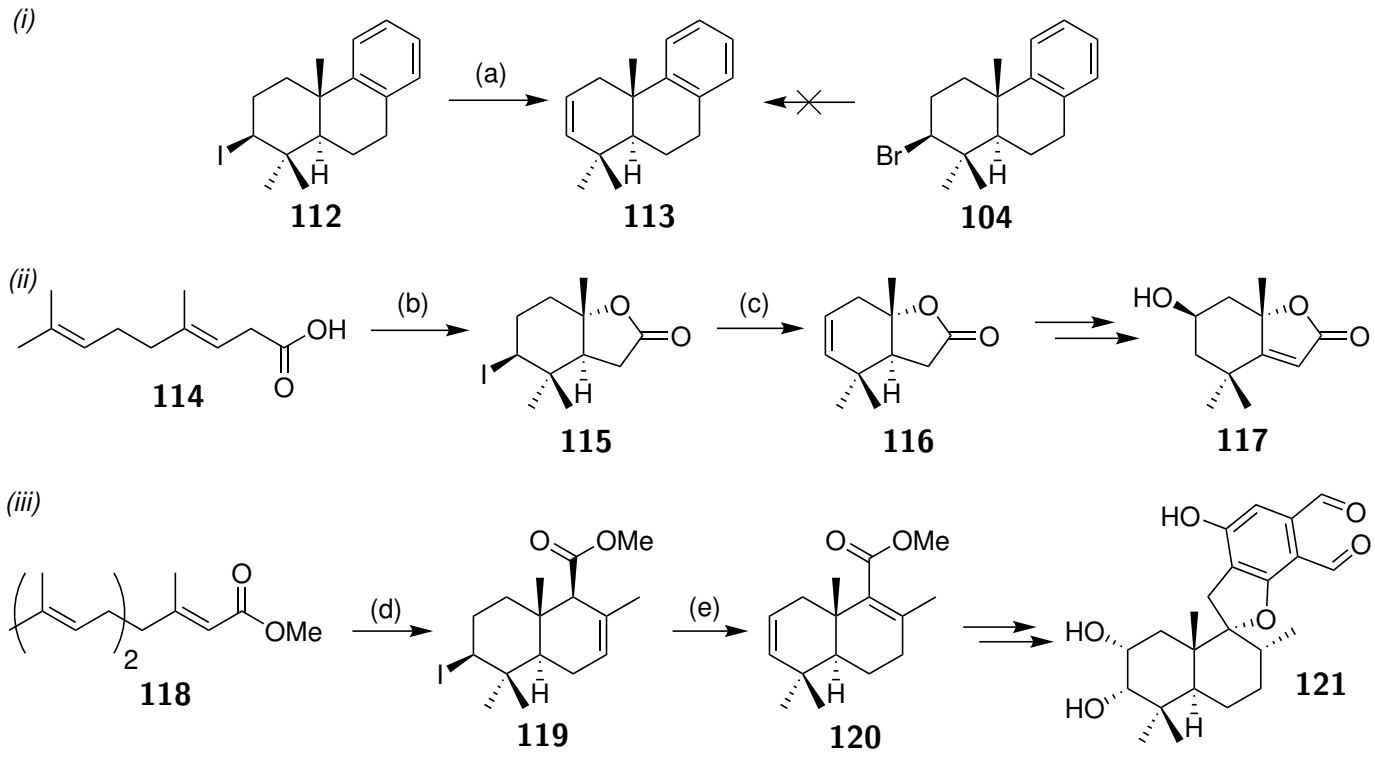
Table 5: Comparison of IDSI to previous protocols.[9]

Entry	Conditions	**109**	**110**	**111**
1	IDSI, $MeNO_2$, –25°C, 5 min	93%	-	-
2	Ipy_2BF_4, HBF_4, CH_2Cl_2, –40°C, 3 h	41%	6%	7%
3	NIS, Ph_3P, CH_2Cl_2, –78 °C, 24 h; –40 °C, 6 h	<5%	0%	64%

While no natural products have been isolated with the iodocyclised framework, Snyder notes the higher reactivity of the resulting alkyl iodides which may aid in further functionalisation. For instance, iodide **112** was eliminated by DBU in pyridine at reflux, while the bromide **104** remained stable under these conditions (Scheme 16*i*).[9] To show the advantages of this protocol, Snyder repeated the syntheses of several compounds which rely on cyclisation and elimination to produce a cyclic alkene.

In the synthesis of loliolide (**117**; Scheme 16*ii*), Snyder intercepted intermediate **116** produced by Rouessac in 3 steps using a mercury(II) triflate cyclisation before elimination in 25% yield. Snyder produced intermediate **116** using IDSI in 77% yield with one fewer step.[9] McMurry produced intermediate **120** in the synthesis of K-76 (**121**) in 4 steps in 53% yield. Snyder's protocol produced intermediate **120** in 2 steps in 66% yield (Scheme 16*iii*).[9] In both cases, avoiding a highly toxic organomercury intermediate is also desirable. In the latter case, Snyder also attempted the other cyclisation protocols listed in Table 5. Each gave a mixture of partially cyclised materials with none of the fully cyclised **120** seen.[9]

CDSC retains the analogous structure to BDSB and is similarly resistant to degradation.[9] Yields were significantly lower in these cyclisations and diastereoselectivity suffered at several carbons – most notably at the quaternary ring junction. Snyder ascribes this to the higher localisation of the chlorine atom in these intermediates than the bridged bromonium and iodonium intermediates invoked in those cyclisations.



Scheme 16: (i) Iodide **112** underwent elimination under reaction conditions but **104** did not.[9] (a) DBU, pyridine, Δ, 86%. (ii) Exploitation of elimination in the formal total synthesis of loliolide (**117**).[9] (b) IDSI, $MeNO_2$, 5 min, 79%, d.r. 19:1. (c) LiCl, DMF, 80 °C, 12 h, 97%. (iii) Formal total synthesis of K-76 (**121**).[9] (d) IDSI, $MeNO_2$, –25 °C, 5 min, 77%. (e) DBU, pyridine, Δ, 12 h, 86%.

Snyder's group produced chiral complexes **122**, **123** and **124** in an attempt to impart enantioselectivity in these transformations.[9] Unfortunately, while these complexes were almost equally competent at promoting halonium cyclisations as the achiral versions, no enantioselectivity was seen. No further reports have been made in the literature.

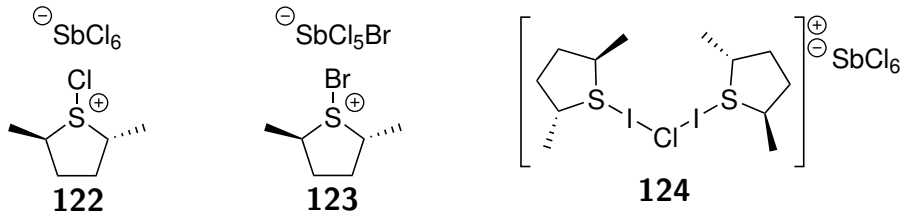


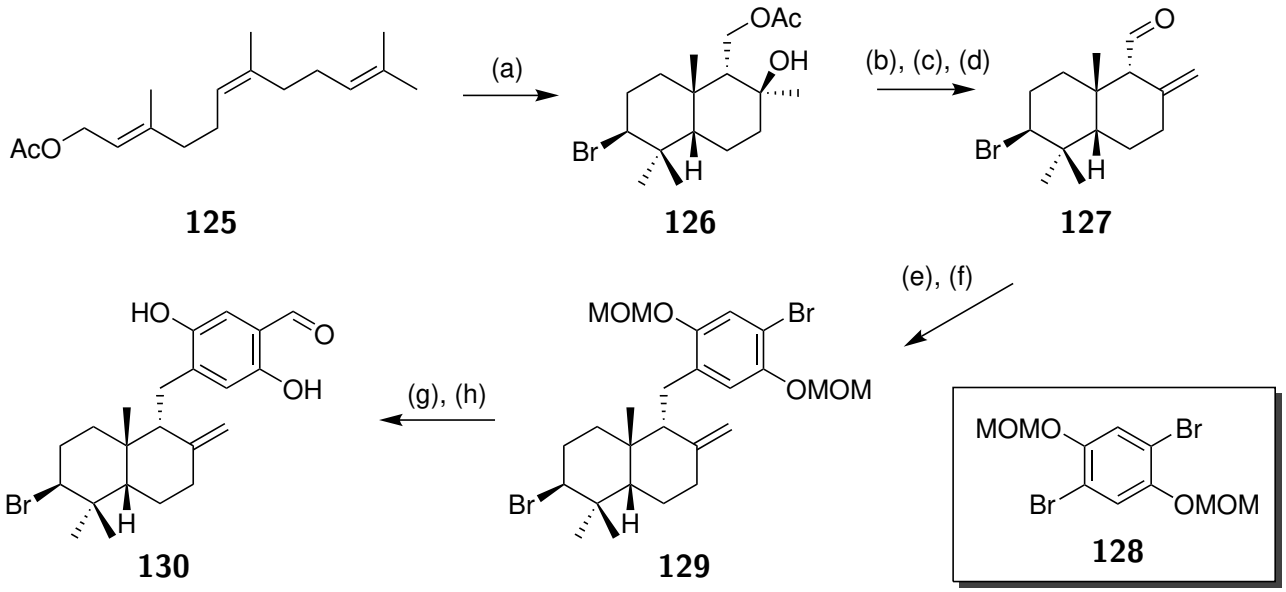
Figure 10: Snyder's chiral halonium complexes.[9]

Snyder has applied this methodology to the synthesis of a series of natural products and their close derivatives.

Firstly, the reported structure of the lead natural compound, peyssonol A (**130**) was synthesised (Scheme 17).[9] Snyder chose this compound specifically because the *cis* stereochemistry across the ring junction was unprecedented. Triene **125** was treated with

BDSB to give the *cis*-decalin **126** in modest yield, a challenging transformation due to the higher strain in the *cis* framework. The related *tert*-butyl carbonate was also subjected to these conditions with similar results.

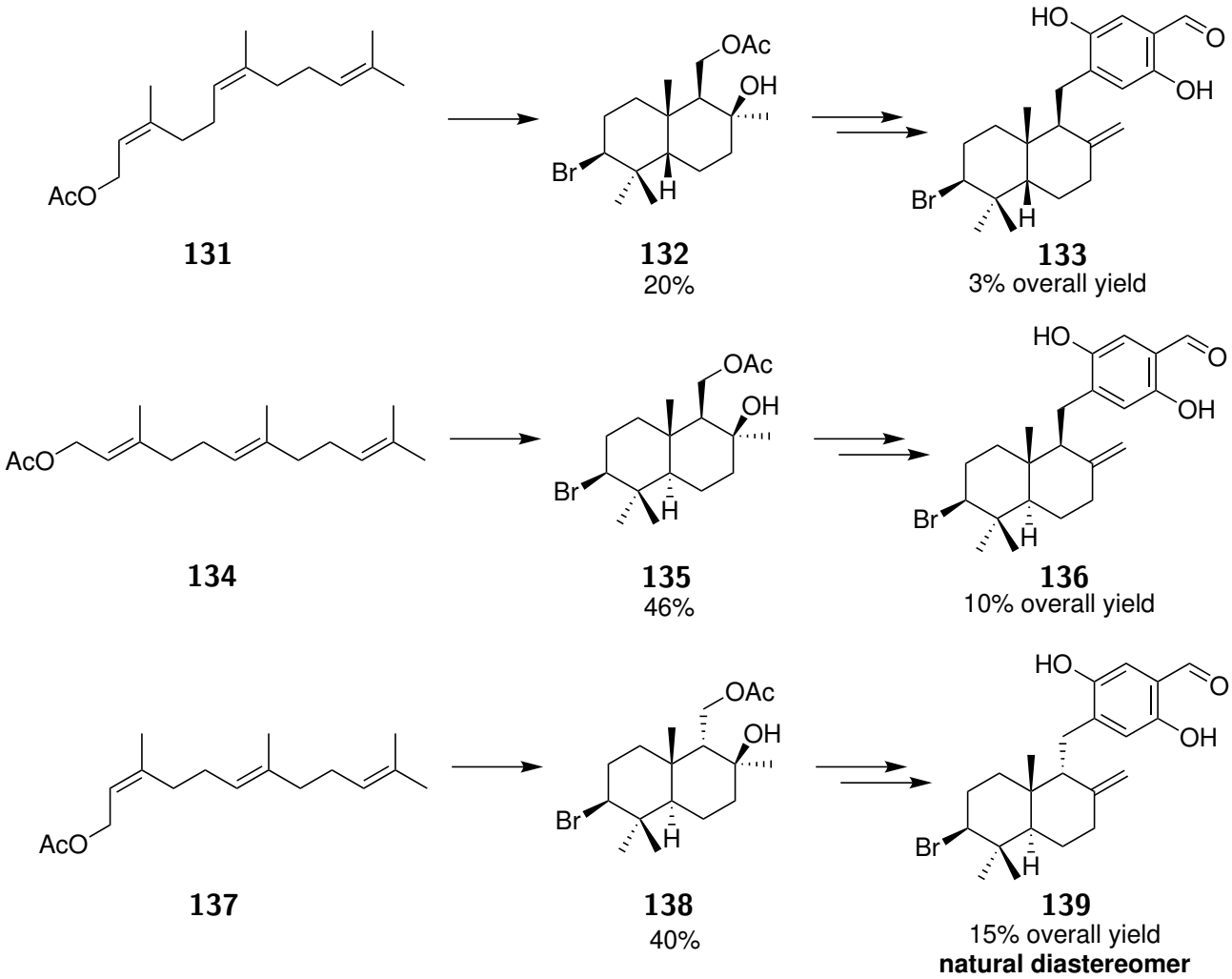
Hydrolysis, oxidation to the aldehyde and elimination to the terminal alkene gave aldehyde **127**, which was coupled with aryl bromide **128** mediated by *n*-butyllithium. Installation of the aryl aldehyde and cleavage of the methoxymethyl ethers gave the proposed structure of peyssonol A (**130**) in only 8 steps from the triene **125** in 7% yield.[9]



Scheme 17: Snyder's synthesis of the proposed natural diastereomer of peyssonol A, **130**.[9] (a) BDSB, $MeNO_2$, 0 °C, 30 s, 34%. (b) K_2CO_3, MeOH, 40 °C, 30 min. (c) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N, –78→–50 °C, 1 h. (d) $SOCl_2$, Et_3N, CH_2Cl_2, –97 °C, 1 h. 91% over 3 steps. (e) **128**, *n*-BuLi, THF, –78 °C, 20 min then **127**, –78 °C, 20 min, 63%. (f) TFA, Et_3SiH, CH_2Cl_2, 90 min, 64%. (g) *n*-BuLi, THF, –78 °C, 20 min, then DMF, –78 °C, 20 min, 62%. (h) TsOH, *t*-BuOH, 65 °C, 2 h, 91%.[9]

Upon producing the proposed structure—the first reported cyclisation of this type giving rise to *cis* stereochemistry—it was discovered that this stereochemical assignment was incorrect. From each of the other three alkene diastereomers, Snyder produced the corresponding diastereomers of peyssonol A using the same sequence (Scheme 18). *trans*-Decalin **139** was shown to be the natural diastereomer.

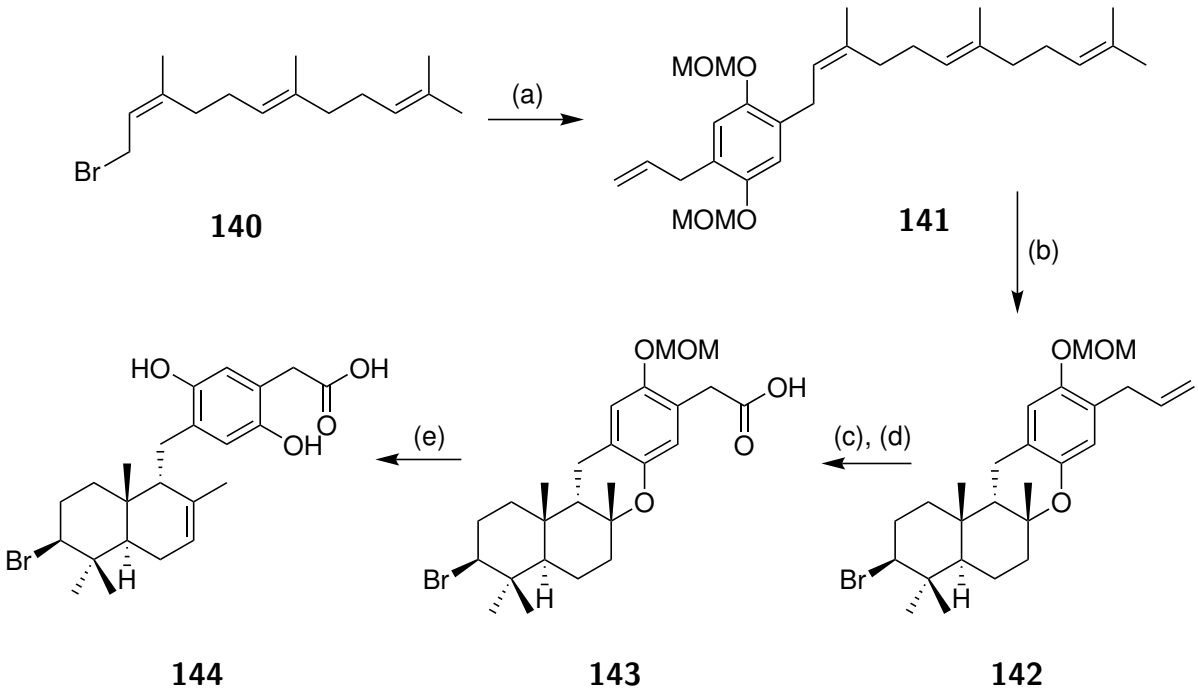
Finally, peyssonoic acid A (**144**) was produced by a similar sequence (Scheme 19).[9] (2*Z*,6*E*)-Farnesyl bromide (**140**) was coupled with aryl bromide **145** and again cyclised to give the benzopyran **142**. The allyl group was oxidised to the aldehyde by Lemieux-Johnson oxidation, then Pinnick oxidation gave the acid **143**. Boron trichloride was used to cleave the cyclic ether and remaining methoxymethyl protecting group, giving peyssonoic



Scheme 18: Snyder's synthesis of the remaining diastereomers of peyssonol A with cyclisation promoted by BDSB as a key step. Diastereomer **139** was found to be the natural diastereomer.[9]

acid A (**144**) in 6 steps from (2*Z*,6*E*)-farnesol in 12% yield.[9]

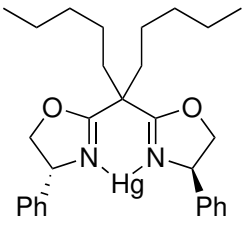
Snyder's work has illustrated the great advantage of polyene cyclisations for the syntheses of these types of terpenoid natural products and their analogues. The strategy can be used to build a number of rings very quickly and different diastereomers can be produced depending on the configuration of the polyene precursor. Total synthesis revealed that the stereochemical assignment of peyssonol A was incorrect.[9] Performing the exact same reaction sequence on the other diastereomers of farnesol gave four diastereomers of the product, revealing the correct stereochemical assignment, but producing this by a "traditional" approach, forming one ring at a time may have required a whole new methodology for each isomer. In addition, a simple change in the aromatic ring used led to the synthesis of a related natural product via the same sequence.



Scheme 19: Snyder's synthesis of peyssonoic acid A.[9] (a) **145**, *n*-BuLi, THF, –78 °C, then **140**, –40→5 °C, 2 h, 74%. (b) BDSB, $MeNO_2$, –25 °C, 5 min, 31%. (c) OsO_4, $NaIO_4$, pyr, THF/*t*-BuOH/H_2O, 0→25 °C, 2 h, 89%. (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*-BuOH/H_2O, 0 °C, 20 min, 81%. (e) BCl_3, CH_2Cl_2, –78 °C, 1h, 72%.

We will apply the same overarching idea to our syntheses of the taiwaniaquinoids and dasyscyphins. If one route fails, we can use the same reaction sequence with a different aryl polyene to reach our desired compounds.

Mercury(II) based-cyclisations



146

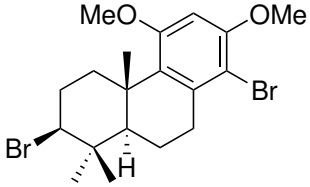
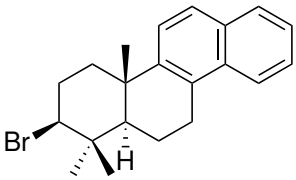
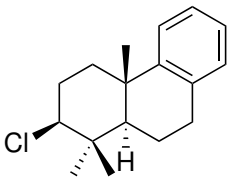
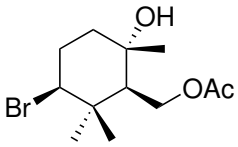
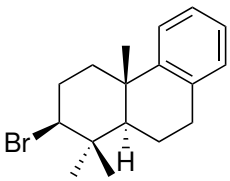
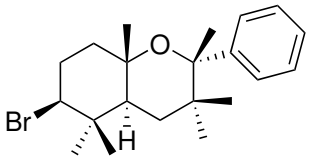
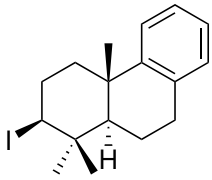
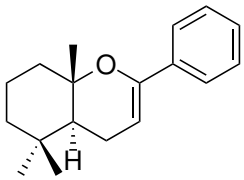
Figure 11: Snyder's mercury(II)-bisoxazoline complex.

Mercury(II) trifluoromethanesulfonate, especially in complex with anilines, is known to mediate polyene cyclisations in a racemic fashion.[27] Since organomercury species can be reacted with a halogen (e.g. bromine) to convert them into the corresponding halide, this can be considered a roundabout way of constructing these bromocyclised compounds. Snyder also developed the use of stoichiometric chiral mercury(II) complexes such as **146**

(Figure 11) to impart enantioselectivity in polyene cyclisations initiated by mercury(II).[28]

Investigation of a series of chiral bisoxazoline ligands led to complexes that provided modest to good enantioselectivity and good yields in various polyene cyclisations (Table 6).

Table 6: Substrate scope for Snyder's mercury-mediated cyclisation.[28] [a] organomercury intermediate was treated with TfOH to fully cyclise. [b] organomercurial was subsequently treated with $NaBH_4$ to effect hydrodemercuration.

#	Product	Yield	ee	#	Product	Yield	ee
147a		79%	72%	**147e**		77%	64%
147b[a]		67%	81%	**147f**		65%	62%
147c[a]		66%	81%	**147g**		80%	28%
147d[a]		72%	81%	**147h**[b]		74%	69%

The organomercury intermediates in Snyder's report are versatile intermediates. While Snyder typically reacts these compounds with a halogen to generate the alkyl halide, it is possible to generate other functionalities; for example, reaction with sodium borohydride generates the demercurated compound **147h**.

This method has a number of obvious drawbacks. While the chiral ligand can be used catalytically, the enantioselectivity is affected negatively.[28] The ligand can be recovered and recycled by flash column chromatography. Mercury is a toxic, environmentally dangerous heavy metal and using it in stoichiometric quantities is particularly undesirable. The highly toxic alkylmercury intermediate generated by this reaction is a safety concern. In addition, triflic acid was needed in examples **147b–d** to

effect full cyclisation following partial bromocyclisation using complex **146**.

Phosphorus-based chiral ligands

A common way of promoting these bromonium-mediated cyclisations is to use a phosphorus-based ligand. Typically these ligands are based on BINOL scaffolds such as those seen in Figure 12.

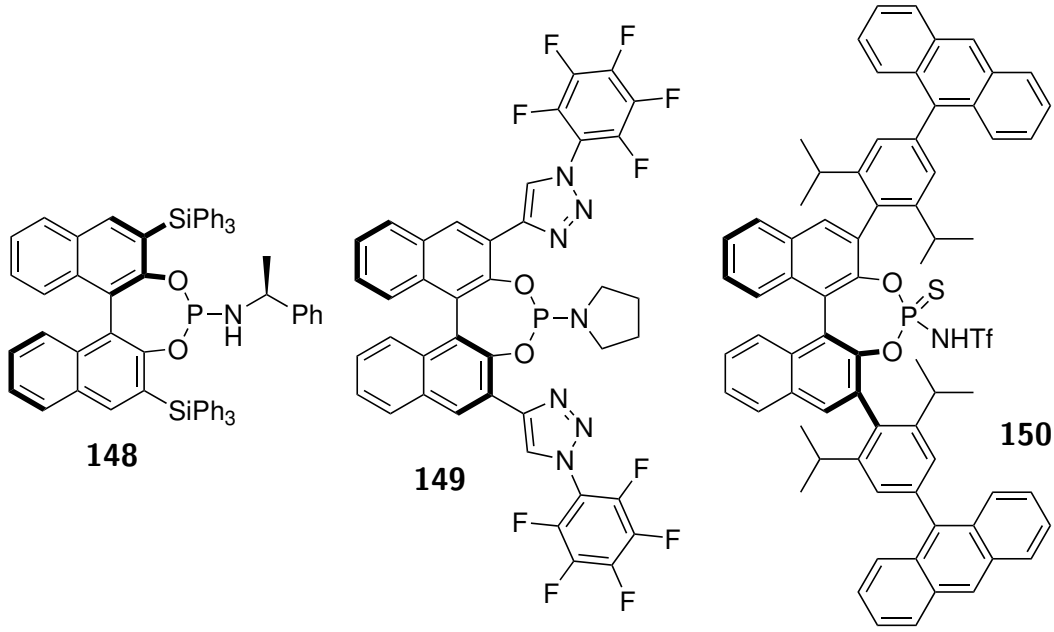


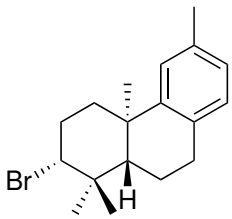
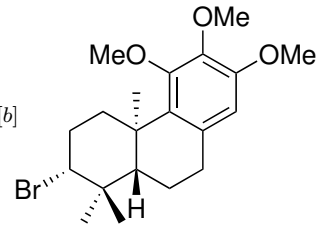
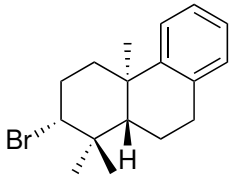
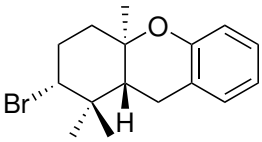
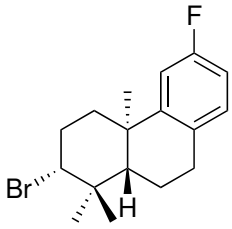
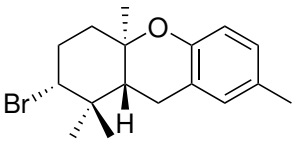
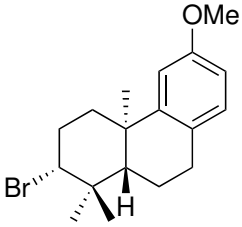
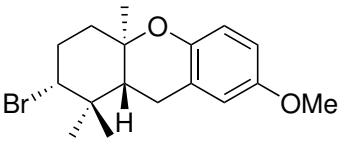
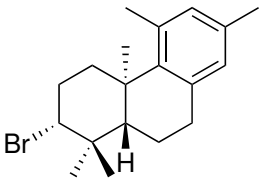
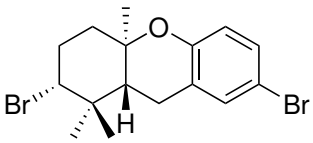
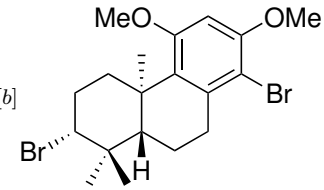
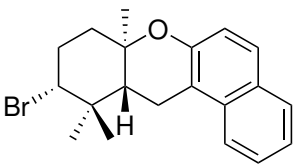
Figure 12: Phosphorus complexes used to guide selectivity of bromination: Ishihara's chiral auxiliary **148**; McErlean group's complex **149**; and Yamamoto's chiral catalyst **150**.

Ishihara was able to use a variety of catalysts to promote the cyclisation of polyenes in conjunction with a stoichiometric amount of an *N*-halosuccinimide.[29] Of note, this reaction did not occur without a catalyst or with amine catalysts such as 1,4-diazabicyclo[2.2.2]-octane (DABCO). It did occur in the presence of phosphines, in particular with phosphoramidite complexes such as **148**. Importantly, stoichiometric amounts of the phosphine were required to impart enantioselectivity: substoichiometric amounts led to an eradication of enantioselectivity and lower yields.

Recent work by the Yamamoto group led to the development of chiral thiophosphoramide catalyst **150**, which can catalyse bromonium-mediated polyene cyclisations using only 5 mol% of catalyst and a stoichiometric amount of dibromodimethylhydantoin (DBDMH) or another bromonium source.[30] In those examples, the product is obtained as the single *trans* diastereomer, with good ee and often in good yield. In contrast to Snyder's examples

with BDSB, additional chlorosulfonic acid was added to completely cyclise mixtures of partially cyclised intermediates to give compounds **151a**–**g**.

Table 7: Yamamoto's enantioselective brominative cyclisation.[30] Conditions: **150** (5 mol%), DBDMH, toluene/CH_2Cl_2 (10:1), –90 °C, 18–24 h. [a] After first step: $ClSO_3H$ (7.5 equiv.) added, –78 °C, 12 h. [b] Reaction worked up, then $ClSO_3H$ (7.5 equiv.), *i*$PrNO_2$, –78 °C, 12 h.

#	Substrate	Yield	ee	#	Substrate	Yield	ee
151a[a]		87%	79%	**151g**[b]		81%	94%
104[a]		98%	78%	**151h**		84%	80%
151c[a]		94%	78%	**151i**		71%	79%
151d[b]		44%	74%	**151j**		41%	69%
151e[b]		64%	79%	**151k**		85%	87%
151f[b]		76%	85%	**151l**		58%	88%

Interestingly, Yamamoto reported that benzopyrans **151h–l** were produced as the single diastereomers, in contrast to the results seen previously with direct acid cyclisation in the presence of Lewis-assisted Brønsted acids built upon BINOL (Table 2).[30] These reactions did not require additional acid to fully cyclise.

Neither Ishihara's nor Yamamoto's catalysts appear to have been used in the synthesis of molecules more complex than the substrate scope shown in their papers.

The McErlean group has previously made efforts to develop chiral phosphoramidite catalysts such as **149** to promote brominative polyene cyclisations and similar reactions such as bromoetherifications.[31] [32] While they are somewhat competent at polyene cyclisations, unfortunately no chiral induction is seen.

These complexes aim to introduce chirality in three ways: first, BINOL is axially chiral and the presence of further bulk at the 3 and 3′ positions additional increases this, as seen in many other examples.[31] The phosphorus-bound amine can also introduce additional chiral units, thus enhancing this effect. Finally, the lone pair of a phosphorus does not undergo inversion at room temperature: it is also chiral. The idea was to chelate a 'bromonium ion' obtained from a typical source such as *N*-bromosuccinimide between the phosphorus atom and a nitrogen atom on the heterocyclic substituents. The steric environment around the bromine atom was envisaged to impart enantioselectivity on a subsequent cyclisation.

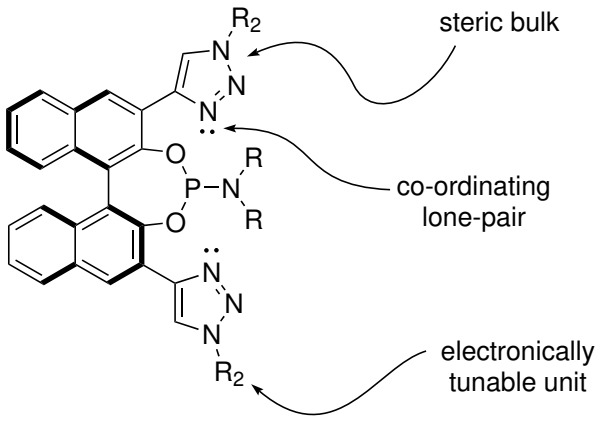
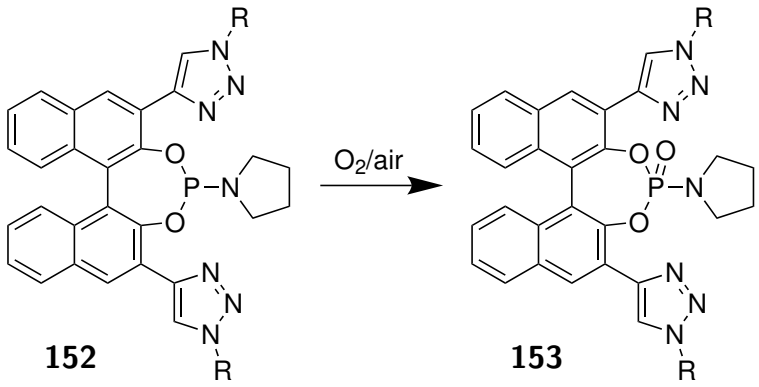


Figure 13: Features of the McErlean group's phosphoramidite catalysts.[31]

Early investigations into 3,3′-substituted BINOL phosphoramidites showed that *N*-heterocyclic substituents led to an unexpected oxidation to the phosphorus(V) compound.[31] The corresponding non-nucleophilic bis(thiophene) compound did not undergo oxidation, thus they expected that the introduction of a triazolyl substituent with a tuneable aryl ring

would be significantly more stable.

These catalysts still readily underwent oxidation to the undesired phosphorus(V) compounds (Scheme 20). Electron-rich aromatic substituents such as 4-methoxyphenyl increased the rate of oxidation (Table 8, entry 4) relative to an unsubstituted phenyl ring, but electron-deficient aromatic substituents suppressed oxidation, particularly the pentafluorophenyl catalyst which saw no oxidation to the corresponding amidophosphate (Table 8, entry 8).



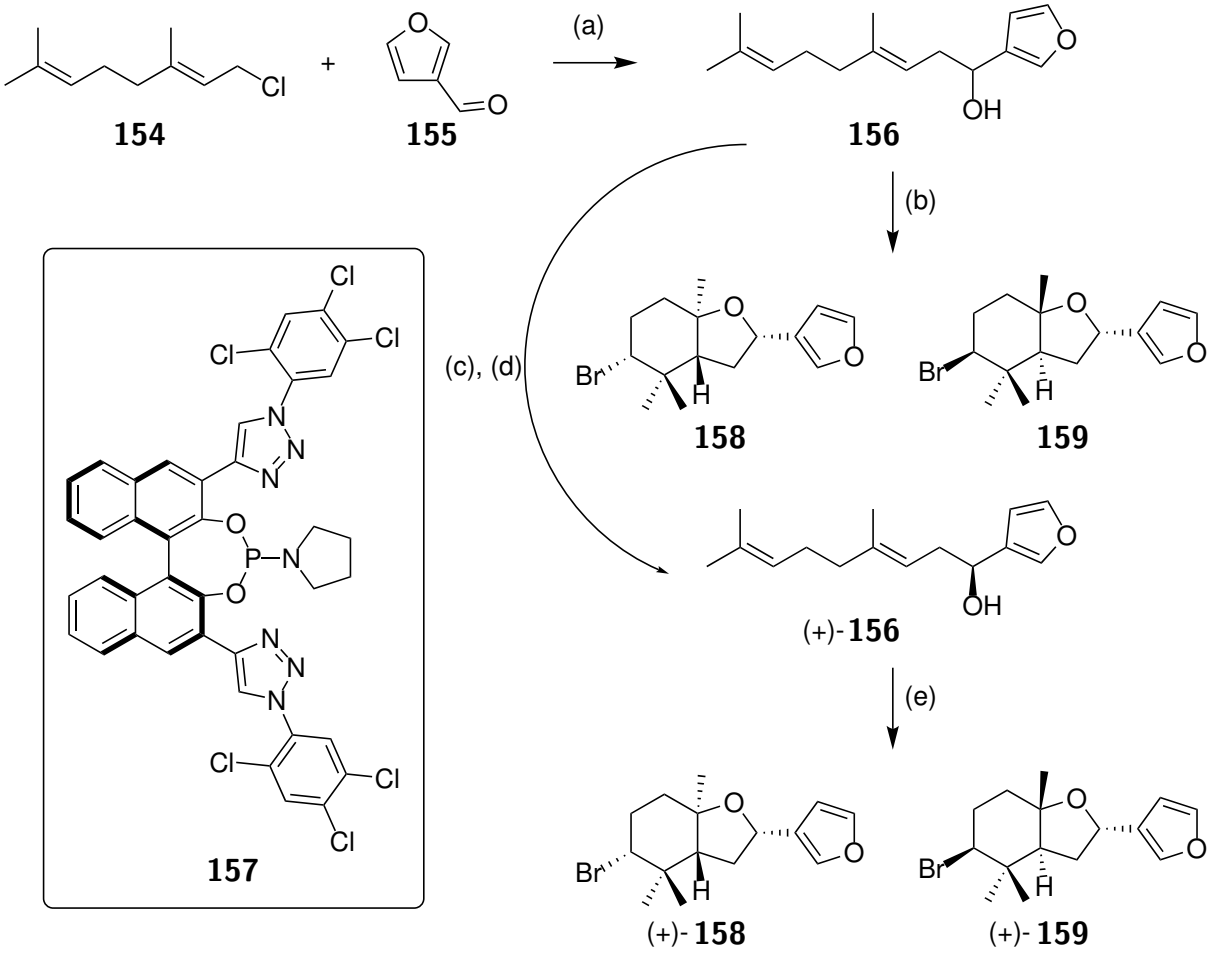
Scheme 20: Oxidation of phosphoramidite **152** to undesired amidophosphate **153**.[31]

Table 8: Oxidation of phosphorus(III) catalysts to inactive phosphorus (V) compounds.[31] Isolated yields after chromatography. [a] Synthesised by alternate method.

Entry	R	Isolated yield		% oxidised
		P(III)	P(V)	
1[a]	benzyl	17%	77%	82%
2	benzyl	36%	40%	52%
3	phenyl	32%	24%	43%
4	4-methoxyphenyl	24%	54%	68%
5	4-bromophenyl	66%	28%	30%
6	4-fluorophenyl	68%	17%	20%
7	2,4,5-trichlorophenyl	59%	10%	14%
8	pentafluorophenyl	89%	0%	0%

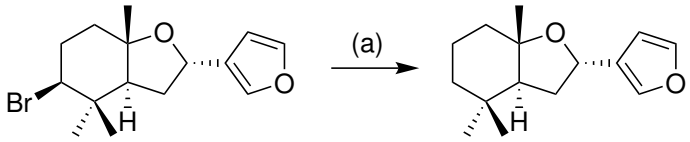
The McErlean group then applied this work to the synthesis of two cyclic terpenoids, luzofuran and ancistrofuran, which contain an easily halogenated furan ring.[33]

Alkylation of 3-furancarboxaldehyde (**154**) with geranyl chloride (**155**) via the organobarium reagent gave alcohol **156**. Cyclisation with phosphoramidite **157** and *N*-bromosuccinimide gave (±)-luzofuran (**158**) in modest yield with a small amount of the C4 epimer **159**.[33] No bromination of the furan was seen under these conditions.



Scheme 21: Synthesis of (±)-luzofuran.[33] (a) BaI, Li, biphenyl, THF, –78 °C. 58% (b) **157**, NBS, CH_2Cl_2, –78 °C. 17% **158**; 4% **159**. (c) Dess-Martin periodinane, CH_2Cl_2, 92%. (d) (*S*,*S*)-RuTsDPEN, $NaHCO_2$, CTAB, EtOAc/H_2O, 72%. (e) **157**, $EtNO_2/CH_2Cl_2$, –78 °C. 29% (+)-**158**; 7% (+)-**159**.

However, alcohol **156** is chiral. Oxidation, followed by Noyori transfer hydrogenation gave enantiopure (+)-**156**. Treatment under slightly modified conditions, using nitroethane as a cosolvent to stabilise the cationic intermediate, gave a higher yield of luzofuran ((+)-**158**; 11% overall yield in 4 steps) and epimer (+)-**159** (3% overall yield in 4 steps) in a similar diastereomeric ratio.[33] Reductive debromination of the minor diastereomer (+)-**159** with activated magnesium in tetrahydrofuran gave (–)-ancistrofuran ((–)-**160**) in 2% overall yield in 5 steps.[33]

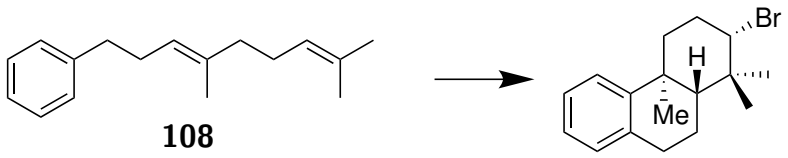


Scheme 22: Synthesis of (–)-ancistrofuran from (+)-**159**.[33] (a) Li, $MgCl_2$, naphthalene, then (+)-**159**, THF, –65 °C, 86%.

These cyclisations are low yielding. However, they represent the straightforward elaboration of an acyclic polyene to a bicyclic compound with four stereogenic centres. In these cases, enantioselectivity was not induced by the catalyst but by the configuration of the starting alcohol **156**.

A comparison of the techniques discussed is shown in Table 9. Early protocols (entries 2–4) gave poor to modest yields and were not enantioselective. The advancements in the past 15 years have shown higher yields, faster reaction times and where applicable, the generation of a single enantiomer with good selectivity.

Table 9: Comparison of brominating reagents - conversion of homogeranylbenzene to cyclised compound **104**; [a] n/a refers to non-chiral methodology while 0% refers to no enantioselectivity seen despite the use of chiral reagents. [b] Significant amounts of monocyclised compounds; performing reaction in toluene gives only monocyclised products.



108 **104**

Entry	Conditions	Yield	ee[a]
1 [26]	BDSB, $MeNO_2$, –25 °C, 5 min	75%	n/a
2 [26]	$Br_2/AgBF_4$, $MeNO_2$	9%	n/a
3 [26]	TBCO, MeCN	27%	n/a
4 [26]	NBS/Ph_3P, CH_2Cl_2	13%	n/a
5 [26]	**123**, $MeNO_2$	72%	0%
6 [28]	**146**, CH_2Cl_2, –78 °C → 0 °C, then aq. NaBr, then Br_2, LiBr, O_2, pyridine	66%	81%
7 [32] [b]	**149**, NBS, CH_2Cl_2 –78 °C, 10 min, 4 Å MS	38%	0%
8 [30]	**150**, DBDMH, toluene/CH_2Cl_2, –90 °C, 18 h, then $ClSO_3H$, –78 °C, 12 h.	98%	78%

1.3.3 Epoxide-mediated polyene cyclisation

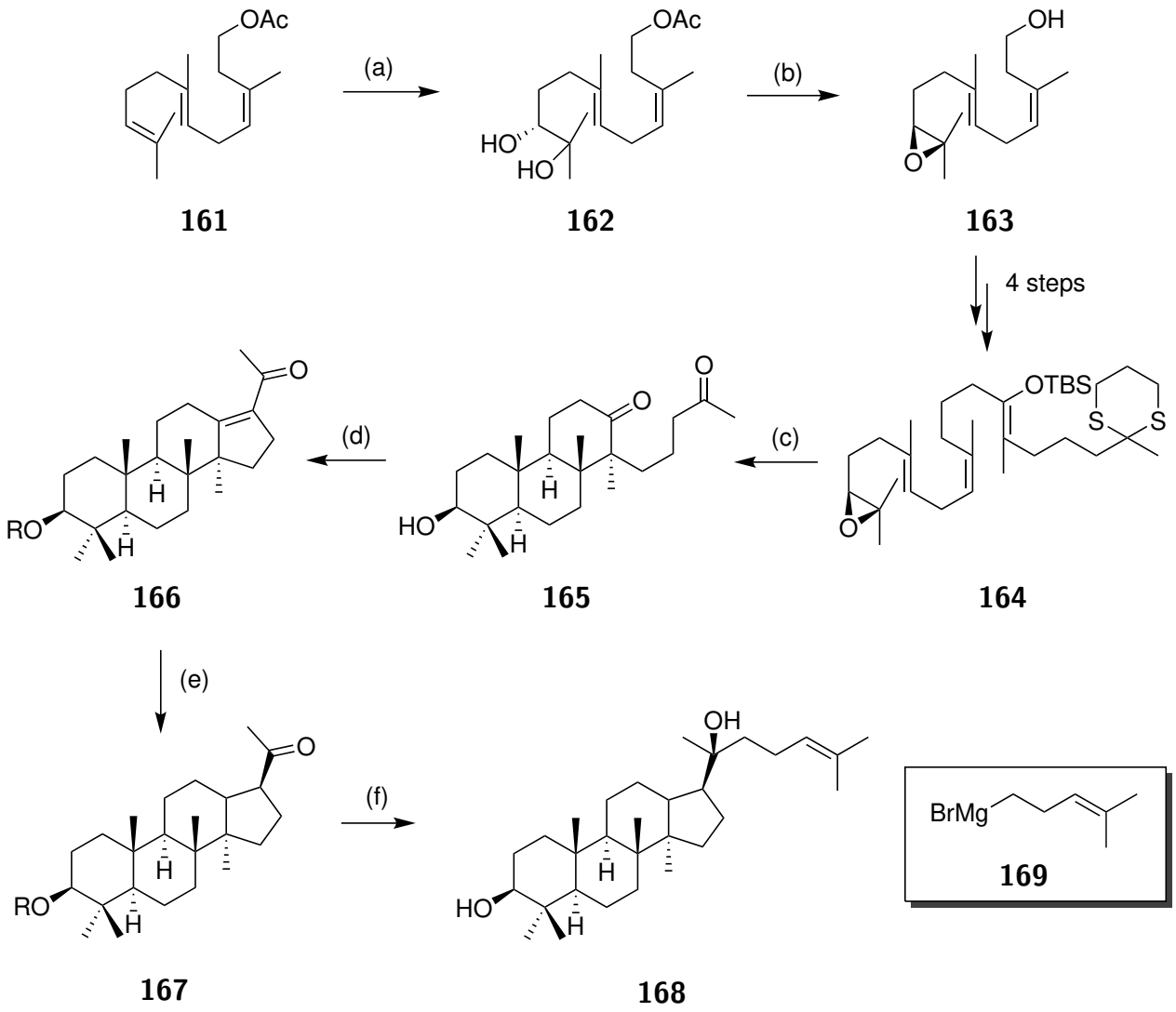
Each of the preceding methods initiated polyene cyclisation from an alkene, but transforming the alkene into another functional group has also been explored.

Converting the distal alkene into an epoxide with subsequent treatment with a suitable oxophilic Lewis acid is an alternative and much more explored route towards terpenoid natural products. A significant advantage of this approach is that chiral epoxidation is a well-established technique, with the enantioselectivity of the cyclised product being determined at this early stage. This contrasts with the previously discussed methods where enantioselectivity occurs during the cyclisation step.

Much of the work in this area was performed by Corey, who reported a series of elegant syntheses of terpenoids using epoxide-opening polyene cyclisation as a key reaction step.

Dammarenediol II (**168**) was one of the earliest syntheses using this epoxide opening approach (Scheme 23).[34] Chiral diol **162** was produced by enantioselective dihydroxylation of (*E*,*E*)-farnesyl acetate (**161**), then mesylation and displacement delivered chiral epoxide **163**. This was further elaborated into the cyclisation precursor **164**. Cyclisation with methylaluminium dichloride, then deprotection of the silyl enol ether and dithiane gave tricyclic diketone **165**. Aldol reaction then installed the cyclopentene D ring in one subsequent step to give the fully cyclised compound **166**. The synthesis was completed by reducing the alkene, then alkylating the exocyclic ketone and deprotection gave dammarenediol II (**168**) in 4% overall yield over 14 steps.[34] Intermediate **166** is closely related to the steroid structures produced by Johnson (**56**; Scheme 9*i*) and Woodward (**61**; Scheme 9*ii*), but Corey accomplished this synthesis in only 8 steps: far shorter than either previous synthesis.

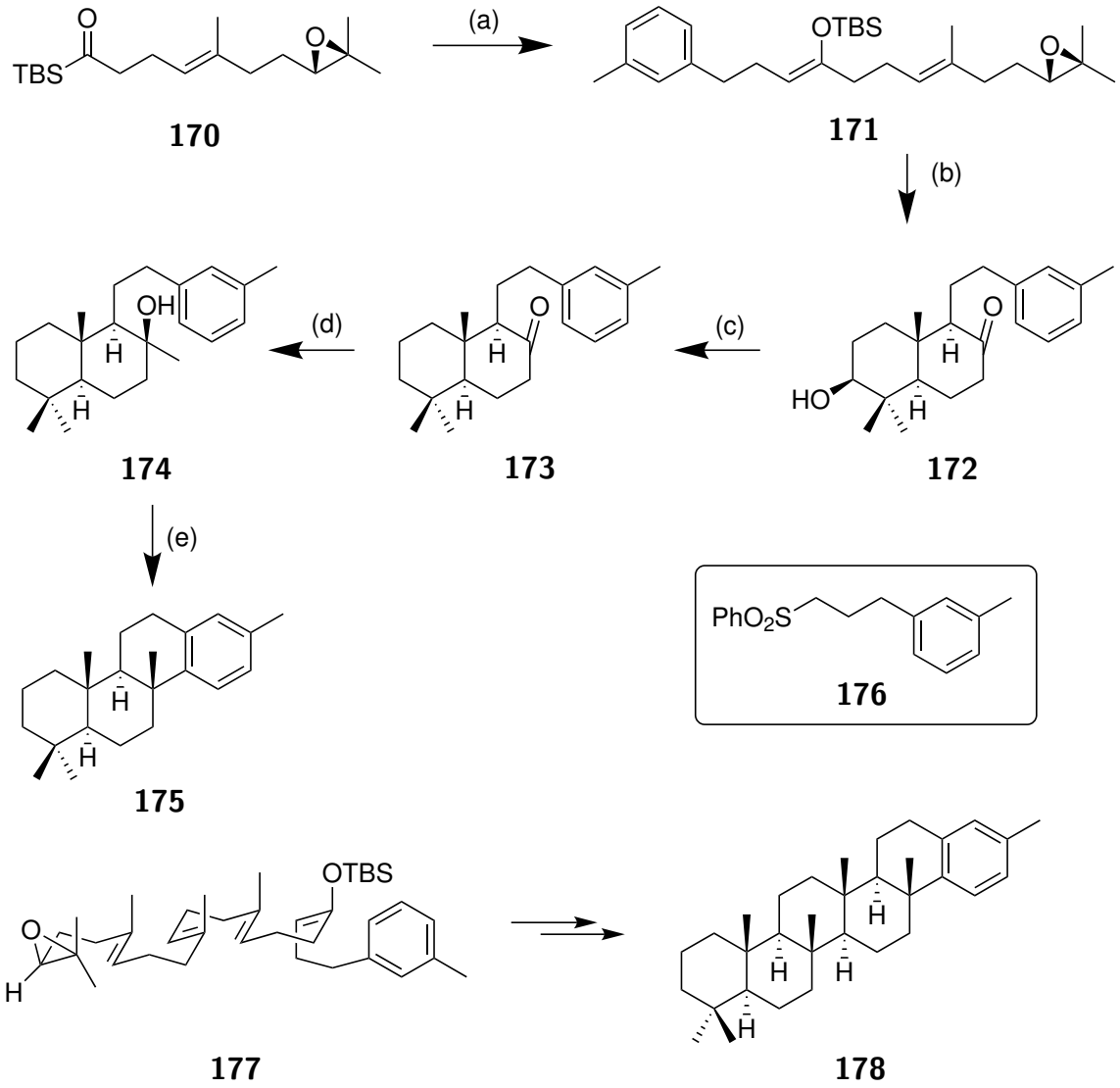
Corey synthesised a series of 6,6 fused terpenoids via epoxide-opening polyene cyclisation (Scheme 24).[35] Silyl ketone **170** derived from geraniol was reacted with phenyl sulfone **176** using *n*-butyllithium, with Brook rearrangement and elimination of the sulfone giving silyl enol ether **171**. Treatment with methyl aluminium dichloride in dichloromethane gave ketone **172**, with the silane acting as a terminating group. Barton-McCombie deoxygenation was performed on the epoxide-derived oxygen to give alkane **173**, which was reacted with methyllithium to generate the tertiary alcohol **174** with a



Scheme 23: Corey's enantioselective synthesis of dammarenediol II (**168**).[34] (a) Noe-Lin catalyst, OsO_4, 80%, 96% ee. (b) MsCl, pyridine, CH_2Cl_2; then K_2CO_3, MeOH/CH_2Cl_2, 95%. (c) $MeAlCl_2$, CH_2Cl_2, –95 °C, 10 min; then HF, MeCN, then PIFA, MeOH/H_2O/*i*PrOH, 42%. (d) PhNCO, pyridine; then TsOH, benzene, Δ, 5 h, 79%. (e) Li/NH_3, ether, 1 h, 60%. (f) **169**, DME/Et_2O, 0 °C; then $LiAlH_4$, THF, Δ, 60%.

methyl group at what would become the ring junction. Methanesulfonic acid in the presence of phosphorus pentoxide performed dehydration and Friedel-Crafts alkylation to give the fully cyclised compound **175**. Again, substrate control gives exclusive *trans* diastereoselectivity across the ring junctions. Corey performed a similar sequence of reactions to produce the longer system **178**.[35]

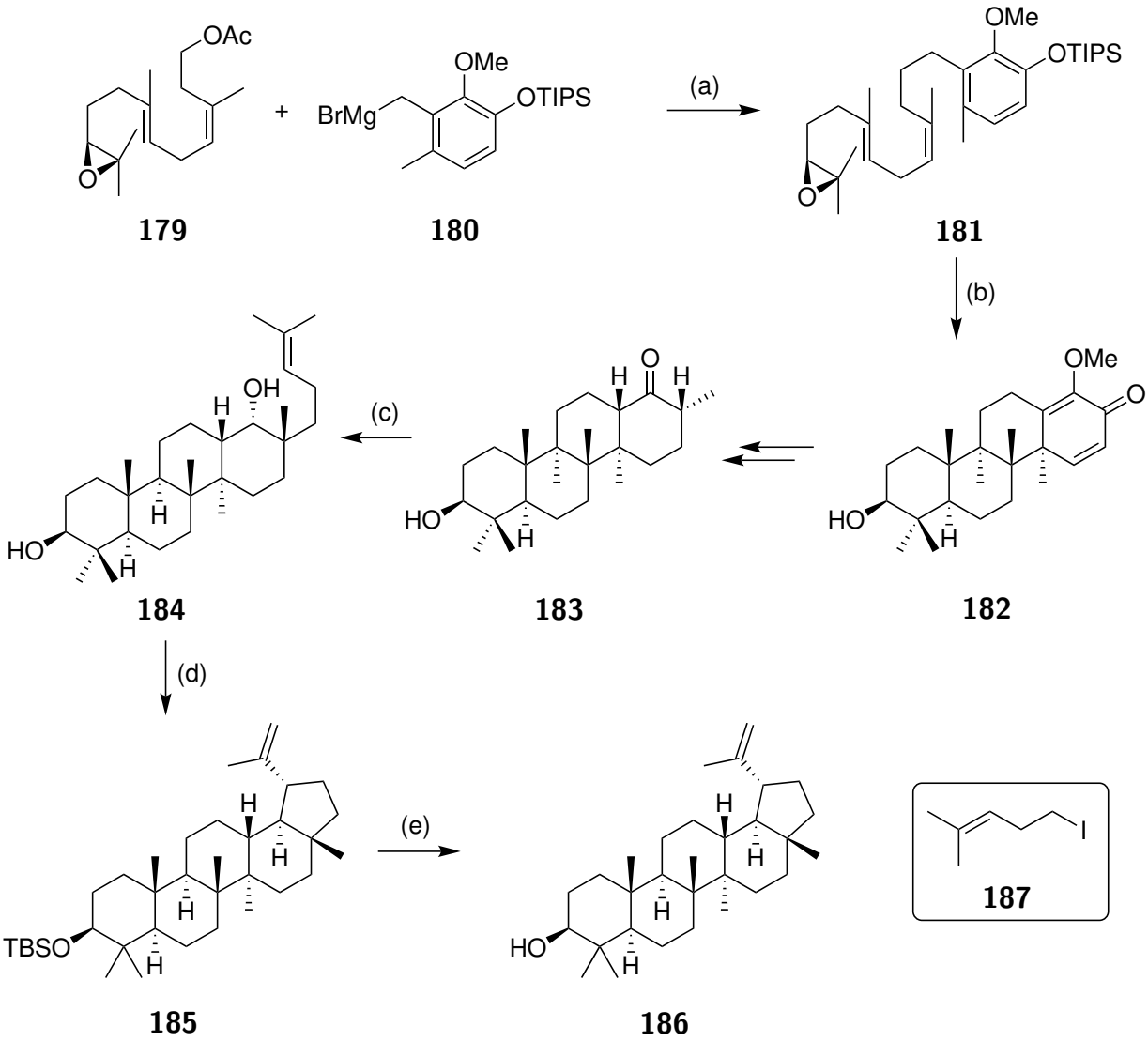
There are a number of explicit criticisms of this approach. We have already seen more efficient syntheses of similar compounds, including by Corey himself (Table 3e–h) and Snyder (Table 4c). In both cases, the homofarnesylbenzene was produced displacing of a farnesyl ester with an organomagnesium reagent. In the above example, Corey used



Scheme 24: Corey's synthesis of diterpene **175** and triterpene **178**.[35] (a) **176**, *n*-BuLi, THF/Et_2O/HMPA, 90%. (b) $MeAlCl_2$, CH_2Cl_2, –94 °C, then HF, MeCN, then KOH, MeOH, 84% (c) C_6F_5OCSCl, then Bu_3SnH, AIBN, 90%. (d) MeLi, THF, 100%. (e) $MeSO_3H$, P_2O_5, 85%.

an epoxide cyclisation but then proceeded to remove the resultant alcohol under Barton-McCombie conditions. At the time of its publication, this approach was the only way of generating these structures enantioselectively, but following Corey's later work using LBAs (Table 3) it is now possible to generate structures like **175** directly as a single enantiomer from the polyene.

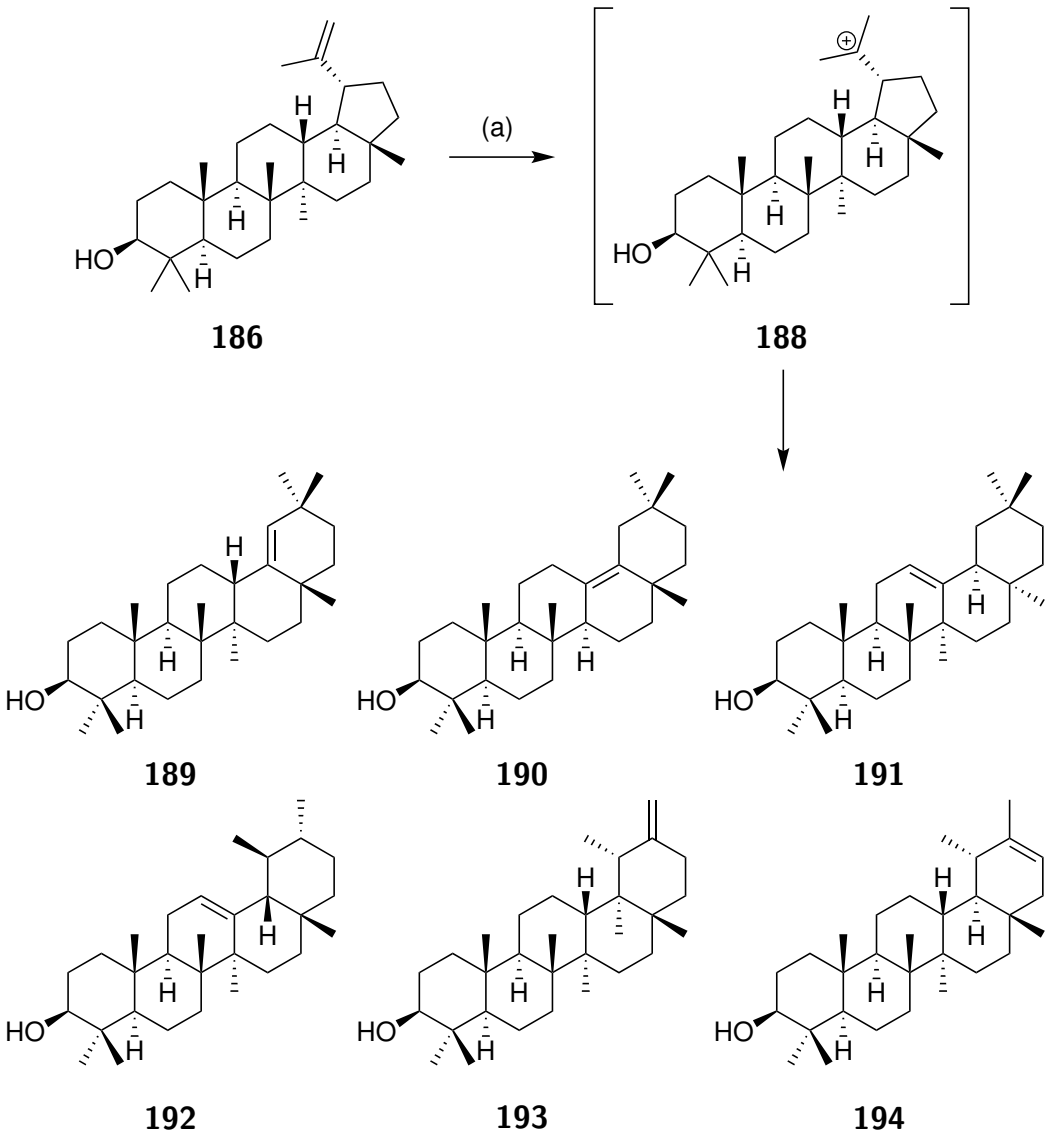
Corey later produced the first enantioselective synthesis of lupeol (**186**) using a sequence that incorporated both an epoxide-opening cationic cascade and a further cationic cyclisation (Scheme 25).[36] Treating epoxide **179** with organomagnesium bromide **180** mediated by lithium tetrachlorocuprate gave the homogeranyl epoxide **181**. This underwent an interesting dearomative cyclisation upon treatment with methyl aluminium



Scheme 25: Corey's synthesis of lupeol.[36] (a) Li_2CuCl_4, THF, 0 °C. 65%. (b) $MeAlCl_2$, Me_2AlCl, CH_2Cl_2, –78 °C; then TBAF, THF, 0 °C, 43%. (c) LiHMDS, THF, 0 °C, then **187**; then $LiBH_4$, THF, 0 °C, 50%. (d) MsCl, Et_3N, CH_2Cl_2, –20→0 °C, 72%. (e) TBAF, THF, 50 °C, 90%.

dichloride and dimethyl aluminium chloride, with subsequent silyl deprotection giving the cyclohexadienone **182**. Further elaboration then provided ketone **183**, which was reacted with iodide **187** to give the alcohol **184**. Treatment with mesyl chloride and elimination furnished the E-ring, with final deprotection giving lupeol (**186**) in 14 steps in 5% overall yield.

Interestingly, treating lupeol with triflic acid in deuterated chloroform gave a mixture of 6,6,6,6,6-fused compounds (Scheme 26).[36] The distribution of these compounds follows the energies derived by computational analysis.[37] This informed Corey's choice of strategy in this synthesis and highlighted a significant drawback to the polyene cyclisation approach where acid-catalysed rearrangement of the desired product is possible and

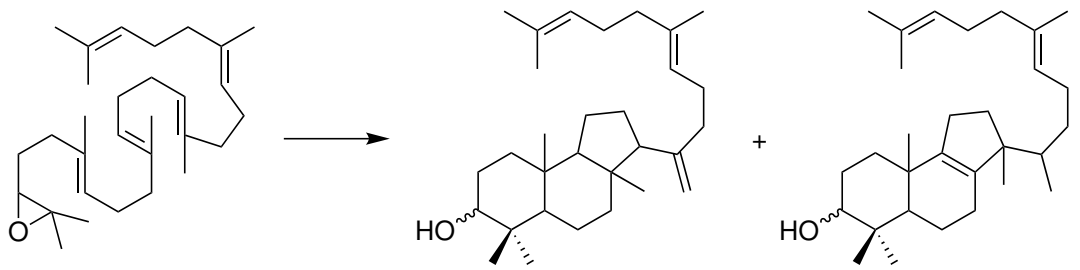


Scheme 26: Acidification of lupeol (**186**) led to products germanicol (**189**; 15%), δ-amyrin (**190**; 12%), 18-epi-β-amyrin (**191**; 17%), α-amyrin (**192**; 10%), taraxasterol (**193**; 10%) and ψ-taraxasterol (**194**; 29%).[36] Conditions: TfOH (20 mM), $CDCl_3$, rt, 24 h.

favourable.

Epoxide-mediated cyclisation suffers many of the same pitfalls as the direct cyclisation approach. van Tamelen cyclised 2,3-epoxysqualene (**195**) with tin(IV) chloride and found, alongside the expected tricyclic compound **196**, a rearranged alkene **197** formed by 1,2-methyl shift (Scheme 27).[38]

In addition, epoxidation can sometimes be problematic. These molecules always contain more than one double bond, all of which are trisubstituted and possess similar electronic character. Chemoselectivity becomes an issue. *m*-CPBA does however selectively oxidise the distal double bond, likely due to the less encumbered steric environment (e.g.



195 **196** **197**

Scheme 27: van Tamelen's cyclisation of 2,3-epoxysqualene (**195**) generates expected compound **196** and rearranged **197**.[12] [38] Conditions: 20 mol% $SnCl_4$, PhH, 10 °C. Yield, ratio and stereochemistry not shown in original paper.

Andersen[8]).

Shi epoxidation is the most common way of installing these epoxides, and the methodology has a number of good characteristics. The catalyst is cheap and easily derived from fructose. The steric encumbrance of the bulky catalyst allows for oxidation with high chemoselectivity for the distal alkene. But high catalytic loadings are often required, the yield can be poor, and reaction rates can be slow.

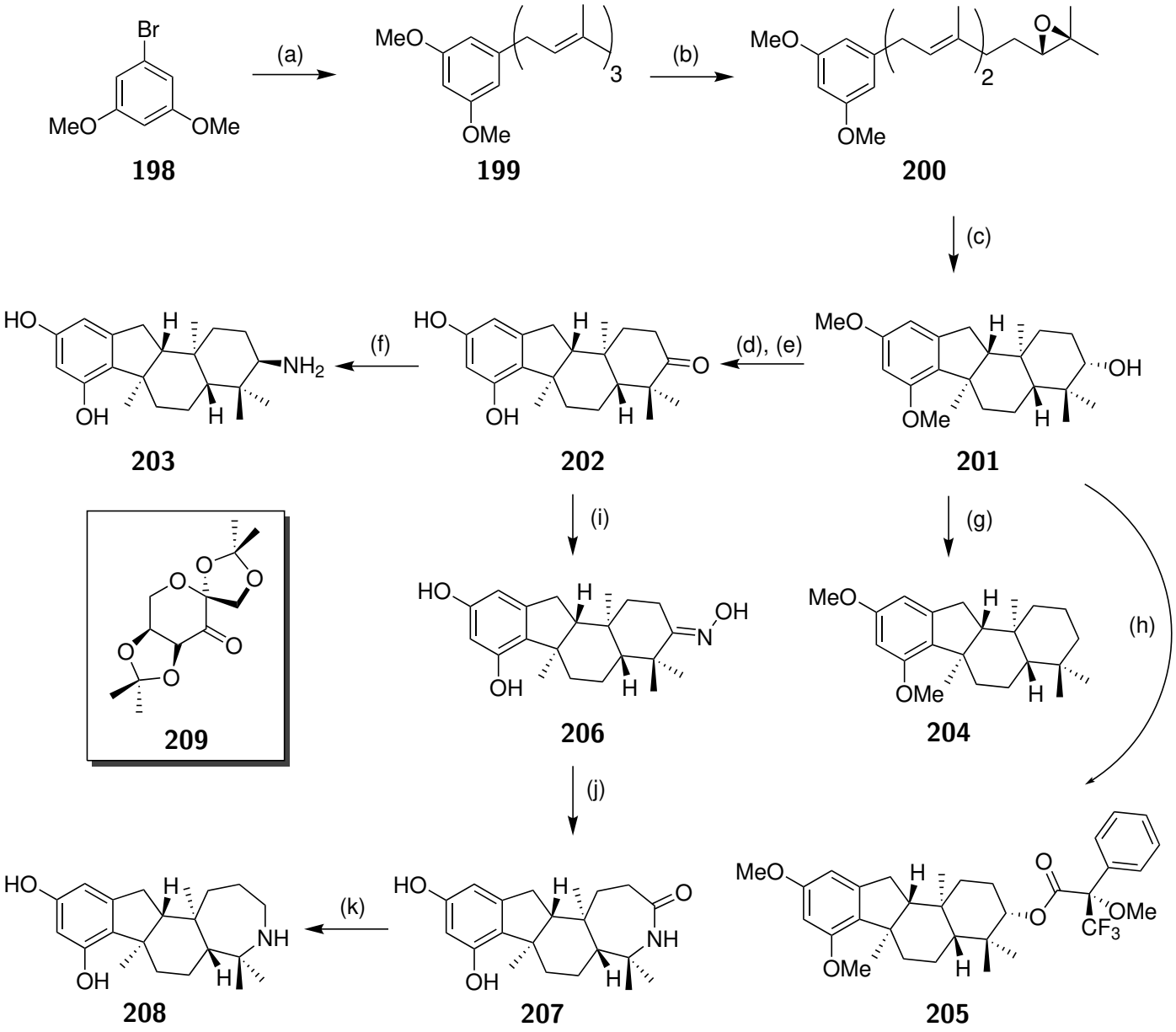
1.3.4 6,5,6-benzofused systems

So far, the examples we have seen deal with 6,6,6-benzofused systems. The focus of this work is on 6,5,6-benzofused systems. By analogy, we may assume that the stereochemistry remains *trans* across the ring junction as with the previous examples. These kinds of cyclisations have been performed several times in the literature, but notably never by directly treating a polyene with acid.

Following the Andersen group's synthesis of pelorol and successful testing as a SHIP-1 inhibitor, a series of analogues were synthesised to improve druglike properties and bioactivity.[8] While the original synthesis relied on condensation with the natural product (–)-sclareolide, the use of polyene cyclisation allowed for the synthesis of the opposite enantiomer (Scheme 28). Converting dimethoxybromobenzene (**198**) to the cuprate using *n*-butyllithium and lithium tetrachlorocuprate, then reaction with farnesyl bromide gave the farnesylarene **199** in good yield in a short sequence. Shi epoxidation gave a poor yield of the enantiomerically pure epoxide **200**. The action of indium(III) bromide fully cyclised the polyene to alcohol **201**.

Again, we see the utility of polyene cyclisations in generating analogues, with the alcohol formed from the ring-opening of an epoxide acting as a synthetic handle. Alcohol **201** was derivatised to a variety of products (Scheme 28).

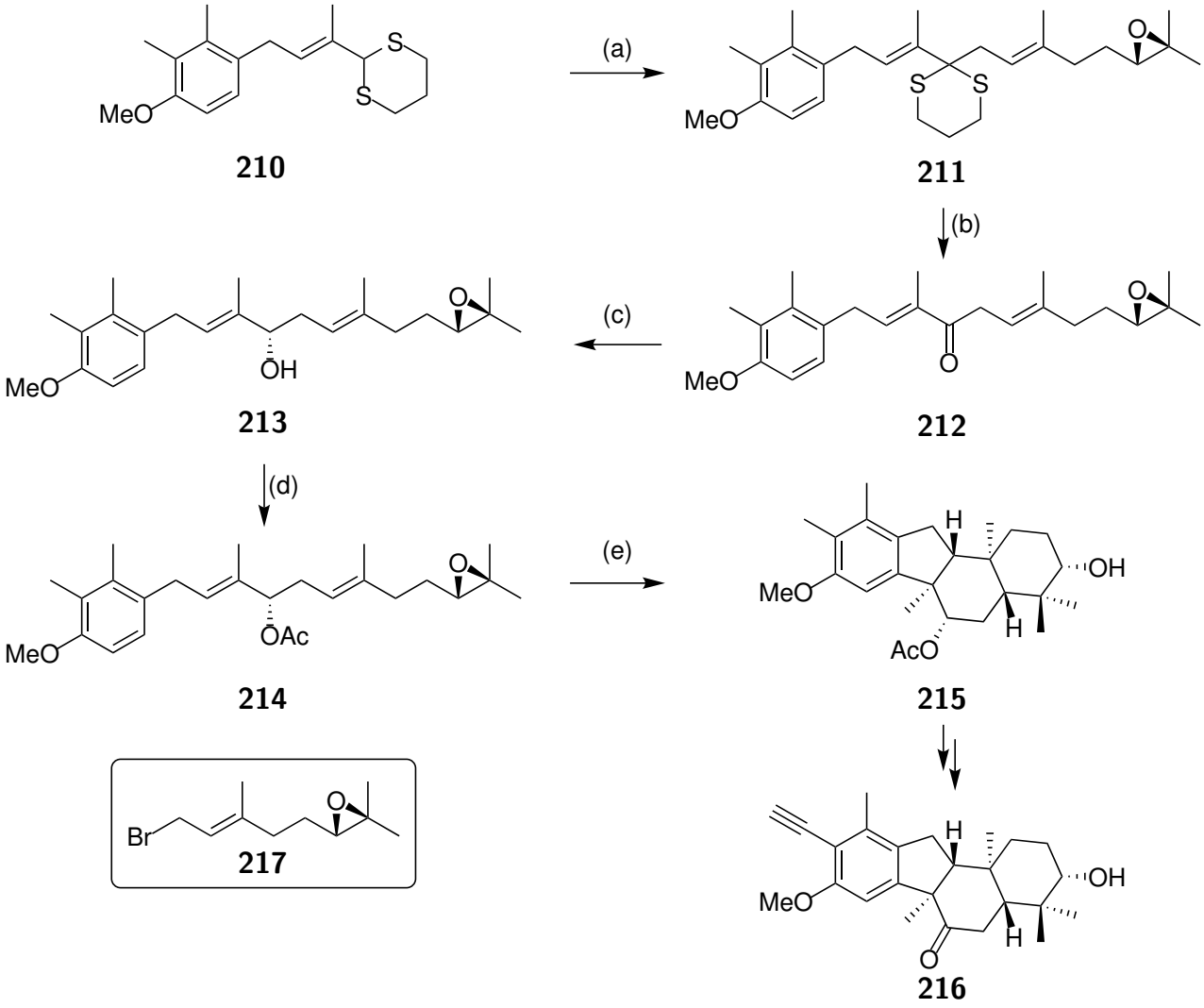
The Mosher ester **205** and its diastereomer were produced to determine the ee of the cyclisation product (er 39:1). Some natural products incorporate an acetate or another ester at this position. Elsewhere, the alcohol **201** was oxidised to ketone **202** and



Scheme 28: Andersen's synthesis of some pelorol analogues.[8] (a) *n*-BuLi, THF, –78 °C, then Li_2CuCl_4, then farnesyl bromide, –78 °C, 65%. (b) **209**, 28%. (c) $InBr_3$, CH_2Cl_2, rt, 24%. (d) Dess-Martin periodinane, CH_2Cl_2, 80%. (e) BBr_3, CH_2Cl_2, 0 °C → rt, 86%. (f) $NaBH_3CN$, NH_4OAc, MeOH, 70 °C, 46%, dr 6.7:1. (g) NaH, CS_2, MeI, THF, then Bu_3SnH, AIBN, PhMe, Δ, 82% over 2 steps. (h) (*R*)-(–)-MTPA-Cl, pyridine, DMAP, CH_2Cl_2, 0 °C, quant.; dr 39:1 (i) $NH_2OH{\cdot}HCl$, pyr, 50 °C, 75%. (j) TFAA, CH_2Cl_2, 0 °C, quant. (k) $LiAlH_4$, THF, Δ, 47%.

further converted into amine **203** by reductive amination. It was also condensed with hydroxylamine to make the oxime **206**. This underwent Beckmann rearrangement to produce the lactam **207**, which further gave the azepine **208** by reduction with lithium aluminium hydride. Alternatively, alcohol **201** could be deoxygenated under Barton-McCombie conditions producing alkane **204**, giving an analogous route to the direct cyclisation of farnesylarene **199** by Lewis acid.

The installation of oxygenation at other positions has also been explored. She and coworkers used a polyene cyclisation in the synthesis of (–)-walsucochin B which contains a hydroxyl on the B-ring (Scheme 29).[39] Dithiane **210** was reacted with enantiopure geranyl bromide-derived epoxide **217**, again made by Shi epoxidation, to give epoxide **211**. Deprotection of the dithiane, Corey-Bakshi-Shibata reduction of the subsequent



Scheme 29: She's synthesis of (–)-walsucochin B.[39] (a) *n*-BuLi, then **217**, THF, –78 °C rt, 86%. (b) I_2, $CaCO_3$, THF, 0 °C, 82%. (c) (*R*)-CBS catalyst, BH_3·THF, 0 °C, 71%, d.r. 4:1. (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 96%. (e) Et_2AlCl, CH_2Cl_2, –78 °C, 62%.

ketone and acetylation gave the acetate **214**, which was subjected to cyclisation by diethylaluminium chloride, again giving the fully cyclised compound **215**. Elaborating the aromatic and oxidation of the proximal oxygen to the ketone, along with necessary protection and deprotection steps, gave the natural product (–)-walsucochin B (**216**).

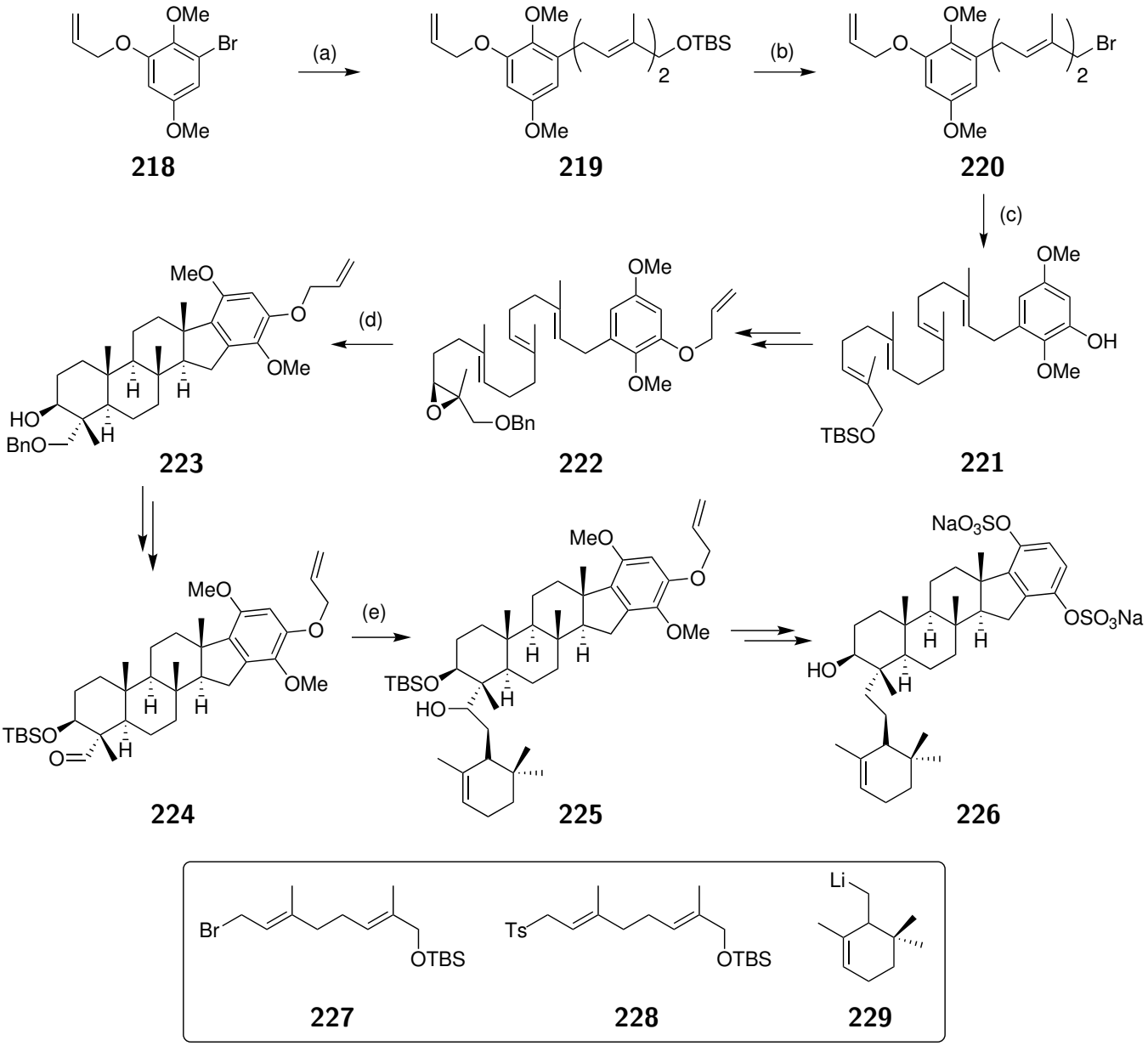
Overman further explored the late-stage derivatisation of these steroid-like fused ring systems in a synthesis of adociasulfate-1 (**226**; Scheme 30).[40] Aryl bromide **218** was coupled with geraniol-derived bromide **227** using *tert*-butyllithium and lithium tetrachlorocuprate to give the geranylarene compound **219**. The TBS ether was deprotected and converted to the bromide **220** to set up for coupling with sulfone **228** using potassium *tert*-butoxide. The sulfone cleavage step incidentally cleaved the allyl ether giving phenol **221**, requiring reprotection. Other protecting group manipulation was also required.

The epoxide was installed under Sharpless conditions giving compound **222**, then full cyclisation was performed using scandium(III) triflate in 15% yield to give alcohol **223**. We again highlight that this transformation involved the formation of four carbon-carbon bonds, leading to four new rings and six new stereogenic centres. Manipulation of the benzyl ether **223** provided an aldehyde for the addition of the pendant cyclohexene **229**, with final deprotection giving adociasulfate-1 (**226**) in 0.6% over 22 steps.

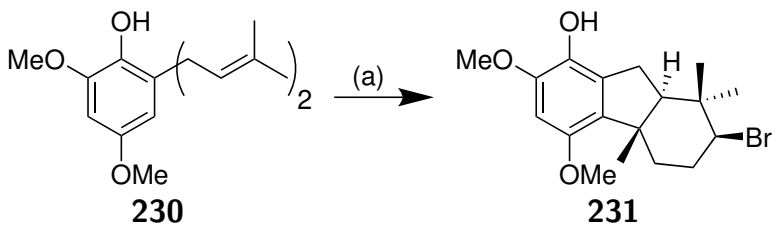
While this is one of the most complex molecules synthesised by a polyene cyclisation, the yield is also one of the lowest seen. Particular criticism lies with the installation of the polyene chain. Most of the polyene chain could have been built up before coupling to the aryl bromide **218**, avoiding protecting group manipulations and reducing the overall step count.

These are all longer systems. Only one example exists of a geranylarene being cyclised to generate the 6,5,6-fused system. Yamamoto treated geranylarene **230** with catalyst **150** and dibromodimethylhydantoin (DBDMH) as a bromonium source (Scheme 31).[30] Cyclised compound **231** was generated with a high yield as the single *trans* diastereomer and with high enantiopurity. This is an interesting case as Friedel-Crafts cyclisation is more favourable than the ether formation seen in compounds **151h–l**.[30] [41]

We will explore these sorts of cyclisations further: of note, all of the reported reactions rely on bromination of the alkene or ring-opening of an epoxide to generate the cationic cyclisation, and not direct acid-mediated polyene cyclisation of an alkene. We will also see



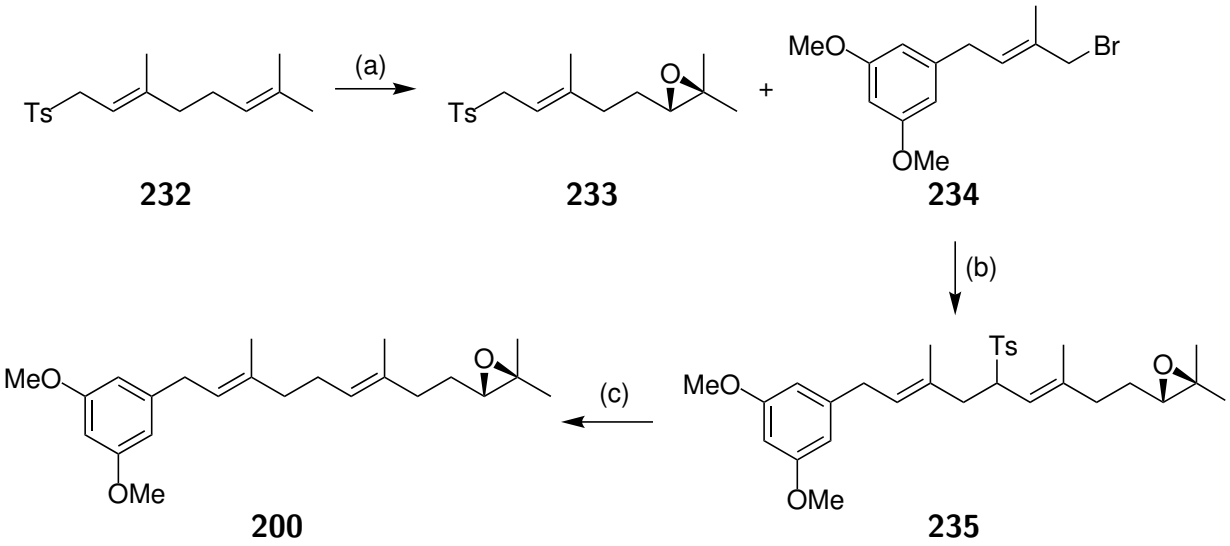
Scheme 30: Overman's synthesis of adociasulfate-1 (**226**).[40] (a) *t*-BuLi, Li_2CuCl_4, then **227**, THF, –78→23 °C, 74%. (b) TBAF, then MsCl, LiBr, 76% over 2 steps. (c) *t*-BuOK, THF/DMF, –20 °C, then Pd(dppp), $LiEt_3BH$, THF, 64%. (d) $Sc(OTf)_3$, CH_2Cl_2, –90→23 °C, 15%. (e) **229**, –78 °C, 79%.



Scheme 31: Enantioselective and diastereoselective cyclisation of polyene **230**.[30] (a) **150**, DBDMH, toluene/CH_2Cl_2, –90 °C, 91%, 99:1 er.

that the stereochemical outcome seen here does not necessarily have to be the case.

We also emphasise the inefficiency in installing the polyene chain in these examples. In Andersen's example (Scheme 28), only 28% of the desired epoxide was seen under Shi epoxidation (albeit with excellent enantiopurity).[8] *m*-Chloroperbenzoic acid gave similarly poor results of the racemate. A second route to epoxide **200** was carried out whereby sulfone **233** was produced by Shi epoxidation of geranyl tolyl sulfone (**232**; Scheme 32. Sulfone **233** was coupled with allylic bromide **234** using potassium *tert*-butoxide as a base and the sulfone was then removed by [1,3-bis(diphenylphopsphino)-propane]palladium(II) dichloride and lithium triethylborohydride to give epoxide **200**. The epoxide moiety was remarkably inert to these conditions and this longer route gave a higher overall yield of epoxide **200**. So it does appear that these lengthier sequences can be advantageous in terms of overall yield at the expense of step count and atom economy.



Scheme 32: Andersen's revised synthesis of epoxide **200**.[8] (a) **209**, oxone, $Na_2B_7O_7$, NH_4HSO_4, K_2CO_3, MeCN/$CH_2(OMe)_2$, 80%, *ee not disclosed.* (b) KO*t*Bu, THF, –78 °C, 97%. (c) $PdCl_2$(dppp), $LiBHEt_3$, THF, 0 °C, 76%.

We have already seen that She used a similar strategy, coupling geranyl bromide-derived epoxide **217** with dithiane **210** to install the similar epoxide **214**; this appears to be the easier course given the presence of oxygenation on the polyene chain.[39]

In Overman's synthesis, an alcohol allylic to the distal alkene allowed for the use of Sharpless epoxidation instead, giving high yields and high ee (Scheme 30).[40] While Sharpless epoxidation is more effective than the other methods mentioned above, it is limited to substrates which allow the titanium catalyst to coordinate near the desired alkene. Again, the polyene chain was built up over several steps already attached to

the aryl ring, requiring protecting group manipulation along the way. We anticipate that prefunctionalising both the arene and polyene chain and coupling these completed building blocks would increase the efficiency of this strategy.

1.4 Aims

The examples discussed above have demonstrated that polyene cyclisation is an effective methodology for the rapid generation of fused ring systems, often with excellent stereocontrol. There are gaps left to be filled. The one of most concern to us is that 6,5,6-fused cyclisations have almost exclusively been performed on longer systems and not the tricyclic architecture of the taiwaniaquinoids. Previous work in the McErlean group delivered only the *cis*-fused diastereomer using this approach and we must explore whether these systems can deliver the desired *trans* stereochemistry at the AB ring junction. Further, the cyclisations above were never performed by direct treatment with acid: they were always initiated by opening of an epoxide or attack onto a bromonium source. The coupling of a suitable polyene fragment is a further cause for concern. In many of these examples, particularly where an epoxide needs to be installed, it takes mulitple steps to elaborate the desired polyene. A general strategy towards families of related natural products and their analogues would be better accomplished by installing this chain in a single step. Finally, these examples only include functionalities that are known to not interfere in the polyene cyclisation step. This may necessitate further elaboration after the cyclisation, again precluding fast, efficient synthesis of many compounds.

This all culminates in the current strategy towards a series of polycyclic terpenoid frameworks. We aim to:

1. Devise a method to synthesise cyclisation precursors expediently through direct coupling between a suitable aromatic and a polyene tail with the necessary functionality.

2. Perform *direct* acid-catalysed cyclisation of the polyenes where applicable, with particular attention paid to examples where the diastereoselectivity at the proximal ring junction is opposite to what is precedented in the literature.

3. Explore the scope of potentially problematic functionalities on either coupling partner.

4. Explore the cyclisation of longer systems than what has been seen before.

5. Target natural products that either are yet to be synthesised or synthesised in inefficient ways.

Chapter 2

Taiwaniaquinoids

2.1 Introduction

The taiwaniaquinones are a family of norditerpenoid and diterpenoid natural products isolated from the tree *Taiwania cryptomerioides*. The tree grows only in Taiwan and Southeast Asia and suffers from slow and temperamental growth and it is an endangered and protected species in these jurisdictions (Figure 14).[1] The wood of *T. cryptomerioides* is widely used in furniture and is known as the coffin tree because of its primary use. It has a pleasant scent and is resistant to degradation by fungus and termites due to the plethora of terpenoids contained within it.[42] Many of these compounds also have synthetically interesting structures and possess intriguing biological activity, making them targets for synthetic chemists and biologists.

Our interest lies in the family known as the taiwaniaquinoids, a collection of fused quinones (the taiwaniaquinones) and similar compounds with the corresponding hydroquinone framework (the taiwaniaquinols), listed in Table 10.[44] As depicted in Figure 15, all of these compounds possess the 6,5,6-fused system shown. However they vary in their configuration across the AB ring junction. Some of the taiwaniaqunoids are unsaturated at the C5–C7 bond. Of the saturated taiwaniaqunoids, all taiwaniaquinones possess the *trans* stereochemistry, while some taiwaniaquinols possess the *cis* stereochemistry.

Typically included in the discussion of the taiwaniaquinoids are related compounds with a similar hexahydrofluorene framework (see Table 10): standishinal (**236**) isolated from

Figure 14: Natural distribution of *Taiwania cryptomerioides*.[43]

Thuja standishii and dichroanals A (**237**), B (**238**) and dichroanone (**239**) isolated from *Salvia dichroantha*.[44] For simplicity, we will refer to these compounds as taiwaniaquinoids regardless of their biological origin.

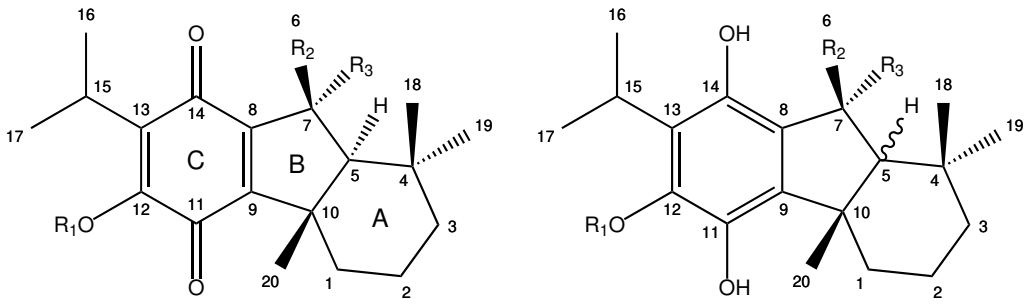
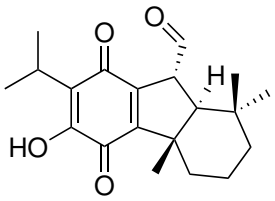
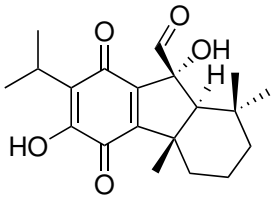
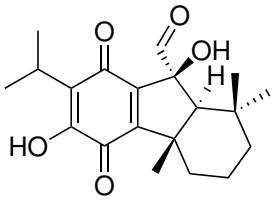
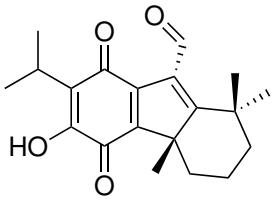
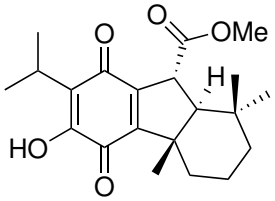
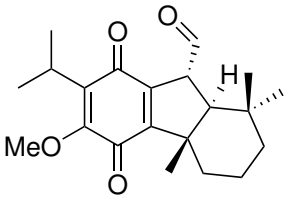
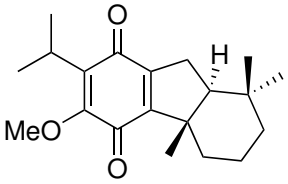
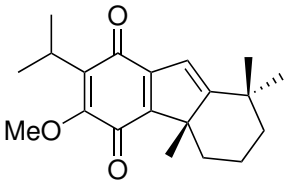
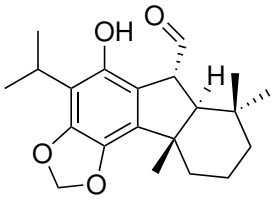
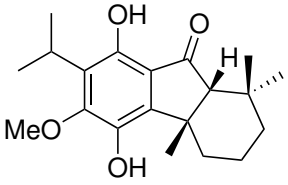
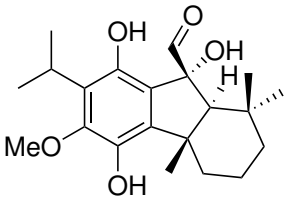
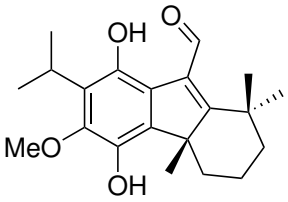
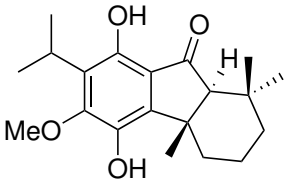
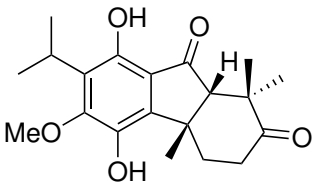
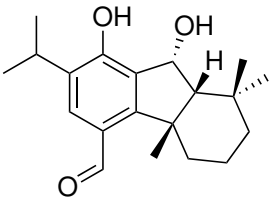
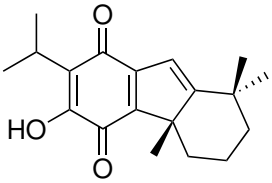
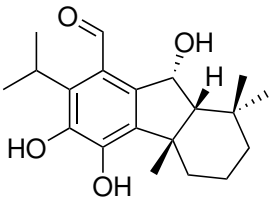


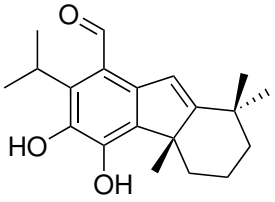
Figure 15: Carbon numbering of the taiwaniaquinoid framework.[2]

Table 10: Known taiwaniaquinoids and similar natural products. Yields and step counts are longest linear sequence. [a] 5-*epi*-taiwaniaquinone G. [b] Formal synthesis: yields and step counts extrapolated from intercepted route. [c] Synthesis begins at an advanced intermediate; prior operations not reported.

Structure	Name	Author	Steps	Yield
		Taiwaniaquinones		
	taiwaniaquinone A (**240**)	Alvarez-Manzaneda[45]	12	23%
		Li[46]	10	11%
	taiwaniaquinone B (**241**)	*none reported*		
	taiwaniaquinone C (**242**)	*none reported*		
	taiwaniaquinone D (**243**)	Banerjee[47]	31	0.8%
		Ozeki[48]	20	3%
	taiwaniaquinone E (**244**)	*none reported*		
	taiwaniaquinone F (**245**)	Alvarez-Manzaneda[45]	13	17%
		Gademann[49]	17	6%
		Li[46]	10	11%

Structure	Name	Author	Steps	Yield
	taiwaniaquinone G (**5**)	Alvarez-Manzaneda[50]	14	25%
		Alvarez-Manzaneda[51]	22	4%
		Bisai[a] [52]	8	24%
		Chang[a] [53]	9	15%
		McErlean[a] [25]	8	11%
	taiwaniaquinone H (**246**)	Alvarez-Manzaneda[54]	12	22%
		Banerjee[47]	18	3%
		Bisai[b] [55]	7	15%
		Gademann[56]	7	19%
		Hartwig[57]	5	27%
		Hu[58]	3	14%
		Node[59]	13	39%
		Qin[b] [60]	15	9%
		Stoltz[b] [61]	10	15%
		Trauner[62]	7	29%
Taiwaniaquinols				
	taiwaniaquinol A (**247**)	Gademann[49]	18	2%
	taiwaniaquinol B (**248**)	Banerjee[47]	28	2%
		Bisai[52]	9	18%
		Chiu[46]	6	35%
		Fillion[63]	15	6%
		Hartwig[57]	10	14%
		Li[46]	11	9%
		Majetich[b][c] [64]		
		She[65]	4	32%
		Trauner[62]	6	27%
	taiwaniaquinol C (**249**)	*none reported*		

Structure	Name	Author	Steps	Yield
	taiwaniaquinol D (**250**)	Li[46]	10	11%
		Majetich[b] [64]	14	2%
		Ozeki[48]	19	11%
		Trauner[62]	8	26%
	taiwaniaquinol E (**251**)	*none reported*		
	taiwaniaquinol F (**252**)	Bisai[52]	8	36%
Other related compounds				
	standishinal (**236**)	Node[66]	16	16%
	dichroanone (**239**)	Alvarez-Manzaneda[54]	7	58%
		Banerjee[47]	17	5%
		Bisai[b] [55]	6	15%
		Majetich[67]	11	44%
		Node[59]	12	40%
		Qin[b] [60]	14	26%
		She[65]	5	18%
		Stoltz[68]	11	4%
		Stoltz[b] [61]	10	4%
		Trauner[62]	7	24%
	dichroanal A (**237**)	*none reported*		

Structure	Name	Author	Steps	Yield
	dichroanal B (**238**)	Banerjee[47]	27	3%
		Majetich[67]	14	9%
		Node[59]	10	50%

Some limited studies have been performed on the biological properties of selected taiwaniaquinoids, notably those that have succumbed to total synthesis and non-natural analogues that were easily obtained by derivatisation or were chemical intermediates in total syntheses of the natural products.

Kuo and coworkers isolated twelve of these compounds and tested all of them for their activity against KB epidermoid carcinoma cells.[2] They found that the compounds containing aldehydes at the C7 position: taiwaniaquinones A (**240**), D (**245**) and F (**245**) and taiwaniaquinols A (**247**), C (**249**) and D (**250**) possessed a cytotoxic effect against these cells. Notably, they did not isolate taiwaniaquinones B (**241**) and C (**242**) and thus did not perform biological studies on these compounds. They would again likely be potent bioactive agents, owing to the presence of an aldehyde. They exist as diastereomers of each other, and would be useful in determining if the configuration at C7 affects activity.

Alvarez-Manzaneda tested taiwaniaquinones A (**240**), F (**245**) and G (**5**), as well as a wide variety of derivatives for their antiproliferative effects against MCF-7 breast tumour cells, T-84 colon tumour cells and A-549 lung tumour cells.[69] The natural products provided modest inhibition against these tumour cell lines, but the artificial analogues provided an even greater effect with IC_{50} values as low as 1 μM. In particular, the presence of a bromine atom at the C12 position significantly enhanced antitumour effects. This bromide functionality is not present in any of the natural taiwaniaquinoids.

In a separate study, Alvarez-Manzaneda tested several taiwaniaquinoids and analogues, including taiwaniaquinone G (**5**) and dichroanone (**239**), for their leischmanicidal and tryptanocidal activity.[70] These compounds are typically more effective than the positive controls and exhibit a far wider selectivity index.

Finally, standishinal (**236**) and its acetate were investigated for their effect against Epstein-Barr virus early antigen and for use as aromatase inhibitors.[66] In both studies they showed

poor efficacy.

As shown in Table 11, data is lacking about the biological properties of these compounds. Notably, no biological studies have been reported for taiwaniaquinones B and C and the dichroanals. Lack of access to these compounds is a significant barrier: no syntheses have been reported for either taiwaniaquinone B or C, nor dichroanal A. Due to the endangered status of *T. cryptomerioides* and the low concentration of all these compounds in biomass, total synthesis is the only way forward.

Due to the lack of biological data, it is apparent that many of the investigators are interested in this family of compounds because of the *synthetic* challenges rather than the compounds' medicinal properties. We are no exception here, but it will be of great value to further biological study to develop an efficient, scalable and general synthesis of the taiwaniaquinoid family.

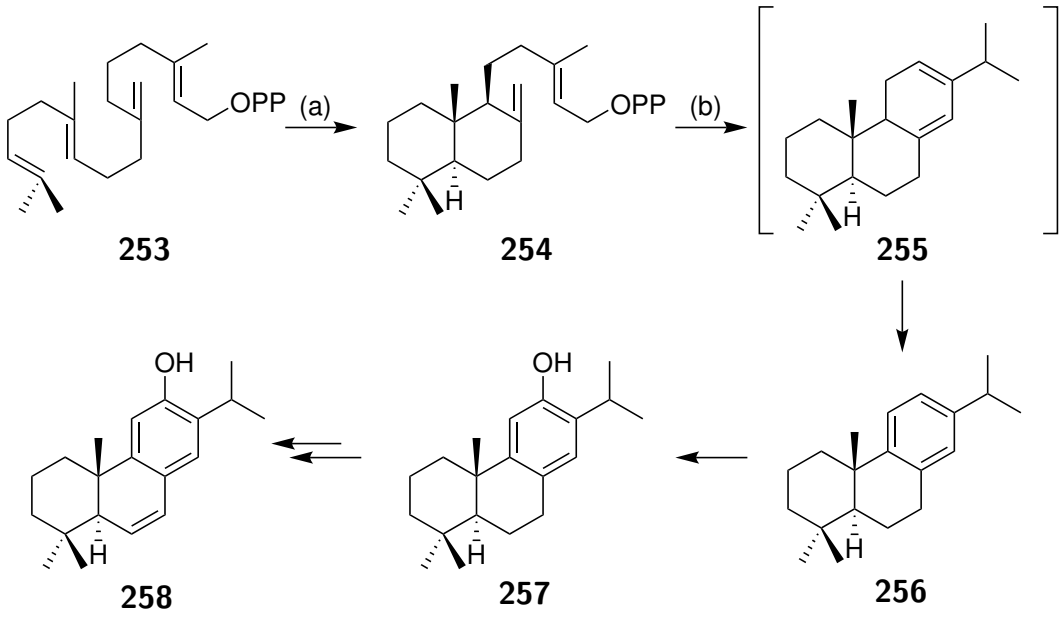
2.1.1 Biosynthesis

While the data about how these compounds affect biological systems is sparse, we have a complete view of how biological systems make the taiwaniaquinoids. The proposed biosyntheses of the taiwaniaquinoid natural products invoke (–)-ferruginol (**257**) as a common intermediate. Geranylgeranyl pyrophosphate (**253**) is partially cyclised to the diene copalyl pyrophosphate (**254**) by Taiwania cryptomerioides copalyl pyrophosphate synthase 4 (TcCPS4). Further cyclisation is performed by Taiwania cryptomerioides kaurene synthase-like synthase (TcKSL3) to the cyclohexadiene levopimaradiene (**255**), which spontaneously aromatises to produce abietriene (**256**).[71] From there, compound **256** is oxidised to (–)-ferruginol (**257**) and installation of a conjugated alkene gives 6,7-dihydroferruginol (**258**). The enzymes involved in these later transformations have not yet been discovered.

Three possible biogenetic pathways have been proposed from compound **258**, a compound that has been isolated from *T. cryptomerioides* (Scheme 34).[72] Cheng proposed dihydroxylation of alkene **258** to 6,7-dihydroxyferruginol (**259**), followed by pinacol rearrangement to give a precursor to taiwaniaquinone A (**262**).[72] Alternatively, oxidative cleavage of alkene **258** could produce dial **260**, a co-isolate from *T. cryptomerioides*.

Table 11: Known biological targets of the taiwaniaquinoid natural products. All values are IC_{50} values in μM. [a] Extracellular forms (promistagotes and epimastigotes) listed. Inhibition data against intracellular forms available in reference. [b] IC_{50} values calculated from reported % inhibition values.

Compound	Kuo[2]	Alvarez-Manzaneda[69]			Alvarez-Manzaneda[a][70]			Node[66]	
	KB	MCF-7	T-84	A-549	*L. infantum*	*L. braziliensis*	*T. cruzi*	EBV-EA[b]	aromatase[b]
Taiwaniaquinones									
taiwaniaquinone A (**240**)	6.9	28.6	30.9	25.1					
taiwaniaquinone B (**241**)									
taiwaniaquinone C (**242**)									
taiwaniaquinone D (**243**)	7.2								
taiwaniaquinone E (**244**)	>10								
taiwaniaquinone F (**245**)	4.4	15.4	11.9	10.1					
taiwaniaquinone G (**5**)	>10	16.8	14.1	30.5	18.3	37.9	41.7		
taiwaniaquinone H (**246**)	>10								
Taiwaniaquinols									
taiwaniaquinol A (**247**)	8.3								
taiwaniaquinol B (**248**)	>10								
taiwaniaquinol C (**249**)	8.1								
taiwaniaquinol D (**250**)	3.5								
taiwaniaquinol E (**251**)	>10								
taiwaniaquinol F (**252**)	>10								
Other related compounds									
standishinal (**236**)								244	60.6
dichroanal A (**237**)									
dichroanal B (**238**)									
dichroanone (**239**)					126.3	55.4	49.9		

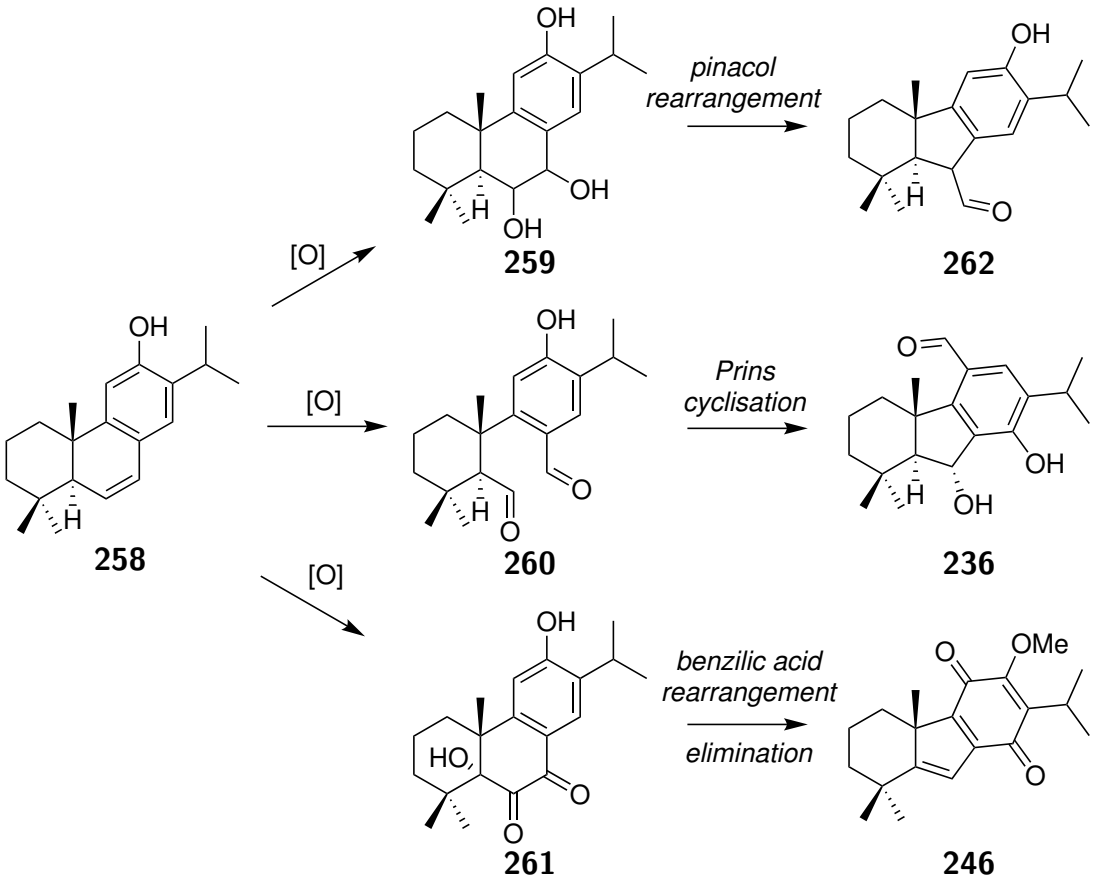


Scheme 33: Biosynthesis of ferruginol (**257**) as an intermediate towards the taiwaniaquinoids.[71] (a) TcCPS4. (b) TcKSL3. Further pathways have been proposed but are not known.

Prins cyclisation of dial **260** gives standishinal (**236**), a result confirmed synthetically by Node.[73] Finally, oxidation of compound **258** to diketone **261**, followed by benzilic acid rearrangement and elimination would give taiwaniaquinone H (**246**), again proposed based on a successful chemical synthesis.[56]

2.1.2 Previous Syntheses

Taiwaniaquinoids are attractive targets due to the challenging fused ring framework. A point of interest is the presence of either diastereomer at the C4–C5 ring junction (Table 10). The *cis*-fused compounds and those with an unsaturated C5–C7 bond have been synthesised many more times than the compounds with the *trans* stereochemistry across the ring junction: more than anything, this likely reflects the difficulty in obtaining the *trans* stereochemistry in these frameworks. While the unsaturated and *cis*-fused compounds are synthesised in fewer overall steps, syntheses of the *trans*-fused compounds are typically lengthy (Table 10) and often involve the inefficient elaboration of existing frameworks.



Scheme 34: Biosynthetic proposals put forth for the production of the taiwaniaquinoids. (a) dihydroxylation followed by pinacol rearrangement.[72] (b) Oxidative cleavage followed by Prins cyclisation.[73] (c) Oxidation, benzilic acid rearrangement and elimination.[56]

Formation of C9–C10 bond

A sensible strategy is to join the A and C rings via the C9–C10 bond, then form the B ring via ring closure in a so-called AC→ABC approach (Figure 16).

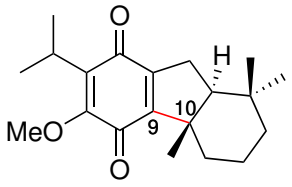
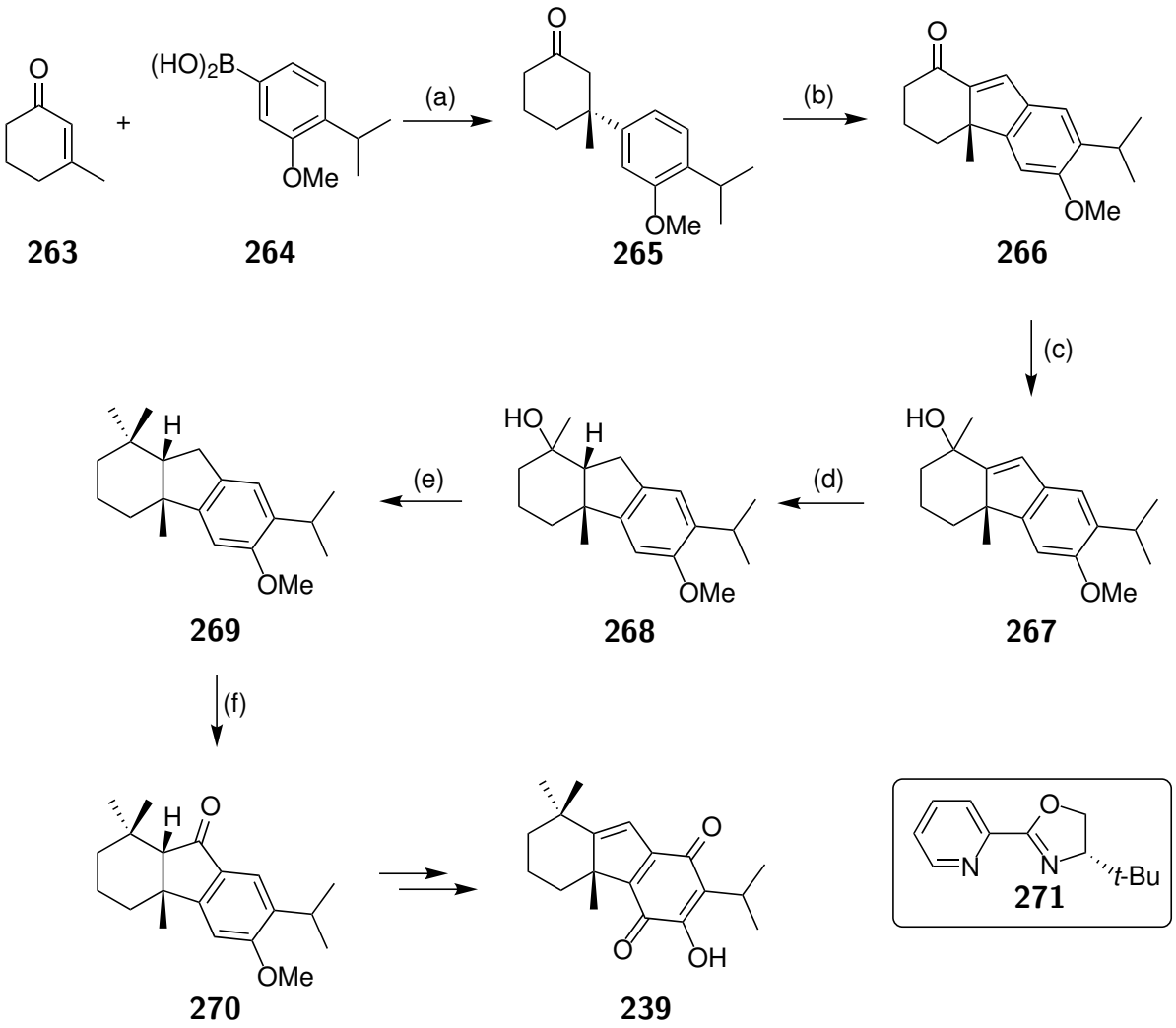


Figure 16: The C9–C10 bond of taiwaniaquinone G.

The Qin group formed this bond using an enantioselective palladium-catalysed conjugate addition (Scheme 35).[60] Treating 3-methylcyclohexenone (**263**) and arylboronic acid **264** with palladium(II) triflate and PyOX ligand **271** gave cyclohexanone **265** in good yield and ee. Treatment with dichlorodimethyl ether and titanium(IV) chloride performed a Friedel-Crafts alkylation and an aldol reaction in one pot to generate the tricyclic compound **266**. The reaction of the cyclic ketone with methylmagnesium iodide generated the

tertiary alcohol **267**, then hydrogenation of the alkene gave the *cis*-fused compound **268**. Dichlorodimethyltitanium was used to install the second methyl group, giving compound **269**. The benzylic ketone **270** was installed by chromium trioxide oxidation, intercepting syntheses by She[65] and Node.[59]

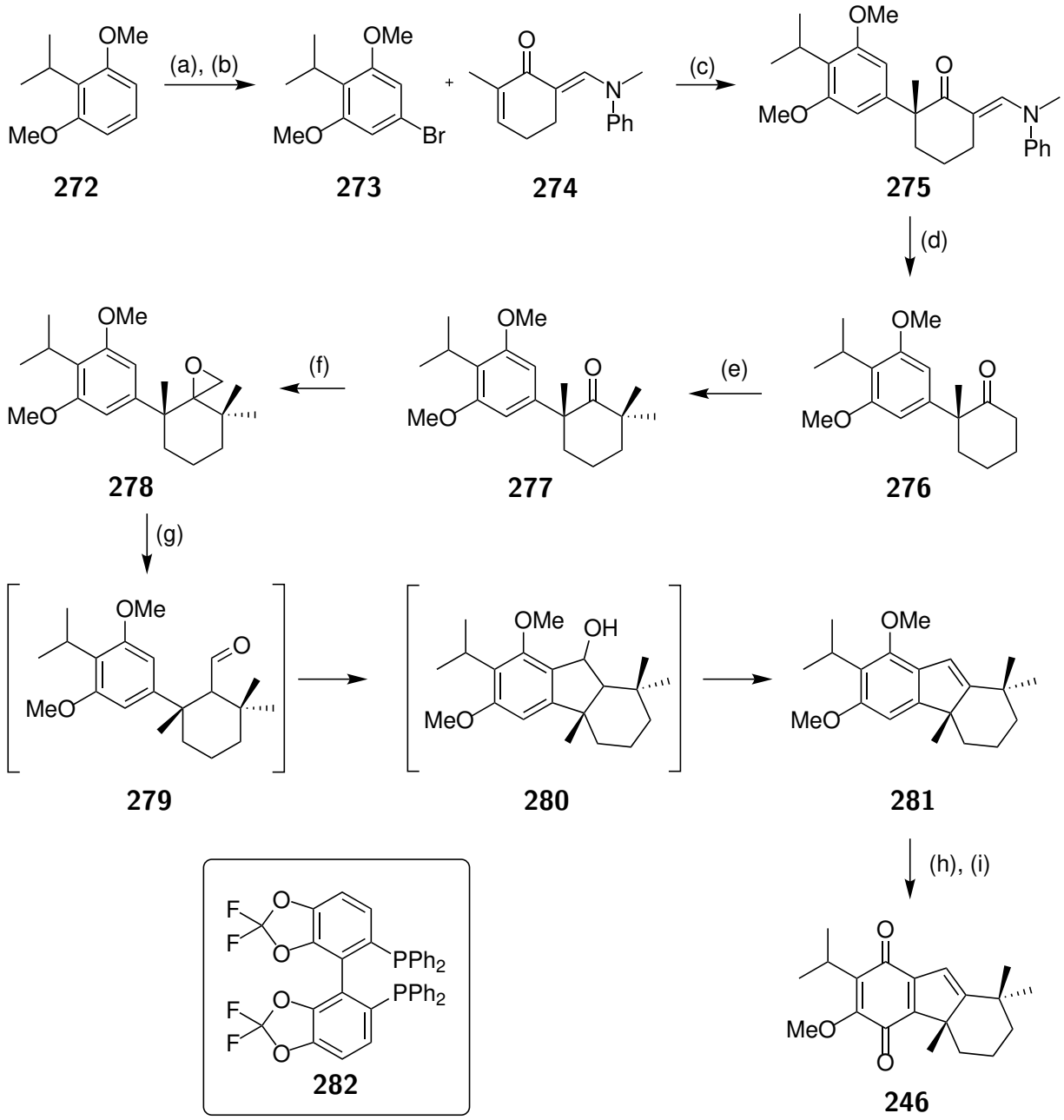


Scheme 35: Qin's formal synthesis of (+)-dichroanone and (+)-taiwaniaquinone H.[60] (a) $Pd(OCOCF_3)_2$, NH_4PF_6, **271**, DCE, 60 °C, 89%, 85% ee (b) Cl_2CHOMe, $TiCl_4$, $CHCl_2$, –78 °C→rt, 76%. (c) MeMgI, Et_2O/THF, 89%. (d) H_2, Pd/C, EtOH/EtOAc, 97%. (e) Me_2Zn, $TiCl_4$, CH_2Cl_2, –30 °C→rt, 72%. (f) CrO_3, AcOH/H_2O, 81%, 83% ee.

Stoltz later attempted to optimise Qin's conjugate addition.[61] This increased the enantiopurity of the final products at the cost of a higher step count due to protecting group manipulations and coincidentally leading to a lower overall yield.

The ability to deliver a single enantiomer at the C10 carbon and a single diastereomer across the C5–C10 bond is a strength of this approach. However, it requires late-stage manipulation of the A-ring following coupling due to the requirement of a cyclic ketone for conjugate addition. Ideally, this should be avoided.

An alternative method was used by Hartwig in the synthesis of taiwaniaquinone H and taiwaniaquinol B (Scheme 36).[57] 2-Isopropyl-1,3-dimethoxybenzene (**272**) was brominated by iridium-catalysed borylation and subsequent displacement with copper(II) bromide to give bromide **273**. This is notable because the bromination occurs selectively at a position that we will later demonstrate to be fairly unreactive. The regioselectivity obtained here is due to the bulk of the large Ir_2-Bpin complex.



Scheme 36: Hartwig's synthesis of taiwaniaquinone H.[57] (a) $[Ir(COD)(OMe)]_2$, *t*-Bu-bpy, THF, 80 °C. (b) $CuBr_2$, H_2O/MeOH, 80 °C, 75% over 2 steps. (c) $Pd(dba)_2$, **282**, NaO*t*-Bu, PhMe, 80 °C, 80%, 94% e.e. (d) HCl (1 M), then NaOH (1 M), 90 °C, 91%. (e) NaHMDS, MeI, THF, 0 °C to rt, 86%. (f) NaH, Me_3SI, 95%. (g) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C, 50–75%. (h) $BBr_3{\cdot}SMe_2$, CH_2Cl_2, 80 °C. (i) O_2, salcomine, DMF, rt, 51% over 2 steps.

Palladium catalysed α-arylation with cyclohexenone **274** gave coupled product **275** in excellent yield and ee. The enamine was removed by hydrolysis to give cyclohexanone **276**, then double methylation with sodium hexamethyldisilazane and methyl iodide gave the *gem*-dimethyl compound **277**. Corey-Chaykovski reaction of the ketone **277** gave epoxide **278**. Treatment of epoxide **278** with boron trifluoride etherate or bismuth(III) chloride triggered a cascade beginning with rearrangement to the aldehyde **279**, then Friedel-Crafts alkylation to form the carbinol **280**, then elimination of the alcohol to form the alkene **281** in good yield. Finally, two-step dealkylation then oxidation to the quinone delivered taiwaniaquinone H (**246**) in 15% over 10 steps.[57]

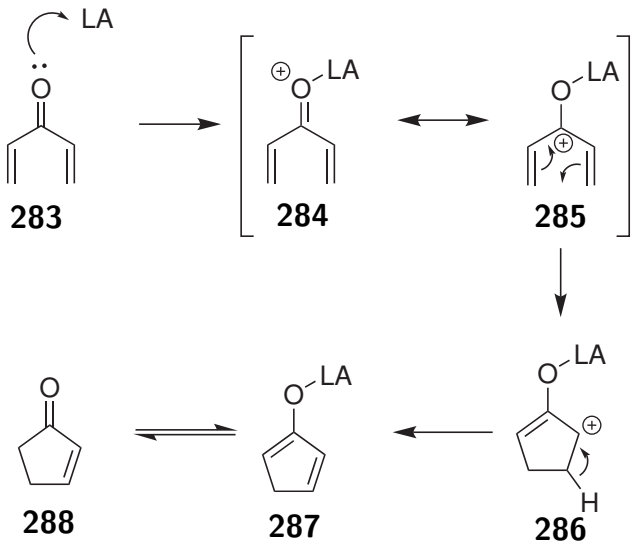
Intermediate **281** could be transformed into (–)-taiwaniaquinol B.[57] Hydroboration-oxidation followed by further oxidation with IBX gave ketone **293**. Boron trichloride demethylation and quinone oxidation/reduction installed the hydroquinone functionality, giving (–)-taiwaniaquinol B (**248**) in 12% over 12 steps.[57]

In Hartwig's synthesis, we again see the need for elaboration of the A-ring after conjugate addition. In this case, an enamine was needed at the C4 carbon and attempts to perform the conjugate addition with other cyclohexenones failed. Given the need for late-stage transformation of the A-ring, it would be prudent to explore instead AC→ABC approaches where the initial coupling event occurs between C7 and C8, and ring closure is performed by a subsequent C9–C10 bond-forming event.

Nazarov cyclisation

The Nazarov reaction is a 4π electrocyclisation of a divinyl ketone to the corresponding cyclopentenone under Lewis acidic conditions (Scheme 37).[74] Treatment with Lewis acid generates the pentadienyl cation **285** which undergoes conrotatory cyclisation to generate the cyclic cation **286**. Elimination reforms the alkene **287**, and tautomerisation gives the ketone **288**.

Nazarov cyclisation is a common and effective methodology for providing the taiwaniaquinoid core, with several groups employing a Nazarov reaction as the key ring-forming step. Trauner's Nazarov triflation provided one of the most direct examples of this methodology, enabling the synthesis of three of the taiwaniaquinoids and the related (±)-dichroanone (**239**).[62] Lithium halogen exchange of aryl bromide **289** and addition to

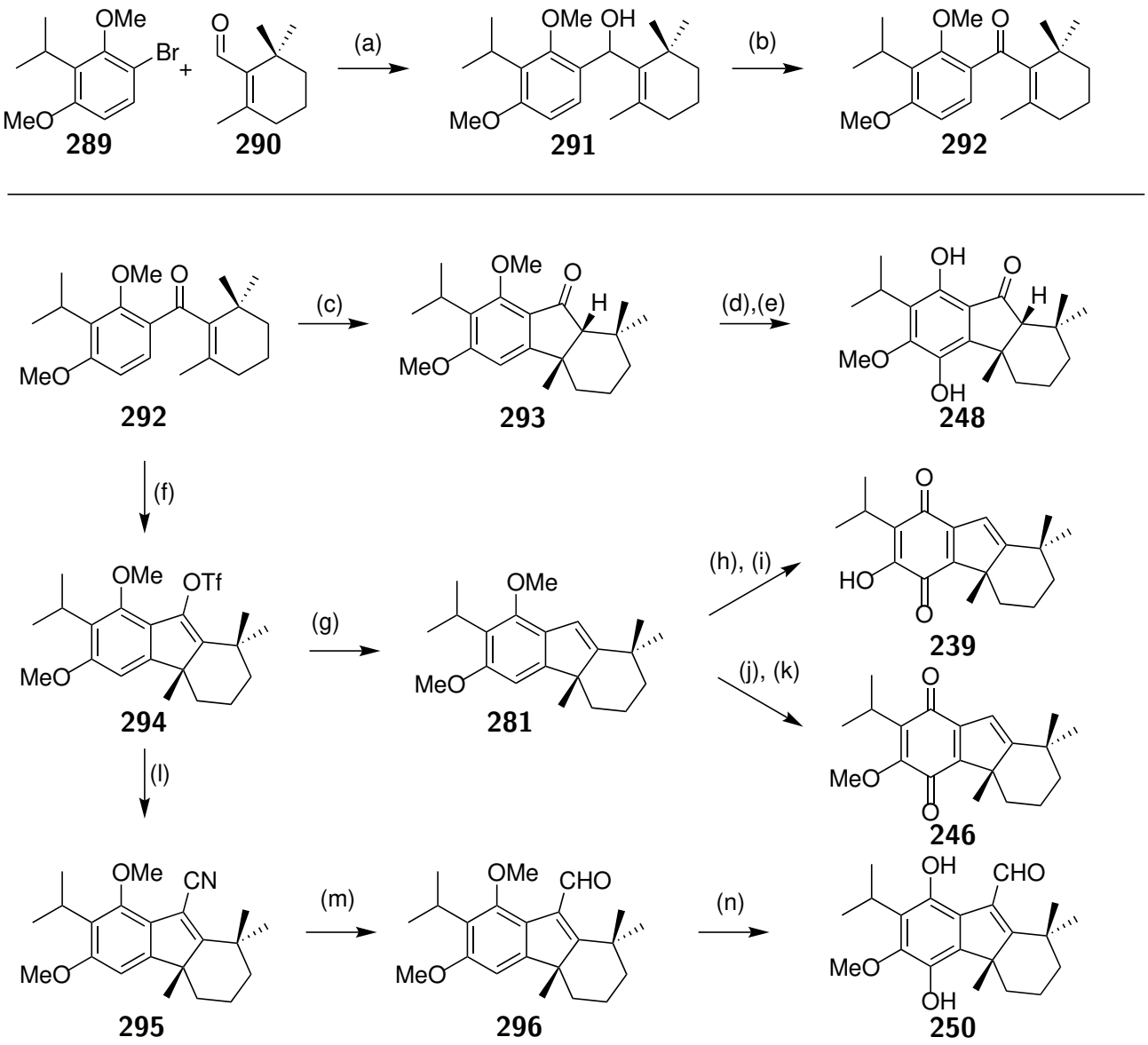


Scheme 37: Mechanism of the Nazarov cyclisation.[74]

β-cyclocitral (**290**) gave the benzyl alcohol **291** with Dess-Martin periodinane giving the ketone **292**. Treatment with trimethylsilyl trifluoroacetate (TMSOTf) performed Nazarov ring closure to compound **293**, with protonation occurring from the sterically available face to give the *cis*-fused compound. Demethylation and quinone oxidation/reduction gave (±)-taiwaniaquinol B (**248**) in 27% over 5 steps from aryl bromide **289**.

Treatment of ketone **292** with triflic anhydride instead gave the ring-closed triflate **294**. Reduction of the triflate with palladium(II) acetate and ammonium formate gave the trisubstituted alkene **281**, which could be converted into (±)-dichroanone (**239**) and (±)-taiwaniaquinone H (**246**) by demethylation and oxidation. Taking triflate **294** and performing a palladium-catalysed cyanation gave the nitrile **295**, which was reduced selectively to the aldehyde **296** with diisobutylaluminium hydride (DIBAL). Demethylation and quinone oxidation/reduction again gave (±)-taiwaniaquinol D (**250**).[62]

Nazarov cyclisation methodologies are only effective for compounds with the *cis* configuration across the AB ring junction or an alkene across the C5–C7 bond. Epimerisation occurs under the reaction conditions, giving only the more stable *cis* stereochemistry.

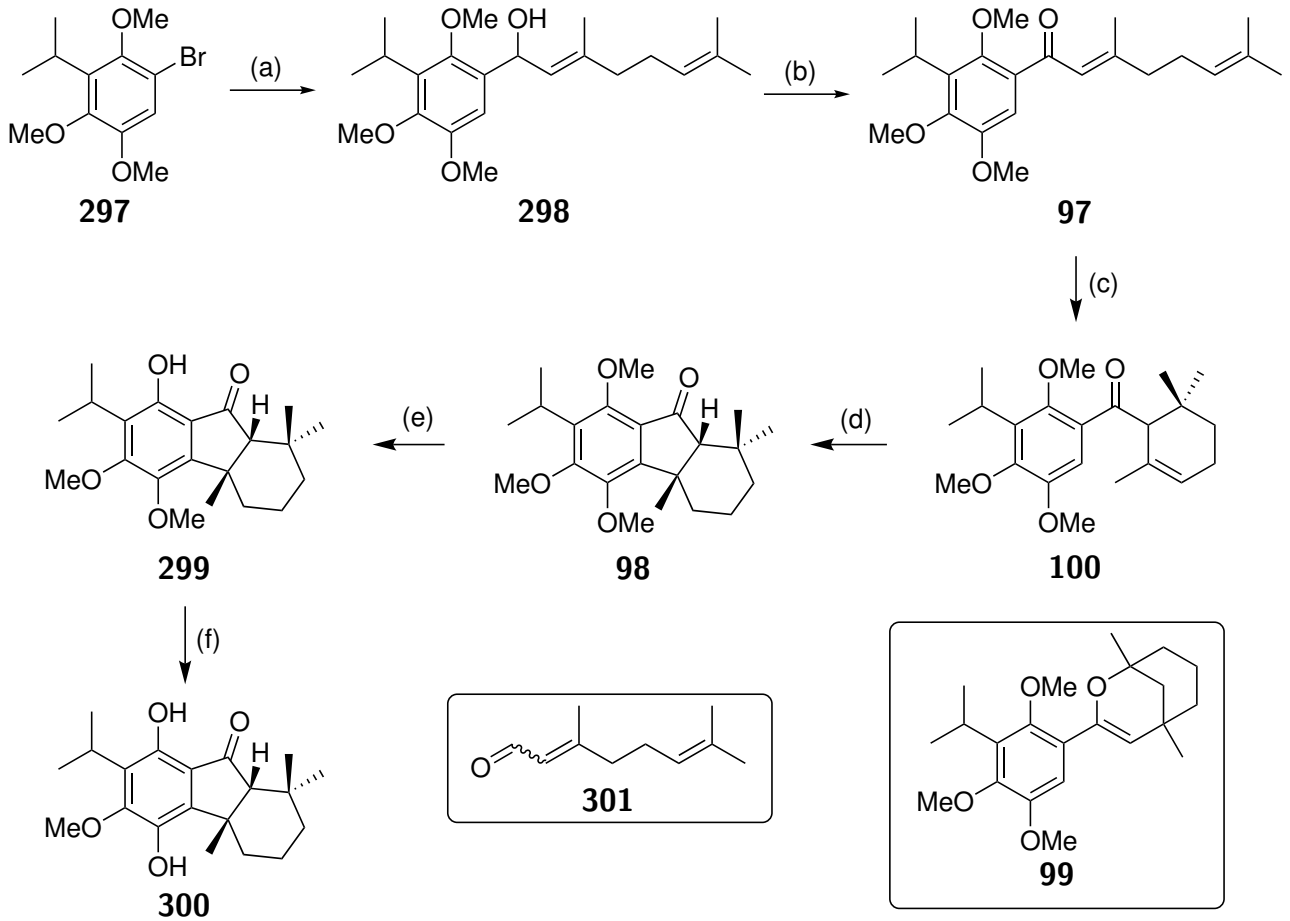


Scheme 38: Trauner's Nazarov triflation.[62] (a) *n*-BuLi, Et_2O, –25 °C→rt, 89%. (b) Dess-Martin, pyr, CH_2Cl_2, 90%. (c) TMSOTf, $MeNO_2$, Δ, 70%. (d), BCl_3, CH_2Cl_2, 95%. (e) CAN, $MeCN/CH_2Cl_2/H_2O$, then $Na_2S_2O_4$, H_2O, 51%. (f) Tf_2O, 2,6-DTBP, $MeNO_2$, Δ, 70%. (g) $Pd(OAc)_2$, $P(OMe)_3$, Et_3N, NH_4HCOO, DMF, 120 °C, 98%. (h) BBr_3, CH_2Cl_2. (i) salcomine, DMF, O_2, 45% over 2 steps. (j) $BBr_3 \cdot SMe_2$, DCE, Δ, 68%. (k) salcomine, DMF, O_2, 80%. (l) $Pd(OAc)_2$, $P(OMe)_3$, TMSCN, DMF, rt, 75%. (m) DIBAL, PhMe, –78 °C, 39%. (n) BBr_3, CH_2Cl_2, 93%.

Polyene cyclisations

Syntheses utilising a Nazarov cyclisation followed an AB→ABC strategy, where pre-formed A and C rings were coupled together in an initial step before B-ring formation. However, the taiwaniaquinone A-ring can be formed by polyene cyclisation. Such a polyene cyclisation would be considered a C→ABC strategy, in which the desired AB ring system is formed in one-pot.

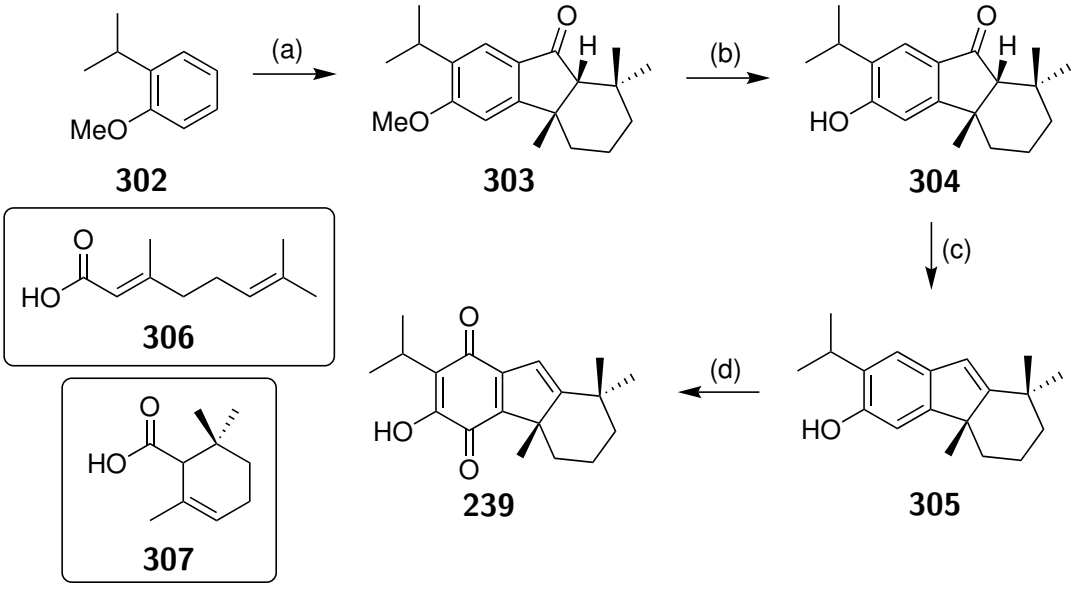
Chiu used a polyene cyclisation in the synthesis of (±)-taiwaniaquinol B.[24] Starting with aryl bromide **297**, lithium halogen exchange and quench with citral (**301**) gave carbinol **298**, which was oxidised to the ketone **97** with manganese dioxide. Tin(IV) chloride monocyclised **97** to the exocyclic ketone **100**, with further treatment with trifluoromethanesulfonic acid giving the fully cyclised compound **98**. Given the structure of ketone **100**, it is likely that this ring closure proceeds via Nazarov reaction. These two reactions could be performed in tandem by using instead trimethylsilyl trifluoromethanesulfonate, albeit in low yield with the production of large amounts of side product **99**. Cleavage of the methyl ether with boron trichloride and oxidation then reduction of the quinone again gave the natural product, (±)-taiwaniaquinol B (**300**) in 6 steps in 35% overall yield.[24]



Scheme 39: Chiu's synthesis of taiwaniaquinol B.[24] (a) *n*-BuLi, Et_2O, then citral, 86%. (b) MnO_2, $CHCl_2$, 78%. (c) $SnCl_4$, $MeNO_2$, 89%. (d) TfOH, $MeNO_2$, 100 °C, 71%. (e) BCl_3, $CHCl_3$, 98%. (f) $PhI(OAc)_2$, $MeCN/H_2O$, then $Na_2S_2O_3$, 85%.

The She group went further with this strategy.[65] Isopropylanisole (**302**) was treated with geranic acid (**306**) in the presence of phosphorus pentoxide in neat methanesulfonic acid which performed a Friedel-Crafts alkylation and polyene cyclisation to tricyclic **303** in

good yield. Reduction and elimination of the ketone and manipulation of the aryl ring gave (±)-dichroanone (**239**) in only five steps in 18% yield. She also treated a number of aromatics with cyclogeranic acid (**307**) under the same reaction conditions to access analogues. As in the example above, the involvement of a Nazarov cyclisation is likely.



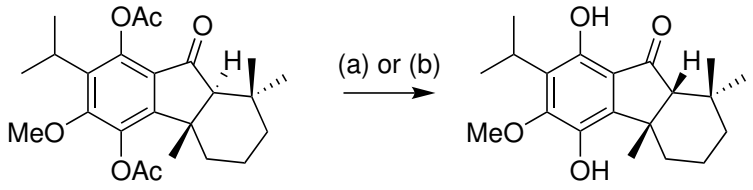
Scheme 40: She's synthesis of (±)-dichroanone.[65] (a) **306**, P_2O_5, $MeSO_3H$, 64%. (b) BBr_3, CH_2Cl_2, 85%. (c) $NaBH_4$, EtOH, then $SOCl_2$, pyridine/$CHCl_2$, 92%. (d) IBX, $CHCl_3$, rt, then C_6F_5SH, rt, then O_2, NaOH, MeOH, 75 °C, 35%.

These are effective sequences and highlight the power of a polyene cyclisation methodology in constructing taiwaniaquinoids. However, given that B-ring formation likely occurs via a Nazarov cyclisation, only the *cis*-fused compounds are available by this approach.

2.1.3 *trans*-Fused taiwaniaquinoids

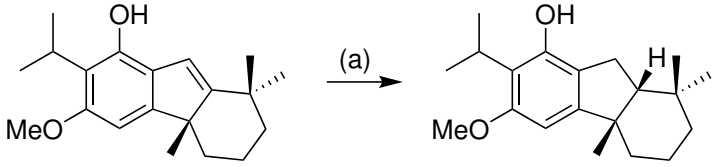
All the strategies we have discussed so far allow for access to the taiwaniaquinoid core in relatively short order and sometimes enantioselectively. However, these all lead to products where the AB ring junction has the *cis* stereochemistry or possesses an alkene. Intermediates that possess a ketone at the benzylic position undergo C5 epimerisation rapidly under acidic or basic reaction conditions to give the more stable *cis* diastereomer (Scheme 41).[51] Likewise, hydrogenation of the alkene intermediates occurs from the sterically available convex face, again leading to the *cis* stereochemistry in the product (Scheme 42).[53]

Efficient routes towards the *trans*-fused taiwaniaquinoids have not yet been discussed.



308 **248**

Scheme 41: Epimerisation of the *trans* compound is facile under both acidic and basic conditions.[51] (a) HCl, MeOH, Δ, 17 h, 88%. (b) KOH, MeOH, 83%.



309 **310**

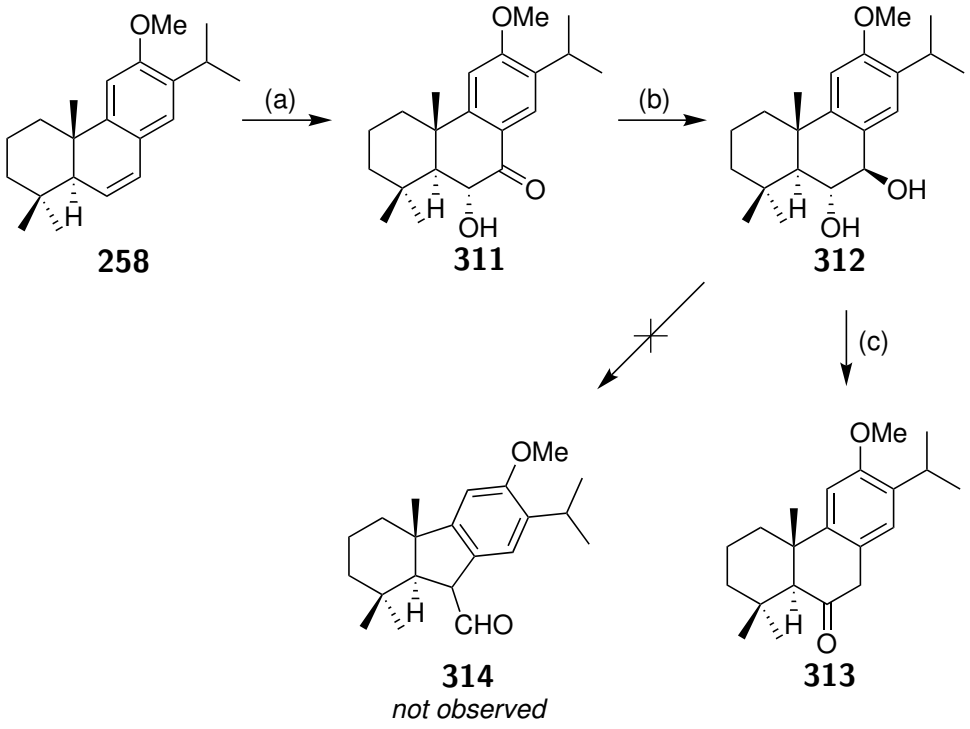
Scheme 42: Hydrogenation of the unsaturated compound gives the *cis* architecture.[53] (a) Pd/C, H_2, MeOH, 40 °C, 30 h, 99%.

We have chosen to specifically target taiwaniaquinone G (**5**), which has been synthesised twice before, both times by the Alvarez-Manzaneda group. It is the simplest *trans*-fused taiwaniaquinoid, exhibiting no functionalisation at the C7 position.

An obvious strategy for the synthesis of taiwaniaquinone G would be to mimic nature, by taking ferruginol or a similar 6,6,6-fused ring system and excising a carbon to generate the 6,5,6-fused ring system. These would be termed ABC→ABC strategies.

Alvarez-Manzaneda investigated the biomimetic synthesis of taiwaniaquinoids from abietanes including *O*-methyl-6,7-dihydroferruginol (**258**; Scheme 43).[51] Treating alkene **258** with osmium tetroxide generated the α-ketoalcohol **311** which was reduced to the *anti*-diol **312** using lithium aluminium hydride. Unfortunately, treatment with a number of acids to generate aldehyde **314** via a Pinacol rearrangement proved unsuccessful. Instead, the ketone **313** was formed by elimination and tautomerisation.

In order to effect the desired biomimetic ring contraction Alvarez-Manzaneda was forced to take a far lengthier course. Starting from (+)-abietic acid (**315**), a series of reactions replaced the alkene with a dioxolane ring and reduced the carboxylic acid to the corresponding alkane. These operations took six steps with a total yield of 40%. The central 6-member ring was opened by ozonolysis and then closed by an aldol reaction to give the 5-member ring. The exocyclic aldehyde was reduced to the alcohol and protected as the acetate, then the tertiary alcohol was eliminated and allylic oxidation was performed



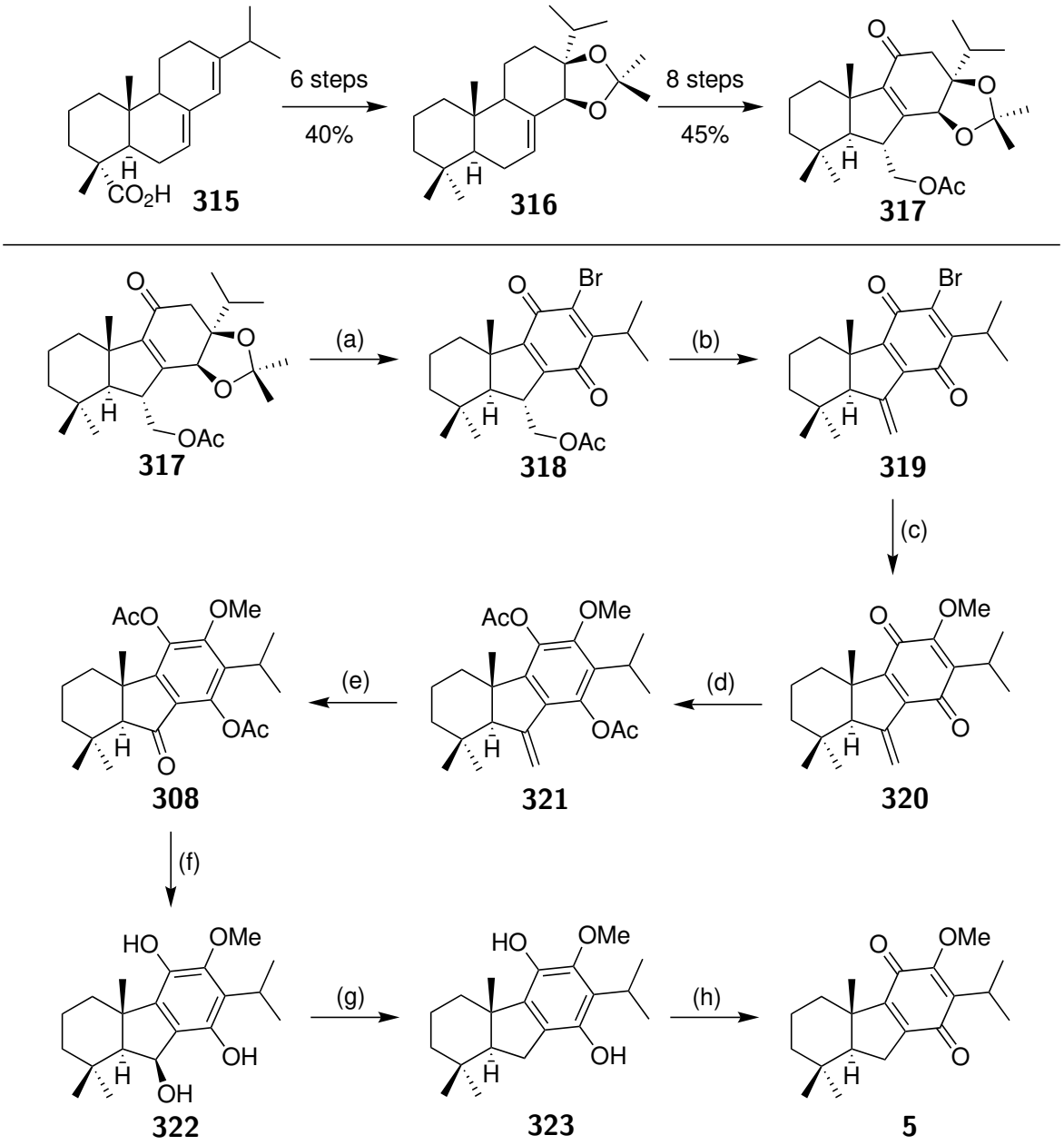
Scheme 43: Alvarez-Manzaneda's attempted Pinacol rearrangement instead gives ketone **313**.[51] (a) OsO_4, Me_3NO, pyridine/*t*-BuOH, Δ, 79%. (b) $LiAlH_4$, THF, 0 °C to rt, 88%. (c) Amberlyst A-15, CH_2Cl_2, rt, 82%.

to produce ketone **317**. This whole process took a further 8 steps with an overall yield of 45%. At this stage, 14 steps had been performed in total giving a mere 18% overall yield. However, this was only a common precursor to some of the taiwaniaquinoids. Further work is needed to elaborate ketone **317** to the desired natural products.

In the case of taiwaniaquinone G, this was a long sequence, involving elimination of the acetate, ozonolysis of the resulting alkene and then reduction to the alkane, with a number of protecting group interconversions and redox manipulations of the quinone to and from the hydroquinone. This took another 8 steps at 20% yield total. Overall, the synthesis of (–)-taiwaniaquinone G, starting from a more complex natural product precursor, took 22 steps with a total yield of only 4%.

This is not an effective strategy for synthesising the taiwaniaquinones. While it is an enantiospecific synthesis, starting from enantiomerically pure (+)-abietic acid, it takes too long to elaborate the abietic acid framework to the 6,5,6-system seen in the taiwaniaquinoids.

Li used a similar ring contraction strategy to deliver the *trans*-fused framework far more efficiently, albeit in a racemic synthesis (Scheme 45).[46] Cyclisation of polyene **326** was



Scheme 44: Summary of Alvarez-Manzaneda's synthesis of (–)-taiwaniaquinone G.[51] (a) Br_2, CH_2Cl_2, 81%. (b) DBU, benzene, 48 h, 85%. (c) NaOMe, MeOH, rt, 96%. (d) $Na_2S_2O_4$, $CHCl_3$, H_2O; then Ac_2O, pyridine, 96%. (e) O_3, MeOH, CH_2Cl_2, –78 °C, then Me_2S, rt, 91%. (f) $LiAlH_4$, Et_2O, 93%. (g) $NaBH_3CN$, ZnI_2, CH_2Cl_2, 82%. (h) MnO_2, $CHCl_3$, 95%.

a key step here. Starting from aldehyde **324**, Wittig reaction with methyltriphenylphosphonium iodide gave the terminal alkene **325**, which was hydroborated and reacted with vinyl iodide **334** to give the homogeranylarene **326**. Cyclisation with bismuth(III) triflate provided the 6,6,6-fused compound **327**, which contained the diastereomerically pure *trans* framework expected from these cyclisations.

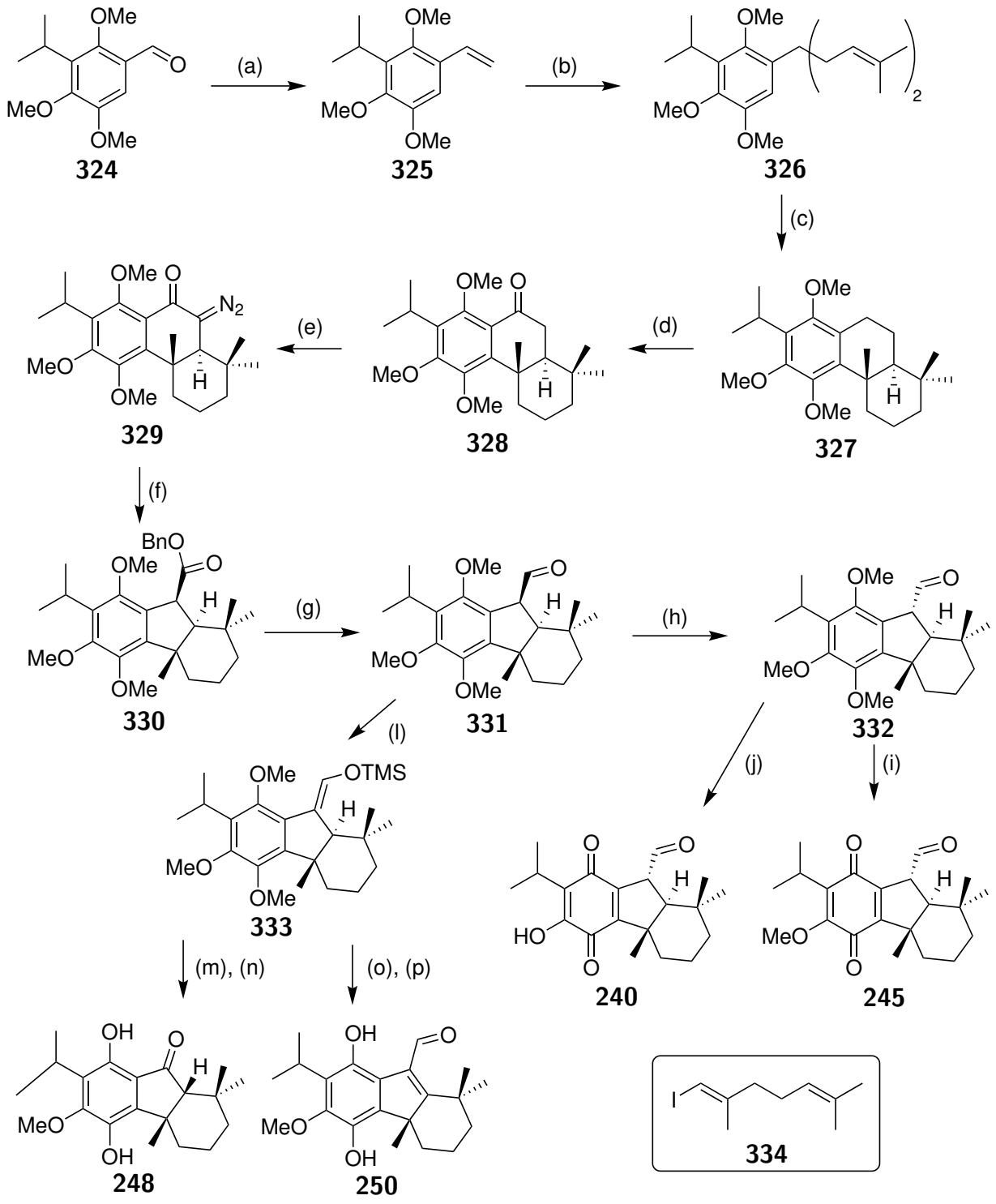
Compound **327** was then elaborated to undergo ring contraction. Chromic acid oxidation gave the phenyl ketone **328** and the α-diazonium unit was installed with 2,4,6-

triisopropylbenzenesulfonyl azide, setting the scene for a Wolff contraction. Benzyl alcohol and 2,4,6-collidine at 160 °C gave the ester **330**, which was reduced with lithium aluminium hydride followed by Dess-Martin periodinane to give the aldehyde **331** with the undesired stereochemistry at the C7 position. Aldehyde **331** proved to be a versatile intermediate. Treating with trimethylsilyl triflate gave the silyl enol ether **333**, which was dihydroxylated with *in situ* diol cleavage, followed by demethylation to give taiwaniaquinol B (**248**) in 9% total yield over 11 steps. However, a trace of an α-hydroxyaldehyde is mentioned, but not isolated or characterised. This uncharacterised aldehyde could likely be a precursor to one of the taiwaniaquinones B (**241**) or C (**242**). Silyl ether **333** was also subjected to Saegusa-Ito oxidation, with demethylation giving taiwaniaquinol D (**250**) in 11% yield over 103 steps.

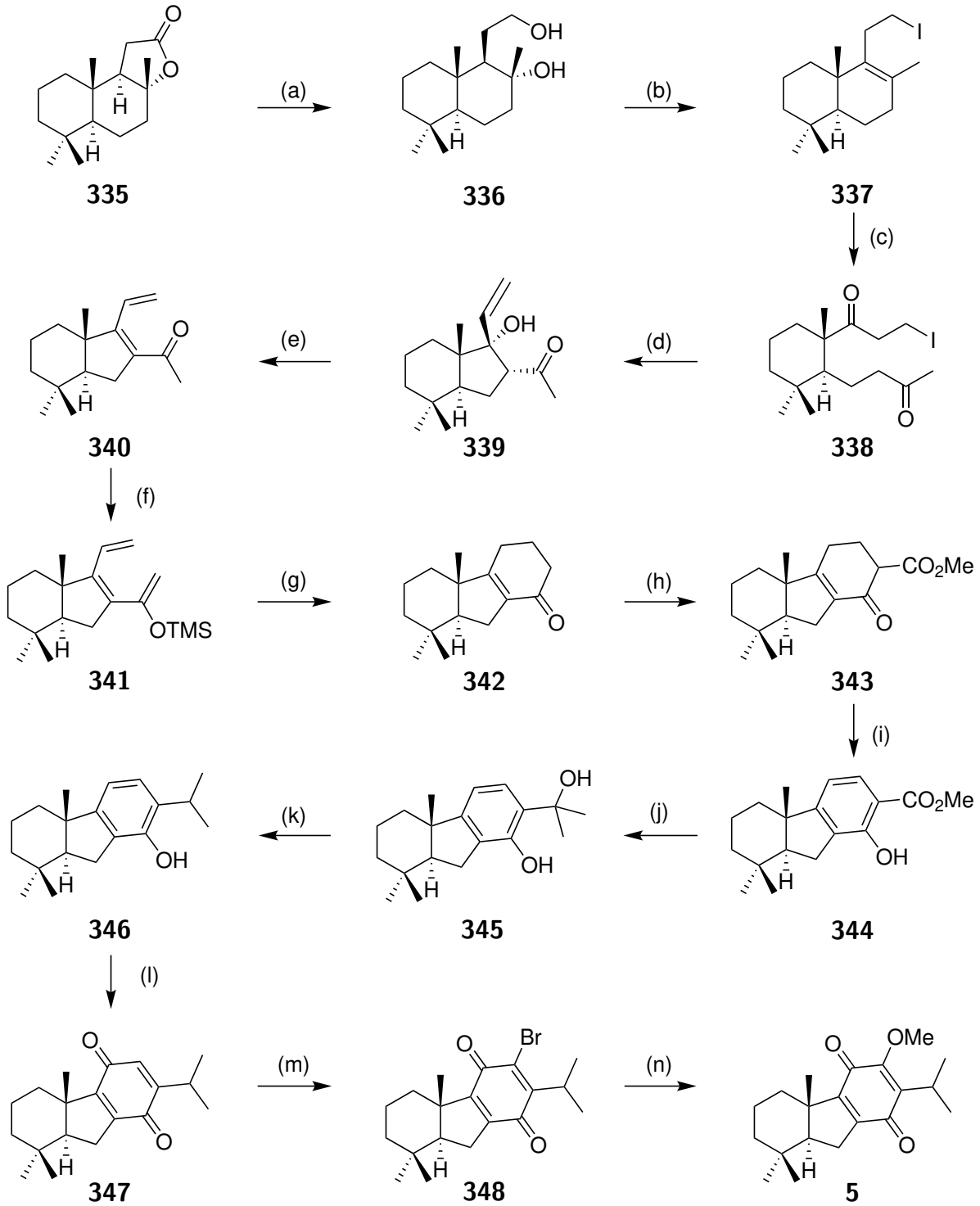
Epimerisation of aldehyde **331** to the desired diastereomer **332** was effected by potassium carbonate in ethanol at reflux. Oxidation of trimethyl ether **332** directly with ceric ammonium nitrate gave taiwaniaquinone F (**245**) in 11% over 10 steps. From aldehyde **332**, non-selective ether cleavage using boron tribromide, followed by aerobic oxidation gave taiwaniaquinone A (**240**) in 11% over 10 steps.

Alvarez-Manzaneda's second synthesis of (–)-taiwaniaquinone G (**5**) is far more direct than the first (Scheme 46).[50] Starting from (+)-sclareolide (**335**), potassium borohydride was used to reductively open the lactone to diol **336**. Treating diol **336** under Appel conditions iodinated the primary alcohol while eliminating the tertiary alcohol to produce alkene **337**. Ozonolysis generated the diketone **338** which was subjected to aldol condensation to produce the cyclopentanol **339**. Subsequent elimination of the tertiary alcohol and silyl enol ether formation gave the triene **341** required for the key electrocyclisation reaction. Heating triene **341** in xylenes at reflux gave the cyclohexenone **342**, which was alkylated under basic conditions with methyl cyanoformate, then the ring was oxidised to the aromatic **344**. The ester was elaborated to the cumene **346** with methylmagnesium bromide and reductive cleavage of the tertiary alcohol. Fremy's salt provided the quinone **347**, with conjugate addition of bromine followed by addition/elimination of methoxide giving (–)-taiwaniaquinone G (**5**) in a shorter 14 steps with a far higher 25% yield.[50]

Diol **336** was also prepared by polyene cyclisation of homofarnesyl acetate with subsequent lipase-catalysed kinetic resolution affording the desired single enantiomer but in far lower yield.[50] Like Li's synthesis, that cyclisation to the decalin system gave the



Scheme 45: Li's synthesis of taiwaniaquinones A & F and taiwaniaquinols B & D.[46] (a) Ph_3MeI, *n*-BuLi, 0 °C, 92%. (b) 9-BBN, $Pd(dppf)Cl_2$, **334**, NaOH, THF 40 °C, 83%. (c) $Bi(OTf)_3$, $MeNO_2$, 80 °C, 71%. (d) CrO_3, 3,5-dimethylpyrazole, –10 °C, 89%. (e) $TrisN_3$, Bu_4NOH, 40 °C, 78%. (f) BnOH, 2,4,6-collidine, 160 °C, 56%. (g) $LiAlH_4$, then Dess-Martin periodinane, 75%. (h) K_2CO_3, EtOH, 80 °C, 93%. (i) CAN, 76%. (j) BBr_3, CH_2Cl_2, –78→–15 °C, air, 76%. (k) TMSOTf, Et_3N, CH_2Cl_2, 92%. (l) $K_2OsO_2(OH)_4$, NMO, MeCN/H_2O, 79%. (m) BBr_3, CH_2Cl_2, –78 °C, then CAN, MeCN/H_2O, then $Na_2S_2O_4$, 81%. (n) $Pd(OAc)_2$, DMSO, 65 °C, 84%. (o) BBr_3, CH_2Cl_2, –78 °C, then CAN, MeCN/H_2O, then $Na_2S_2O_4$, 80%.

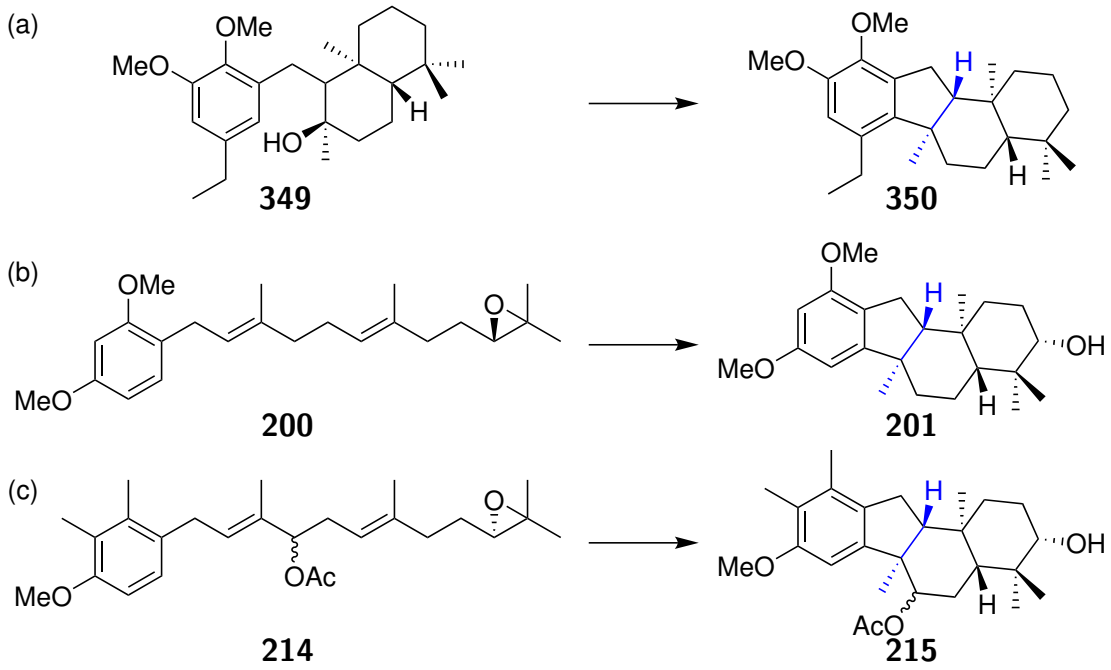


Scheme 46: Alvarez-Manzaneda's second synthesis of (–)-taiwaniaquinone G using a key 6π electrocyclisation.[50] (a) KBH_4, EtOH, Δ, 96%. (b) I_2, PPh_3, CH_2Cl_2, 83%. (c) O_3, CH_2Cl_2, –78 °C, then Me_2S, 75%. (d) DBU, PhH, 90%. (e) H_2SO_4, dioxane, 73%. (f) TMSOTf, *i*PrNEt$_2$, CH_2Cl_2, 0 °C, quant. (g) Xylene, Δ, 92%. (h) LDA, THF, –78 °C, then NCCOOMe, THF, –78 °C, 97%. (i) DDQ, dioxane, Δ, 94%. (j) MeMgBr, THF, 97%. (k) Et_3SiH, TFA, CH_2Cl_2, –40 °C, 95%. (l) Fremy's salt, acetone, 94%. (m) Br_2, AcOH, 89% (n) NaOMe, MeOH, 97%.

desired *trans* stereochemistry. In all three of these syntheses, the *trans* stereochemistry at this important ring junction was set early in the sequence.

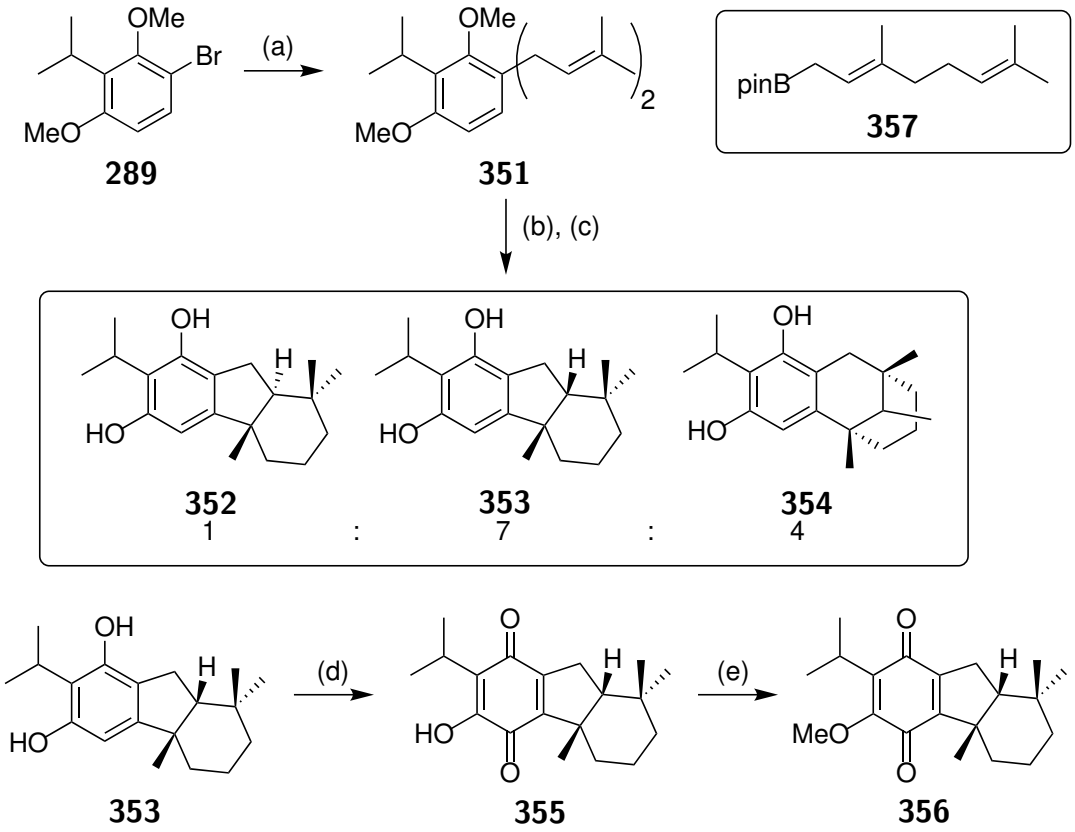
We propose that these methods cannot possibly be the most efficient routes to the *trans*-fused taiwaniaquinoids. Much as Chiu's[24] and She's[65] work provided the *cis*-fused taiwaniaquinoids in short order by a polyene cyclisation strategy, a similar strategy without the benzylic ketone should provide the *trans*-fused system. Precedent for this comes from the synthesis of similar tetracyclic compounds where Friedel-Crafts alkylation is a key ring-forming event.

In Andersen's synthesis of pelorol, the decalin moiety was obtained directly from (+)-sclareolide, with further elaboration giving alcohol **349**.[75] Treatment with tin(IV) chloride eliminated the alcohol and allowed for ring closure to the *trans*-fused compound **350** (Scheme 47). Later work by Andersen on analogues of pelorol[8] showed that epoxide-mediated polyene cyclisation of compound **200** again delivered the *trans*-fused compound **201**. She's synthesis of (–)-walsucochin B[39] using a similar epoxide-mediated polyene cyclisation resulted again in the *trans*-fused compound **215**.



Scheme 47: Cyclisations of similar compounds during the synthesis of (a) pelorol[75] (b) the synthesis of pelorol anologues[8] and (c) the synthesis of (–)-walsucochin B.[39]

This work inspired the McErlean group's previous synthesis of (±)-5-epi-taiwaniaquinone G (Scheme 48), in an effort to access quickly the *trans*-configured compounds.[25] Suzuki coupling between aryl bromide **289** and boronate **357** delivered the geranylarene **351**.



Scheme 48: McErlean group synthesis of 5-epi-taiwaniaquinone G.[25] (a) **357**, $Pd(PPh_3)_4$, NaOH, PhMe/H_2O, 100°C, 73%. (b) $BF_3{\cdot}OEt_2$, $EtNO_2$. (c) BBr_3, CH_2Cl_2, 21% over 2 steps. (d) Fremy's salt, KH_2PO_4, acetone/H_2O, 98%. (e) MeI, K_2CO_3, MeCN, 35%.

While formation of the A ring was facile, Friedel-Crafts type alkylation to form the B ring was more difficult. Bismuth(III) triflate at elevated temperatures or boron trifluoride etherate at room temperature, each in nitromethane, were found to catalyse the full cyclisation of polyene **351**, which was immediately cleaved to the diol to facilitate HPLC separation. In opposition to expectations, the *cis* isomer **353** was highly favoured in a 7:1 ratio with the *trans* isomer **352**. Rearrangement product **354** was also present. Oxidation with Fremy's salt gave quinone **355** with the methyl ether being reinstalled with methyl iodide and potassium carbonate to give (±)-5-epi-taiwaniaquinone G in 11% yield over eight steps.[25] This is the shortest reaction sequence reported in the literature for these compounds, although in lower yield than Alvarez-Manzaneda's synthesis.[62] The final methyl ether formation is key for the loss of material here: intermediate **355** is produced in 31% yield over seven steps.

The *cis* stereochemistry observed here is surprising. All the examples of polyene cyclisations we have seen so far deliver a *trans* configuration at the proximal ring junction, with the closest comparison being Yamamoto's bromonium cyclisation reported after the

inception of our group's work.[30] In Yamamoto's example, *none* of the *cis* configured compound was seen (Table 12).

Table 12: Previously reported cyclisations to 6,5,6 compounds.

SM	Lewis acid	Solvent	T/°C	Yield	*cis*:*trans*
230[30]	**150**, DMDBH	PhMe/CH_2Cl_2	–90	91%	0:1
351[25]	$Bi(OTf)_3$	$MeNO_2$	80	20%	7:1
351[25]	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt	21%	7:1

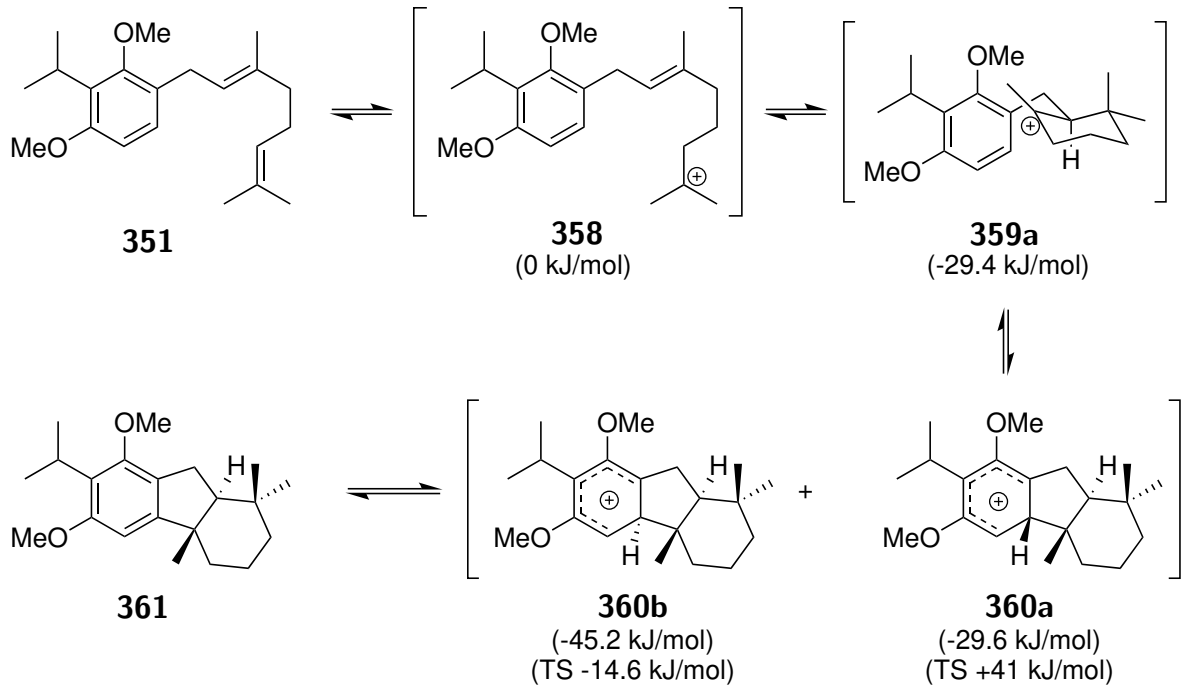
McErlean investigated the factors behind this puzzling selectivity by computational modelling.[41] It is assumed that this reaction follows a discrete, stepwise pathway: many sets of conditions produced the monocyclised cyclohexene only and indeed monitoring by ^{1}H NMR spectroscopy shows stepwise formation of the cyclohexene followed by a second alkylation to generate the fully cyclised compound **352**. Indeed, McErlean could not find a transition state for the concerted cyclisation using DFT methods.

As seen with Snyder's syntheses of the four diastereomers of peyssonol (Scheme 18), the configuration of each alkene can have significant impact on the diastereoselectivity of the final product.[9] Diastereomerically pure (*E*)-geraniol (**374**) was employed, but we anticipated isomerisation could occur under strongly acidic conditions leading to each of the diastereomers of taiwaniaquinone G.

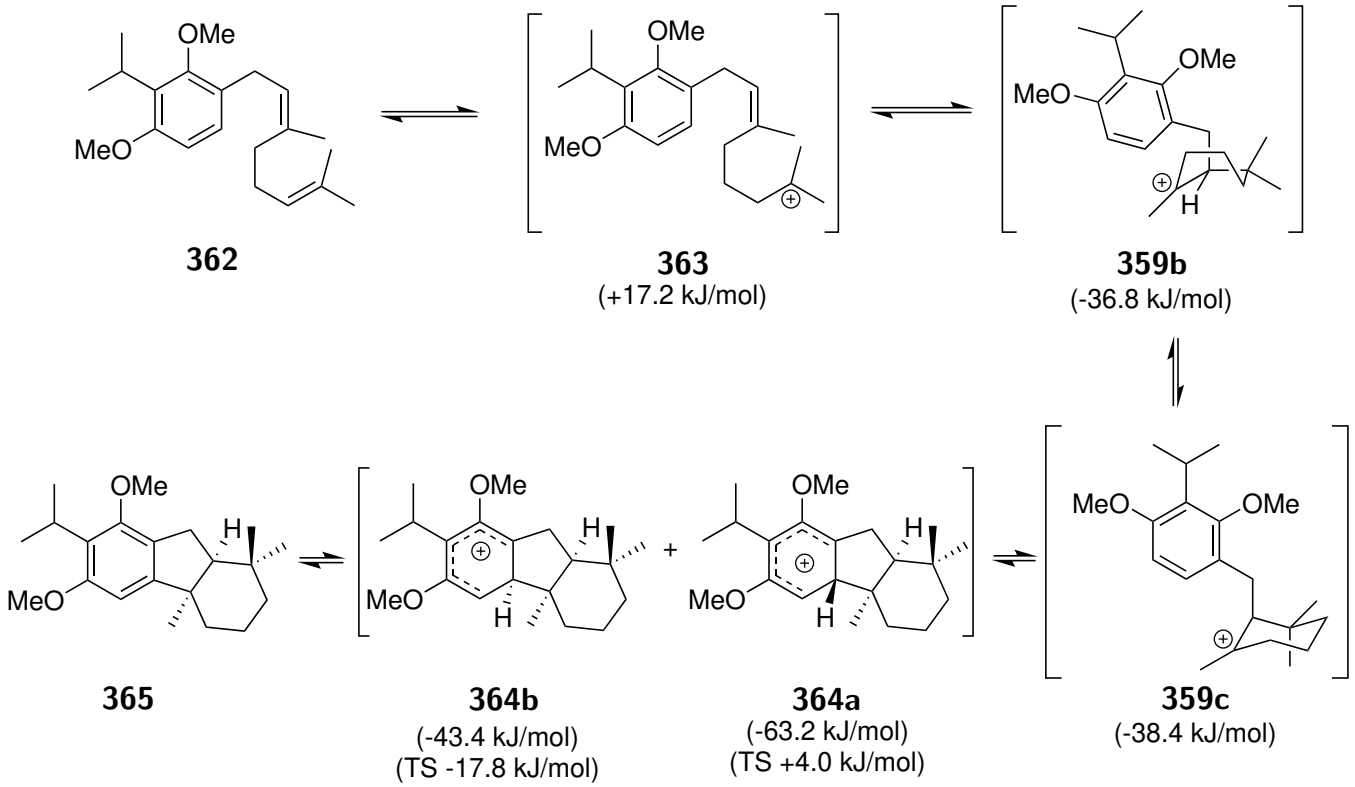
McErlean performed computational experiments to determine whether isomerisation from the (*E*)-configured alkene **351** to the (*Z*)-configured alkene **362** was a significant factor in the resulting *cis* selectivity.[41] Protonation of (*E*)-alkene **351** led to carbocation **358**, with monocyclisation to the A-ring proceeding through a chair-like transition state to produce cyclised carbocation **359a**, where the benzyl substituent was in a pseudoequatorial position. Cyclisation led to the *trans*-configured compound **361** through the Wheland intermediates **360**.

As for the (*Z*)-alkene **362**, protonation delivered carbocation **363** which was 17 kJ/mol higher in energy than carbocation **358**.[41] Cyclisation would proceed through a high-energy boat-like transition state, giving cyclised boat-like carbocation **359b** which would isomerise to the more stable chair configured compound **359c**. In this case, the benzyl substituent was pseudoaxially disposed, leading to the *cis*-configured core **365**.

It seemed unlikely that cyclisation was proceeding via initial isomerisation of the (*E*)-



Scheme 49: Cyclisation of (*E*)-configured polyene **351** should lead to *trans*-configured compound **361**.[41]



Scheme 50: Cyclisation of (*Z*)-configured polyene **362** should lead to *cis*-configured compound **365**.[41]

configured alkene **351** to the (*Z*)-configured alkene **362**: not only was the activation barrier to cyclisation far higher in energy, so was the carbocation **363**. Indeed, we separately obtained experimental evidence for this: we saw no change upon treating polyene **351** with Wilkinson's catalyst in tetrahydrofuran at reflux for several days and again saw no change in a ^{1}H NMR experiment in which we monitored change in the alkene protons after treating a solution of polyene **351** in deuterated chloroform with concentrated hydrochloric acid.

Carbocation **359c**, which possesses a pseudoaxially disposed benzyl substituent, is 9 kJ/mol lower in energy than carbocation **359a**, where the benzyl substituent is disposed pseudoequatorially and these two carbocations would lead to each diastereomer of the cyclised core. Thus the unusual diastereomeric outcome was due to interconversion between these two intermediates.

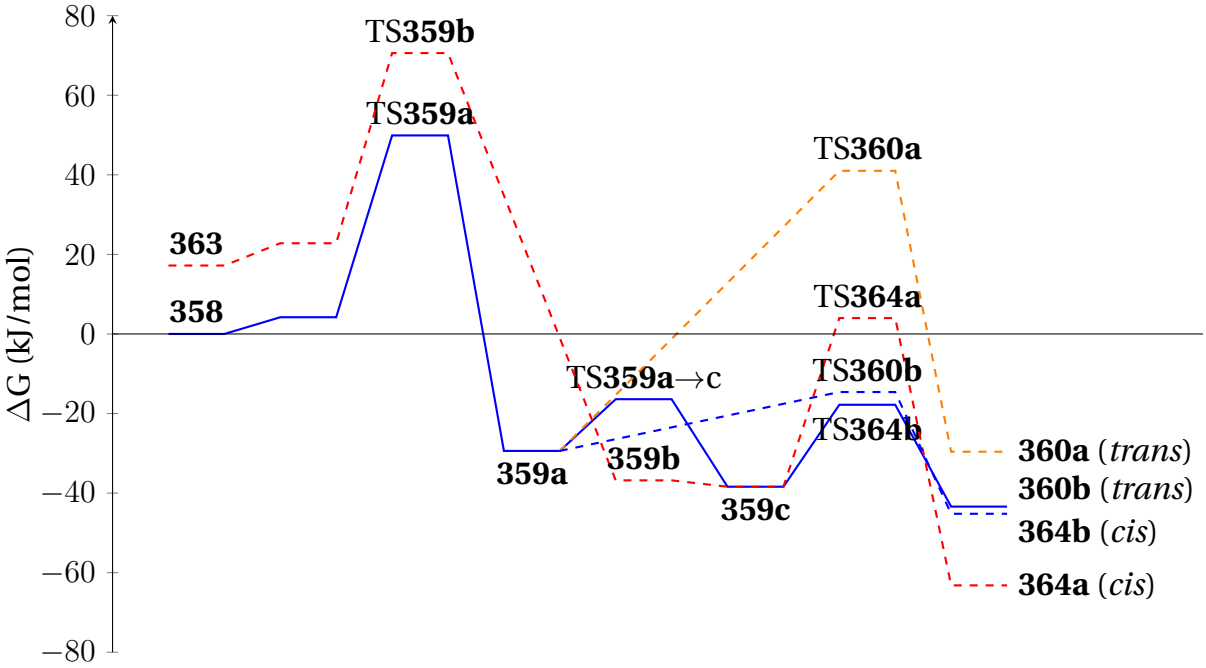
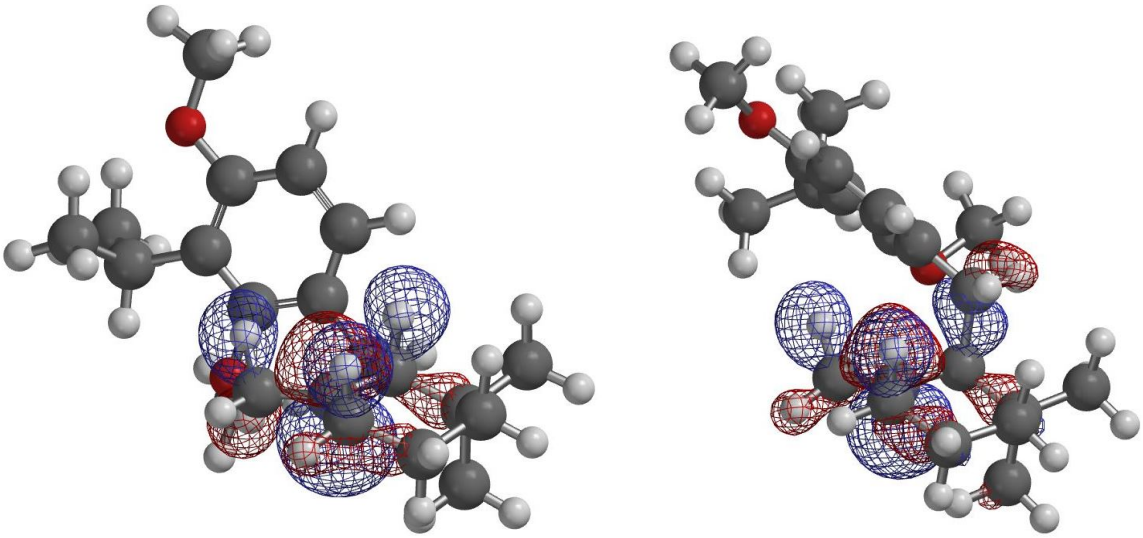


Figure 17: Reaction energy profile for the cyclisation of **351**. Solid line indicates preferred energy pathway to the experimentally observed product. Adapted from ref. 41.

This does not explain why pseudoaxial carbocation **359c** was more stable. We expect pseudoequatorial carbocation **359a** to be more stable due to 1,3-diaxial strain. The answer lies in an unusual hyperconjugative stabilisation of carbocation **359c**, with backdonation from the electron rich C-C σ bond of the benzyl unit and in turn into the vacant p orbital of the carbocation. There is less stabilisation of the cation in the equatorial diastereomer **359a**. A more rigorous treatment using gas-phase DFT calculation of the LUMO confirms this, with the bond connecting the benzylic carbon to the cyclohexane lengthening from

1.547 Å to 1.604 Å, signifying that it is weakened by electron donation into the LUMO (Figure 18).[41]

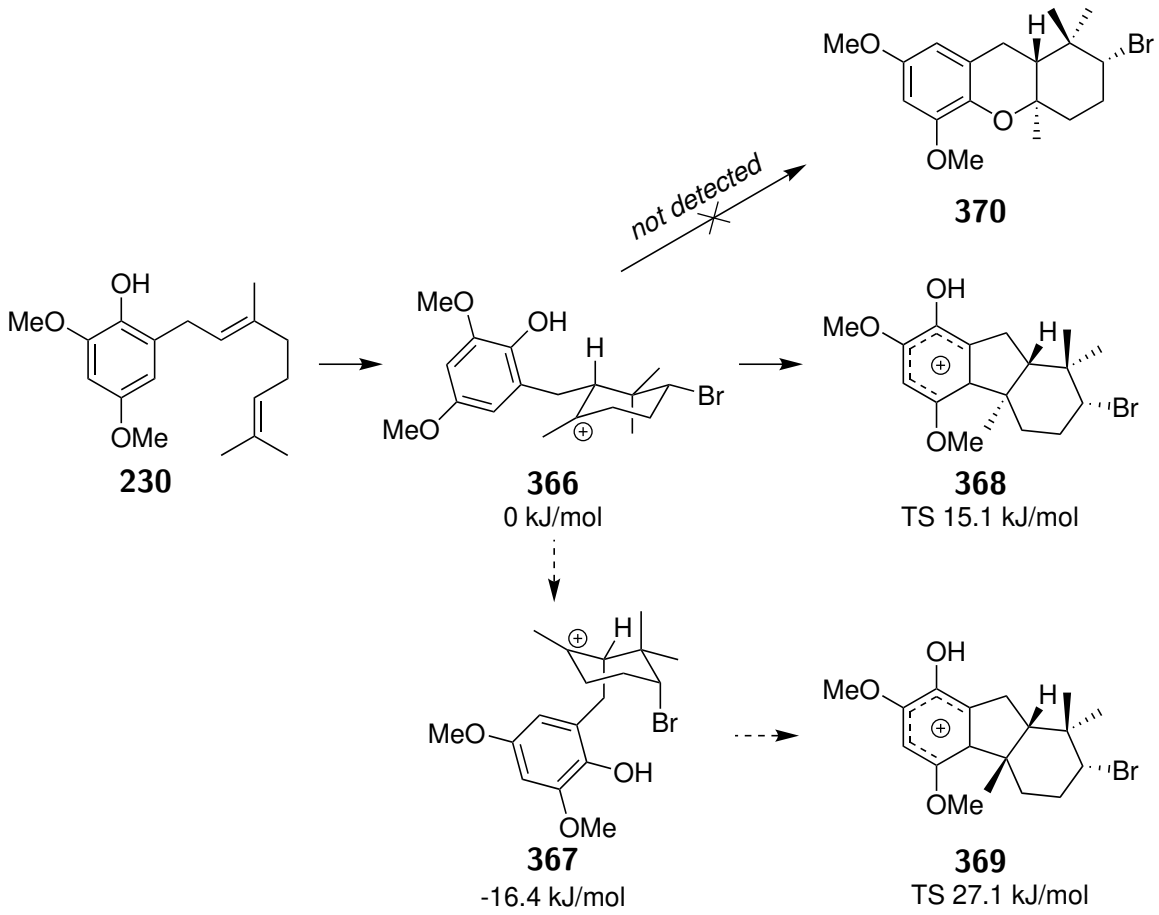


359a **359c**

Figure 18: LUMO orbitals of equatorial conformer **359a** and axial conformer **359c**. Adapted from ref. 41.

McErlean also studied the factors behind the exclusive *trans*-selectivity in Yamamoto's work.[30] [41] Again, this cyclisation proceeds through a stepwise mechanism to intermediate carbocations **366** and **367**, with pseudoaxial isomer **367** again being lower in energy by 16.4 kJ/mol (Scheme 51). But the aryl ring is so nucleophilic that the transition state associated with cyclisation of isomer **366** to the *trans* compound is only 15.1 kJ/mol: far lower than our system. Thus, Friedel-Crafts reaction occurs before isomerisation to the axial conformer **367**. Indeed, the aromatic ring is so electron rich that this cyclisation happens faster than cyclisation from the phenol oxygen to form the corresponding benzopyran **370** (c.f. Table 7) and any effect that the bromide atom plays is insignificant.

We had two avenues to explore in order to improve on the *cis*/*trans* selectivity of this cyclisation: we could attempt other cyclisations of compound **351**, or we could modify our substrate to provide a more nucleophilic aromatic. The first was simpler and we began with this approach.

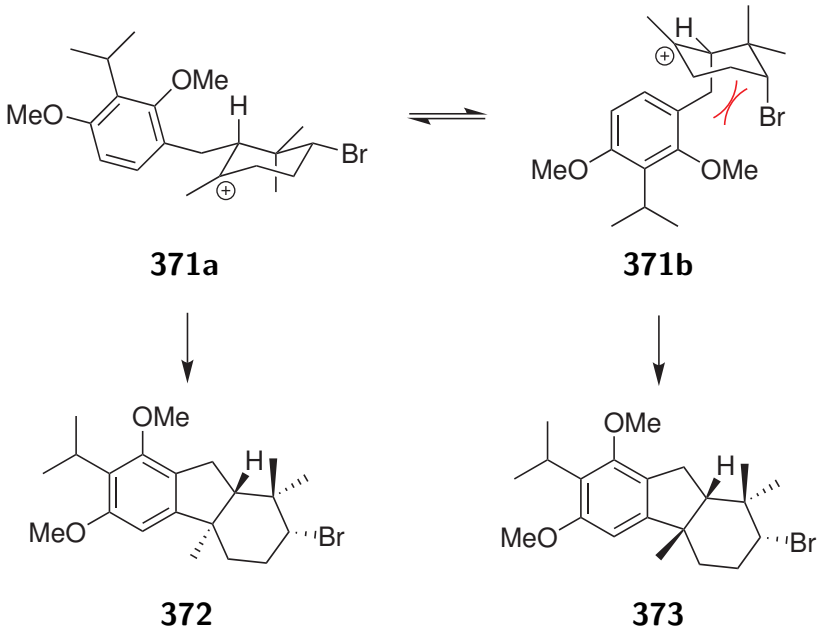


Scheme 51: Computational analysis of Yamamoto's bromonium-mediated cyclisation of polyene **230**.[30] [41]

2.2 Taiwaniaquinone G

Our first point of investigation was to alter the cyclisation methodology we employed. In addition to Lewis or Brønsted acid catalysis, we can initiate a cationic cyclisation by ring-opening of an epoxide, or by direct reaction of the polyene with a bromonium source or a suitable mercury(II) salt. Upon monocyclisation to a compound such as **371**, the heteroatom may destabilise the pseudoaxial conformer **371b**. This would force the large benzyl group to remain pseudoequatorial (**371a**), generating the preferred *trans* diastereomer **372** (Scheme 52).

Synthesis of the polyene **351** was performed in a similar manner to the literature procedure (Scheme 54).[25] Alkylation of 1,3-dimethoxybenzene (**376**) was performed by *ortho*-lithiation followed by addition to acetone, giving alcohol **377**, which was reduced to isopropylbenzene **272**. This was first performed under the previously reported ammonium formate transfer hydrogenation conditions, however hydrogenolysis of later

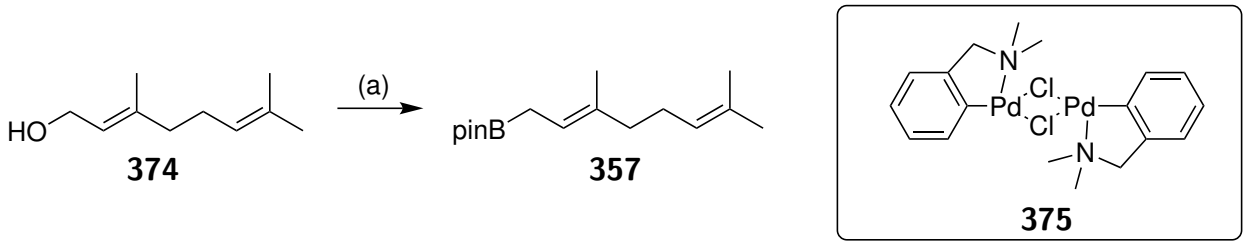


Scheme 52: Cyclisation with a heteroatom such as a bromine at the 3 position should provide a conformational constraint leading to *trans*-fused compound **372** over *cis* diastereomer **373**.

analogues proved troublesome. Instead, hydrochloric acid was used to eliminate the alcohol *in tandem* with palladium-on-carbon under a hydrogen atmosphere to reduce the resulting alkene. Not only did this provide higher and more reproducible yields even in the case of alcohol **377**, but it was also operationally simpler as we avoided portionwise addition of ammonium formate to a reaction mixture at reflux.

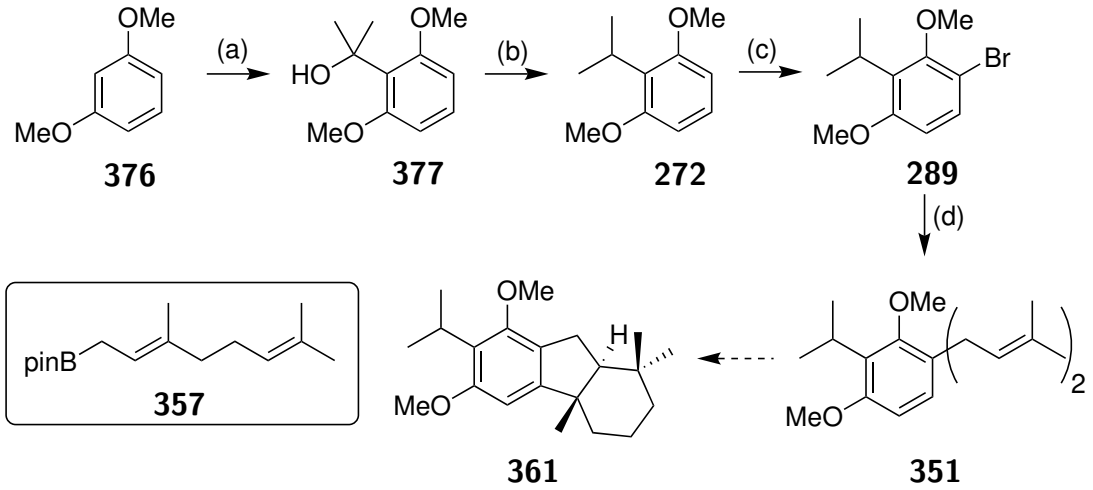
Aromatic bromination of cumene **272** to aryl bromide **289** with *N*-bromosuccinimide was performed in dichloromethane instead of dimethylformamide, with the succinimide byproduct removed by passing the reaction mixture through a silica plug rather than aqueous extraction. Reaction times were accelerated and removal of the reaction solvent became easier.

Geranyl pinacol boronate (**357**) was synthesised in one step from geraniol using palladium catalyst **375** and bis(pinacolato)diboron (Scheme 53).[76]



Scheme 53: Borylation of geraniol. (a) B_2pin_2, TsOH, **375**, MeOH/DMSO (1:1), 50 °C, 72%.

Suzuki reaction between aryl bromide **289** and boronate **357** was performed under the same conditions, which would later prove robust for other analogues (Scheme 54). A significant difference is that while polyene **351** was purified by high-performance liquid chromatography (HPLC) in the original report,[25] we found that flash column chromatography using dichloromethane/hexanes mixtures gave satisfactory results. This allowed us to produce polyene **351** more quickly on a larger scale. With the desired intermediate **351** in hand, we set out to investigate different cyclisation strategies in an attempt to produce the desired *trans*-fused tricycle **361**.



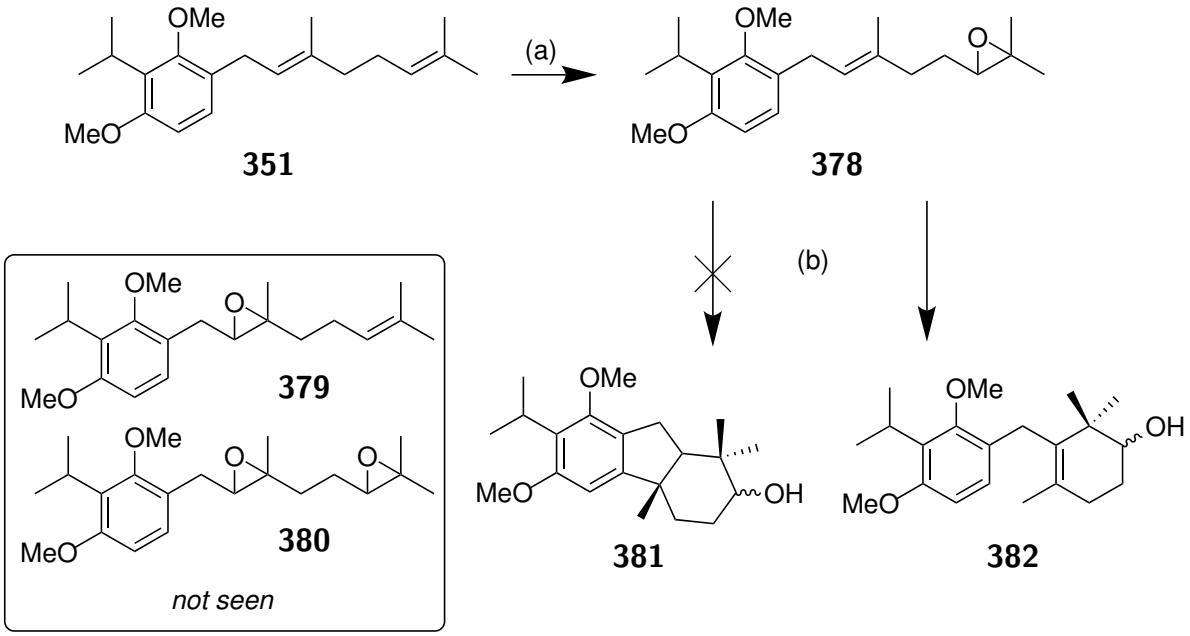
Scheme 54: Synthesis of polyene **351**. (a) *n*-BuLi, TMEDA; then acetone, 84%. (b) H_2, Pd/C, HCl, EtOH, quant. (c) NBS, CH_2Cl_2, 75%. (d) **357**, $Pd(PPh_3)_4$, NaOH, PhMe/H_2O, 100 °C, 78%.

2.2.1 Epoxide-opening strategy

Epoxide-opening cationic cascades are the most common polyene cyclisation methodology found in the literature. An advantage of this approach is that we would require little change to deliver the single enantiomer, facilitating a stereoselective synthesis of (–)-taiwaniaquinone G. A direct chiral acid-mediated approach would require careful optimisation of reaction conditions, whereas in the epoxide-mediated process, chirality is determined by the chirality of the intermediate epoxide.

Epoxidation was performed using *meta*-chloroperbenzoic acid (*m*CPBA) to obtain monoepoxide **378** in 40% yield (Scheme 55). Varying the temperature and concentration of the reaction did not affect the yield. Purifying *m*CPBA by washing with pH 7.5 phosphate buffer and drying allowed us to add strictly one equivalent to the reaction, but again this

led to no increase in yield. In any case, no epoxidation of the proximal alkene to either monoepoxide **379** or diepoxide **380** was observed.



Scheme 55: Epoxidation and attempted cyclisation of polyene **351**. (a) *m*CPBA, CH_2Cl_2, 0 °C, 40%. (b) *Table 13*.

From here, we treated epoxide **378** with a number of Lewis acids. We did not observe any conversion to the fully cyclised compound **381**, however in some cases were able to see the formation of one ring, followed by the formation of the internal alkene to give compound **382**. Elimination producing partially cyclised compound **382** was favoured over Friedel-Crafts alkylation to give fully cyclised compound **381**, even under conditions leading to full cyclisation in the direct approach (Table 13, entries 3 & 7). Longer reaction times or subsequent treatment with a stronger acid did not lead to full cyclisation but instead alternative degradation pathways. In many cases a rearranged product or series of rearranged products was seen as the major or sole product. We were unable to effect the Friedel-Crafts cyclisation. Elimination of the A-ring alcohol likely outcompetes cyclisation under forcing conditions, resulting in a series of rearranged products.

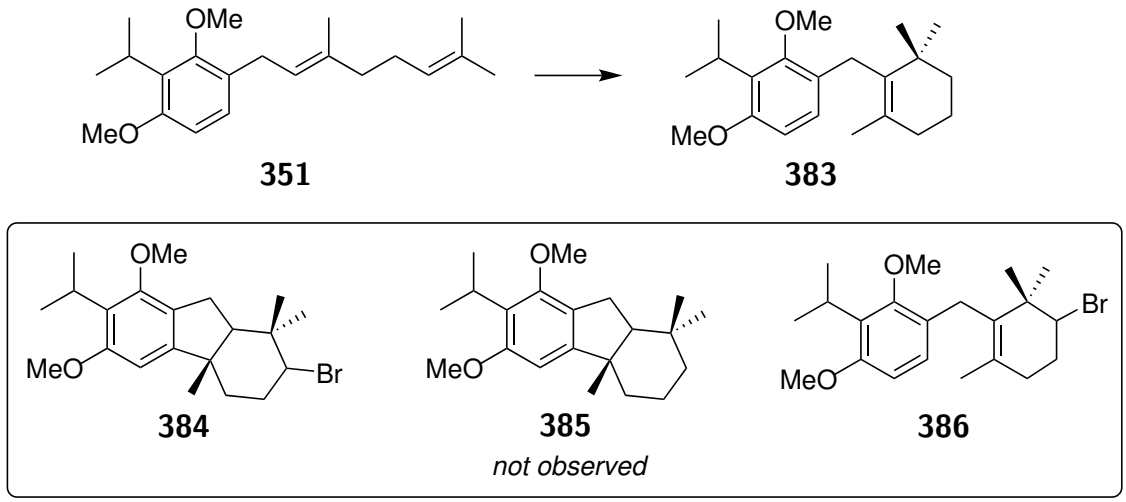
Given the failure of many conditions to generate the desired fully cyclised compound **381**, other strategies were employed, such as treating polyene **351** with a bromonium source.

Table 13: Attempted conditions for epoxide-opening polyene cyclisation (Scheme 55).

Entry	Acid	Solvent	T/°C	**382**	**378** (SM)
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	rt	X	X
2	$BF_3{\cdot}OEt_2$	PhMe	70	X	✓
3	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt	✓	X
4	$Bi(OTf)_3$	CH_2Cl_2	rt	✓	X
5	$Bi(OTf)_3$	PhMe	70	X	X
6	$Bi(OTf)_3$	$MeNO_2$	rt	✓	X
7	$Bi(OTf)_3$	$MeNO_2$	70	X	✓
8	$Bi(OTf)_3$	$MeNO_2$	–30	X	✓
9	TsOH	CH_2Cl_2	rt	X	X
10	TsOH	PhMe	70	X	X
11	TsOH	$MeNO_2$	rt	X	X
12	$FeCl_3$	CH_2Cl_2	rt	X	X
13	$AlCl_3$	CH_2Cl_2	rt	X	X
14	Me_2AlCl	CH_2Cl_2	–78	X	X
15	$Sn(OTf)_2$	$MeNO_2$	rt	X	✓

2.2.2 Bromonium-based strategies

Interestingly, when polyene was treated with **351** with *N*-bromosuccinimide in dichloromethane, monocyclised unbrominated compound **383** was formed. Using triphenylphosphine as a catalyst did not change this outcome, consistent with Ishihara's results.[29] Treatment with BDSB also led to the production of unbrominated compound **383**. Combined, these results suggest the possibility that intermediate **371** was formed, but reductive workup with sodium sulfite led to the removal of the bromide. It is also possible that cyclohexene **383** was formed directly by Lewis acid catalysis. Treatment by Gulder's protocol using *N*-bromosuccinimide and morpholine in hexafluoroisopropanol gave unreacted polyene **351**.[77]



Scheme 56: Attempted bromocyclisation led only to non-halogenated partially cyclised compound **383**.

Table 14: Attempts to cyclise polyene **351** via bromonium sources.

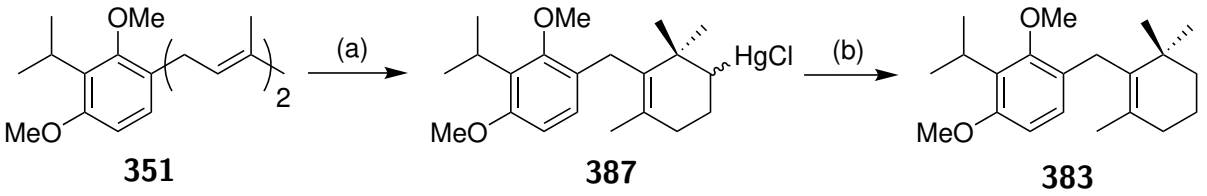
Br^+ source	Solvent	T (°C)	**384**	**385**	**383**	**351** (SM)
NBS	CH_2Cl_2	rt	X	X	✓	X
NBS	$MeNO_2$	100	X	X	✓	X
DBDMH	CH_2Cl_2	rt	X	X	✓	X
BDSB	$MeNO_2$	–15	X	X	✓	X
NBS	PhMe	110	X	X	X	✓

2.2.3 Mercury(II) trifluoromethanesulfonate

To this point, we had explored epoxide opening and bromonium mediated polyene cyclisations as a means to overcome the inherent bias for the *cis*-isomer in the Friedel-Crafts cyclisation. We also explored the use of mercury(II) trifluoromethanesulfonate in initiating this polyene cyclisation (Scheme 57). Under a number of reaction conditions, treating polyene **351** with mercury(II) trifluoromethanesulfonate led to either monocyclic organomercurial **387** or decomposition. In practice, this was typically treated *in situ* with sodium borohydride to generate alkane **383**, avoiding the need to isolate a likely extremely toxic organomercurial compound. This contrasts with Snyder's methodology which always treated the organomercurial with a halogen to generate the desired alkyl halide.[28]

Treating the organomercurial **387** with strong acid in nitromethane led to no further cyclisation. Given the highly toxic nature of the organomercury compounds generated

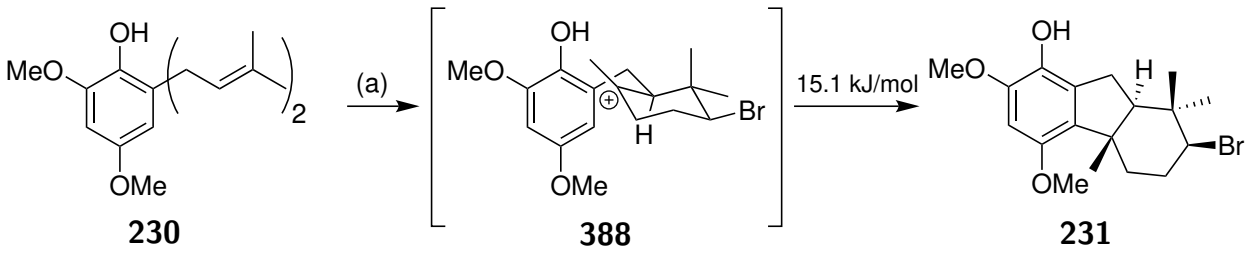
by this approach, we did not want to pursue it any further and instead tried less hazardous and more promising approaches. Our attempts to access the *trans*-configured 6,5,6-fused framework by altering the mode of polyene cyclisation had been unsuccessful. Instead, we turned our attention to the cyclisation substrate.



Scheme 57: Mercury-mediated cyclisation of polyene **351**. (a) HgO, Tf_2O, MeCN, –78 °C, then NaCl, H_2O, rt. (b) $NaBH_4$, NaOH.

2.2.4 Changing the substrate

During this work, Yamamoto published the first example of enantioselective brominative cyclisation, which included an example of a 6,5,6-tricyclic framework with exclusive *trans* selectivity.[30] It was unclear why this substrate delivered such a high level of *trans* selectivity compared to the McErlean group's *cis* selective efforts. Computational analysis by McErlean revealed that the activation energy for Friedel-Crafts alkylation in this system was only 15.4 kJ/mol – far lower than the activation barrier in the previous cyclisation using polyene **351**.[41]



Scheme 58: An example of high *trans*-selectivity in this type of polyene cyclisation.[30] (a) **150**, DBDMH, toluene/CH_2Cl_2, –90 °C, 91%, 99:1 er.

McErlean performed density-functional calculations to determine the energy barrier to Friedel-Crafts alkylation in systems that would be more relevant to us: phenol **389**, trimethoxybenzene **390** and dimethoxyphenol **391** (Figure 19).[41]

Cyclisation onto the methoxyphenol **389**, a close analogue of precursor **351** used in the previous synthesis was associated with a high transition state energy of 36.2 kJ/mol.

This is so high that cyclisation would be expected to occur onto the phenol oxygen to form the chromane rather than the desired carbocycle. This is well-precedented. For the trimethoxy compound **390**, the transition state leading to *trans* compound **393** is significantly lower at 21.4 kJ/mol, and the dimethoxyphenol **391** lower still at 13.5 kJ/mol. The latter two substrates would deliver higher levels of *trans*-selectivity and we hoped that this diastereomer would predominate.

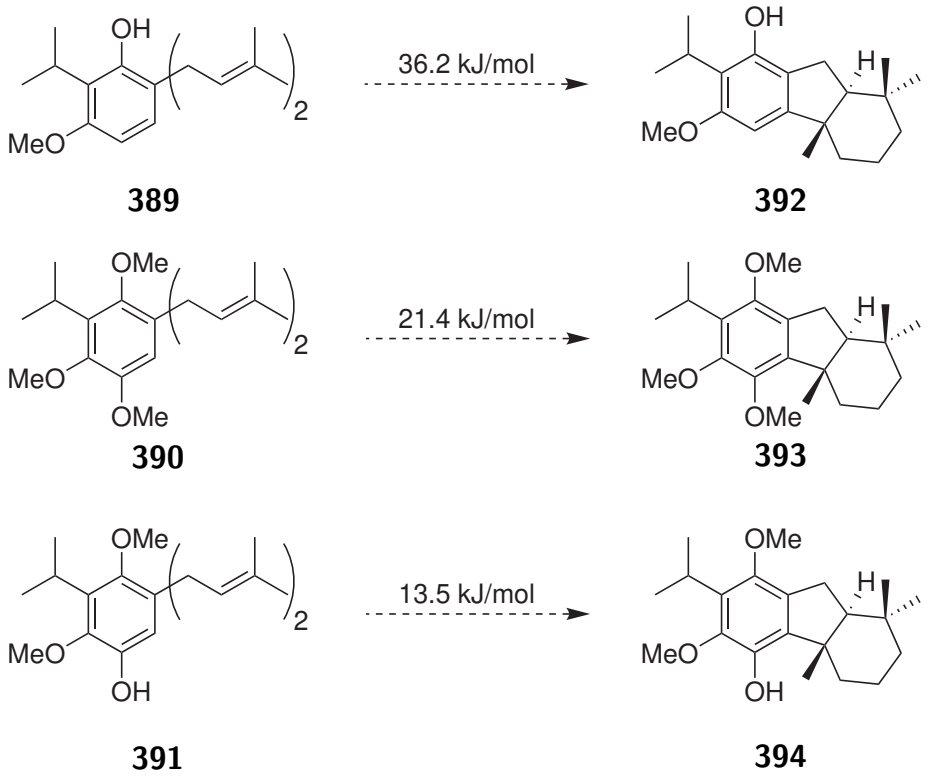
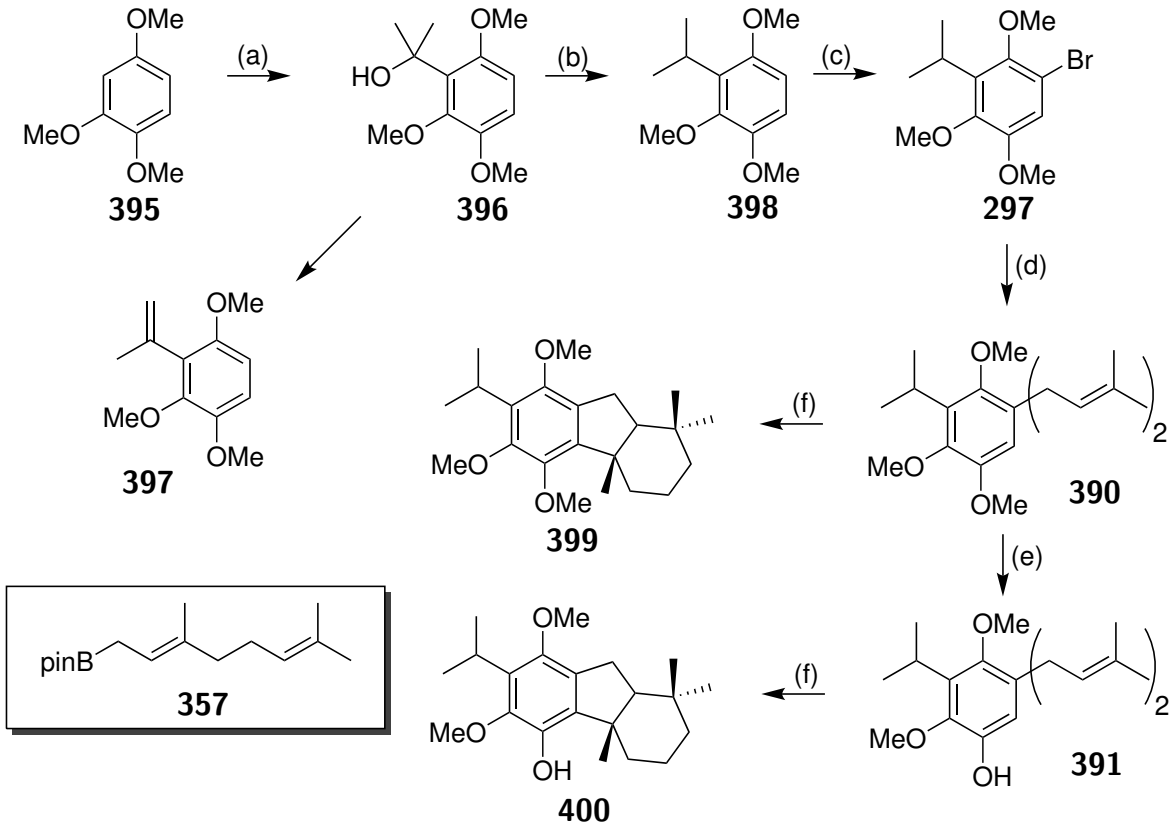


Figure 19: Polyenes used in the computational analysis, with activation energies for the Friedel-Crafts alkylation step shown.[41]

Synthesis of the trimethoxy analogue **390** was performed in much the same manner as the previous route to dimethoxy polyene **351** (Scheme 59). The addition of lithiated trimethoxybenzene (**395**) to acetone was more difficult to perform than the alkylation of 1,3-dimethoxybenzene (**376**). We considered the possibility that the acetone used had become wet, thus quenching the lithiated species before it could react productively. Removing water from acetone is a non-trivial task: it undergoes aldol reactions under even the mildly basic or acidic conditions provided by most common desiccants, such as molecular sieves. Distilling acetone immediately prior to use through a packed column of calcium sulfate did not appreciably increase the yield of the reaction, but did improve reproducibility. We suggest that the sterically encumbered environment here makes this reaction difficult. Longer reaction times at room temperature did not appreciably increase

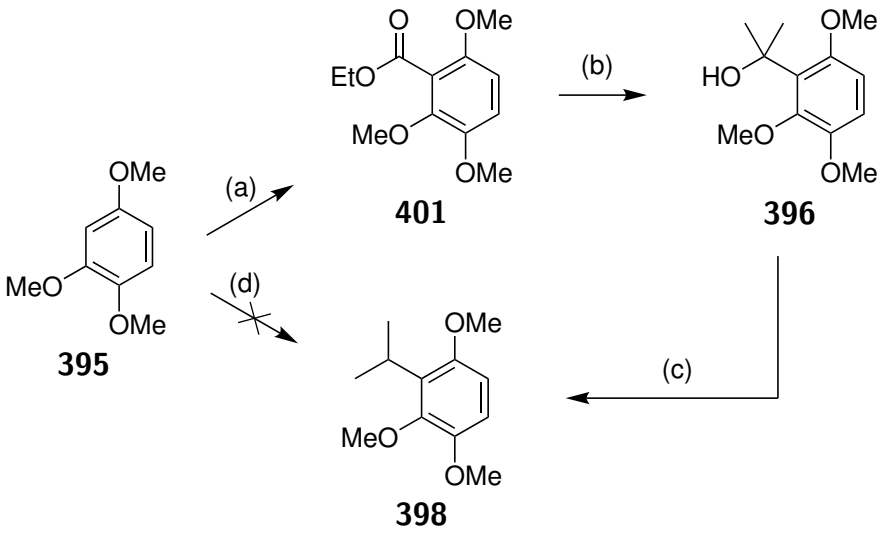
yield, nor did holding the reaction at –40 °C overnight to avoid thermal degradation of the organolithium species.



Scheme 59: Synthesis of polyenes **390** and **391**. (a) *n*-BuLi, TMEDA, THF, –78 °C; then acetone, –78 °C→rt, 50%. (b) H_2, Pd/C, HCl, EtOH, 59%. (c) NBS, CH_2Cl_2, 91%. (d) **357**, $Pd(PPh_3)_4$, NaOH, PhMe/H_2O, 100 °C, 67%. (e) L-selectride, THF, Δ, 48%. (f) *Table 15*.

We also attempted quenching the lithium anion of aryl ring **395** with ethyl chloroformate and subsequently reacting the isolated ester with methyllithium, as per Bisai's report.[55] This did not improve the yield significantly and led to an additional reaction and purification step. Likewise, an attempt to quench the organolithium species with 2-chloropropane to form the isopropyl group directly led to no reaction. This compound is far too large to react with the sterically congested organolithium. Similarly, other attempts at Friedel-Crafts alkylation were unsuccessful: reactions between trimethoxybromobenzene (**634**) and 2-chloropropane or isopropanol under Lewis or Brønsted acid catalysis returned starting materials. Addition of acetone to the aryllithium species seems to be the most effective approach towards cumene **398**, as evidenced by the lack of reports of the alternative methods.

As mentioned earlier, hydrogenolysis of the newly formed tertiary alcohol **396** by the conditions in McErlean's original synthesis of *epi*-taiwaniaquinone G led to issues. The



Scheme 60: Attempted improved syntheses of **398**. Conditions: (a) *n*-BuLi, TMEDA, THF, –78 °C, then $ClCO_2Et$, 64%. (b) MeLi, THF, –78 °C, %. (c) H_2, Pd/C, HCl, EtOH, 59%. (d) *n*-BuLi, TMEDA, THF, –78 °C, then 2-chloropropane, –78 °C→rt, 18 h, nr.

extra steric bulk made this reaction sluggish and often alkene **397** was present, either as a sole product or as the major component of a mixture with desired product **398**. This could often not be pushed to complete conversion, except by work-up and treatment of the crude reaction mixture with palladium-on-carbon again, this time in methanol under a hydrogen atmosphere. Treating alcohol **396** with ethanolic hydrochloric acid and *in situ* hydrogenation using palladium-on-carbon under a hydrogen atmosphere led to more reliable production of cumene **398**.

Bromination exclusively at the desired position was again performed with *N*-bromosuccinimide in dichloromethane, reacting more quickly due to the improved nucleophilicity of this aryl ring. Suzuki reaction using tetrakis(triphenylphosphine) palladium(0) in hot toluene/water gave our desired polyene **390** in comparable yields to the previous synthesis.

Cyclisation of polyene **390** was conducted under the previous successful conditions in McErlean's synthesis of 5-*epi*-taiwaniaquinone G (Table 15). We also found that chlorosulfonic acid successfully effected the polyene cyclisation in comparable yields. While not as successful as anticipated, the diastereomeric ratio decreased from 7:1 to 2.7:1, still in favour of the undesired *cis* isomer **407**. While not obtaining *trans* selectivity, the high level of *cis* selectivity was disrupted. Conducting this reaction at lower temperatures did not affect *cis*/*trans* selectivity.

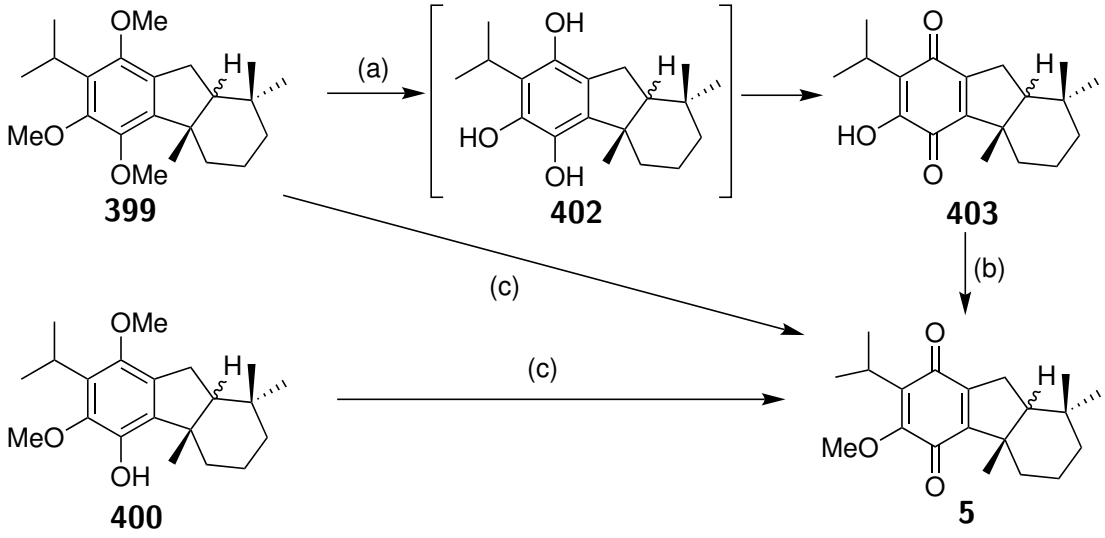
We could also treat this precursor **390** with L-Selectride in tetrahydrofuran at reflux, selectively demethylating the least hindered methyl ether to give exclusively phenol **391** (Scheme 59). Treating polyene **391** with either boron trifluoride etherate or chlorosulfonic acid, we found a further slightly higher preference for the *trans* isomer, with a dr of 2.1:1 still in favour of the undesired *cis* isomer.

Table 15: Summary of all cyclisation reactions. Previous literature is shaded grey. [a] *cis*/*trans* ratios for cyclisations from polyenes **351**, **390** and **391** determined by ^{1}H NMR analysis. [b] hydroxyquinone **403** obtained from this reaction.

SM	Lewis acid	Solvent	T /°C	Yield	cis:trans[a]
230[30]	**150**, DMDBH	PhMe/CH_2Cl_2	–90	91%	0:1
351[41]	$Bi(OTf)_3$	$MeNO_2$	80	20%	7:1
351[41]	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt	21%	7:1
390	$Bi(OTf)_3$	$MeNO_2$	80	87%	2.8:1
390	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt	61%	2.7:1
390	$ClSO_3H$	$MeNO_2$	rt	64%	2.8:1
390	$BF_3{\cdot}OEt_2$	$MeNO_2$	–5	66%	2.8:1
390	$ClSO_3H$	$MeNO_2$	–5	40%	2.7:1
391	$BF_3{\cdot}OEt_2$	$EtNO_2$	–5	22%	2.1:1
391	$ClSO_3H$	$EtNO_2$	–5	10%	2.1:1
391[b]	$SbCl_5$, **404**	CH_2Cl_2	rt	20%	3:1
		Failed reactions			
390	TsOH	$EtNO_2$	–40	nr	
390	$ClSO_3H$	$EtNO_2$	–78→–40	monocyclised	
390	$SnCl_4$	$EtNO_2$	–40	nr	
390	$BF_3{\cdot}OEt_2$	PhMe	rt	monocyclised	
390	$BF_3{\cdot}OEt_2$	CH_2Cl_2	rt	monocyclised	
390	$BF_3{\cdot}OEt_2$	$EtNO_2$	–78→–40	nr	
390	$BF_3{\cdot}OEt_2$	$EtNO_2$	–78→–40	nr	
390	$BF_3{\cdot}OEt_2$	$EtNO_2$	0	monocyclised	

In both cases, oxidation to the quinone could be carried out in a similar method to the McErlean group's previous synthesis. Boron tribromide non-selectively cleaved the methyl ethers to produce triol **402**, which spontaneously oxidised in air to the hydroxyquinone **403**. The remaining methyl ether could be installed with methyl iodide and potassium carbonate. However, because these intermediates also possessed oxygenation at the C11 position, a more efficient sequence was possible.

Pleasingly, oxidation of the mixture of trimethoxy compound **399** and phenol **400** to taiwaniaquinone G could be effected with cerium ammonium nitrate in good yield. This provided the natural product, taiwaniaquinone G, as a mixture with the *cis*-configured epimer in a racemic fashion.



Scheme 61: Late-stage oxidation of hexahydrofluorenes **399** and **400**. (a) BBr_3, $CHCl_2$, –78 °C. (b) MeI, K_2CO_3, MeCN, 32%. (c) CAN, MeCN/H_2O, 0 °C→rt, 86%.

With access to the racemate, we next sought access to the naturally occurring stereoisomer of taiwaniaquinone G (**5**). Inspired by Corey's work on enantioselective polyene cyclisation using antimony complexes,[21] we treated polyene **391** with (*S*)-*o,o*′-diiodo-BINOL (**404**) and antimony pentachloride in dichloromethane.

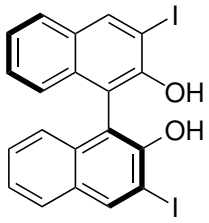
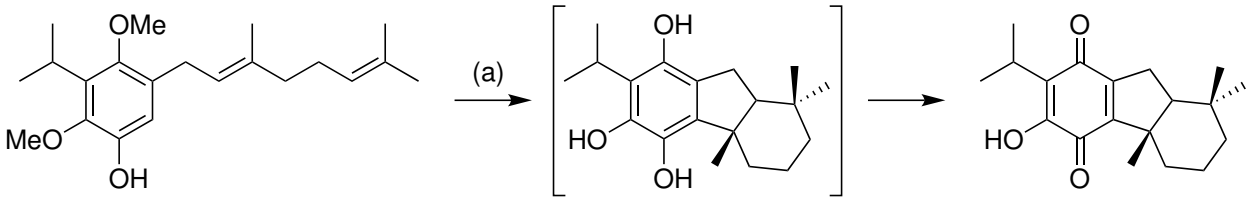


Figure 20: (*S*)-*o,o*′-diiodo-BINOL (**404**).

Interestingly, not only did the cyclisation occur in a modest 3:1 dr in favour of the *cis* isomer, this occurred with *in situ* demethylation to give, upon aerobic oxidation during workup, hydroxyquinone **403**. Given the modest dr and lack of *O*-cyclised material, demethylation likely occurred after the Friedel-Crafts cyclisation step. Disappointingly, no enantioinduction was seen for this polyene cyclisation.

Overall, the best conditions gave a mixture of taiwaniaquinone G and its epimer in only six steps, albeit with a yield of only 11% for the mixture of diastereomers and merely 3%



Scheme 62: One-pot cyclisation and demethylation with antimony pentachloride gives hydroxyquinone **403**. Conditions: **404**, $SbCl_5$, CH_2Cl_2, 20%.

for the natural epimer. Much of the poor yield can be ascribed to the difficulty in installing the isopropyl group in the early stages, which is a problem we have been unable to rectify.

Flash column chromatography was unsuccessful at separating taiwaniaquinone G from its epimer, but a diastereomerically pure sample of taiwaniaquinone G was obtained using preparative high-performance liquid chromatography.

^{1}H and ^{13}C NMR spectra of the synthesised taiwaniaquinone G closely matched that of naturally isolated taiwaniaquinone G (Figure 22) apart from the coupling constants between the C5 proton and benzylic protons 7a and 7b.[2] We suggest Kuo misreported this data, but we could not verify this as the authors provided no raw NMR spectra. Alvarez-Manzaneda reported two syntheses of taiwaniaquinone G. In one report, the provided characterisation data is clearly for a different compound.[51] NMR data was not reported in the second synthesis but raw NMR spectra were provided, which aligned closely with our own.[50]

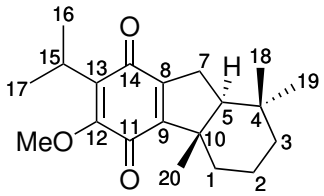


Figure 21: Carbon numbering for taiwaniaquinone G.[2]

While the McErlean group's previous synthesis provided a route to 5-*epi*-taiwaniaquinone G in 11% yield over 8 steps with a trace of the natural taiwaniaquinone G, we were able to shorten this to 6 steps, with 11% yield for the 3:1 mixture of epimers, giving a yield of 3% for the natural epimer. These epimers could be isolated after HPLC separation, giving an expedient, albeit low-yielding route to (±)-taiwaniaquinone G. This was generally in agreement with the literature and we were able to correct the coupling constant data provided by the Kuo group[2] for the naturally isolated taiwaniaquinone G.

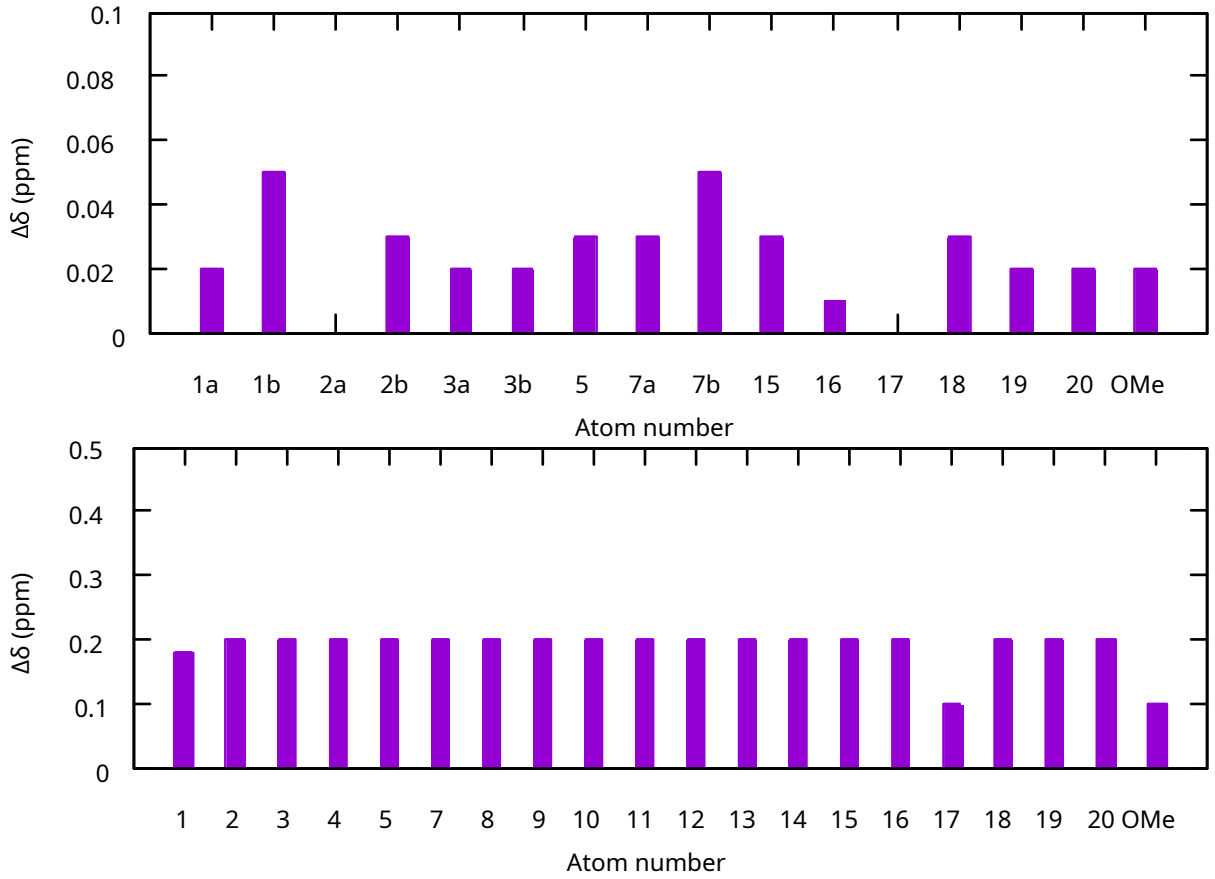


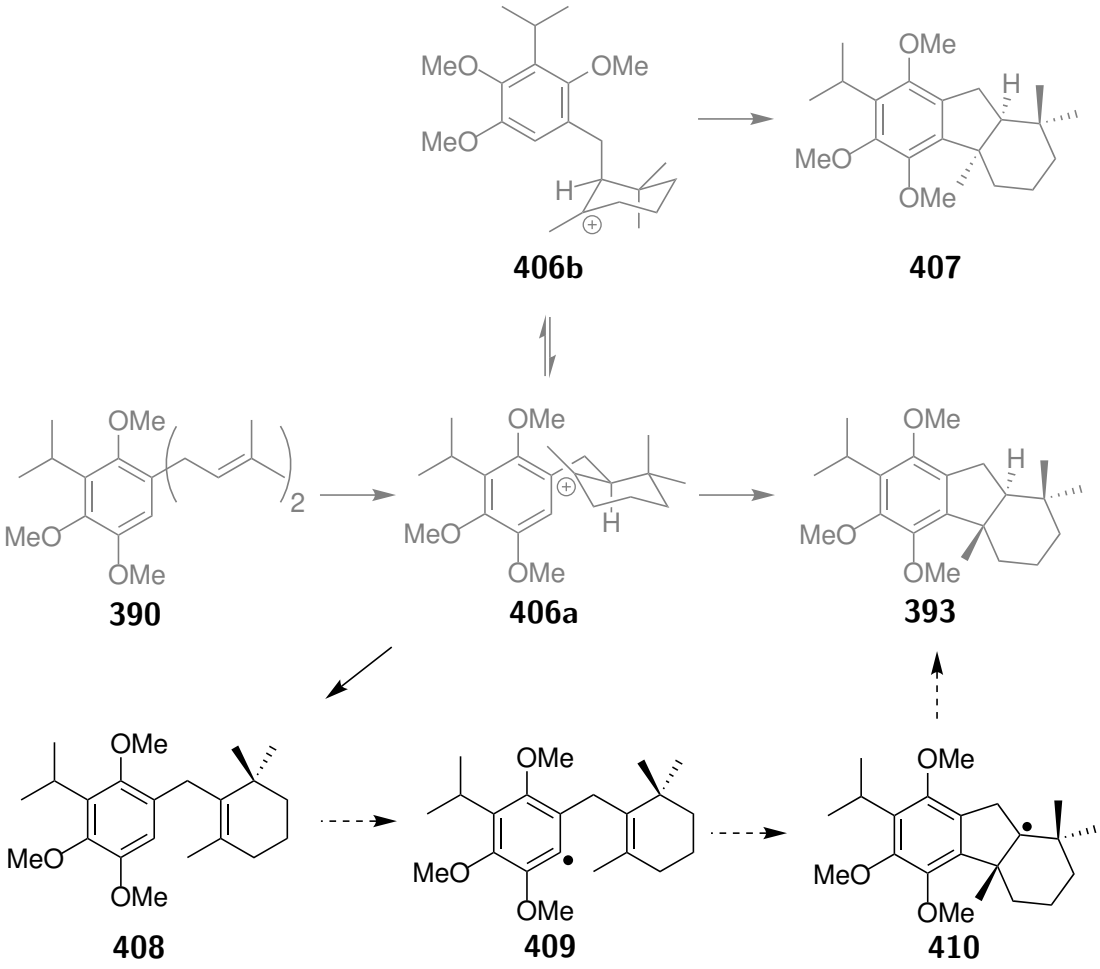
Figure 22: Comparison to reported ^{1}H and ^{13}C NMR spectra of taiwaniaquinone G isolated from *T. cryptomerioides*.[2]

2.2.5 Photoredox radical cyclisation

Efforts towards taiwaniaquinone G using a cationic cyclisation were successful but somewhat disappointing. We had to revisit what was happening during the reaction: upon protonation of polyene **390**, cyclisation to carbocation **406a** occurs. Then, the next likely event is isomerisation to the pseudoaxial conformer **406b**. But if elimination occurs instead, forming alkene **408**, the benzyl substituent would be attached to an sp^2-hybridised centre. This would set up for cyclisation giving the *trans*-configured diastereomer.

A sound strategy would be to perform a cyclisation onto alkene **408**. After generating an aryl radical **409**, cyclisation would generate radical **410**, which could be quenched by a hydrogen source to give the *trans*-configured compuond **393**.

The key to this strategy was access to alkene **408**. We are able to produce this compound through monocyclisation of polyene **390**, but installing the cyclohexene in a single step would be more succinct, so we attempted direct coupling between the aromatic and



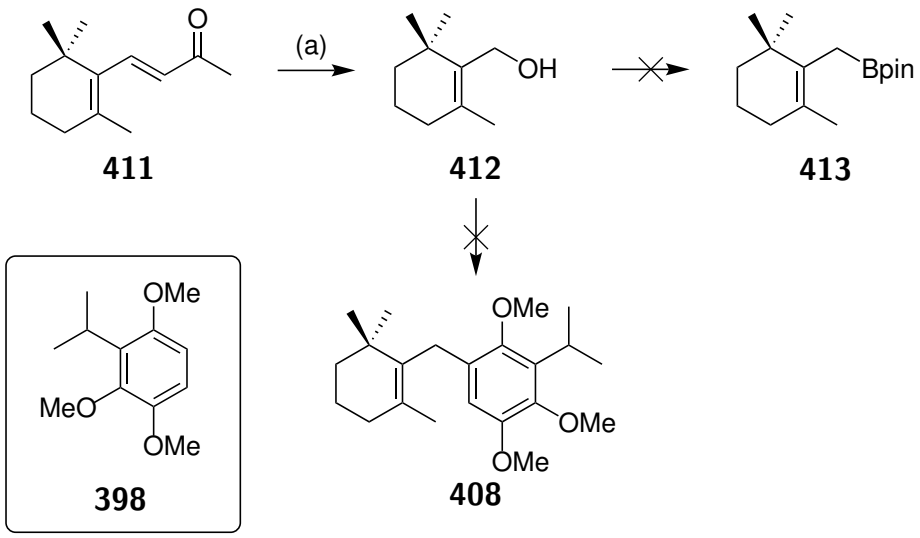
Scheme 63: Cyclisation of polyene **390** could be achieved by radical means to avoid formation of *cis*-fused product **407**.

cyclohexene fragments.

Cyclogeraniol (**412**) was produced by ozonolysis of β-ionone with a reductive quench using sodium borohydride. We attempted borylation of alcohol **412** using our standard conditions, but no reaction was seen. Dethe and coworkers used boron trifluoride etherate to couple alcohol **412** with a number of aromatic rings directly.[78] Unfortunately, when we used these reaction conditions to couple alcohol **412** with aromatic unit **398**, the only product was unreacted aromatic **398**. Alcohol **412** likely underwent elimination, then the volatile alkene product evaporated during workup.

Nevertheless, we could still produce compound **408** by partially cyclising polyene **390** using boron trifluoride etherate in dichloromethane. Aromatic iodination would deliver the cyclisation precursor.

Chemoselectivity was not a significant concern here: our desired path was iodination of



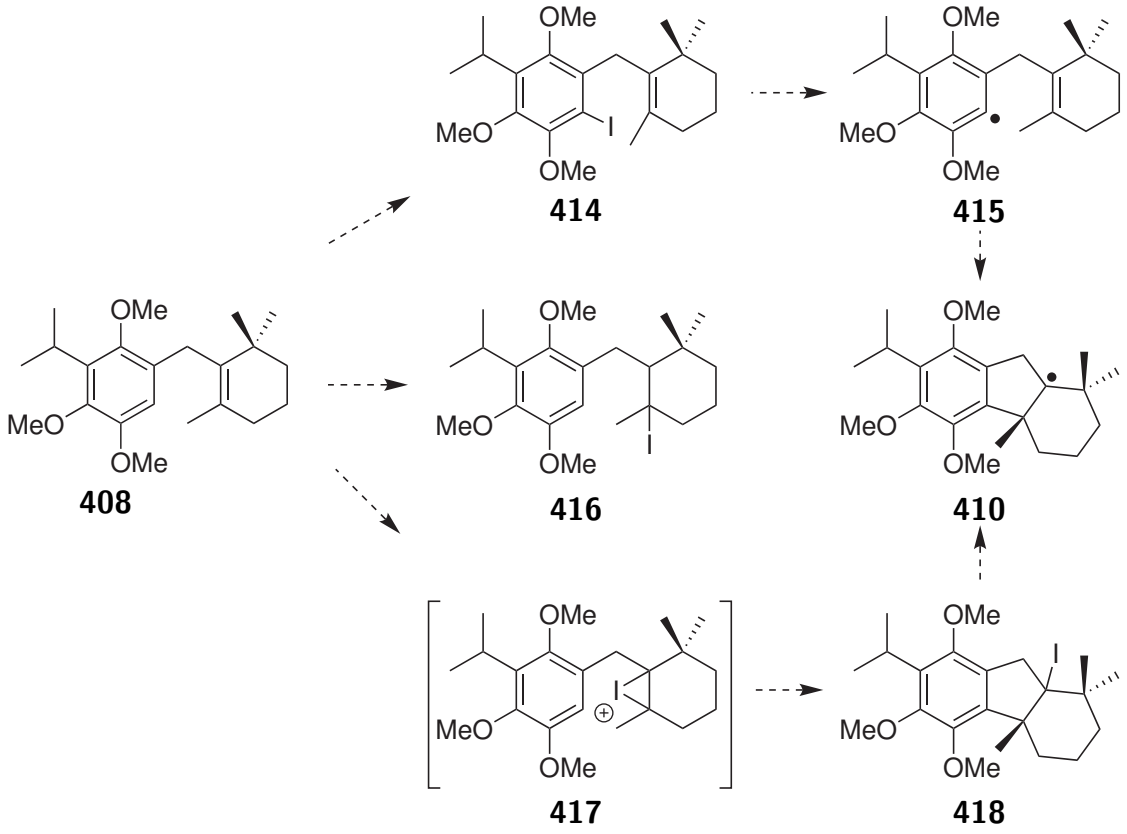
Scheme 64: Direct synthesis of **397** failed. Conditions: (a) O_3, MeOH, –78 °C, 8 h, then $NaBH_4$, N_2, 0 °C→rt 89%.

the aromatic to generate aryl iodide **414**, but we may first hydroiodinate the alkene to give alkyl iodide **416**, which could easily be eliminated to reform the alkene. There is a slight chance we could produce a fully cyclised structure **418** by the attack of the intermediate iodonium **417** by the proximal aromatic. This could be homolysed to form radical **409**. Iodination under various conditions led to none of these outcomes: the challenging steric environment seemed to hinder reaction.

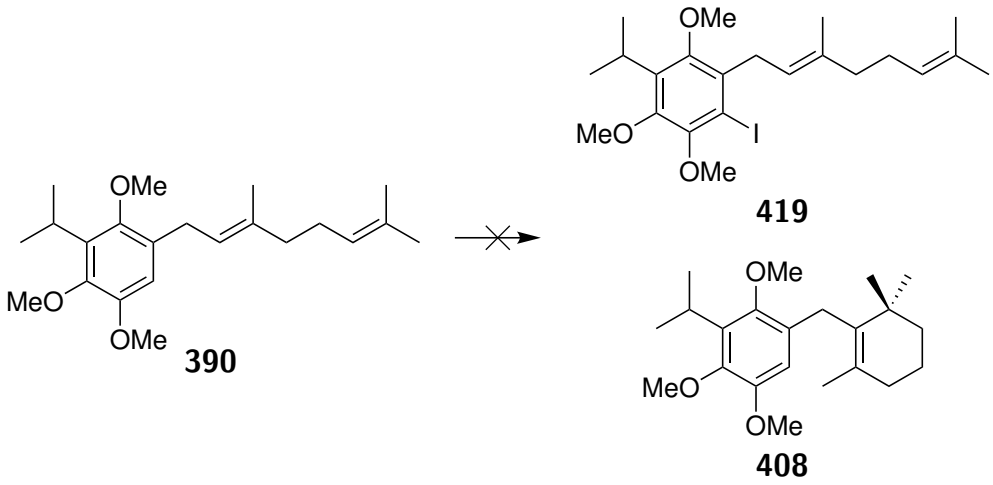
This meant that we would have to install an iodine before cyclisation and perhaps before the Suzuki coupling. Treating polyene **390** under several iodination conditions led to no reaction. The aromatic is insufficiently nucleophilic at the available position. Unlike with *N*-bromosuccinimide, using *N*-iodosuccinimide or iodine as a halonium source did not lead to any cyclisation. This is in line with Ishihara's results that demonstrated that NIS itself is insufficient to initiate a cationic cyclisation.[29]

Treating polyene **390** with *n*-butyllithium followed by quenching with iodine also led to recovery of starting material. Three equivalents were used to first deprotonate both benzylic positions, then deprotonate directly on the aromatic. The colour of the iodine solution faded until an excess was added: this suggests that some reaction with iodine was occurring, whether it was reacting with *n*-butyllithium or the lithiated substrate followed by removal upon reductive workup.

Our only move left was to install a different photolabile group onto aryl bromide **297**. This could not be done directly: an *ortho*-dihalide would likely decompose to the benzyne and



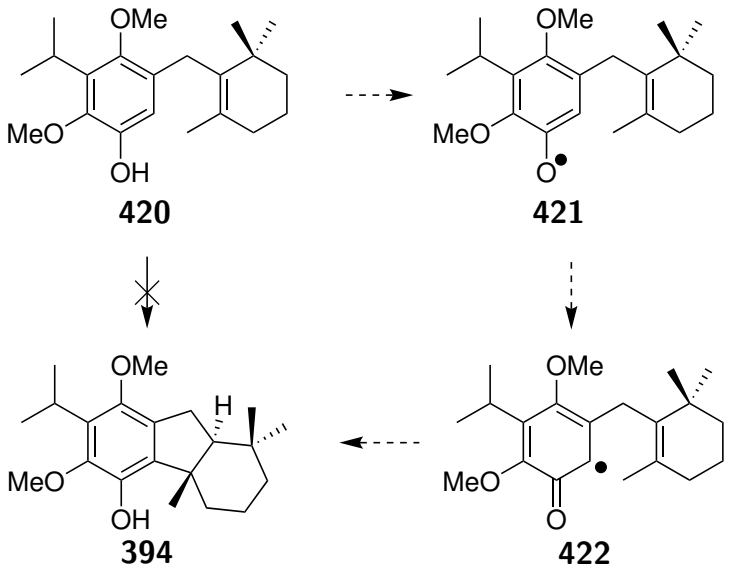
Scheme 65: Iodination of compound **408** could proceed in a number of ways, two of which would produce the desired radical **410**.



Scheme 66: Iodination of polyene **390** did not lead to aromatic iodination or cyclisation. Conditions: NIS, DMF, rt, 48 h, I_2, AgOTf, 48 h or *n*-BuLi, then I_2, THF.

regardless, would prove troublesome in the subsequent Suzuki coupling. We attempted nitration of aryl ring **297**, intending to convert the nitro group to a diazonium or aryl iodide later. Treatment of aryl bromide **297** with a mixture of sulfuric and nitric acids or using copper(II) nitrate led only to an uncharacterised mixture of highly coloured products. It is likely that demethylative oxidation to the quinone occurred.

Finally, we attempted ring closure using Luo's eosin Y-promoted cyclisation. In some cases it is suggested that O–H abstraction can occur at a phenol, isomerising to the carbon-centred radical which could perform our desired reaction (Scheme 67).[22] Treatment of phenol **420** under these photocatalytic conditions led to no reaction.



Scheme 67: Luo's eosin Y photoredox cyclisation did not lead to any reaction. Conditions: eosin Y, HFIP, CFL bulb.

Clearly, the synthesis of a precursor to generate a radical at the free aromatic carbon is challenging. We were therefore unable to investigate whether a radical cyclisation would lead to the desired diastereomeric outcome. A different strategy was warranted.

2.2.6 Forming a different bond

Our attempts thus far have focused on forming the C9–C10 bond last (Figure 23a), which has led to a mixture of diastereomers favouring the undesired *cis* stereochemistry. If we instead formed this bond earlier, and formed the C7–C8 bond later (Figure 23b), then the stereochemistry would be set early, perhaps by epimerisation of a pendant carbonyl, and

we should obtain the desired *trans* stereochemistry. In contrast to the strategies we have previously discussed, we will attempt conjugate addition between the aromatic C-ring and an A-ring with an exocyclic carbonyl, avoiding the later stage elaboration of the A-ring that hampered those syntheses by Hartwig[57] and Qin.[60]

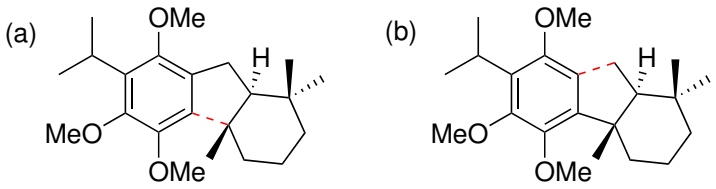
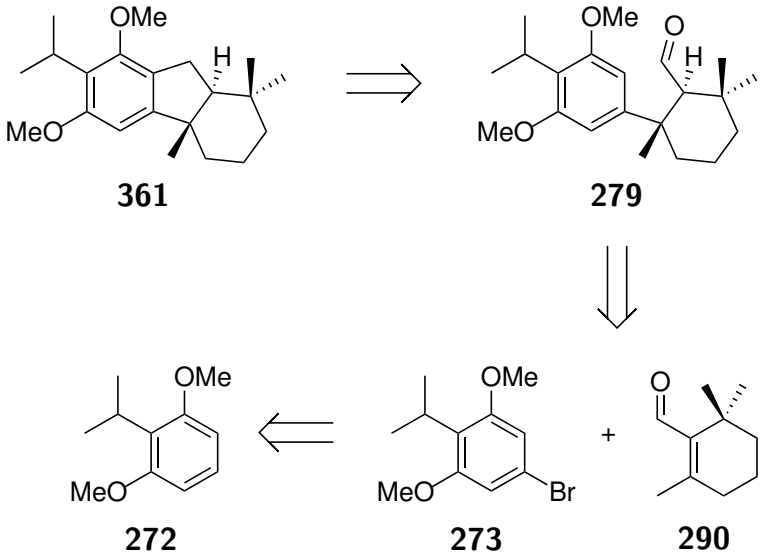


Figure 23: (a) Previous strategy forming the C9–C10 bond last, highlighted in red. (b) New strategy, with ring closure by C7–C8 bond formation.

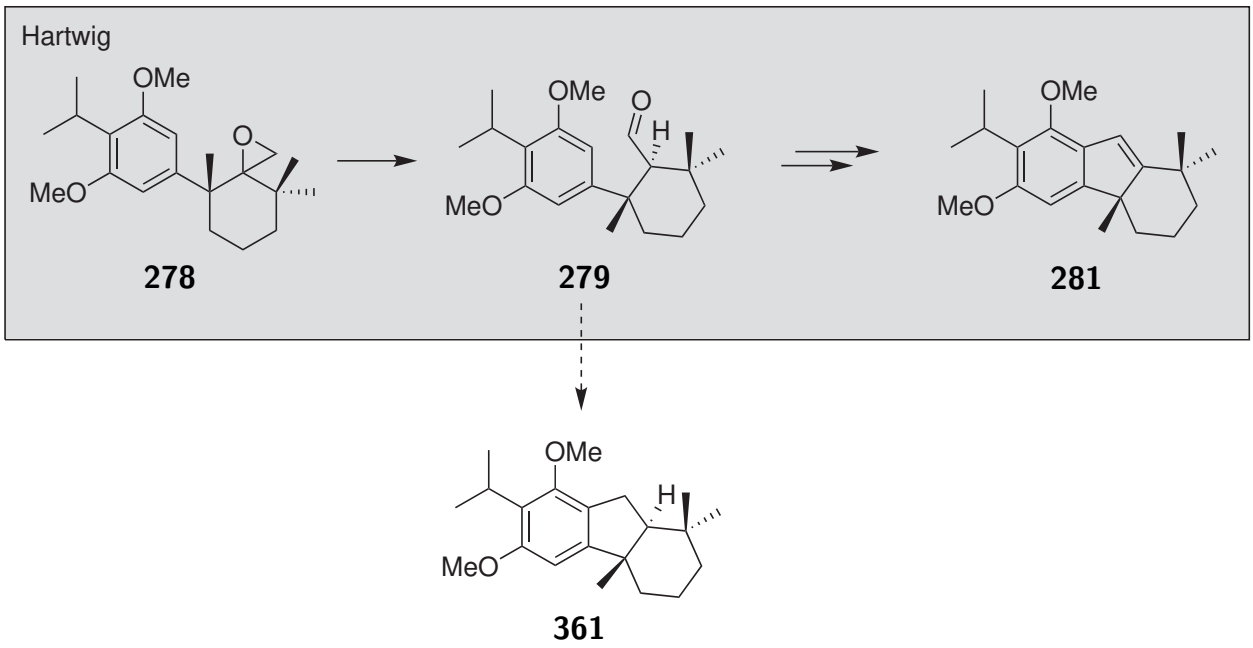
Retrosynthetically, from the benzofused compound **399**, disconnection of the top bond would occur first to give *trans*-fused aldehyde **279** (Scheme 68). This would be formed by conjugate addition of aryl bromide **273** to β-cyclocitral (**290**). Synthesis of the aryl bromide would be difficult, given the lack of nucleophilicity at the 5-position which constantly hampered our efforts thus far, but it has been synthesised by Hartwig using iridium catalysis from 2-isopropyl-1,3-dimethoxybenzene (**272**),[57] an intermediate we have already made.



Scheme 68: Retrosynthesis of *trans*-fused tricyclic compound **361**.

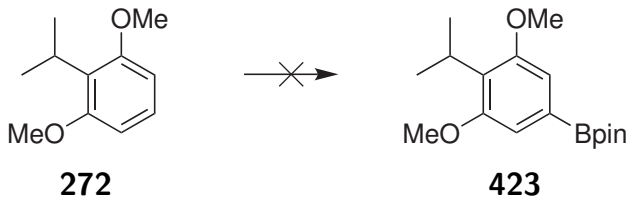
This synthesis would intercept Hartwig's intermediate **279**, which was never isolated in that reaction sequence.[57] It was generated *in situ* from epoxide **278** and under the strongly acidic reaction conditions subsequent cyclisation and elimination of the alcohol occurred, giving fully cyclised alkene **281** (Scheme 69). Rather than producing the

unsaturated compound **281**, we expect that isolating the aldehyde should give us access to the *trans* configured taiwaniaquinoids.



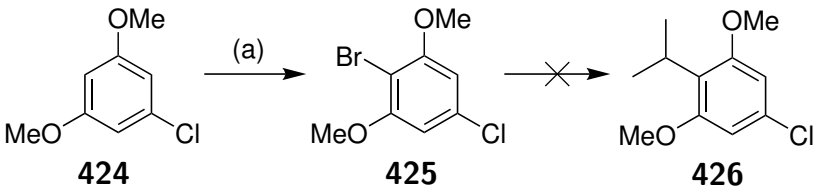
Scheme 69: Isolating aldehyde **279** should allow us to produce the *trans* architecture.

Unfortunately, in our hands treating compound **272** under Hartwig's conditions did not produce the desired boronate **423**. The high cost of iridium compounds made this approach unappealing for scale-up despite the low catalyst loading. Further, Hartwig's work was performed in a glovebox, which we did not have access to, instead opting to use Schlenk techniques to avoid the introduction of water and oxygen. As a result, this approach was abandoned.



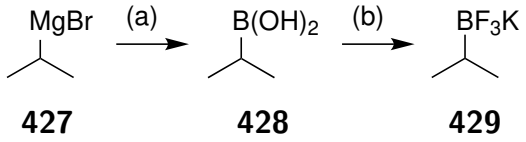
Scheme 70: Regioselective borylation of aryl compound **272** gave no reaction.
Conditions: $[Ir(cod)Cl]_2$, B_2pin_2, MeOH, rt.

Our next approach looked at having a halide attached prior to installation of the isopropyl group, for instance starting with 1-chloro-3,5-dimethoxybenzene **424**. Clearly, this group could not be installed via *ortho*-lithiation, given the ability of the chlorine atom to undergo lithium-halogen exchange. Instead, we brominated selectively at the 4-position using bromine in dichloromethane, then attempted to use the aryl bromide **425** as a coupling partner in a Suzuki reaction to install the isopropyl group to produce chloroarene **426**.



Scheme 71: Synthesis of aryl chloride **425**. (a) Br_2, CH_2Cl_2, 50%.

Potassium isopropyltrifluoroborate (**429**) was synthesised by reacting isopropylmagnesium bromide (**427**) with trimethylborate, with subsequent hydrolysis giving the boronic acid **428**. Reaction with potassium bifluoride and isolation using a Soxhlet apparatus gave trifluoroborate salt **429**.



Scheme 72: Synthesis of potassium isopropyltrifluoroborate. (a) $B(OMe)_3$, THF, –78 °C, then HCl (1 M), rt. (b) KHF_2, $MeOH/H_2O$, then Soxhlet extraction, MeCN, 27% over 2 steps.

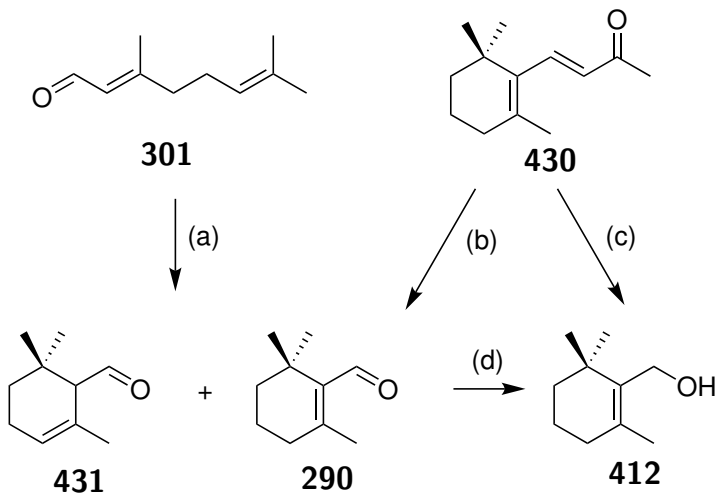
Unfortunately, treating aryl bromide **425** under several conditions led to no formation of the desired cumene (Table 16). In all cases, the bromine atom remained attached, suggesting the challenging steric environment led to no insertion of the large palladium catalyst into the C-Br bond. Likewise, we attempted lithium-bromine exchange of aryl bromide **425**. Despite being less active, the chlorine atom was more sterically available and thus we only saw exchange at the chlorine, giving the undesired isomer.

Table 16: Attempted reaction conditions for the Suzuki reaction of aryl bromide **425** to cumene **426**.

Entry	Catalyst	Solvent	Base	T (°C)
1	$Pd(PPh_3)_4$	$PhMe/H_2O$	NaOH	90
2	$Pd(PPh_3)_4$	dioxane	NaOH	80
3	$Pd_2(dba)_3$/RuPhos	$PhMe/H_2O$	K_2CO_3	110

The strategy from here was to install the isopropyl group later and instead aim to attach chlorobenzene **424** directly to the A-ring. This could be achieved either through forming the cuprate and performing conjugate addition onto β-cyclocitral or through a palladium catalysed reaction with the aryl halide and β-cyclogeraniol.

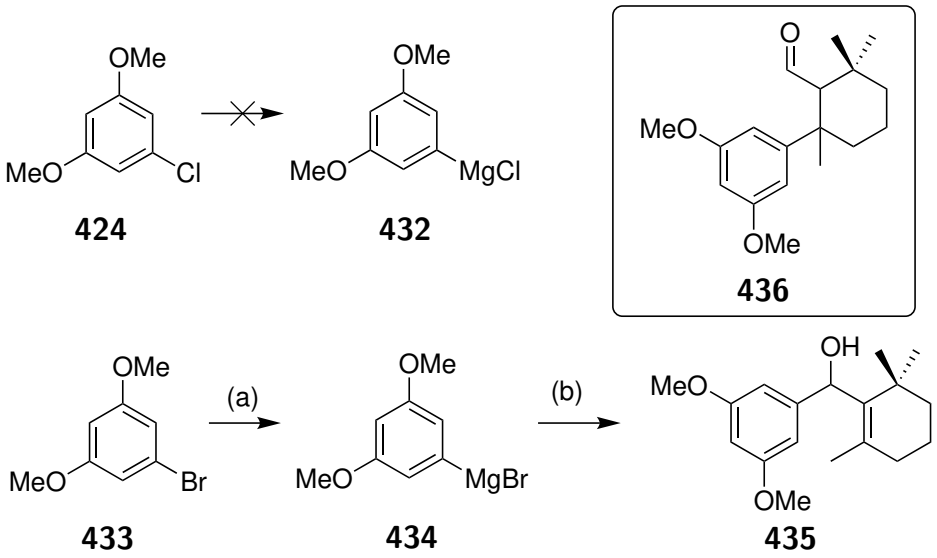
β-Cyclocitral (**290**) was produced by ozonolysis of β-ionone (**430**) and quenching with triphenylphosphine. Subsequently (when we did not have access to an ozone generator) β-ionone (**430**) was produced by cyclisation of the pyrrolidine imine by reaction of citral with pyrrolidine in ether in the presence of magnesium sulfate, followed by slow decanting of the ethereal imine solution into 95% sulfuric acid. This led to a mixture of α-cyclocitral (**431**) and β-cyclocitral (**290**), which could be isomerised to the pure β isomer **290** by sodium hydroxide in methanol. β-Cyclogeraniol (**412**) could be synthesised by reduction of aldehyde **290** with sodium borohydride. This would be performed by reductive quenching of the ozonolysis reaction mixture but could also be achieved by reduction of isolated β-cyclocitral (**290**) in isopropanol/ethanol.



Scheme 73: Synthesis of β-cyclocitral. (a) pyrrolidine, Et_2O, then H_2SO_4. (b) NaOH, MeOH, rt, 57% over 2 steps. (c) O_3, then PPh_3, MeOH, –40 °C. 57% (d) O_3, then $NaBH_4$, MeOH, –40→rt, 89% (e) $NaBH_4$, *i*PrOH/MeOH, 0 °C, 89%.

Aryl chloride **424** proved difficult to work with (Scheme 74). Lithium-halogen exchange using *n*-butyllithium, followed by addition of stoichiometric copper(I) iodide and α,β-unsaturated aldehyde **290** led only to addition of *n*-butyllithium at the 2-position. Similarly, reaction with isopropylmagnesium chloride to effect magnesium-halogen exchange returned starting material.

No reaction was seen with magnesium metal with catalytic iodine, despite activating magnesium by washing with 1 M hydrochloric acid, ethanol and ether followed by drying. Switching to the aryl bromide **433**, we successfully synthesised aryl Grignard reagent **434** using the same batch of magnesium metal. Unfortunately, treating this Grignard reagent with stoichiometric copper(I) iodide and reacting with aldehyde **290** again led to addition at the carbonyl.



Scheme 74: Addition of aryl bromide **433** to aldehyde **290** lead to the 1,2 adduct **435**.

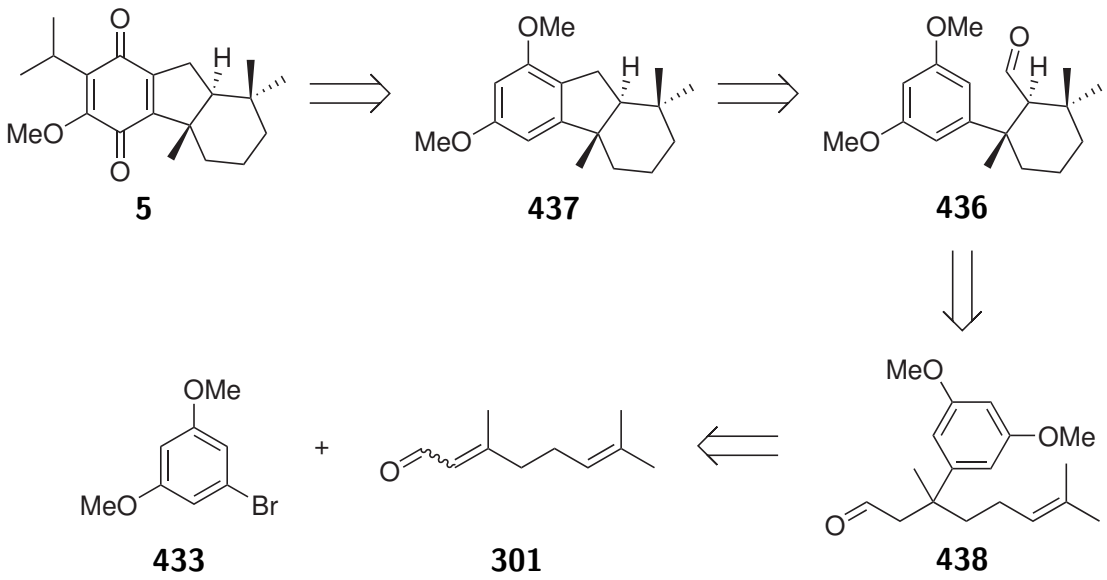
Heck arylation of β-cyclogeraniol would also give us the desired compound **436**. Aryl chloride **424** was inert to all attempted conditions (Table 17). Aryl bromide **433** was similarly unreactive. The lack of reactivity is likely due to the challenging steric environment around the tetrasubstituted alkene.

Table 17: Conditions for Heck reaction between aryl halides **424** or **433** and β-cyclogeraniol (**412**).

Entry	Arene	Catalyst	Base	Solvent	T (°C)	Result
1	**433**	$Pd(PPh_3)_4$	Et_3N	MeCN	80	nr
2	**433**	$Pd(PPh_3)_4$	Et_3N	dioxane	80	nr
3	**433**	$Pd(OAc_2)$/SPhos	K_2CO_3	MeCN	80	nr
4	**433**	$Pd(PPh_3)_4$	K_2CO_3	$PhMe/H_2O$	100	nr

Conjugate addition of bis(pinacolato)diboron to α,β-unsaturated aldehyde **290** under copper catalysis, to give a boronate that could be used in a subsequent Suzuki coupling reaction, was also unsuccessful.

Looking at these results, we considered installing the aryl ring onto a linear precursor, i.e. citral (**301**). Retrosynthetically, elaboration of the aryl ring would occur at a late-stage. The central five member ring would be formed by Friedel-Crafts alkylation from aldehyde **279**, in turn formed from the citral derivative **438** obtained by Gilman addition onto citral. As with the previous strategy, this cuprate addition could be performed enantioselectively in the future.



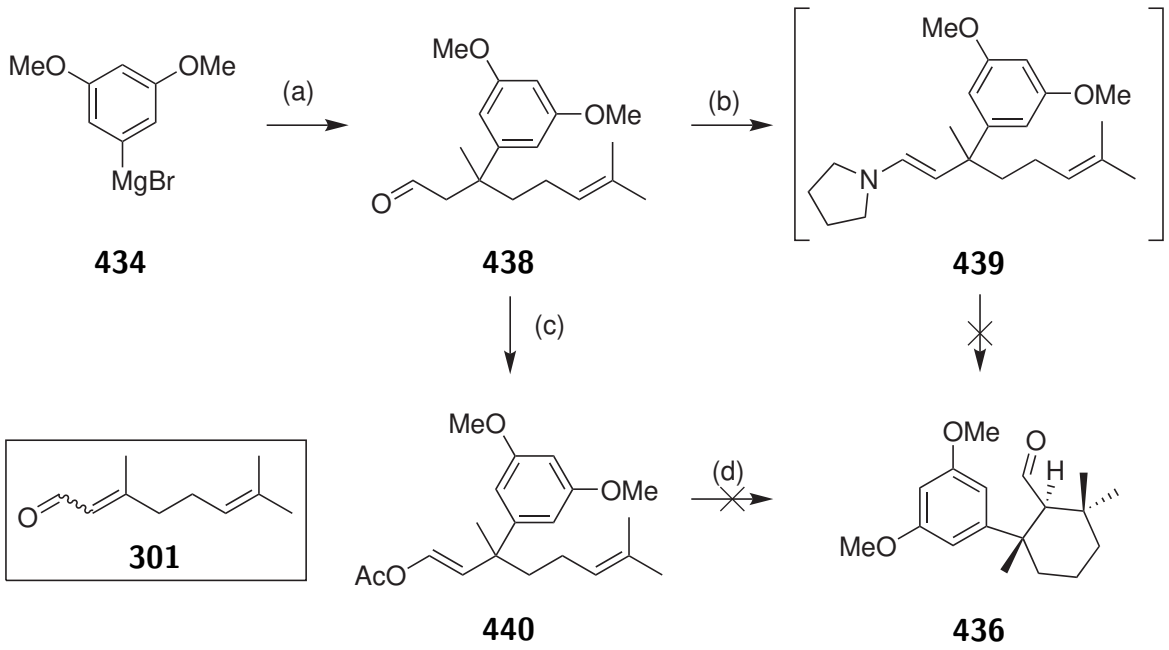
Scheme 75: Retrosynthesis starting from citral.

Unlike with β-cyclocitral, the desired conjugate addition onto citral (**301**) occurred with ease using either copper(I) iodide or copper(I) bromide dimethylsulfide complex. Unfortunately, treating aldehyde **438** with pyrrolidine followed by sulfuric acid did not give the desired cyclised compound, unlike the reaction with citral itself. Thin layer chromatography analysis reveals transformation of aldehyde **438** to a new compound which reverted to the starting material upon workup. This suggests that formation of the enamine took place, but that cyclisation could not be effected, perhaps due to steric hindrance around the proximal quaternary carbon.

Table 18: Attempted cyclisation of enol acetate **440** to aldehyde **436**.

Acid	Solvent	T (°C)	**440**	**438**	**436**
H_3PO_4	PhMe	80	✓	X	X
$BF_3{\cdot}OEt_2$	CH_2Cl_2	rt	X	✓	X
$Bi(OTf)_3$	CH_2Cl_2	rt	✓	X	X
$SnCl_4$	CH_2Cl_2	rt	X	✓	X
H_2SO_4	CH_2Cl_2	rt	X	✓	X
TFA	CH_2Cl_2	rt	✓	X	X
$ZrCl_4$	CH_2Cl_2	rt	✓	X	X

Work by Simmons, who cyclised enantiopure citronellal *via* the enol acetate, provided an alternative route forward.[79] Treating the 1,4-adduct **438** with acetic anhydride in the presence of triethylamine and potassium acetate gave the corresponding enol acetate **440** in high yield. Heating enol acetate **440** with 85% phosphoric acid in toluene overnight



Scheme 76: Attempted synthesis of monocyclised aldehyde **436**. (a) CuI, THF, –78 °C, then citral, 55%. (b) pyrrolidine, Na_2SO_4, Et_2O, then H_2SO_4. *Not isolated.* (c) Et_3N, KOAc, Ac_2O, 120 °C. *Not isolated.* (d) Table 18.

remarkably returned us the starting material, suggesting that it is quite resistant to hydrolysis. The acetate was hydrolysed under more strongly acidic conditions, but no cyclisation to aldehyde **436** ever occurred. Clearly, the steric environment around the enol ester or enamine functional group prevented reaction with the distal alkene.

We successfully produced taiwaniaquinone G with an increased amount of the desired *trans* diastereomer, but our only successful method towards the taiwaniaquinoid core was using polyene cyclisation. It seemed that any further investigation should focus on the divergent synthesis of other taiwaniaquinoids with a key ring closure performed by polyene cyclisation.

2.3 Other Taiwaniaquinoids

2.3.1 Benzylic oxidation strategies: (±)-taiwaniaquinol B

Up to this point, attempts to generate selectively the natural *trans* diastereomer of (±)-taiwaniaquinone G were somewhat disappointing, but we had a way of generating the *cis* diastereomer **365** with good stereocontrol. Two of the taiwaniaquinols possess

the *cis* stereochemistry: taiwaniaquinol B (**248**) and taiwaniaquinol F (**252**). Both compounds contain a benzylic ketone, likely the cause of the *cis* stereochemistry via epimerisation. They differ only in the presence of a ketone α to the geminal dimethyl group in taiwaniaquinol F.

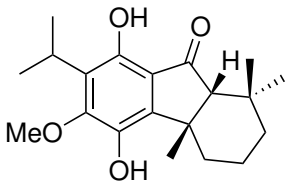
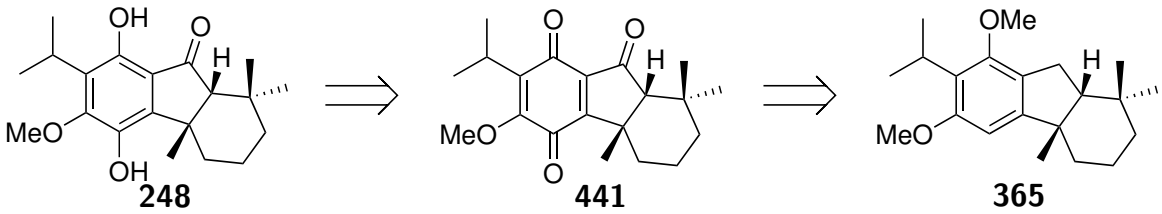


Figure 24: Taiwaniaquinol B (**248**).

We envisioned we could obtain taiwaniaquinol B from dithionite reduction of quinone **441**, which we hoped to obtain in a single step by one-pot benzylic oxidation and subsequent quinone oxidation of intermediate **365** (Scheme 77).

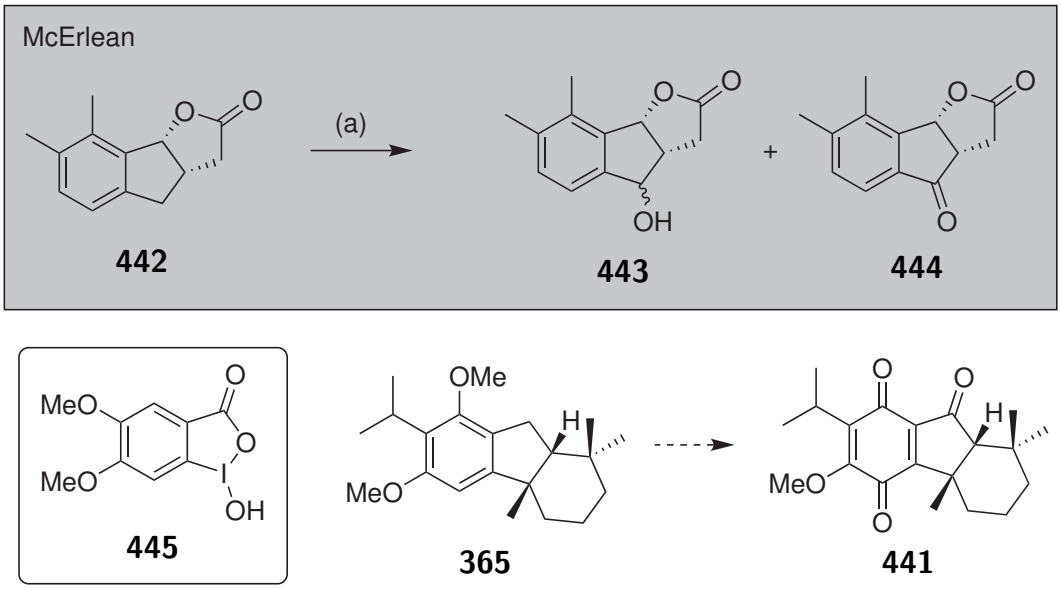


Scheme 77: Retrosynthesis for taiwaniaquinol B up to the previously synthesised *cis*-fused tricycle **365**.

A number of reagents should perform both of the desired oxidations. We first attempted mild conditions using the hypervalent iodine reagent 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (**445**), using a photoredox protocol developed by Liu and Chen.[80]

Previous work in the McErlean group used this protocol in the synthesis of (–)-solanacol.[81] Treating indane **442** with iodoxolone **445** in the presence of *tris*-bipyridine ruthenium(II) chloride and blue light generated a modest yield of the desired alcohol **443** with a significant amount of a ketone byproduct **444**. Careful optimisation reduced the amount of this ketone and importantly, only minor oxidation of the benzylic methyl groups was seen.

In this case, we want the ketone. Compound **365** was obtained according to the McErlean group's original synthesis of 5-*epi*-taiwaniaquinone G. We treated tricycle **365** with 5 equivalents of benziodoxolone **445** and *tris*-bipyridineruthenium(II) chloride under blue LED using a MacMillan photoreactor. A mixture of products was obtained. No highly



Scheme 78: Photoredox oxidation of benzylic positions using benziodoxolone **445**.[81] (a) $Ru(bpy)_3Cl_2$, **445**, MeCN, 465 nm LED.

coloured quinone products were seen, and further, ^{1}H NMR spectroscopy showed the methyl ethers were intact and there was no loss of the characteristic benzylic protons.

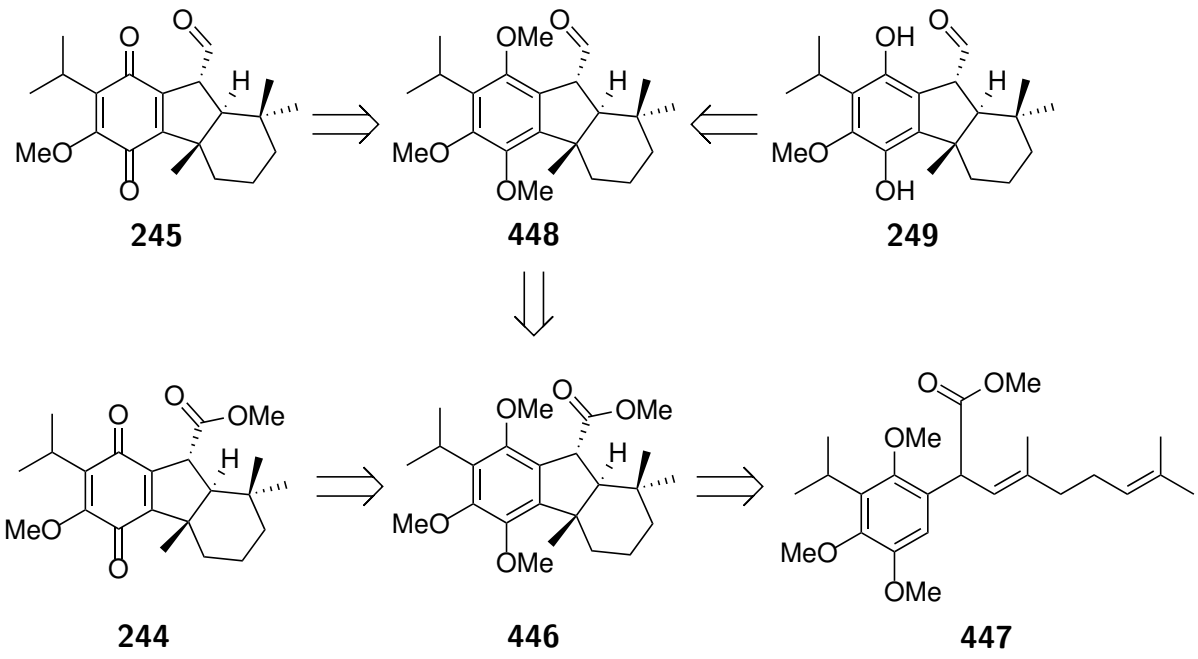
We then attempted more traditional, more hazardous methods. No reaction was seen upon treatment with sodium dichromate. This was expected given previous work by Alvarez-Manzaneda[54] and Banerjee.[47]

We also attempted oxidation by catalytic selenium dioxide with *tert*-butylhydroperoxide as a stoichiometric oxidant. While selenium dioxide may perform the benzylic oxidation, *tert*-butylhydroperoxide should oxidise the aromatic to the quinone. Again, no reaction occurred after several days.

We considered a modification of this route with no substitution at the *ortho* position, which would allow more room for an oxidant such as Cr(VI) to react at the desired benzylic position. Regiochemical issues, particularly with bromination, would be troublesome. Benzylic oxidation of compound **365** could not be performed, thwarting efforts to synthesise taiwaniaquinol B (**248**) by this method. Later efforts detail the attempted synthesis of taiwaniaquinol B (**300**) as a product of a more extensive divergent synthetic strategy of the taiwaniaquinoids.

2.3.2 Substitution at C7

Most of the taiwaniaquinoids have some functionality at the C7 position. We have already attempted to produce the compounds containing a ketone at this position (e.g. taiwaniaquinol B), but often there is instead a pendant carbonyl group at this position. These compounds provide an opportunity to assess the effect of an electron withdrawing group at the C7 position on the diastereoselectivity of a polyene cyclisation. Removing electron density from the LUMO should weaken the hyperconjugative stabilisation which previously led to the *cis*-fused products **365** and **407**. Cyclisation would instead favour the *trans*-fused products.

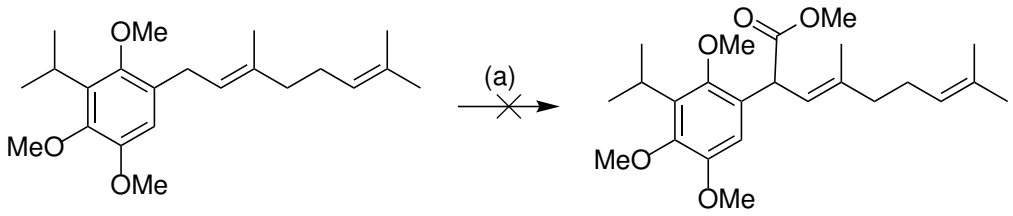


Scheme 79: Polyene **447** should give us the *trans*-fused compound **446** which can be elaborated to taiwaniaquinone E (**244**) and the aldehyde containing taiwaniaquinoids **245** and **249**.

Taiwaniaquinone E (**244**) seems an ideal candidate, with a pendant methyl ester at the C7 position and the *trans* stereochemistry across the ring junction. Further, taiwaniaquinones A and F should be accessible by reduction to the aldehyde, then taiwaniaquinones B or C and taiwaniaquinone D by α-bromination of the aldehyde and substitution or elimination.

The linchpin in this strategy towards taiwaniaquinone E was the ester **447**. The simplest way to obtain this compound would be to deprotonate the benzylic, allylic proton and quench with methyl chloroformate. Unfortunately, when that was attempted no reaction

was seen. We suggest the lithium anion was too sterically encumbered to react with methyl chloroformate and was quenched upon workup.

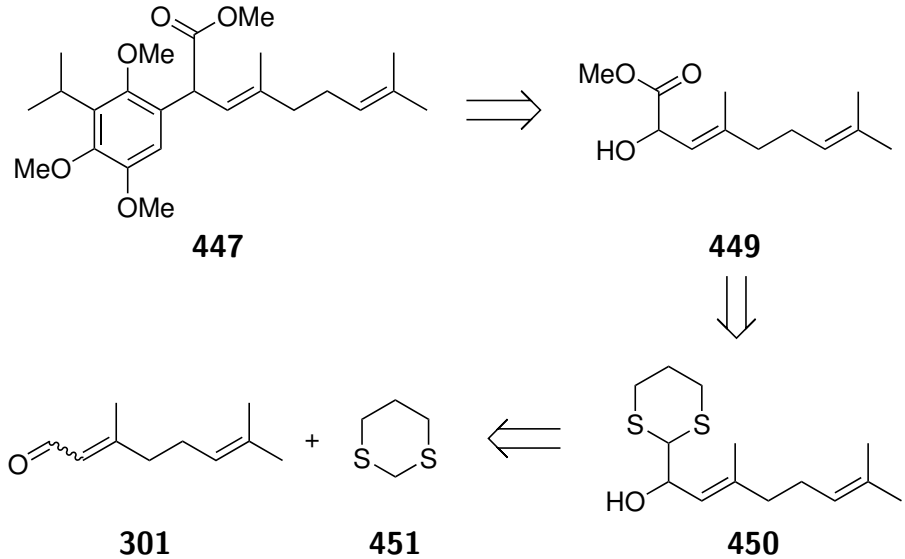


390 **447**

Scheme 80: Direct installation of the methyl ether onto **390** failed. (a) *n*-BuLi, THF, –78 °C, then $ClCO_2Me$.

Dithiane strategy

We then decided to modify our polyene coupling partner. A retrosynthesis is presented in Scheme 81. To produce the desired ester **447**, we could make secondary alcohol **449** and attempt cross-coupling. We could then use an *umpolung* strategy, obtaining alcohol **449** from deprotection and oxidation of the aldehyde surrogate **450**, formed in turn by addition of *m*-dithiane (**451**) onto citral (**301**).

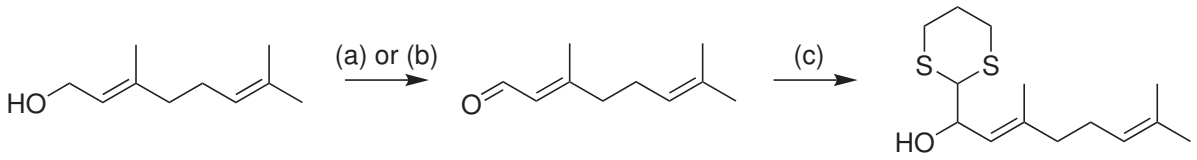


447 **449** **301** **451** **450**

Scheme 81: Retrosynthesis of intermediate **447** by an *umpolung* strategy.

Commercially sourced citral is an inseparable mixture of the (*E*) and (*Z*) configured aldehydes, geranial and neral. The neral-derived (*Z*) diastereomer of **447** could potentially lead to the *cis*-fused compound. Chiu used commercially sourced citral in the synthesis of taiwaniaquinol B and separated the diastereomers at a later stage,[24] but the synthesis of diastereomerically pure (*E*)-geraniol is a simple task.

Geranial (**452**) was obtained as the single diastereomer by oxidation of geraniol (Scheme 82). Manganese dioxide has been used to perform this reaction adequately in the literature.[82] But manganese dioxide requires a large excess; to avoid this on a multigram scale we later opted to use the Stahl oxidation: use of a copper(I)/copper(II) catalyst and TEMPO as a co-catalyst, with oxygen from air as a stoichiometric oxidant.[83] Both methods gave good yields of geranial with clean reaction by ^{1}H NMR analysis. Geranial was then reacted with the anion produced from deprotonation of *m*-dithiane with *n*-butyllithium to give the α-hydroxydithiane **450** in good yield.

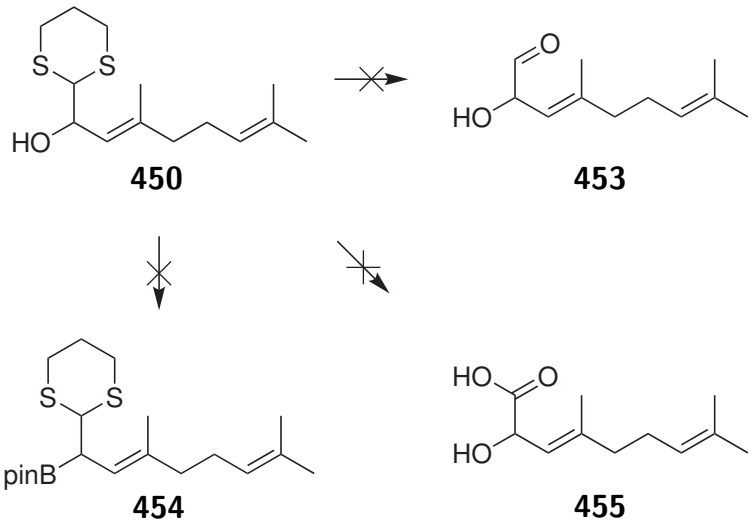


374 **452** **450**

Scheme 82: Synthesis of dithiane **450**. (a) CuBr, bpy, TEMPO, NMI, MeCN, air, rt, 3 d, 92%. (c) *m*-dithiane, *n*-BuLi, –78 °C, THF, 1 h, then **452**, –78 °C→rt, 3 h, 58%.

From here, we attempted deprotection of dithiane **450** (Scheme 83). Pinnick conditions have been shown to generate the carboxylic acid through oxidative deprotection with oxidation of the resultant aldehyde occurring in one pot.[84] Pinnick oxidation of aldehydes to acids has always been successful on the polyene substrates we have used it on. We expected this would be no different. Unfortunately, dithiane **450** was resistant to oxidation under these conditions. Methylative deprotection of dithiane **450** using methyl iodide and sodium bicarbonate in aqueous acetonitrile is a protocol widely used in our group which should have delivered the corresponding aldehyde **453**. ^{1}H NMR analysis showed the disappearance of dithiane protons, but no resulting aldehyde. We believed that the α-hydroxyaldehyde **453** was produced but was highly unstable and degraded rapidly, and coupling should be attempted before deprotection.

Treating alcohol **450** under our borylation conditions led to no reaction: the presence of sulfur so close to the reaction centre poisoned the palladium catalyst. We expect a subsequent Suzuki reaction using boronate **454** would be equally troublesome if it could be obtained. Any coupling with alcohol **450** or a dithiane-containing derivative would also be complicated by the bulk of the dithiane. We abandoned this approach and attempted to arylate a suitable polyene by other means.

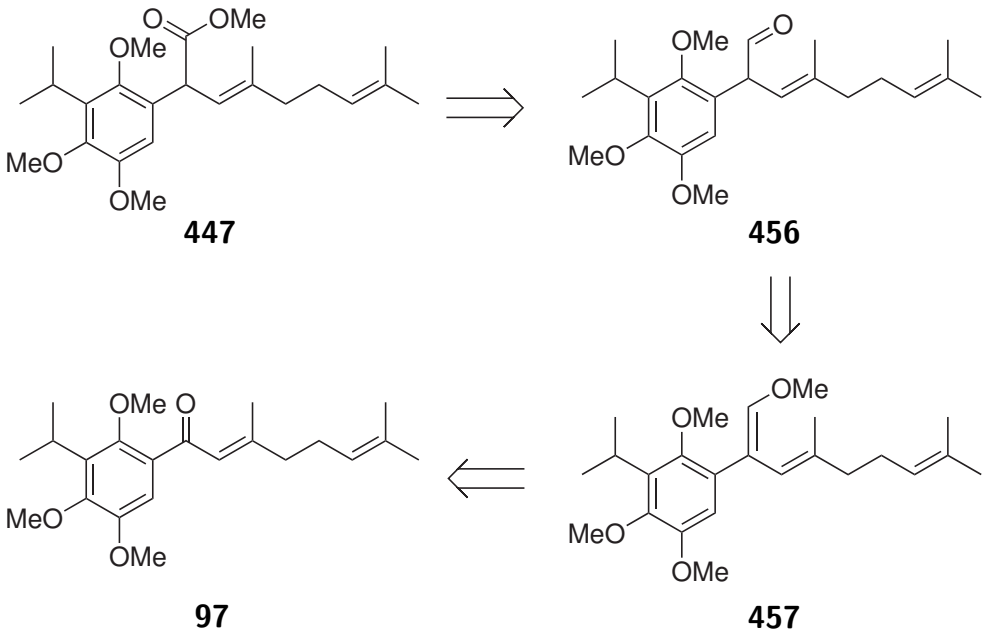


Scheme 83: We were unable to derivatise dithiane **450** further. Deprotection and borylation both failed.

Wittig olefination

We were unable to produce the compound **447** using an *umpolung* strategy. Nevertheless, compound **447** could prove to be a key intermediate in a divergent synthesis of the taiwaniaquinoids.

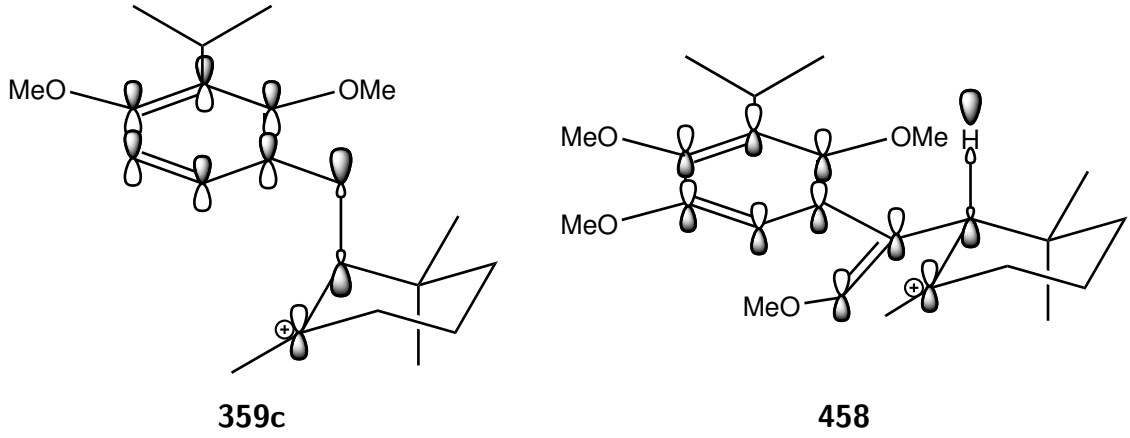
Alternatively, we could obtain compounds **447** and **456** through a Wittig olefination of ketone **97**, an intermediate from Chiu's synthesis of taiwaniaquinol B.[24]



Scheme 84: We could obtain polyenes **447**, **456** and **457** from Chiu's intermediate **97**.

We expect that cyclisation of these compounds would lead to higher selectivity for the

trans isomer by weakening the hyperconjugative stabilisation in the cationic intermediate. However, we now have another compound to consider. If polyene **457** is compatible with our polyene cyclisation reaction conditions, it should deliver high levels of *trans* selectivity due to similar hyperconjugative factors (Figure 25). In contrast to our previous cyclisations, the extended styrenyl π system would donate electron density into the *axial* C–H σ^* orbital and in turn into the vacant carbocation *p* orbital, thereby stabilising the equatorial conformer **458**.



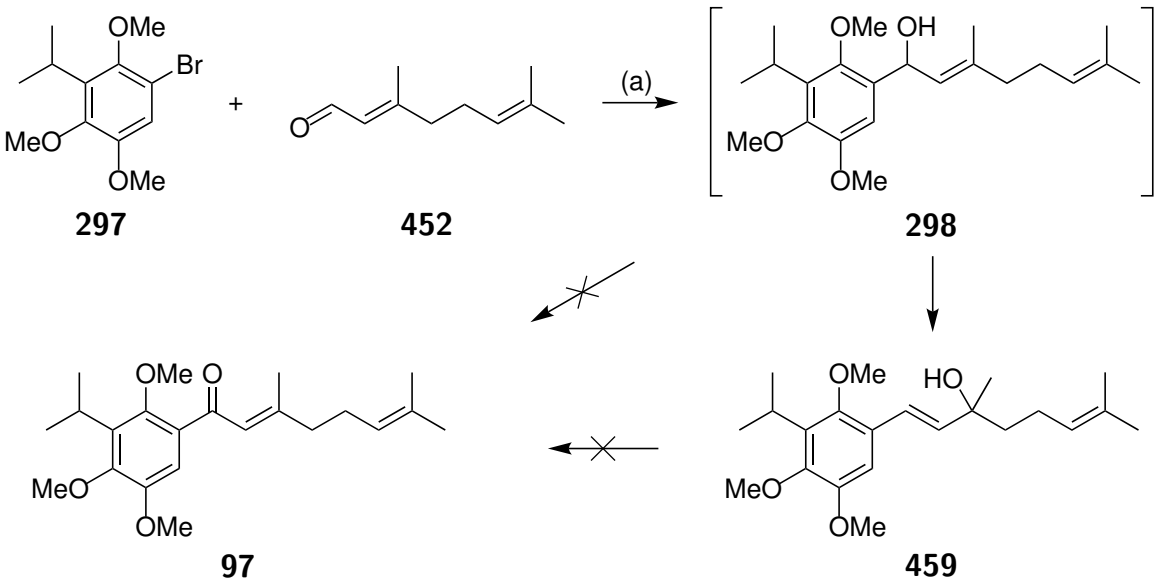
359c **458**

Figure 25: Hyperconjugative effects delivered the axial conformer **359c**. Hyperconjugative effects should instead stabilise the equatorial conformer **458**, giving the *trans* product.

In Chiu's report, aryl bromide **297** was coupled with citral *via* the aryllithium, with the (*E*) and (*Z*) diastereomers being separated by careful column chromatography.[24] We had already obtained diastereomerically pure geranial (**452**), which was reacted in the same way to give the alcohol **298** (Scheme 85). This *n*-BuLi mediated coupling was complicated by the instability of intermediate **298**, which would isomerise to the tertiary alcohol **459** immediately upon contact with acidic media. We could not rectify this despite workup with sodium bicarbonate as an especially weak proton source, avoidance of column chromatography and immediate treatment with manganese dioxide as a mild oxidant. Attempted oxidative rearrangement using iodoxybenzoic acid or pyridinium chlorochromate also failed. We have been unable to produce compound **97**.

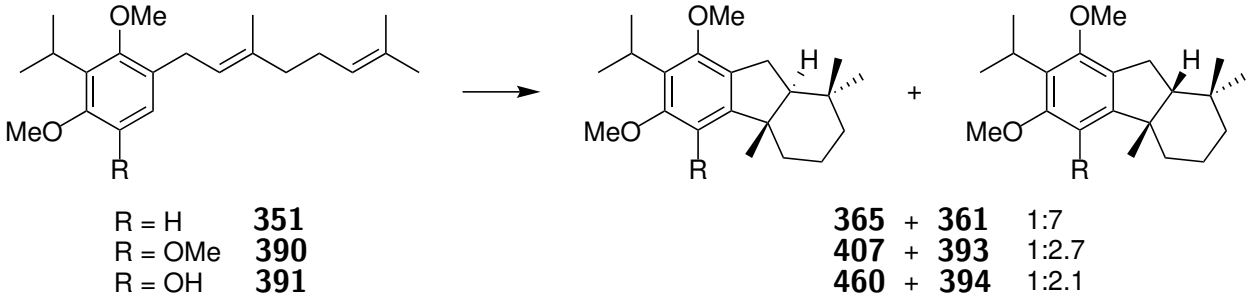
2.4 Conclusion

This chapter describes work on taiwaniaquinone G that was able to decrease the undesired inherent diastereoselectivity of the key cyclisation of polyene **351** from 7:1 to 2.7:1 via



Scheme 85: After coupling, alcohol **298** rapidly isomerised to tertiary alcohol **459**. We were unable to produce ketone **97**.

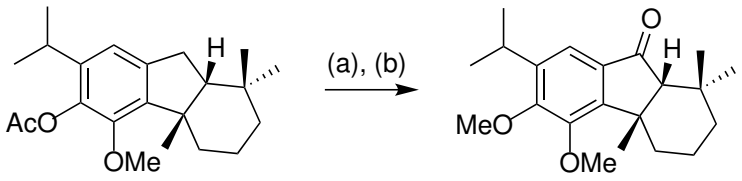
compound **390**. We saw a further improvement to 2.1:1 using phenol **391**, demonstrating that the stereochemical outcome of these polyene cyclisations can be controlled by altering the nucleophilicty of the terminating aromatic ring. However, in no case was exclusive *trans* selectivity achieved, unlike in the case of Yamamoto's work.[30]



Scheme 86: Summary of all cyclisation reactions including diastereomeric ratios.

Given that we have been able to obtain good selectivity for the *cis* diastereomer of this framework, we attempted to produce the *cis*-fused natural products that possess a ketone at the C7 position, by way of benzylic oxidation. This proved impossible. Other groups such as Ozeki's have successfully used chromium(VI) reagents to effect benzylic oxidation on substrates that lack a methoxy group at the C14 position (Scheme 87).[48] Such compounds may be more amenable to other oxidation methodologies that avoid the use of carcinogenic and highly toxic chromium(VI) compounds. Ozeki's oxidation also does not oxidise the aromatic unit to the quinone, which we attempted to achieve in one pot.

We also tried a series of alternative syntheses in an attempt to obtain the *trans*



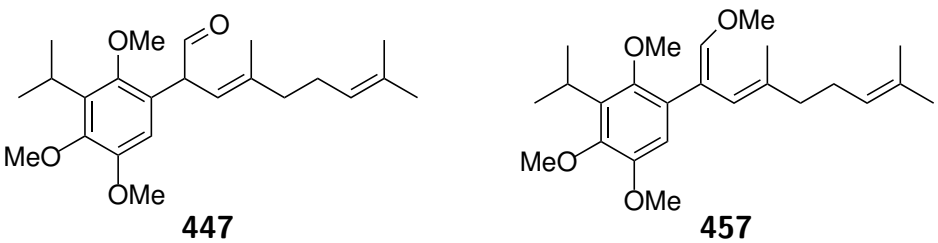
461 **462**

Scheme 87: Ozeki's Benzylic oxidation of substrate **461** proceeds in good yield.[48] (a) PCC, Celite, benzene. (b) K_2CO_3, MeI, acetone/MeOH. 83% over 2 steps.

diastereomer of taiwaniaquinoid G in a more efficient manner that was substantially different from the existing syntheses of the *trans*-taiwaniaquinoids. Unfortunately, these were uniformly unsuccessful.

Nevertheless, we did successfully synthesise (±)-taiwaniaquinone G and obtain a diastereomerically pure sample of the natural isomer. We accomplished this in only six steps, leading to the shortest synthesis of taiwaniaquinone G and one of the shortest syntheses of any of the taiwaniaquinoids. Rapid construction of fused ring systems is the key advantage of polyene cyclisation and our synthesis highlights this advantage. The total yield is only 3% for the *trans* diastereomer, but the cyclisation step is not the problem in this approach. The yield for this step from polyene **390** is far higher than the McErlean group's previous synthesis of 5-*epi*-taiwaniaquinone G owing to the higher nucleophilicity of compound **390**, which also leads to suppression of an alternatively cyclised byproduct. We were also able to provide *correctly* reported ^{1}H NMR data for taiwaniaquinone G, which was previously lacking in the literature.

The possibility of installing an aldehyde or alkene at the C7 position (shown in Figure 26) was intriguing, as this would act to minimise the hyperconjugative stabilisation that hindered production of *trans*-fused taiwaniaquinone G. If successful, compounds such as polyene **447** would be possible precursors to most of the taiwaniaquinoids. Unfortunately, we could not synthesise a suitable precursor.

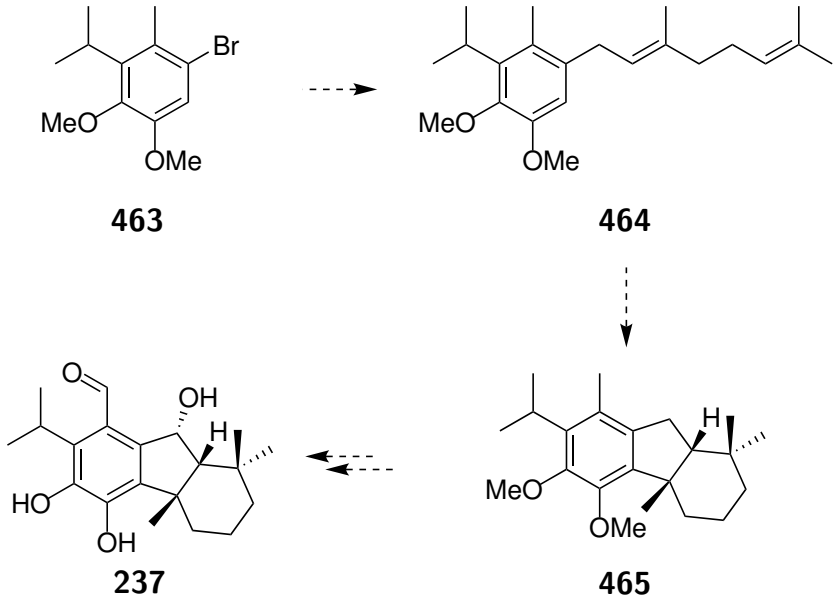


447 **457**

Figure 26: Polyenes which we project will deliver *trans* selectivity in a subsequent cyclisation.

Nevertheless, the polyene cyclisation approaches demonstrated here and by other authors should apply to the synthesis of other compounds, including those that are yet to be synthesised.

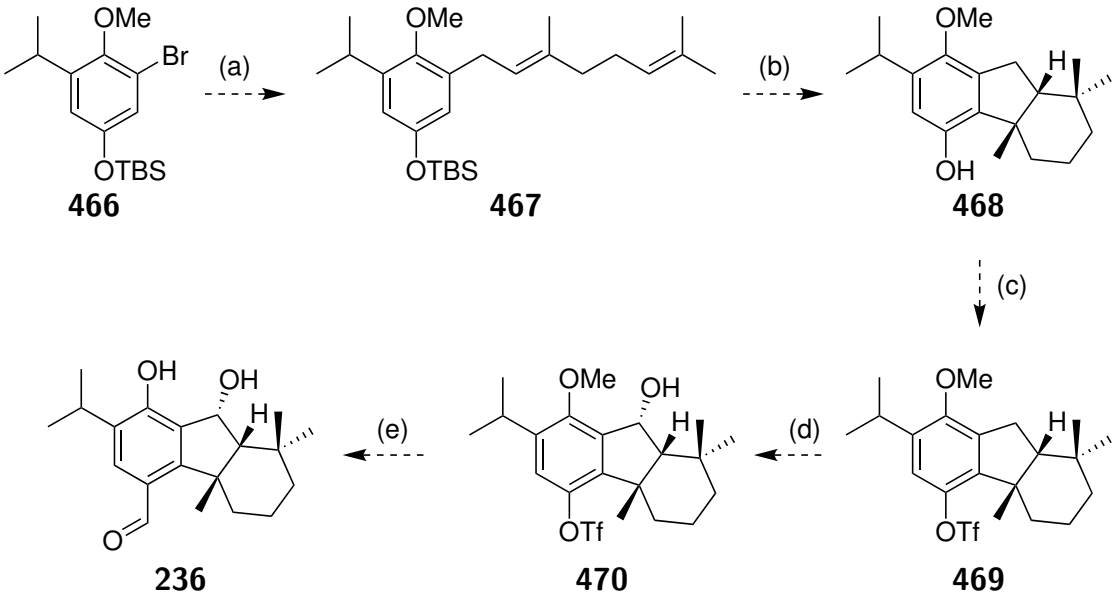
Dichroanal A is one such example. This would require synthesis of aryl bromide **463**, which could then be subjected to Suzuki coupling with geranyl pinacol boronate as per our work to produce polyene **464**. Cyclisation would deliver a mixture of diastereomers of hexahydrofluorene **465**, heavily favouring the *cis* diastereomer. Benzylic oxidation of the toluene methyl group to the corresponding aldehyde and benzylic oxidation at the cyclopentane ring, followed by cleavage of the phenyl methyl ethers should deliver dichroanal A (**237**) in a short synthesis.



Scheme 88: Proposed synthesis of dichroanal A.

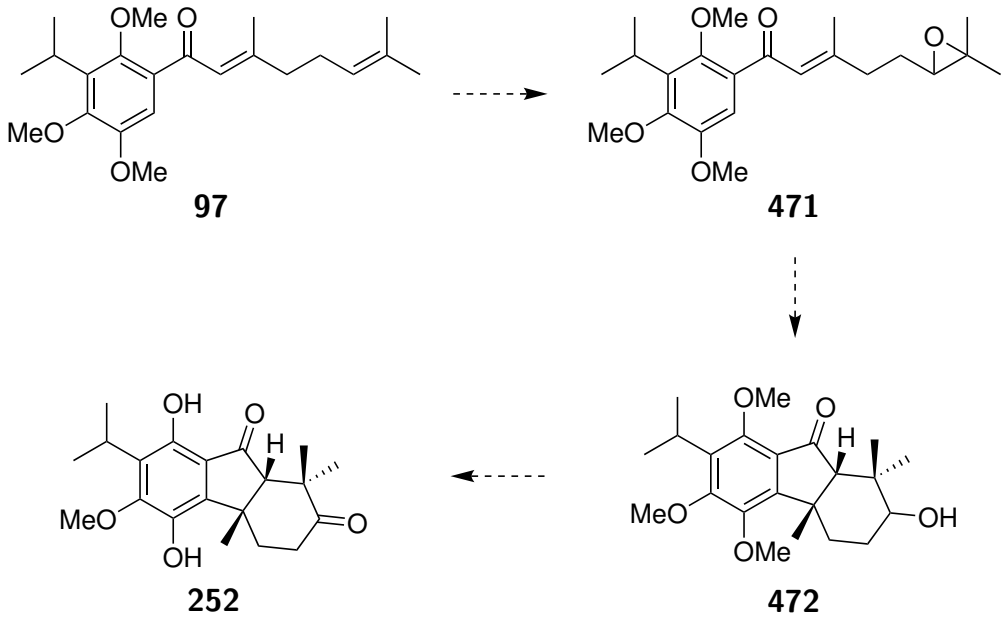
Standishinal (**236**), previously synthesised only by Node,[66] may also be produced by this methodology. Again, Suzuki coupling between aryl bromide **466** and geranyl pinacol boronate would deliver the desired polyene **467**. Polyene cyclisation may be more difficult on this substrate due to the lesser oxygenation, but the *cis*-fused product **468** should be highly favoured. We may then protect the free phenol as the triflate **469** and perform benzylic oxidation of the cyclopentane to deliver alcohol **470**. Trauner performed palladium-catalysed cyanation of an enol triflate at the C7 position with subsequent hydrolysis furnishing the aldehyde;[62] we expect this sequence or direct carbonylation would install the benzaldehyde, with methyl ether cleavage delivering standishinal (**236**).

These two syntheses rely on benzylic oxidation to install alcohols and aldehydes, but our



Scheme 89: Proposed synthesis of standishinal. (a) $Pd(PPh_3)_4$, **357**, $PhMe/H_2O$, 100 °C. (b) $ClSO_3H$, $MeNO_2/H_2O$. (c) Tf_2O, (d) *benzylic oxidation* (e) *Pd-catalysed carbonylation*, then BBr_3.

foray into this area in an attempt to synthesise taiwaniaquinol B was unsuccessful.



Scheme 90: Proposed synthesis of taiwaniaquinol F (**252**) beginning from ketone **97**.

Chiu's methodology, which installs the benzylic ketone prior to cyclisation,[24] also provides an opportunity to produce taiwaniaquinol F (**252**), which has not yet been synthesised. From ketone **97**, oxidation of the distal alkene provides epoxide **471**, with subsequent cyclisation delivering exclusively *cis*-fused alcohol **472**. Oxidation of the alcohol and cleavage of the methyl ethers would deliver taiwaniaquinol F (**252**). However, we have had difficulties in producing ketone **97**.

By far the most important avenue of investigation, however, would be to produce a polyene containing a pendant aldehyde (e.g. **447**) or alkene (e.g. **457**) at the C7 position. We expect that cyclisation of these compounds would be selective for the *trans* diastereomer. This should facilitate the synthesis of most of this family of compounds, including some of those yet to be produced by total synthesis. So far we have been unable to produce these polyenes.

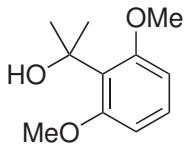
2.5 General experimental

Unless otherwise stated, all reactions were performed under an inert atmosphere (nitrogen or argon) in oven dried glassware. Acetonitrile, dichloromethane, *N,N*-dimethylformamide, tetrahydrofuran and toluene were purified using an Innovative Technology, Inc. Puresolv^{TM} solvent purification system. Triethylamine was distilled from potassium hydroxide. *p*-Toluenesulfonic acid was recrystallised from anhydrous methanol. Diisopropylamine and *N,N,N',N'*-tetramethylethylenediamine were purified by passage through a basic alumina column. Nitromethane and nitroethane were purified by passage through a neutral or acidic alumina column. All other solvents and reagents were used as received from commercial sources. Melting points were determined using a Stanford Research Systems DigiMelt melting point apparatus and are uncorrected. Infrared spectra were acquired on a Bruker ALPHA FT-IR, neat. Absorption maxima are expressed in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform or DMSO-d_6 on a Bruker AVANCE 500, Bruker AVANCE III 400, Bruker AVANCE DPX300 or Bruker DPX200 spectrometer (^{1}H frequencies 500, 400, 300, 200 MHz; ^{13}C frequencies 125, 100, 75 and 50 MHz respectively). ^{1}H NMR chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 7.26) or DMSO (δ 2.50) as an internal reference and are reported as chemical shift (δH); relative integral; multiplicity (s = singlet, br = broad, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, q = quartet, m = multiplet); and coupling constants (J) reported in Hz. ^{13}C NMR chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 77.16) as an internal reference and are reported as chemical shift (δC). NMR chemical shifts of other nuclei are expressed as parts per million (ppm) with no internal reference and are reported as chemical shift. Low resolution electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI) mass spectra were recorded on a Bruker amazon SL mass spectrometer. Low resolution electron impact (EI) mass spectra were obtained using a Finnigan PolarisQ ion trap mass spectrometer at 40 or 70 eV, coupled to gas chromatography using a Perkin Elmer Clarus GC-Q-MS equipped with a 30 m column with a diameter of 250 mm. High resolution mass spectra were recorded on a Bruker Apex II Fourier Transform Ion Cyclotron Resonance mass spectrometer with a 7.0 T magnet, fitted with an off-axis Analytica electrospray source or a Solarix 2XR FTICR

mass spectrometer with a 7.0 T magnet, fitted with an off-axis Analytica electrospray source. Column chromatography was performed using Grace Davison or Merck 40–63 μm (230-400 mesh) silica gel. Analytical thin layer chromatography was performed using preconditioned plates (Merck TLC silica gel 60 F254 on aluminium) and visualised using UV light (254 nm and 365 nm), ethanolic anisaldehyde, potassium permanganate solution, dinitrophenylhydrazine or bromocresol green.

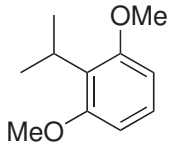
2.6 Experimental

2-(2,6-Dimethoxyphenyl)propan-2-ol (377) [25]



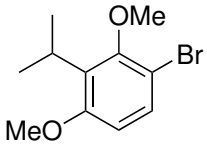
To a solution of 1,3-dimethoxybenzene (2.6 mL, 20 mmol) and *N,N,N,N*-tetramethylethylenediamine (3.8 mL, 25 mmol) in tetrahydrofuran (100 mL) at –78 °C was added *n*-butyllithium (1.8 M in hexanes, 14 mL, 25 mmol) and stirred for 1 h at room temperature. The reaction was cooled to –78 °C and acetone (4.5 mL, 60 mmol) was added. The reaction mixture was stirred overnight, warming to room temperature, then saturated aqueous ammonium chloride solution (50 mL) was added and the reaction mixture was stirred vigorously for 5 min. The reaction mixture was then extracted with ethyl acetate (3 $\times$ 50 mL) and the combined organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give *title compound* **377** (3.3 g, 17 mmol, 85%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (1 H, *t*, *J* = 8.4 Hz), 6.60 (2 H, *d*, *J* = 8.4 Hz), 3.82 (6 H, *s*), 1.65 (6 H, *d*, *J* = 7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 157.9, 127.6, 124.4, 106.0, 74.1, 56.1, 31.1 ppm. MS (ESI): *m/z* (%): 179 $[M\text{-}OH]^+$ (100).

2-Isopropyl-1,3-dimethoxybenzene (272) [25]



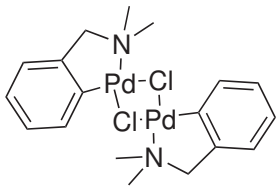
Alcohol **377** (3.6 g, 18 mmol) and palladium-on-carbon (10%, 0.19 g, 0.18 mmol) were dissolved in absolute ethanol (50 mL) and hydrochloric acid (10 M, 2.0 mL) was added. The reaction mixture was sparged with hydrogen for 5 min before stirring for 24 h under a hydrogen atmosphere. The reaction mixture was then sparged with nitrogen before opening to the air. The reaction mixture was filtered over Celite, eluting with ethyl acetate (2 $\times$ 50 mL). The solvent was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (100 mL) and aqueous sodium bicarbonate solution (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 $\times$ 50 mL). The solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give *title compound* **272** (3.3 g, 18 mmol, 100%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (1 H, *t*, *J* = 8.4 Hz), 6.61 (2 H, *d*, *J* = 8.4 Hz), 3.86 (6 H, *s*), 3.71 (1 H, *septet*, *J* = 7.2 Hz), 1.38 (6 H, *d*, *J* = 7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 158.8, 126.6, 124.6, 104.7, 55.8, 24.2, 20.8. MS (ESI): *m/z* (%): 203 $[M+Na]^+$ (100).

1-Bromo-3-isopropyl-2,4-dimethoxybenzene (289) [25]



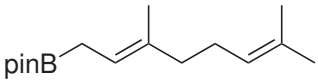
Compound **272** (3.2 g, 18 mmol) and *N*-bromosuccinimide (3.2 g, 18 mmol) were dissolved in dichloromethane (100 mL) and stirred in the dark for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 5% ether in hexanes to give *title compound* **289** (3.5 g, 14 mmol, 75%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (2 H, *d*, *J* = 8.8 Hz), 6.55 (2 H, *d*, *J* = 8.8 Hz), 3.79 (6 H, *s*), 3.51 (1 H, *septet*, *J* = 7.1 Hz), 1.32 (6 H, *d*, *J* = 7.1 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 155.2, 131.9, 130.4, 108.9, 108.8, 61.6, 55.7, 26.3, 21.0 ppm. MS (ESI): *m/z* (%): 281/283 $[M+Na]^+$ (100).

Di-μ-chlorobis[2-[(dimethylamino-κN)methyl]phenyl-κC]dipalladium (375) [85]



Palladium(II) chloride (1.0 g, 6 mmol) was dissolved in methanol (60 mL) and *N*,*N*-dimethylbenzylamine (1.7 mL, 12 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, then the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and filtered over a silica plug, eluting with dichloromethane to give *title compound* **375** (1.6 g, 2.8 mmol, 94%) as a light yellow powder. m.p. 160–170 °C (decomp; lit. 185–187 °C) [85] ^{1}H NMR (300 MHz, $CDCl_3$): 7.23–7.12 (2 H, *m*), 7.00–6.93 (2 H, *m*), 6.91–6.82 (4 H, *m*), 3.93 (4 H, *s*), 2.86 (6 H, *s*), 2.83 (6 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 147.0, 143.2, 133.3, 125.3, 121.6, 73.4, 53.0, 52.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3056, 3001, 2968, 2909, 2884, 2854, 2827, 1577, 1446, 1285, 1043, 1018, 982, 861, 846, 733, 515, 422 cm^{-1}

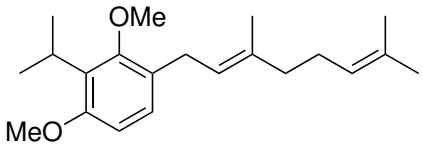
Geranyl pinacol boronate (357) [25]



Geraniol (1.8 mL, 12 mmol), bis(pinacolato)diboron (5.8 g, 23 mmol), *p*-toluenesulfonic acid (0.12 g, 0.68 mmol) and catalyst **375** (0.32 g, 0.56 mmol) were dissolved in methanol (24 mL) and dimethylsulfoxide (24 mL) and heated to 50 °C overnight, then diluted with water (30 mL) and ether (30 mL). The layers were separated and the aqueous layer extracted with ether (2 $\times$ 30 mL), then the combined organic layers were washed with water (50 mL) and brine (50 mL), then dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 2% ether in hexanes to give geranyl pinacol boronate (**357**) (2.3 g, 8.6 mmol, 72%) as a clear, colourless to yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.26–5.20 (1 H, *m*), 5.10 (1 H, *m*). 2.06–1.99 (4 H, *m*), 1.68–1.58 (2 H, *m*), 1.67 (3 H, *s*), 1.59 (3 H, *s*), 1.58 (3 H, *s*), 1.25 (12 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 131.1, 124.5, 118.5, 83.0, 39.8, 26.8, 25.7, 24.7, 24.6, 17.7, 15.9 ppm. Unable to obtain

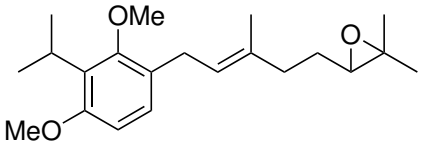
MS by ESI or APCI. IR (neat): $\tilde{\nu}_{max}$ = 2958, 2924, 2856, 1450, 1370, 1321, 1145, 967, 885, 845 cm^{-1}.

(*E*)-1-(3,7-Dimethylocta-2,6-dien-1-yl)-3-isopropyl-2,4-dimethoxybenzene (351) [25]



Aryl bromide **289** (0.37 g, 1.4 mmol), geranyl pinacol boronate (**357**; 0.75 g, 2.8 mmol), tetrakis (triphenylphosphine)palladium(0) (0.086 g, 0.074 mmol) and powdered sodium hydroxide (1.1 g, 28 mmol) were dissolved in toluene (30 mL) and water (7.5 mL), placed under an argon atmosphere and sparged with argon for 10 min. The reaction mixture was then heated to 100 °C for 18 h, then cooled to room temperature and diluted with hexanes (30 mL) and water (20 mL). The reaction mixture was extracted with ether (30 mL), then the combined organic extracts were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 15% dichloromethane in hexanes to give *title compound* **351** (0.36 g, 1.1 mmol, 79%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (1 H, *d*, *J* = 8.4 Hz), 6.62 (1 H, *d*, *J* = 8.4 Hz), 5.34–5.28 (1 H, *m*), 5.15–5.09 (1 H, *m*), 3.78 (3 H, *s*), 3.71 (3 H, *s*), 3.49 (1 H, *septet*, *J* = 7.1 Hz), 3.33 (2 H, *d*, *J* = 7.2 Hz), 2.18–2.02 (4 H, *m*), 1.72 (3 H, *s*), 1.69 (3 H, *s*), 1.61 (3 H, *s*), 1.34 (6 H, *d*, *J* = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 156.4, 135.9, 132.6, 131.5, 129.5, 127.2, 126.9, 124.5, 107.6, 61.7, 55.5, 39.9, 27.9, 26.7, 25.9, 25.7, 21.2, 17.8, 16.2 ppm. MS (ESI) *m/z* (%): 339 $[M+Na]^+$ (100).

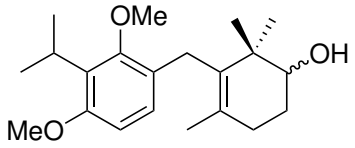
(*E*)-3-(5-(3-Isopropyl-2,4-dimethoxyphenyl)-3-methylpent-3-en-1-yl)-2,2-dimethyl oxirane (378)



Polyene **351** (0.28 g, 0.89 mmol) was dissolved in dichloromethane (5 mL) and *m*-chloroperbenzoic acid (85% w/w; 0.18 g, 0.90 mmol) was added portionwise at 0 °C, then stirred at 0 °C for 2.5 h. The reaction mixture was diluted with dichloromethane (30 mL)

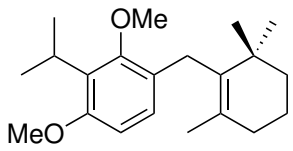
and poured onto saturated aqueous sodium bicarbonate solution (30 mL), the layers were separated and the organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 3% ethyl acetate in hexanes to give *title compound* **378** (0.12 g, 0.36 mmol, 40%) as a white paste. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (1 H, *d*, *J* = 8.4 Hz), 6.60 (1 H, *d*, *J* = 8.4 Hz), 5.40-5.30 (1 H, *m*), 3.78 (3 H, *s*), 3.70 (3 H, *s*), 3.47 (1 H, *septet*, *J* = 7.0 Hz), 3.32 (2 H, *d*, *J* = 7.2 Hz), 2.72 (1 H, *t*, *J* = 6.0 Hz), 2.30-2.04 (2 H, *m*), 1.75-1.55 (6 H, *m*), 1.33 (6 H, *d*, *J* = 7.2 Hz), 1.28 (3 H, *s*), 1.26 (3 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 156.3, 134.9, 129.6, 127.2, 126.7, 124.2, 107.6, 64.3, 61.7, 58.4, 55.4, 36.5, 28.1, 27.6, 25.7, 24.9, 21.2, 18.8, 16.3 ppm. MS (ESI) *e/z* (%): 355 ($[M+Na]^+$, 100), 687 ($[2M+Na]^+$, 20). HRMS (ESI): calcd. for $C_{21}H_{32}O_3Na^+$ 355.22437; found 355.22427. IR (neat): $\tilde{\nu}_{max}$ = 2956, 1596, 1453, 1250, 1104, 1075, 801 cm^{-1}.

3-(3-Isopropyl-2,4-dimethoxybenzyl)-2,2,4-trimethylcyclohex-3-en-1-ol (382)



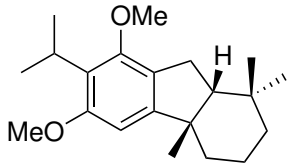
Epoxide **378** (0.050 g, 0.15 mmol) was dissolved in nitromethane (2 mL), then boron trifluoride etherate (1 drop) was added at 0 °C and the reaction mixture was stirred for 18 h, warming to room temperature. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give *title compound* **382** (0.090 g, 0.027 mmol, 18%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (1 H, *d*, *J* = 8.6 Hz), 6.56 (1 H, *d*, *J* = 8.6 Hz), 3.77 (3 H, *s*), 3.74 (3 H, *s*), 3.57 (1 H, *dd*, *J* = 3.0, 9.0 Hz), 3.48 (1 H, *septet*, *J* = 7.0 Hz), 3.38 (2 H, *s*), 2.21–2.15 (2 H, *m*), 1.92–1.71 (2 H, *m*), 1.55 (3 H, *s*), 1.34 (6 H, *d*, *J* = 7.0 Hz), 0.951 (3 H, *s*), 0.945 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 156.1, 133.1, 129.30, 129.25, 125.96, 125.88, 107.1, 76.3, 61.1, 55.4, 40.3, 29.8, 27.4, 26.7, 26.4, 25.7, 21.9, 21.30, 21.27, 20.4 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}O_3Na^+$ 355.22437; found 355.22451.

2-Isopropyl-1,3-dimethoxy-4-((2,6,6-trimethylcyclohexen-1-en-1-yl)methyl)benzene (383)



Polyene **351** (0.60 g, 0.81 mmol) was dissolved in nitromethane (10 mL) and bismuth triflate (13 mg, 0.020 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, then diluted with saturated aqueous sodium bicarbonate solution (20 mL) and extracted with ether (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 20% dichloromethane in hexanes to give *title compound* **383** (0.14 g, 0.19 mmol, 23%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (1 H, *d*, *J* = 8.4 Hz), 6.57 (1 H, *d*, *J* = 8.4 Hz), 3.78 (3 H, *s*), 3.75 (3 H, *s*), 3.49 (1 H, *septet*, *J* = 7.2 Hz), 3.37 (2 H, *s*), 2.10-2.02 (2 H, *m*), 1.72-1.60 (3 H, *m*), 1.54-1.45 (4 H, *m*), 1.35-1.25 (10 H, *m*), 0.92 (6 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 156.0, 134.4, 129.8, 128.9, 126.2, 126.0, 106.8, 60.9, 55.2, 39.9, 35.0, 32.7, 28.6, 27.2, 25.6, 21.2, 20.5, 19.6 ppm. MS (APCI) *m/z* (%): 317 $[M+H]^+$ (100), 369 $[M+MeOH+Na]^+$ (40).

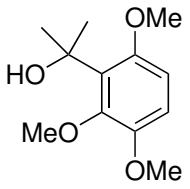
7-Isopropyl-6,8-dimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-fluorene (365) [25]



Polyene **351** (2.3 g, 7.3 mmol) was dissolved in nitromethane (70 mL) and boron trifluoride etherate (0.090 mL, 0.73 mmol)) was added at 0 °C. The reaction mixture was stirred for 24 h at room temperature, then saturated aqueous sodium bicarbonate solution (50 mL) was added. The organic layer was extracted with ether (2 × 30 mL), then the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 20% dichloromethane in hexanes to give *title compound* **365** (0.49 g, 1.6 mmol, 21%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.44 (1 H, *s*), 3.81 (3 H, *s*), 3.78 (3 H, *s*), 3.51 (1 H, *septet*, *J* = 7.2 Hz), 2.85 (1 H, *dd*, *J* = 7.7, 15.0 Hz), 2.69 (1 H, *dd*, *J* = 11.0, 15.0 Hz), 1.86

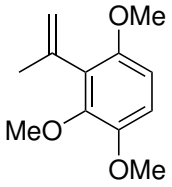
(1 H, *dd*, *J* = 7.7, 11.0 Hz), 1.72–1.59 (2 H, *m*), 1.44 (3 H, *s*), 1.41–1.22 (4 H, *m*), 1.33 (6 H, *dd*, *J* = 2.2, 7.2 Hz), 1.14 (3 H, *s*), 0.98 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4, 155.0, 154.1, 126.4, 124.6, 101.1, 60.5, 57.6, 55.9, 45.6, 36.4, 35.3, 32.3, 31.2, 30.8, 29.6, 25.6, 25.1, 21.5, 19.1 ppm. HRMS (APCI): calcd. for $C_{21}H_{33}O_3$ 317.24751; found 317.24745. IR (neat): $\tilde{\nu}_{max}$ = 2930, 1583, 1452, 1411, 1301, 1190, 1101, 1052, 920, 828 cm^{-1}.

2-(2,3,6-Trimethoxyphenyl)propan-2-ol (396) [86]



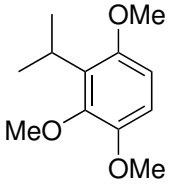
1,2,4-Trimethoxybenzene (980 mg, 5.8 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.0 mL, 6.8 mmol) were dissolved in tetrahydrofuran (58 mL) and cooled to -78 °C. *n*-Butyllithium (2.0 M in hexanes, 3.0 mL, 6.0 mmol) was added dropwise and stirred for 1 h, warming to room temperature. The reaction mixture was again cooled to -78 °C, then acetone (1.3 mL, 1.8 mmol) was added dropwise, then the mixture was stirred for 2 h, warming to room temperature. Saturated aqueous ammonium chloride solution (20 mL) was added, then the mixture was extracted with ethyl acetate (3 $\times$ 30 mL) and the combined extracts were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **396** (0.65 g, 2.9 mmol, 50%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (1 H, *d*, *J* = 9.0 Hz), 6.63 (1 H, *d*, *J* = 9.0 Hz), 5.89 (1 H, *s*), 3.85 (3 H, *s*), 3.81 (6 H, *s*), 1.66 (6 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 148.2, 147.5, 130.2, 110.7, 107.5, 74.4, 61.5, 56.4, 56.3, 31.4 ppm. MS (ESI) *m/z* (%): 249 $[M+Na]^+$ (100).

2-(2,3,6-Trimethoxyphenyl)prop-1-ene (397) [86]



Alcohol **396** (0.62 mg, 2.8 mmol) and palladium-on-carbon (10 wt%, 0.041 g, 0.038 mmol) were dissolved in glacial acetic acid (6 mL) and the reaction mixture was heated to 100 °C. Ammonium formate (0.88 g, 14 mmol) was added portionwise at 100 °C with gas evolution observed and the reaction mixture was stirred at 100 °C for 3 h. The reaction mixture was then cooled to room temperature and filtered through Celite, eluting with ethyl acetate (3 × 20 mL), then washed with water (2 × 100 mL) and brine (100 mL) and the solvent was removed *in vacuo* to give *title compound* **397** (0.47 g, 2.3 mmol, 81%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (1 H, *d*, *J* = 8.9 Hz), 6.57 (1 H, *d*, *J* = 8.9 Hz), 5.32-5.29 (1 H, *m*), 4.90-4.88 (1 H, *m*), 3.82 (3 H, *s*), 3.79 (3 H, *s*), 3.76 (3 H, *s*), 2.05-2.04 (3 H, *m*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 147.4, 147.0, 139.2, 128.1, 115.7, 110.9, 106.0, 61.3, 56.4, 56.3, 23.9 ppm.

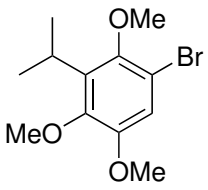
2-Isopropyl-1,3,4-trimethoxybenzene (398) [86]



Alcohol **396** (2.0 g, 8.9 mmol) and palladium-on-carbon (10 wt%, 0.38 g, 0.36 mmol) were dissolved in ethanol (60 mL) and hydrochloric acid (10 M, 2.0 mL) was added. The reaction mixture was stirred for 5 h under an atmosphere of hydrogen, then the reaction mixture was sparged before opening to the air and filtering over Celite, eluting with ethanol (50 mL). The solvent was removed *in vacuo*, then the residue was dissolved in ether (50 mL), washed with saturated aqueous sodium bicarbonate solution (50 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give *title compound* **398** (1.1 g, 5.3 mmol, 59%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (1 H, *d*, *J*= 8.9 Hz), 6.56 (1 H, *d*, *J* = 8.9 Hz), 3.81 (3 H, *s*), 3.80 (3 H, *s*), 3.76 (3 H, *s*), 3.54

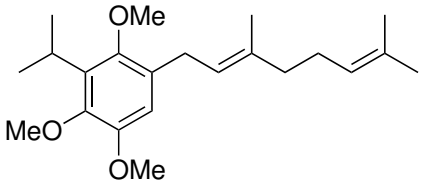
(1 H, *septet*, J = 7.1 Hz), 1.31 (6 H, *d*, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 148.0, 147.5, 131.1, 109.7, 106.5, 61.1, 56.3, 56.0, 25.3, 21.3 ppm. MS (APCI): *m/z* (%): 210 $[M]^+$ (100).

1-Bromo-3-isopropyl-2,4,5-trimethoxybenzene (297) [86]



To a solution of aromatic **398** (0.24 g, 1.2 mmol) in dichloromethane (10 mL) was added *N*-bromosuccinimide (0.21 g, 1.2 mmol). The reaction mixture was stirred at room temperature for 2 h, then the solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 5% ether in hexanes to give *title compound* **297** (0.30 g, 1.0 mmol, 91%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (1 H, *s*), 3.83 (3 H, *s*), 3.81 (3 H, *s*), 3.77 (3 H, *s*), 3.46 (1 H, *septet*, J = 7.2 Hz), 1.33 (6 H, *d*, J = 7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 149.1, 148.2, 136.9, 114.3, 110.9, 61.7, 60.9, 56.2, 26.9, 21.9 ppm. MS (ESI): *m/z* (%): 311/313 $[M+Na]^+$ (100).

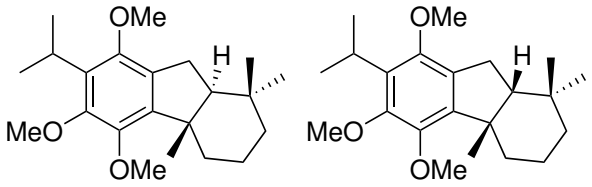
(*E*)-1-(3,7-Dimethylocta-2,6-dien-1-yl)-3-isopropyl-2,4,5-trimethoxybenzene (390)



Aryl bromide **297** (0.61 g, 2.1 mmol), geranyl pinacol boronate (**357**; 0.56 g, 2.1 mmol), powdered sodium hydroxide (1.0 g, 25 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.23 g, 0.20 mmol) were dissolved in toluene (30 mL) and water (7.5 mL), placed under an argon atmosphere and sparged with argon for 10 min. The reaction mixture was heated to 90 °C for 20 h, then cooled to room temperature, diluted with hexane (30 mL) and water (20 mL), separated and the aqueous layer was extracted with diethyl ether (30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over

silica gel, eluting with 30% dichloromethane in hexanes to give *title compound* **390** (0.49 g, 1.4 mmol, 67%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (1 H, *s*), 5.31 (1 H, *tq*, *J* = 7.1 Hz, 1.4 Hz), 5.12 (1 H, *tt*, *J* = 6.6 Hz, 1.3 Hz), 3.83 (3 H, *s*), 3.80 (3 H, *s*), 3.67 (3 H, *s*), 3.44 (1 H, *septet*, *J* = 7.2 Hz), 3.35 (2 H, *d*, *J* = 7.1 Hz), 2.19-2.03 (4 H, *m*), 1.73 (3 H, *s*), 1.67 (3 H, *s*), 1.59 (3 H, *s*), 1.35 (6 H, *d*, *J* = 7.2 Hz) ppm. ^{13}H NMR (100 MHz, $CDCl_3$): δ = 149.8, 149.6, 146.9, 136.3, 134.9, 131.6, 129.5, 124.3, 123.3, 111.2, 61.9, 60.8, 55.9, 39.9, 28.3, 26.9, 26.2, 25.8, 22.2, 17.8, 16.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{34}O_3Na^+$ 369.24002; found 369.24044. IR (film): $\tilde{\nu}_{max}$ = 2955, 2931, 2872, 2833, 1591, 1482, 1454, 1426, 1343, 1253, 1226, 1111, 1042, 1015, 981, 846, 789, 720 cm^{-1}.

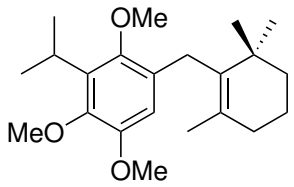
7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene (399)



Polyene **390** (0.30 g, 0.87 mmol) was dissolved in nitroethane (9 mL) and cooled to 0 °C. Boron trifluoride etherate (0.020 mL, 0.15 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. Saturated aqueous sodium bicarbonate solution (5 mL) was added, then the reaction mixture was extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 35% dichloromethane in hexanes to give *title compound* **399** as an inseparable mixture of diastereomers at the C5 position (2:1 *cis*:*trans*) (0.15 g, 0.43 mmol, 50%). *cis isomer:*[52] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (3 H, *s*), 3.79 (3 H, *s*), 3.72 (3 H, *s*), 3.39 (1 H, *septet*, *J* = 7.2 Hz), 2.83 (1 H, *dd*, *J* = 15.4, 7.9 Hz), 2.62 (1 H, *dd*, *J* = 15.4, 11.3 Hz), 1.81 (1 H, *dd*, *J* = 11.3, 7.9 Hz), 1.80–1.74 (1 H, *m*), 1.61 (3 H, *s*), 1.46–1.42 (1 H, *m*), 1.42–1.36 (2 H, *m*), 1.32 (6 H, *d*, *J* = 7.2 Hz), 1.29–1.24 (2 H, *m*), 1.13 (3 H, *s*), 0.93 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 150.3, 146.4, 144.3, 132.3, 128.9, 60.5, 60.4, 56.6, 47.2, 35.2, 35.0, 32.2, 31.3, 31.1, 25.6, 25.5, 22.24, 22.20, 18.7 ppm. *trans isomer (partial data; some resonances obscured):*[52] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (3 H, *s*), 3.75 (3 H, *s*), 3.39 (1 H, *septet*, *J* = 7.2 Hz), 2.74 (1 H, *dd*, *J* = 14.3, 6.3 Hz), 2.55 (1 H, *dd*, *J* = 14.3, 12.9 Hz), 2.39 (1 H, *m*), 1.73 (1 H, *dd*, *J* = 12.9, 6.3 Hz), 1.58–1.53 (2 H, *m*), 1.24–1.17 (1

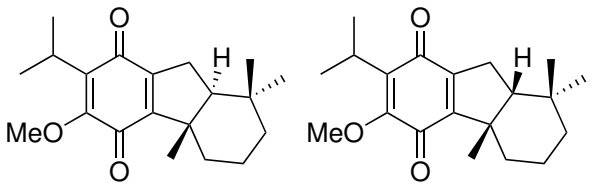
H, *m*), 1.12 (3 H, *s*), 1.03 (3 H, *s*), 0.96 (3 H, *s*) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 150.5, 145.5, 144.9, 131.8, 129.4, 59.7, 47.0, 41.4, 36.8, 33.3, 33.1, 27.2, 21.1, 20.3, 20.1 ppm. HRMS (ESI): calcd. for $C_{22}H_{34}O_3Na^+$ 369.24002; found 369.24035.

3-Isopropyl-1,2,4-trimethoxy-5-((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)benzene (408)



Partially cyclised *title compound* **408** was commonly found as a side-product of the above procedure under shorter reaction times. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53 (1 H, *s*), 3.83 (3 H, *s*), 3.74 (3 H, *s*), 3.71 (3 H, *s*), 3.43 (1 H, *septet*, *J* = 7.2 Hz), 3.39 (2 H, *s*), 2.06 (2 H, *dd*, *J* = 6.3, 6.3 Hz), 1.69-1.64 (2 H, *m*), 1.54 (3 H, *s*), 1.51-1.47 (2 H, *m*), 1.36 (3 H, *s*), 1.34 (3 H, *s*), 0.92 (6 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 149.3, 146.6, 134.7, 134.5, 130.3, 129.2, 110.7, 61.2, 60.8, 55.9, 40.1, 35.2, 32.9, 28.7, 27.6, 26.2, 22.3, 20.8, 19.7 ppm. HRMS (ESI): calcd. for $C_{22}H_{34}O_3Na^+$ 369.24002; found 369.24035.

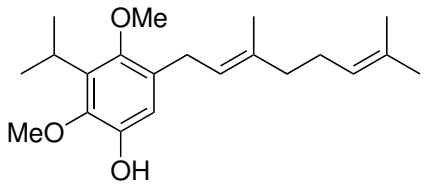
Taiwaniaquinone G (5) and 5-epi-taiwaniaquinone G (356)



Compound **399** (0.12 g, 0.35 mmol) was dissolved in acetonitrile (3 mL) and cooled to 0 °C. A solution of ceric ammonium nitrate (0.95 g, 1.7 mmol) in water (1 mL) was added dropwise and stirred 1 h, warming to room temperature. Saturated aqueous sodium sulfite solution (10 mL) was added and the reaction was extracted with ether (2 $\times$ 20 mL), dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 25% dichloromethane in hexanes to give taiwaniaquinone G and 5-epi-taiwaniaquinone G as a mixture (0.094 g, 0.30 mmol, 86%). A diasteromerically pure sample of taiwaniaquinone G was obtained by

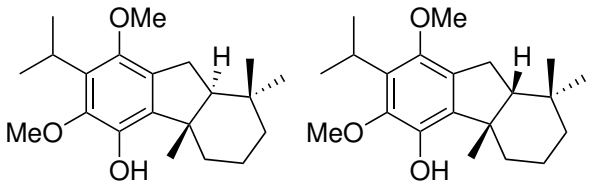
preparative HPLC (water/acetonitrile 25:75 isocratic, Sunfire C_{18}) as a yellow oil. *Data for pure* trans *isomer*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (3 H, *s*), 3.22 (1 H, *septet*, *J* = 7.1 Hz), 2.59 (1 H, *dd*, *J* = 6.4, 16.8 Hz), 2.31 (1 H, *dd*, *J* = 12.7, 16.8 Hz), 2.30–2.26 (1 H, *m*), 1.82–1.71 (1 H, *m*), 1.64 (1 H, *dd*, *J* = 6.4, 12.7 Hz), 1.65–1.59 (1 H, *m*), 1.51–1.48 (1 H, *m*), 1.45 (1 H, *dd*, *J* = 4.2, 12.8 Hz), 1.21 (3 H, *d*, *J* = 7.1 Hz), 1.20 (3 H, *d*, *J* = 7.1 Hz), 1.14 (1 H, *dd*, *J* = 4.8, 13.9), 1.08 (3 H, *s*), 0.99 (3 H, *s*), 0.93 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.4, 182.4, 156.3, 153.9, 148.5, 137.3, 61.2, 58.4, 48.2, 41.2, 35.0, 33.2, 32.9, 27.2, 24.7, 21.2, 20.8, 20.7, 19.8, 18.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}O_3Na^+$ 339.19307; found 339.19331.

(*E*)-5-(3,7-Dimethylocta-2,6-dien-1-yl)-3-isopropyl-2,4-dimethoxyphenol (391)



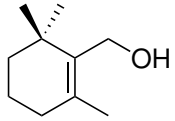
Polyene **390** (0.35 g, 1.0 mmol) was dissolved in tetrahydrofuran (10 mL) and L-Selectride (1.0 M in THF, 3.0 mL, 3.0 mmol) was added. The reaction mixture was heated at reflux and stirred for 24 h, then cooled to room temperature and saturated aqueous ammonium chloride solution (20 mL) was added. The reaction mixture was extracted with ether (3 $\times$ 30 mL) and the combined organic layers were dried over magnesium sulfate and solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 30% dichloromethane in hexanes to give *title compound* **391** as a yellow oil (0.16 g, 0.48 mmol, 48%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.53 (1 H, *s*), 5.62 (1 H, *s*), 5.32–5.26 (1 H, *m*), 5.18–5.08 (1 H, *m*), 3.83 (3 H, *s*), 3.67 (3 H, *s*), 3.42 (1 H, *septet*), 3.32 (2 H, *d*, *J* = 7.2 Hz), 2.20–2.02 (4 H, *m*), 1.73 (3 H, *s*), 1.67 (3 H, *s*), 1.60 (3 H, *s*), 1.38 (6 H, *d*, *J* = 7.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.9, 143.3 (2 C), 136.1, 131.6, 127.2, 124.8, 124.4, 123.7, 109.1, 62.0, 56.3, 39.9, 28.1, 26.9, 26.0, 25.8, 20.9, 17.8, 16.3 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}O_3Na^+$ 355.22437; found 355.22483. IR (film): $\tilde{\nu}_{max}$ = 3539, 2956, 2925, 2853, 1486, 1455, 1421, 1339, 1288, 1242, 1213, 1103, 1039, 987, 847, 780, 457 cm^{-1}.

7-Isopropyl-6,8-dimethoxy-1,4,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluoren-5-ol (400)



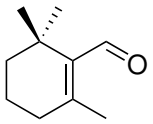
Polyene **391** (0.050 g, 0.15 mmol) was dissolved in nitroethane (1.5 mL) and boron trifluoride etherate (0.020 mL, 0.15 mmol) was added. The reaction was stirred at –5 °C for 3 days, then saturated aqueous sodium bicarbonate solution (5 mL) was added and the reaction mixture was warmed to room temperature, then extracted with ether (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 25% dichloromethane in hexanes to give *title compound* **400** as an inseparable mixture of diastereomers at the C5 position (2:1 *cis:trans*) (0.011 mg, 0.033 mmol, 22%) as a yellow oil. *cis isomer:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (1 H, *s*), 3.75 (3 H, *s*), 3.71 (3 H, *s*), 3.40 (1 H, *septet, J* = 7.1 Hz), 2.81 (1 H, *dd, J* = 15.1, 7.7 Hz), 2.62 (1 H, *dd, J* = 15.1, 10.9 Hz), 1.80 (1 H, *dd, J* = 10.9, 7.3 Hz), 1.66–1.61 (2 H, *m*), 1.60 (3 H, *s*), 1.47–1.41 (2 H, *m*), 1.34 (6 H, *dd, J* = 7.1, 6.0 Hz), 1.30–1.24 (2 H, *m*), 1.11 (3 H, *s*), 0.91 (3 H, *s*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.9, 147.2, 143.1, 140.4, 125.4, 125.1, 62.2, 60.8, 57.5, 47.3, 35.4, 35.3, 32.4, 30.9, 29.9, 25.6, 25.4, 21.3, 21.2, 18.9 ppm. *trans isomer (partial data; some resonances obscured):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (1 H, *s*), 3.77 (3 H, *s*), 3.73 (3 H, *s*), 3.40 (1 H, *septet, J* = 7.1 Hz), 2.72 (1 H, *dd, J* = 14.1, 6.2 Hz), 2.54 (1 H, *dd, J* = 14.1, 12.5 Hz), 2.35–2.30 (1 H, *m*), 1.70 (1 H, *dd, J* = 12.5, 6.2 Hz), 1.54–1.48 (2 H, *m*), 1.32 (6 H, *d, J* = 7.2 Hz), 1.23–1.14 (2 H, *m*), 1.12 (3 H, *s*), 1.03 (3 H, *s*), 0.96 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 146.9, 144.6, 139.1, 125.5, 124.9, 62.3, 60.8, 60.1, 47.1, 41.2, 36.9, 33.5, 33.2, 31.0, 27.0, 21.4, 21.3, 20.5, 20.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}O_3Na^+$ 355.22437; found 355.22483. IR (neat): $\tilde{\nu}_{max}$ = 3523, 2930, 2868, 1456, 1422, 1336, 1260, 1100, 1037, 887 cm^{-1}.

β-Cyclogeraniol (412) [87]



β-Ionone (7.0 g, 36 mmol) was dissolved in methanol (70 mL) and cooled to –78 °C. A stream of ozone/oxygen was bubbled through the reaction for 8 h, then the reaction mixture was purged with nitrogen, warmed to 0 °C and sodium borohydride (6.0 g, 160 mmol) was added portionwise. The reaction mixture was stirred for 18 h, then the solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (100 mL) and water (100 mL). The mixture was acidified with hydrochloric acid (10 M), then the layers were separated and the aqueous layer was extracted with dichloromethane (2 $\times$ 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **412** (5.0 g, 32 mmol, 89%) as a waxy solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.12 (2 H, *s*), 1.96 (2 H, *t*, *J* = 6.3 Hz), 1.73 (3 H, *s*), 1.62–1.55 (2 H, *m*), 1.46–1.41 (2 H, *m*), 1.03 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.8, 133.7, 59.0, 39.5, 34.1, 32.9, 28.6, 19.7, 19.4 ppm. MS (APCI): *m/z* (%): 177 $[M+H]^+$ (100).

β-Cyclocitral (290) [88]

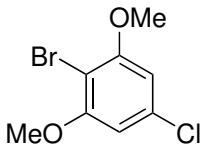


Citral (10 mL, 58 mmol) was dissolved in ether (12 mL) and aniline (6.4 mL, 70 mmol) was added. The reaction mixture was stirred for 1 h, then dried with anhydrous sodium sulfate. The reaction mixture was decanted into sulfuric acid (95%, 70 mL) at 0 °C and stirred for 1 h, then poured onto ice, extracted with ether (2 $\times$ 100 mL) and washed with saturated aqueous sodium bicarbonate solution (100 mL). The solvent was then removed *in vacuo*, giving a mixture of α- and β-cyclocitral.

The residue was dissolved in a solution of potassium hydroxide (3.0 g, 5.3 mmol) in methanol (100 mL) at 0 °C and stirred for 30 min. The reaction mixture was diluted

with brine (200 mL) and extracted with ether (2 × 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give *title compound* **290** (5.1 g, 33 mmol, 57%) as a colourless to pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.12 (1 H, *s*), 2.18 (3 H, *t*, *J* = 6.3 Hz), 2.08 (3 H, *s*), 1.64–1.58 (2 H, *m*), 1.45–1.42 (2 H, *m*), 1.19 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.3, 156.1, 140.7, 40.6, 35.8, 33.1, 27.9, 19.4, 18.7 ppm. MS (APCI): *m/z* (%): 153 $[M]^+$ (100).

2-Bromo-5-chloro-1,3-dimethoxybenzene (425) [89]



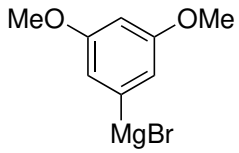
1-Chloro-3,5-dimethoxybenzene (1.5 g, 10 mmol) was dissolved in chloroform (20 mL) and bromine (1.7 mL, 33 mmol) was added dropwise. The reaction mixture was heated at reflux for 2 h, then cooled to room temperature and saturated aqueous sodium sulfite solution (30 mL) was added. The reaction mixture was extracted with ethyl acetate (2 × 50 mL), dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo* to give *title compound* **425** (1.3 g, 5.0 mmol, 50%) as a white solid. m.p. 198.4–203.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.45 (2 H, *s*), 3.92 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 136.6, 104.5, 95.4, 56.9 ppm. MS (APCI): *m/z* (%): 250/252 $[M]^+$ (100).

Potassium isopropyltrifluoroborate (429) [90]

Trimethylborate (4.2 mL, 38 mmol) was dissolved in tetrahydrofuran (50 mL) and isopropylmagnesium chloride (1.3 M in tetrahydrofuran, 20 mL, 26 mmol) was added at –78 °C. The reaction mixture was stirred for 1 h at –78 °C, then stirred for 1 h at room temperature. Hydrochloric acid (3 M, 50 mL) was added and the reaction mixture was stirred for 30 min, then the reaction mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*.

The residue was dissolved in methanol (50 mL) and cooled to 0 °C. Saturated aqueous potassium bifluoride solution (18 mL; 6.3 g, 81 mmol) was added dropwise and stirred for 1 h at room temperature. The solvent was removed *in vacuo*, then the residue was purified by extraction into acetonitrile (80 mL) using a Soxhlet apparatus. The solvent was removed until some precipitation was seen, then ether (10 mL) was added. The precipitate was collected by filtration to give *title compound* **429** (1.1 g, 7.1 mmol, 27%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.66 (6 H, *d*, *J* = 7.2 Hz), 0.18 (1 H, *br s*) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 145.0–145.9 (*m*) ppm. ^{11}B NMR (160 MHz, DMSO-d_6): δ = 5.07 (*q*, *J* = 64 Hz) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.59 (*d*, *J* = 1.3 Hz) ppm. Masses corresponding to the parent ion or expected degradation products were not seen by mass spectroscopy (ESI or APCI).

3,5-Dimethoxyphenylmagnesium bromide (434)

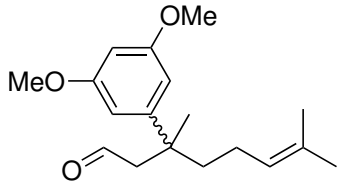


Magnesium was prepared by washing with 1 M hydrochloric acid until lustrous, followed by ethanol, then ether. It was then dried under vacuum and stored under argon. Magnesium stored this way remained active for several months. Magnesium not prepared in this way did not undergo the reaction.

Magnesium (0.68 g, 28 mmol) and iodine (0.058 mg, 0.23 mmol) were dissolved in tetrahydrofuran (13 mL) and stirred 5 min, then a solution of 1-bromo-3,5-dimethoxy benzene (5.0 g, 23 mmol) in tetrahydrofuran (20 mL) was added. The reaction mixture was heated at reflux for 18 h, then cooled to room temperature, at which time the magnesium had been consumed.

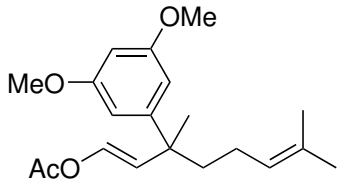
The organomagnesium bromide was titrated as follows: an oven-dried flask was charged with iodine (0.13 g, 0.50 mmol) and lithium chloride (0.063 g, 1.5 mmol), then tetrahydrofuran (3 mL) was added and the reaction mixture was stirred until fully dissolved. Organomagnesium bromide solution was added until the reaction mixture turned colourless. A concentration of 0.45 M was obtained (40% yield).

3-(3,5-Dimethoxyphenyl)-3,7-dimethyloct-6-enal (438)



Copper(I) bromide dimethylsulfide complex (1.5 g, 7.5 mmol) was dissolved in tetrahydrofuran (30 mL) and cooled to –15 °C. 3,5-Dimethoxyphenylmagnesium bromide (0.45 M in tetrahydrofuran, 30 mL, 14 mmol) was added dropwise and stirred for 1 h, then a solution of citral (1.2 g, 8.0 mmol) in tetrahydrofuran (30 mL) was added dropwise and stirred for 1 h at –15 °C. Saturated aqueous ammonium chloride solution (30 mL) was added, then the reaction mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting wtih 5% ether in hexanes to give *title compound* **438** (1.2 g, 4.1 mmol, 55%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.52–9.48 (1 H, *m*), 6.71 (1 H, *d*, *J* = 2.2 Hz), 6.50–6.45 (2 H, *m*), 5.06–4.97 (1 H, *m*), 3.84 (6 H, *s*), 2.76 (1 H, *dd*, *J* = 15.2, 2.3 Hz), 2.49 (1 H, *dd*, *J* = 15.2, 3.4 Hz), 1.89–1.73 (4 H, *m*), 1.64 (3 H, *s*), 1.49 (3 H, *s*), 1.45 (3 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 203.2, 161.1, 131.9, 124.0, 105.7, 105.1, 99.6, 53.4, 43.6, 40.2, 37.1, 25.7, 24.8, 22.7, 17.7 ppm. HRMS (APCI): calcd for $C_{18}H_{27}O_3^+$ 291.19602, found 291.19598. IR (neat): $\tilde{\nu}_{max}$ = 2934, 1717, 1589, 1454, 1202, 1153, 1051, 830 cm^{-1}.

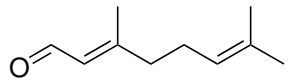
3-(3,5-Dimethoxyphenyl)-3,7-dimethylocta-1,6-dien-1-yl acetate (440)



Aldehyde **438** (0.60 g, 2.0 mmol) was dissolved in acetic anhydride (3 mL), then triethylamine (0.60 mL, 2.0 mmol) and potassium acetate (0.030 g, 0.3 mmol) were added. The reaction mixture was heated to 120 °C and stirred for 18 h. The reaction mixture was then poured onto saturated aqueous sodium bicarbonate solution (30 mL) and extracted with ether (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give crude *title compound* **440** (0.28 g, 0.84

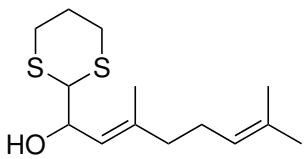
mmol, 42%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (1 H, *d*, *J* = 12.7 Hz), 6.71 (1 H, *d*, *J* = 2.2 Hz), 6.50–6.45 (2 H, *m*), 5.67 (1 H, *d*, *J* = 12.7 Hz), 5.10–5.03 (1 H, *m*), 3.84 (6 H, *s*), 2.13 (3 H, *s*), 1.90–1.70 (4 H, *m*), 1.65 (3 H, *s*), 1.52 (3 H, *s*), 1.40 (3 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 161.1, 149.9, 143.6, 135.2, 131.7, 124.4, 123.7, 99.6, 55.5, 55.4, 42.0, 41.8, 25.8, 23.4, 20.9, 17.7 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}NaO_4^+$ 355.18789; found 355.18820. IR (neat): $\tilde{\nu}_{max}$ = 2936, 1752, 1589, 1202, 1153, 1062, 1048, 730 cm^{-1}.

Geranial (452) [91]



Geraniol (11 mL, 65 mmol) was dissolved in acetonitrile (300 mL). Copper(I) bromide (0.46 g, 3.2 mmol), 2,2‘-bipyridine (0.50 g, 3.2 mmol), TEMPO (500 mg, 3.2 mmol) and *N*-methylimidazole (0.50 mL, 6.3 mmol) were added and the reaction mixture was stirred vigorously, open to air for 3 d. The reaction mixture was washed with water (2 × 100 mL), then dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give geranial (**452**; 9.2 g, 60 mmol, 92%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.00 (1 H, *d*, *J* = 8.0 Hz), 5.88 (1 H, *d*, *J* = 8.0 Hz), 5.15–5.05 (1 H, *m*), 2.28–2.19 (4 H, *m*), 2.17 (3 H, *s*), 1.69 (3 H, *s*), 1.61 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 163.5, 132.6, 127.1, 122.3, 40.3, 25.5, 25.4, 17.4, 17.3 ppm. MS (APCI): *m/z* (%): 153 $[M+H]^+$ (100).

1-(1,3-Dithan-2-yl)-3,7-dimethylocta-2,6-dien-1-ol (450)



m-Dithiane (0.60 g, 5.0 mmol) was dissolved in tetrahydrofuran (30 mL) and cooled to –78 °C. *n*-Butyllithium (1.2 M in hexanes, 4.5 mL, 5.4 mmol) was added and the reaction mixture was stirred at –78 °C for 1 h. A solution of geranial (0.85 mL, 5.0 mmol) in tetrahydrofuran (20 mL) was added and the reaction mixture was stirred for 4 h, slowly

warming to room temperature. Saturated aqueous ammonium chloride solution (20 mL) was added, then the layers were separated and the organic layer was extracted with ether (30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **450** (0.78 g, 2.9 mmol, 58%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.30 (1 H, *ddd*, *J* = 1.2, 8.8, 22 Hz), 5.18–5.06 (1 H, *m*), 4.62–4.55 (1 H, *m*), 3.96 (1 H, *dd*, *J* = 7.0, 22 Hz), 2.97–2.86 (2 H, *m*), 2.83–2.72 (2 H, *m*), 2.36–2.21 (2 H, *m*), 2.18–2.05 (4 H, *m*), 1.77 (3 H, *dd*, *J* = 1.2, 15.9 Hz), 1.70–1.67 (3 H, *m*), 1.62–1.59 (3 H, *m*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.4, 131.9, 124.0, 123.7, 69.4, 52.7, 39.8, 28.8, 28.1, 26.4, 25.83, 25.81, 17.9, 17.3 ppm. MS (ESI): *m/z* (%): 295 $[M+Na]^+$ (100).

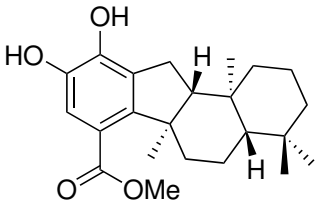
Chapter 3

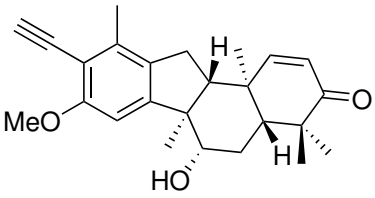
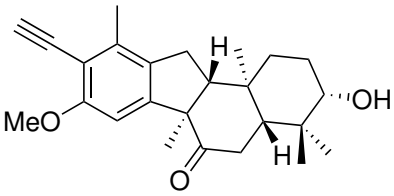
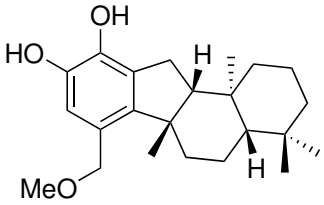
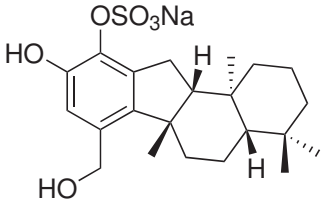
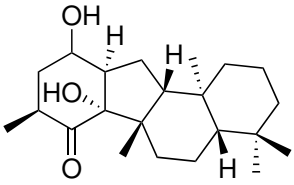
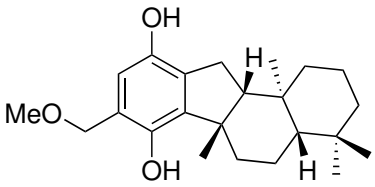
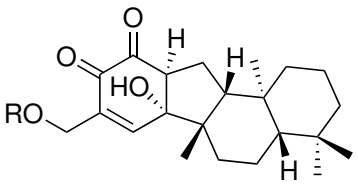
Longer Polyenes

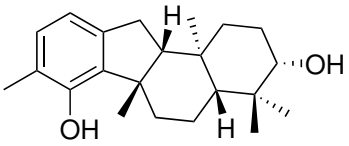
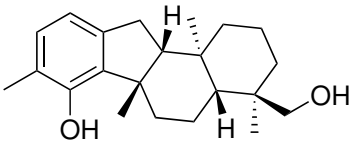
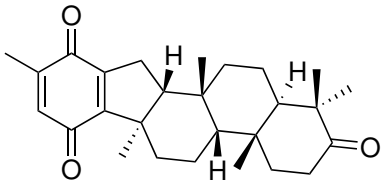
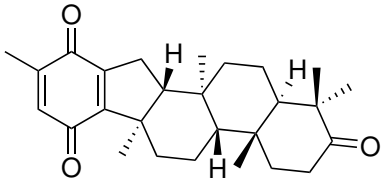
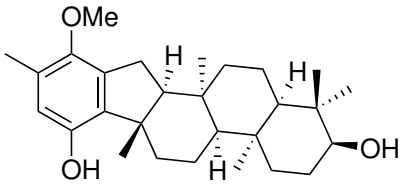
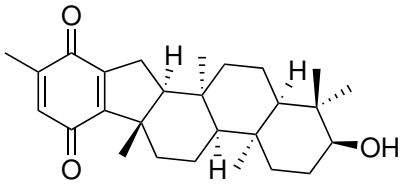
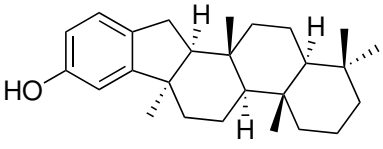
3.1 Introduction

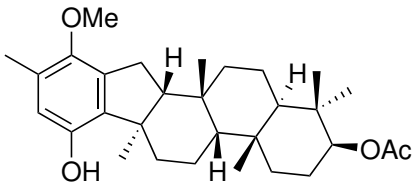
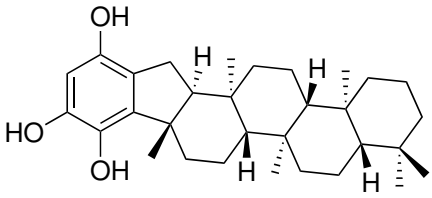
In the preceding chapter, we successfully produced the three ring-containing compounds (±)-taiwaniaquinone G and its C5 epimer. If this is a truly general strategy, we should be able to extend the scope of this reaction to longer polyenes, generating frameworks with four or more fused rings. Some of these frameworks have been synthesised before using a polyene cyclisation strategy. However, in all these cases the cyclisation has been initiated by opening of an epoxide and the products always possess the *trans* configuration at the 5,6 ring junction. We have highlighted the inefficient ways that the polyene chains are produced in many of these syntheses as a clear opportunity for improvement.

Table 19: A summary of the known longer polycyclic compounds containing an aromatic or quinone. Yields and step counts are longest linear sequence.

Structure	Name	Author	Steps	Yield
trans-Fused Tetracyclic Compounds				
	pelorol (**473**)	Andersen[75]	11	6%
		Baran[92]	11	9%
		Gui[93]	11	4%

Structure	Name	Author	Steps	Yield
	walsucochin A (**474**)	*none reported*		
	walsucochin B (**475**)	She[39]	22	5%
cis-Fused Tetracyclic Compounds				
	akaol A (**476**)	Alvarez-Manzaneda[94]	15	26%
		Bisai[86]	12	8%
		Qin[95]	13	11%
	akaol B (**477**)	*none reported*		
	dasyscyphin A (**478**)	*none reported*		
	dasyscyphin B (**6**)	Alvarez-Manzaneda[96]	25	6%
	dasyscyphin C (**479**)	*none reported*		

Structure	Name	Author	Steps	Yield
	dasyscyphin D (**480**)	She[97]	9	23%
	dasyscyphin E (**481**)	Alvarez-Manzaneda[98]	17	23%
		Alvarez-Manzaneda[99]	14	32%
Five contiguous rings				
	atomarianone A (**482**)	*none reported*		
	atomarianone B (**9**)	*none reported*		
	flabellinol (**483**)	*none reported*		
	flabellinone (**484**)	*none reported*		
	habiterpenol (**8**)	*none reported*		

Structure	Name	Author	Steps	Yield
	zonaquinone acetate (**485**)	*none reported*		
Six contiguous rings				
	disidein (**7**)	*none reported*		

We have chosen to investigate cationic polyene cyclisations as a methodology to access a few of these compounds as interesting exemplars of the broad family. As previously discussed, only the *trans*-fused diastereomers of these larger compounds have been produced by polyene cyclisation. As such, we will target the *cis*-fused dasyscyphin B. Indeed, the immediate reason for this work is that we were able to obtain selectively the *cis*-fused taiwaniaquinoid framework, and we want to investigate the stereocontrol of related longer systems.

Of the 5 and 6 ring containing compounds, only adociasulfate-1 (**226**) has been synthesised (Scheme 30).[40] Overman's synthesis of adociasulfate-1 (**226**) used an epoxide-mediated cascade, again highlighting the utility of that reaction. But this means no direct cyclisations have been performed to produce pentacyclic systems. Habiterpenol (**8**) has no oxygenation on the A ring and would give us an opportunity to explore direct acid-catalysed cyclisation of longer systems. The pentacyclic oxygen-containing molecules exemplified by flabellinol (**483**) differ only in their oxidation state and the diastereochemistry of their shared carbon framework: we may investigate whether treating a suitable epoxide under various conditions will result in these different diastereomers. We expect that atomarianone B (**9**) may be the only possible product of polyene cyclisation by any of the three commonly employed methodologies. Finally, disidein (**7**) contains six rings, the longest compound of this type yet reported. Again, no synthesis of disidein has been reported.

3.1.1 Tetracyclic compounds

Far more is known about the tetracyclic compounds than their longer analogues. All possess the *trans* stereochemistry across the AB ring junction (Figure 27). However, some compounds possess the *cis* stereochemistry at the BC ring junction, while others possess the *trans* stereochemistry (Table 19). In the *trans*-fused diastereomer, the ring-junction methyl groups lie *syn* to each other; in the *cis*-fused diastereomer, they lie *anti* to each other. So unlike our work on the taiwaniaquinoids, we cannot obtain the *cis*-fused diastereomers of larger systems by epimerisation of the C9 hydrogen of a *trans*-fused compound.

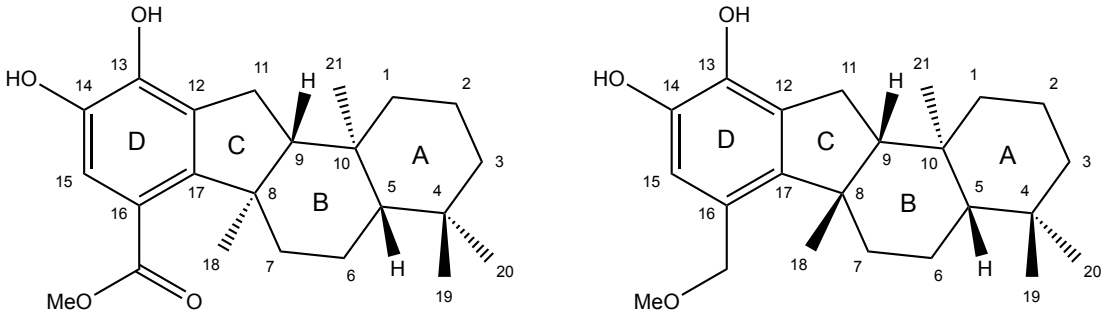


Figure 27: Carbon numbering of the tetracyclic compounds as labeled on *trans*-fused pelorol (**473**) and *cis*-fused akaol A (**476**).

Pelorol (**473**) is a *trans*-configured compound isolated from the sponges *Dactylospongia elegans* and *Petrosaspongia metachromia.*[75] Andersen has evaluated pelorol and a series of analogues (Scheme 28) for their ability to activate SHIP phosphatases, which show promise as anti-inflammatory agents and treatments for blood diseases.[8] [75]

Walsucochins A (**474**) and B (**500**) were isolated from *Walsura cochinchinensis.*[100] They are unusual due to the presence of oxygenation on the B-ring, potentially a sign of a unique biosynthetic pathway. Pretreatment of cells with either walsucochin A or B leads to higher cell viability upon treatment with hydrogen peroxide.

Akaols A (**476**) and B (**477**) are *cis*-fused compounds isolated from sea sponge *Aka* sp.[101] No biological activity is known. A number of partially cyclised compounds were co-isolated with the fully cyclised akaols.

The dasyscyphins are found in the fungus *Dasyscyphus niveus.*[102] [103] All of these compounds are *cis*-configured at the B–C ring junction. Dasyscyphins B (**6**), D (**480**) and

E (**481**) possess an aromatic D-ring, while dasyscyphin A (**478**) contains a cyclohexanone D-ring and dasyscyphin C (**479**) contains a cyclohexadienone D-ring. Anke and coworkers screened dasyscyphins B and C for their antimicrobial and cytotoxic effects, finding good cytotoxic properties against human cancer cell lines and weak antibiotic activity against a range of microbes.[102] Dasyscyphin A (**478**) was ineffective against all the microorganisms

Table 20: Antimicrobial effects of dasyscyphins B (**6**) and C (**479**).[102]

Organism	MIC (μg/mL)	
	6	**479**
Bacteria		
Bacillus brevis	100	100
Bacillus subtilis	10	20
Corynebacterium islandicum	>100	5
Enterobacter dissolvens	>100	>100
Micrococcus luteus	n/a	5
Mycobacterium phlei	5	5
Yeasts		
Candida glabrata	>100	>100
Candida krusei	>100	>100
Candida lusitaniae	n/a	100
Candida parapsilosis	>100	>100
Nadsonia fulvescens	5	50
Nematospora coryli	5	>100
Saccharomyces cerevisiae	>100	>100
Filamentous fungi		
Absidia glauca (+)	1	50
Absidia glauca (–)	1	100
Alternaria porri	100	100
Ascochyta pisi	100	20
Aspergilus ochraceus	100	20
Fusarium fujikuroi	>100	100
Fusarium oxysporum	>100	100
Paecilomyces varioti	100	50
Penicillium islandicum	10	50
Penicillium notatum	5	20
Zygorhynchus moelleri	1	100

Table 21: Cytotoxic effects of dasyscyphins B (**6**) and C (**479**).[102]

Human cell line	IC_{50} (μg/mL)	
	6	**479**
Colo 320	2	0.8
HeLa S3	1	0.8
Hep G2	3	0.9
U 937	1	0.7
Jurkat	2	0.6

and cell lines tested.

Dasyscyphins B–E all showed antifungal effects, inhibiting conidial germination of *Magnaporthe grisea* at 20–25 μg/mL but not affecting other fungi.[103] Dasyscyphins D and E showed no cytotoxic activity.

Along with these fully cyclised compounds, there are also partially cyclised compounds with potent bioactivity. Snyder evaluated peyssonol A and a range of natural and non-natural analogues for inhibition of HIV-1 and demonstrated that they were highly potent HIV-1 reverse transcriptase inhibitors.[10] Unfortunately, these compounds are also highly cytotoxic.

3.1.2 Pentacyclic compounds

A group of five natural products have been isolated from various species which differ only in their diastereochemistry and oxidation state. All have been shown to have potent medicinal effects.

Atomarianone A (**482**) and B (**9**) are quinone meroditerpenoids.[104] They are diastereomers of each other at the C7 position (Figure 31), isolated from *Taonia atomaria*, found in the Aegean Sea. Both isomers were found to be cytotoxic against NSCLC-N6 and A549 lung cancer cells with IC_{50} values of less than 7.35 μM.

The structurally related compounds flabellinone (**484**) and flabellinol (**483**) are metabolites of brown algae *Stypopodium flabelliforme* from Papua New Guinea.[105] They have been found to possess cytotoxic effects against NCI-H460 lung cancer cells. They also exhibit

sodium channel blocking activity at 2 μM for flabellinol and 7 μM for flabellinone.

Zonaquinone acetate (**485**) has been isolated from the related *Stypopodium zonale* found in Jamaica.[106] Flabellinone was also isolated from this species. They were found to have insignificant antioxidant activity but again exhibited cytotoxic effects on par with approved drugs.

All of these compounds possess oxygenation at the A ring and as such could be obtained from an epoxide-mediated cyclisation.

Habiterpenol (**8**) is a similar natural product possessing a *cis*-fused C-D ring junction, with all other ring junctions possessing the *trans* stereochemistry.[107] It was isolated from the bacterium *Phytohabitans suffuscus* and unlike the other compounds has no oxygenation on the A ring, thus is likely biosynthesised by direct cyclisation. It possesses minor antimicrobial activity against *Bacillus subtilus* but not against 13 other microorganisms.[108]

Other examples exist with unusual cyclisation motifs containing the same pentacyclic core (Figure 28). As in Overman's synthesis, they may be obtained synthetically by further elaboration following a cyclisation to the pentacyclic framework. The adociasulfates contain either a pendant cyclohexene or an extended ring system where this cyclohexene has undergone cyclisation with the alcohol to generate an oxepane.[40] The haliclotriols are similar oxepane containing compounds with a pendant isoprenyl group.[109] Both families

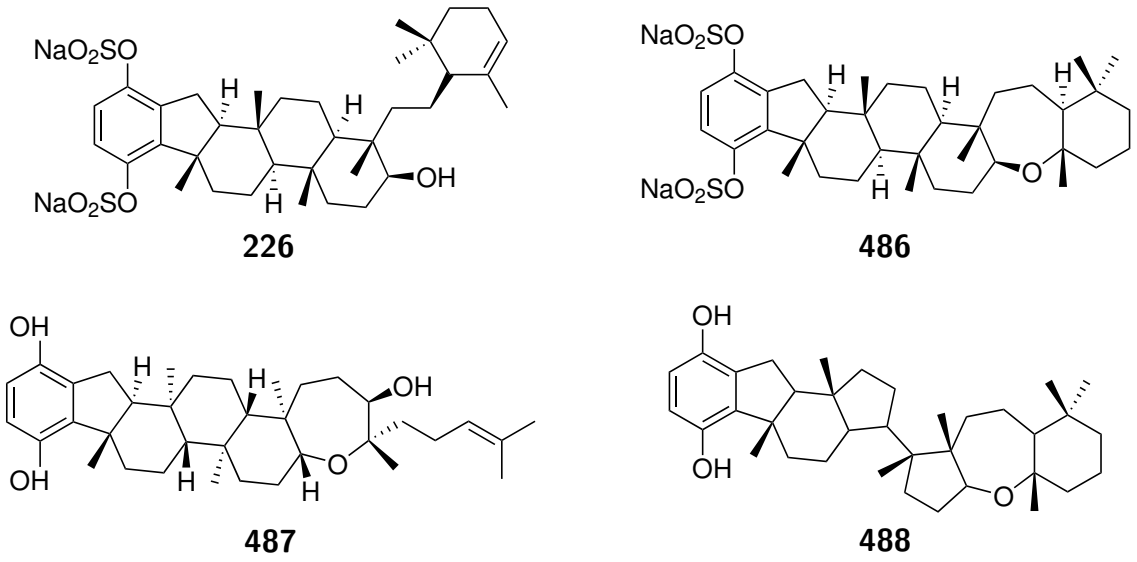


Figure 28: Oxepane-containing terpenoid natural products: adociasulfate-1 (**226**), adociasulfate-2 (**486**), haliclotriol B (**487**) and toxicol B (**488**).

of compounds are found within the sea sponge genus *Haliclona*. The toxicols, substances found in *Toxiclona toxius* possess an unprecedented framework containing two non-fused cylopentanes.[110] These compounds are less amenable to synthesis by our methodology.

3.1.3 Disidein

Disidein (**7**) is a merosesterpenoid isolated from the marine sponge *Disidea pallescens* found in the bay of Naples.[111] It contains six contiguous rings and is the largest natural product reported containing this structural motif. In this case, unlike the compounds above containing five rings, analysis by 2D NMR and X-ray crystal structure has determined that disidein has the *trans* stereochemistry across all ring junctions, making it a highly attractive target for our synthetic methodology.[112] Disidein and its triacetate were assessed for their analgesic activity in mice but no effect was found.[113] No further biological testing has been reported, so biological examination of these longer fused 6,5,6-ring systems provides impetus for accessing them via synthetic methods.

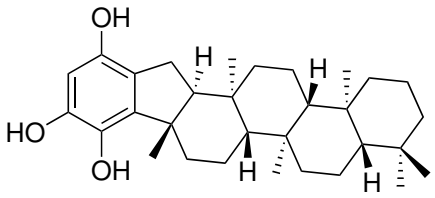
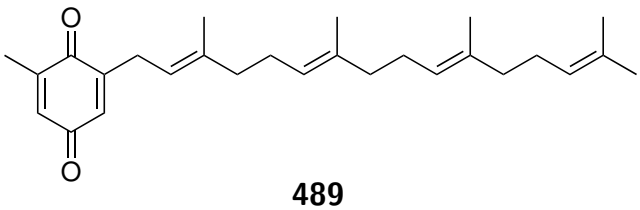


Figure 29: Disidein (**7**).

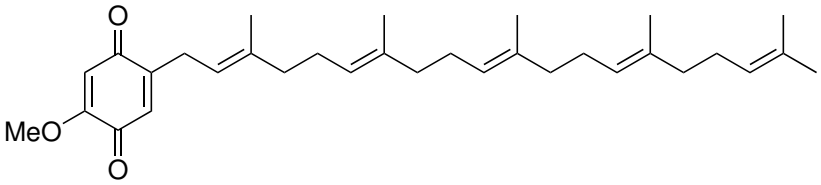
3.1.4 Biosynthesis

Not much is known about the biosynthesis of these understudied compounds. We do have one clue: polyene quinones **489** and **490** were isolated along with the cyclised natural products from *Stypopodium flabelliforme* and *Disidea pallescens* (**??**).[105] [111]

In contrast to the taiwaniaquinoids, it is likely that the 6,5,6-fused compounds are not produced by excision of a carbon atom from a 6-member ring but by cyclising polyenes **489** and **490** (or probably the corresponding hydroquinones) directly.[105] These precursors should lead not only to our compounds of interest, but also the benzopyran analogues (e.g. epitaondiol; **492**) and spirocyclised compounds like styptotriol (**493**). Compounds



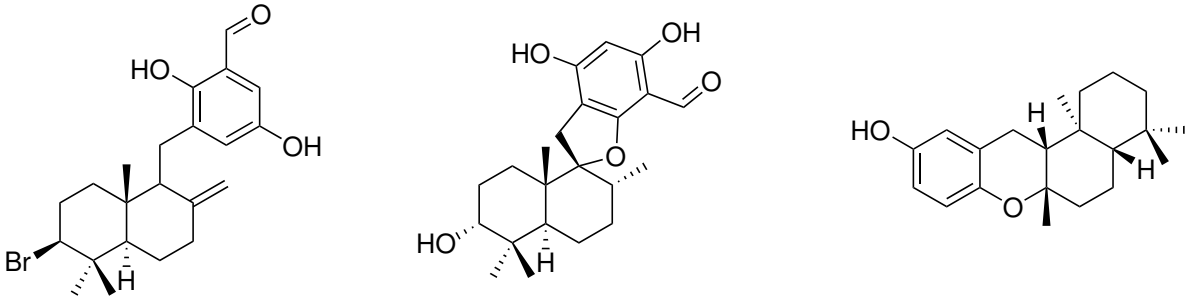
489



490

492 and **493** have been found alongside flabellinol and flabellinone in *S. flabelliforme*, but the analogous compounds have not been found in other species. Scheme 91 highlights the unusual conformations required for these hypothesised cyclisations. Many of these compounds are likely to be inaccessible without the strict conformational demands enforced by a cyclase enzyme.

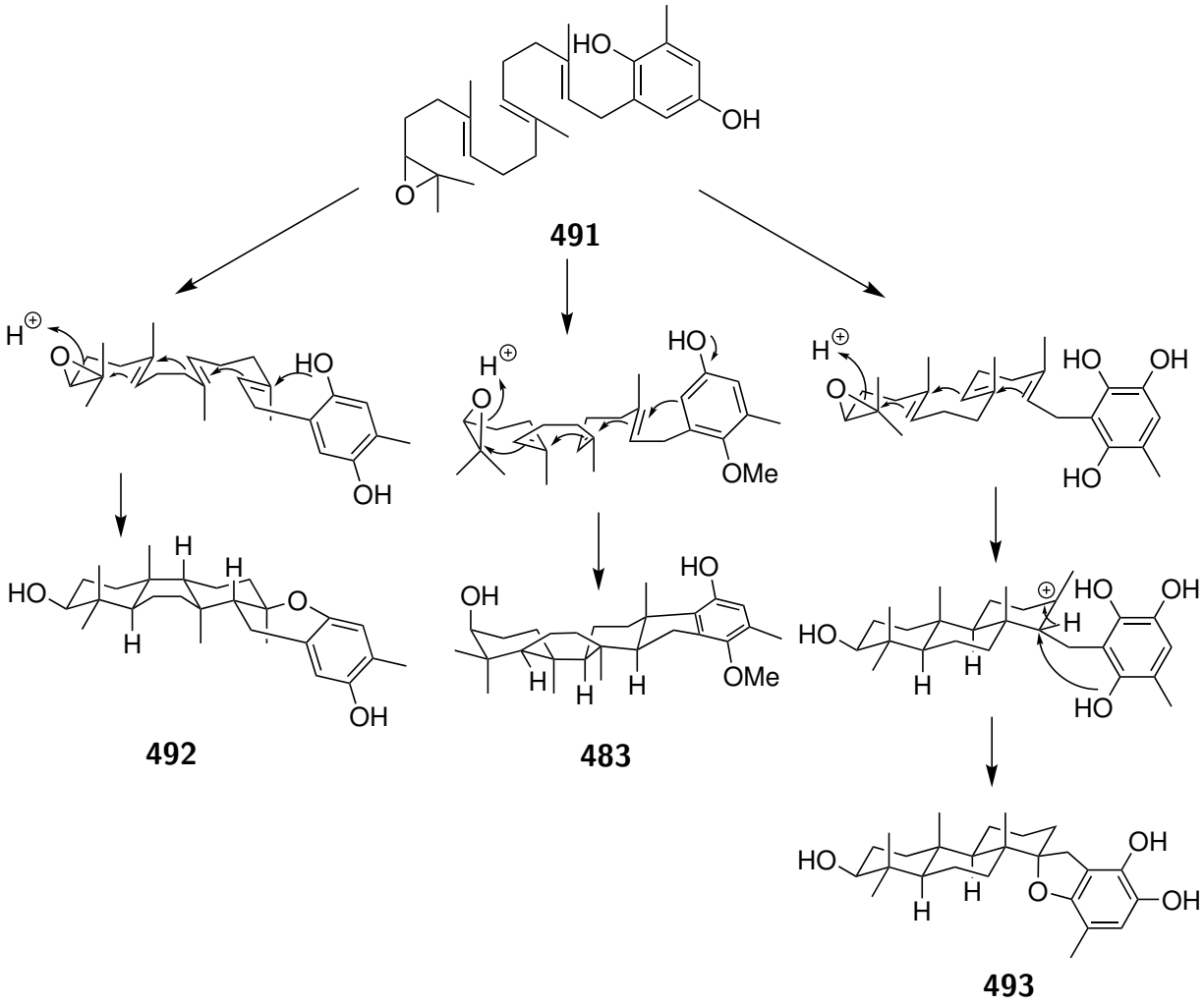
While similar farnesylquinones have been found in other species, they have not been co-isolated with the cyclised products. Partially cyclised alkenes (e.g. peyssonol A; **494**), spirocyclic compounds (e.g. stachybotrysin A; **495**) and benzopyran compounds (e.g. chromazonarol; **83**) have also been found in various species (Figure 30).[114] [115] [116] This gives credence to the idea that the tetracyclic compounds are produced by cyclisation of a farnesylhydroquinone.



494 **495** **83**

Figure 30: Other natural products which could arise from a farnesylhydroquinone cyclisation: peyssonol A (**494**),[114] stachybotrysin A (**495**)[115] and chromazonarol (**83**).[116]

Yue proposes a different pathway for the walsucochins, starting from a steroid also found in the *Walsura* genus (Scheme 92).[100] Piscidinol D (**496**) is dehydrated to compound **497**, then the C and D rings are rearranged to the desired sizes giving compound **499**. Aromatisation gives walsucochin A (**474**), which is further converted into walsucochin B



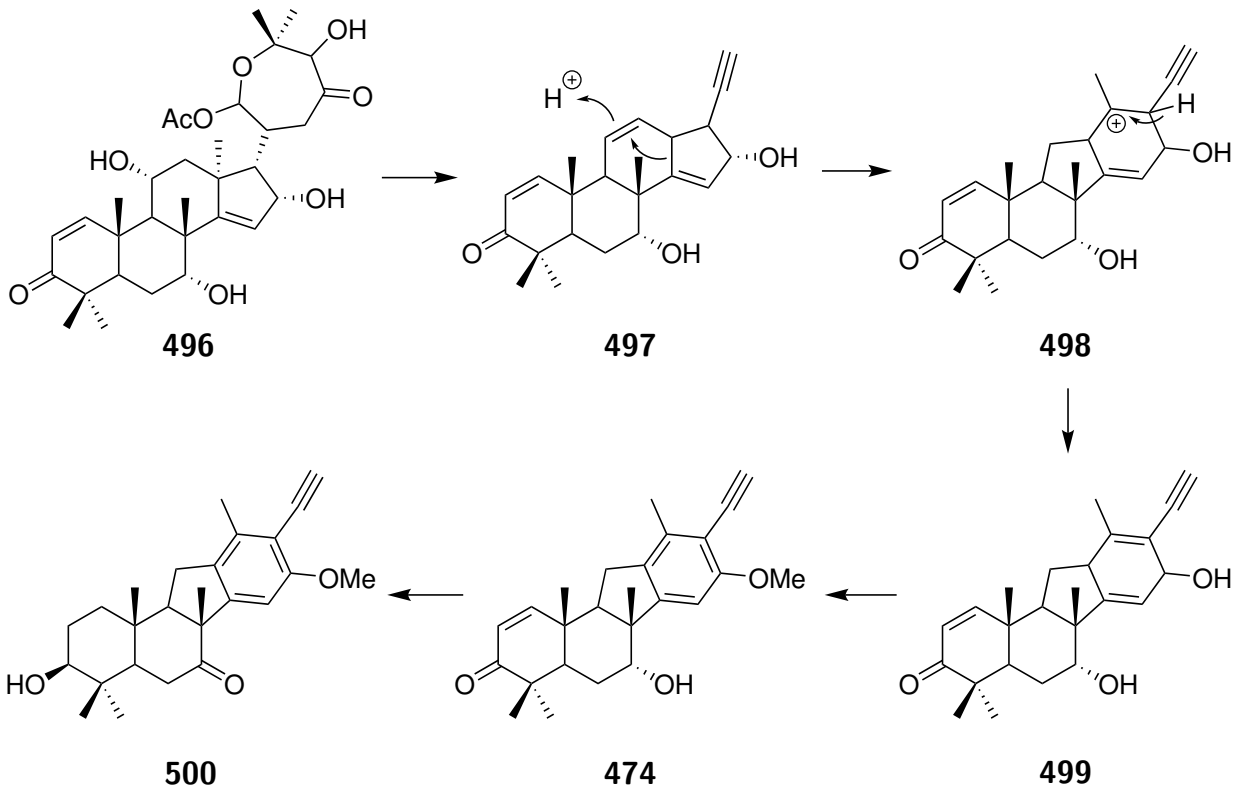
Scheme 91: Polyene **491** can be cyclised to pyran **492**, 6,5-fused compound **483** or spirocycle **493**. Adapted from ref. 105.

(**500**). It is plausible that more of these tetracyclic compounds can be synthesised from the rearrangement of a suitable steroid. Of course, steroids are ultimately produced by polyene cyclisation of squalene (Scheme 4).

3.1.5 Previous syntheses

We have already discussed the three previously reported syntheses of longer 6,5,6,6 systems by polyene cyclisation: walsucochin B by She,[39] adociasulfate-1 by Overman[40] and the route towards analogues of pelorol by Andersen.[8] These compounds all contain the *trans* stereochemistry at the 5,6 ring junction and all the cyclisations are mediated by epoxide-opening events.

Sclareolide (**335**) is a common chiral pool material used in other strategies. It is a

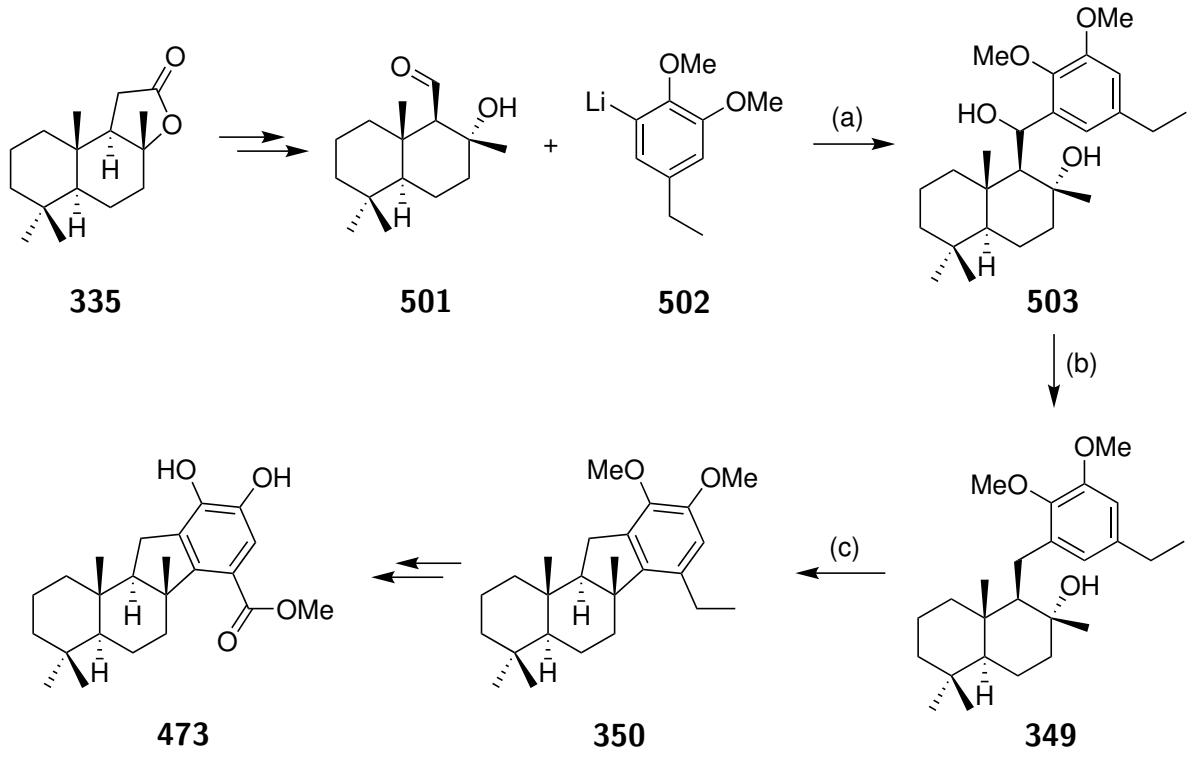


Scheme 92: Proposed biosynthesis of the walsucochins by rearrangement of the steroid piscidinol D (**496**).[100]

commercially available natural product with the desired A and B rings already complete with the desired *trans,trans* stereochemistry.

Andersen began his synthesis of (–)-pelorol (**473**) with aldehyde **501**, which was derived from sclareolide (Scheme 93).[75] Aldehyde **501** was reacted with aryllithium **502** to give the diol **503**, which was removed by hydrogenolysis to give the tertiary alcohol **349**. This sets up for the key Friedel-Crafts alkylation, using tin(IV) chloride in dichloromethane to perform the final ring closure giving the *trans*-fused compound **350**. This was further elaborated to give the final natural product, (–)-pelorol (**473**) in 11 steps with an overall yield of 6%.[75]

McErlean has provided computational analysis of the Friedel-Crafts step, explaining the resulting *trans* stereochemistry (Scheme 94).[41] Tin(IV) chloride eliminates the tertiary alcohol of **349**, generating carbocation **504**. McErlean computed two conformations of the intermediate carbocation. The chair-like carbocation **504** holds the benzyl group in a pseudoequatorial configuration, so nucleophilic attack by the aryl ring generates the *trans* diastereomer **350**. Note that due to conformational locking by the decalin system, no ring flip to a chair-like diastereomer with a pseudoaxial benzyl group is possible. However,

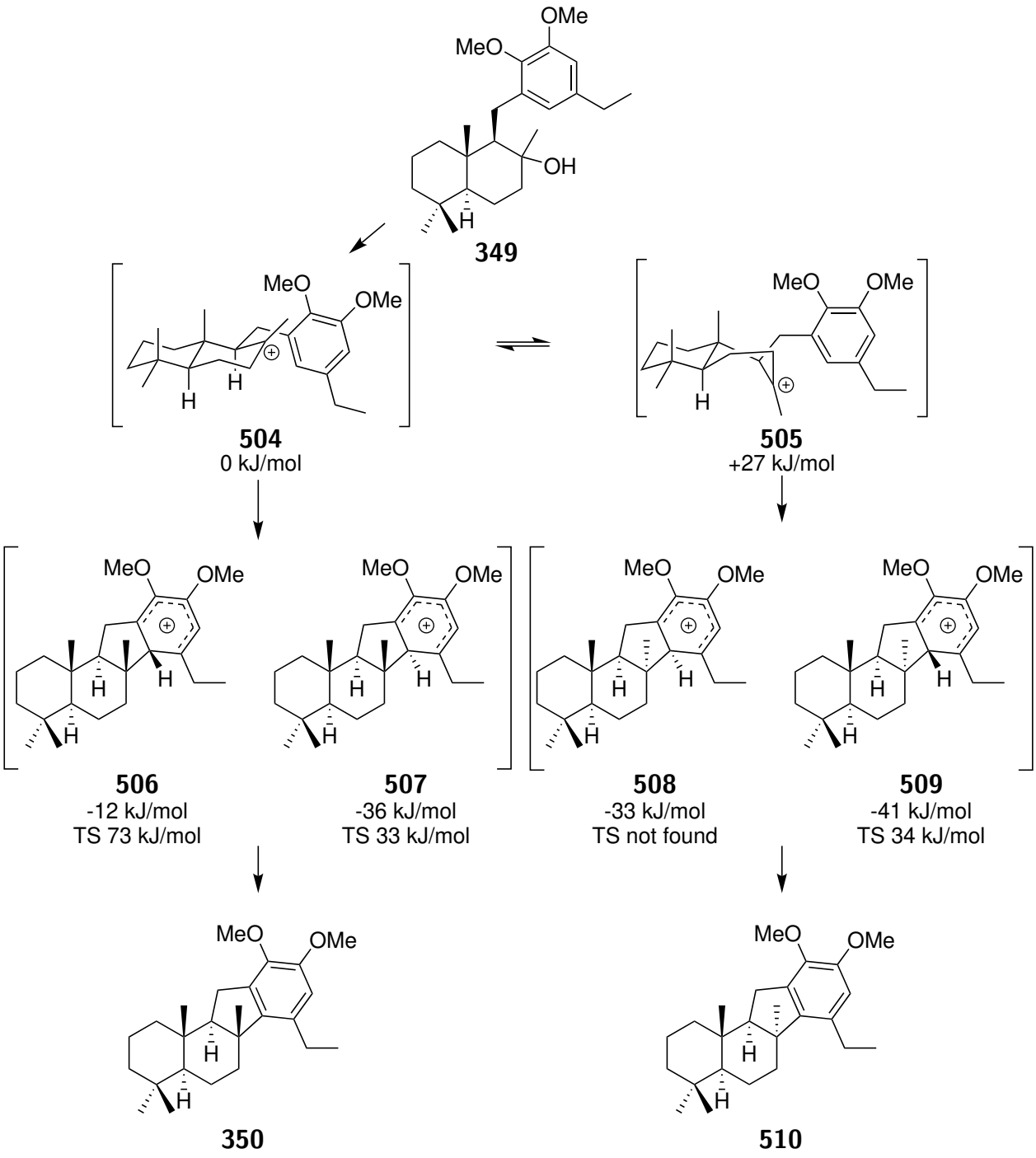


Scheme 93: Andersen's synthesis of pelorol.[75] (a) THF, –78 °C, 68%. (b) H_2, Pd/C, EtOAc, rt, 87%. (c) $SnCl_4$, CH_2Cl_2, –20 °C, 76%.

isomerisation to the boat-like carbocation **505** is possible, in which the benzyl group is oriented axially. Friedel-Crafts alkylation from this conformation would lead to the *cis*-configured ring system **510**. While the hyperconjugative effect is in play, the contribution from steric interactions and ring strain means that this conformer is 27 kJ/mol higher in energy. Thus the *trans* diastereomer **350** is the only observed product.

Nazarov cyclisation appears to be a sound strategy for synthesising the *cis* diastereomer. Syntheses of taiwaniaquinoids using a key Nazarov cyclisation gave the *cis* diastereomer because they proceeded through a cyclopentene intermediate. The resulting alkene was then hydrogenated selectively from the less hindered face (Scheme 42).[53]

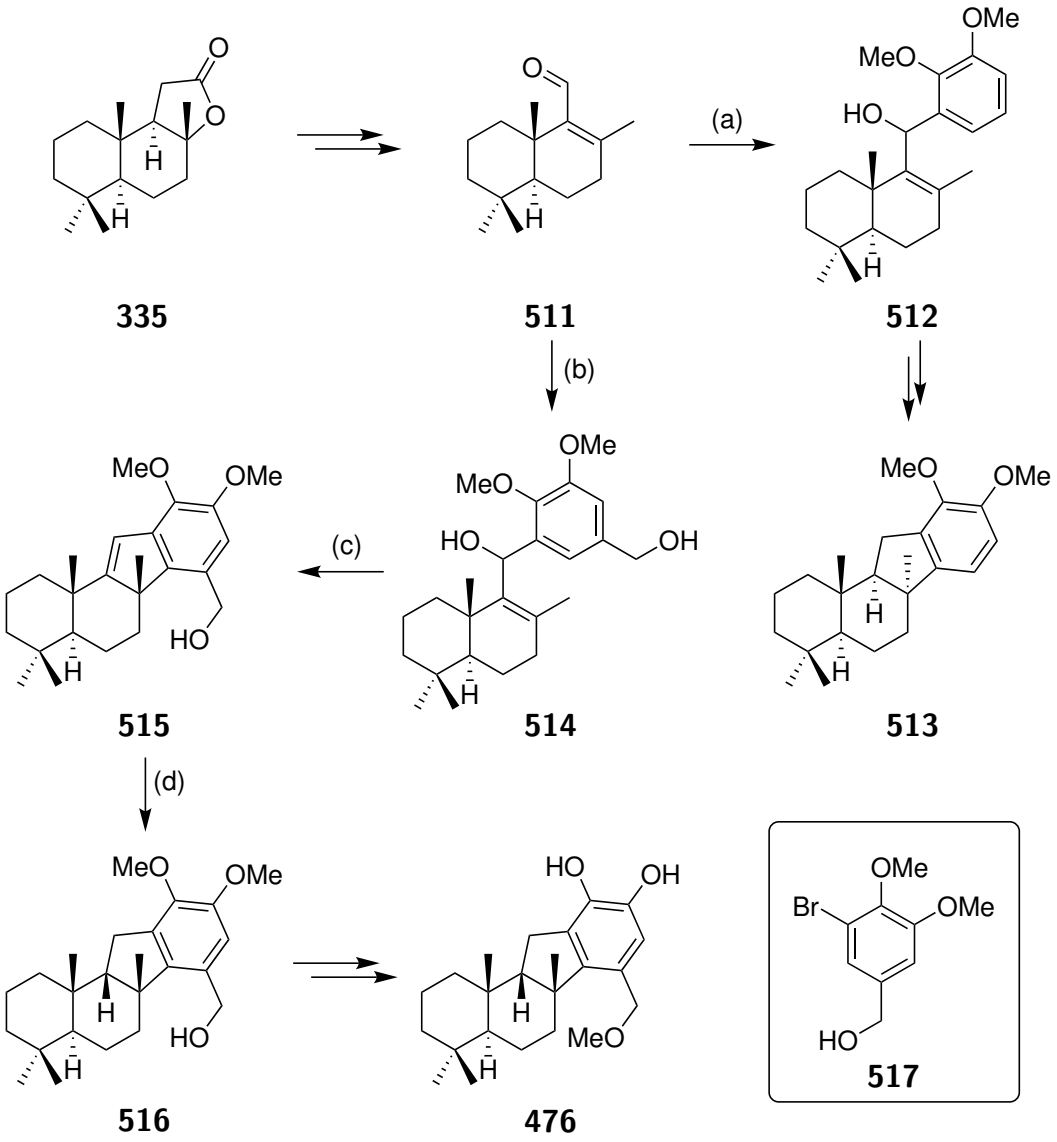
Bisai's group had previously synthesised a series of taiwaniaquinoids using a Nazarov cyclisation strategy.[86] Like us, they wanted to extend their methodology to the longer rings: in this case, akaol A. They chose again to start from (+)-sclareolide, elaborating to aldehyde **511** over four steps. *n*-Butyllithium mediated coupling with 1,2-dimethoxybenzene gave carbinol **512**, which was subjected to Nazarov cyclisation to give the undesired C9 epimer **513**. Coupling instead with aryl bromide **517** containing a pendant benzyl alcohol gave a 1.2:1 mixture of diastereomers in favour of the desired epimer. Hydrogenation gave each epimer's *cis* stereochemistry and these compounds were now



Scheme 94: McErlean's computational analysis of Andersen's Friedel-Crafts cyclisation towards pelorol (**473**).[41]

separable by chromatography. Taking the desired epimer **516**, final decoration of the aromatic gave akaol A (**476**) in 8% overall yield in 12 steps. The lack of stereoselection during the Nazarov cyclisation is a significant obstruction to this approach's success.

Qin used an ingenious conformational constraint strategy to synthesise akaol A.[95] In contrast to the chair-like intermediate carbocation invoked in Andersen's cyclisation, the cyclohexenol **518** forced the carbocation to take a boat-like conformation (Scheme 96).

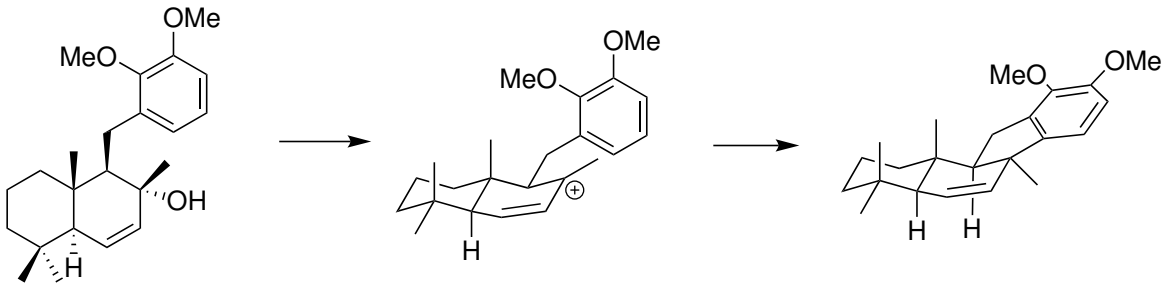


Scheme 95: Bisai's synthesis of akaol A using a Nazarov cyclisation.[86] (a) 1,2-dimethoxybenzene, *n*-BuLi, TMEDA, THF, –78 °C, then **511**, 74%. (b) **517**, *n*-BuLi, THF, –78 °C, then **511**, 58%. (c) $Bi(OTf)_3$, DCE, 80 °C, 96%, dr 1.2:1. (d) H_2, Pd/C, MeOH, 49% (*single diastereomer*).

Thus, *cis*-fused compound **520** was formed instead of the corresponding *trans*-fused compound.

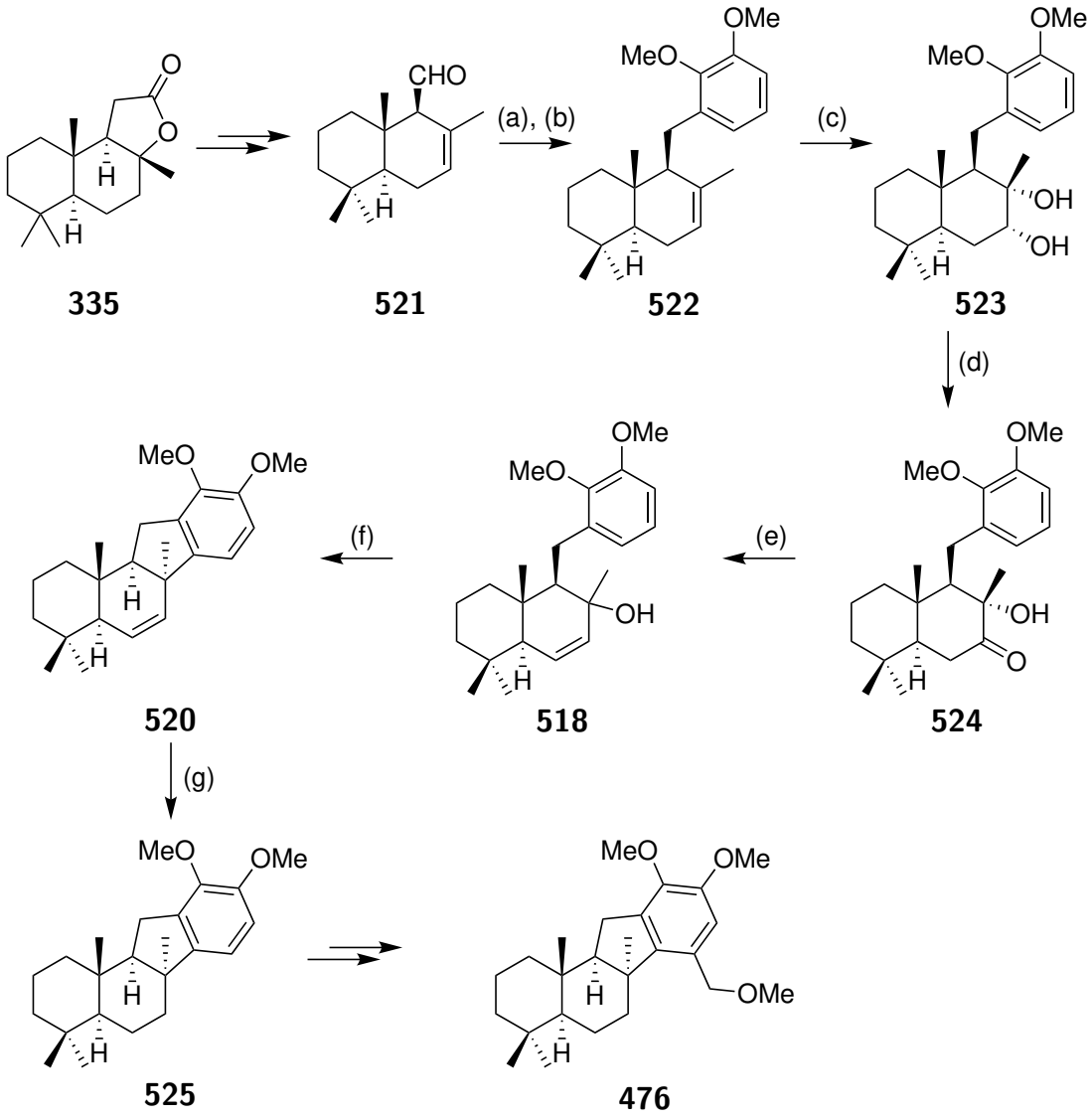
The issue with this strategy lay in elaborating sclareolide to the desired alkene (Scheme 97). It already took 4 steps to obtain aldehyde **521** from sclareolide at a mere 35% overall yield and this compound marks the *beginning* of Qin's reported synthesis. Aldehyde **521** was coupled with 1,2-dimethoxybenzene via *ortho*-lithiation and addition to the intermediate aryllithium and the resulting alcohol was cleaved under Birch conditions to give compound **522**.

Isomerisation to the desired alkene took a less than optimal sequence. Alkene **522** was



518 **519** **520**

Scheme 96: Proposed conformation of carbocation **519**, leading to alkene **520**.[95]



335 **521** **522** **523** **524** **518** **520** **525** **476**

Scheme 97: Qin's synthesis of (–)-akaol A (**476**) via a conformational constraint strategy.[95] (a) *n*-BuLi, 1,2-dimethoxybenzene, TMEDA, THF, –78 °C, then **521**. (b) Li, NH_3 (l), THF, –78 °C. 70% over 2 steps. (c) OsO_4, NMO, acetone/H_2O, 79%. (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78 °C, 82%. (e) NH_2NHTs, PPTS, THF, then *n*-BuLi, THF, 0 °C, 59%. (f) TFSI-H, CH_2Cl_2, 0 °C, 86%. (g) PtO_2, H_2 (22 bar), AcOH, rt, 96%.

dihydroxylated to give diol **523**, then Swern oxidation gave the α-hydroxyketone **524**. Shapiro olefination gave a mixture of epimers of the tertiary alcohol **518**. Elimination of alcohol **518** and cyclisation using bistriflimide gave compound **520**, exclusively with the desired *cis* stereochemistry. Hydrogenation of alkene **520** to compound **525** and late-stage decoration of the aromatic gave akaol A (**476**) in 11% overall yield over 13 steps.

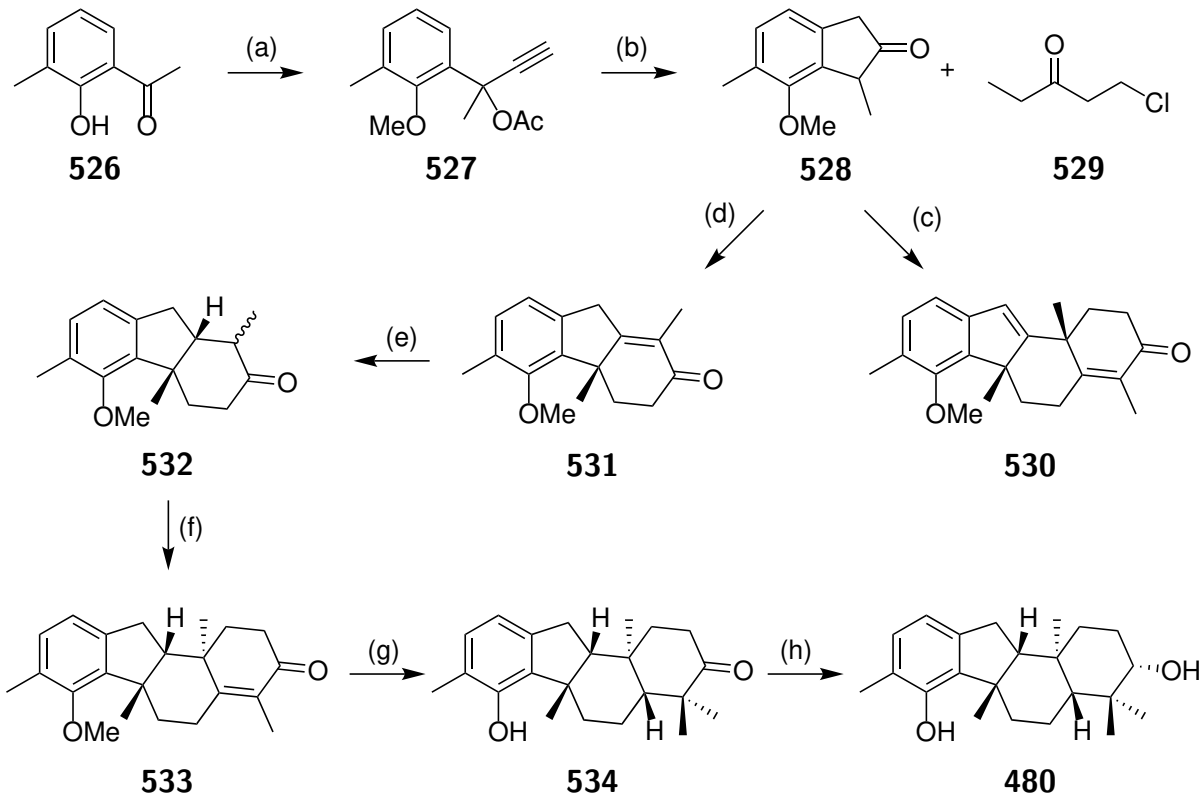
Forcing the bicyclic intermediate carbocation into a boat-like conformation like **519** is vital to obtaining the desired *cis* stereochemistry, but we are not convinced that Qin's method is the best way of getting there. We hope to develop an alternative way to coax a carbocation obtained by polyene cyclisation into a boat-like conformation, which would deliver the *cis* configured compound.

One other intriguing strategy towards the *cis*-fused four-ring compounds was developed by the She group using an iterative Robinson annulation (Scheme 98).[97] Acetophenone **526** was protected as the methyl ether, then the ketone was reacted with ethynylmagnesium bromide and the alcohol was immediately acetylated to give propargyl acetate **527**. Platinum dichloride catalysed pentannulation and hydrolysis delivered indanone **528**, set up for the first Robinson annulation.

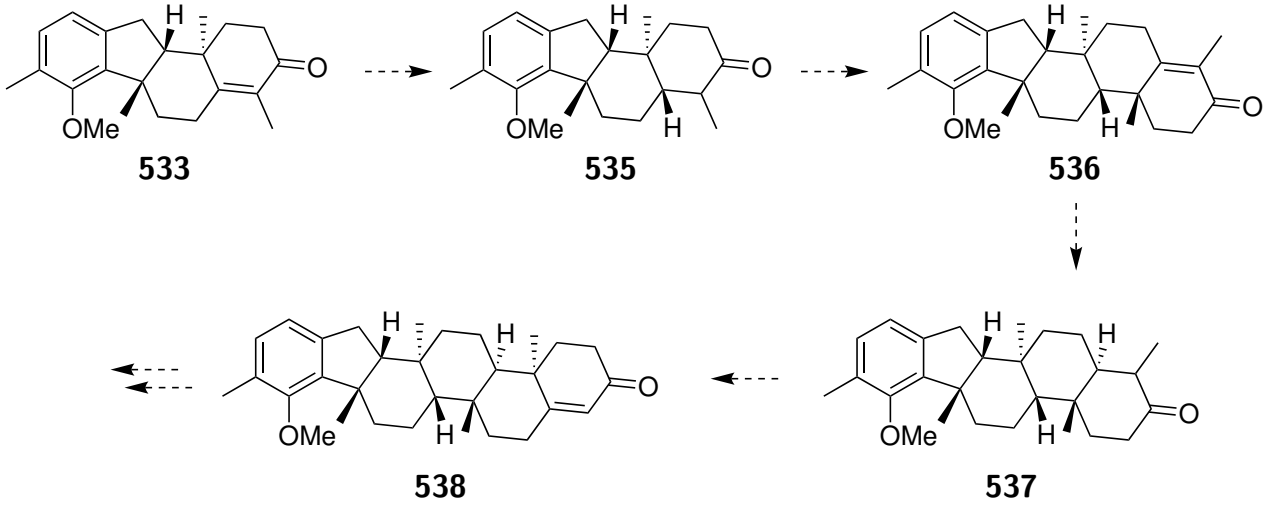
Treating ketone **528** with 1-chloro-3-pentanone (**529**) and *para*-toluenesulfonic acid in toluene at reflux gave the tricycle **531** in excellent yield. Reacting ketone **528** with more equivalents of compound **529** gave exclusively the undesired diastereomer **530**; likewise, treating isolated enone **531** under basic conditions gave a mixture of diastereomers, favouring in a 5:1 ratio again the undesired isomer **530**.

Instead, reducing the double bond of enone **531** under dissolving metal conditions gave ketone **532** with the expected *cis* stereochemistry across the ring junction. Treating ketone **532** again with compound **529** and *p*-toluenesulfonic acid in benzene at reflux gave the desired diastereomer **533**. Then Birch reduction, followed by alkylation with methyl iodide gave the geminal dimethyl containing compound **534**. Cleavage of the methyl ether and reduction of the ketone gave ($\pm$)-dasyscyphin D (**480**) in 9 steps, with 23% overall yield.

This is an effective sequence. Again from enone **533**, another Birch reduction could be performed, followed by another annulation giving compound **536**. This could proceed *ad infinitum*, giving a molecule of any desired size. At a certain point, this would be less efficient than a one-step polyene cyclisation, but nevertheless, this represents an



Scheme 98: She's synthesis of dasyscyphin D (**480**).[97] (a) MeI, K_2CO_3, acetone, then HC≡CMgBr, THF, then Ac_2O, pyridine, CH_2Cl_2, 95% over 3 steps. (b) $PtCl_2$, PhMe, 60 °C, 72%. (c) **529** (2.5 equiv), TsOH, PhMe, Δ, 12 h, 76%. (d) **529** (1.5 equiv), TsOH, PhMe, Δ, 3 h, 87%. (e) Li, NH_3 (l), THF, –78 °C, 88%, dr 6:1 (f) **529** (1.5 equiv), TsOH, PhH, Δ, 55%. (g) Li, NH_3 (l), MeI, THF, –78 °C, then BBr_3, CH_2Cl_2, –78 °C, 68% over 2 steps. (h) $NaBH_4$, MeOH, –20 °C, 92%.



Scheme 99: The same sequence of reactions could be repeated to produce ring systems of larger size.

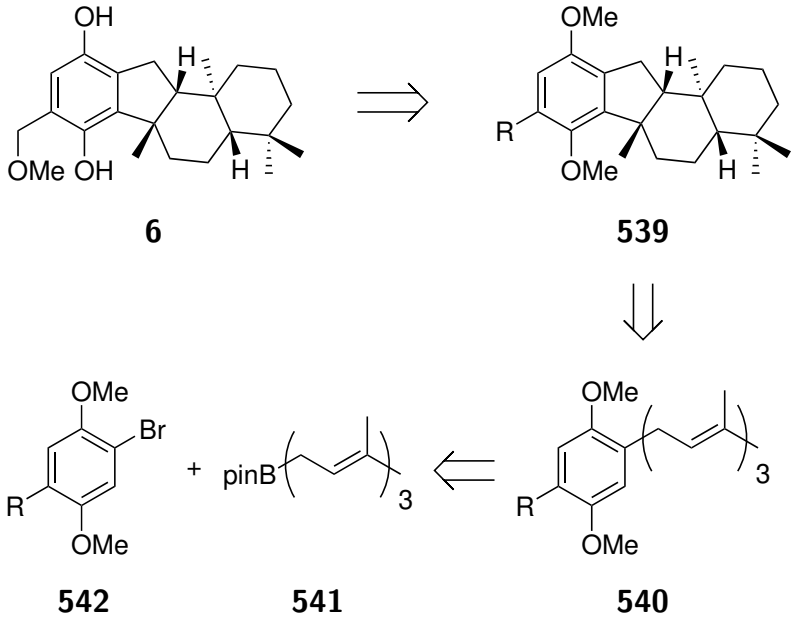
intriguing strategy.

It has been highlighted throughout this thesis that a key advantage of our polyene cyclisation strategy is its efficiency and the speed at which we can produce a variety of polycyclic compounds. Following synthesis of the required aryl bromide and polyprenyl boronate coupling partners, we should obtain the desired natural products in short order *via* Suzuki reaction, cyclisation and late-stage decoration.

3.2 Results

3.2.1 Dasyscyphin B

The first goal was to investigate polyene cyclisations leading to the dasyscyphin B ring system. The retrosynthetic plan towards the longer polyenes is much the same as for the taiwaniaquinoids (Scheme 100). Dasyscyphin B (**6**) would be obtained by late-stage manipulation of a fully cyclised structure **539**, the product of a key polyene cyclisation event of precursor **540**. Polyene **540** would again be produced by Suzuki coupling between farnesyl pinacolboronate (**541**) and a suitable aryl bromide (**542**).

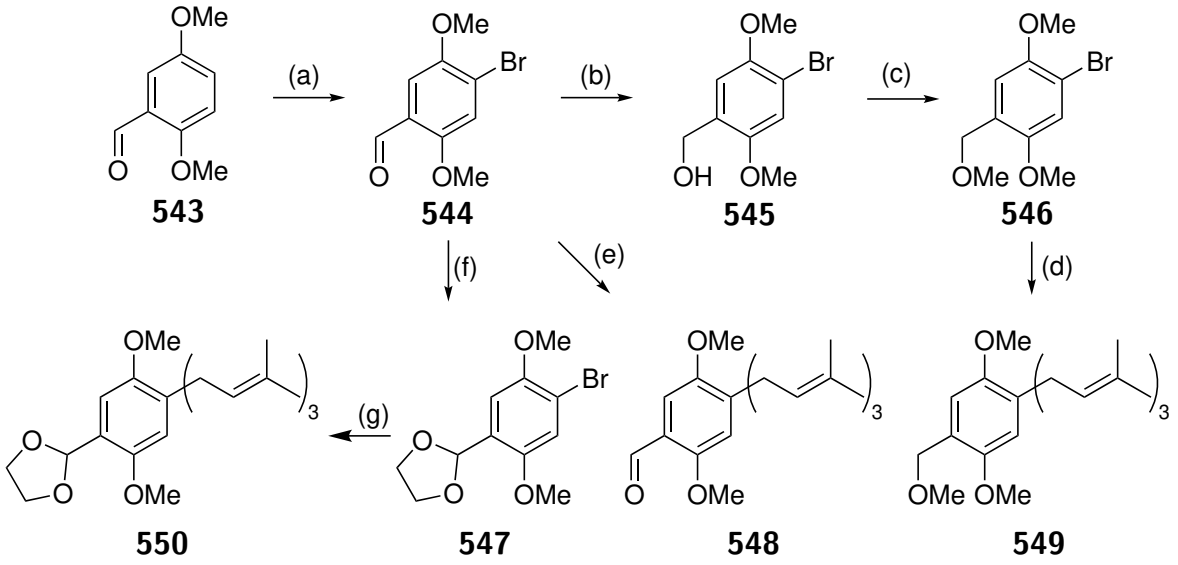


Scheme 100: Retrosynthesis of dasyscyphin B (**6**).

The most suitable aromatic would be a derivative of benzaldehyde **544**, which was produced by bromination of commercially available 2,5-dimethoxybenzaldehyde (**543**)

with bromine in dichloromethane in excellent yield and purity.

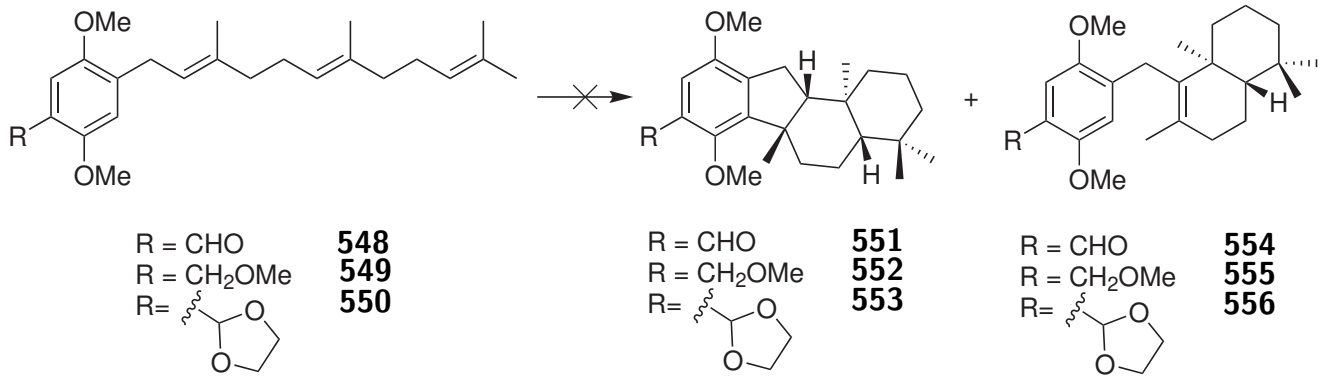
Marlowe Graham attempted some early work on dasyscyphin B and reported problems in directly coupling benzaldehyde **544** and boronate **541**. Protecting this aldehyde functionality was an important next step. We were able to protect the aldehyde as the dioxolane **547** by treatment with ethylene glycol and toluenesulfonic acid in toluene at reflux under Dean-Stark conditions (**??**). Suzuki reaction under the conditions employed for the taiwaniaquinones project gave the corresponding polyene **550**. The acetal is unstable in air, particularly after coupling and gave a poor yield of compound **550** as a mixture with the corresponding aldehyde **548**. Attempts to cyclise the mixture of compounds **550** and **548** were unsuccessful.



Scheme 101: Synthesis of polyenes **548** and **549**. (a) Br_2, CH_2Cl_2, 76%. (b) $NaBH_4$, MeOH, quant. (c) MeI, K_2CO_3, MeCN, 52 %. (d) **541**, $Pd(PPh_3)_4$, NaOH, PhMe/H_2O, Δ, 47%. (e) **541**, $Pd(PPh_3)_4$, NaOH, PhMe/H_2O, Δ, 81%. (f) ethylene glycol, TsOH, PhMe, Δ, 62%. (g) **541**, $Pd(PPh_3)_4$, NaOH, PhMe/H_2O, Δ, 34%.

Since the methyl ether is present in the final product, this seemed to be an ideal way of avoiding the apparent problems with Suzuki coupling with the aldehyde and potential side reactions with the polyene cyclisation. Reduction of benzaldehyde **544** with sodium borohydride in methanol gave benzyl alcohol **545** which was methylated with methyl iodide and potassium carbonate, giving ether **546**. Again, Suzuki reaction under our standard conditions gave polyene **549**.

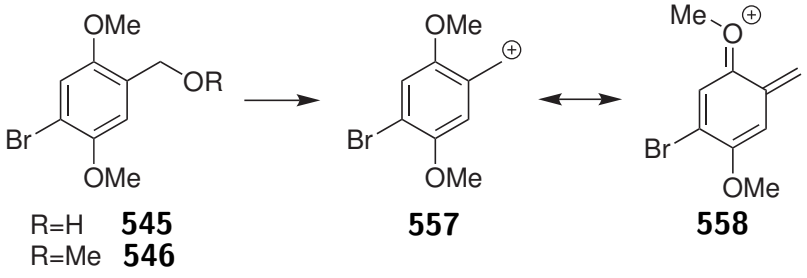
There were no issues when coupling benzaldehyde **544** directly with boronate **541** to give polyene **548**.



Scheme 102: None of compounds **551**–**553** or partially cyclised **554**–**556** were seen under the conditions reported in Table 22.

With polyenes in hand, we investigated the cationic cyclisation. Cyclisation did not occur in any of the conditions listed in Table 22. The only outcome was decomposition or a complex reaction mixture in which none of the desired cyclised compounds **551**–**553** or partially cyclised **554**–**556** could be identified by NMR spectroscopy. No masses corresponding to the parent ion could be seen by mass spectrometry. Similar results were seen employing other methodologies: BDSB led to decomposition, as did mercury(I) triflate, with or without dimethylaniline as a ligand.

We expect that many issues arise from the lability of these masked aldehyde equivalents under strongly acidic conditions. Elimination and formation of the highly reactive *ortho*-quinone methide seems an obvious degradation pathway. Supporting this hypothesis is that the major mass seen by APCI mass spectrometry analysis of compounds **545** and **546** is cation **557** formed by the elimination of methanol. We expect the formation of similar intermediate species may occur during attempted cyclisation of the polyenes **548**, **549** and **550**. Loss of the methyl ether and aldehyde functional groups were observed in ^{1}H NMR analysis of crude reaction mixtures from attempted cyclisations of polyenes **548** and **549**.

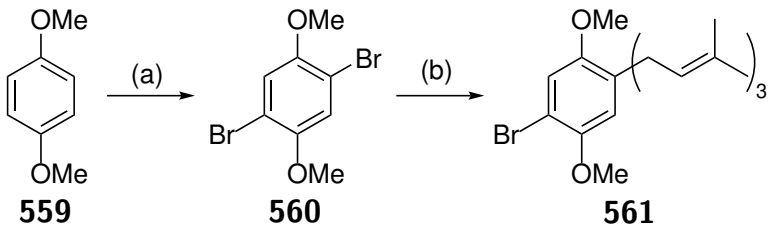


Scheme 103: Decomposition of aryl bromides **545** and **546** under APCI mass spectrometry conditions.

Table 22: Attempted polyene cyclisation of **548**, **549** and **550** by direct acid-catalysed cyclisation. All reactions resulted in decomposition to complex reaction mixtures with no distinguishable resonances in the ^{1}H NMR spectra.

Entry	Polyene	Acid	Solvent	T (°C)
1	**548**	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt
2	**548**	$Bi(OTf)_3$	$MeNO_2$	rt
3	**548**	$ClSO_3H$	$MeNO_2$	rt
4	**549**	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt
5	**549**	$Bi(OTf)_3$	$MeNO_2$	rt
6	**549**	MsOH	$MeNO_2$	rt
7	**549**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	rt
8	**549**	$Bi(OTf)_3$	CH_2Cl_2	rt
9	**549**	MsOH	CH_2Cl_2	rt
10	**550**	$Bi(OTf)_3$	$EtNO_2$	rt
11	**550**	$Bi(OTf)_3$	$MeNO_2$	100
12	**550**	$ClSO_3H$	$EtNO_2$	rt
13	**550**	$BF_3{\cdot}OEt_2$	$EtNO_2$	rt
14	**550**	$Bi(OTf)_3$	CH_2Cl_2	rt
15	**550**	$ClSO_3H$	CH_2Cl_2	rt
16	**550**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	rt

Replacing this troublesome functionality with a bromine atom was projected to be a good strategy while retaining a synthetic handle for subsequent regioselective functionalisation. Treatment of 1,4-dimethoxybenzene (**559**) with two equivalents of bromine gave the dibromobenzene **560**. Unfortunately, Suzuki coupling under the normal conditions did not deliver the farnesylated compound **561** as expected. A short screening (Table 23) revealed that a change of solvent to tetrahydrofuran or dimethylformamide while retaining tetrakis(triphenylphosphine)palladium(0) as the palladium source and sodium hydroxide as base gave the desired product in acceptable yields.



559 **560** **561**

Scheme 104: Synthesis of polyene **561**. (a) Br_2, CH_2Cl_2. (b) *Table 23*.

Table 23: Conditions for Suzuki reaction between aryl bromide **560** and boronate **541**.

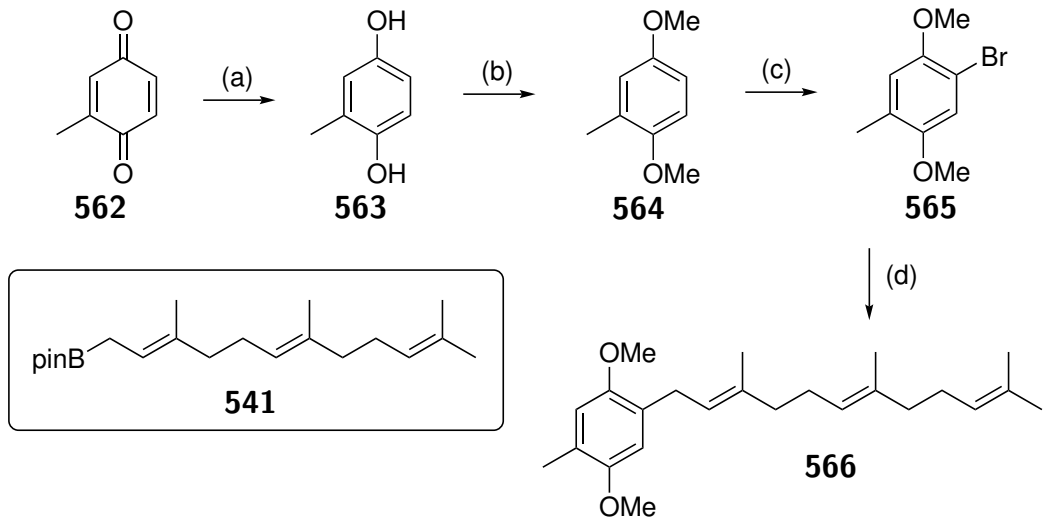
Entry	Catalyst	Solvent	Base	Yield
1	$Pd(PPh_3)_4$	$PhMe/H_2O$	NaOH	decomp.
2	$Pd(PPh_3)_4$	THF	NaOH	51%
3	$Pd(PPh_3)_4$	DMF	NaOH	35%
4	$Pd(dppf)_2Cl_2$	DMF	K_2CO_3	n.r.
5	$Pd(OAc)_2$	$PhMe/H_2O$	K_2CO_3	n.r.
6	$Pd(OAc)_2$	THF	K_2CO_3	n.r.
7	$Pd(PPh_3)_2Cl_2$	$PhMe/H_2O$	NaOH	decomp.

Attempted cyclisation under a number of conditions (Table 24) resulted only in the decomposition of polyene **561**.

Table 24: Attempted cyclisation conditions for cyclisation of **561**. All resulted in complex reaction mixtures with no identifiable cyclised products.

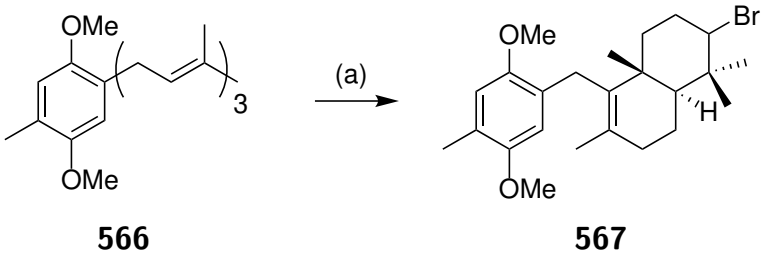
Entry	Acid	Solvent	T (°C)
1	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt
2	$Bi(OTf)_3$	$MeNO_2$	rt
3	$ClSO_3H$	$MeNO_2$	rt
4	$BF_3{\cdot}OEt_2$	CH_2Cl_2	rt
5	$Bi(OTf)_3$	CH_2Cl_2	rt
6	$ClSO_3H$	CH_2Cl_2	rt
7	$ClSO_3H$	$EtNO_2$	–78
8	$BF_3{\cdot}OEt_2$	$EtNO_2$	80
9	$Bi(OTf)_3$	$EtNO_2$	80

As the final cyclisation precursor, we synthesised the toluene **566**, which could be converted into the natural product by oxidation of the toluene methyl group following cyclisation. Shaking *para*-toluquinone (**562**) in tetrahydrofuran with aqueous sodium dithionite solution gave the hydroquinone (**563**). The reaction mixture was then separated and the organic layer was dried, filtered and treated directly with methyl iodide and potassium carbonate to give the dimethyl ether **564**. Methylation could also be performed on commercially sourced toluhydroquinone (**563**) under similar conditions. Treating ether **564** with bromine in dichloromethane gave the aryl bromide **565**. Subjecting aryl bromide **565** and farnesyl pinacolboronate (**541**) to our standard Suzuki reaction conditions furnished the desired polyene **566** in good yield.

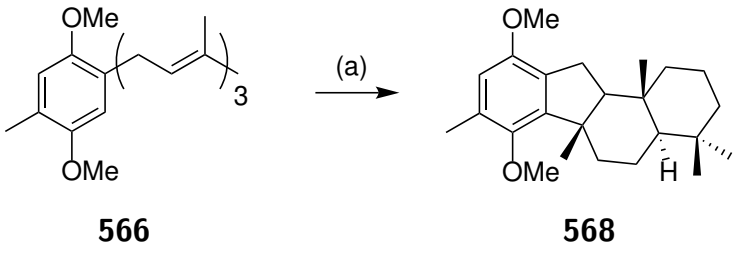


Scheme 105: Synthesis of polyene **566**. (a) $Na_2S_2O_4$, THF/H_2O (b) K_2CO_3, MeI, THF, 66% over 2 steps. (c) Br_2, CH_2Cl_2, 76%. (d) **541**, $Pd(PPh_3)_4$, NaOH, PhMe/H_2O, 72%.

In this case, treatment with BDSB gave a complex reaction mixture, which clearly contained a significant amount of the bicyclised alkene **567** (Scheme 106). All attempts at direct cyclisation using Lewis acid were unsuccessful (Table 25).



Scheme 106: Treatment of polyene **566** with BDSB gave a complex reaction mixture containing partially cyclised compound **567**.



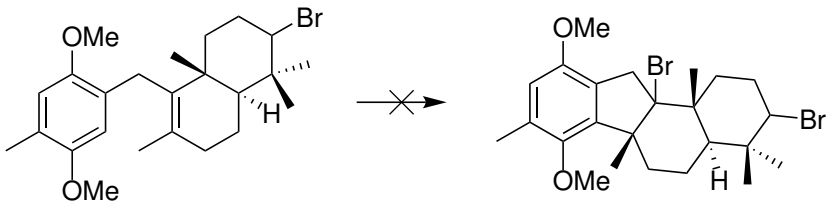
Scheme 107: Polyene **566** could not be cyclised by Lewis acid. Attempted conditions in Table 25.

We might optimise this reaction to give the fully cyclised compound, except it would almost certainly result in the *trans* configuration given the results of Andersen's Friedel-Crafts alkylation towards pelorol and the computational analysis of that step by McErlean. Obtaining this compound gave us a prime opportunity to explore how to generate the desired *cis* stereochemistry instead.

Table 25: Attempted cyclisation conditions of polyene **566**. All resulted in complex reaction mixtures with no yield of the desired cyclised compound, except entry 6 which led to no reaction.

Entry	Acid	Solvent	T (°C)
1	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt
2	$Bi(OTf)_3$	$MeNO_2$	rt
3	$ClSO_3H$	$MeNO_2$	rt
4	$SnCl_4$	$MeNO_2$	rt
5	$Bi(OTf)_3$	$MeNO_2$	60
6	$BF_3{\cdot}OEt_2$	CD_3CN	rt

It may be possible to obtain a *cis*-fused compound by treating alkene **567** again with BDSB: this would generate a bromine atom at the ring junction, giving dibromo compound **569** (Scheme 108). The carbon-bromine bond could be homolysed and may lead to the *cis*-fused compound due to the ability to deliver a hydrogen atom from the less sterically congested face. Surprisingly, we saw no reaction even under forcing conditions.

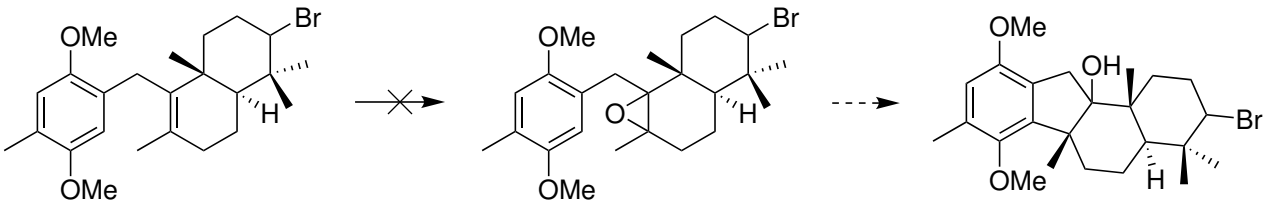


567 **569**

Scheme 108: Treating decalin **567** again with BDSB led to no further reaction.

Likewise, ring closure via epoxide **570** would produce compound **571** with an alcohol at the ring junction (Scheme 109). We anticipated removing the alcohol under Barton-McCombie conditions, possibly again delivering the *cis* stereochemistry. Attempted oxidation with *m*-CPBA or DMDO again led to no reaction. These two results together suggest that this tetrasubstituted alkene is far too sterically congested to undergo reaction.

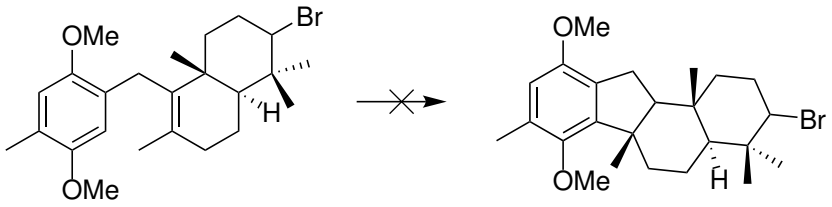
The only other option was to treat this compound with an acid to undergo Friedel-Crafts alkylation; a reaction which should generate the *trans*-configured compound, but some set of conditions may be able to coax the carbocation into a high energy boat-like conformation. Treatment of alkene **567** with boron trifluoride etherate in various solvents led to no reaction, while treatment with chlorosulfonic acid led to decomposition (Scheme 110). ^{1}H NMR analysis revealed the loss of resonances associated with both the



567 **570** **571**

Scheme 109: Failed epoxidation of compound **567** to form epoxide **570**, which is the precursor to tertiary alcohol **571**.

benzylic proton and the alkyl bromide proton. Elimination of both the aromatic unit and the bromide appears to have occurred. Conducting the reaction at low temperature in nitromethane led to no reaction.



567 **572**

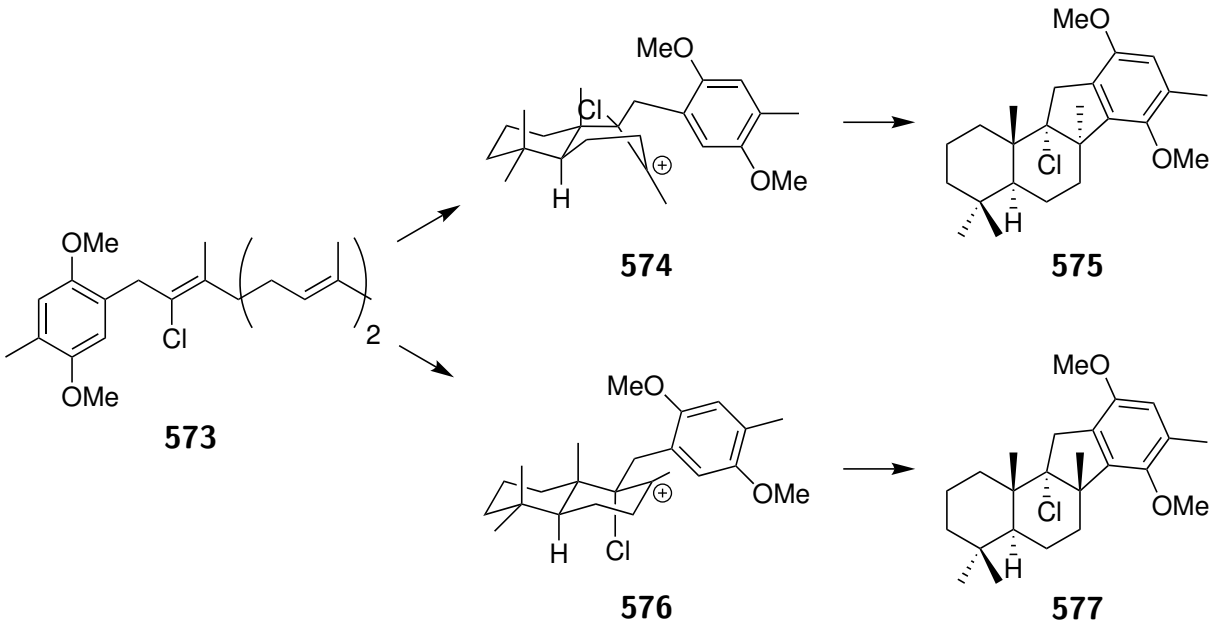
Scheme 110: Treating decalin **567** with a series of Lewis acids led to no further reaction or decomposition.

Table 26: Treatment of decalin **567** with acid to effect ring closure to compound **572** led to the recovery of starting material **567** or decomposition.

Entry	Acid	Solvent	T (°C)	SM	Decomp.
1	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt	✓	X
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	rt	✓	X
3	$BF_3{\cdot}OEt_2$	PhMe	rt	✓	X
4	$ClSO_3H$	$MeNO_2$	rt	X	✓
5	$ClSO_3H$	CH_2Cl_2	rt	X	✓
6	$ClSO_3H$	PhMe	rt	X	✓
7	$ClSO_3H$	$EtNO_2$	–78	✓	X

At this stage, there was no clear pathway towards a *cis*-selective synthesis. Perhaps if we installed a chlorine atom at the carbon that would become part of the ring junction, it would force the carbocation into the boat conformation **574**. By analogy to the conformer **505** in McErlean's computational modelling of Andersen's Friedel-Crafts reaction (Scheme 94),[41] we may then be able to generate the *cis* isomer.

Retrosynthetically, we should obtain the *cis* configured system **578** by homolysis of

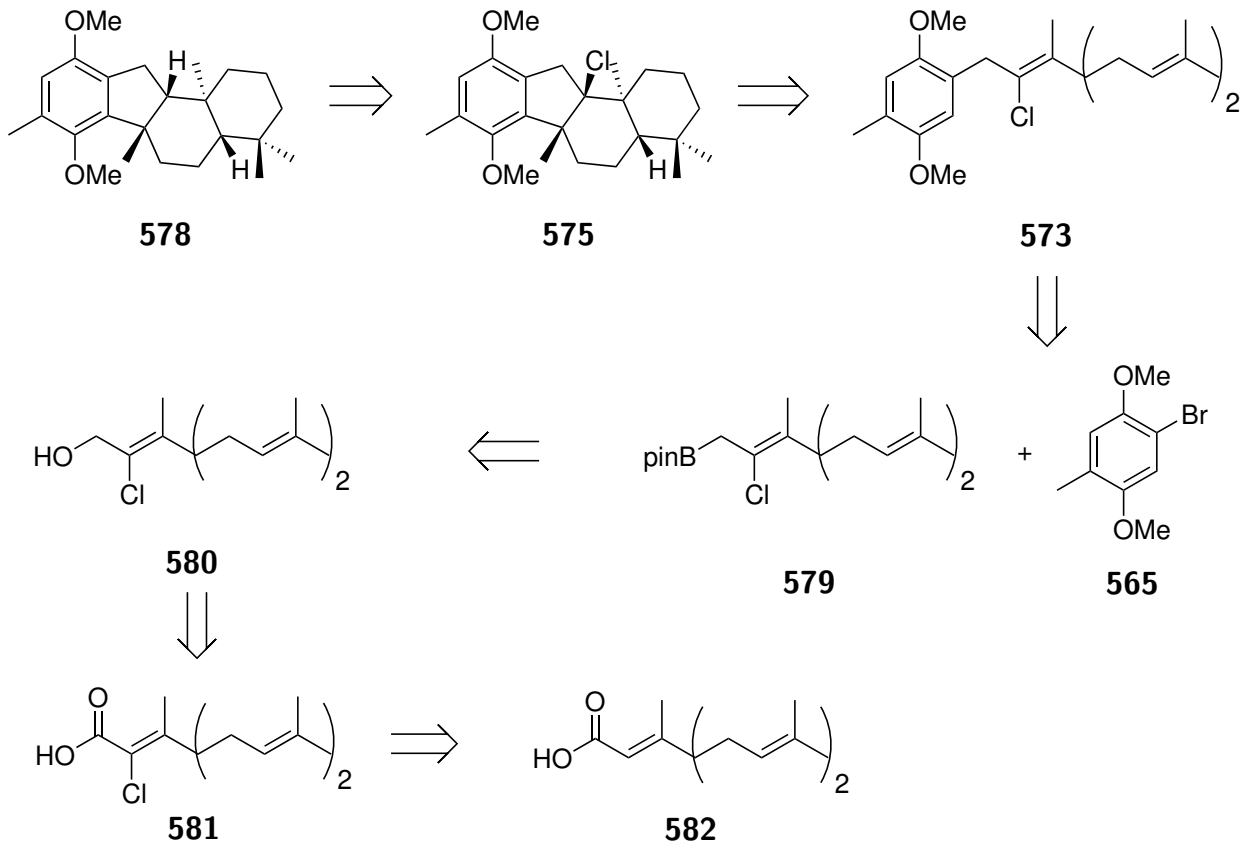


Scheme 111: A chlorine atom at the ring junction will allow the cyclisation to proceed through boat-like intermediate **574** rather than chair-like intermediate **576**, leading to the desired *cis*-fused architecture.

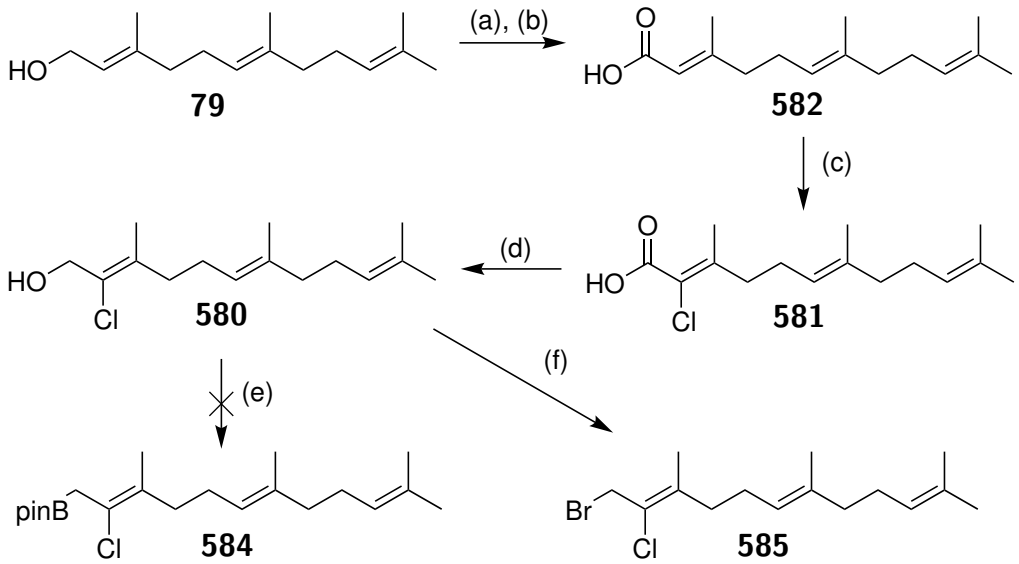
chloride **575** (Scheme 112). This would be obtained by full cyclisation of the chlorinated polyene **573** formed by Suzuki reaction between aryl bromide **565** and boronate **584**. Boronate **584** for this coupling would be obtained from chlorofarnesol (**580**) by the palladium catalysed borylation we have successfully applied to allyl alcohols of various lengths. Alcohol **580** can be obtained from the reduction of chlorofarnesoic acid (**581**), given by the reaction of farnesoic acid (**582**) with *N*-chlorosuccinimide.

Farnesoic acid (**582**) can be purchased commercially but is a niche product and correspondingly prohibitively expensive. It could easily be made by two-step oxidation of farnesol (**79**; Scheme 113): activated manganese dioxide gave farnesal (**583**) in quantitative yield, then Pinnick oxidation with 2-methyl-2-butene gave excellent yields of farnesoic acid (**582**). Treatment of acid **582** with *N*-chlorosuccinimide in chloroform at reflux gave chlorofarnesoic acid (**581**) in good yield. Subsequent reduction with lithium aluminium hydride was unsuccessful at room temperature in ether, but reduction in tetrahydrofuran at reflux gave the alcohol **580** in good yield.

Unfortunately, borylation under our usual conditions led to dechlorination catalysed by palladium(0) so we opted to employ a more simple S_N2 displacement of chlorofarnesyl bromide (**586**) instead. Treatment of alcohol **580** with phosphorus tribromide gave alkyl bromide **586** in excellent yield. Using the conditions employed by Andersen[8]—treating

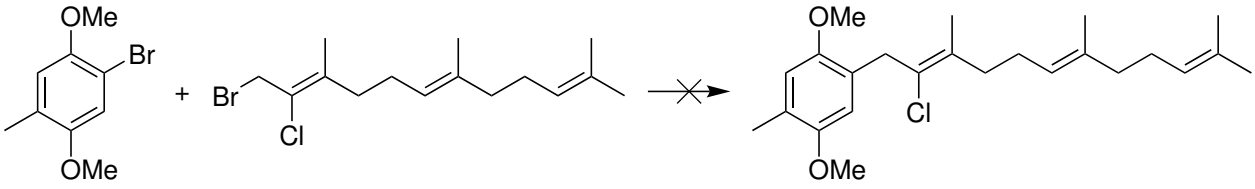


Scheme 112: Retrosynthesis of chlorinated dasyscyphin analogue **578**.



Scheme 113: Synthesis of chlorofarnesol (**580**) and attempts to convert to a useful coupling partner. (a) MnO_2, hexane, 95%. (b) 2-methyl-2-butene, NaH_2PO_4, $NaClO_2$, acetone/H_2O, 60%. (c) NCS, $CHCl_3$, Δ, 18 h, 63%. (d) $LiAlH_4$, THF, Δ, 18 h, 69%. (e) **375**, B_2pin_2, TsOH, DMSO/MeOH, 50 °C.

aryl bromide **565** with *n*-butyllithium then using catalytic Li_2CuCl_4 to displace alkyl bromide **586**—led only to protodehalogenation of aryl bromide **565** and decomposition of alkyl bromide **586**. This has been a consistent problem in our attempts to use cuprates derived from organolithium reagents, and we do not suspect interference from water due to the red colour of the anhydrous Li_2CuCl_4 solution and addition of excess *n*-butyllithium to react with adventitious water. We instead generated the Grignard reagent of aryl bromide **565** using magnesium/iodine in tetrahydrofuran at reflux, but again subjecting the pre-formed Grignard reagent to copper-mediated coupling conditions led to quenching of the organomagnesium and no coupling.



565 **586** **573**

Scheme 114: Attempted coupling of chlorofarnesyl bromide (**586**) to aryl bromide **565**. Conditions: *n*-BuLi, Li_2CuCl_4, THF, –78 °C; or Mg, Br_2, THF, Δ, then **565**, 0 °C→rt.

This is likely to be a useful method for polyene cyclisation delivering the desired diastereomer of the dasyscyphin skeleton, but we have been unable to effect coupling between chlorofarnesol (**580**) and the aryl bromide **565**. Without this key step, there is no way to test whether a chlorinated polyene chain would deliver our desired *cis*-diastereomer.

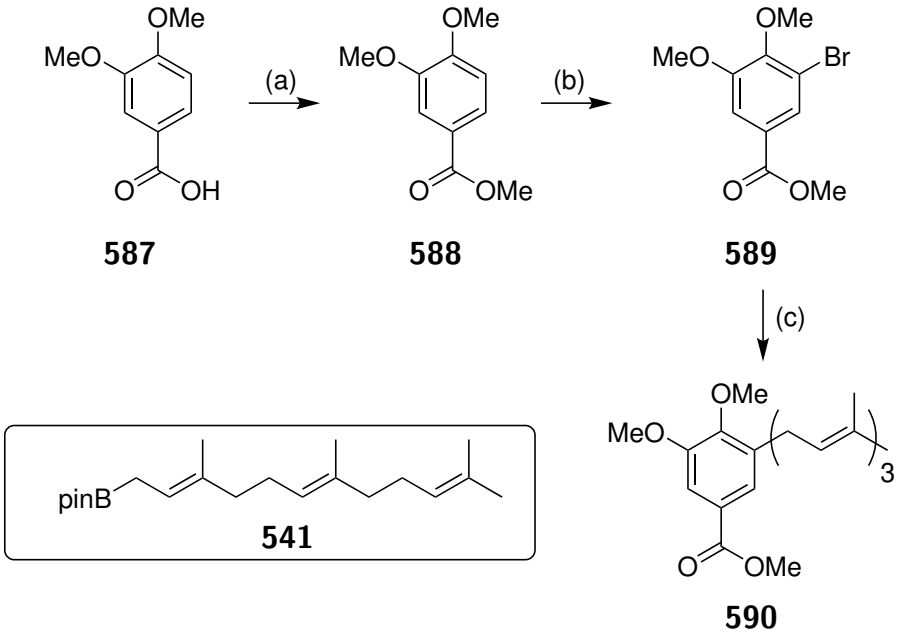
Our attempts at a *cis*-selective polyene cyclisation to generate a fused 6,5,6,6-fused ring system were unsuccessful. Our efforts towards a rapid *cis*-selective method were impeded by the steric encumberance of partially cyclised material and the undesired reactivity of chlorine-containing analogues.

3.2.2 Pelorol

Given that we were able to partially cyclise polyene **566** to the decalin system **567**, a compound we have determined would deliver the *trans*-fused system, we decided to pursue an expedient synthesis of the *trans*-fused natural product pelorol (**473**).

Our synthesis started with the bromination of methyl 3,4-dimethoxybenzoate (**588**) to aryl

bromide **589** using bromine in methanol (Scheme 115), which was subsequently used in a Suzuki coupling with farnesyl pinacolboronate (**541**) under the usual conditions, giving polyene **590** which could be used in the key cyclisation reaction.

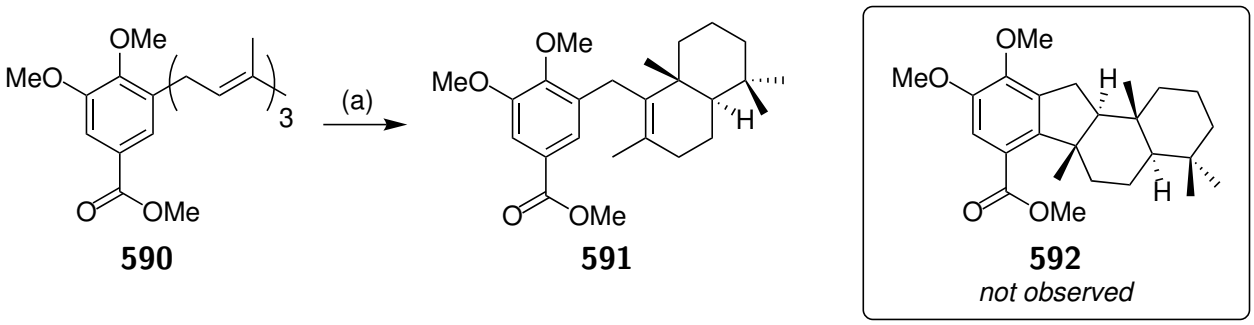


Scheme 115: Synthesis of polyene **590**. (a) H_2SO_4, MeOH, Δ, 87%. (b) Br_2, MeOH, rt, 34% (c) **541**, NaOH, $Pd(PPh_3)_4$, PhMe/H_2O, 100 °C, 35%.

When polyene **590** was treated with catalytic boron trifluoride etherate in nitromethane at room temperature overnight, we observed formation of bicyclised compound **591** (entry 1; Table 27). This type of partial cyclisation has only been reported through the use of BDSB and indeed is something we were unable to achieve during our work on dasyscyphin except using BDSB.[9] Like our cyclisations of taiwaniaquinone G precursors, this was not a clean reaction and we could not isolate compound **591** by column chromatography. Analytical HPLC traces suggest that the isolation of decalin **591** could be achieved on reverse-phase preparatory HPLC, but we did not have access to preparatory HPLC at this stage.

The next step would be to perform *full* cyclisation of polyene **590** to pelorol dimethyl ether (**592**). Unfortunately, performing the cyclisation at 60 °C using boron trifluoride etherate did not lead to ring closure and decomposition occurred instead (entry 2; Table 27). Treatment with a series of other acids also led to decomposition (entries 3-5; Table 27).

Treatment of polyene **590** with BDSB led to decomposition. This is in contrast to dasyscyphin B precursor **566**, which was cyclised successfully with BDSB to the partially cyclised alkene **567**, but did not undergo cyclisation after treatment with boron trifluoride



590 **591** **592**

Scheme 116: Cyclisation of polyene **590** led to formation of decalin **591** but not fully cyclised compound **592**. Conditions: (a) Table 27.

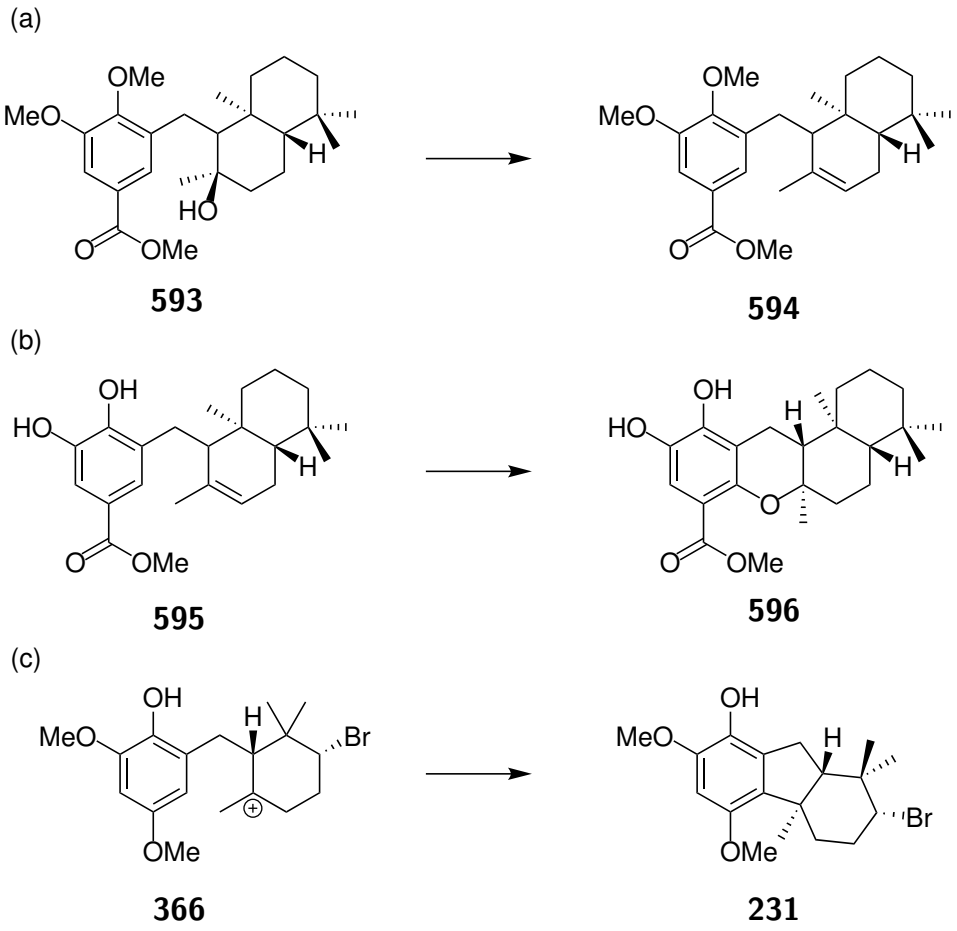
Table 27: Conditions for attempted cyclisation of polyene **590**.

Acid	Solvent	T/°C	time (h)	**592**	**591**	**590**
$BF_3{\cdot}OEt_2$	$MeNO_2$	rt	18	X	✓	X
$BF_3{\cdot}OEt_2$	$MeNO_2$	60	18		*decomp.*	
$SnCl_4$	$MeNO_2$	rt	18		*decomp.*	
$ClSO_3H$	$MeNO_2$	rt	18		*decomp.*	
$Bi(OTf)_3$	$MeNO_2$	60	18		*decomp.*	

etherate.

Decalin **591** is also a close relative of the natural product smenodiol (**595**), which could be synthesised by alkene isomerisation to compound **594** and cleavage of the methyl ethers by boron tribromide. A patent search reveals the synthesis of smenodiol proceeding through tertiary alcohol **593**.[117] Alcohol **593** is closely related to Andersen's intermediate **349**, yet treating alcohol **593** with tin(II) triflate for significantly longer reaction times at higher temperatures than Andersen's protocol led only to dehydration.[117] Similarly, treatment of smenodiol (**595**) with hydrochloric acid in ethanol leads to cyclisation at the phenol.[118] This is in contrast to Yamamoto's cyclisation of polyene **230** (Scheme 51): in that case, McErlean has demonstrated that cyclisation at the aryl carbon is energetically favourable to cyclisation at the phenol.[30] [41] Full cyclisation may be impossible in the presence of a bulky ester group *ortho* to the nucleophilic aryl carbon.

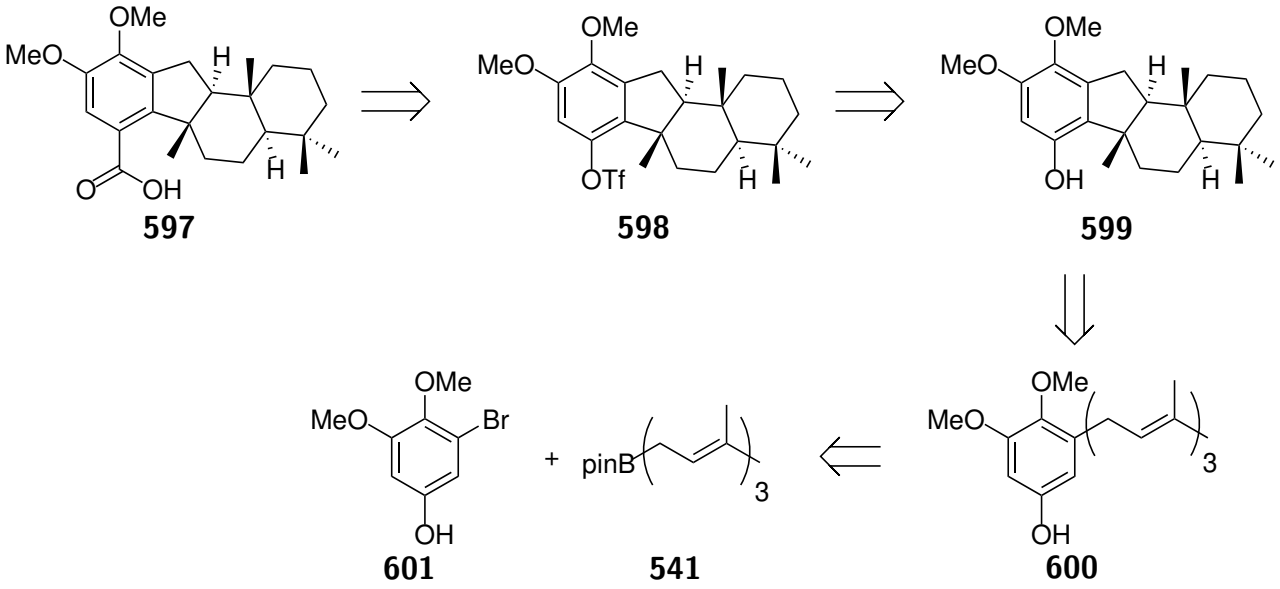
Nevertheless, while we were unable to effect full cyclisation of polyene **590** to dimethylpelorol (**592**), we were finally able to effect partial cyclisation by a direct acid-catalysed approach. This is, to our knowledge, the first cyclisation of this type reported. We were able to produce intermediate **591**, a close relative to another natural product, smenodiol



Scheme 117: (a) Wu's treatment of alcohol **593** led to elimination instead of cyclisation.[117] Conditions: $Sn(OTf)_2$, CH_2Cl_2, 6 h, 93%. (b) Crews' cyclisation of smenodiol (**595**) led to *O*-cyclisation.[118] Conditions: HCl, EtOH, Δ, 57%. (c) Yamamoto's bromocyclisation gave *C*-cyclised compound **231**.[30] Conditions: **150**, DBDMH, toluene/CH_2Cl_2, –90 °C, 91%.

(**595**). A total synthesis of smenodiol could be achieved by alkene transposition and methyl ether cleavage.

We have hypothesised that the failure of polyene **590** to undergo full cyclisation to dimethylpelorol (**592**) is due to the steric environment around the aromatic ring, leading to formation instead of decalin **591**. It could also be due to the deactivating effect of the ester moiety. To that end, we attempted cyclisation of polyene **600**, which would be both less sterically shielded at the nucleophilic carbon and more activated. To produce pelorol from here would be a lengthier sequence (Scheme 118). Retrosynthetically, from Andersen's advanced intermediate **597**, we could perform carboxylation of triflate **598** obtained by triflation of phenol **599**, the product of cyclisation of polyene **600**. We envision producing polyene **600** by Suzuki coupling between farnesyl pinacolboronate (**585**) and aryl bromide **601**.

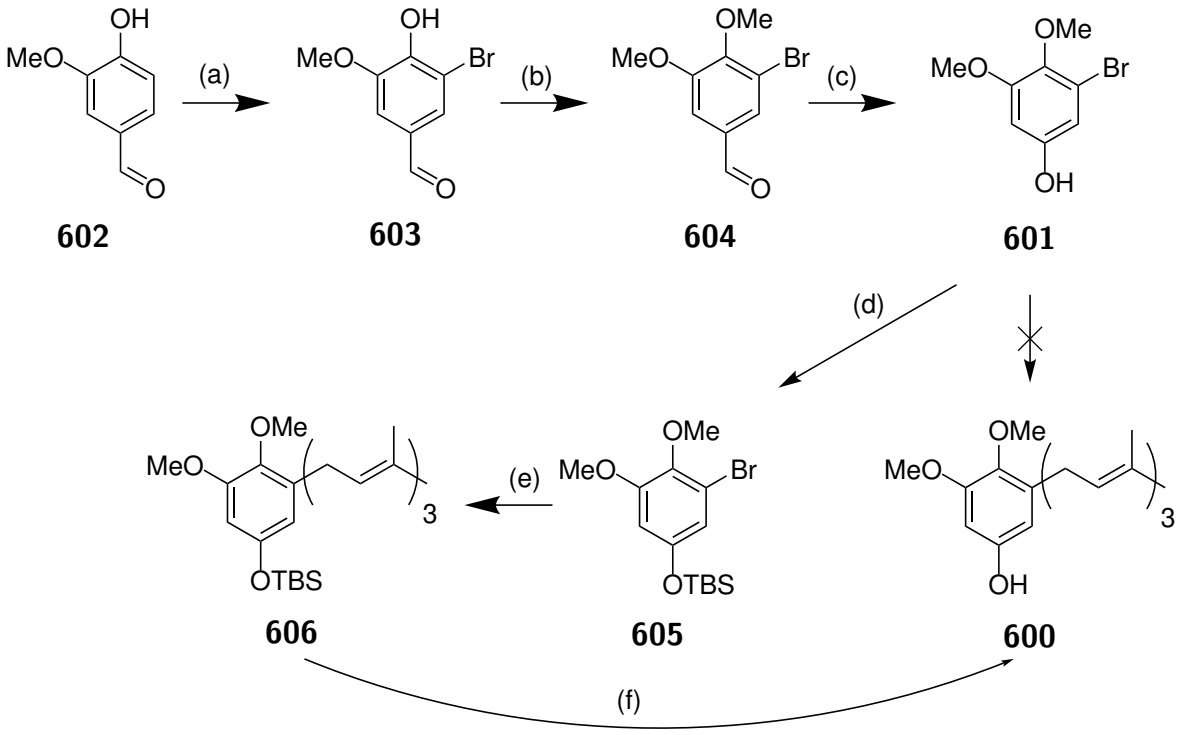


Scheme 118: Retrosynthesis of intermediate **597**, a late-stage intermediate in Andersen's synthesis of pelorol (**473**).

Our synthesis of aryl bromide **601** began with vanillin (**602**; Scheme 119). Bromination with DBDMH occurred selectively at the 5-position to give aryl bromide **603**, followed by methylation of the phenol with methyl iodide and potassium carbonate. Aldehyde **604** was subjected to Dakin oxidation with *m*CPBA, giving aryl bromide **601**.

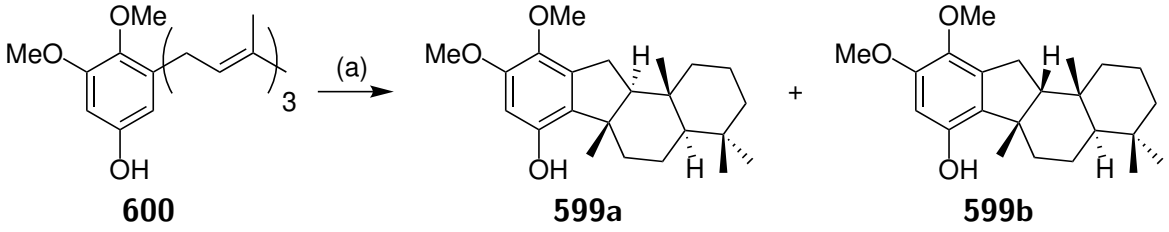
Unfortunately, we could not couple aryl bromide **601** to farnesyl pinacolboronate (**585**) using our standard conditions for these couplings. Deprotonation of the phenol likely led to partitioning into the aqueous layer and deactivation towards the initial oxidative addition step. Fortunately, protection of the phenol using TBS chloride and imidazole gave the silyl ether **605**, which then participated in Suzuki coupling, giving the polyene **606** in an acceptable yield. Cleavage of the TBS ether was then effected with tetrabutylammonium fluoride (TBAF), giving phenol **600**.

Pleasingly, treatment of polyene **600** with boron trifluoride etherate in nitromethane at room temperature delivered the fully cyclised compound **599** in good yield (Scheme 120). This is, to our knowledge, the first reported direct acid-catalysed polyene cyclisation of a farnesylarene to a 6,5,6,6 fused ring system. Interestingly, in contrast to Andersen's cyclisation, we obtained a mixture of diastereomers at the C9 position, as determined by HSQC and HMBC NMR studies and comparison to the known literature data for compounds possessing this ring system.[8] [86] A third compound was identified in trace quantities. By ^{1}H NMR analysis, this compound possessed the same characteristic



Scheme 119: Synthesis of polyene **600**. (a) DBDMH, MeCN, 18 h, 45%. (b) MeI, K_2CO_3, DMF, 73%. (c) *m*CPBA, $CHCl_3$, Δ, 2 h, then HCl (1 M), MeOH, rt. 22%. (d) TBSCl, imidazole, THF, rt, 18 h, 46%. (e) **541**, $Pd(PPh_3)_4$, NaOH, $PhMe/H_2O$, Δ, 18 h, 16%. (f) TBAF (1 M in THF), THF, rt, 18 h, 62%.

splitting pattern at the C11 benzylic hydrogens, but we were unable to confirm the structure of this molecule due to its low concentration.



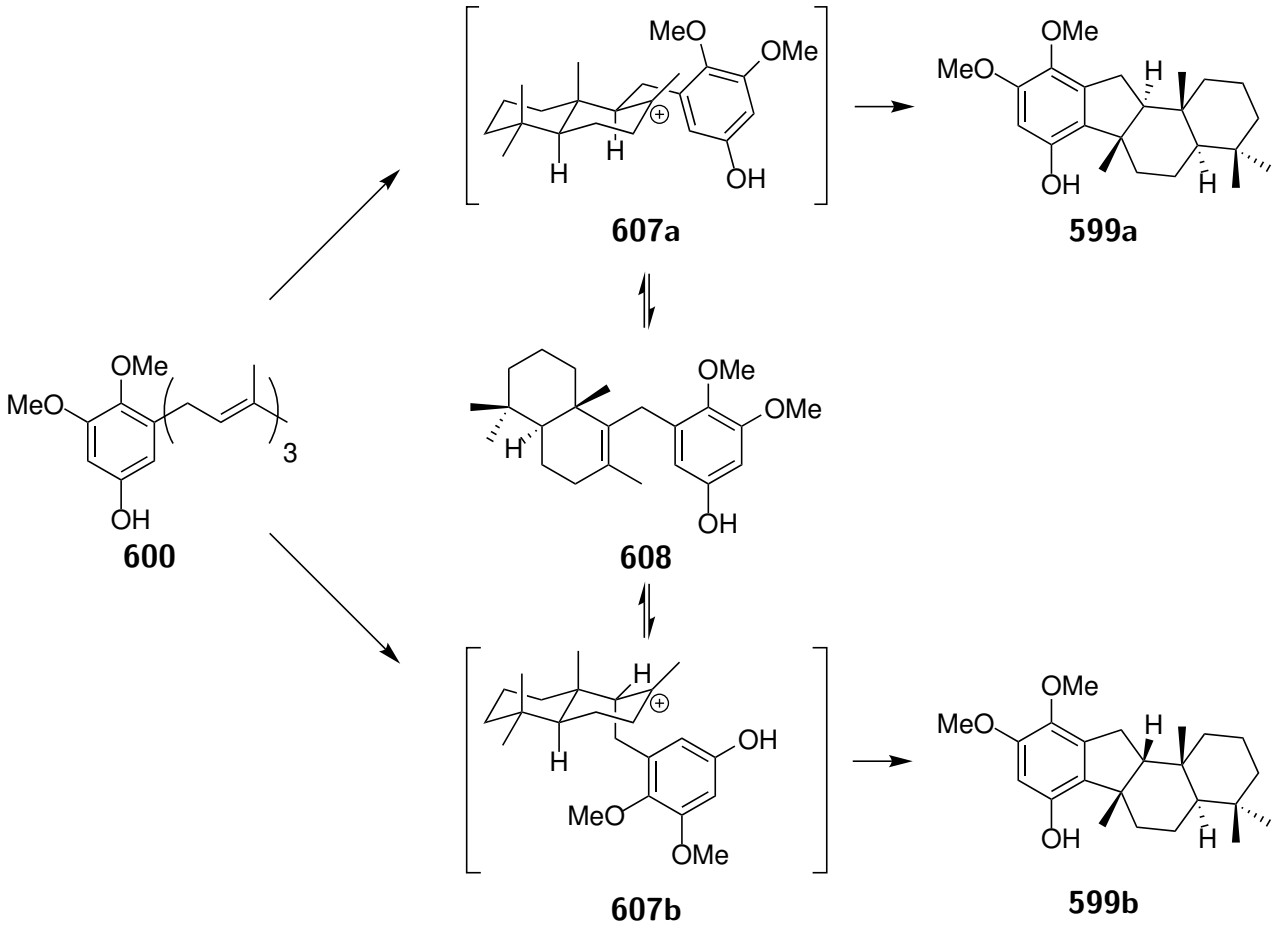
Scheme 120: Cyclisation of polyene **600** led to a mixture of diastereomers **599a** and **599b**. (a) $BF_3{\cdot}OEt_2$, $MeNO_2$, rt, 19%.

cis-Fused diastereomer **599b** must arise from a chair-like carbocation where the aryl unit is in an axial position and these intermediates are made more stable by the hyperconjugative effect that likewise promoted the formation of the *cis*-fused intermediates in the synthesis of 5-*epi*-taiwaniaquinone G. It appears that in our case, rearrangement of carbocation **607a** to **607b** is possible, leading to a 1:1 mixture of both the *cis* and *trans* fused diastereomers (Scheme 121).

This is also the highest level of *trans*-selectivity we have achieved in polyene cyclisations.

We should expect that interconversion between carbocations **607a** and **607b** should be slower than that between cyclohexane intermediates such as **359**, leading to a mixture enriched in the *trans* isomer. However, Andersen's cyclisation of a pre-formed decalin system **349** delivered exclusively *trans*-configured product.[75] Likewise, Andersen's later work on analogues using an epoxide-mediated cyclisation and other groups' epoxide mediated cyclisations led to exclusive *trans*-selectivity.[8] [39] Yamamoto's bromonium-mediated cyclisation towards the tricyclic system also delivered exclusive *trans*-selectivity and this is notable because the aromatic unit in this reaction is nearly identical to the one employed here.[30] The presence of a C3 substituent in these cyclisations must have a role to play here.

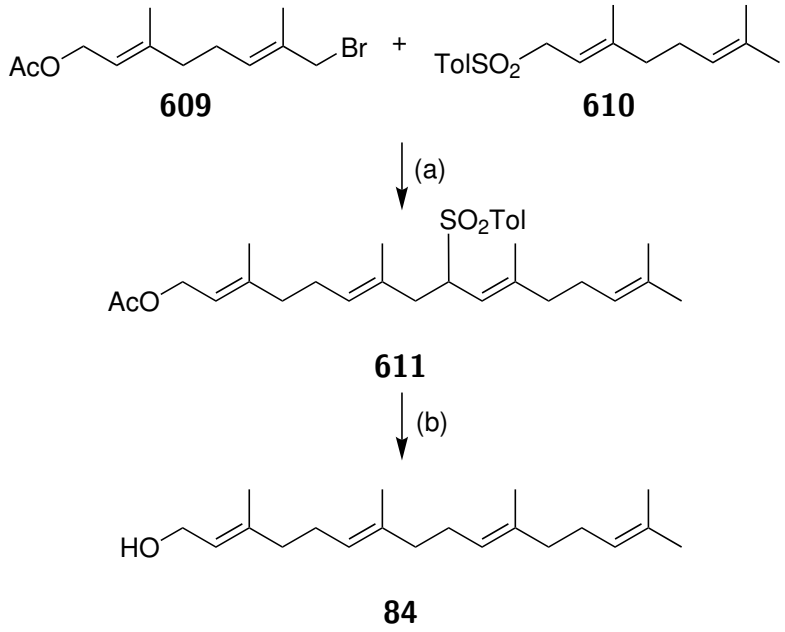
Nevertheless, we have successfully delivered the first examples of both partial cyclisation (in the case of compound **591**) and complete cyclisation (in the case of **599**) by direct, acid-catalysed means.



Scheme 121: Polyene cyclisation of **600** produces carbocations **607a** and **607b** which can interconvert, leading to both products **599**.

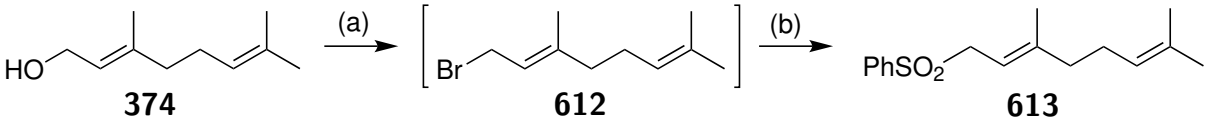
3.2.3 Polyprenol synthesis

With the ability to successfully synthesise the tetracyclic 6,5,6,6 system, we set to making larger derivatives, those with 5 and 6 rings total. In the previous cyclisations towards of taiwaniaquinone G and dasyscyphin B, we were able to use geraniol and farnesol as commercially available and relatively inexpensive sources of the polyprenoid chain, but the longer chains needed for the syntheses of larger fused ring systems are not as easily available as geraniol and farnesol. Geranylgeraniol is more than 250 times more expensive and available in less than gram quantities. Geranylfarnesol is even more difficult to find commercially. We chose to adopt a strategy performed by Chen, using Julia-type coupling followed by desulfurisation to give a series of polyprenols (Scheme 122).[119] But we needed to make some modifications.



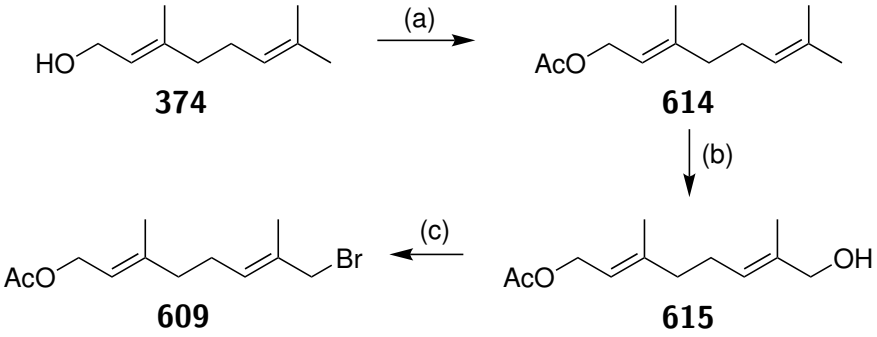
Scheme 122: Chen's synthesis of geranylgeraniol.[119] (a) NaH, DMF, –5 °C, 78%. (b) $Pd(dppp)Cl_2$, $LiBHEt_3$, THF, 0 °C→ rt, 90%.

Geranyl phenyl sulfone (**613**) was synthesised via the alkyl bromide **612**. In Chen's report, geranyl bromide (**612**) was produced by Appel reaction using solid-supported triphenylphosphine to assist in workup.[119] We instead used solution-phase triphenylphosphine under similar conditions, with a more complicated workup procedure involving trituration with ether, then filtration. We later found that using phosphorus tribromide gave a comparable yield with a simpler workup, cleaner reaction products and of course, far higher atom economy. The bromide was immediately subjected to S_N2 displacement to give the desired sulfone **610** in excellent yield.



Scheme 123: Our synthesis of geranyl phenyl sulfone (**613**). (a) PBr_3, CH_2Cl_2, 0 °C→rt. (b) $PhSO_2Na$, DMF, 0 °C→rt, 18 h, 79% over 2 steps.

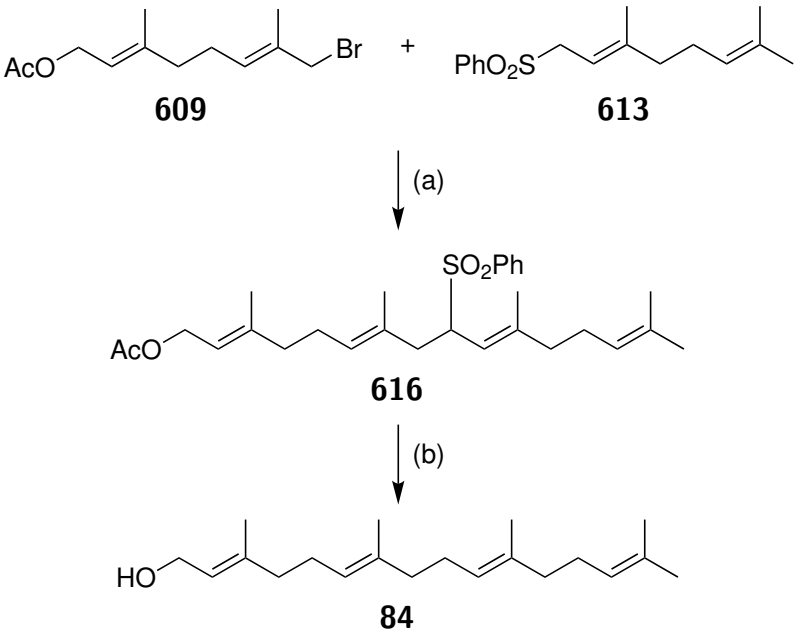
Our other coupling partner was allylic bromide **609**. As shown in Scheme 124, Geraniol was first acetylated in quantitative yield by acetic anhydride in pyridine. Catalytic selenium dioxide with *tert*-butyl hydroperoxide as a stoichiometric oxidant performed the allylic oxidation, giving desired alcohol **615** as the (*E*) diastereomer. A significant amount of an overoxidised side product was present; this could be suppressed with a lower catalytic loading of selenium dioxide and lesser excess of *tert*-butyl hydroperoxide. Alcohol **615** was subjected to Appel reaction again, with the same modifications as above to give alkyl bromide **609**. Column chromatography was required here, and the presence of a closely eluting impurity made the subsequent reaction troublesome. Phosphorus tribromide improved this sequence, with formation of the impurity being suppressed and alkyl bromide **609** was isolated.



Scheme 124: Our synthesis of alkyl bromide **609**. (a) Ac_2O, pyridine, rt, 98%. (b) SeO_2, TBHP, salicylic acid, CH_2Cl_2, 52%. (c) PBr_3, Et_2O, –15 °C→rt, 75%.

Coupling between sulfone **613** and alkyl bromide **609** was difficult, which was surprising due to the many reports of this strategy in the literature. Chen reported using sodium hydride in dimethylformamide,[119] a combination which has been reported to lead to runaway exotherm on scale.[120] We felt it wise to consider other solvents, but found that this reaction did not produce the desired sulfone **616** in any of the conditions screened. We finally had success with lithium bases, with reaction occurring using *n*-butyllithium as well as dimsyllithium and lithium diisopropylamide (LDA), prepared fresh by addition of *n*-butyllithium solution to a solution of dimethylsulfoxide or diisopropylamine, respectively. LDA gave the cleanest reaction product and highest

yield, but we still had problems with poor reproducibility until we began synthesising bromide **609** using phosphorus tribromide. Careful column chromatography is vital for reproducibility of this reaction: phosphorus tribromide gives a cleaner reaction with no removal of the triphenylphosphine oxide byproduct necessary, making purification far easier.



Scheme 125: Coupling of alkyl bromide **609** and sulfone **613** to produce alcohol **84**. (a) LDA, THF, –78 °C, 3 h, 96%. (b) *Table 29*.

Table 28: Attempted conditions for coupling alkyl bromide **609** and sulfone **613**.

Entry	Base	Solvent	T (°C)	**616**
1	NaH	THF	0	X
2	NaH	DMSO	0	X
3	*t*-BuOK	THF	0	X
4	*n*-BuLi	THF	–78	✓
5	LDA	THF	–78	✓
6	LiDMSO	THF	–78	✓

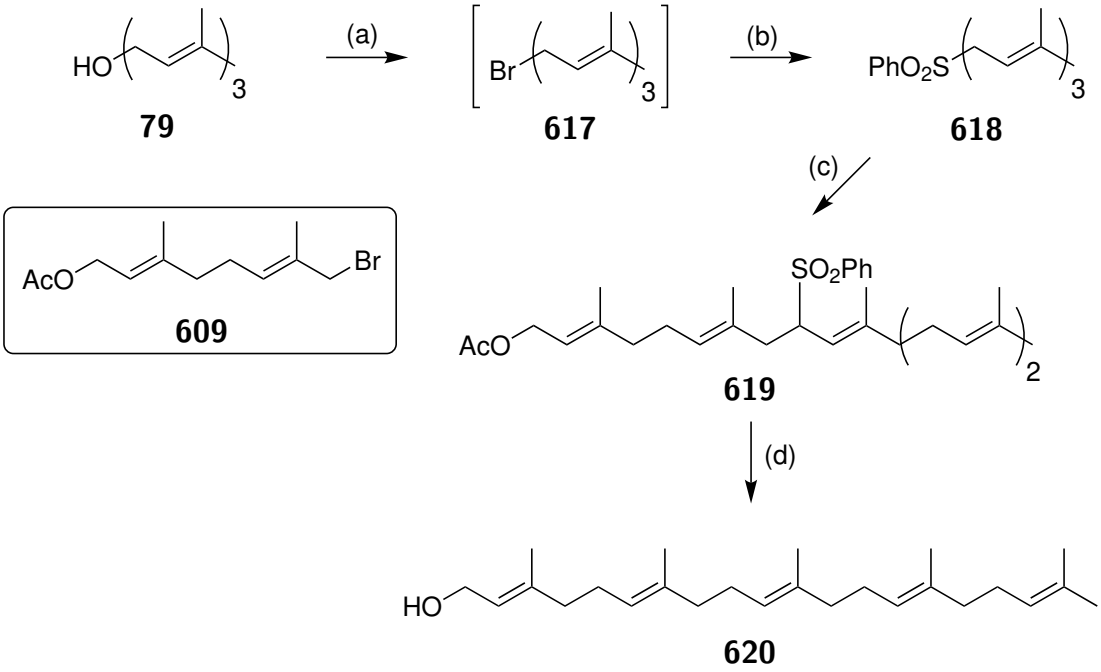
Desulfurisation provided another challenge. The widely reported conditions for performing this desulfurisation are L-Selectride with catalytic [1,3-bis(diphenylphosphino)propane] palladium(0),[119] but we had no access to this catalyst. Following saponification by sodium hydroxide in methanol, we attempted palladium catalysed desulfurisation with tetrakis (triphenylphosphine)palladium(0) using L-selectride as a hydride source but no reaction occurred.

Sulfone **616** was reacted with sodium naphthalenide, generated by addition of sodium metal to a solution of naphthalene in tetrahydrofuran. This gave a low yield of the desired geranylgeraniol (**84**), with some difficulty removing naphthalene from the isolated product **84**. Pleasingly, none of the isomerised product was seen. Sodium metal in a tetrahydrofuran/ethanol mixture gave far higher yields, again with no isomerised product. Sodium ethoxide is clearly produced as a result of the reaction: the acetate is cleaved *in situ.*

Table 29: Conditions for desulfurisation of sulfone **616**.

Entry	Conditions	Yield
1	$Pd(PPh_3)_4$, $LiBHEt_3$, THF, 0 °C→rt	n.r.
2	Na, naphthalene, THF, rt	20%
3	Na, EtOH, THF, rt	58%

With successful synthesis of geranylgeraniol (**84**) achieved, we performed the same sequence to produce geranylfarnesol (**620**), coupling alkyl bromide **609** instead with farnesyl phenyl sulfone (**618**; Scheme 126). Yields for these two processes were comparable.



Scheme 126: Synthesis of geranylfarnesol. (a) PBr_3, Et_2O. (b) $PhSO_2Na$, DMF, 68% over 2 steps. (c) LDA, THF, then **609**, 67%. (d) Na, EtOH, THF, 50%.

3.2.4 Pentacyclic compounds

We have identified a series of compounds (Figure 31) which differ from each other only in their oxidation state and stereochemistry. Atomarianone B (**9**) seems the likely outcome from an epoxide-mediated cyclisation, with the *trans-cis-trans* stereochemistry being delivered from a series of low energy chair-like transition states. We were interested in whether we could coax this reaction to deliver the other, unusual diastereomers. These other diastereomers probably arise naturally from being held in a particular conformation inside a cyclase enzyme, a feat far more difficult to achieve using a simple Lewis acid in solution.

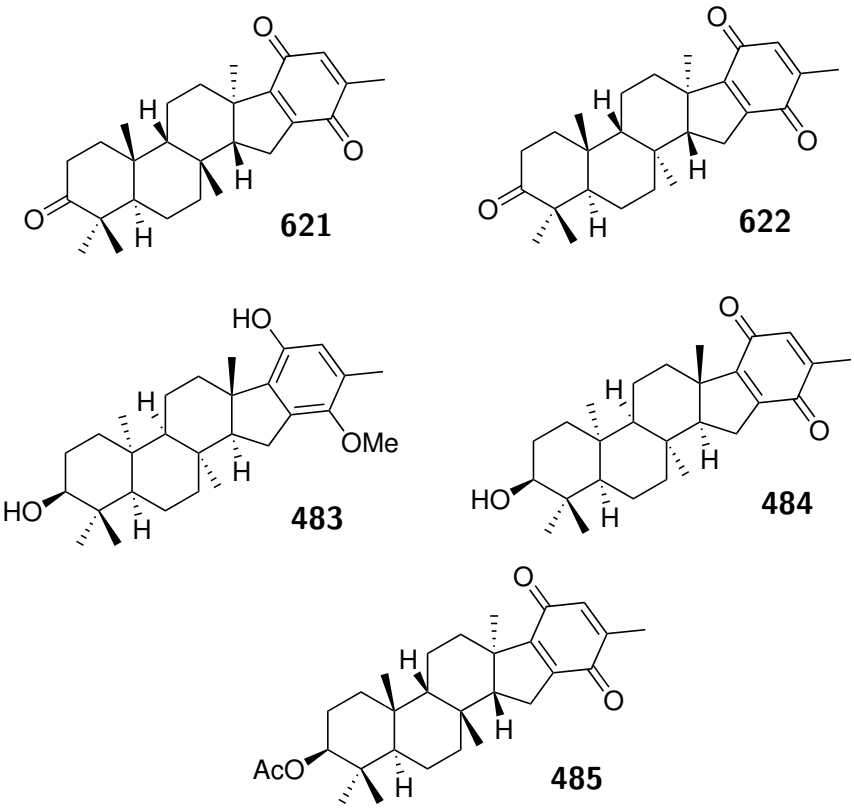
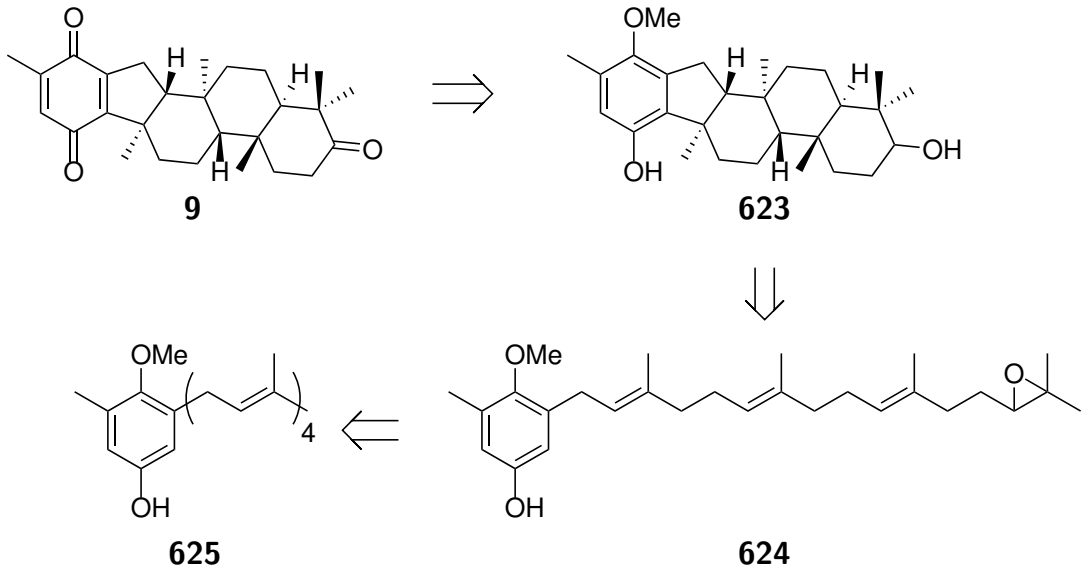


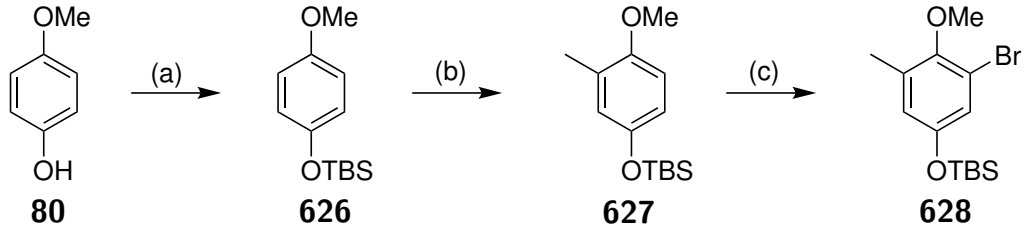
Figure 31: Natural products atomarianone A (**621**) and B (**622**), flabellinol (**483**), flabellinone (**484**) and zonaquinone acetate (**485**).

The synthesis of this carbon skeleton would take place using a similar strategy to the other compounds (Scheme 127). It was anticipated that the most likely diastereomer of the compound obtained by a polyene cyclisation would be atomarianone B (**9**), which would be obtained through a late stage oxidation of compound **623** from cyclisation of polyene **625** via epoxide **624**. This would again be formed by coupling between the aryl bromide and a boronate derived from geranylgeraniol.



Scheme 127: Retrosynthesis of atomarianone B (**9**).

The strategy towards these diastereomeric compounds began with synthesis of a suitable aryl bromide (Scheme 128). The *tert*-butyldimethylsilyl ether would block the positions *ortho* to the phenol and force methylation at the desired *meta* position. Treating 4-methoxyphenol (**80**) with *tert*-butyldimethylsilyl chloride with imidazole as a catalyst gave the protected phenol **626** in excellent yield. We could *ortho*-lithiate TBS ether **626** using *n*-butyllithium and quench with methyl iodide, giving a good yield of the toluene **627**, then bromination was performed using bromine in dichloromethane to give the desired aryl bromide **628** as a single regioisomer (as determined by 2D NMR), again in excellent yield and purity.



Scheme 128: Synthesis of aryl bromide coupling partner. (a) TBSCl, imidazole, CH_2Cl_2, 91%. (b) *n*-Buli, TMEDA, THF, 0 °C, 2 h, then MeI, 0 °C→rt, 18 h. 52%. (c) Br_2, CH_2Cl_2, rt, 85%.

Borylation of geranylgeraniol proceeded as with the shorter analogues, giving us a good yield of the desired geranylgeranyl pinacolborate (**629**; Scheme 129). We initially had problems with this route and attempted coupling via geranylgeranyl bromide mediated by *n*-butyllithium, but this was unsuccessful. Later attempts at borylation were reliable and high yielding, as per the previous work. Suzuki coupling under our standard conditions,

with tetrakis(triphenylphosphine)palladium(0) in hot toluene/water gave a good yield of the desired geranylgeranylarene **630**.

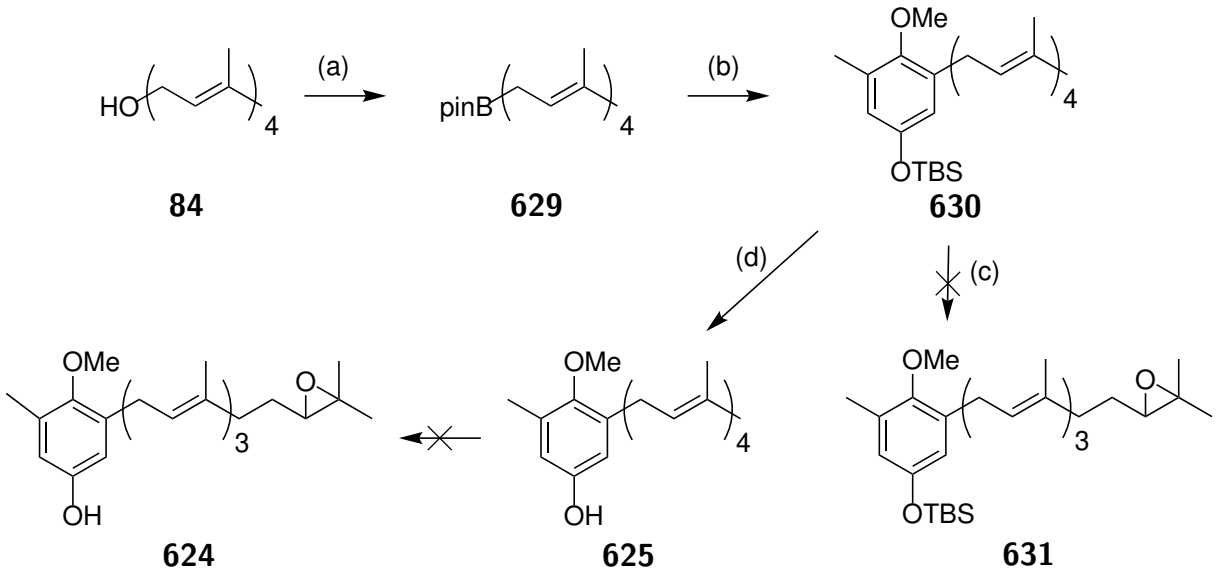
Since these natural products have oxygenation on the A ring, the most obvious strategy is to use an epoxide-mediated coupling. However, when we attempted epoxidation using *m*-CPBA, we saw only degradation of the starting material with none of the desired epoxide. Other epoxidation strategies include using *N*-bromosuccinimide and water, to generate the epoxide via the bromohydrin: despite long reaction times and forcing conditions, no reaction was seen. Likewise, treating polyene **630** with DMDO, produced *in situ* from a mixture of acetone, Oxone and potassium carbonate gave no reaction. We attempted bromocyclisation using BDSB, with the only identifiable compound being a trace of starting material.

Table 30: Attempted epoxidation of TBS-protected compound **630**.

Conditions	**631**	**630**
*m*CPBA, CH_2Cl_2, –20 °C	X	X
NBS, THF/H_2O, rt	X	✓
Oxone, $NaHCO_3$, acetone, CH_2Cl_2/H_2O	X	✓

Unfortunately, we were unable to produce the desired precursor **631** for this epoxide-mediated cyclisation. Direct acid-catalysed cyclisation would not be appropriate here, given that this family of natural products incorporates an oxygen atom at the A-ring. Cyclisation by BDSB in order to install a bromine atom, which we expect could be later converted to the alcohol, also failed. We may have more success in future with a different aromatic unit.

It seemed possible that the TBS ether was sensitive to our oxidation conditions and the powerful BDSB reagent. Cleavage of TBS ether **630** was performed with tetrabutylammonium fluoride, giving us the free phenol **625**. Unfortunately, we were still unable to cleanly effect epoxidation of deprotected polyene **625** to the corresponding epoxide to set up for cyclisation. A stepwise synthesis of polyene **625** by methods like those carried out by Andersen (Scheme 32)[8] or Overman (Scheme 30)[40] may be more appropriate in this case.



Scheme 129: Synthesis of polyene epoxide **624**. (a) **375**, B_2pin_2, MeOH/DMSO, 50 °C, 63%. (b) **628**, $Pd(PPh_3)_4$, NaOH, PhMe/H_2O, 100 °C, 50%. (c) Table 30; n.r. or decomp. (d) TBAF, THF, 0 °C, 25%.

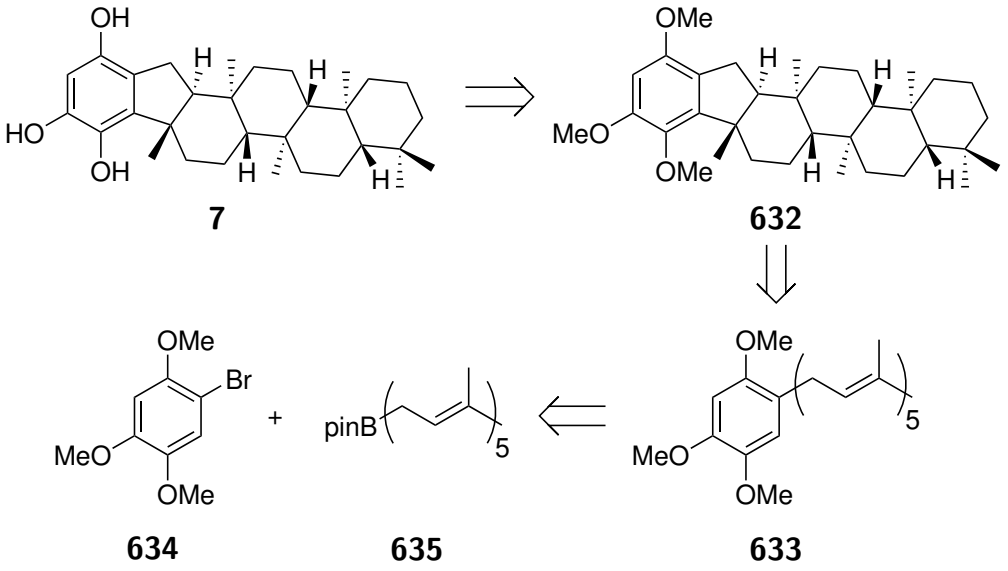
3.2.5 Disidein

Disidein contains one of the simplest aromatics that we have applied to our strategy. It is also the largest compound, comprising six fused rings and eight stereocentres. A successful cyclisation towards disidein would be the longest polyene cyclisation reported to date.

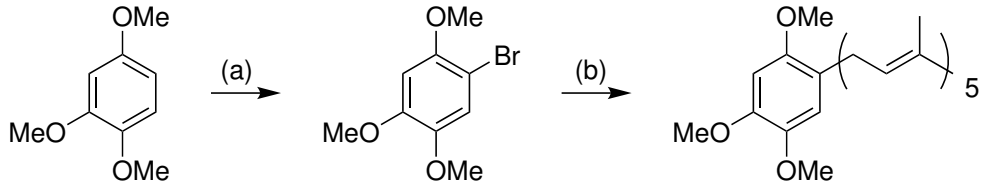
Our retrosynthetic plan remained as before: disidein would be obtained by cleavage of the methoxy ethers in compound **632**, which would in turn by produced by polyene cyclisation of compound **633**. This polyene would be obtained by Suzuki coupling between aryl bromide **634** and geranylfarnesyl pinacol boronate (**635**).

Geranylfarnesyl pinacol boronate was produced using the same palladium catalysed borylation that has been highly successful for the other unfunctionalised polyprenols. Aryl bromide **634** was produced as a single regioisomer by treating trimethoxybenzene (**395**) with bromine, delivering aryl bromide **634** as a single regioisomer in excellent yield and purity. Suzuki coupling was effected using our standard conditions to give polyene **633**.

Polyene **633** was a suitable precursor for cyclisation towards intermediate **632**. But under a number of conditions, again none of the desired fully cyclised compound was observed. In all cases, complex reaction mixtures were seen from which no distinct compound could be isolated. ^{1}H NMR analysis of the crude reaction mixture likewise shows no



Scheme 130: Retrosynthesis of disidein.



Scheme 131: Synthesis of aryl bromide **634**. (a) Br_2, CH_2Cl_2, 90%. (b) **635**, $Pd(PPh_3)_4$, NaOH, $PhMe/H_2O$, 100 °C, 37%.

useful compounds. In particular, we looked for a characteristic signal associated with the benzylic hydrogens: a doublet would indicate uncyclised material, while a singlet would indicate a tricyclised compound and a doublet of doublets would indicate that the benzylic hydrogens were locked in the desired cyclopentane system. None of these resonances were seen, however resonances characteristic of aromatic hydrogens were found, suggesting elimination as a prominent reaction pathway. BDSB similarly led to decomposition of polyene **633**.

Table 31: Conditions for attempted direct cyclisation of polyene **633**. All led to complex reaction mixtures with none of the desired compound **632** seen by analysis of the ^1H NMR spectra.

Lewis acid	Solvent	T (°C)
$BF_3{\cdot}OEt_2$	$MeNO_2$	rt
$AlCl_3$	$MeNO_2$	rt
TfOH	$MeNO_2$	rt
$Bi(OTf)_3$	$MeNO_2$	100

Unfortunately, synthesis of the larger terpenoid compounds by polyene cyclisation

remains an elusive goal.

3.3 Conclusion

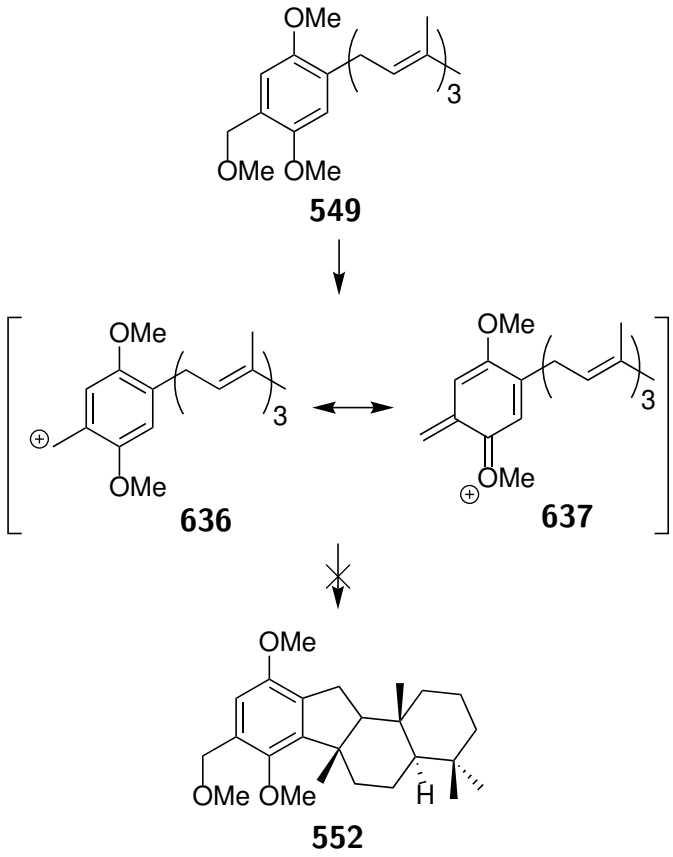
Most of the cyclisations attempted on longer polyene chains were unsuccessful. Several reactions in the cyclisation of farnesylarenes were successful: firstly, BDSB-mediated cyclisation of dasyscyphin B precursor **566**, a feat already accomplished in the literature. Direct acid-catalysed cyclisation was achieved in two cases: polyene **590** delivered the partially cyclised decalin **591**, but then polyene **600** gave the fully cyclised tetracyclic compound **600**. Both of these acid-catalysed cyclisations have, to our knowledge, no precedent in the literature.

The latter cyclisation was again influenced by a hyperconjugative effect that weakens the expected *trans*-selectivity in this cyclisation. In comparison to Andersen's cyclisation of alcohol **349** invoking an analogous carbocationic intermediate, a 1:1 mixture of the *trans* and *cis*-fused isomers **599a** and **599b** was obtained by using the polyene **600** instead.

The aromatics **548**, **549** and **550** contain functionalities incompatible with polyene cyclisation due to the formation of highly reactive *ortho*-quinone methide species such as **637**. Strategies that include such functional groups *ortho* to a phenyl ether or phenol should be avoided.

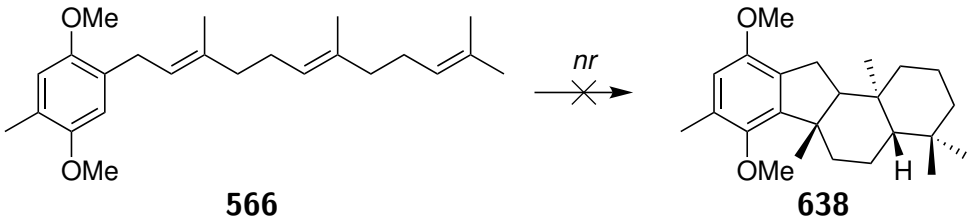
While polyene cyclisation has been shown to be useful for the construction of the taiwaniaquinoids, it is far less successful for their larger counterparts. Overman noted the failure of less oxygenated arenes to undergo the final Friedel-Crafts step, with a series of partially cyclised products being produced.[40] Full cyclisation was only achieved with the addition of a further allyl ether *para* to the nucleophilic carbon. It is possible that the compounds employed are similarly unsuitable: the two polyenes that were cyclised with direct acid catalysis contained oxygen atoms at both the positions *ortho* and *para* to the nucleophilic carbon and these may have a role to play in not only activating the aromatic for nucleophilic attack, but also stabilising against elimination of the aryl unit, which was a prominent degradation pathway in the failed experiments.

NMR experiments may shed some light on what occurs in these failed reactions.



Scheme 132: Cyclisation of polyene **549** leads to formation of *ortho*-quinone methide **637** which precludes cyclisation to compound **552**.

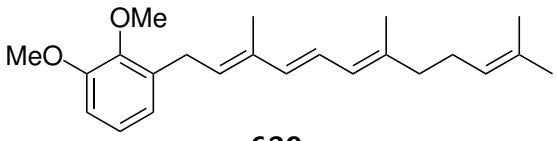
Attempted monitoring of the cyclisation of polyene **566** to **638** in d_3-acetonitrile revealed that no reaction occurred (Scheme 133). d_3-Acetonitrile was chosen due to its similar properties to nitromethane, the solvent used in successful cyclisations, but d_3-nitromethane is prohibitively expensive. Attempted cyclisation in other common solvents including *d*-chloroform may provide more insights.



Scheme 133: Attempted NMR monitoring of cyclisation of **566**. Conditions: $BF_3{\cdot}OEt_2$, CD_3CN, rt, 18 h, nr.

Dasyscyphin B (**6**) was chosen as a target due to the *cis* fusion at the BC ring junction. However, attempts to cyclise the polyene precursor **566** led to partial cyclisation with traces of the *trans*-fused compound. An approach using a chlorine substituent to attempt to coax the intermediate into a boat-like conformation fell short when we were unable

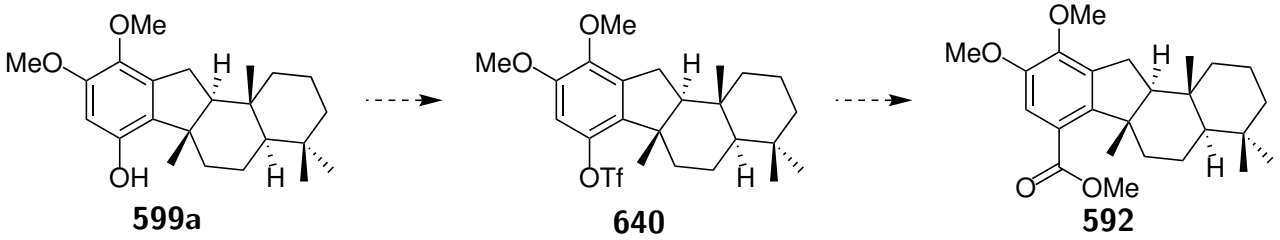
to couple chlorofarnesol with aryl bromide **565**. We could take a page from Qin's book here, placing an alkene at the C7–C8 position of the polyene to give triene **639** but we suspect that this would be a difficult compound to synthesise and further, issues would arise during polyene cyclisation, least of all suspected instability of the triene moiety.



639

Figure 32: Compound **639**, with incorporation of an alkene at the C7–C8 position.

Our work towards the natural product pelorol (**473**) is clearly unfinished. This synthesis could be completed fairly rapidly: triflation of phenol **599a** would deliver triflate **640** which can engage in metal-catalysed carboxylation, with esterification delivering dimethylpelorol (**592**). This procedure could be projected to produce pelorol in the same number of steps as Andersen at a lower overall yield, however we have clear avenues for improvement. In particular, avoiding the use of a silyl protecting group in the sequence producing **600** from **601** would remove two steps from this synthesis. Clearly, the polyene cyclisation of **600** needs to be explored more thoroughly.

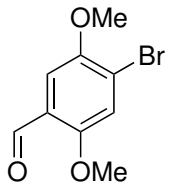


Scheme 134: *trans*-Fused isomer **599a** could carboxymethylated via triflate **640** to produce dimethylpelorol (**592**).

We also should continue to investigate cyclisation towards the hexacyclic compound disidein (**7**). Substitution at the aromatic ring has a profound effect on the success or failure of these reactions and a more activated aromatic ring may deliver a positive result. The possibility of producing this compound in such an efficient manner is intriguing.

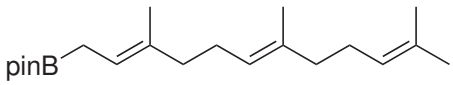
3.4 Experimental

4-Bromo-2,5-dimethoxybenzaldehyde (544) [121]



2,5-Dimethoxybenzaldehyde (1.2 g, 7.0 mmol) was dissolved in dichloromethane (35 mL) and bromine (0.40 mL, 7.8 mmol) was added at 0 °C. The reaction mixture was stirred for 18 h, warming to room temperature, then aqueous saturated sodium sulfite solution (30 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to give *title compound* **544** (1.2 g, 5.3 mmol, 76%) as a yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.39 (1 H, *s*), 7.33 (1 H, *s*), 7.24 (1 H, *s*), 3.90 (1 H, *s*), 3.89 (1 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.9, 156.3, 150.6, 124.3, 120.4, 117.8, 109.8, 56.9, 56.5 ppm. MS (ESI) *m/z* (%): 267/269 $[M+Na]^+$ (100).

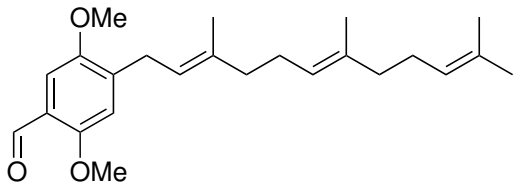
Farnesyl pinacol boronate (541)



Farnesol (2.7 g, 12 mmol), bis(pinacolato)diboron (5.8 g, 24 mmol), *p*-toluenesulfonic acid (0.12 g, 0.68 mmol) and catalyst **375** (0.32 g, 0.56 mmol) were dissolved in dimethylsulfoxide (24 mL) and methanol (24 mL) and heated to 50 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with water (30 mL) and extracted with ether (2 $\times$ 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 2% ether in hexanes to give farnesyl pinacol boronate (**541**; 3.5 g, 11 mmol, 88%) as a colourless to yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.28–5.21 (1 H, *m*), 5.16–5.05 (2 H, *m*), 2.11–1.93 (8 H, *m*), 1.67 (6 H, *s*), 1.61–1.55 (6 H, *s*), 1.23 (12 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.3, 134.9, 131.3, 124.58,

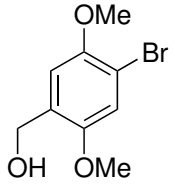
124.57, 124.54, 83.2, 39.91, 39.88, 26.9, 26.8, 25.8, 24.9, 17.8, 16.11, 16.06 ppm. ^{11}B NMR (160 MHz, $CDCl_3$): δ = 33.5 ppm. MS (APCI): *m/z* (%): 205 $[M\text{-}Bpin]^+$ (40), 333 $[M+H]^+$ (100).

2,5-Dimethoxy-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzaldehyde) (548)



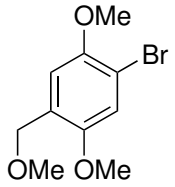
Aryl bromide **544** (0.13 g, 0.53 mmol), farnesyl pinacol boronate (0.20 g, 0.60 mmol), tetrakis(triphenylphosphine)palladium(0) (0.035 g, 0.030 mmol) and powdered sodium hydroxide (0.30 g, 6.0 mmol) were dissolved in toluene (8 mL) and water (2 mL). The reaction mixture was heated to 100 °C and stirred vigorously for 18 h, then cooled to room temperature. The reaction mixture was diluted with ether (30 mL) and water (30 mL), separated and the aqueous layer was extracted with ether (30 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with 3% ethyl acetate in hexanes to give *title compound* **548** (0.16 g, 0.43 mmol, 81%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.32 (1 H, *s*), 7.19 (1 H, *s*), 6.74 (1 H, *s*), 5.25–5.19 (1 H, *m*), 5.10–4.97 (2 H, *m*), 3.79 (3 H, *s*), 3.75 (3 H, *s*), 3.29 (2 H, *d*, *J* = 7.3 Hz), 2.10–1.85 (8 H, *m*), 1.63 (3 H, *s*), 1.60 (3 H, *s*), 1.51 (6 H, *m*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.4, 157.0, 151.7, 140.0, 137.8, 135.3, 131.4, 124.4, 124.1, 122.9, 121.0, 113.5, 108.1, 56.2, 56.0, 39.9, 39.8, 29.2, 26.9, 26.8, 25.8, 17.8, 16.3, 16.1 ppm. HRMS (APCI): calcd. for $C_{24}H_{34}O_3^+$ 371.25807; found 371.26080. IR (neat): $\tilde{\nu}_{max}$ = 2965, 2932, 2863, 1715, 1610, 1407, 1208, 1034, 876 $cm^{-}1$.

(4-Bromo-2,5-dimethoxyphenyl)methanol (545) [122]



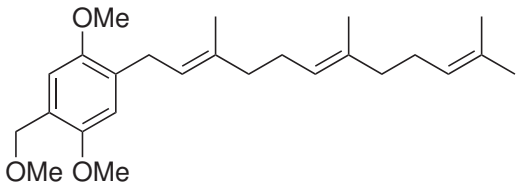
Aldehyde **544** (1.0 g, 4.0 mmol) was dissolved in methanol (40 mL) and cooled to 0 °C. Sodium borohydride (0.16 g, 4.0 mmol) was added and the reaction was stirred for 2 h at 0 °C, then hydrochloric acid (1 M, 5.0 mL) was added and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and washed with saturated aqueous sodium hydrogen carbonate solution (50 mL) then dried over magnesium sulfate, filtered and the solvent was remove *in vacuo* to give *title compound* **545** (0.98 mg, 4.0 mmol, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): 7.06 (1 H, *s*), 6.93 (1 H, *s*), 3.86 (3 H, *s*), 3.81 (3 H, *s*), 1.57 (2 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 151.6, 150.3, 129.4, 115.9, 113.0, 110.5, 61.6, 47.1, 56.2 ppm. MS (APCI): *m/z* (%): 229/231 $[M\text{-}OH]^+$ (100), 245/247 $[M\text{-}H]^-$.

1-Bromo-2,5-dimethoxy-4-(methoxymethyl)benzene (546)



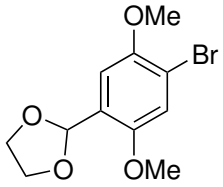
Alcohol **545** (0.98 g, 5.0 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled to 0 °C. Sodium hydride (65% dispersion in mineral oil; 0.20 g, 5.0 mmol) was added and the reaction mixture was stirred for 10 min before adding methyl iodide (0.31 mL, 5.0 mmol) dropwise at 0 °C. The reaction mixture was stirred for 18 h, warming to room temperature. Saturated aqueous ammonium chloride solution (30 mL) was added, then the reaction mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography, eluting with 2% ether in hexanes to give *title compound* **546** (0.67 g, 2.6 mmol, 52%) as yellow needles. m.p. 60.5–64.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.04 (1 H, *s*), 6.99 (1 H, *s*), 4.44 (2 H, *s*), 3.86 (3 H, *s*), 3.78 (3 H, *s*), 3.43 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 151.3, 150.2, 127.1, 115.9, 112.8, 110.3, 69.1, 58.6, 57.0, 56.3 ppm. MS (APCI) *m/z* (%): 229/231 $[M\text{-}OMe]^+$ (100), 260/262 $[M+H]^+$ (10).

1,4-Dimethoxy-2-(methoxymethyl)-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (549)



Aryl bromide **546** (0.67 g, 2.6 mmol), farnesyl phenyl boronate (**541**; 0.86 g, 2.6 mmol), powdered sodium hydroxide (1.0 g, 26 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.090 g, 0.078 mmol) were dissolved in toluene (21 mL) and water (5 mL). The reaction mixture was degassed with argon for 5 min, then stirred at 100 °C for 18 h. The reaction mixture was then cooled to room temperature, water (20 mL) was added and the reaction mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*, then the residue was purified by column chromatography over silica gel, eluting with 15% dichloromethane in hexanes to give *title compound* **549** (0.47 g, 1.2 mmol, 47%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.88 (1 H, *s*), 6.70 (1 H, *s*), 5.35–5.25 (1 H, *m*), 5.20–5.05 (2 H, *m*), 4.46 (2 H, *s*), 3.80 (3 H, *s*), 3.78 (3 H, *s*), 3.42 (3 H, *s*), 2.15–2.00 (3 H, *s*), 1.71 (3 H, *s*), 1.67 (3 H, *s*), 1.59 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.3, 151.1, 136.4, 135.0, 131.3, 130.2, 124.4, 124.3, 124.2, 122.4, 112.6, 111.9, 69.4, 58.3, 56.18, 56.19, 39.8, 39.7, 28.3, 26.8, 26.6, 25.7, 17.7, 16.2, 15.9 ppm. MS (APPI): *m/z* (%): 355 $[M\text{-}OMe]^+$ (100), 386 $[M]^+$ (77). IR (neat): $\tilde{\nu}_{max}$ = 2925, 2854, 1499, 1462, 1402, 1208, 1093, 1044, 866 $cm^{-}1$.

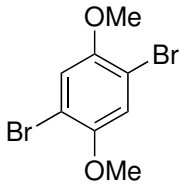
2-(4-Bromo-2,5-dimethoxyphenyl)-1,3-dioxolane (547)



Aldehyde **544** (0.98 g, 4.0 mmol) and ethylene glycol (1.0 mL, 20 mmol) were dissolved in toluene (20 mL). *p*-Toluenesulfonic acid (0.034 g, 0.20 mmol) was added and the reaction mixture was heated at reflux under Dean-Stark conditions for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give *title compound* **547** (0.72 g, mmol, 62%) as

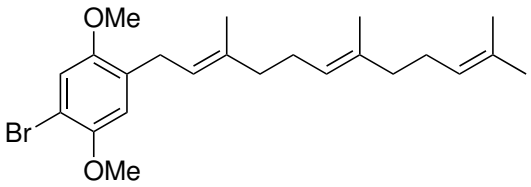
a colourless oil which reverted to **544** in air. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.14 (1 H, *s*), 7.11 (1 H, *s*), 6.06 (1 H, *s*), 4.18–4.00 (4 H, *m*), 3.87 (3 H, *s*), 3.82 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.2, 150.3, 126.0, 116.7, 112.7, 110.9, 98.9, 65.5, 63.4, 57.0, 56.6 ppm. MS (APCI): *m/z* (%): 289/291 $[M+H]^+$ (100).

1,4-Dibromo-2,5-dimethoxybenzene (560) [123]



1,4-Dimethoxybenzene (5.0 g, 36 mmol) was dissolved in dichloromethane (75 mL) and cooled to 0 °C. A solution of bromine (5.0 mL, 97 mmol) in dichloromethane (25 mL) was added dropwise over 20 min, then the reaction was stirred at 0 °C for 3 h, then warmed to room temperature and stirred 18 h. Saturated aqueous sodium sulfite (30 mL) was added and the reaction was extracted with dichloromethane (3 $\times$ 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo* to give *title compound* **560** (10 g, 35 mmol, 95%) as a white solid. m.p. 143.5–146.2 °C (lit. 144.0-144.5 °C) [123] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (2 H, *s*), 3.83 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.5, 117.2, 110.5, 57.1 ppm. MS (EI): *m/z* (%): 294/296/298 $[M]^+$ (100), 279/281/283 $[M\text{-}CH_3]^+$ (70), 185/187 $[M\text{-}C_2H_6Br]^+$ (50).

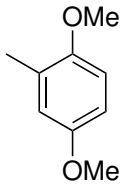
1-Bromo-2,5-dimethoxy-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (561)



Farnesyl pinacol boronate (**541**; 2.9 g, 8.7 mmol), aryl bromide **560** (2.9 g, 10 mmol), powdered sodium hydroxide (2.0 g, 50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.34 g, 0.30 mmol) were dissolved in tetrahydrofuran (50 mL) and the solution was sparged with argon for 20 min. The reaction was heated at reflux overnight, then cooled

to room temperature, diluted with water (50 mL) and extracted with ether (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 1% ether in hexanes to give *title compound* **561** (3.1 g, 7.4 mmol, 85%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (1 H, *s*), 6.75 (1 H, *s*), 5.30–5.23 (1 H, *m*), 5.16–5.05 (2 H, *m*), 3.82 (3 H, *s*), 3.78 (3 H, *s*), 3.28 (2 H, *d*, *J* = 7.2 Hz), 2.16–1.92 (8 H, *m*), 1.68 (3 H, *s*), 1.59 (3 H, *s*), 0.87 (3 H, *s*), 0.86 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 150.1, 137.1, 135.3, 131.5, 130.6, 124.5, 121.8, 118.4, 115.9, 114.2, 108.4, 57.1, 56.3, 41.5, 39.9, 29.2, 26.9, 25.8, 22.8, 17.8, 16.1, 11.6 ppm. HRMS (APCI): calcd. for $C_{23}H_{34}BrO_2^+$ 421.17367; found 421.17381. IR (neat): $\tilde{\nu}_{max}$ = 2964, 2931, 2840, 1491, 1435, 1209, 1022, 851, 730 cm^{-}1.

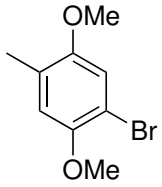
2,5-Dimethoxytoluene (564) [124]



p-Toluquinone was first purified by silica plug, eluting with dichloromethane to give a yellow powder.

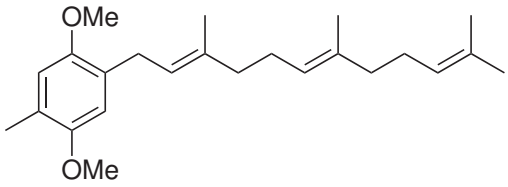
p-Toluquinone (2.5 g, 20 mmol) was dissolved in tetrahydrofuran (100 mL) and shaken with a solution of sodium dithionite (9.4 g, 54 mmol) in water (100 mL) until the organic layer was colourless. The organic layer was separated and dried over anhydrous magnesium sulfate and filtered. Potassium carbonate (8.3 g, 60 mmol) and methyl iodide (3.7 mL, 60 mmol) were added and the reaction was stirred overnight. Water (100 mL) was added and the reaction mixture was stirred vigorously for 5 min, then the layers were separated. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with dichloromethane to give *title compound* **564** (2.0 g, 13 mmol, 66%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.78-6.74 (2 H, *m*), 6.70 (1 H, *dd*, *J* = 8.9, 2.9 Hz), 3.79 (3 H, *s*), 3.77 (3 H, *s*), 2.23 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.5, 152.2, 127.9, 117.2, 111.0, 110.8, 56.0, 55.7, 16.5 ppm. MS (APCI): *m/z* (%): 153 $[M+H]^+$ (100), 154 $[M+H]^+$ (9).

1-Bromo-2,5-dimethoxy-4-methylbenzene (565) [125]



Aromatic **564** (1.1 g, 7.0 mmol) was dissolved in dichloromethane (35 mL) and bromine (0.40 mL, 7.8 mmol) was added. The reaction was stirred 18 h, then saturated aqueous sodium sulfite solution (50 mL) was added. The organic layer was separated and dried over anhydrous magnesium sulfate. The residue was recrystallised from ethanol to give *title compound* **565** (1.2 g, 5.3 mmol, 76%) as a white solid. m.p. 89.9–95.2 °C (lit 92–94 °C).[125] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 (1 H, *s*), 6.74 (1 H, *s*), 3.84 (3 H, *s*), 3.78 (3 H, *s*), 2.18 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.3, 149.9, 127.0, 115.6, 115.4, 108.2, 57.1, 56.2, 16.4 ppm. MS (APCI) *m/z* (%): 230 $[M+H]^+$.

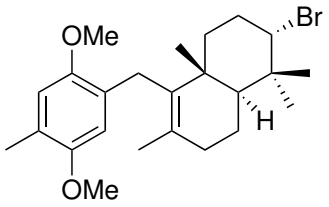
1,4-Dimethoxy-2-methyl-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (566) [126]



Aryl bromide **565** (0.42 g, 1.8 mmol), farnesyl pinacol boronate (**541**; 0.56 g, 1.7 mmol), powdered sodium hydroxide (720 mg, 18 mmol) and tetrakis(triphenylphosphine) palladium(0) (0.10 g, 0.087 mmol) were dissolved in toluene (16 mL) and water (4 mL). The reaction mixture was sparged with argon for 5 min, then stirred at 100 °C for 18 h. The reaction mixture was then cooled to room temperature, water (20 mL) was added and the reaction mixture was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*, then the residue was purified by column chromatography over silica gel, eluting with 20% dichloromethane in hexanes to give *title compound* **566** (0.45 g, 1.3 mmol, 72%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.69–6.66 (2 H, *m*), 5.33 (1 H, *t*, *J* = 7.5 Hz), 5.14 (1 H, *t*, *J* = 7.5 Hz), 5.11 (1 H, *tt*, *J* = 6.8 Hz, 1.3 Hz), 3.78 (3 H, *s*), 3.78 (3 H, *s*), 3.31 (2 H, *d*, *J* = 7.2 Hz), 2.21 (3 H, *s*), 2.15–2.10 (2 H, *m*), 2.10–2.02 (5 H, *m*), 2.02–1.96 (1 H, *m*), 1.73

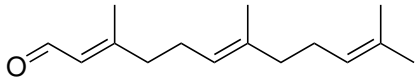
(3 H, *s*), 1.69 (3 H, *s*), 1.60 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.8, 151.2, 136.2, 135.1, 131.4, 128.2, 125.2, 124.5, 124.4, 122.9, 114.2, 112.6, 55.4, 55.2, 39.9, 32.2, 28.3, 26.9, 25.9, 25.8, 17.8, 16.3, 16.2, 16.1 ppm. HRMS (ESI): calcd. for $C_{24}H_{36}O_2Na^+$ 379.26075; found 379.26130. IR (neat): $\tilde{\nu}_{max}$ = 2925, 2852, 1504, 1464, 1208, 1046, 857, 447 cm^{-1}.

3-Bromo-8-(2,5-dimethoxy-4-methylbenzyl)-4,4,7,8a-tetramethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene (567)



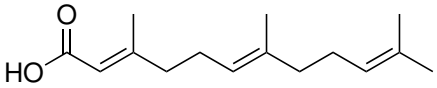
Polyene **566** (0.10 g, 0.28 mmol) was dissolved in nitromethane (25 mL) and cooled to –20 °C. A solution of bromodiethylsulfonium bromopentachloroantimonate (0.17 g, 0.31 mmol) in nitromethane (1 mL) was added at once and stirred 2 min, then water (0.05 mL, 2.8 mmol) was added and the reaction mixture was stirred for 1 h, warming to room temperature. Saturated aqueous sodium bicarbonate solution (10 mL) and saturated aqueous sodium sulfite solution (10 mL) were added and the reaction mixture was stirred vigorously for 18 h. Saturated aqueous sodium potassium tartrate solution (20 mL) was added and the reaction mixture was extracted with ethyl acetate (3 $\times$ 30 mL). Treatment by column chromatography over silica gel, eluting with 30% dichloromethane in hexanes gave a complex mixture of compounds containing *title compound* **572** (0.011 g, 0.025 mmol, 9%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.64 (1 H, *s*), 6.56 (1 H, *s*), 3.90 (1 H, *dd*, *J* = 12.7, 4.3 Hz), 3.78 (3 H, *s*), 3.77 (3 H, *s*), 3.71 (3 H, *s*), 3.33 (1 H, *d*, *J* = 17.5 Hz), 3.20 (1 H, *d*, *J* = 17.5 Hz), 2.95 (1 H, *dd*, *J* = 14.4, 5.9 Hz), 2.32 (1 H, *dd*, *J* = 14.1, 5.9 Hz), 2.19 (3 H, *s*), 1.95 (1 H, *dd*, *J* = 13.7, 4.0 Hz), 1.64–1.56 (2 H, *m*) 1.51 (3 H, *s*), 1.32–1.28 (1 H, *m*), 1.19–1.14 (1 H, *m*), 1.10 (3 H, *s*), 1.05 (3 H, *s*), 0.97 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.5, 150.9, 136.7, 129.2, 127.1, 124.1, 113.3, 112.3, 69.8, 56.5, 56.0, 53.1, 39.8, 39.0, 37.5, 33.8, 31.2, 30.6, 26.6, 20.7, 20.3, 20.2, 18.4, 16.0 ppm. HRMS (ESI): calcd. for $C_{24}H_{35}BrO_2Na^+$ 434.18149; found 434.18183.

Farnesal (583)



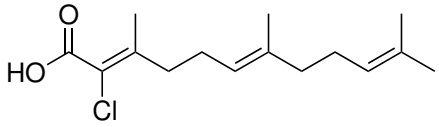
Farnesol (2.2 g, 10 mmol) was dissolved in *n*-hexane (50 mL) and activated manganese dioxide (8.7 g, 100 mmol) was added. The reaction mixture was stirred vigorously at room temperature for 18 h, then filtered over Celite, eluting with dichloromethane (50 mL). The solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give farnesal (**583**; 2.1 g, 9.5 mmol, 95%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.98 (1 H, *d*, *J* = 8.2 Hz), 5.88 (1 H, *d*, *J* = 8.0 Hz), 5.14–5.03 (2 H, *m*), 2.09–1.94 (8 H, *m*), 1.68 (3 H, *s*), 1.67 (3 H, *s*), 1.59 (6 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.4, 163.9, 136.7, 131.6, 127.6, 124.2, 122.6, 40.7, 39.7, 32.1, 26.7, 25.8, 23.4, 17.7, 16.1 ppm. MS (APCI): *m/z* (%): 221 $[M+H]^+$ (100).

Farnesoic acid (582)



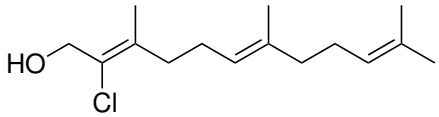
Farnesal (2.6 g, 12 mmol) was dissolved in acetone (50 mL) and 2-methyl-2-butene (5.0 mL, 47 mmol), then a solution of sodium dihydrogen phosphate (2.8 g, 23 mmol) and sodium chlorite (2.1 mg, 23 mmol) in water (20 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 18 h, warming to room temperature, then the acetone and 2-methyl-2-butene were removed *in vacuo*. Hydrochloric acid (1 M, 30 mL) was added and the reaction mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give farnesoic acid (1.7 g, 7.2 mmol, 60%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.69 (1 H, *s*), 5.18–5.04 (2 H, *m*), 2.22–2.15 (8 H, *m*), 1.71–1.66 (6 H, *m*), 1.62–1.59 (6 H, *m*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 163.1, 136.4, 131.6, 124.3, 122.8, 115.4, 41.3, 39.8, 26.8, 26.1, 25.8, 19.3, 17.8, 16.2 ppm. MS (ESI): *m/z* (%): 235 $[M-H]^-$ (100).

Chlorofarnesoic acid (581)



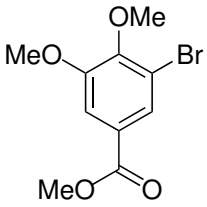
Farnesoic acid (**582**; 2.3 g, 10 mmol) was dissolved in chloroform (50 mL) and *N*-chlorosuccinimide (1.3 g, 10 mmol) was added. The reaction mixture was heated at reflux for 18 h, then the reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **581** (1.7 g, 6.3 mmol, 63%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.70 (1 H, *s*), 5.05–5.00 (1 H, *m*), 4.93–4.89 (1 H, *m*), 2.18 (3 H, *s*), 2.16–1.85 (8 H, *m*), 1.81 (3 H, *s*), 1.62 (3 H, *s*), 1.43 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 162.7, 130.6, 129.6, 126.5, 124.1, 114.3, 41.2, 36.8, 34.9, 27.1, 26.0, 19.3, 17.2, 14.3 ppm. MS (ESI): *m/z* (%): 269 $[M-H]^-$ (100), 270 $[M-H]^-$ (20), 271 $[M-H]^-$ (35), 272 $[M-H]^-$ (5).

Chlorofarnesol (580)



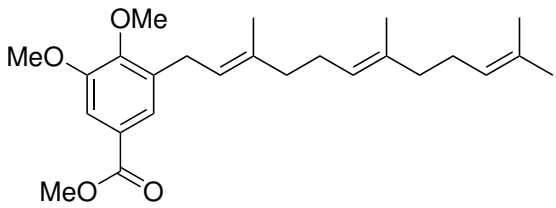
Acid **581** (1.4 g, 5.2 mmol) was dissolved in tetrahydrofuran (50 mL) and lithium aluminium hydride (0.59 g, 16 mmol) was added slowly at 0 °C. The reaction mixture was then heated at reflux for 18 h, then cooled to room temperature and aqueous sodium hydroxide solution (10%, 50 mL) was added. The layers were separated and the aqueous layer was extracted with ether (50 mL), then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel eluting with 10% ethyl acetate in hexanes to give *title compound* **580** (0.93 g, 3.6 mmol, 69%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.43–5.38 (1 H, *m*), 5.18–5.07 (1 H, *m*), 4.14 (2 H, *d*, *J* = 6.8 Hz), 2.25–1.84 (11 H, *m*), 1.67 (6 H, *s*), 1.59 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6, 144.5, 134.9, 124.9, 124.1, 114.3, 66.4, 41.2, 36.8, 35.0, 29.9, 26.1, 19.3, 17.2, 16.1 ppm. MS (ESI): *m/z* (%): 279 $[M+Na]^+$ (100), 281 $[M+Na]^+$ (33).

Methyl 3-bromo-4,5-dimethoxybenzoate (589) [127]



Methyl 3,4-dimethoxybenzoate (6.8 g, 35 mmol) was dissolved in methanol (100 mL) and bromine (1.8 mL, 35 mmol) was added. The reaction mixture was stirred for 3 h, then poured onto ice (300 mL). The precipitate was collected by filtration and dried *in vacuo* to give *title compound* **589** (3.3 g, 12 mmol, 34%) as an off-white powder. m.p. 74.2–79.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (1 H, *s*), 7.08 (1 H, *s*), 3.90 (3 H, *s*), 3.89 (3 H, *s*), 3.88 (3 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 152.0, 147.8, 122.9, 117.0, 114.2, 114.0, 56.3, 56.2, 52.2 ppm. MS (APCI): *m/z* (%): 275/277 $[M+H]^+$ (100).

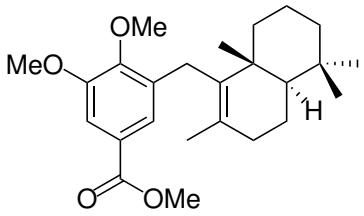
Methyl 3,4-dimethoxy-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzoate (590)



Aryl bromide **589** (1.1 g, 4.0 mmol), farnesyl pinacolboronate (1.3 g, 4.0 mmol), powdered sodium hydroxide (1.6 g, 40 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.23 g, 0.20 mmol) were dissolved in toluene (40 mL) and water (10 mL) and the reaction mixture was heated to 100 °C. The reaction mixture was stirred at 100 °C for 18 h, then cooled to room temperature and diluted with water (20 mL). The reaction mixture was extracted with ether (2 $\times$ 30 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 30% dichloromethane in hexanes to give *title compound* **590** (0.55 g, 1.4 mmol, 35%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (1 H, *s*), 6.75 (1 H, *s*), 5.33–5.26 (1 H, *m*), 5.20–5.05 (2 H, *m*), 3.89 (6 H, *s*), 3.87 (3 H, *s*), 3.70 (2 H, *d*, *J* = 6.9 Hz), 2.20–1.92 (8 H, *m*), 1.72 (3 H, *s*), 1.67 (3 H, *s*), 1.58 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 152.0, 146.6, 138.3, 136.5, 135.2, 131.4, 124.5, 124.4, 124.2, 123.3, 121.0, 113.7, 56.2,

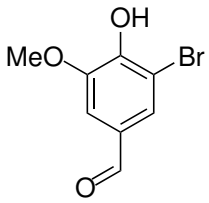
55.9, 51.9, 39.9, 32.5, 26.9, 26.8, 26.7, 25.8, 17.8, 16.5, 16.1 ppm. HRMS (ESI): calcd. for $C_{25}H_{36}O_4Na^+$ 423.25058; found 423.25062. IR (neat): $\tilde{\nu}_{max}$ = 2914, 2849, 1715, 1514, 1433, 1264, 1206, 1146, 1003, 776 cm^{-1}

Methyl 3,4-dimethoxy-5-((2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)benzoate (591)



Polyene **590** (0.050 g, 0.13 mmol) was dissolved in nitromethane (1 mL) and boron trifluoride etherate (1 drop) was added. The reaction mixture was stirred for 18 h at room temperature, then poured onto saturated aqueous sodium bicarbonate solution (20 mL). The mixture was extracted with ether (2 × 20 mL), then the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was treated by column chromatography over silica gel, eluting with 50% dichloromethane in hexanes to give a complex reaction mixture which contained *title compound* **591** (0.0065 g, 0.016 mmol, 13%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (1 H, *s*), 6.91 (1 H, *s*), 3.93 (3 H, *s*), 3.92 (3 H, *s*), 3.85 (3 H, *s*), 3.50 (1 H, *d*, *J* = 16.1 Hz), 2.93 (1 H, *d*, *J* = 16.1 Hz), 2.10–2.03 (2 H, *m*), 1.97–1.89 (1 H, *m*), 1.68–1.56 (3 H, *m*), 1.50–1.37 (4 H, *m*), 1.25 (3 H, *s*), 0.99 (3 H, *s*), 0.98 (3 H, *s*) 0.89 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 151.1, 146.3, 136.02, 135.99, 133.2, 123.2, 113.5, 113.2, 56.1, 56.0, 51.9, 45.6, 45.2, 42.1, 39.9, 38.1, 28.2, 27.0, 26.6, 26.5, 22.7, 21.6, 21.3, 20.1 ppm. HRMS (ESI): calcd. for $C_{25}H_{36}O_4Na^+$ 423.25058; found 423.25067.

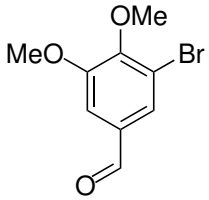
5-Bromovanillin (603) [128]



Vanillin (6.1 g, 40 mmol) was dissolved in acetonitrile (200 mL) and dibromodimethyl hydantoin (5.7 g, 20 mmol) was added. The reaction mixture was stirred for 18 h, then

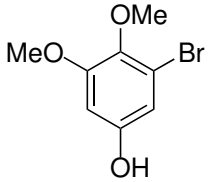
diluted with ether (50 mL) and washed with water (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give *title compound* **603** (4.3 g, 18 mmol, 45%) as a white powder. m.p. 155.5–162.3 °C (lit. 160–162 °C).[128] ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.77 (1 H, *s*), 7.11 (1 H, *d*, *J* = 1.7 Hz), 7.41 (1 H, *d*, *J* = 1.7 Hz), 3.91 (3 H, *s*) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 190.3, 149.8, 148.6, 128.9, 128.6, 109.6, 109.2, 56.3 ppm. MS (ESI): *m/z* (%): 229/231 $[M\text{-}H]^-$ (100).

5-Bromoveratraldehyde (604) [129]



5-Bromovanillin (2.4 g, 10 mmol), potassium carbonate (1.4 g, 10 mmol) and methyl iodide (0.62 mL, 10 mmol) were dissolved in dimethylformamide (50 mL). The reaction mixture was stirred for 48 h, then poured onto ice water (300 mL). The precipitate was collected by filtration to give *title compound* **604** (1.8 g, 7.3 mmol, 73%) as a white powder. m.p. 52.3–57.4 °C (lit. 61–62 °C).[129] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.84, 7.65 (1 H, *d*, *J* = 1.8 Hz), 7.39 (1 H, *d*, *J* = 1.8 Hz), 3.95 (3 H, *s*), 3.93 (3 H, *s*) ppm. ^{13}C NMR (75 MHz, DMSOd_6): δ = 190.9, 153.8, 150.6, 133.1, 127.0, 117.0, 111.6, 60.4, 56.3 ppm. MS (APCI): *m/z* (%): 245/247 $[M+H]^+$ (100).

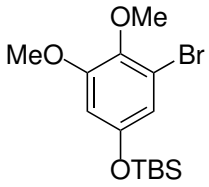
3-Bromo-4,5-dimethoxyphenol (601) [130]



5-Bromoveratraldehyde (1.8 g, 7.3 mmol) and *m*CPBA (77% w/w; 2.5 g, 11 mmol) were dissolved in chloroform (50 mL) and heated at reflux for 2 h. The reaction mixture was cooled to room temperature and washed with saturated aqueous sodium sulfite solution (50 mL), saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*.

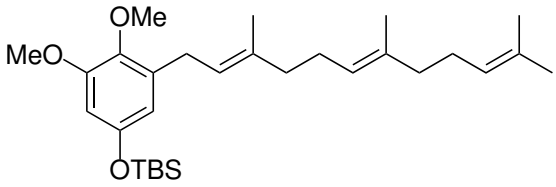
The residue was dissolved in methanol (50 mL) and hydrochloric acid (1 M, 10 mL) was added. The reaction mixture was stirred at room temperature for 18 h, then the solvent was removed. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **601** (0.37 g, 1.6 mmol, 22%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (1 H, *d*, *J* = 2.7 Hz), 6.41 (1 H, *d*, *J* = 2.7 Hz), 3.81 (3 H, *s*), 3.77 (3 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 153.2, 140.3, 117.5, 110.8, 100.4, 60.8, 56.1 ppm. HRMS (APCI): calcd. for $C_8H_{10}BrO_3^+$ 232.98078; found 232.98094.

(3-Bromo-4,5-dimethoxyphenoxy)(*tert*-butyl)dimethylsilane (605)



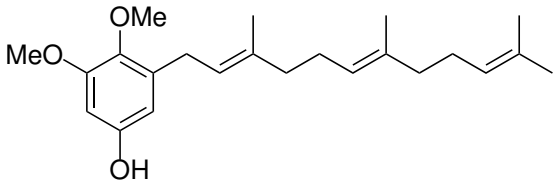
Phenol **601** (1.3 g, 5.6 mmol), *tert*-butyldimethylchlorosilane (0.90 g, 6.0 mmol) and imidazole (0.41 g, 6.0 mmol) were dissolved in tetrahydrofuran (50 mL). The reaction mixture was stirred for 18 h, then diluted with ether (10 mL) and washed with water (30 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*, then the residue was purified by column chromatography over silica gel, eluting with 2% ether in hexanes to give *title compound* **605** (0.90 g, 2.6 mmol, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.60 (1 H, *d*, *J* = 2.7 Hz), 6.35 (1 H, *d*, *J* = 2.7 Hz), 3.81 (3 H, *s*), 3.79 (3 H, *s*), 0.98 (9 H, *s*), 0.20 (6 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.0, 152.5, 141.3, 117.3, 115.5, 104.8, 60.8, 56.1, 25.7, 18.3, –4.4 ppm. HRMS (APCI): calcd. for $C_{14}H_{24}BrO_3Si^+$ 349.06518; found 349.06516.

***tert*-Butyl(3,4-dimethoxy-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)phenoxy) dimethylsilane (606)**



Aryl bromide **605** (0.44 g, 1.3 mmol), boronate **541** (0.42 g, 1.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.044 g, 0.037 mmol) were dissolved in toluene (10 mL) and aqueous sodium hydroxide solution (1 M, 2 mL, 2 mmol) was added and the reaction mixture was heated at reflux and stirred for 18 h. The reaction mixture was cooled to room temperature, then the reaction mixture was diluted with water (30 mL) and extracted with ether (2 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 20% dichloromethane in hexanes to give *title compound* **606** (0.089 g, 0.21 mmol, 16%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.28–6.25 (1 H, *m*), 6.25–6.22 (1 H, *m*), 3.80 (3 H, *s*), 3.74 (3 H, *s*), 3.30 (2 H, *d*, *J* = 7.2 Hz), 2.18–1.92 (8 H, *m*), 1.71 (3 H, *s*), 1.68 (3 H, *m*), 1.60 (6 H, *m*), 0.98 (9 H, *s*), 0.19 (6 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 151.8, 141.5, 136.3, 135.7, 135.1, 131.3, 124.5, 124.3, 122.8, 112.1, 102.9, 60.7, 55.8, 39.9, 39.8, 32.1, 28.2, 26.9, 25.9, 23.5, 18.3, 17.8, 16.3, 16.1, –4.3 ppm. HRMS (ESI): calcd. for $C_{29}H_{49}O_3Si^+$ 473.34455; found 473.34442. IR (neat): $\tilde{\nu}_{max}$ = 2928, 1590, 1487, 1340, 1086, 1022, 838, 779 cm^{-1}.

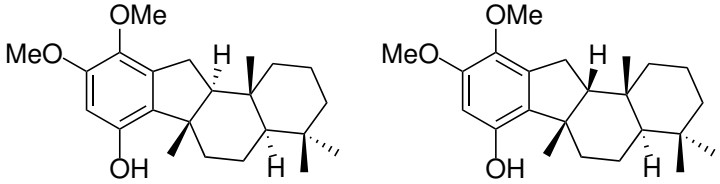
3,4-Dimethoxy-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)phenol (600)



Polyene **606** (0.089 g, 0.21 mmol) was dissolved in tetrahydrofuran (2 mL) and tetrabutylammonium fluoride solution (1 M in THF; 0.30 mL, 0.30 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, then diluted with ether (30 mL) and water (30 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*, then the residue was purified by column chromatography over silica gel, eluting

with dichloromethane to give *title compound* **600** (0.046 g, 0.13 mmol, 62%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.29 (1 H, *d*, *J* = 2.6 Hz), 6.21 (1 H, *d*, *J* = 2.6 Hz), 5.30–5.21 (1 H, *m*), 5.19–5.06 (2 H, *m*), 3.78 (3 H, *s*), 3.74 (3 H, *s*), 3.31 (2 H, *d*, *J* = 7.2 Hz), 2.17–1.93 (8 H, *m*), 1.71 (3 H, *s*), 1.68 (3 H, *s*), 1.60 (6 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.5, 152.2, 140.7, 136.4, 136.2, 135.2, 131.5, 124.5, 124.3, 122.6, 107.4, 98.5, 60.8, 55.8, 39.8, 32.1, 28.2, 26.8, 26.7, 25.8, 17.2, 16.2, 16.1 ppm. HRMS (APCI): calcd. for $C_{23}H_{35}O_3^+$ 359.25807; found 359.25809. IR (neat): $\tilde{\nu}_{max}$ = 2917, 1596, 1471, 1431, 1146, 999, 836, 774 cm^{-1}.

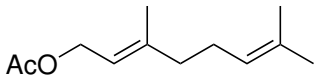
9,10-Dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[a]fluoren-7-ol (599)



Polyene **600** (0.042 g, 0.12 mmol) was dissolved in nitromethane (1 mL) and boron trifluoride etherate (1 drop) was added. The reaction mixture was stirred for 18 h at room temperature, then diluted with ether (10 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The reaction mixture was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with dichloromethane to give *title compound* **599** (0.083 g, 0.023 mmol, 19%) as a yellow oil as a mixture of diastereomers at the C9 position (1:1). *trans diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.20 (1 H, *s*), 4.53 (1 H, *s*), 3.78 (3 H, *s*), 3.77 (3 H, *s*), 2.69 (1 H, *dd*, *J* = 14.8, 6.1 Hz), 2.49 (1 H, *dd*, *J* = 14.8, 12.6 Hz), 2.32 (1 H, *dd*, *J* = 11.8, 3.0 Hz), 1.84–1.78 (1 H, *m*), 1.75 (1 H, *dd*, *J* = 12.8, 6.2 Hz), 1.77–1.72 (1 H, *m*), 1.71–1.66 (1 H, *m*), 1.63–1.58 (1 H, *m*), 1.58–1.53 (1 H, *m*), 1.45–1.38 (2 H, *m*), 1.21–1.16 (1 H, *m*), 1.18 (3 H, *s*), 1.14 (3 H, *s*) 1.04 (3 H, *s*), 1.04–0.98 (2 H, *m*), 0.87 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.5, 146.6, 139.9, 136.8, 131.0, 99.7, 64.6, 60.8, 57.4, 56.1, 46.5, 42.6, 40.2, 38.6, 36.8, 33.5, 33.2, 25.9, 21.1, 20.3, 19.7, 18.4, 16.2 ppm. *cis diastereomer (partial data; some resonances obscured)*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.15 (1 H, *s*), 4.56 (1 H, *s*), 3.78 (3 H, *s*), 3.77 (3 H, *s*), 2.92 (1 H, *dd*, *J* = 16.0, 8.2 Hz), 2.72 (1 H, *dd*, *J* = 16.4, 10.6 Hz), 2.03–1.98 (1 H, *m*), 1.83 (1 H, *dd*, *J* = 11.9, 8.0 Hz), 1.68 (3 H, *s*), 1.44–1.29 (3 H, *m*), 1.29–1.22 (2 H, *m*), 1.22 (3 H, *s*), 1.20–1.15 (1 H, *m*), 0.87 (3 H, *s*), 0.86 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.3, 147.7, 139.0, 135.8, 131.4, 100.4, 62.5, 60.7, 56.2, 48.1, 46.8, 42.7, 38.6, 37.2, 33.7,

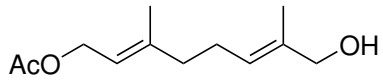
33.1, 30.9, 29.8, 25.7, 24.5, 22.0, 18.5 ppm. HRMS (APCI): calcd. for $C_{23}H_{35}O_3^+$ 359.25807; found 359.25806. IR (neat): $\tilde{\nu}_{max}$ = 3380, 2931, 2864, 1599, 1495, 1448, 1262, 1016, 703 cm^{-1}.

Geranyl acetate (614) [119]



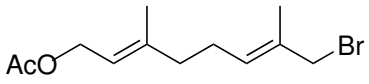
Geraniol (8.8 mL, 50 mmol) was dissolved in pyridine (8 mL) and cooled to 0 °C. Acetic anhydride (8.0 mL, 85 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured onto ice water (50 mL) and extracted with ether (3 × 50 mL), then washed with hydrochloric acid (1 M, 100 mL) and brine (50 mL). The organic layer was then dried over magnesium sulfate and filtered. The volatiles were removed *in vacuo* to give *title compound* **614** (9.7 g, 49 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.35–5.30 (1 H, *m*), 5.09–5.03 (1 H, *m*), 4.57 (2 H, *d*, *J* = 7.1 Hz), 2.13–1.99 (7 H, *m*), 1.68 (3 H, *s*), 1.66 (3 H, *s*), 1.58 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 142.3, 131.9, 123.8, 118.4, 61.5, 39.6, 26.4, 25.1, 21.1, 17.7, 16.5 ppm. MS (ESI): *m/z* (%): 219 $[M+H]^+$ (100).

(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate (615) [119]



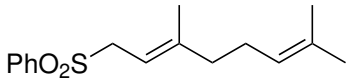
Selenium dioxide (0.033 g, 0.30 mmol), salicylic acid (0.140 g, 1.0 mmol) and *tert*-butylhydroperoxide solution (3.2 g, 25 mmol) were dissolved in dichloromethane (15 mL) and stirred 15 min, then geranyl acetate (2.0 g, 10 mmol) was added and the reaction mixture was stirred 18 h at room temperature. The reaction mixture was washed with aqueous potassium hydroxide solution (10%, 30 mL), water (30 mL) and brine (30 mL), then purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **615** (1.1 g, 5.2 mmol, 52%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.38–5.28 (2 H, *m*), 4.56 (2 H, *d*, *J* = 7.0 Hz), 3.96 (2 H, *s*), 2.19–2.05 (4 H, *m*), 2.03 (3 H, *s*), 1.68 (3 H, *s*), 1.64 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 141.8, 135.4, 125.3, 118.8, 68.9, 61.5, 39.1, 25.8, 21.1, 16.5, 13.8 ppm. MS (ESI): *m/z* (%): 235 $[M+Na]^+$ (100).

(2*E*,6*E*)-8-Bromo-3,7-dimethylocta-2,6-dien-1-yl acetate (609) [119]



Alcohol **615** (3.3 g, 16 mmol) was dissolved in ether (80 mL) and cooled to 0 °C. Phosphorus tribromide (0.76 mL, 8.0 mmol) was added dropwise and the reaction mixture was stirred for 3 h at room temperature. Saturated aqueous sodium hydrogen carbonate solution (100 mL) was added slowly, then the layers were separated and the aqueous layer was extracted with ether (100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **609** (3.3 g, 12 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.54 (1 H, *t*, *J* = 6.7 Hz), 5.39–5.31 (1 H, *m*), 4.56 (2 H, *d*, *J* = 7.2 Hz), 3.93 (2 H, *s*), 2.18–2.05 (4 H, *m*), 2.03 (3 H, *s*), 1.73 (3 H, *s*), 1.68 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 141.3, 132.5, 130.5, 119.0, 61.3, 41.6, 38.6, 26.5, 21.1, 16.5, 14.7 ppm. MS (ESI): *m/z* (%): 297/299 $[M+Na]^+$.

Geranyl phenyl sulfone (613) [131]



Method A

Geraniol (2.1 mL, 12 mmol) was dissolved in dichloromethane (25 mL) and cooled to 0 °C. Carbon tetrabromide (5.2 g, 16 mmol) then triphenylphosphine (4.7 g, 18 mmol) were added, then the reaction mixture was stirred for 3 h at room temperature. Ether (50 mL) was added to precipitate triphenylphosphine oxide which was removed by vacuum filtration. The filtrate was collected and the solvent was removed *in vacuo*.

The residue was dissolved in *N*,*N*-dimethylformamide (20 mL) and sodium benzenesulfinate (3.2 g, 19 mmol) was added at 0 °C. The reaction mixture was stirred overnight, then diluted with ether (50 mL) and washed with water (2 × 100 mL) and brine (50 mL), dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue

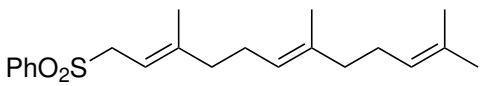
was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **613** (2.9 g, 10 mmol, 86%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.83 (2 H, *m*), 7.65–7.59 (1 H, *m*), 7.55–7.49 (2 H, *m*), 5.20–5.14 (1 H, *m*), 5.05–4.98 (1 H, *m*), 3.79 (2 H, *d*, *J* = 7.9 Hz), 2.00–1.97 (4 H, *m*), 1.67 (3 H, *s*), 1.57 (3 H, *s*), 1.30 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 138.8, 133.6, 132.1, 129.0, 128.6, 123.5, 110.4, 56.2, 39.8, 26.3, 25.8, 17.8, 16.2 ppm. MS (ESI): *m/z* (%): 279/280/281 (100) $[M+H]^+$.

Method B

Geraniol (5.0 mL, 29 mmol) was dissolved in ether (50 mL) and cooled to –20 °C. Phosphorus tribromide (1.4 mL, 15 mmol) was added and the reaction was stirred, warming to room temperature. Saturated aqueous sodium hydrogen carbonate solution (30 mL) was added, the layers were separated and the aqueous layer was extracted with ether (50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was removed *in vacuo*.

The residue was dissolved in dimethylformamide (50 mL) and sodium benzenesulfinate (5.7 g, 35 mmol) was added. The reaction mixture was stirred overnight, then diluted with ether (50 mL) and washed with water (2 $\times$ 100 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **613** (6.5 g, 23 mmol, 79%) as a colourless oil. Characterisation data was identical to Method A.

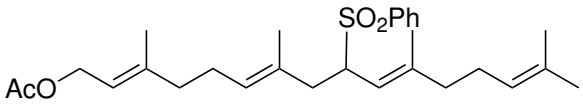
Farnesyl phenyl sulfone (618) [132]



Farnesol (3.0 mL, 12 mmol) was dissolved in dichloromethane (25 mL) and cooled to 0 °C. Carbon tetrabromide (5.2 g, 16 mmol), then triphenylphosphine (4.7 g, 18 mmol) were added, then the reaction mixture was stirred 6 h at room temperature. The reaction mixture was filtered over Celite, washing with dichloromethane (50 mL), then the filtrate was collected and the solvent removed *in vacuo*.

The residue was dissolved in *N,N*-dimethylformamide (20 mL) and sodium benzenesulfinate (3.2 g, 19 mmol) was added at 0 °C. The reaction mixture was stirred overnight, then diluted with ether (50 mL) and washed with water (2 × 100 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give farnesyl phenyl sulfone (2.8 g, 8.2 mmol, 68%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85–7.82 (2 H, *m*), 7.62–7.57 (1 H, *m*), 7.52–7.47 (2 H, *m*), 5.20–5.12 (1 H, *m*), 5.10–4.99 (2 H, *m*), 3.78 (3 H, *s*), 3.77 (3 H, *s*), 2.06–1.90 (8 H, *m*), 1.69 (3 H, *s*), 1.64–1.58 (6 H, *m*), 1.33 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.5, 138.8, 135.8, 133.6, 131.5, 129.0, 128.7, 124.3, 123.4, 110.4, 56.2, 39.8, 39.8, 32.0, 26.8, 26.3, 25.8, 17.8, 16.3, 16.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{30}O_2SNa^+$ 369.18587; found 369.18539.

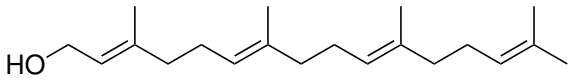
(2*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-9-(phenylsulfonyl)hexadeca-2,6,10,14-tetraen-1-yl acetate (616)



Diisopropylamine (0.89 mL, 6.0 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled to –78 °C. *n*-Butyllithium (1.5 M in hexane, 4.0 mL, 6.0 mmol) was added and the reaction mixture was stirred at –78 °C for 5 min. A solution of geranyl phenyl sulfone (**613**; 1.3 g, 4.7 mmol) in tetrahydrofuran (10 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min, then a solution of alkyl bromide **609** (1.3 g, 4.7 mmol) in tetrahydrofuran (10 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h, then saturated aqueous ammonium chloride solution (30 mL) was added and the reaction mixture was warmed to room temperature. The layers were separated and the aqueous layer was extracted with ether (30 mL), then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **616** (1.9 g, 4.5 mmol, 96%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (2 H, *d*, *J* = 7.4 Hz), 7.60 (1 H, *t*, *J* = 7.4 Hz), 7.49 (2 H, *dd*, *J* = 7.4, 7.4 Hz), 5.28 (1 H, *t*, *J* = 6.9 Hz), 5.12 (1 H , *t*, *J* = 6.7 Hz), 5.02-4.97 (1 H, *m*), 4.89 (1 H, *d*, *J* = 10.3 Hz), 4.55 (2 H, *d*, *J* = 7.1 Hz), 3.87 (1 H, *td*, *J* = 10.8, 3.0 Hz), 2.86 (1 H, *d*, *J* = 13.1 Hz),

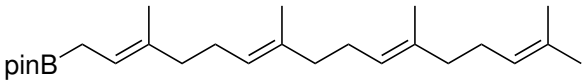
2.26 (1 H, *dd*, *J* = 13.0, 11.7 Hz), 2.13–1.89 (11 H, *m*), 1.66 (3 H, *s*), 1.65 (3 H, *s*), 1.57 (3 H, *s*), 1.51 (3 H, *s*), 1.15 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 145.1, 141.9, 138.1, 133.4, 132.0, 130.5, 129.4, 128.8, 127.7, 123.7, 118.6, 117.4, 63.6, 61.4, 39.8, 39.3, 37.5, 26.4, 26.4, 25.8, 21.1, 17.8, 16.5, 16.4, 16.0 ppm. HRMS (ESI): calcd. for $C_{28}H_{40}O_4SNa^+$ 495.25395; found 495.25353.

Geranylgeraniol (84) [119]



Sulfone **616** (1.9 g, 4.5 mmol) was dissolved in tetrahydrofuran (40 mL) and ethanol (5 mL) and cooled to 0 °C. Sodium (1.0 g, 45 mmol) was added and the reaction mixture was stirred vigorously for 24 h, warming to room temperature. Excess ethanol was added to quench any remaining sodium, then the solvent was removed *in vacuo*. The residue was dissolved in ether (50 mL) and water (50 mL), separated and the aqueous layer was extracted with ether (50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give geranylgeraniol (0.69 g, 2.4 mmol, 53%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.42–5.37 (1 H, *m*), 5.15–5.06 (3 H, *m*), 4.12 (2 H, *d*, *J* = 6.9 Hz), 2.14–1.90 (12 H, *m*), 1.66 (6 H, *s*), 1.60–1.56 (9 H, *m*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.6, 135.4, 135.0, 131.3, 124.5, 124.2, 123.9, 123.5, 59.3, 39.8, 39.7, 39.6, 26.8, 26.7, 26.4, 25.7, 17.7, 16.3, 16.1, 16.0 ppm. MS (ESI): *m/z* (%): 313 (100) $[M+H]^+$.

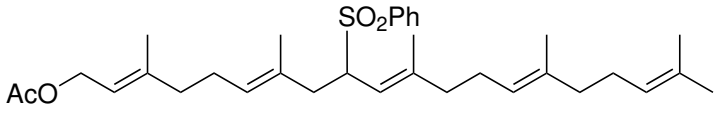
Geranylgeranyl pinacol boronate (629)



Geranylgeraniol (0.69 g, 2.4 mmol), bis(pinacolato)diboron (1.2 g, 4.8 mmol), *p*-toluenesulfonic acid (0.058 g, 0.35 mmol) and catalyst **375** (0.18 g, 0.24 mmol) were dissolved in methanol (12 mL) and dimethylsulfoxide (12 mL). The reaction mixture was stirred at 50 °C for 18 h, then diluted with water (30 mL) and extracted with ether (2 × 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and the

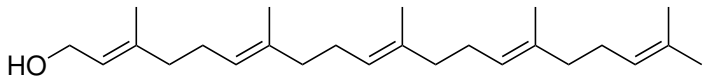
solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 2% ether in hexanes to give geranylgeranyl pinacol boronate (**629**; 0.60 g, 1.5 mmol, 63%) as a faint yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.31–5.22 (1 H, *m*), 5.18–5.07 (3 H, *m*), 2.10–1.93 (14 H, *m*), 1.68 (3 H, *s*), 1.59 (6 H, *s*), 1.30–1.22 (20 H, *m*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.3, 135.0, 134.9, 131.3, 125.0, 124.58, 124.56, 124.5, 83.2, 40.0, 39.90, 39.88, 27.0, 26.93, 26.86, 25.8, 24.9, 17.8, 16.1, 16.0, 14.3 ppm. Unable to obtain mass spectrum by EI, ESI or APCI. IR (neat): $\tilde{\nu}_{max}$ = 2976, 2920, 2855, 1446, 1370, 1321, 1144, 967, 885, 846 cm^{-1}.

(2*E*,6*E*,10*E*,14*E*)-3,7,11,15,19-Pentamethyl-9-(phenylsulfonyl)icosa-2,6,10,14,18-pentaen-1-yl acetate (619)



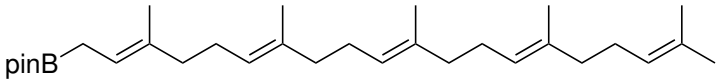
Diisopropylamine (0.47 mL, 3.3 mmol) was dissolved in tetrahydrofuran (15 mL) and cooled to –78 °C. *n*-Butyllithium (0.55 M in hexanes, 6.0 mL, 3.3 mmol) was added and the reaction was stirred for 5 min before adding a solution of farnesyl phenyl sulfone (1.0 g, 3.0 mmol) in tetrahydrofuran (5 mL), then the reaction mixture was stirred for 30 min. Alkyl bromide **609** (0.83 g, 3.0 mmol) was added as a solution in tetrahydrofuran (5 mL), then the reaction was stirred for 1 h at –78 °C. Saturated aqueous ammonium chloride solution (30 mL) was added, the reaction mixture was warmed to room temperature and the layers were separated. The aqueous layer was extracted with ether (3 $\times$ 30 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give *title compound* **619** as a colourless oil (1.1 g, 2.0 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.80 (2 H, *m*), 7.58–7.53 (1 H, *m*), 7.49–7.43 (2 H, *m*), 5.29 (1 H, *td*, *J* = 7.1, 1.0 Hz), 5.16–5.00 (3 H, *m*), 4.94–4.87 (1 H, *m*), 4.54 (2 H, *d*, *J* = 7.3 Hz), 3.87 (1 H, *td*, *J* = 10.8, 2.9 Hz), 2.88 (1 H, *d*, *J* = 13.3), 2.31–2.23 (1 H, *m*), 2.09–1.88 (15 H, *m*), 1.66 (3 H, *s*), 1.64 (3 H, *s*), 1.57 (3 H, *d*, *J* = 4.7 Hz), 1.51 (3 H, *s*), 1.15 (3H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7, 144.9, 141.5, 138.1, 135.4, 133.2, 130.3, 129.2, 128.9, 128.6, 128.1, 127.5, 123.4, 118.5, 117.3, 63.4, 61.1, 39.6, 39.1, 34.6, 31.5, 26.6, 26.2, 25.5, 25.2, 22.6, 20.8, 17.5, 16.2, 15.8, 14.0 ppm. MS (ESI): *m/z* (%): 563 (100) [M+H]$^{+}$

Geranylfarnesol (620) [132]



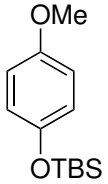
Sulfone **619** (0.31 g, 0.55 mmol) was dissolved in tetrahydrofuran (5 mL) and ethanol (0.50 mL). Sodium (0.12 g, 5 mmol) was added portionwise at 0 °C and stirred for 18 h. Water (30 mL) was added slowly and the reaction mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give geranylfarnesol (0.095 g, 0.27 mmol, 50%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.44–5.39 (1 H, *m*), 5.16–5.07 (4 H, *m*), 4.14 (2 H, *d*, *J* = 6.9 Hz), 2.16–1.91 (16 H, *m*), 1.68 (9 H, *s*), 1.61–1.58 (9 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.0, 135.5, 135.1, 135.0, 131.4, 124.6, 124.4, 124.3, 123.9, 123.5, 59.5, 39.86, 39.85, 39.7, 39.6, 26.9, 26.80, 26.79, 26.5, 25.8, 17.8, 16.4, 16.16, 16.15, 16.14 ppm. MS (ESI): *m/z* (%): 381 (100) $[M+Na]^+$.

Geranylfarnesyl pinacol boronate (635)



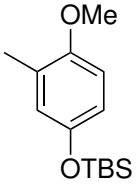
Geranylfarnesol (0.60 g, 1.7 mmol), bis(pinacolato)diboron (0.85 g, 3.4 mmol), catalyst **375** (0.093 g, 0.17 mmol) and *p*-toluenesulfonic acid (0.043 g, 0.25 mmol) were dissolved in methanol (8 mL) and dimethylsulfoxide (8 mL) and heated to 65 °C for 18 h. The reaction mixture was cooled to room temperature and diluted with water (30 mL) and ether (30 mL). The layers were separated and the aqueous layer was extracted with ether (30 mL), then the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with 30% dichloromethane in hexanes to give *title compound* **635** (0.76 g, 1.6 mmol, 94%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.27–5.22 (1 H, *m*), 5.17–5.07 (4 H, *m*), 2.12–1.94 (16 H, *m*), 1.70–1.57 (18 H, *m*), 1.24 (12 H, *s*), 0.96 (2 H, *d*, *J* = 6.6 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.3, 135.1, 135.0, 134.9, 131.4, 125.4, 124.56, 124.55, 124.52, 124.4, 83.2, 40.2, 39.94, 39.89, 39.87, 26.92, 26.87, 26.83, 26.77, 25.8, 24.9, 17.8, 16.14, 16.13, 14.2 ppm. Could not obtain mass spectrum via EI, ESI or APCI. IR (neat): $\tilde{\nu}_{max}$ = 2921, 1449, 1370, 1320, 1124 cm^{-1}.

***tert*-Butyl(4-methoxyphenoxy)dimethylsilane (626)** [133]



4-Methoxyphenol (4.0 g, 32 mmol) was dissolved in dichloromethane (30 mL) and *tert*-butyldimethylchlorosilane (5.3 g, 35 mmol) and imidazole (2.4 g, 35 mmol) were added. The reaction mixture was stirred at room temperature for 2 h, then washed with water (10 mL) and the organic layer was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to give *title compound* **626** (7.0 g, 29 mmol, 91%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.57 (4 H, *s*), 3.56 (3 H, *s*), 0.79 (9 H, *s*), –0.03 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.2, 149.5, 120.7, 114.6, 55.7, 25.9, –4.4 ppm. MS (APCI): *m/z* (%): 239 ($[M+H]^+$, 80), 240 ($[M+H]^+$, 16), 241 ($[M+H]^+$, 4).

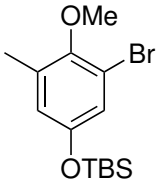
***tert*-Butyl(4-methoxy-3-methylphenoxy)dimethylsilane (627)**



Aromatic **626** (2.0 g, 8.4 mmol) and *N,N,N',N'*-tetramethylethylenediamine (1.3 mL, 8.4 mmol) were dissolved in tetrahydrofuran (10 mL) and cooled to 0 °C. *n*-Butyllithium (1.3 M in hexanes, 8.4 mL, 11 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then cooled to 0 °C and methyl iodide (0.62 mL, 10 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. Saturated aqueous ammonium chloride solution (10 mL) was added, then the layers were separated and the aqueous layer was extracted with ether (30 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 1% ether in hexanes to give *title compound* **627** (1.1 g, 4.4 mmol, 52%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.77–6.60 (3 H, *m*), 3.78 (3 H, *s*), 2.18 (3 H, *s*), 0.99 (9 H, *s*), 0.18 (6 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.5, 149.1, 127.7, 122.7, 117.3, 110.9,

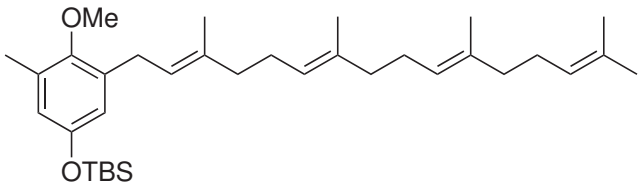
55.9, 25.9, 18.3, 16.4, –4.3 ppm. MS (APCI): *m/z* (%): 253 ([M+H]$^+$), 80), 254 ([M+H]$^+$, 16), 255 ([M+H]$^+$, 4). HRMS (ESI): calcd. for $C_{14}H_{25}O_2Si^+$ 253.16183; found 253.16174.

(3-Bromo-4-methoxy-5-methylphenoxy)(*tert*-butyl)dimethylsilane (628)



Aromatic **627** (1.1 g, 4.4 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. A solution of bromine (0.25 mL, 4.9 mmol) in dichloromethane (2 mL) was added dropwise and the reaction mixture was stirred for 2 h, warming to room temperature. The reaction mixture was washed with saturated aqueous sodium sulfite solution (20 mL) and the organic layer was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to give *title compound* **628** (1.2 g, 3.7 mmol, 85%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96 (1 H, *s*), 6.71 (1 H, *s*), 3.79 (3 H, *s*), 2.16 (3 H, *s*), 1.07 (9 H, *s*), 0.25 (6 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 152.6, 146.1, 126.9, 122.4, 114.9, 111.3, 56.0, 25.9, 18.4, 16.2, –4.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{24}BrO_2Si^+$ 353.05429; found 353.05411.

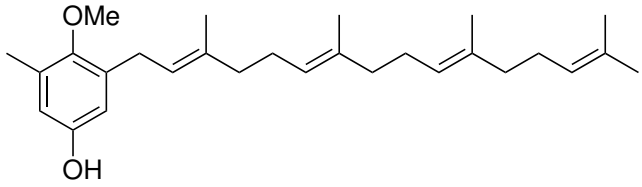
***tert*-Butyl(4-methoxy-3-methyl-5-((2*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl)phenoxy)dimethylsilane (630)**



Aryl bromide **628** (0.39 g, 1.1 mmol), geranylgeranyl pinacol boronate (0.45 g, 1.1 mmol), powdered sodium hydroxide (0.44 g, 11 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.060 mg, 0.05 mmol) were dissolved in toluene (7.5 mL) and water (2.5 mL). The reaction mixture was degassed with argon, then heated to 100 °C for 18 h. The reaction mixture was cooled to room temperature, then diluted with water (30 mL) and extracted with ether (2 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column

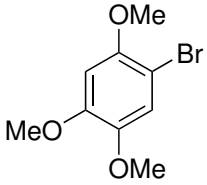
chromatography over silica gel, eluting with 20% dichloromethane in hexanes to give *title compound* **630** (0.29 mg, 0.55 mmol, 50%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.61 (1 H, *s*), 6.59 (1 H, *s*), 5.36–5.30 (1 H, *m*), 5.14–5.07 (3 H, *m*), 3.75 (3 H, *s*), 3.28 (2 H, *d*, *J* = 7.1 Hz), 2.18–1.91 (15 H, *m*), 1.70 (3 H, *s*), 1.67 (3 H, *s*), 1.60 (9 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1, 147.7, 147.3, 146.6, 136.2, 131.3, 125.0, 124.5, 123.0, 121.1, 121.0, 112.0, 111.9, 111.0, 56.1, 44.3, 39.8, 28.6, 26.9, 26.7, 26.4, 26.0, 25.8, 18.8, 18.3, 17.8, 16.1, 16.0, 1.1, –3.41, –4.0 ppm. HRMS (ESI): calcd. for $C_{34}H_{56}O_2SiNa^+$ 547.39418; found 547.39465.

4-Methoxy-3-methyl-5-((2*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl)phenol (625)



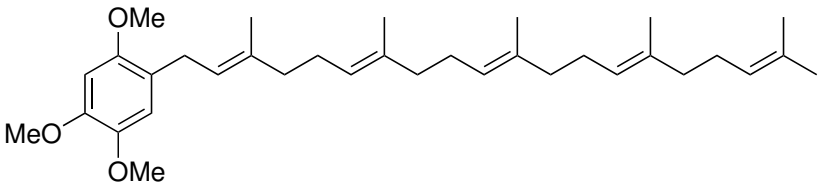
Polyene **630** (2.1 g, 4.0 mmol) was dissolved in tetrahydrofuran (40 mL) and cooled to 0 °C. Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 4.0 mL, 4.0 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ether (30 mL) and washed with water (50 mL), then the organic layer was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 20% dichloromethane in hexanes to give *title compound* **625** (0.43 g, 1.0 mmol, 25%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.63 (1 H, *s*), 6.60 (1 H, *s*), 5.38–5.28 (1 H, *m*), 5.18–5.08 (3 H, *m*), 4.80 (1 H, *s*), 3.78 (3 H, *s*), 3.34 (2 H, *d*, *J* = 7.1 Hz), 2.23–1.94 (15 H, *m*), 1.79 (3 H, *s*), 1.70 (3 H, *s*), 1.62 (9 H, *s*) ppm. ^{13}C NMR (MHz, $CDCl_3$): δ = 151.9, 147.8, 138.3, 135.7, 135.0, 131.4, 125.7, 124.53, 124.46, 124.4, 123.8, 122.1, 118.5, 112.4, 56.2, 39.85 (2 C), 39.80, 30.0, 26.9, 26.7, 26.6, 25.8, 17.8, 16.4, 16.2, 16.1, 15.9 ppm. HRMS (ESI): calcd. for $C_{28}H_{42}O_3Na^+$ 449.30262; found 449.30277. IR (neat): $\tilde{\nu}_{max}$ = 3428, 2918, 2853, 1510, 1450, 1409, 1198, 1021, 863, 834, 449 cm^{-1}.

1-Bromo-2,4,5-trimethoxybenzene (634) [134]



1,2,4-Trimethoxybenzene (5.0 g, 30 mmol) was dissolved in dichloromethane (100 mL) and cooled to 0 °C, then bromine (1.6 mL, 31 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, then saturated aqueous sodium sulfite solution (100 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to give *title compound* **634** (6.7 g, 27 mmol, 90%) as a brown solid. m.p. 51.9–52.7 °C. (lit m.p. 52–54 °C) [134] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 (1 H, *s*), 6.52 (1 H, *s*), 3.84 (3 H, *s*), 3.82 (3 H, *s*), 3.79 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.3, 149.1, 143.8, 116.5, 101.1, 98.9, 57.2, 56.6, 56.3 ppm. MS (ESI) *m/z* (%): 269/271 $[M+Na]^+$ (100).

1,2,4-Trimethoxy-5-((2*E*,6*E*,10*E*,14*E*)-3,7,11,15,19-pentamethylicosa-2,6,10,14,18-pentaen-1-yl)benzene (633)



Aryl bromide **634** (0.37 g, 1.5 mmol), geranylfarnesyl pinacol boronate (**635**; 0.71 g, 1.5 mmol), powdered sodium hydroxide (0.60 g, 15 mmol) and tetrakis(triphenylphosphine) palladium(0) (0.087 g, 0.075 mmol) were dissolved in toluene (12 mL) and water (3 mL) and the reaction mixture was stirred vigorously at 100 °C for 18 h. The reaction mixture was cooled to room temperature and extracted with ether (3 × 30 mL), then dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 30% dichloromethane in hexanes to give *title compound* **633** (0.28 g, 0.55 mmol, 37%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.71 (1 H, *s*), 6.52 (1 H, *s*), 5.34–5.06 (5 H, *m*), 3.87 (3 H, *s*), 3.82 (3 H, *s*), 3.80 (3 H, *s*), 3.27 (2 H, *d*, *J* = 7.2 Hz), 2.19–1.92 (16 H, *m*), 1.76–1.53 (18 H, *m*) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.5, 147.8, 143.2, 136.2, 135.2, 135.1, 135.0, 131.4, 124.6, 124.4, 124.4, 124.3, 122.9, 122.0, 114.0, 98.3, 56.8, 56.7, 56.5, 40.0, 39.9, 32.1, 27.8, 27.0, 26.9, 26.9, 26.8, 25.9, 25.8, 23.5, 17.8, 16.3, 16.2, 16.1 ppm. HRMS (ESI): calcd. for $C_{34}H_{52}O_3Na^+$ 531.38087; found 531.38092. IR (neat): $\tilde{\nu}_{max}$ = 2961, 2919, 2851, 1607, 1507, 1203, 1037, 806 cm^-1.

Chapter 4

Polycyclic ethers

4.1 Introduction

The last foray into the synthesis of fused ring systems involved an entirely separate, non-terpenoid family of compounds: the polycyclic marine ethers. These exhibit an entirely different architecture with their own challenges and structural complexities.

The polycyclic marine ethers are a family of compounds produced by dinoflagellate marine algae such as *Karenia brevis* and *Gambierdiscus toxicus*. Over 50 of these compounds have been identified, ranging in size from hemibrevetoxin all the way to maitotoxin, which at 3422 g/mol is the largest non-biopolymer natural product yet to be identified.[135] They all consist of an array of fused oxygen-containing rings ranging in size between six and nine rings, with all exocyclic substituents and hydrogens at the ring junctions being axially oriented. This leads to a characteristic *trans,syn,trans* stereochemistry which gives rise to their alternative name, ladder polyethers (Figure 33). These interesting structural features and the sheer size of many polycyclic ethers make them a challenging target for chemical synthesis.

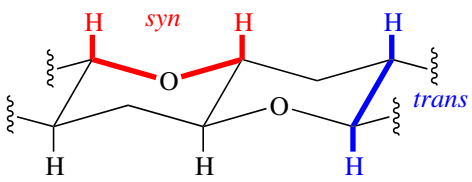


Figure 33: Characteristic ladder configuration of the polycyclic ether natural products.

Interest in these compounds is not just academic: the polycyclic ethers are extremely toxic compounds. Along with being the largest non-biopolymer natural product discovered, maitotoxin is also the most toxic, with an LD_{50} of only 0.13 μg.[135] Brevetoxin B can exert toxic effects at picomolar concentrations and prymnesin can kill a population of *Tanichthys albonubes* minnow at a concentration of only 3 nM.[136] Effects of polycyclic ether toxicity range from nausea and muscle pain to a paradoxical feeling of hot and cold, paraesthesia and even death.[137]

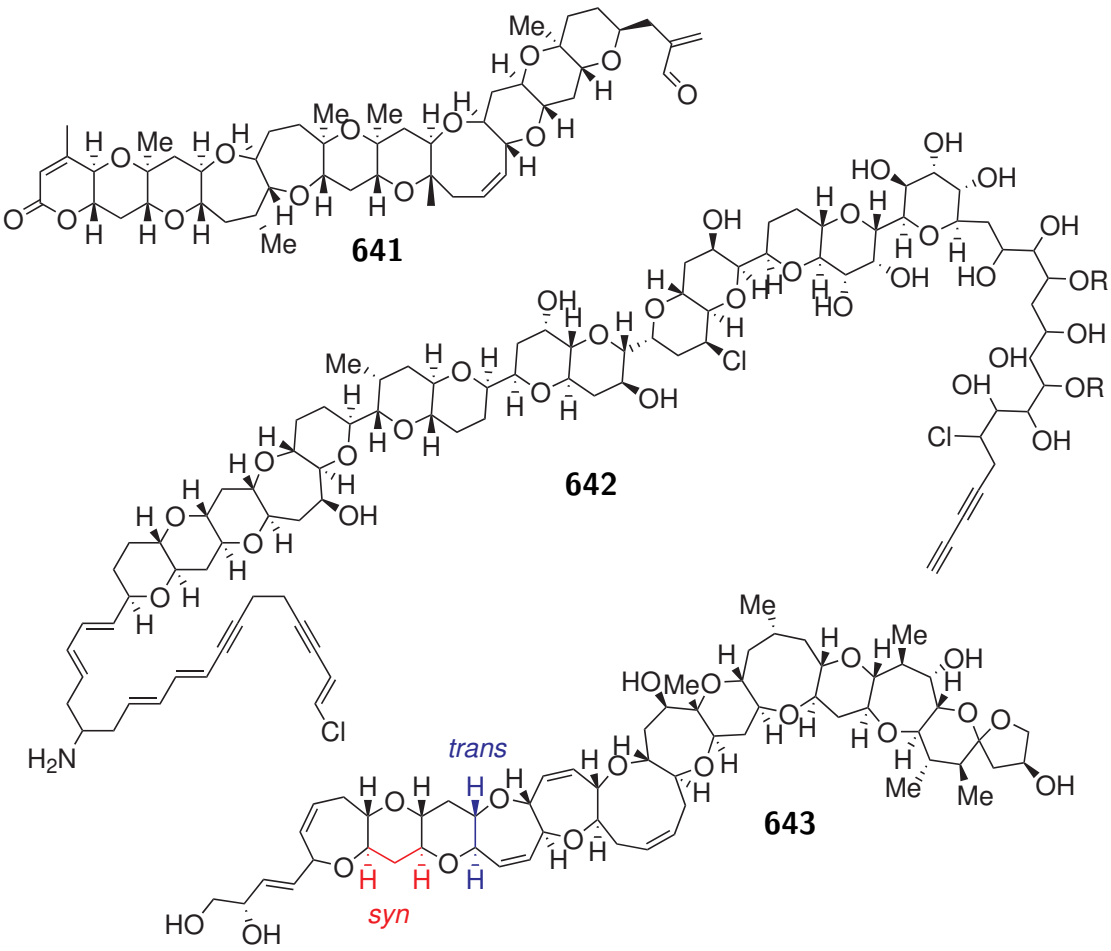


Figure 34: Example polycyclic ethers: brevetoxin B (**641**), prymnesin (**642**) and ciguatoxin (**643**). The characteristic *syn,trans* stereochemistry is highlighted on structure **643**.

Because of the low active concentrations of these compounds, methods for their detection in food sources are severely lacking. Liquid chromatography-mass spectrometry can be successful, but is of little value to poorer regions where this technology may be unavailable and prohibitively expensive. Folk heuristic methods, which are unreliable, are commonly used in its place.

Not only are they highly toxic at minute concentrations, but they can be dispersed over a wide area by algal blooms.[137] These algae then bioaccumulate into larger fish. This

poses a serious problem as some of the areas affected are the world's poorest: island communities in the Pacific and the Caribbean rely on fish as a source of protein. Indeed, in some places in the Pacific Islands, polycyclic ether contamination means that 90% of consumed fish is imported as canned fish.[137]

Despite the overwhelming damage these compounds can do to human health, the surrounding ecosystem and the economy of some of our most underprivileged countries, the polycyclic ethers hold great promise as therapeutic agents. Ciguatoxin and gambieric acid are highly potent antifungal agents, with ciguatoxin being 400 times more potent than amphotericin B, the gold standard clinical antifungal agent.[138] Brevenal and some brevetoxin derivatives may reverse the respiratory effects of inhaled brevetoxins. This antagonistic effect may also lead to treatments for respiratory diseases such as cystic fibrosis.[139]

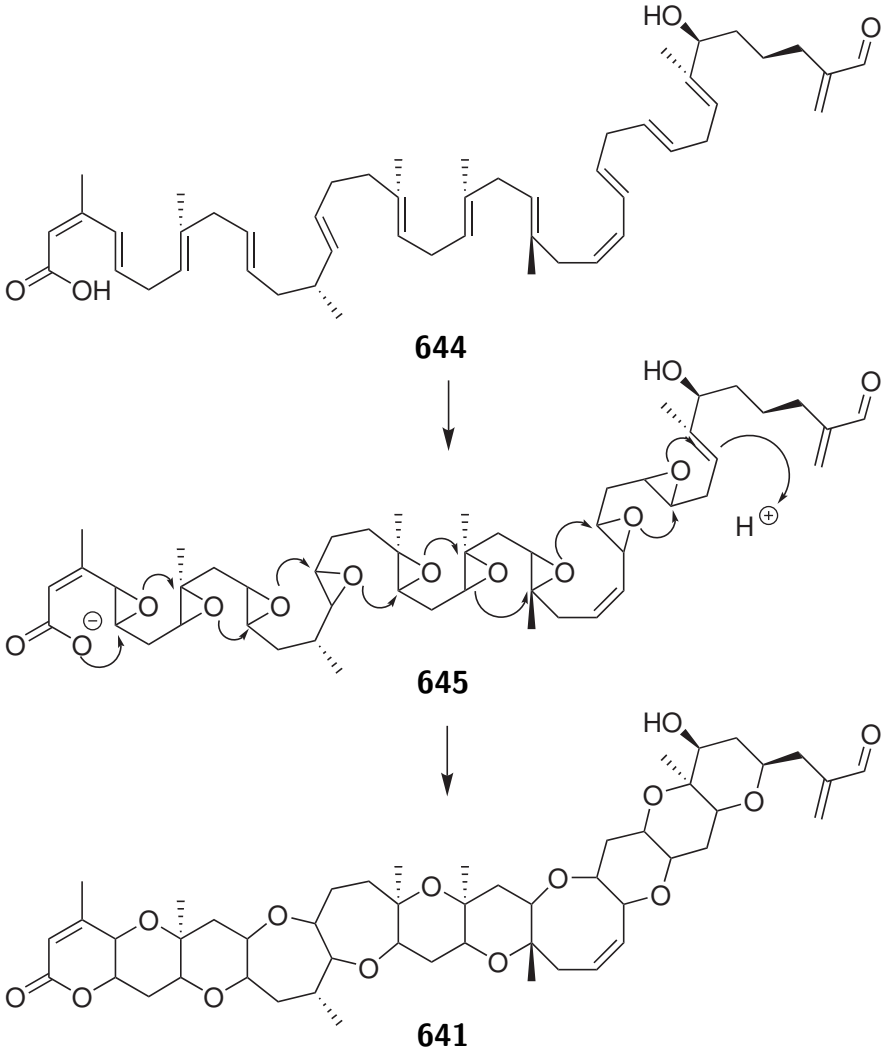
This situation is complicated by the low concentrations of these incredibly complex natural products. Isolation of small amounts of the polycyclic ethers requires obscene amounts of material. Extraction of 50 L (or 500 million cells) of *K. brevis* led to a mere 5 mg of brevetoxin B and even less of brevetoxins A and C.[140] In another example, extraction of an incredible four tonnes of moray eels led to only 350 μg of ciguatoxin.[141] If isolation from cell culture or the environment is not feasible, then chemical synthesis becomes imperative in order to unravel the unique properties of these compounds.

4.1.1 Biosynthesis

The polycyclic ethers are clearly not terpenoids: they do not follow the biogenetic isoprene rule. Labelling studies have determined that they are polyketide in origin.[142] Nakanishi proposes that a linear polyene **644** is epoxidised enzymatically to give compound **645**. Polyepoxide **645** is then cyclised through a cascade of *endo*-selective epoxide ring openings to give the fully cyclised brevetoxin B (**641**) in a single step (Scheme 135).

The synthetic trouble with this proposal is that the necessary *6-endo-tet* cyclisation is kinetically disfavoured according to Baldwin's rules and no enzyme has been found that catalyses such a reaction. Further, the hypothesis itself has never been experimentally verified. Nevertheless, investigators who have adopted biomimetic strategies have had

some success in overcoming the issues with selectivity.



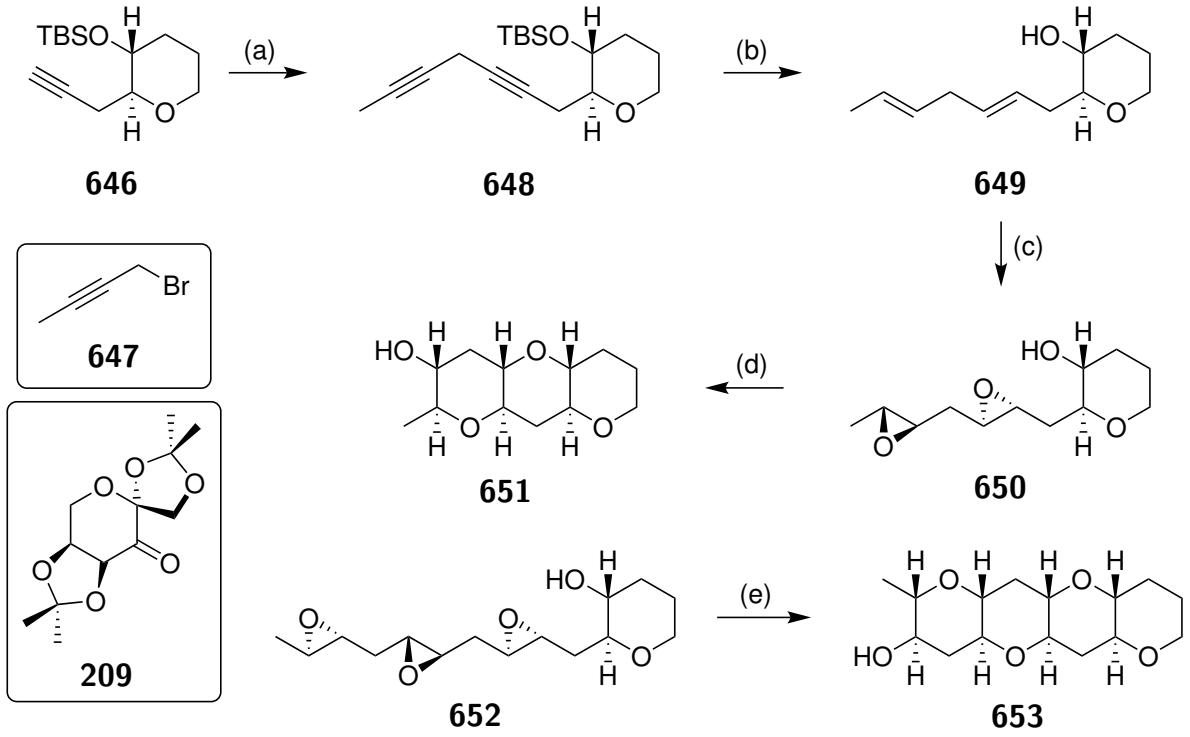
Scheme 135: Hypothesised biosynthesis of brevetoxin B (**641**).[142]

4.1.2 Previous syntheses

Our work on the terpenoids has focused on a biomimetic cascade, sometimes initiated by opening of an epoxide, which generates a fully cyclised product in a single step. Inspired by Nakanishi's hypothesis, the polycyclic ethers could very well be produced by a somewhat similar anionic epoxide opening cascade. Indeed, Jamison has investigated the synthesis of polycyclic ether compounds using an epoxide-opening cascade.[143] [144]

Jamison reported a synthesis of a series of non-natural polycyclic ether fragments.[143] Coupling of pyran **646** with propargyl bromide **647** gave the diyne **648**. Partial reduction gave the diene **649** which was immediately epoxidised under Shi conditions to give epoxide **650**. Heating this compound in water for 24 h gave the fully cyclised compound as

a single diastereomer with an astonishing 87% yield per epoxide-opening event. A similar set of reactions gave the triepoxide **652**, which could again be fully cyclised to tetracycle **653** in water in a single step.

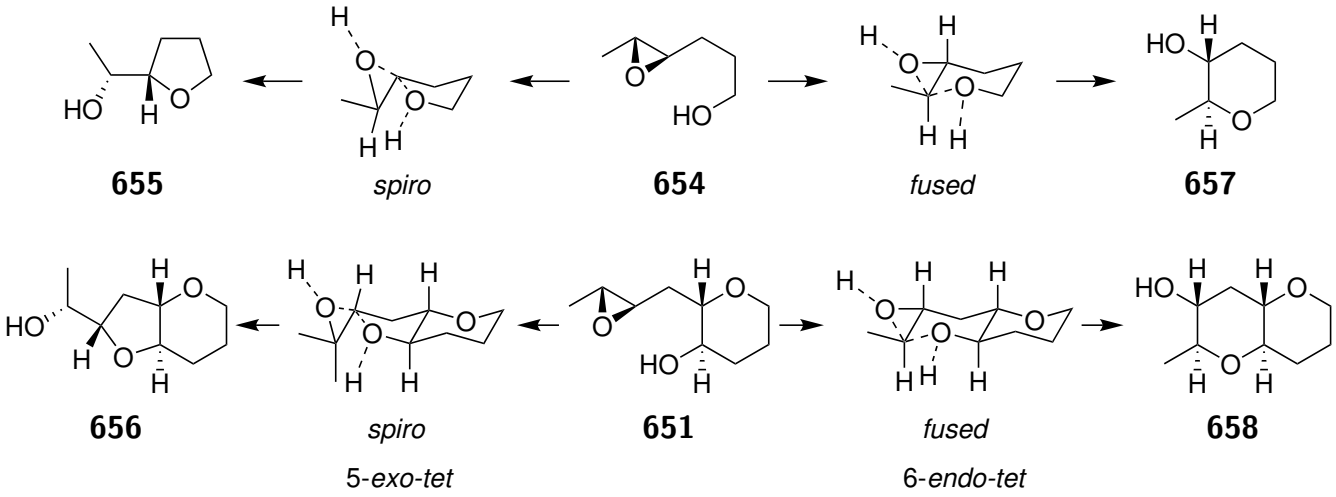


Scheme 136: Jamison's synthesis of non-natural polycyclic ether **651**.[143] (a) **647**, Cs_2CO_3, CuI, NaI, DMF, 87%. (b) Li, NH_3. (c) **209**, Oxone, $Na_2B_4O_7$, Na_2EDTA, *n-Bu*$NHSO_4$, K_2CO_3, MeCN/DMM, 50% over 2 steps, dr 4:1. (d) H_2O, 70 °C, 24 h, 60%.

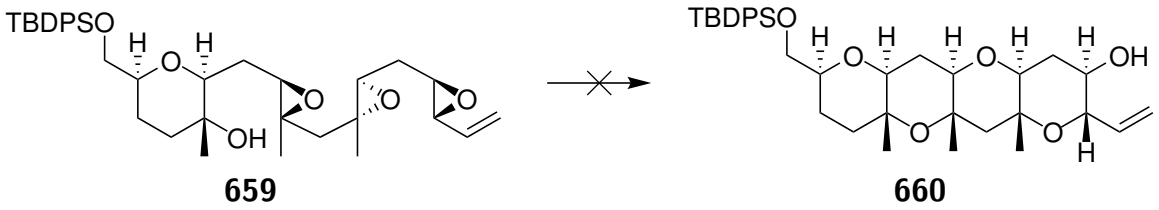
Pre-organisation is the key to the regioselectivity in this reaction (Scheme 137). The *spiro* transition state is favoured in a linear system, giving the furan product. However, in a system with a preformed chair-like ring, the *fused* transition state is more favoured giving the desired pyran. Hydrogen bonding seems to be an important factor here: in anhydrous tetrahydrofuran, the dr is 2:1, but in 100% water the dr increases to 6:1.[143]

Producing a compound like polyene **644** or its corresponding polyepoxide **645** is no small feat and there is no guarantee that a more complicated system will deliver the desired result. Indeed, a similar epoxide cascade set up by Nicolaou did not deliver the desired cyclised compound (Scheme 138).[145] Under Jamison's reported conditions as well as a variety of other anionic and cationic conditions, none of the desired compound **660** was seen. Starting material **659** was often recovered and mixtures of compounds formed by direct ring-opening attack by water were observed.

This is not the optimal strategy. Given the repeated cyclic ether motif across the molecule,



Scheme 137: Rationale for regioselectivity in Jamison's epoxide opening cascades.[143]

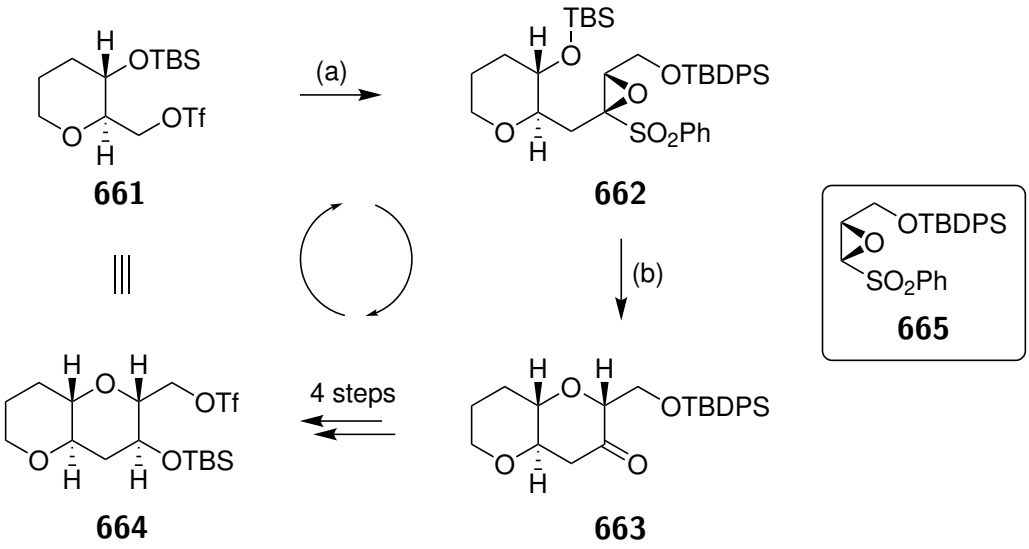


Scheme 138: Nicolaou attempted the cyclisation of polyepoxide **659** to tetracycle **660** under a wide variety of conditions leading only to recovery of starting material or polyhydroxylated side products.[145]

an iterative strategy may be more appropriate. The same sequence of transformations may be repeated *ad infinitum* to produce a molecule of the desired size, leading to a generic strategy for the entire family of polycyclic ether compounds. We have already seen examples of this type of strategy in the work on terpenoids: She's synthesis of dasyscyphin D (Scheme 98)[97] and Chen's synthesis of polyene alcohols (Scheme 122).[119]

Mori has reported an iterative synthesis of the polycyclic ethers that still uses a bio-inspired epoxide-opening cyclisation (Scheme 139).[146] Triflate **661** is displaced by the anion of sulfone **665** to produce compound **662**. Treating epoxide **662** with *p*-toluenesulfonic acid deprotects the silyl ether and activates the epoxide for cyclisation, producing ketone **663**. A series of protecting group manipulations produces compound **664**, which completes the cycle and allows for the same set of reactions to be repeated, generating a further ring. In this case, *6-endo-tet* cyclisation is enforced through charge stabilisation α to the sulfone.

This strategy requires six steps per iterative cycle, to produce only the six-member ring with no substitution at the ring junctions. For brevetoxin, a compound containing ten



Scheme 139: Mori's iterative cycle.[146] (a) **665**, *n*-BuLi, DMPU. (b) TsOH.

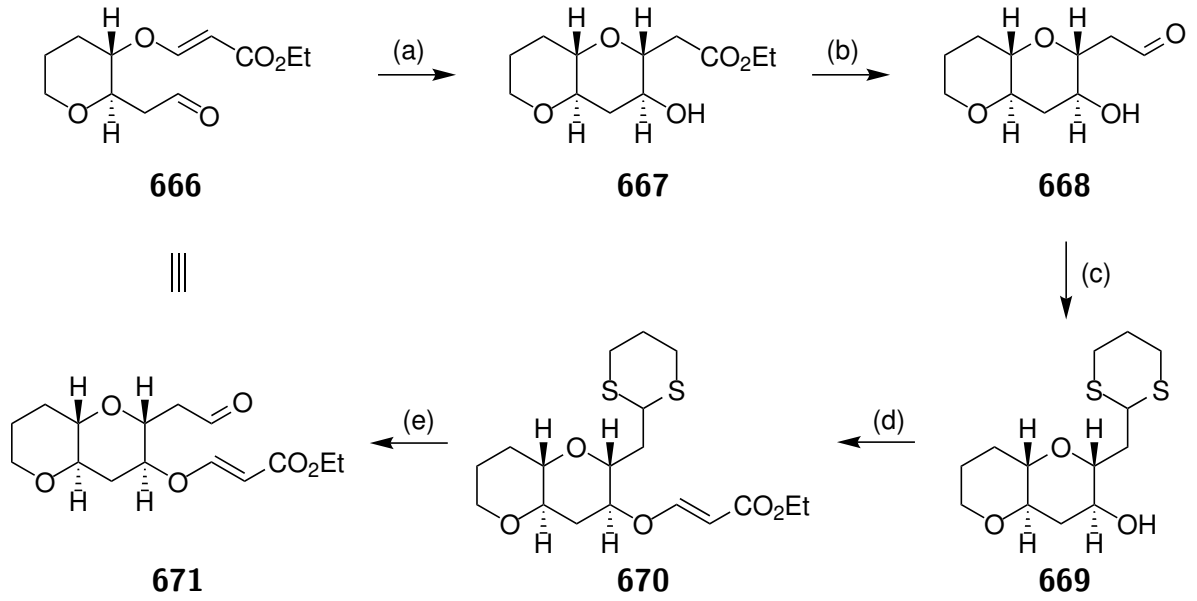
rings, that would still require sixty steps to produce the core compound even before extensive elaboration including ring expansion and methylation at ring junctions.

One of the most efficient iterative syntheses of the polycyclic ether framework was developed by Nakata by moving away from biology (Scheme 140).[147] Aldehyde **666** is cyclised by samarium(II) iodide to give alcohol **667**, then the ester is reduced to the aldehyde **668** and protected as the dithiane **669**. *N*-Methylmorpholine catalysed coupling between alcohol **669** and ethyl propiolate gives ester **670**, containing all the necessary carbons for another ring. Deprotection of the dithiane gives aldehyde **671**, allowing for another cycle to be performed.

Nakata has successfully applied this methodology to synthesise a number of polycyclic ether natural products. A highlight is the synthesis of brevetoxin B.[147] Nicolaou's first synthesis took 12 years and 123 steps with a paltry overall yield of 9.2×10^{-4}%.[3] Nakata produced this exceptionally large molecule in 90 steps with a far higher yield of 0.15%. Despite the low overall yields, this is still far improved from biomass isolation and previous synthetic approaches.

4.1.3 McErlean group efforts

Nakata's synthetic strategy is the most efficient to date, but it is far from optimal. Samarium(II) iodide, used in the key cyclisation step, is expensive and often temperamental.



Scheme 140: Nakata's samarium(II) iodide iterative strategy.[147] (a) SmI_2, MeOH, THF. (b) DIBAL. (c) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$. (d) $HC{\equiv}CCO_2Et$, NMM. (e) MeI.

Other reagents which are far easier to handle can also effect similar transformations. The use of a dithiane protecting group is particularly undesirable. 1,3-Propanedithiol used in its installation is toxic with a foul odour. Methyl iodide used in its deprotection is carcinogenic and the sulfide byproduct of deprotection is also foul smelling. A protecting-group free strategy would avoid these undesirable reagents and should make the iterative cycle more efficient through a lower step count.

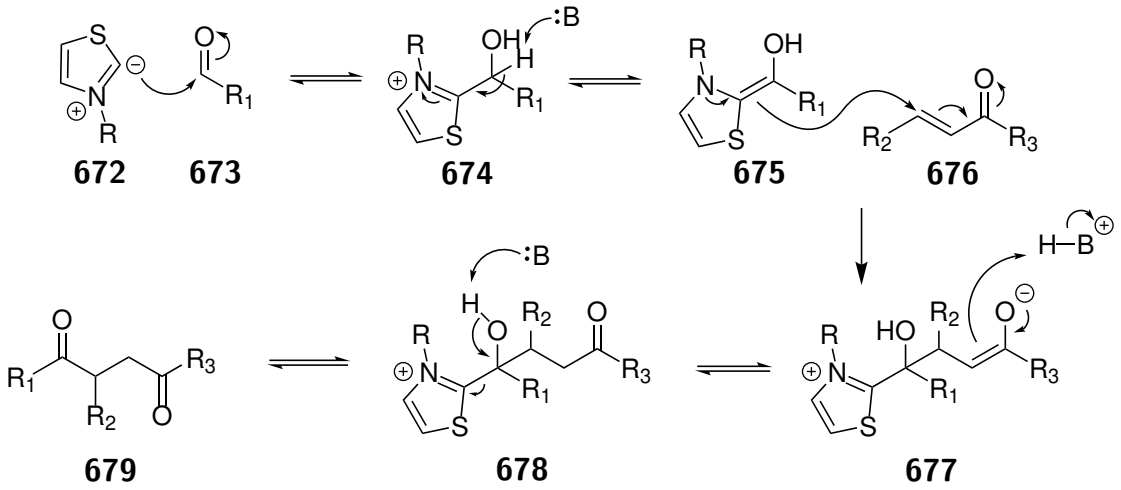
There has been an ongoing project in the McErlean group to deliver an improved synthesis of the polycyclic ethers and Nakata's strategy lays a good groundwork for this. Our group's focus has been on avoiding the use of protecting groups and using alternative reagents to samarium(II) iodide, particularly the Stetter reaction.

Stetter reaction

The Stetter reaction is an organocatalytic reaction in which an aldehyde undergoes addition to a Michael acceptor. It is a form of *umpolung* chemistry whereby a normally electrophilic aldehyde carbon is converted into a nucleophile by the action of an organocatalyst, typically an *N*-heterocyclic carbene.[148]

In a typical example, an NHC such as thiazolium **672** reacts first with an aldehyde **673** (Scheme 141). An adduct **674** is formed, which tautomerises to the Breslow intermediate

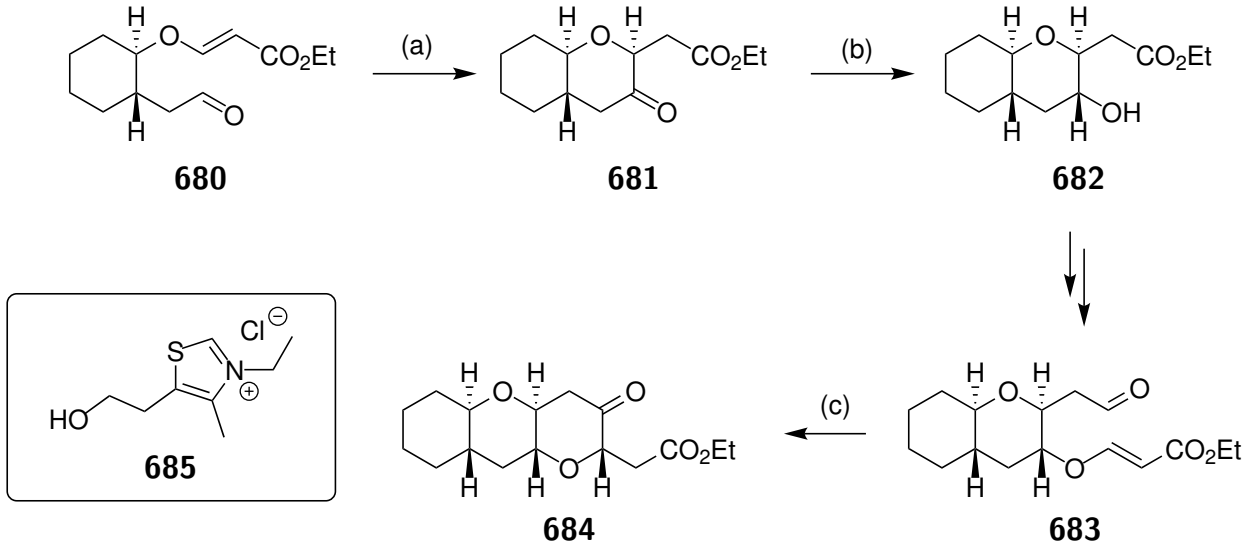
675. The aldehyde carbon is now nucleophilic and can react with Michael acceptor **676**, forming adduct **677**. Tautomerisation to ketone **678** and elimination of the NHC leads to the regeneration of the catalyst and formation of the adduct **679**.[148]



Scheme 141: Mechanism of the Stetter reaction.[148]

McErlean's first foray into using the intramolecular Stetter reaction to produce polycyclic ether scaffolds relied on ester **680** (Scheme 142).[149] Esters were previously understood to be unreactive under these conditions and an aryl aldehyde or a malonate acceptor was required for the reaction to proceed. The presence of a β-oxygen substituent was also expected to be troublesome. Nevertheless, treatment of aldehyde **680** with a superstoichiometric amount of catalyst **685** delivered the desired ring-closed compound **681** in excellent yield. Importantly, ring-closed compound **681** was produced as a single isomer and the subsequent reduction of the cyclic ketone also gave the desired stereochemistry, giving the *trans*-configured compound **682**. After elaborating alcohol **682** to aldehyde **683**, Stetter reaction under the same conditions was performed again, pleasingly giving tricyclised compound **684**.

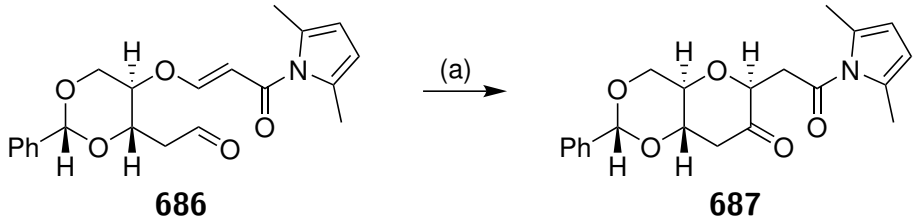
McErlean was able to demonstrate that the intramolecular Stetter reaction was possible on esters such as compound **680** and that the reaction delivered the desired *trans,syn,trans* stereochemistry. This did not lead to any increase in efficiency: McErlean required the same reaction sequence to produce aldehyde **683** from alcohol **682**, with a further reduction step now included. We should be able to abbreviate this sequence by using a different Michael acceptor, as the protecting group manipulation needed to regenerate an aldehyde from the ester is inefficient.



Scheme 142: McErlean's first successful cyclisation using the Stetter reaction for production of polycyclic ethers.[149] (a) **685**, DBU, THF, Δ, 98%. (b) $NaBH_4$, 94%. (c) **685**, DBU, THF, Δ, 81%.

N-acylpyrroles

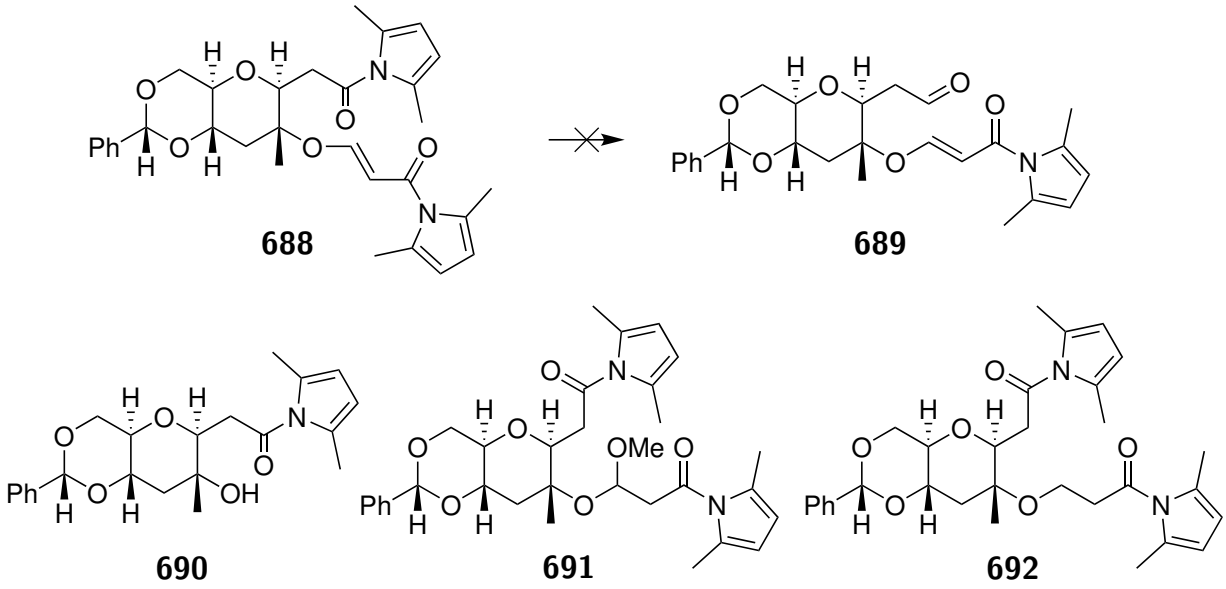
A key advancement within the McErlean group has been replacing the ester moiety in Nakata's synthesis with an *N*-acylpyrrole functionality. Far from being standard amides, pyrrolic amides are far more electron withdrawing due to the aromaticity of the pyrrole unit.[150] An important advantage is that the tetrahedral intermediate formed by hydride reduction is stable. Combined, this means that reduction can be effected with even a weak reductant such as sodium borohydride and will lead selectively to a carbinol intermediate which can be successively collapsed to the aldehyde. The McErlean group successfully applied the Stetter reaction to unsaturated *N*-acylpyrroles such as **686** (Scheme 143).[151]



Scheme 143: Cyclisation of *N*-acylpyrrole **686** under Stetter conditions to give the desired diastereomer **687**.[151] (a) **695**, Et_3N, THF, Δ, 86%.

Later work within the McErlean group elaborated the cyclised ketone **687** to di-*N*-acylpyrrole **688**, with the aim of selectively reducing the saturated *N*-acylpyrrole to aldehyde **689** *via* the carbinol, allowing for further cyclisation.[152] Unfortunately, none of the reducing agents tried were able to reduce bis-*N*-acylpyrrole **688** to aldehyde **689**.

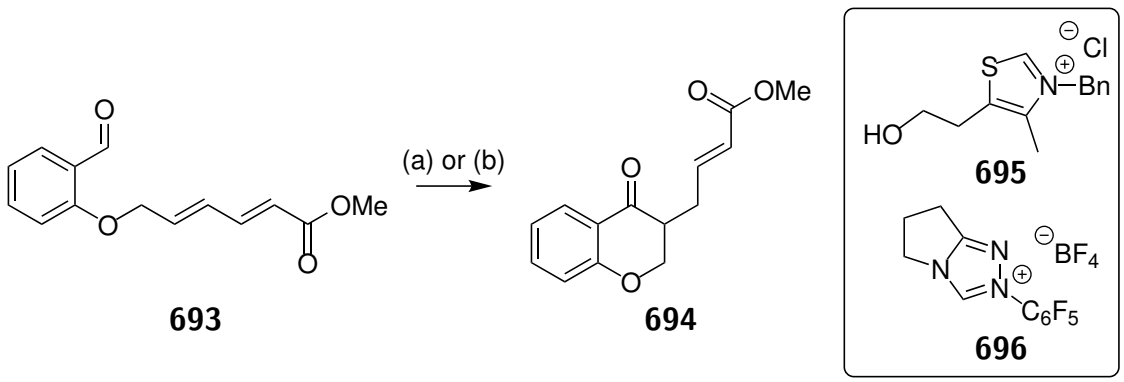
Under a range of conditions, either eliminated product **690** or reduced products **691** or **692** were found. Only upon treatment with DIBAL could trace amounts of aldehyde **689** be found (Scheme 144).



Scheme 144: The desired reduction of *N*-acylpyrrole **688** could not be effected.

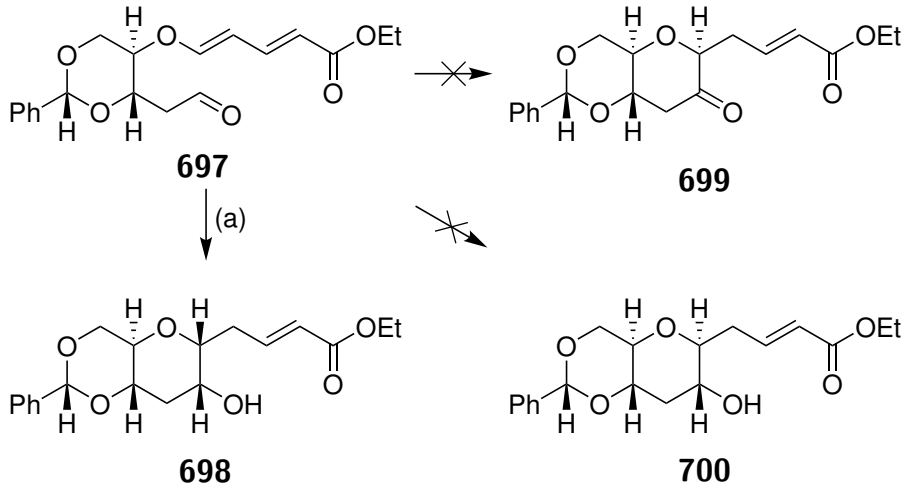
Our suspicion was that the pyrrolic methyl group blocks the C–O π* antibonding orbital of the carbonyl, preventing attack by hydride. We will pursue a route to the 2,5-unsubstituted *N*-acylpyrrole where the π* antibonding orbital of the carbonyl is accessible to reducing agents.

In addition, this strategy only applies to the synthesis of 6-member rings. The McErlean group later developed the vinylogous Stetter reaction, in which an acyl anion equivalent was added to an $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compound such as **693** to generate the 1,6 adduct **694** (Scheme 145).[153]



Scheme 145: Vinylogous Stetter reaction producing chromanone **694**.[153] (a) **695**, Cs_2CO_3, PhMe, 70 °C, 52%. (b) **696**, DBU, PhMe, rt, 76%.

The extended Stetter methodology could not be successfully applied to the synthesis of polycyclic ethers via ester **697**, but reductive cyclisation of aldehyde **697** using samarium(II) iodide generated an undesired diastereomer of alcohol **699** (Scheme 146). We want to revisit this result using alternative conditions which avoid the difficulties of samarium(II) iodide. These alternative conditions should also deliver the desired diastereomer **699**.



Scheme 146: Vinylogous Stetter reaction of ester **697** failed but samarium(II) iodide reaction proceeded with the undesired stereochemistry. (*unreported results*) (a) SmI_2, THF, MeOH, –15 °C, 25%.

Further exploration of this idea lead to a cassette strategy, where the cyclised compound **701** could be elaborated in a variety of ways, leading to different substitution and ring sizes (Figure 35). Reduction of the ketone should lead to spontaneous lactonisation delivering compound **702**, which could be derivatised further to continue the iterative synthesis. Conjugate addition onto the α,β-unsaturated carbonyl and subsequent cyclisation could install functionality at the 4 position (compound **703**), while hydroboration might deliver a synthetic handle at the 3-position (compound **704**). Finally, dihydroxylation of the remaining alkene to give a compound like **705** would mask an aldehyde for a subsequent Stetter reaction, with elaboration giving aldehyde **706**. Compound **701** could prove to be a versatile intermediate towards a number of ring architectures with different substitution patterns.

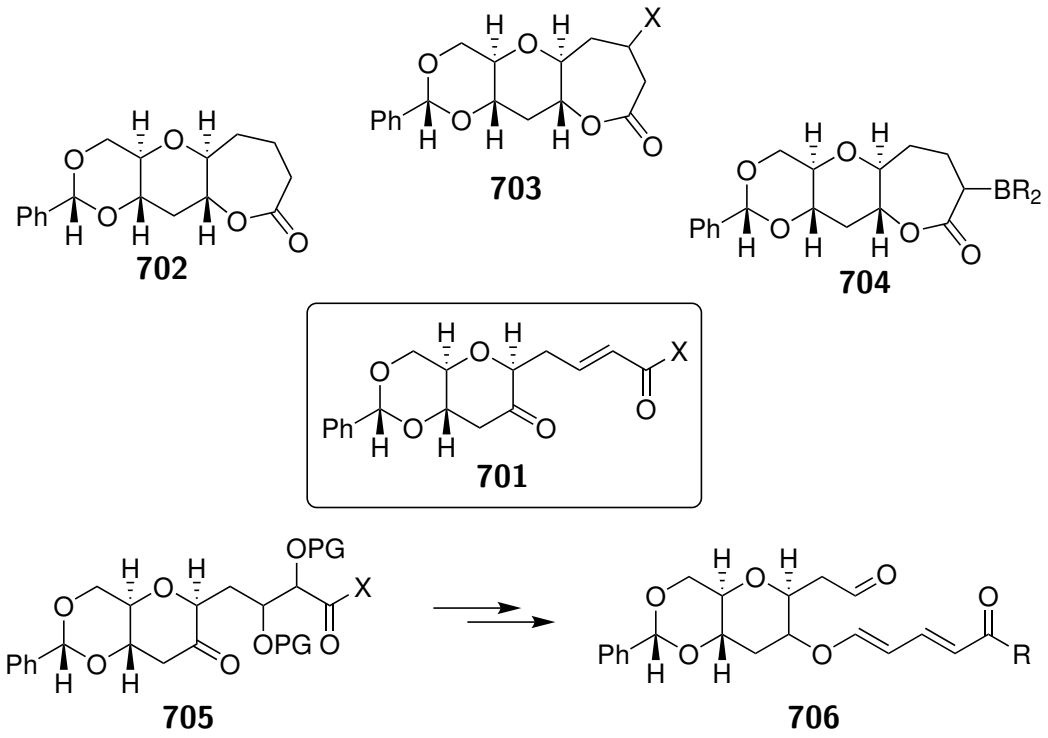


Figure 35: Cyclised compound **701** could be elaborated to a number of frameworks.

4.2 Goals

Above, we have discussed a number of shortcomings of Nakata's polycyclic ether methodology and we expect that the methodology could be made more efficient. We will focus on the following points:

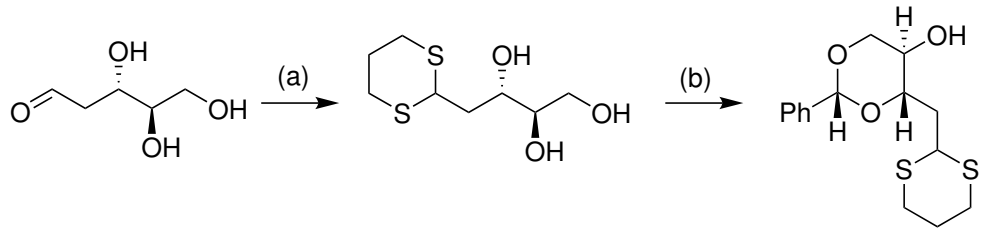
1. Investigate alternative methodologies for ring closure of known substrate.
2. Expand on the McErlean group's previous use of unsubstituted *N*-acylpyrroles.
3. Investigate the use of α-ketoesters as masked aldehyde surrogates in the Stetter reaction.
4. Use the vinylogous Stetter reaction to expand the variety of available cyclised intermediates as viable parts of a reiterative strategy.

These avenues should lead to a successful, more efficient iterative strategy for the construction of polycyclic ethers, leading to a final aim:

5. Construct a polycyclic marine ether compound; or an advanced intermediate or fragment that could be used as part of a convergent synthesis of the polycyclic ethers.

4.3 Results

The starting point for our investigations is the scaffold **709** used by Nakata in his synthesis of brevetoxin B and other polycyclic ether fragments (Scheme 147).[147] 2-Deoxy-D-ribose (**707**) was protected as the dithiane **708** by treating with 1,3-propanedithiol in a mixture of chloroform and 6 M hydrochloric acid. Treating ribose derivative **708** with benzaldehyde dimethyl acetal in the presence of catalytic *para*-toluenesulfonic acid selectively gave the dioxane **709**. The McErlean group has always produced compound **709** with trace impurities, with complete purification occurring following the coupling of an acetylene to the free alcohol.



707 **708** **709**

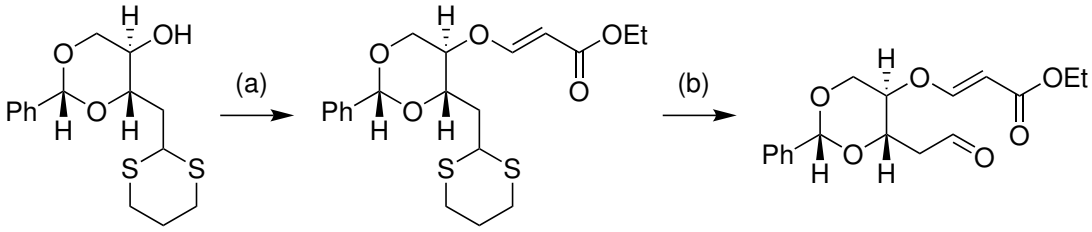
Scheme 147: Synthesis of initial ring **709**. (a) 1,3-propanedithiol, HCl (6 M), $CHCl_3$, 52%. (b) $PhCH(OMe)_2$, TsOH, EtOAc, >90%.

4.3.1 Cyclisation methodology

Other cyclisation methodologies should open up new options for an iterative strategy towards the polycyclic ethers. Different reagents and reaction pathways may allow selectively reaction at one site over another, allowing us to bypass troublesome protecting groups or open up new strategies.

The emerging field of photoredox catalysis is one such idea. We can abstract the hydrogen from an aldehyde, forming an acyl radical which could add onto an electron deficient alkene to form a cyclised ring in a similar fashion to the existing Stetter and samarium(II) iodide methodologies. The known compound **711** would act as a testbed for these methodologies. Coupling alcohol **709** with ethyl propiolate using *N*-methylmorpholine as a catalyst gave compound **710**, which was deprotected using methyl iodide to reveal the aldehyde **711** (Scheme 148).

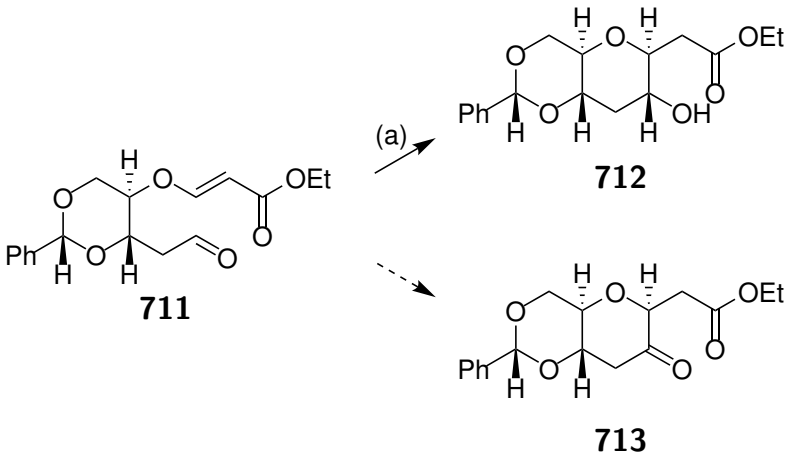
From Nakata's work, we know that aldehyde **711** cyclises to alcohol **712** by the action of



709 **710** **711**

Scheme 148: Synthesis of cyclisation precursor **711**. (a) NMM, HC≡CCO_2Et, CH_2Cl_2, 92% over 2 steps. (b) MeI, $NaHCO_3$, $MeCN/H_2O$, 78%.

samarium(II) iodide.[147] We could also form the corresponding ketone **713** via the Stetter reaction of the same aldehyde **711** (Scheme 149).

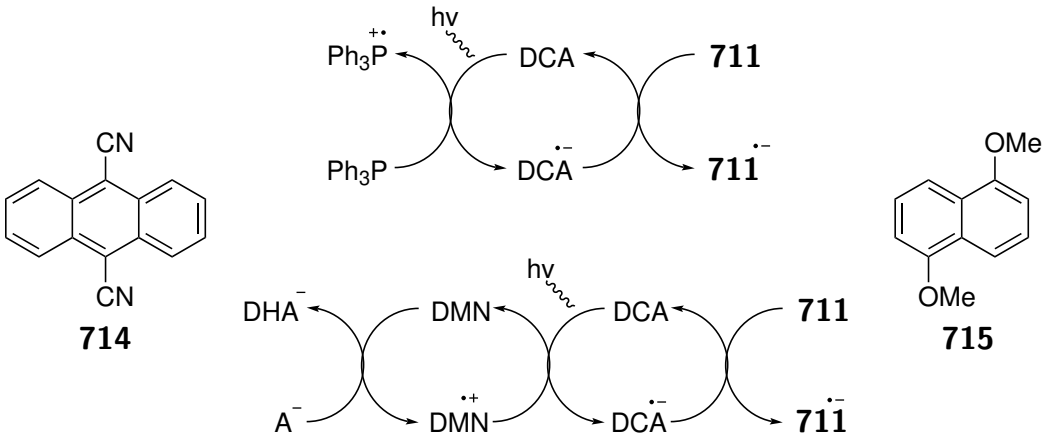


711 **712** **713**

Scheme 149: We wanted alternative cyclisation methodologies to perform the reactions to alcohol **712** and ketone **713**. (a) SmI_2, MeOH, THF, 0 °C, 95%.[147]

Under a wide range of reaction conditions using photocatalysis, we were unable to produce the cyclised compounds **712** or **713**. Pandey had introduced a photoredox process exciting 9,10-dicyanoanthracene (DCA; **714**) with light to generate the radical anion which could reduce an aldehyde to the ketyl radical (Scheme 150), providing a similar reaction pathway to samarium(II) iodide.[154] The nucleophilic ketyl radical could attack a suitable electron withdrawing alkene intramolecularly, in a compound such as ester **711**. We saw no reaction under either of the photocatalytic systems they describe: using triphenylphosphine as a sacrificial electron donor (Table 32, entry 1) or using 1,5-dimethoxynaphthalene (DMN; **715**) as a primary electron donor and ascorbic acid as a sacrificial electron donor (Table 32; entry 2).

Nicewicz reported metathesis between diphenyldisulfide (**717**) and ditolyldisulfide (**718**) under irradiation by visible light (450 nm).[155] They concluded that this was a homolytic



Scheme 150: Pandey's photoredox process.[154] A = ascorbate; DCA = 9,10-dicyanoanthracene (**714**); DHA = dehydroascorbate; DMN = 1,5-dimethoxynaphthalene (**715**).

cleavage process and we hoped we could initiate a radical reaction using blue light and diphenyldisulfide, with the resulting thiophenyl radical acting as a hydrogen shuttle (Scheme 151).

We could not replicate this result on compound **711**, either by itself (Table 32; entries 3–4) or in the presence of an inorganic photocatalyst, either tris(bipyridine)ruthenium(III) chloride (Table 32; entries 5–7) or tris(phenylpyridine)iridium(III) (Table 32; entries 10–11). The addition of other hydrogen atom sources such as Hantzsch ester (**716**) or dodecanethiol did not lead to any change, nor did the addition of potassium persulfate as a one-electron oxidant.

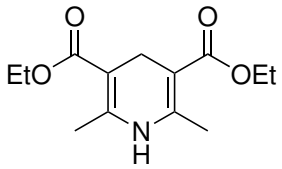
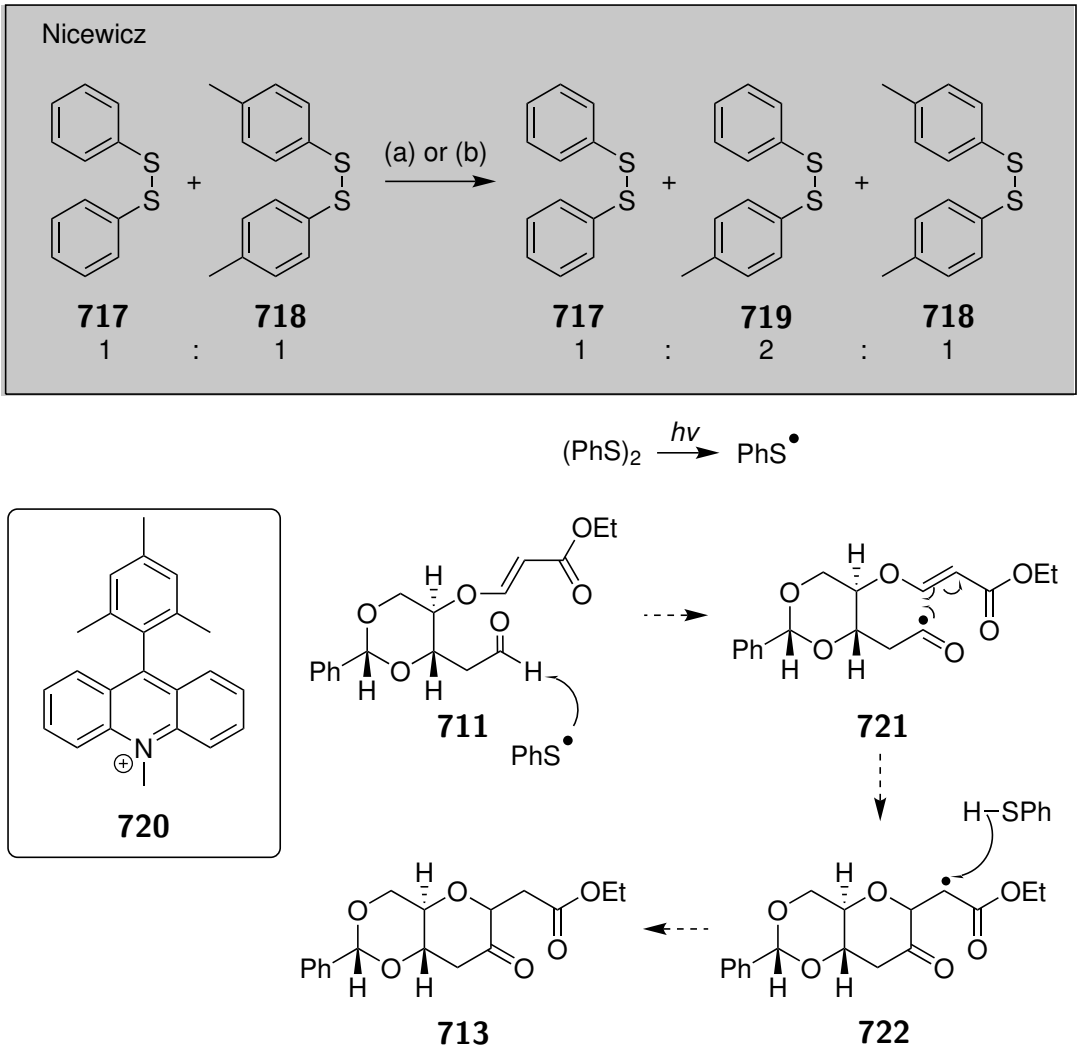


Figure 36: Hantzsch ester (**716**).

Other photoredox systems initiated by tris(bipyridine)ruthenium(III) chloride (Table 32; entries 8–9) or tris(phenylpyridine)iridium(III) (Table 32; entries 12–13) also led to no reaction.

Finally, we attempted to use tetrabutylammonium decatungstate (TBADT; **723**) as a photocatalyst. TBADT is easily prepared from tetrabutylammonium bromide and sodium tungstate in water and can abstract an aldehyde hydrogen to form the acyl radical. While it absorbs in the UV spectrum, it can be activated conveniently by sunlight rather than using

a UV lamp.[156]



Scheme 151: Nicewicz's metathesis of disulfides **717** and **718** under blue light.[155] We envisioned using the same strategy to generate a thiophenyl radical which could initiate radical cyclisation of aldehyde **711**. (a) blue LED (450 nm), DCE. (b) **720**, blue LED (450 nm), DCE.

TBADT synthesised by us using Fagnoni's method was difficult to activate in sunlight and led to no reaction (Table 32; entry 14). The same happened when treating a reaction directly with a UV lamp (Table 32; entry 15). However, treating a solution of TBADT with no reactants under the same conditions led to activation as identified by the deep blue colour of the activated complex.

We could not find any set of photoredox conditions which would effect the desired coupling of an aldehyde onto the α,β-unsaturated ester. We would have to rely on the Stetter reaction or samarium(II) iodide for these transformations.

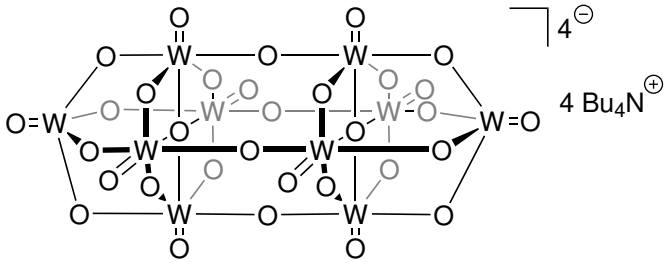


Figure 37: Tetrabutylammonium decatungstate (**723**).

Table 32: Attempted photoredox cyclisation conditions. All sets of conditions led to no reaction and full recovery of starting material. Blue LED λ_{max} = 465 nm; UV λ_{max} = 365 nm. CFL = compact fluoresecent lamp; DCA = 9,10-dicyanoanthracene; DMN = 1,5-dimethoxynaphthalene; TBADT = tetrabutylammonium decatungstate.

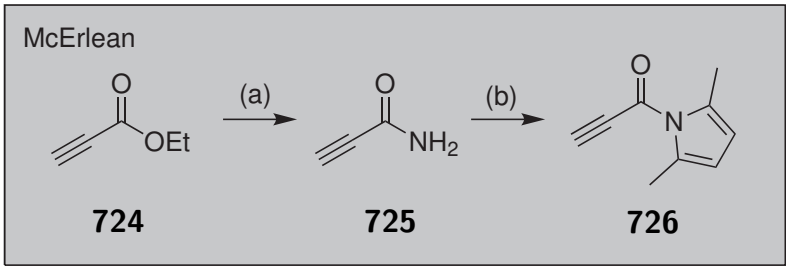
#	Photocatalyst	Solvent	Additives	Light source
1	DCA	DMF/*iPr*OH/H_2O	Ph_3P	CFL
2	DCA	DMF/*iPr*OH/H_2O	DMN, sodium ascorbate	CFL
3	$(PhS)_2$	DCE	–	Blue LED
4	$(PhS)_2$	DCE	–	CFL
5	$Ru(bpy)_3Cl_2$	MeCN	$(PhS)_2$	Blue LED
6	$Ru(bpy)_3Cl_2$	MeCN	$(PhS)_2$, $K_2S_2O_8$	Blue LED
7	$Ru(bpy)_3Cl_2$	MeCN	$(PhS)_2$, **716**	Blue LED
8	$Ru(bpy)_3Cl_2$	MeCN	$K_2S_2O_8$, **716**	Blue LED
9	$Ru(bpy)_3Cl_2$	MeCN	$K_2S_2O_8$, dodecanethiol	Blue LED
10	$Ir(ppy)_3$	MeCN	$(PhS)_2$	Blue LED
11	$Ir(ppy)_3$	MeCN	$(PhS)_2$, **716**	Blue LED
12	$Ir(ppy)_3$	MeCN	$K_2S_2O_8$, **716**	Blue LED
13	$Ir(ppy)_3$	MeCN	$K_2S_2O_8$, dodecanethiol	Blue LED
14	TBADT	MeCN	–	sunlight
15	TBADT	MeCN	–	UV lamp

4.3.2 Unsubstituted *N*-acylpyrroles

Given the requirement for dithiane protecting groups in Nakata's approach using α,β-unsaturated esters as intramolecular electrophiles,[147] the McErlean group has for some time attempted to apply Nakata's iterative strategy to α,β-unsaturated N-acylpyrroles as a surrogate Michael acceptor.[151]

The McErlean group's efforts using N-acylpyrroles has typically relied on the 2,5-dimethyl

substituted compound **726** for two reasons. Firstly, synthesis was far more convenient, requiring only a Paal-Knorr condensation onto propiolamide (**725**; Scheme 152). This is low yielding but step efficient. Second, the unsubstituted *N*-propiolylpyrrole (**731**) is highly volatile, leading to difficulties in synthesis, isolation and storage. We suspect that the methyl groups at the 2 and 5 positions block direct reduction of the carbonyl, leading to unexpected reaction at other functionalities. To test this idea, we needed to synthesise the unsubstituted compound **731**.

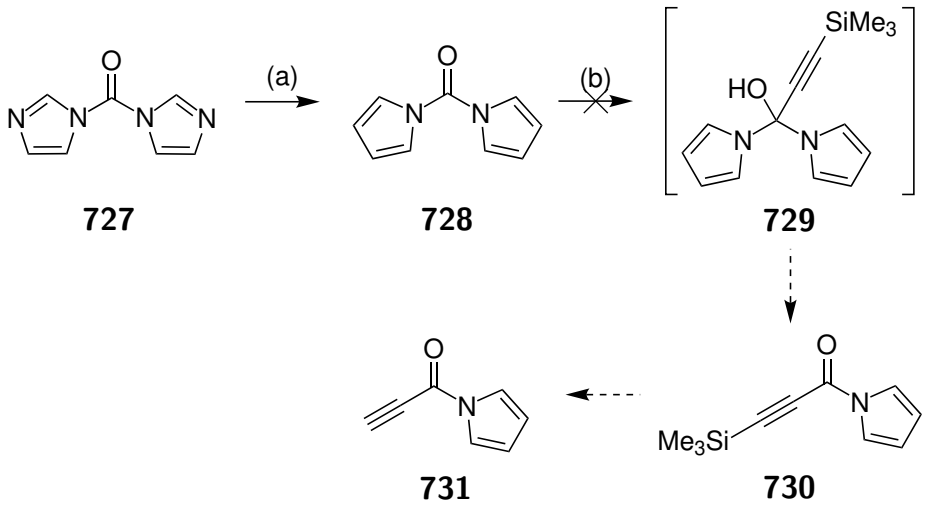


Scheme 152: Reported conditions for synthesising *N*-acylpyrrole **726**.[151] (a) NH_3 (aq.), –20 °C, 52%. (b) 2,5-hexanedione, TsOH, PhH, Δ, 47%.

Direct amidation of propiolic acid with pyrrole in these conditions does not work. Pyrrole is a weak nucleophile and standard amidation conditions using dicyclohexylcarbodiimide and similar reagents led to no reaction. Addition of dimethylaminopyridine as a nucleophilic catalyst led to polymerisation, as did addition of base to initially deprotonate pyrrole.

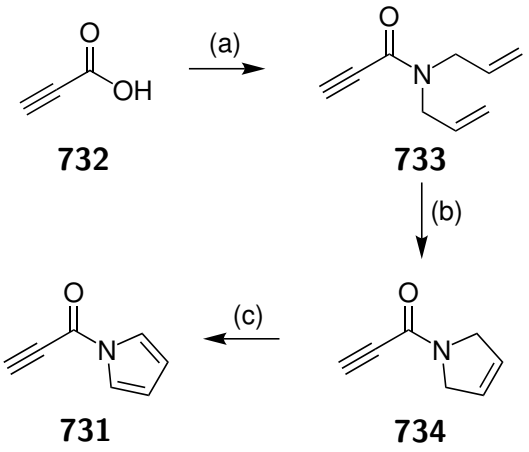
Therefore, we attempted to use carbonyldipyrrole (**728**) as a source of the *N*-acylpyrrole functionality. Carbonyldipyrrole was produced by heating carbonyldiimidazole in pyrrole at reflux. Treating trimethylsilylacetylene with *n*-butyllithium, followed by addition of carbonyldipyrrole should have led to the alkynylsilane **730**, but no reaction was seen.

Given the difficulties in making *N*-acylpyrrole **731**, we took a different approach. Coupling between propiolic acid (**732**) and *N,N*-diallylamine using DCC gave diallylamide **733** (Scheme 154). Diallylamide **733** was then subjected to ring closing metathesis using Grubbs first generation catalyst. Strangely, the reaction proceeded normally for about one hour, at which time the reaction stalled, suggesting build-up of a substance which inhibited the catalyst and giving us a low yield of the ring-closed compound **734**. Grubbs-Hoveyda first generation catalyst and Grubbs second generation catalyst both led to no production of amide **734**. Additives such as acetic acid did not prevent the reaction from stalling, nor did heating at reflux or changing reaction solvent.



Scheme 153: Attempted synthesis of **731**. (a) pyrrole, Δ, 43%. (b) TMS-C$\equiv$CH, *n*-BuLi, THF, then **728**.

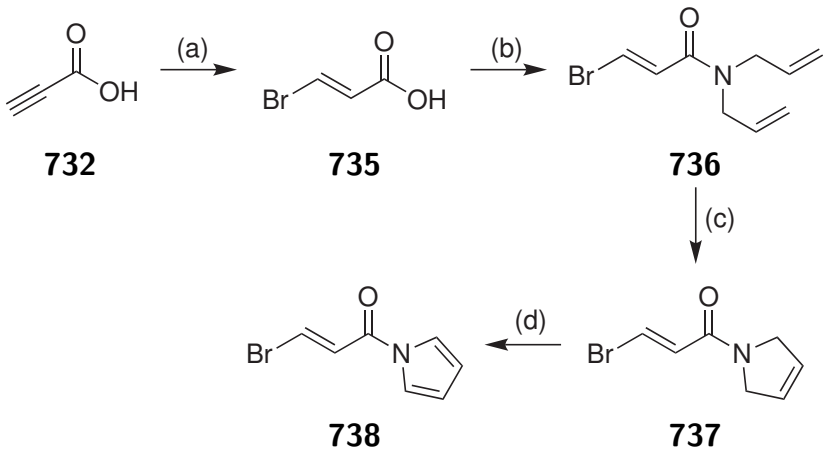
Oxidation was performed using DDQ in tetrahydrofuran at reflux, however the product was too volatile and could not be isolated, as with the attempt in Scheme 153. We could not couple propiolyl amide **734** directly with alcohol **709**. Amide **734** was not reactive enough under these conditions.



Scheme 154: Synthesis of **734**. (a) DCC, diallylamine, CH_2Cl_2, 81%. (b) Grubbs I, CH_2Cl_2, 27%. (c) DDQ, THF, Δ, 0%.

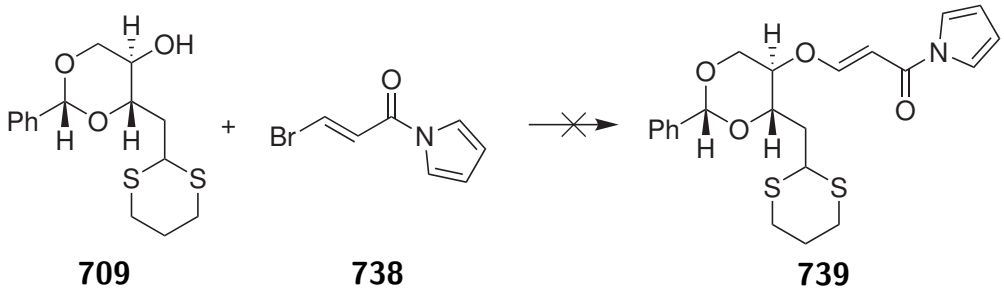
Bromoacrylamide **738** should be easier to handle. The addition of a bromine atom should make this compound less volatile than amide **731**. Treating propiolic acid with aqueous hydrobromic acid at reflux gave bromoacrylic acid (**735**) as the single (*E*) diastereomer in good yield (Scheme 155). Amidation of acid **735** with diallylamine was performed using dicyclohexylcarbodiimide to give acrylamide **736** in an acceptable yield. Again, ring closing metathesis with Grubbs generation I stopped after an hour, giving a modest yield of amide **737** with unrecovered starting material being recovered. Oxidation with DDQ

converted the dihydropyrrole **737** to the *N*-acylpyrrole **738**, which was a solid and not a volatile compound.



Scheme 155: Synthesis of **738**. (a) HBr, Δ, 65%. (b) diallylamine, DCC, CH_2Cl_2, 57%. (c) Grubbs I, CH_2Cl_2, 32%. (d) DDQ, THF, Δ, 53%.

Unfortunately, we could not couple bromoacrylamide **738** with alcohol **709** under a variety of acidic and basic conditions. With the inability to couple an unsaturated *N*-acylpyrrole to alcohol **709**, we determined that this strategy was not viable: we could not circumvent the shortcomings of Nakata's synthesis by employing sterically unhindered *N*-acylpyrroles.



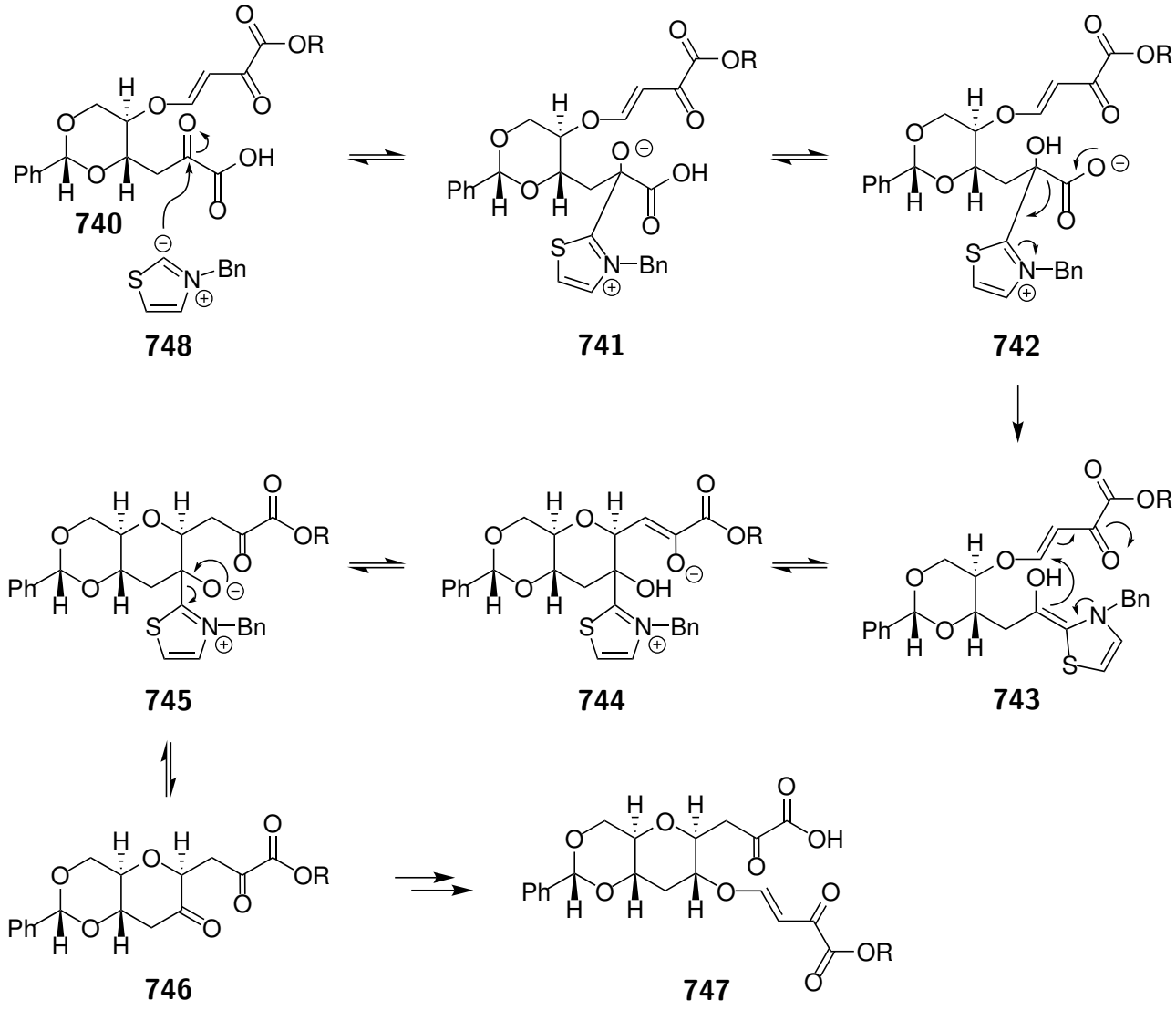
Scheme 156: Coupling between alcohol **709** and bromoalkene **738** was unsuccessful under a range of conditions. (Table 33)

Table 33: Coupling conditions between alcohol **709** and vinyl bromide **738**.

Reagent	Solvent	T (°C)	Outcome
NMM	CH_2Cl_2	rt	n.r.
AgOTf	CH_2Cl_2	rt	n.r.
CuI	CH_2Cl_2	rt	n.r.
DBU	CH_2Cl_2	rt	decomp. + **709**

4.3.3 α-Ketoacid strategy

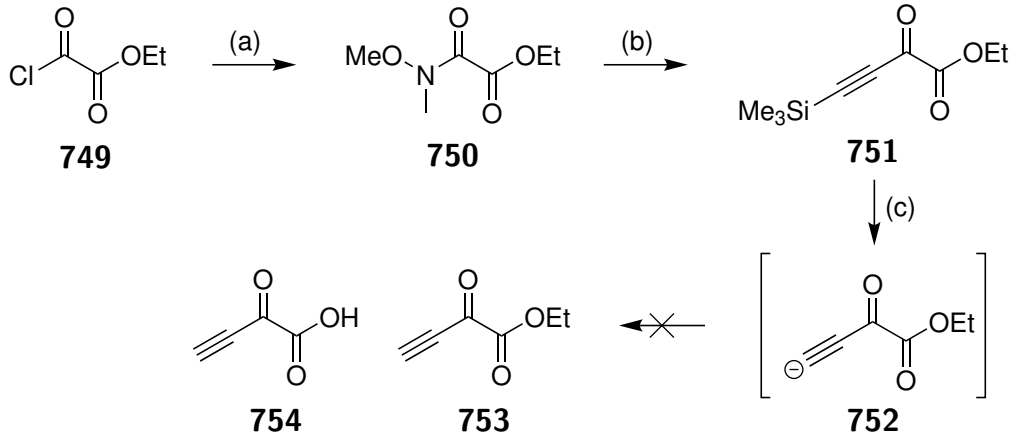
The thiazolium catalyst commonly employed for Stetter reactions is a synthetic mimic for thiamine, which acts as a cofactor for pyruvate decarboxylase in transforming pyruvate into acetaldehyde in biology. We can exploit this reactivity *ex-vivo*: we could react a similar α-ketoacid **740** with an *N*-heterocyclic carbene **748** giving adduct **741** which loses carbon dioxide to form the active Breslow intermediate **743**. Cyclisation would proceed via the normal Stetter pathway to give cyclised compound **746** (Scheme 157). We could then elaborate cyclised compound **746** to give α-ketoacid **747**, which could undergo another cyclisation.



Scheme 157: Decarboxylative Stetter reaction on α-ketoacid **740** would generate compound **746** as part of an iterative strategy.

We needed to produce a route to the alkyne coupling partner **753** for this strategy to work (Scheme 158). Starting from ethyl oxalyl chloride (**749**), reaction with *N,O*-dimethylhydroxylammonium hydrochloride gave the Weinreb amide **750**. Then trimethyl silylacetylene was deprotonated using *n*-butyllithium and reacted with Weinreb amide **750** to give compound **751**. Unfortunately, all attempts to deprotect the silyl group to give ester **753** or acid **754** failed (Table 34). Even the mildest basic conditions, dissolving ester **751** in methanol that had been passed over the basic alumina column in a PureSolv solvent purification system, led to rapid decomposition with no compounds isolated from the reaction mixture. Dissolving silane **751** in wet methanol from the School's drum stock gave no reaction. Using tetrabutylammonium fluoride in THF also led to rapid decomposition. The intermediate acetylide anion **752** appears to be too unstable and decomposes during the reaction conditions.

We finally attempted to form ester **753** directly by reacting Weinreb amide **750** with lithium acetylide ethylenediamine complex. This is a bench-stable form of acetylide anion, but requires strong conditions to free the anion from the ethylenediamine complex. Unfortunately, our attempts led to no reaction.



Scheme 158: Synthesis of α-ketoester coupling partner failed. (a) (MeO)MeNH·HCl, Et_3N, CH_2Cl_2, 62%. (b) TMS-C≡CH, *n*-BuLi, THF, –78 °C, then **750**, 52%. (c) Table 34.

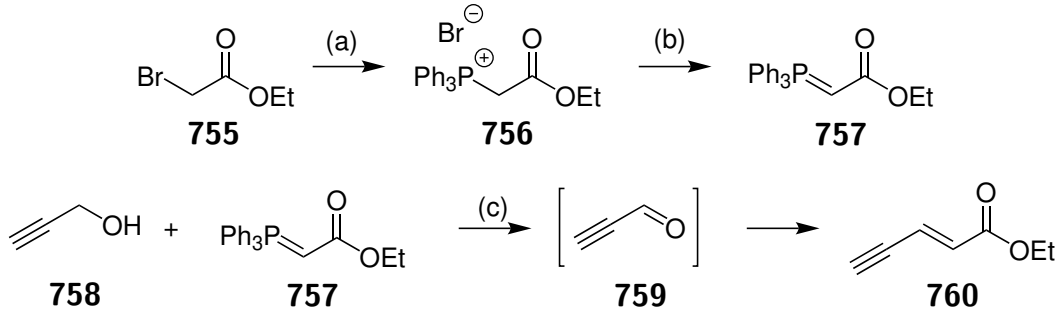
With no ability to produce the desired alkyne for coupling, we were unable to test whether the decarboxylative Stetter approach was successful or not. The ability to generate large amounts of alkene **753** or **754** is necessary for this approach to be successful in the minimum number of steps.

Table 34: Conditions for deprotection of silane **751** to ester **753** or acid **754**.

Entry	Reagent	Solvent	T (°C)	**754**	**753**	**751** (SM)
1	NaOH	MeOH/H_2O	rt	X	X	X
2	TBAF	THF	0	X	X	X
3	Na_2CO_3	MeOH/H_2O	rt	X	X	X
4	–	MeOH (from PureSolv)	rt	X	X	X
5	–	MeOH (drum stock)	rt	X	X	✓

4.3.4 Extended Stetter reaction: cassette strategy

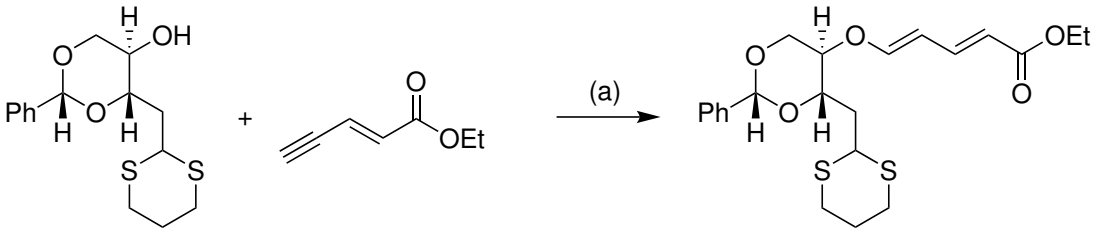
Previous results had shown coupling between alcohol **709** and enyne **760** was possible using *N*-methylmorpholine, but low yielding and slow. We produced enyne **760** by tandem manganese dioxide oxidation/Wittig reaction between propargyl alcohol and phosphorane **757** (Scheme 159). Phosphorane **757** was in turn synthesised by the reaction of ethyl bromoacrylate and triphenylphosphine followed by deprotonation. This was necessary as the intermediate propargyl aldehyde (**759**) is highly unstable.



Scheme 159: Synthesis of phosphorane **756** and subsequent tandem manganese dioxide oxidation/Wittig reaction to give enyne **760**. (a) PhMe, 16 h, 88%. (b) NaOH, CH_2Cl_2, 89%. (c) MnO_2 (10 eq.), CH_2Cl_2, 77%.

Coupling had previously been very slow and low yielding. Tejedor systematically analysed nucleophilic catalysts for the coupling of alcohols with propiolic acid derivatives and found that 1,4-diazabicyclo[2.2.2]octane (DABCO) in dichloromethane gave superior yields.[157] Applying this to the 1,6 addition here improved our yield of ester **761** significantly, with reaction times reduced to only one hour (Scheme 160).

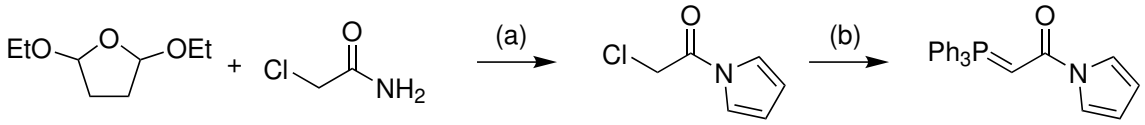
Other $\alpha,\beta,\gamma,\delta$-unsaturated carboxylic acid derivatives may successfully participate in the vinylogous Stetter reaction. We attempted to produce stabilised phosphorane **765** by a similar route to phosphorane **757** (Scheme 161). Chloroacetamide (**763**) was reacted with diethoxytetrahydrofuran (**762**) in hot glacial acetic acid, which gave a low yield of the



709 **760** **761**

Scheme 160: 1,6 Coupling between alcohol **709** and enyne **760**. (a) DABCO, CH_2Cl_2, 1 h, 76%. *Alternative conditions:* NMM, CH_2Cl_2, 48 h, 26%.

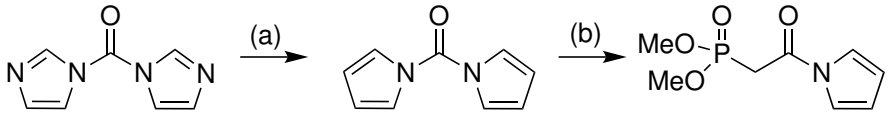
desired *N*-acylpyrrole **764** with significant polymerisation occurring during the reaction. This was to be expected. The reaction of *N*-acylpyrrole **764** with triphenylphosphine and deprotonation to give the phosphorane yielded only 9% of the desired Wittig reagent **765**. It was clear that this route was not suitable for scale-up.



762 **763** **764** **765**

Scheme 161: Synthesis of phosphorane **765**. (a) AcOH, 100 °C, 2 h. 18%. (b) Ph_3P, PhMe, 18 h, then NaOH (aq.), CH_2Cl_2, 9%.

Production of the related phosphonate (**766**) was straightforward (Scheme 162). 1,1′-Carbonyldipyrrole (**728**) was synthesised by heating 1,1′-carbonyldiimidazole (**727**) in pyrrole at reflux. Reaction between dimethyl methylphosphonate and *n*-butyllithium gave an anion that did not react with 1,1′-carbonyldipyrrole by the normal Horner-Wadsworth-Emmons pathway but instead gave phosphonate **766** in excellent yield, as expected.

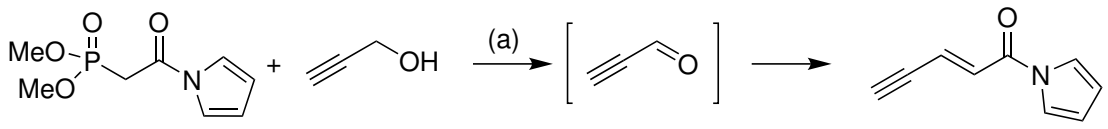


727 **728** **766**

Scheme 162: Synthesis of phosphonate **766**. (a) pyrrole, Δ, 43%. (b) dimethyl methylphosphonate, *n*-BuLi, THF, –78 °C, then **728**, 87%.

Tandem manganese dioxide oxidation/Horner-Wadsworth-Emmons processes are more difficult than the corresponding tandem Wittig reaction using a stabilised phosphorane. Nevertheless, treating propargyl alcohol and phosphonate **766** with a procedure using lithium hydroxide as the base in the presence of 4 Å molecular sieves gave us the desired enyne **767** in acceptable yield (Scheme 163). Yields are significantly lower than the tandem

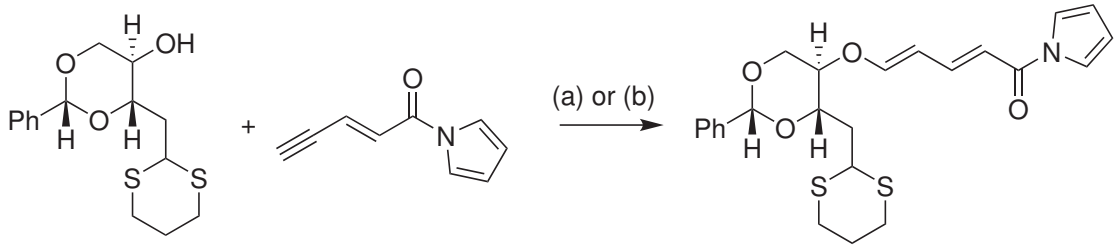
manganese dioxide oxidation/Wittig reaction to produce ester **760** due to the instability of propargylaldehyde (**759**) under basic conditions.



766 **758** **759** **767**

Scheme 163: Synthesis of enyne **767** by tandem MnO_2/HWE reaction. (a) LiOH, MnO_2, THF, 4 Å MS, Δ, 8 h, then rt, 18 h. 42%.

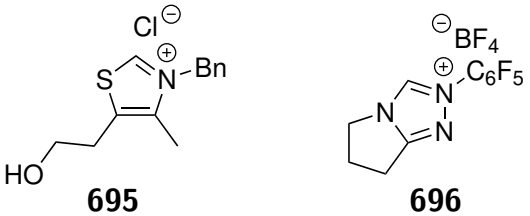
From here, addition of enyne **767** to alcohol **709** was performed using either *N*-methylmorpholine or DABCO (Scheme 164). *N*-Methylmorpholine again gave poor yields and long reaction times, while DABCO proved quicker and higher yielding.



709 **767** **768**

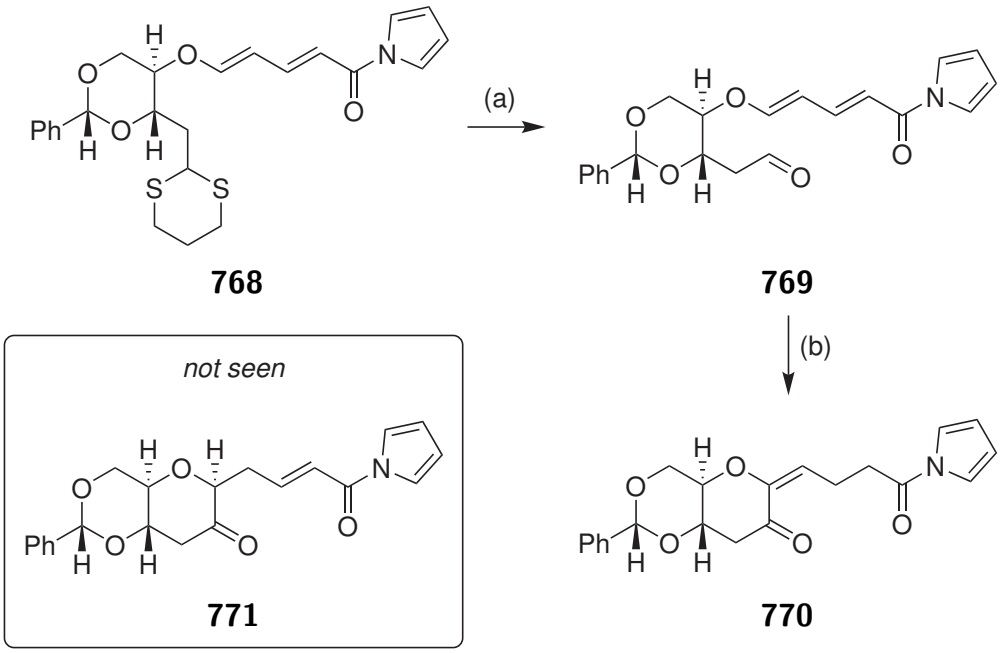
Scheme 164: 1,6 Coupling between alcohol **709** and enyne **767**. (a) NMM, CH_2Cl_2, 3 d, 30%. (b) DABCO, CH_2Cl_2, 1 h, 50%.

Dithiane **768** was deprotected using methyl iodide to reveal aldehyde **769**, setting up for cyclisation. Like the previous ester compound, aldehyde **769** was unable to be purified by column chromatography and carried through as crude material which was relatively pure by ^{1}H NMR analysis. Vinylogous Stetter reaction of *N*-acylpyrrole **769** gave the undesired alkene isomer **770** (Scheme 165). Alkene isomerisation occurs because the ketone is more electron-withdrawing than the *N*-acylpyrrole. This suggests that reduction of the ketone would occur selectively over reduction of the *N*-acylpyrrole, which would be key to continuing our reiterative strategy.



695 **696**

Figure 38: NHC precatalysts used in the vinylogous Stetter reaction.



Scheme 165: Vinylogous Stetter reaction gives the undesired alkene **770**. (a) MeI, $NaHCO_3$, MeCN/H_2O. (b) **695**, Et_3N, THF, Δ, 19% over 2 steps.

Table 35: Attempted conditions for the extended Stetter reaction of aldehyde **769** to ketone **771**.

#	Precatalyst	Base	Solvent	T (°C)	Outcome
1	**695**	Et_3N	THF	65	**770** (19%)
2	**696**	DBU	PhMe	rt	decomp.
3	**695**	Cs_2CO_3	PhMe	70	**770** (22%)
4	**695**	Cs_2CO_3	THF	65	decomp.
5	**695**	Cs_2CO_3	PhMe	rt	SM

We could likely reduce the alkene and ketone of compound **770**, giving the saturated alcohol which would likely spontaneously lactonise to give compound **702**. However, without the alkene at the desired position, conjugated to the *N*-acylpyrrole moiety, we no longer have rapid access to the intermediates that made our cassette route so compelling.

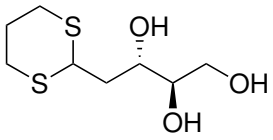
4.4 Conclusion

We made very little progress on the polycyclic ethers project. The large size of the natural products puts some stringent demands on synthetic strategy. To improve on the current strategies, we require a high yielding reaction with excellent stereoselectivity and regioselectivity. In the McErlean group's strategies using the extended Stetter reaction, we have achieved either one or the other.

Our other strategies have been similarly unsuccessful. The unsubstituted *N*-acylpyrrole **731** was too volatile to be useful, and regardless we have shown that the later reduction would have been unsuccessful. Extending our cyclisation methodologies to include photoredox methods, in order to extend the possibilities of substrates we can use, was also unsuccessful. We could not produce the α-ketoester **753** which would enable a decarboxylative Stetter strategy. Unfortunately, it appears that we have exhausted our avenues to an improved synthesis of the polycyclic ether natural products built upon Nakata's methodology.

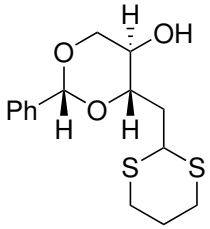
4.5 Experimental

(2*S*,3*R*)-1-(1,3-Dithian-2-yl)butane-2,3,4-triol (708) [151]



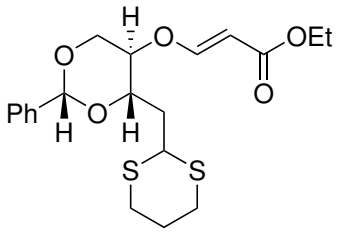
2-deoxy-D-ribose (3.2 g, 23 mmol) was suspended in chloroform (11 mL). The mixture was cooled to 0 °C and hydrochloric acid (6 M, 17 mL) was added, followed by 1,3-propanedithiol (3.2 mL, 53 mmol), then the reaction mixture was stirred for 18 h. The precipitate was collected by filtration and dried by phosphorus pentoxide under vacuum with a solid calcium hypochlorite scrubber to give *title compound* **708** (2.8 g, 12 mmol, 52%) as a white solid. m.p. 124.5 °C (lit. 125.3 °C).[151] $[\alpha]_D$ = –32.5 (*c* = 1.09, MeOH). ^{1}H NMR (300 MHz, MeOD): δ = 2.78 (dt, *J* = 11.1 Hz, 2.9 Hz, 1 H), 2.37–2.27 (m, 1 H), 2.26–2.17 (m, 1 H), 2.11–2.01 (m, 1 H), 1.97-1.89 (m, 1 H), 1.86–1.78 (m, 2 H), 1.51–1.28 (m, 4 H), 0.67–0.55 (m, 2 H), 0.41–0.19 (m, 2 H) ppm. ^{13}C NMR (125 Hz, MeOD): δ = 76.4, 69.8, 64.7, 44.8, 40.3, 31.2, 30.5, 27.4 ppm. MS (ESI): 247 $[M+Na]^+$ (100).

(2*R*,4*S*,5*R*)-2-Phenyl-1,4-[(1,3-dithian-2-yl)methyl]-1,3-dioxan-5-ol (709) [147]



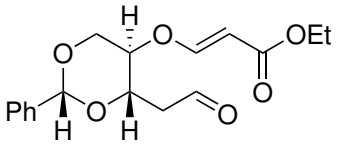
To a mixture of diol **708** (1.0 g, 4.5 mmol) and ethyl acetate (9 mL) was added *p*-toluenesulfonic acid (0.076 g, 0.45 mmol, 10 mol%) and benzaldehyde dimethyl acetal (0.87 mL, 5.8 mmol, 1.3 equiv.). The reaction was stirred overnight, then triethylamine (0.22 mL, 1.6 mmol) was added and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 40% ethyl acetate in hexanes, giving *title compound* **709** (1.3 g) as an impure colourless oil which was used directly in the next reaction.

Ethyl (*E*)-3-(((2*R*,4*S*,5*R*)-4-((1,3-dithian-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yl)oxy) acrylate (710) [147]



Alcohol **709** (1.7 g) was dissolved in dichloromethane (20 mL) and ethyl propiolate (0.60 mL, 6 mmol, 2 equiv.) and *N*-methylmorpholine (1.3 mL, 12 mmol, 4 equiv.) were added. The reaction was stirred at room temperature overnight, then the solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **710** (1.7 g, 4.1 mmol, 92% over 2 steps) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.47 (3 H, *m*), 7.40–7.38 (3 H, *m*), 5.53 (1 H, *s*), 5.40 (1 H, *d*, *J* = 12.4 Hz), 4.40 (1 H, *dd*, *J* = 10.8, 5.2 Hz), 4.28 (1 H, *dd*, *J* = 10.8, 4.0 Hz), 4.25–4.15 (2 H, *m*), 4.11 (1 H, *td*, *J* = 9.6, 2.2 Hz), 3.92 (1 H, *td*, *J* = 9.9, 5.1 Hz), 3.69 (1 H, *t*, *J* = 10.8 Hz), 2.94–2.78 (4 H, *m*), 2.27 (1 H, *td*, *J* = 10.6, 2.2 Hz), 2.15–2.01 (2 H, *m*), 1.97–1.85 (1 H, *m*), 1.28 (3 H, *t*, *J* = 8.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 160.7, 137.1, 129.1, 128.3, 126.2, 101.2, 99.3, 75.8, 74.9, 68.1, 60.0, 42.2, 37.5, 29.9, 29.4, 25.9, 14.4 ppm. MS (ESI): 433 $[M+Na]^+$ (100).

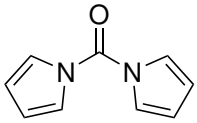
Ethyl (*E*)-3-(((2*R*,4*S*,5*R*)-4-(2-oxoethyl)-2-phenyl-1,3-dioxan-5-yl)oxy)acrylate (711) [147]



Dithiane **710** (1.6 g, 3.9 mmol) was dissolved in acetonitrile (40 mL) and water (7 mL). Sodium bicarbonate (3.0 g, 35 mmol) and methyl iodide (2.2 mL, 35 mmol) were added and the reaction mixture was stirred at room temperature for 3 d. The reaction mixture was poured onto water (50 mL) and extracted with ethyl acetate (3 × 50 mL), then the combined organic layers were concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in hexanes to give *title compound* **711** (0.98 g, 3.1 mmol, 78%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.83 (1 H, *t*, *J* = 1.7 Hz), 7.52–7.33 (6 H, *m*), 5.57 (1 H, *s*), 5.39 (1 H, *d*, *J* = 12.0 Hz), 4.45 (1 H, *dd*, *J* = 11.0, 5.0 Hz), 4.39 (1 H, *ddd*, *J* = 9.6, 8.3, 3.7 Hz), 4.18 (2 H, *q*, *J* = 7.0 Hz), 3.99 (1 H, *ddd*, *J* = 10.5, 9.6, 5.0 Hz), 3.73 (1 H, *dd*, *J* = 10.5, 10.5 Hz), 2.81 (1 H, *ddd*, *J* = 17.0, 8.3, 1.6 Hz), 1.28 (3 H, *t*, *J* = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.7, 167.1, 160.2,

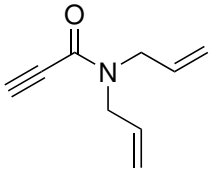
136.6, 129.2, 128.3, 126.0, 101.3, 99.7, 74.5, 74.1, 68.2, 60.1, 45.4, 14.3 ppm. MS (ESI): *m/z* (%): 343 $[M+Na]^+$ (100).

Carbonyldipyrrole (728) [158]



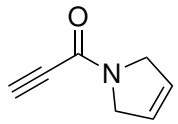
Carbonyldiimidazole (5.0 g, 31 mmol) and pyrrole (6.1 g, 93 mmol) were heated at 130 °C for 90 min. Volatiles were removed by rotary evaporation, then the residue was dissolved in ethyl acetate (100 mL) and washed with hydrochloric acid (1 M, 20 mL) and water (3 × 20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to a volume of 30 mL. Hexanes were added until the solution began to appear cloudy (ca. 100 mL), then the reaction was cooled to –78 °C. The precipitate was collected by filtration to give carbonyldipyrrole (2.1 g, 13 mmol, 43%) as a grey solid. m.p. 60.0–64.8 °C. (lit. m.p. 59–61 °C) [158] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.30 (4 H, *m*), 6.39–3.66 (4 H, *m*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.1, 122.1, 113.3 ppm. MS (ESI): *m/z* (%): 199 $[M+K]^+$ (100).

N,N-Diallylpropiolamide (733) [159]



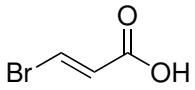
Dicyclohexylcarbodiimide (2.5 g, 12 mmol) was dissolved in dichloromethane (100 mL). Propiolic acid (0.62 mL, 10 mmol) and diallylamine (1.3 mL, 12 mmol) were added at 0 °C. The reaction mixture was stirred for 3 h at room temperature, then the solvent was removed *in vacuo*. The residue was dissolved in hexane (30 mL) then filtered, washing with hexane and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **733** (1.2 g, 8.1 mmol, 81%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82–5.67 (2 H, *m*), 5.26–5.13 (4 H, *m*), 4.15 (2 H, *td*, *J* = 1.5, 5.7 Hz), 3.99 (2 H, *td*, *J* = 1.5, 5.7 Hz), 3.08 (1 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.3, 132.5, 131.9, 118.4, 118.3, 78.6, 75.8, 50.7, 46.4 ppm. MS (ESI) *m/z* (%): 150 $[M+H]^+$ (15), 172 $[M+Na]^+$ (46), 321 $[M_2+Na]^+$ (100).

1-(2,5-Dihydro-1*H*-pyrrol-1-yl)prop-2-yn-1-one (734) [160]



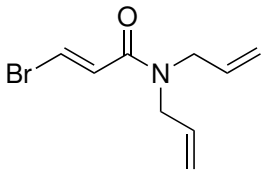
Grubbs generation I catalyst (0.068 g, 0.080 mmol) was dissolved in dichloromethane (200 mL) and *N,N'*-diallylpropiolamide (1.2 g, 8.1 mmol) was added. The reaction mixture was stirred 1 h, then the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10-20% ethyl acetate in hexanes to give starting material (0.70 g, 4.7 mmol) as a yellow oil and *title compound* **734** (0.27 g, 2.2 mmol, 27%; 65% brsm) as an off-white solid. m.p. 93.1–95.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.81–5.74 (2 H, *m*), 4.38–4.35 (2 H, *m*), 4.18–4.15 (2 H, *m*), 3.08 (1 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.4, 125.4, 124.9, 77.7, 76.4, 54.6, 52.3 ppm. MS (ESI): *m/z* (%): 144 $[M+Na]^+$ (100). HRMS (ESI): calcd. for $(C_7H_7N_1O_1)_3Na^+$ 386.14751; found 386.14864.

(*E*)-3-Bromoacrylic acid (735) [161]



Propiolic acid (1.2 mL, 20 mmol) was dissolved in hydrobromic acid (8.9 M, 8 mL) and the reaction mixture was heated at reflux for 1.5 h, then cooled to 0 °C. The precipitate was collected by filtration and washed with water (50 mL) to give (*E*)-3-bromoacrylic acid (2.0 g, 13 mmol, 65%) as a white solid. m.p. 115.1–119.3 °C (lit. 117.5–118.5 °C).[161] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.4 (1 H, *br s*), 7.76 (1 H, *d*, *J* = 13.9 Hz), 6.54 (1 H, *d*, *J* = 13.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 130.1, 128.3 ppm. MS (ESI): *m/z* (%): 148/150 $[M-H]^-$ (100).

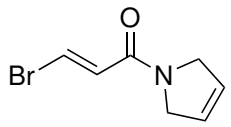
***N,N*-Diallyl-(*E*)-3-bromoacrylamide (736)**



(*E*)-3-bromoacrylic acid (1.5 g, 10 mmol) and dicyclohexylcarbodiimide (2.5 g, 12 mmol) were dissolved in dichloromethane (100 mL) and cooled to 0 °C. Diallylamine (1.3 mL, 12 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed

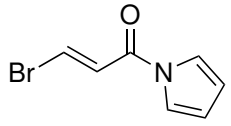
in vacuo and the residue was dissolved in hexane (30 mL). The mixture was filtered, washing with hexane, then the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes to give *title compound* **736** (1.3 g, 5.7 mmol, 57%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (1 H, *d*, *J* = 13.2 Hz), 6.84 (1 H, *d*, *J* = 13.2 Hz), 5.83–5.72 (2 H, *m*), 5.27–5.12 (4 H, *m*), 4.04–3.89 (4 H, *m*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5, 132.8, 132.7, 128.2, 124.5, 117.9, 117.3, 49.3, 48.6 ppm. MS (ESI): *m/z* (%): 252/254 $[M+Na]^+$ (6), 379/381 $[M_2\text{-Br+H}]^+$ (100).

(*E*)-3-Bromo-1-(2,5-dihydro-1*H*-pyrrol-1-yl)prop-2-en-1-one (737)



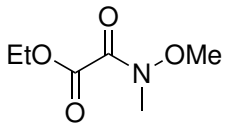
Grubbs generation I catalyst (0.096 g, 0.12 mmol) was dissolved in dichloromethane (50 mL) and diene **736** (1.3 g, 5.7 mmol) was added. The reaction mixture was stirred 3 h, then the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10-20% ethyl acetate in hexanes to give *title compound* **737** (0.36 g, 1.8 mmol, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (1 H, *d*, *J* = 13.3 Hz), 6.81 (1 H, *d*, *J* = 13.0 Hz), 5.93–5.86 (1 H, *m*), 5.84–5.77 (1 H, *m*), 4.32 (4 H, *d*, *J* = 14.3 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1, 128.7, 126.2, 124.6, 124.1, 53.3, 53.0 ppm. HRMS (ESI): calcd. for $C_7H_8BrNONa^+$ 223.96815; found 223.96829.

N-Pyrrolyl-(*E*)-3-bromoacrylamide (738)



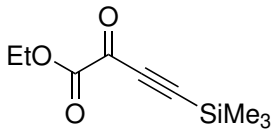
Amide **737** (0.39 g, 1.9 mmol) and DDQ (0.57 g, 2.5 mmol) were dissolved in tetrahydrofuran (20 mL). The reaction mixture was heated at reflux and stirred for 18 h, then diluted with ether (30 mL) and washed with saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 2% ether in hexanes to give *title compound* **738** (0.20 g, 1.0 mmol, 53%) as an off-white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.89 (1 H, *d*, *J* = 13.4 Hz), 7.34 (2 H, *t*, *J* = 2.2 Hz), 7.24 (1 H, *d*, *J* = 13.4 Hz), 6.36 (2 H, *t*, *J* = 2.2 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 129.9, 127.2, 119.4, 114.2 ppm. MS (ESI): *m/z* (%): 241 $[M_2\text{-Br}_2\text{+H}]^+$ (54).

Ethyl 2-(methoxy(methyl)amino)-2-oxoacetate (750) [162]



N-Methoxy-*N*-methylammonium chloride (1.5 g, 16 mmol) and ethyl oxalyl chloride (2.5 g, 19 mmol) were dissolved in dichloromethane (30 mL) and triethylamine (3.1 g, 37 mmol) was added slowly at 0 °C. The reaction mixture was stirred 30 min at room temperature, then methanol (5 mL) was added. The solvent was removed *in vacuo* and the residue was dissolved in tetrahydrofuran (10 mL), filtered and washed with tetrahydrofuran (10 mL). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in hexanes to give *title compound* **750** (1.5 g, 9.6 mmol, 62%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.29 (2 H, *q*, *J* = 7.1 Hz), 3.70 (3 H, *s*), 3.17 (3 H, *s*), 1.30 (3 H, *t*, *J* = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 162.1, 62.3, 62.1, 31.4, 14.0 ppm. MS (ESI): *m/z* (%): 184 $[M+Na]^+$ (100), 345 $[M_2+Na]^+$ (60).

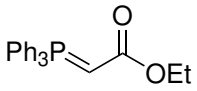
Ethyl 2-oxo-4-(trimethylsilyl)but-3-ynoate (751) [163]



Ethynyltrimethylsilane (0.42 mL, 3.0 mmol) was dissolved in tetrahydrofuran (30 mL) and cooled to –78 °C. *n*-Butyllithium (2.4 M in hexanes; 1.3 mL, 3.0 mmol) was added and the reaction mixture was stirred for 30 min. Amide **750** (0.48 g, 3.0 mmol) was added and the reaction mixture was stirred for 1 h at –78 °C.

Saturated aqueous ammonium chloride solution (25 mL) was added and the reaction mixture was warmed to room temperature. The reaction mixture was extracted with ether (3 × 30 mL), then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 2% ether in hexanes to give *title compound* **751** (0.31 g, 1.6 mmol, 52%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.36 (2 H, *q*, *J* = 7.1 Hz), 1.38 (3 H, *t*, *J* = 7.1 Hz), 0.28 (9 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 159.0, 106.8, 100.2, 63.3, 14.0, –0.9 ppm. Compound decomposed under ESI MS. Plausible decomposition products detected: 253 $[C_{12}H_{17}O_4Si]^+$ (91), 333 $[C_{14}H_{22}O_4Si_2Na]^+$ (100). IR (neat): $\tilde{\nu}_{max}$ = 2961, 2153, 1740, 1682, 1251, 1091, 843 cm^{-1}.

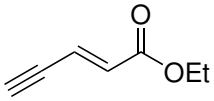
(Carbethoxymethylene)triphenylphosphorane (757) [164]



Triphenylphosphine (2.0 g, 7.5 mmol) was dissolved in toluene (20 mL) and ethyl bromoacetate (0.75 mL, 6.7 mmol) was added dropwise at room temperature. The reaction was stirred overnight, during which time a white precipitate formed. The precipitate was collected by vacuum filtration and washed with toluene to give the phosphonium salt (2.5 g, 5.9 mmol, 88%). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.94–7.71 (15 H, *m*), 5.32 (2 H, *d*, *J* = 14.5 Hz), 4.04 (2 H, *q*, *J* = 7.1 Hz), 0.97 (3 H, *t*, *J* = 7.1 Hz) ppm.

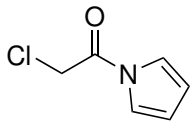
The phosphonium salt was then dissolved in dichloromethane (20 mL) and aqueous sodium hydroxide solution (1 M, 20 mL) was added. The reaction was stirred for 15 min at room temperature, then the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo* to give *title compound* **757** (1.9 g, 5.3 mmol, 89%). m.p. 125 °C (lit. m.p. 115–120 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99–7.61 (15 H, *m*), 5.62 (2 H, *d*, *J* = 20.4 Hz), 4.04 (2 H, *q*, *J* = 10.8 Hz), 1.08 (3 H, *t*, *J* = 10.8 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 133.0, 131.9, 128.7, 74.0, 57.9, 31.0, 14.8 ppm. MS (ESI): *m/z* (%) = 349 $[M+H]^+$ (100).

Ethyl (*E*)-pent-2-en-4-ynoate (760) [165]



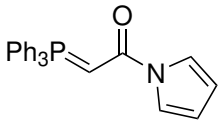
Propargyl alcohol (0.18 mL, 3.0 mmol), phosphorane **757** (1.2 g, 3.5 mmol) and activated manganese dioxide (2.5 g, 30 mmol) were mixed with dichloromethane (50 mL) and the reaction mixture was stirred for 3 d. The reaction mixture was filtered over Celite, eluting with dichloromethane (100 mL) and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 5% ether in hexanes to give *title compound* **760** (0.28 g, 2.3 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70 (1 H, *d*, *J* = 15.9 Hz), 6.30 (1 H, *d*, *J* = 15.9 Hz), 4.20 (2 H, *q*, *J* = 7.1 Hz), 3.33 (1 H, *s*), 1.28 (3 H, *t*, *J* = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 132.5, 123.9, 85.8, 80.2, 60.9, 14.1 ppm. MS (APCI): *m/z* (%): 97 $[M\text{-}OEt+H_2]^+$ (100), 125 $[M+H]^+$ (81).

N-2′-Chloroacetylpyrrole (764)



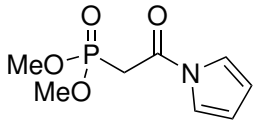
To a solution of 2-chloroacetamide (2.0 g, 21 mmol) in glacial acetic acid (5 mL) was added diethoxytetrahydrofuran (5.0 mL, 24 mmol). The reaction was stirred at 100 °C for 2 hours, during which time the reaction mixture turned to a brown intractable tar. After returning to room temperature, the reaction mixure was poured onto water (100 mL) and neutralised with sodium hydrogen carbonate. The mixture was filtered and the filtrate was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in hexanes, to give *title compound* **764** (0.54 g, 3.8 mmol, 18%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (2 H, *br*), 6.35 (2 H, *br*), 4.5 (2 H, *s*). The instability of this compound precluded further characterisation.

N-[(Triphenylphosphoranylidene)acetyl]pyrrole (765) [166]



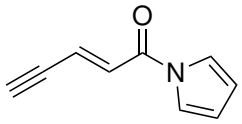
To a solution of triphenylphosphine (1.1 g, 4.2 mmol) in toluene (5 mL) was added chloroacetylpyrrole (0.54 g, 3.8 mmol). The reaction was stirred overnight, during which time a white precipitate formed. This precipitate was collected and dissolved in water (50 mL). Aqueous sodium hydroxide solution (1 M, 50 mL) was added and the reaction was stirred for two hours at room temperature to give a white precipitate. This white precipitate was filtered and washed with water to give *title compound* **765** as a white solid (0.15 g, 0.41 mmol, 9%), m.p. 190–198 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.78–7.39 (15 H, *m*), 7.39–7.30 (2 H, *m*), 6.23–6.13 (2 H, *m*), 3.74 (1 H, *br*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5 (*d*, *J* = 10.2 Hz), 133.1 (*d*, *J* = 10.1 Hz), 132.3 (*d*, *J* = 2.9 Hz), 128.9 (*d*, *J* = 12.4 Hz), 126.6 (*d*, *J* = 92.3 Hz), 118.5 (*d*, *J* = 0.8 Hz), 109.5, 38.2 (*d*, *J* = 125 Hz) ppm. MS (ESI): *m/z* (%): 370 $[M+H]^+$ (100), 392 $[M+Na]^+$ (30).

Dimethyl (2-oxo-2-(1*H*-pyrrol-1-yl)ethyl)phosphonate (766) [153]



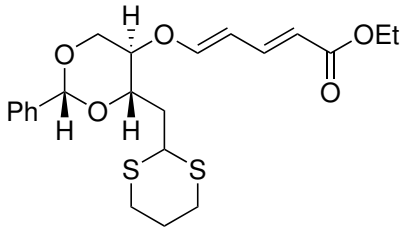
Dimethyl methylphosphonate (0.92 mL, 8.5 mmol) was dissolved in tetrahydrofuran (30 mL) and cooled to –78 °C. *n*-Butyllithium (2.4 M in hexanes, 8.5 mmol, 3.6 mL) was added slowly, then the reaction mixture was warmed to –65 °C and stirred for 2 h. A solution of carbonyldipyrrole (1.3 g, 7.8 mmol) in tetrahydrofuran (3.5 mL) was added slowly, then stirred for 1 h before stirring for a further 1 h at room temperature. Saturated aqueous ammonium chloride solution (15 mL) was added and the reaction mixture was stirred vigorously for 1 h. The reaction mixture was extracted with ethyl acetate (3 $\times$ 30 mL), then the combined organic layers were washed with brine (30 mL) and dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo*, then the residue was purified by column chromatography over silica gel, eluting with 50-100% ethyl acetate in hexanes to give *title compound* **766** (1.5 g, 6.8 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.21 (2 H, *m, overlapping solvent resonance*), 6.26–6.22 (2 H, *m*), 3.75 (3 H, *s*), 3.72 (3 H, *s*), 3.40 (2 H, *d*, $^{2}J_{HP}$ = 22 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6 (*d*, $^{2}J_{CP}$ = 5.9 Hz), 119.8, 113.9, 53.4 (*d*, $^{2}J_{CP}$ = 6.5 Hz), 34.8 (*d*, $^{1}J_{CP}$ = 135 Hz) ppm. ^{31}P NMR (200 MHz, $CDCl_3$): δ = 20.77 ppm. MS (ESI): *m/z* (%): 240 $[M+Na]^+$ (74), 457 $[M_2+Na]^+$ (100).

(*E*)-1-(1*H*-Pyrrol-1-yl)pent-2-en-4-yn-1-one (767)



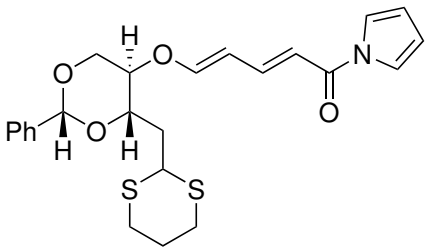
Propargyl alcohol (0.19 mL, 3.1 mmol) was dissolved in tetrahydrofuran (15 mL), then lithium hydroxide (0.15 g, 6.2 mmol), manganese dioxide (2.7 g, 31 mmol), 4 Å molecular sieves (1.7 g) and phosphonate **766** (0.80 g, 3.7 mmol) were added. The reaction mixture was heated at reflux and stirred for 8 h, then stirred for 18 h at room temperature. The reaction mixture was filtered over Celite, eluting with ether, then the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 2% ether in pentane to give *title compound* **767** (0.19 g, 1.3 mmol, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (2 H, *br s*), 7.10–6.95 (2 H, *m*), 6.35 (2 H, *br s*), 3.49 (1 H, *s*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 130.0, 126.6, 119.2, 113.9, 87.6, 80.5 ppm. Compound decomposed under ESI MS. Major peak detected at 413.

Ethyl (2*E*,4*E*)-5-(((2*R*,4*S*,5*R*)-4-((1,3-dithian-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yl)oxy) penta-2,4-dienoate (761)



Alcohol **709** (0.31 g, 1.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.011 g, 0.10 mmol) were dissolved in dichloromethane (1.5 mL), then a solution of enyne **760** (0.16 g, 1.3 mmol) in dichloromethane (1 mL) was added. The reaction mixture was stirred at room temperature for 1 h, then the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in hexanes to give *title compound* **761** (0.33 g, 0.76 mmol, 76%). $[\alpha]_D$ = –11.9 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.25 (5 H, *m*), 7.13 (1 H, *dd*, *J* = 11.4, 15.0 Hz), 6.68 (1 H, *d*, *J* = 12.0 Hz), 5.80–5.63 (2 H, *m*), 5.45 (1 H, *s*), 4.31 (1 H, *dd*, *J* = 10.8, 4.8 Hz), 4.20 (1 H, *dd*, *J* = 10.5, 3.9 Hz), 4.12 (2 H, *q*, *J* = 3.9 Hz), 4.06–3.96 (1 H, *m*), 3.77 (1 H, *td*, *J* = 9.9 Hz, 4.8 Hz), 3.61 (1 H, *t*, *J* = 10.5 Hz), 2.88–2.67 (5 H, *m*), 2.28–2.14 (1 H, *m*), 2.10–1.75 (4 H, *m*), 1.21 (3 H, *t*, 7.2 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 155.4, 141.6, 137.2, 129.1, 128.3, 126.1, 117.3, 107.6, 101.1, 75.9, 74.5, 68.5, 60.1, 42.3, 37.5, 29.9, 29.4, 25.9, 14.3 ppm. MS (ESI): *m/z* (%): 459 $[M+Na]^+$ (100). HRMS (ESI): calcd. for $C_{22}H_{28}O_5S_2Na^+$ 459.12704; found 459.12691. IR (neat): ν_{max} = 2976, 2933, 2901, 2867, 1703, 1631, 1367, 1309, 1235, 1184, 1122, 1087, 1026, 988, 910, 865, 817, 750, 698 cm^{-1}.

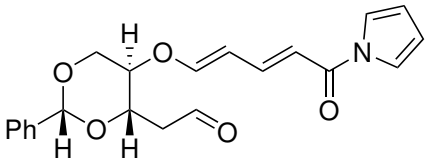
(2*E*,4*E*)-5-(((2*R*,4*S*,5*R*)-4-((1,3-Dithian-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yl)oxy)-1-(1*H*-pyrrol-1-yl)penta-2,4-dien-1-one (768)



Alcohol **709** (0.31 g, 1.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.11 g, 0.10 mmol) were dissolved in dichloromethane (1.5 mL), then a solution of enyne **767** (0.19 g, 1.3 mmol) in dichloromethane (1 mL) was added. The reaction mixture was stirred at room temperature for 1 h, then the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting

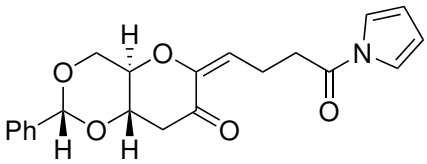
with 5–15% ethyl acetate in hexanes to give *title compound* **768** (0.23 g, 0.50 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.45 (3 H, *m*), 7.45–7.33 (5 H, *m*), 6.92 (1 H, *d*, *J* = 12.1 Hz), 6.48 (1 H, *d*, *J* = 14.6 Hz), 6.31 (2 H, *s*), 5.98 (1 H, *dd*, *J* = 12.0 Hz, 12.0 Hz), 5.54 (1 H, *s*), 4.41 (1 H, *dd*, *J* = 4.9, 10.9 Hz), 4.29 (1 H, *dd*, *J* = 3.9, 10.5 Hz), 4.11 (1 H, *dd*, *J* = 9.0, 9.0 Hz), 3.89 (1 H, *ddd*, *J* = 5.1, 14.6, 14.6 Hz), 3.78–3.66 (1 H, *m*), 2.96–2.77 (4 H, *m*), 2.35–2.21 (1 H, *m*), 2.19–2.00 (2 H, *m*), 1.99–1.83 (1 H, *m*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3, 157.6, 145.0, 137.9, 129.2, 128.4, 126.2, 119.2, 114.8, 113.0, 108.1, 101.3, 76.1, 74.9, 68.6, 42.4, 37.6, 30.1, 29.6, 26.0 ppm. HRMS (ESI): calcd. for $C_{24}H_{27}NO_4S_2Na^+$ 480.12737; found 480.12812.

2-((2*R*,4*S*,5*R*)-5-(((1*E*,3*E*)-5-Oxo-5-(1*H*-pyrrol-1-yl)penta-1,3-dien-1-yl)oxy)-2-phenyl-1,3-dioxan-4-yl)acetaldehyde (769)



Dithiane **768** (0.31 g, 0.70 mmol) was dissolved in acetonitrile (15 mL) and water (5 mL). Sodium bicarbonate (0.55 g, 7.0 mmol) and methyl iodide (0.41 mL, 7.0 mmol) were added and the reaction mixture was stirred at room temperature for 3 d. The reaction mixture was then diluted with brine (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*, giving crude *title compound* **769** (0.13 g, 0.35 mmol, 50%). Compound **769** decomposed during column chromatography and was used crude in the next step. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.84 (1 H, *s*), 7.63–7.31 (8 H, *m*), 6.90 (1 H, *d*, *J* = 11.9 Hz), 6.49 (1 H, *d*, *J* = 11.8 Hz), 6.38–6.26 (2 H, *m*), 5.97 (1 H, *dd*, *J* = 11.9, 11.9 Hz), 5.58 (1 H, *s*), 4.58–4.30 (2 H, *m*), 4.08–3.89 (1 H, *m*), 3.84–3.68 (1 H, *m*), 2.97–2.73 (2 H, *m*) ppm.

(2*R*,4a*R*,8a*S*,*E*)-6-(4-Oxo-4-(1*H*-pyrrol-1-yl)butylidene)-2-phenyltetrahydropyrano[3,2-*d*][1,3]dioxin-7(6*H*)-one (770)



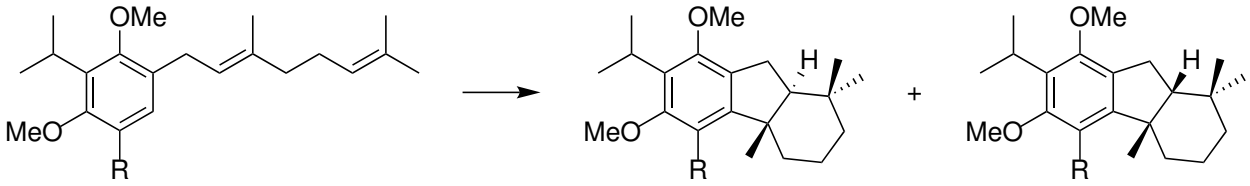
Thiazolium catalyst **695** (0.0042 g, 16 μmol) and triethylamine (0.0022 mL, 16 mmol) were dissolved in tetrahydrofuran (1.4 mL) and degassed with argon for 30 min, then a solution of aldehyde **769**

(0.050 g, 0.14 mmol) in tetrahydrofuran (2.6 mL) was added. The reaction mixture was degassed with argon for a further 30 min then heated at reflux and stirred for 15 h. The reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 × 20 mL), then the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with 5–15% ethyl acetate in hexanes to give *title compound* **770** (0.010 g, 0.027 mmol, 19%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.34 (5 H, *m*), 7.30 (2 H, *br s*), 6.30 (2 H, *t*, *J* = 2.3 Hz), 6.02 (1 H, *t*, *J* = 8.1 Hz), 5.60 (1 H, *s*), 4.49–4.45 (1 H, *m*), 4.15–4.06 (2 H, *m*), 3.90–3.79 (2 H, *m*), 3.07 (1 H, *dd*, *J* = 6.0, 18.0 Hz), 2.96 (1 H, *td*, *J* = 2.3, 7.5 Hz), 2.69–2.59 (2 H, *m*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.6, 169.5, 149.7, 136.9, 129.5, 128.6, 126.3, 119.1, 116.1, 113.4, 101.5, 73.9, 70.5, 68.9, 42.6, 33.4, 20.1 ppm. HRMS (APCI): calcd. for $C_{21}H_{22}NO_5^+$ 368.14925; found 368.14984.

Chapter 5

Conclusion

We have devised a strategy for rapidly synthesising the desired polyenes, as shown above. Decoration of the aryl unit is usually a simple affair and with most of the functionality lying on the aromatic unit in the natural products we aimed to synthesise, this is an ideal strategy. A series of polyene boronates provide the carbon atoms necessary to produce the other part of these molecules, facilitating the rapid synthesis of an array of natural products. Indeed, at only six steps, our successful synthesis of taiwaniaquinone G is the shortest reported.



R = H **351**
R = OMe **390**
R = OH **391**

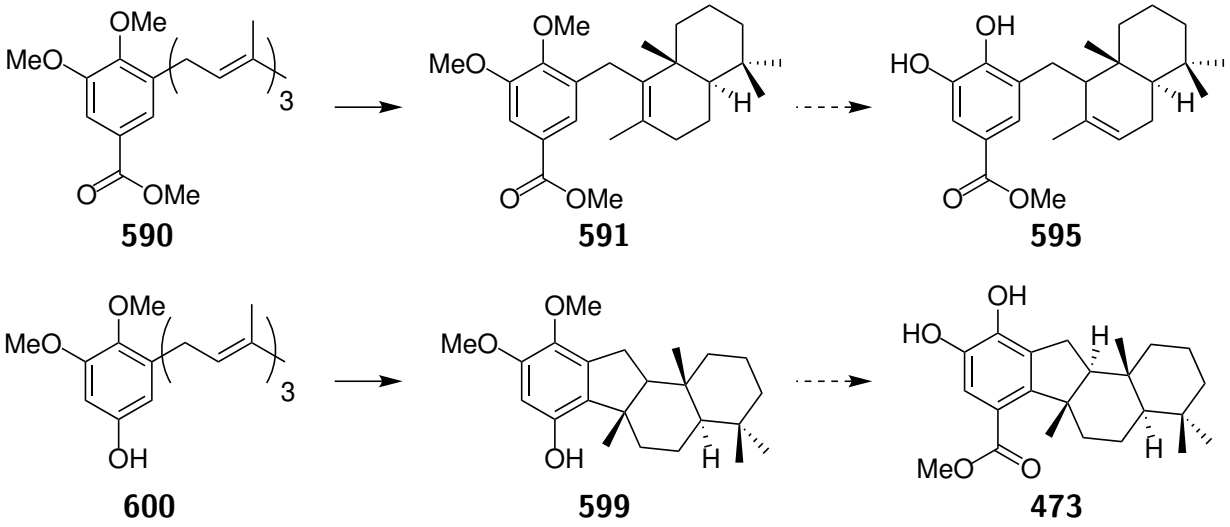
365 + **361** 1:7
407 + **393** 1:2.7
460 + **394** 1:2.1

Scheme 166: Summary of all cyclisation reactions towards taiwaniaquinone G including diastereomeric ratios.

We have had limited success in extending this methodology to larger molecules. In the work towards dasyscyphin B, polyene **566** was partially cyclised by BDSB. We foresaw this as a possible precursor to dasyscyphin B, however we were unable to produce a fully fused ring system from this compound and, in any case, our efforts would likely have led to the *trans* configured compound.

This led us to pursue a synthesis towards the *trans*-fused compound pelorol. Firstly,

polyene **590** produced the partially cyclised compound **591** by direct acid-catalysed cyclisation. This has no precedent to our knowledge. Decalin **591** is an advanced intermediate to not only pelorol, but also partially cyclised natural product smenodiol. We expect that this synthesis could be accomplished in a step-efficient manner. We suspected that the presence of the ester moiety on polyene **590** hindered full cyclisation to dimethylpelorol, so pursued an alternative route, replacing this ester with a phenol and for the first time we performed a direct, acid-catalysed cyclisation of a farnesylarene **600** to the tetracyclic system. We envision that cyclised compound **599a** could be transformed rapidly into the natural product pelorol (**473**).



Scheme 167: Polyene **590** produced partially cyclised compound **591**, which may be transformed into smenodiol (**595**). Polyene **600** was fully cyclised to compound **599** (dr 1:1), which may be transformed into pelorol (**473**).

As with our work with geranylarenes, levels of *trans*-selectivity are far lower than we would have expected. Hyperconjugation plays a role in both cases. Yamamoto's brominative cyclisation with a similar aromatic terminator delivered exclusively the *trans*-fused compound,[30] as did epoxide-mediated cyclisations with other compounds by Andersen and She.[8] [39] We expect that substitution at the C3 atom leads to higher levels of *trans* selectivity through higher diaxial strain (see Scheme 52) and this vindicates our first attempts at delivering *trans* selectivity in tricyclic compounds via those methods. We should explore whether an even lower activation barrier to Friedel-Crafts alkylation would lead to even higher levels of *trans*-selectivity in these cyclisations.

Our attempts to produce the BC *cis*-fused compound dasyscyphin B by this strategy have not been as fruitful. We were able to synthesise chlorofarnesol, but attaching

this to the desired aromatic has not been accomplished. It appears impossible to use the same palladium-catalysed borylation/Suzuki reaction sequence on chlorofarnesol to effect coupling and attempts using organolithium or organomagnesium reagents have been equally unsuccessful.

In addition, we have determined that some functional groups are incompatible with acid-catalysed polyene cyclisation. Functional groups such as benzaldehydes and easily eliminable moieties such as aryl methoxymethyl units form reactive *ortho*-quinone methides which prevent formation of the desired cyclised products. One strategy to avoid this problem is to install methyl groups at these positions and perform late-stage benzylic oxidation to install these functionalities. Unfortunately, while these methodologies exist, our attempts to oxidise a sterically congested cyclopentyl carbon in a synthesis of taiwaniaquinol D failed.

Our attempts at cyclising larger polyenes to produce compounds such as disidein (**7**), the largest of this class of compounds, have similarly been met with only failure. This is a challenging transformation and a more thorough reaction screening should be performed, because the possibility of synthesising a molecule with six rings and eight stereogenic carbons in only five steps is too exciting to pass up.

We did not make much progress on an iterative strategy towards the polycyclic marine ether compounds. It appears we may have exhausted this approach. Further work on the polycyclic ethers within the McErlean group has deviated significantly from Nakata's methodology in favour of more promising leads.

References

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