Biomimetic Studies towards the Polycyclic Diterpene Bielschowskysin

by

Joseph Rogers

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Doctor of Philosophy

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Declaration

I declare that the substance of this Thesis has not been submitted, nor is concurrently being submitted, in candidature for any other degree. I also declare that the work embodied in this Thesis is the result of my own investigations. Where the work of other investigators has been used, this has been fully acknowledged in the text.

Joseph Rogers

G. Pattenden

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Contents

Abstract

This Thesis describes synthetic studies directed towards evaluating the biosynthetic relationships between several novel polycyclic diterpenes, including bielschowskysin **1**, verrillin **2**, plumarellide **3** and intricarene **4**, and their probable furanobutenolide – based cembrane precursors, *e.g.* bipinnatin J (**5**) and bipinnatin G (**6**). These interesting natural products have all been isolated from marine corals in recent years.

The **Introduction** describes a general overview of biologically active compounds isolated from natural sources, followed by the isolation, structure and biological profile of the aforementioned marine natural products.

The **Discussion** section introduces the family of furanobutenolide – based cembrane natural products and then discusses the structures of bielschowskysin **1**, verrillin **2**, plumarellide **3** and intricarene **4** and their proposed biogenetic origins from simple furanocembranes *via* transannular pericyclic cycloaddition processes. A synthetic study towards the model bielschowskysin structures **106** and **132** from rubifolide analogues, *i.e.* **102** and **125** is then described. Difficulties with the stabilities of various substrates led to abandonment of this route, but an alternative strategy produced the 14-membered furanocembrane structure **142** which lacked a $\Delta^{11,12}$-alkene bond. Further manipulation of **142** into the modified bielschowskysin structure **125** could not be achieved, due to the dearth of material.

The oxidation chemistry of 2-alkenylfurans was next studied. Model studies established that treatment of the alkenylfuran **162** with peroxy reagents led to the *Z*-dienedione **163**. When **163** was left in the presence of *p*-TSA in THF-H_2O it was first

converted into the β-hydroxyketone **165** and then into the vicinal diol **178**, presumably *via* the transient enol ether species **166**. In complementary studies, treatment of the *Z*-dienedione **163** with K_2CO_3 in THF-H_2O led to the 4-hydroxycyclopent-2-enone **193** (53%), and isomerisation in the presence of iodine gave the corresponding *E*-isomer **194** (90%). These observations may have significance for the origins of coralloidolide F (**195**) and the macrocyclic *E*-dienedione **196** from furanocembrane precursors in corals.

A brief review of the syntheses of furanobutenolide – based cembranes is presented and then two synthetic approaches towards deoxybipinnatin G (**188b**/ **188e**), using Aldol/Stille/Nozaki-Hiyama-Kishi (NHK) and ring-closing metathesis (RCM)/Stille/NHK reactions, are presented. The RCM/Stille/NHK approach produced the macrocyclic precursor **275b** which, unfortunately, upon exposure to $CrCl_2$ in THF, produced the acyclic intermediate **318**. In contemporaneous studies, attempts were made to form the furanobutenolide – based cembrane *bis*-deoxylopholide **319** *en route* to plumarellide **3**, *via* a RCM approach. Unfortunately, exposure of the vinyl furan **322** to Grubbs 2nd generation catalyst in refluxing DCM only led to the phenylvinylfuran **338** and to the dimer **339**.

In a separate study, treatment of isoepilophodione B (**159**), derived from bipinnatin J (**5**) *via* rubifolide **49**, with *p*-TSA in THF-H_2O led to the novel and unusual 19-hydroxyrubifolide **353**, presumably *via* the enol ether intermediate **354** and allylic transposition.

The **Experimental** section contains full details of the preparative work carried out, and collects together spectroscopic and analytical data for all the new compounds described.

Abbreviations

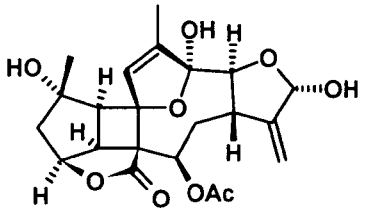
Å	Angstrom (10^{-10} meters)
Acac	acetoacetone
AIBN	2,2′-azobis-*iso*-butyronitrile
cat.	catalytic
conc.	concentrated
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAl-H	di-*iso*-butylaluminium hydride
DIPEA	di-*iso*-propylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyl dioxrane
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess Martin periodane
DMSO	dimethyl sulfoxide
dppe	di(phenylphosphine)ethane

dppf	1,1′-bis(diphenylphosphino)ferrocene
eq.	equivalents
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphorus triamide
Im	imidazole
^{i}Pr	*iso*-propyl
LDA	lithium di-*iso*-propylamide
*m*CPBA	*meta*-chloroperbenzoic acid
Mes	mesityl
MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	methoxymethyl
Ms	mesyl/ methanesulfonyl
MS	molecular sieves
NBS	*N*-bromosuccinimide
NHK	Nozaki-Hiyama-Kishi
NMO	4-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PPTS	pyridinium *para*-toluenesulphonate
p-TSA	*para*-toluenesulfonic acid
Py	pyridine
RCM	ring-closing metathesis
TBAF	*tert*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl

TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Trisylimid	1-(2,4,6-triisopropylbenzenesulfonyl)imidazole
Ts	tosyl

INTRODUCTION

The work presented in this Thesis describes synthetic investigations directed towards understanding the biosynthetic interrelationships between the novel polycyclic diterpenes bielschowskysin **1**,[1] verrillin **2**,[2] plumarellide **3**[3] and intricarene **4**[4] recently isolated from the gorgonian corals of the genius *Pseudopterogorgia* and *Plumarella*. These natural products co-occur with a variety of macrocyclic furanobutenolide – based cembranes, *viz* **5**[5] and **6**,[6] which are believed to be their biological precursors by oxidation of an alkenylfuran substituent followed by a series of intriguing transannular cycloaddition reactions. In addition to their novel structural features the diterpenoids **1-4** exhibit a variety of biological activities, *e.g.* antitumour, antimalarial and hemolytic activity, which adds to their interest as significant targets for synthesis and possible scope in medicine.



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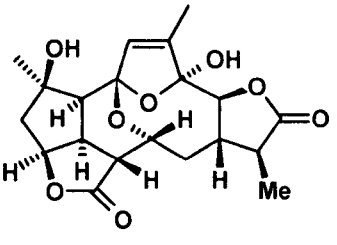

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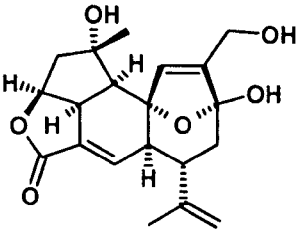

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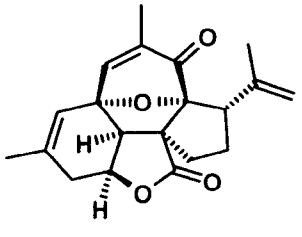

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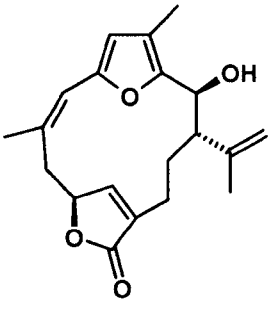

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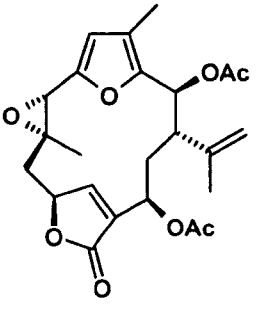

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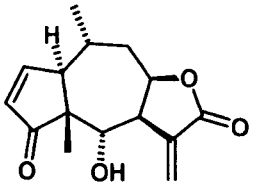
Indeed, biologically active natural products are present in a wide array of organisms and they have been utilised for making herbal remedies and ancient medicines for centuries. One example is arnica, isolated from *Arnica montana*, which is a herbaceous, perennial species belonging to the sunflower species. Arnica is applied

topically to the skin in order to reduce bruising and inflammation.[7] There are two active components within the mixture, helenalin **7** from the main body of the plant and thymol **8** from the roots. Helenalin **7** is a sesquiterpene lactone with potent anti-inflammatory and antitumour activity.[8,9] This compound has also been shown to be highly toxic, but only when large quantities of the plant are ingested. Thymol **8** is a simple monoterpene-derived phenol[10] and is a strong antiseptic.[11] The combined application of henenalin (anti-inflammatory) and thymol (antiseptic) allow faster transport of blood and fluid away from the affected region due to dilation of the subcutaneous blood capillaries.[12] For this reason arnica has been used to treat bruising, strains and sprains for centuries.



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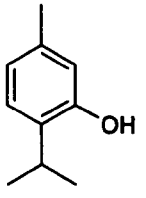

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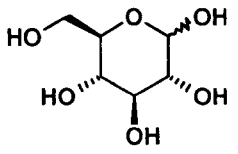
The physiological results obtained from herbal medicines led chemists to begin isolating the active constituents found in plants and their fruits. One of the first natural products to be isolated was the sugar, glucose **9**. This carbohydrate was isolated in 1747 by Marggraf from raisins,[13] although it wasn't until later that Lavoisier determined its elemental composition. *D*-Glucose **9** is a simple monosaccharide, along with *L*-mannose **10** and *β*-*L*-fructose **11**, which act as a rapid source of energy and metabolic intermediate for all living cells.[14] It is also one of the main products from photosynthesis and initiates cellular respiration.[15] The simple monosaccharides **9**, **10** and **11** are complemented by polysaccharides, *e.g.* starch **12**,[16] which offer long-term energy storage for organisms.



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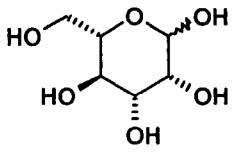

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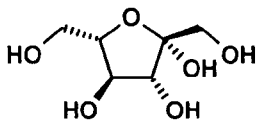

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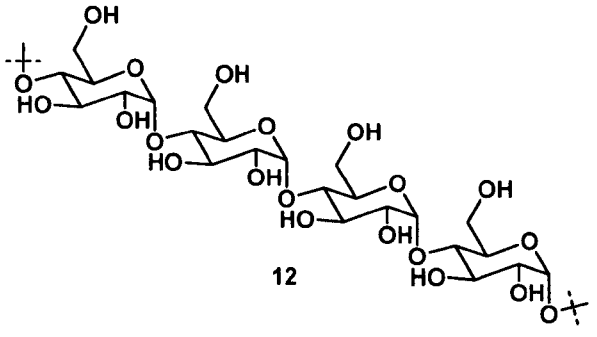
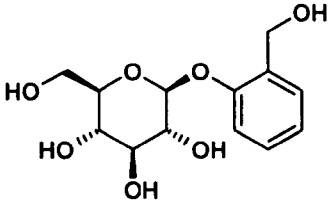


12

Another important medicine, derived from natural sources, which emerged and became the most successful medication in history, was aspirin **15**.[17] Aspirin **15** has analgesic and anti-inflammatory properties.[18,19] The natural precursor to aspirin **15** is salicin **13** which is produced by the bark of the willow tree and has been utilised since ancient Egyptian times as a pain relieving agent.[20] In 1828 Andreas was able to prepare a relatively pure sample of salicin **13** which, in 1838, was transformed by Piria *et al.* into salicylic acid **14**,[21] a precursor to aspirin **15**. Aspirin **15** was first synthesised in 1853 by Gerhardt but he was unable to purify the compound or identify the structure.[22] Finally, in 1897, Hoffmann prepared a pure sample of acetylsalicylic acid (later trademarked as aspirin) which was free from the impurities which caused side-effects like gastrointestinal ulcers.



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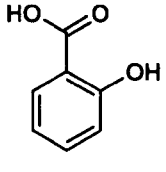

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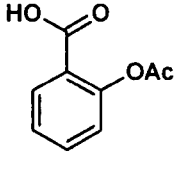

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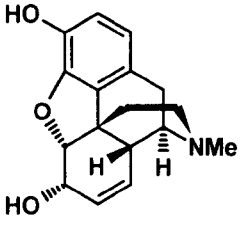
In 1803, the alkaloid morphine **16** was isolated from crude opium by Sertürner.[23] Crude opium gum is formed upon drying the milky solution extruded from the

unripened seed-head of the opium poppy. Morphine **16** has analgesic properties and it is a narcotic due to its ability to bind to the central nervous system thereby inducing pain relief.[24-27] Other opiates, *e.g.* codeine **17**, also occur naturally in the opium poppy and display similar biological activity.[28] In 1874 the synthetic opiate diacetylmorphine **18** (more commonly known as heroin) was formed in a similar process to the production of aspirin **15** from salicylic acid **14**. Heroin **18** was initially used as a treatment for morphine addiction but it soon became apparent that it was even more addictive[29] and was later classified as an illegal drug. In 1855, Gaedcke identified the tropane alkaloid cocaine **19** from coca leaves.[30] Cocaine is used medically as a stimulant of the central nervous system and acts by inhibiting the uptake of catecholamine by nerve endings. Due to its mode of action, cocaine **19** is also addictive.[31,32] Later, the extremely toxic alkaloid strychnine **20** was extracted from the seeds of the *Strychnos nux vomica* tree,[33] and initially found use as a pesticide due to its ability to cause asphyxiation *via* intense muscular convulsion.[34-36] The difficult task of synthesising the complex structure of strychnine **20** was first achieved in 1954 by Woodward,[37,38] who was later awarded the Nobel prize in chemistry.



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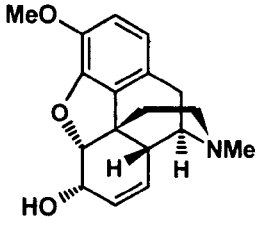

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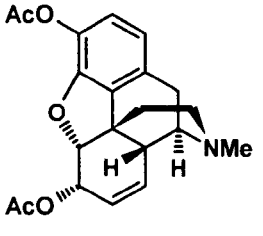

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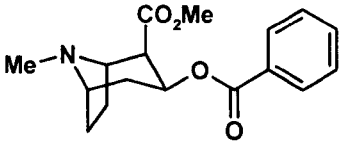

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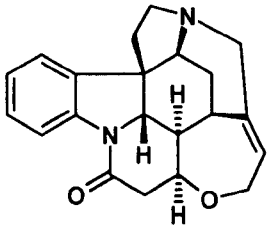

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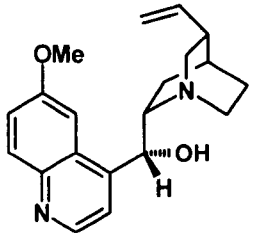
Many toxic compounds like strychnine **20** have been isolated from plants, but other natural products with equally beneficial medical usage have also been isolated. The alkaloid quinine **21**, for example, has a wide variety of biological properties ranging from antipyretic (fever-reducing),[39] analgesic[40] to anti-inflammatory activity but it is most commonly known for its antimalarial properties.[41] Quinine **21** has long been used by the quechua indians of Peru to treat fevers. The natural product is produced within the bark of the cinchona tree[42] which is native to the forest of the Andes mountains, and was isolated by Pelletier and Caventou in 1817. Since the 1940s alternative antimalarial drugs have been developed, *e.g.* chloroquine **22** and pyrimethamine **23**, which are now used in preference to quinine **21**.



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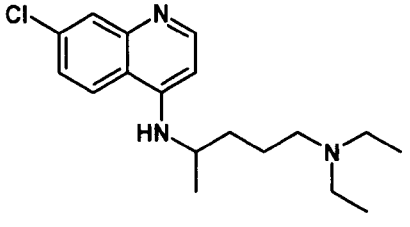

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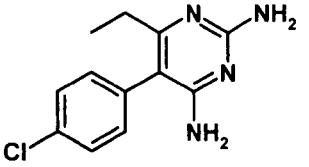

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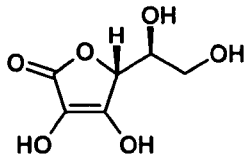
The active components of food, *i.e.* vitamins, became a fascination during the 1920s. In 1921, both Szent-Györgyi and Zilva prepared crude samples of ascorbic acid **24** from lemon juice and the bovine adrenal cortex, respectively. Pure ascorbic acid crystals, commonly known as vitamin C (**24**) were later obtained by Szent-Györgyi[43,44] by the extraction of peppers and the compound was first synthesised independently by Haworth and by Reichstein in 1933.[45] Vitamin C (**24**) was the first vitamin to be mass-produced in an industrial process by Hoffmann-La Roche, and in 1934 it became available to the public. Vitamin C (**24**) acts as an anti-oxidant and is an essential nutrient for a balanced diet.[46] If vitamin C is not consumed, the deficiency causes scurvy, a disease which induces bleeding from mucous membranes.[47,48] Many

other essential vitamins are now commercially available as dietary supplements, *e.g.* vitamin B_6 (**25**) and vitamin D_2 (**26**).



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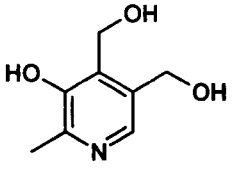

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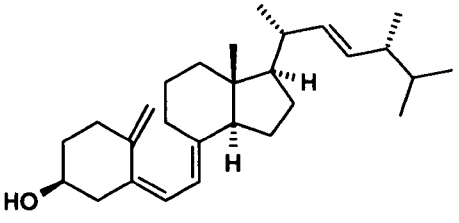

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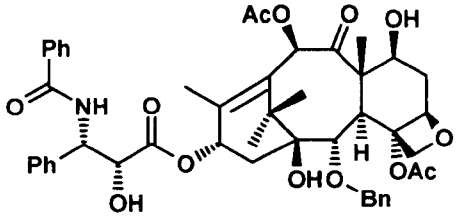
Taxol® **27** is another important natural product which was shown to have anti-cancer activity.[49] Taxol® **27** was isolated from the bark of the Pacific yew tree genus *Taxus brevifolia* in 1962, but it was not until 1971 that its structure was established by x-ray crystallography.[50,51] It took 1200 kg of bark in order to accumulate 10 g of pure taxol, and harvesting caused the death of the tree. Later Potier discovered that the foliage of the European yew tree, *Taxus baccata*, represented a renewable source of 10-deacetylbaccatin III (**28**),[52] which upon a short synthetic sequence could produce taxol® **27**.[53] The natural product **27**, along with its derivative Taxotere® (docetaxel) **29**[54] (which has an improved pharmacological profile) are mitotic inhibitors used in cancer chemotherapy, due to their ability to stabilise microtubules during cell division.[55-57] This mode of action constituted an entirely new mechanism of intervention during cell division from the previous microtubule-destabilising agents which result from known natural products.

In the early 1990s another group of natural products was discovered, which matched the anti-cancer properties of taxol® **27**, although publication was delayed until 1996. Hofle and Reichenbach extracted epothilones A (**30**) and B (**31**) from a culture of myxobacterium *Sorangium cellulosum* found in the banks of the Zambezi river.[58] These polyketide-derived epothilones were tested against multiple cancer cell lines

and were shown to exhibit antitumour activity even against taxol®-resistant tumour cells,[59,60] with epothilone B (**31**) being the most potent naturally occurring compound. They act in an identical mode to taxol® **27**, stabilising microtubules by binding to the same site on the same protein target.



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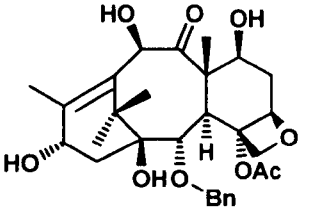

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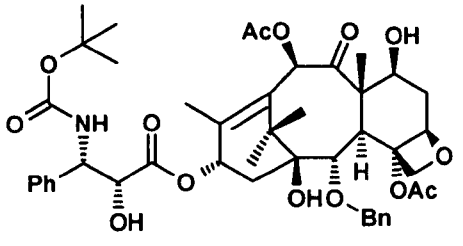

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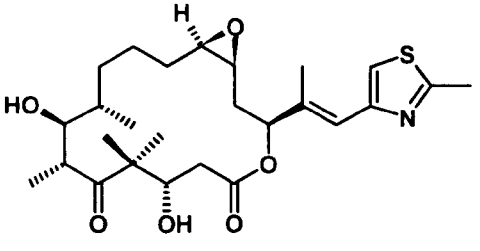

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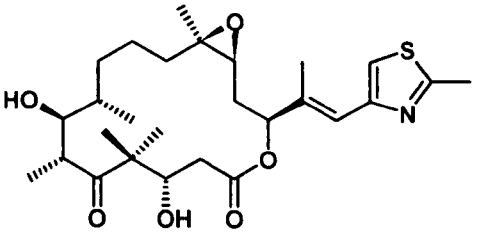
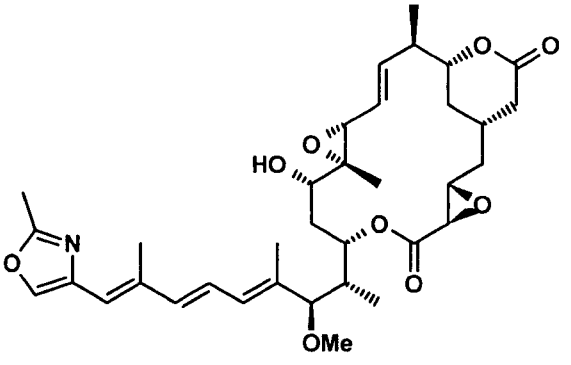


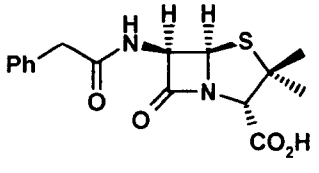
31

Another group of natural products which exhibit anti-cancer activity is rhizoxin **32** and its analogues. The rhizoxins are produced by *Rhizopus microsporus*, a pathogenic plant fungus.[61] The natural products possess antimitotic activity, acting by disrupting the formation of microtubules during cell division and they can also depolymerise pre-formed microtubules.[62-64]



32

Initially plants constituted the main source of natural products. Later attention turned to microorganisms and animals to determine which active components they accommodated. In 1928, penicillin **33**, possibly the most important natural product to be discovered was isolated by Fleming[65] from the fungus, *Penicillium notatum*.[66] Fleming noticed that a culture of the mold formed on nutritional agar had no bacterial colonies surrounding its periphery.[67] Later, Fleming demonstrated the mold extruded a substance with antibiotic properties (the active component being named penicillin), which caused cell death to bacteria upon exposure.[68,69] Penicillins G (**33**) and V (**34**) are β-lactam antibiotics which are widely used for the treatment of bacterial infections, along with thienamycin **35** and amoxycillin **36**.[70]



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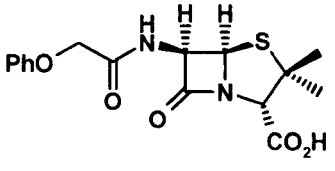

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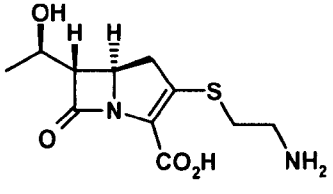

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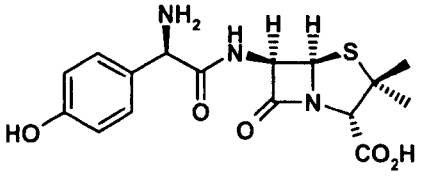

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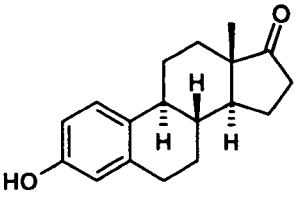
Humans have also been indirectly analysed for natural products. Oestrogens, *e.g.* oestrone **37**, are steroids which were first isolated from the urine of pregnant women,

independently by Doisy and by Butenandt in 1928.[71,72] The most potent oestrogen is oestradiol **38**, which was isolated by Doisy in 1936 by processing 4 tons of fresh sow ovaries in order to gain 25 mg of the steroid.[73] The oestrogens are sex hormones, produced in the ovaries and are responsible for female sex characteristics.[74-76] Further isolation and characterisation revealed several other steroidal compounds, *e.g.* progesterone **39**, discovered in 1934.[77] Progesterone is another female sex hormone involved in the menstrual cycle.[76,78,79] The main steroid found in man was reported in 1935, and is the sex hormone, testosterone **40**,[80] which is produced in the testes and is responsible for virilization and anabolism.[76,81]



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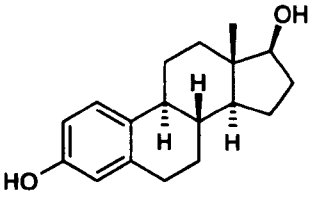

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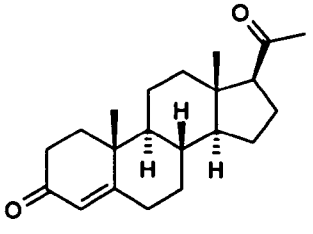

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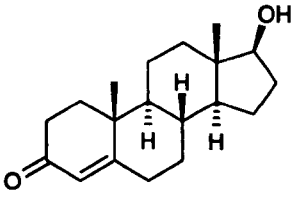

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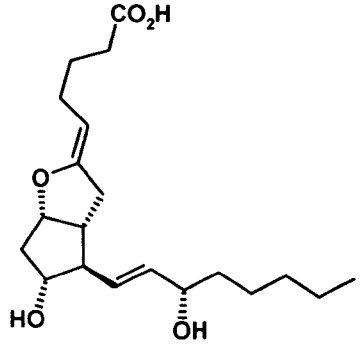
Another family of complex natural products which are produced within the human body and help its self-regulation are the prostaglandins. Prostaglandins were first discovered in 1934 by von Euler from prostate gland secretions of sheep.[82,83] Later it was discovered that prostaglandins were not solely formed within the prostate gland but within every nucleated cell and they perform a variety of functions. In 1971, simple aspirin-like drugs were shown to inhibit prostaglandin production.[84] Each prostaglandin has a unique biological function, *e.g.* prostaglandin I_2 (PGI_2) (**41**)[85] causes dilation of vascular smooth muscle cells, inhibits platelet aggregation and

dilation of smooth muscle in the lungs. PGE_2 (**42**) has numerous applications, from gastric acid/ mucus secretion to uterus contraction, and $PGF_{2\alpha}$ (**43**) functions by inducing contraction of the smooth muscle within the lungs.[86] The prostaglandin family is also supplemented by synthetic compounds, *e.g.* latanoprost **44**, which is used for the treatment of glaucoma.



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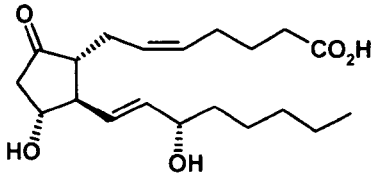

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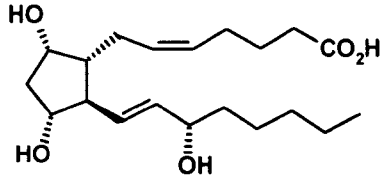

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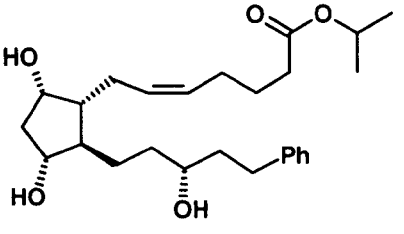

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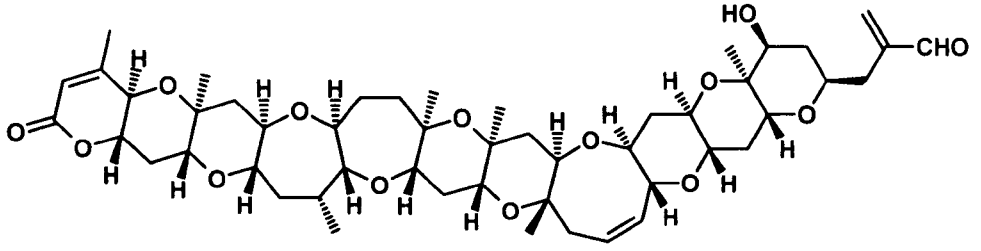
It was not until the late 1960s that the attentions of natural product chemists turned to the seas and the oceans as a source of biologically active compounds. Over the past 50 years thousands of biologically active compounds have been isolated from sponges, corals, plants, fish and marine bacteria. In 1981, for example Clardy and Nakanishi isolated brevetoxin B (**45**) from blooming monocellular algae,[87] which cause a phenomenon known as "red tides". The red colouration of the tide is produced by a dense growth of algae which contain the carotenoid pigment, peridinin. The brevetoxins are produced by phytoplankton of the genus *Ptychodiscus brevis*. This family of polycyclic ether compounds exhibit neurotoxic activity,[88] causing the death

of fish and the poisoning of mollusks by activating the sodium channels within neurons, causing a continuous influx of sodium ions which disable the neurons.[89]

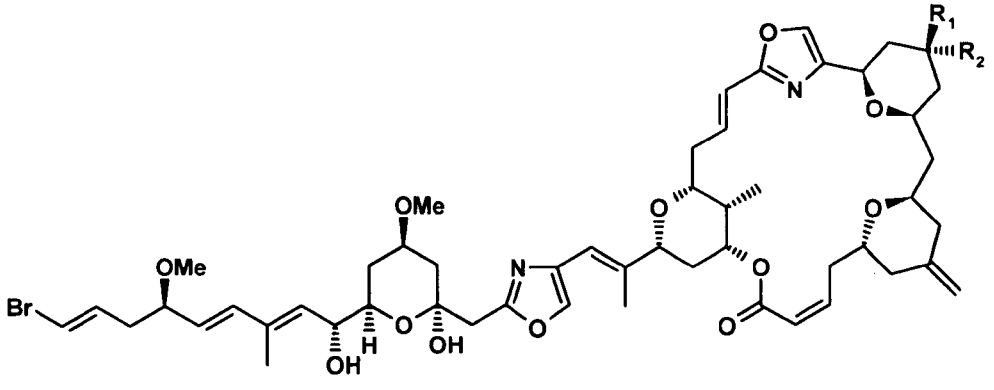


45

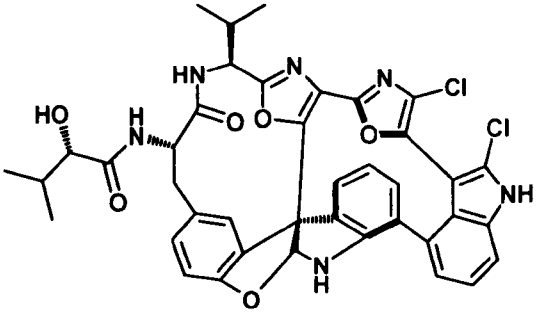
There are other natural products which have been isolated from marine sources which have beneficial medicinal properties, for example the phorboxazole family of compounds. The 21-membered macrolide structures of phorboxazole A (**46**) and B (**47**) were described in 1993 by Molinski from the marine sponge *Phorbas sp.* Extraction of 236 g of the sponge yielded only 95 mg of phorboxazole A (**46**) and 41 mg of phorboxazole B (**47**). Both phorboxazole A (**46**) and B (**47**) exhibit antifungal and anti-cancer activity by causing cell arrest in the S-phase.[90] Another marine natural product which shows anti-cancer activity is the macrocyclic peptide diazonamide A (**48**). This natural product was isolated from the ascidian *Diazona angulata* by Fenical and Clardy in 1991.[91] Initially the structure of diazonamide A was assigned incorrectly, but re-evaluation gave the true structure of the natural product which was later confirmed in synthetic studies by Harran[92-94] and by Nicolaou.[95] Diazonamide A (**48**) was shown to exhibit antimicrobial, antiviral and cytotoxic activity against ovarian and breast cancer, along with taxol®-resistant cancer cell lines by inhibiting tubulin assembly into microtubules.

Natural products provide a synthetic challenge to chemists due to their diverse structural array and complexity, and their varied biological activity. Chemists have been fascinated with natural products since they were first isolated and characterised.

The chemical synthesis of natural products allows access to these complex structures when their abundance in Nature is low, *e.g.* oestradiol **38** and phorboxazole A (**46**) and B (**47**). This access enables further biological evaluation and pharmaceutical trials, where previously these would not have been feasible. Total synthesis has also allowed the confirmation of the structure of natural products like diazonamide A (**48**). Indeed, chemical synthesis has now become an essential part of the natural product process.



46, Phorboxazole A: R_1 = H, R_2 = OH
47, Phorboxazole B: R_1 = OH, R_2 = H



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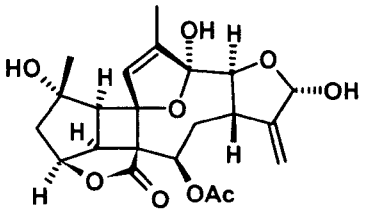
The gorgonian octocorals are marine organisms of the class *Anthozoa*, of which, *Pseudopterogorgia kallos*, *Gersemia rubiformis*, *Lophogorgia* and *Pseudopterogorgia bipinnata*, are just a few examples. Several research groups have studied and analysed these Caribbean octocorals for biologically active compounds, and a range of diverse and structurally intriguing natural products have been discovered. The novel polycyclic diterpenes bielschowskysin **1**,[1] verrillin **2**,[2] intricarene **4**[4] (discovered by

Rodriguez *et al.*) and plumarellide **3**[3] (discovered by Stonik *et al.*) were isolated from octocorals between 2000 and 2005. They each possess unusual, unprecedented polycyclic structures, and demonstrate interesting biological activity. Bielschowskysin **1**[1] was reported in 2004 from the gorgonian octocoral, *Pseudopterogorgia kallos* in the south western Caribbean sea. It possesses a tricyclo[9.3.0.$0^{2,10}$]-tetradecane ring system containing a cyclobutane ring at its core, a 5-membered lactol and a cyclic hemi-ketal function. This compound also exhibited interesting biological activity in the NCI antitumour screening program, namely antimalarial activity against *Plasmodium falciparum*, and strong anticancerous properties against lung and renal cancer cell lines. Verrillin **2**[2] was reported in 2000 from the gorgonian octocoral *Pseudopterogorgia bipinnata* found close to Colombia. This compound contains a *cis*-bicyclo[9.3.0]-tetradecane nucleus encompassing two 5-membered lactone units, a 6-membered ring containing an ether-bridge and a dihemi-ketal functionality. Unfortunately, due to lack of material, the biological activity of verrillin **2** could not be fully analysed. Plumarellide **3**[3] was reported in 2002 from the coral species *Plumarella* in the North-Western Pacific Ocean. This diperpene contains a pentasubstituted-cyclohexene at its core, a 5-membered lactone unit and a hemi-ketal functionality. Biological testing demonstrated this compound produced moderate hemolytic activity. Intricarene **4** reported in 2005 from *Pseudopterogorgia kallos* off the coast of Providencia island, Columbia,[4] has a carbon skeleton containing a novel tetracyclic core with a lactone, an α,β-unsaturated ketone and an ether bridge substituent. The biological activity of intricarene **4** was tested against tuberculosis but showed no appreciable toxicity. Unfortunately further analysis could not be achieved due to the dearth of material.



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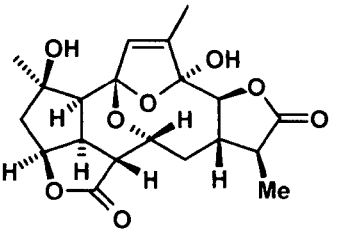

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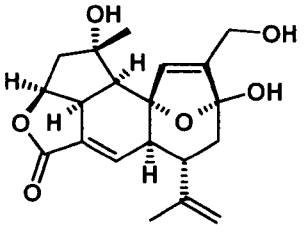

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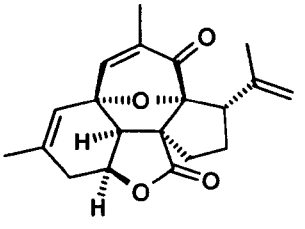


4

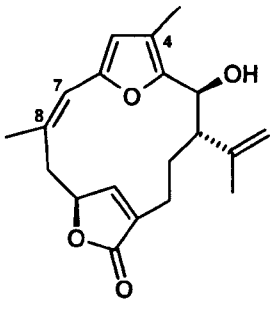
We believe that bielschowskysin **1**, verrillin **2**, plumarellide **3** and intricarene **4** show a unique and interesting biosynthetic relationship. As indicated at the beginning of the *Introduction*, the aim of the work described in this Thesis was to probe this relationship by examining routes to the total synthesis of **1**, **2** and **3** using a design based on biosynthetic speculation from a furanobutenolide – based cembrane precursor, *viz* **5** and **6**.

DISCUSSION

The polycyclic diterpenes bielschowskysin 1, verrillin 2, plumarellide 3 and intricarene 4, and their furanobutenolide cembrane congeners

The complex polycyclic diterpenes bielschowskysin **1**,[1] verrillin **2**,[2] plumarellide **3**[3] and intricarene **4**[4] co-occur with less complex furanobutenolide – based cembrane structures in corals. Naturally occurring furanobutenolide – based cembranes can be divided into two categories, *i.e.* those that are substituted at the C4 position by CH_3 and those that have a higher oxidation state, *i.e.* CH_2OH, CHO or CO_2Me. The former category is represented by bipinnatin J (**5**),[5] bipinnatin G (**6**),[6] and rubifolide **49**,[96] and the latter by lophotoxin **50**,[97] pukalide **51**,[98] and providencin **52**.[99] Pukalide **51** occupies a special place in natural product chemistry since it was the first member of the family of furanobutenolide – based cembranoids to be described, in 1975, from corals, *i.e. Sinnlaria abrupta*.[98] Since then pukalide **51** has been isolated from many other coral species,[100] and has also been found in the dendronoid nudibranch *Tochuina tetraquetra*, together with rubifolide **49**.[101]

Analysis of the structures and stereochemistries of naturally occurring, oxidised furanocembranes,[102] reveals a number of interesting features. Thus: i) the natural products containing a C7,C8 epoxide, *e.g.* bipinnatin G (**6**)[6] and D (**53**),[103] are derived from $\Delta^{7,8}$-alkene bond precursors which have the *E*-configuration; ii) the compounds containing a C7,C8-epoxy furan are present with both a methyl group and the electron withdrawing ester and aldehyde substituents, at the C3-furan position, *e.g.* bipinnatin G (**6**) and leptolide **54**;[104] iii) all of the *Z*-$\Delta^{7,8}$-alkene bond cembranoids that have been



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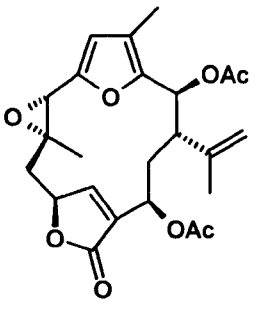

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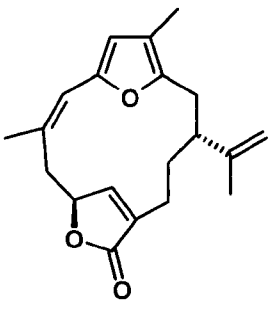

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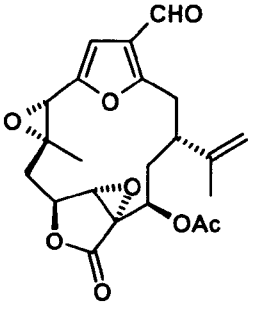

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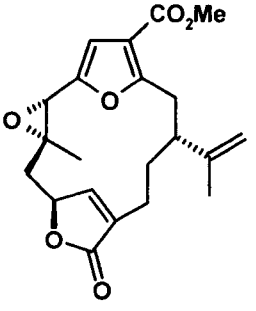

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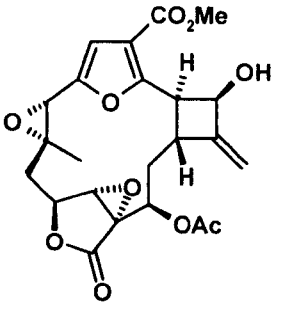
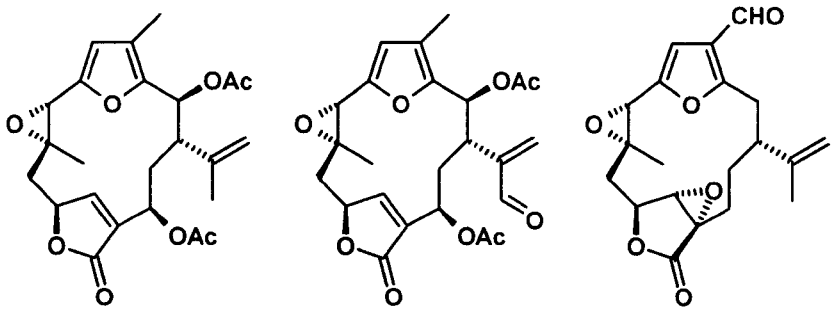


52

isolated from marine corals, and characterised, carry a methyl rather than an electron withdrawing group on their alkene units, *e.g.* bipinnatin J (**5**)[5] and rubifolide **49**.[96] These structural features combine to highlight the importance of the stereochemistry of the $\Delta^{7,8}$-alkene bond, and the nature of the substitution at the C4 position in determining the patterns of oxidation of alkenylfuranocembranes *in vivo*, and the subsequent transformations of the oxidised members leading to the rich variety of unusual polycyclic diterpenes produced in corals.

The furanocembranes within the "lophotoxin" family are biologically active and exhibit neurotoxicity. Lophotoxin **50** and other family members act by irreversibly binding to the nicotinic acetylcholinergic receptors on the Tyr-190 amino acid in the α-subunit of the autonomic ganglia receptor, causing paralysis and asphyxiation. The neurotoxicity of lophotoxin is thought to be associated with the structural similarity between its butenolide fragment and acetylcholine **55**.[105,106]



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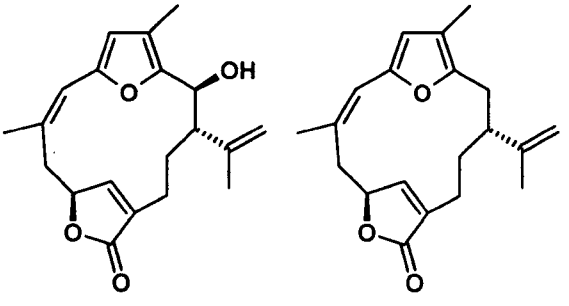

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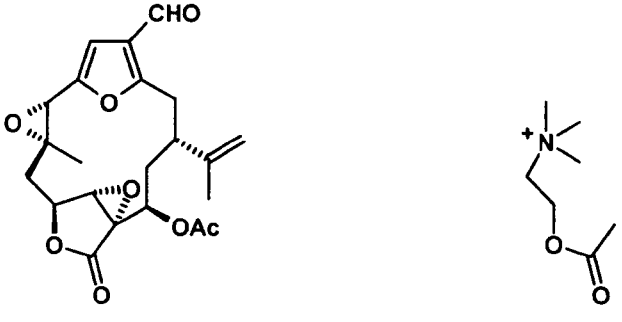
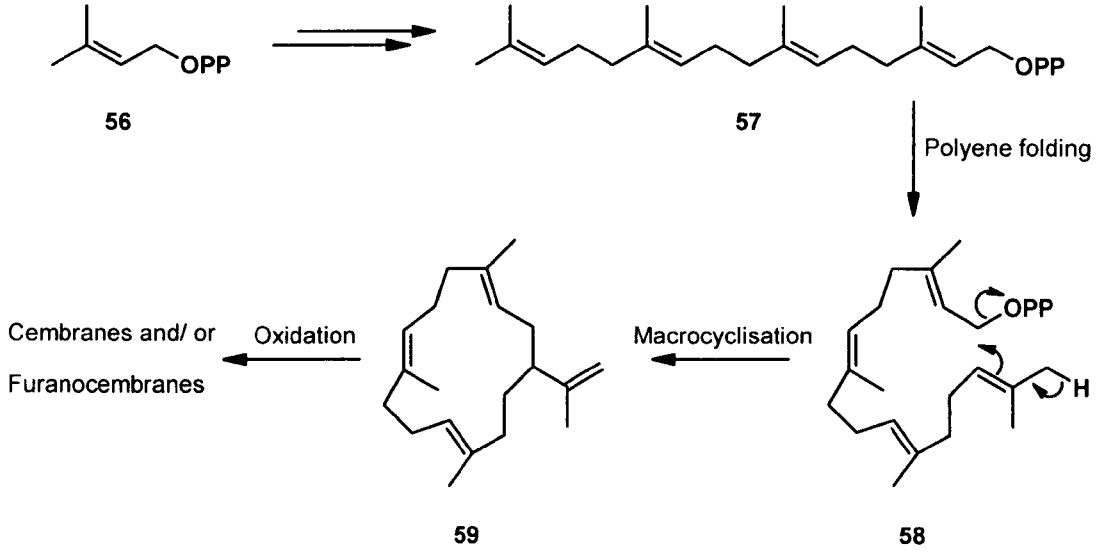


50 55

The gorgonian octocoral reefs are relatively abundant in the temperate waters of the Caribbean, but predation within these reefs is scarce apart from some specialist feeders (*e.g.* butterflyfish, molluscs, etc.). Field studies on twenty eight species demonstrated that the gorgonian octocorals major defence utilises the furanocembranolide diterpenes, *e.g.* pukalide **51**, lophotoxin **50** and other metabolites, as potent feeding deterrents.[107-109] Within the gorgonians species of soft coral, the cembrane and furanocembrane structures are produced biosynthetically from the common starting material dimethylallyl pyrophosphate **56** (Scheme 1). The isoprene unit is first elongated to the C20 diterpene, geranylgeranyl pyrophosphate **57**. This

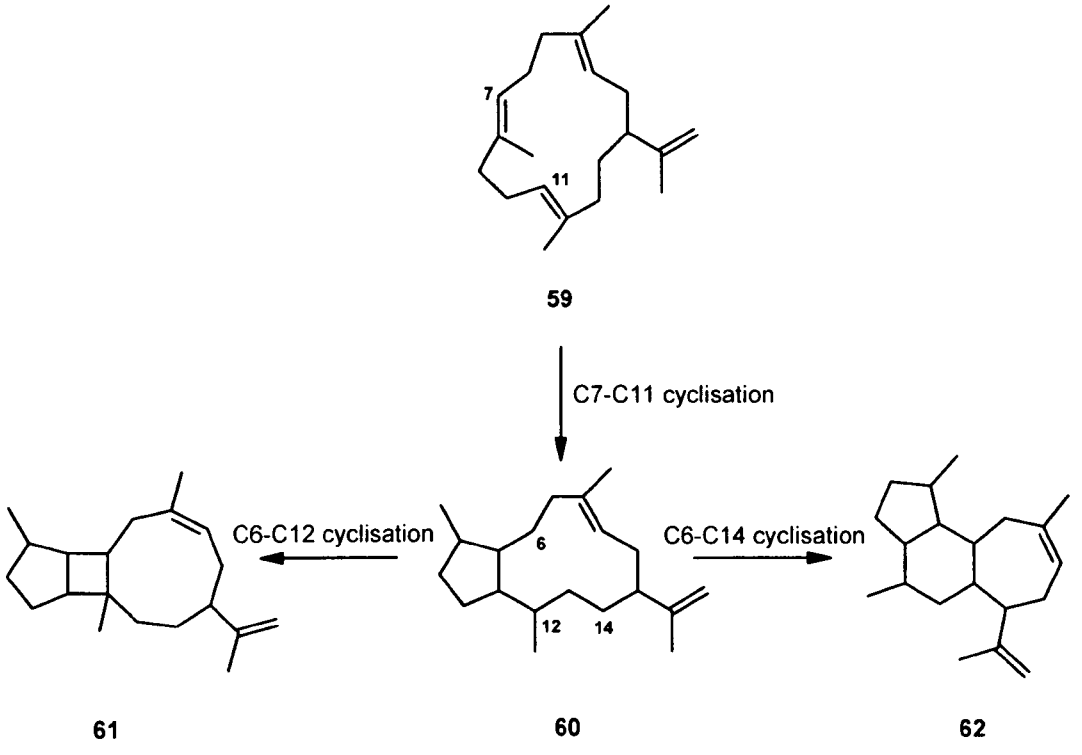
key intermediate **57** folds into the conformation **58** which then undergoes an intramolecular electrophilic cyclisation between the terminal alkene and the pyrophosphate to produce a macrocyclic intermediate **59**. Upon oxidation of the neocembrane structure **59**, depending on the level of oxidation achieved, either a cembrane or a furanocembrane is finally produced. Further oxidation produces a butenolide, various epoxide/ alkene functionality and the alcohols seen in furanocembrane natural products (**5**, **6** and **49-54**).[5,6,96-104]



Scheme 1. Biosynthesis of a furanocembrane structure.

In Nature, we believe that the complex structures of bielschowskysin **1**, verrillin **2** and plumarellide **3** are synthesised by cyclisations of the intermediate 14-membered neocembrane ring **59** (Scheme 2). Cyclisation across the C7,C11 position reveals a verrillane carbon skeleton **60** and by a further cyclisation procedure across the C6,C12 positions the bielschowskyane carbon skeleton **61** is produced. Alternatively, cyclisation between the C6,C14 positions of the verrillane carbon skeletal intermediate **60** produces the 6-membered ring at the core of the plumarellide carbon skeleton **62**. Further elaboration of these basic verrillane **60**, bielschowskyane **61** and

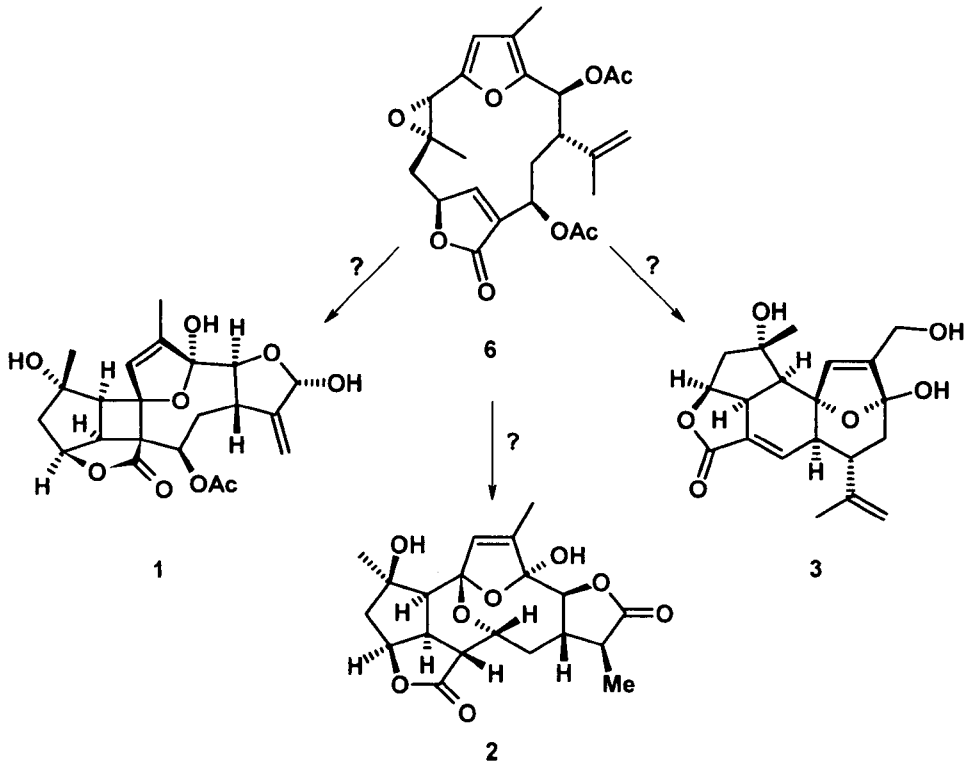
plumarellide **62** structures *via* enantioselective and regiospecific enzymatic oxidations would produce the novel natural products.[1]



Scheme 2. Biosynthesis of the skeletal structures of bielschowskysin **61**, verrillin **60** and plumarellide **62**.

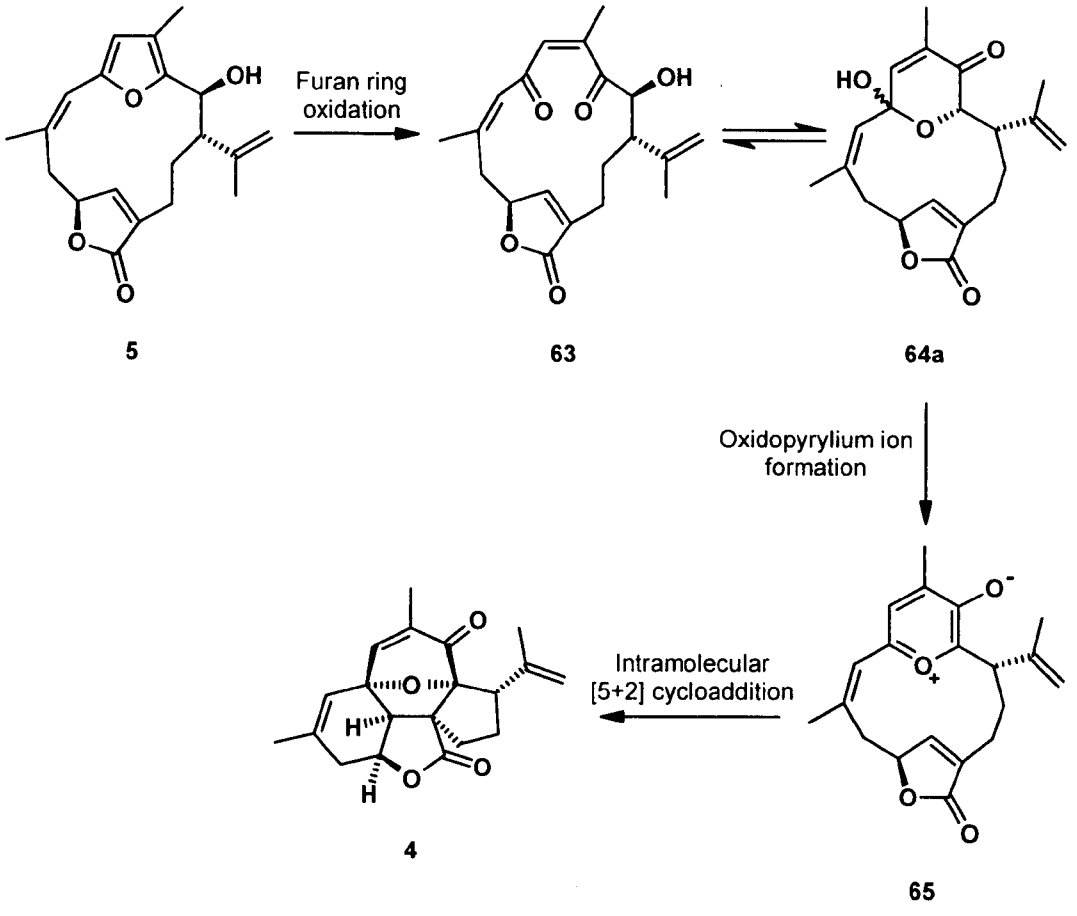
It is plausible that the octocorals enzymatically oxidise the basic skeleta, *i.e.* **60**, **61** and **62**, to the natural products, bielschowskysin **1**, verrillin **2** and plumarellide **3**. With the furanobutenolide family of compounds being co-metabolites within the corals, it is possible enzymatic oxidation occurs on the basic cembrane **59** in order to produce furanobutenolide – based cembrane structures which could, in-turn, be transformed into the three more complex polycyclic compounds (Scheme 3).

The idea of transforming a furanobutenolide – based cembrane into a polycyclic diterpene was supported by contemporaneous work within our research group[110] and work from the group of Trauner[111] on the total synthesis of (+)-intricarene **4**. The



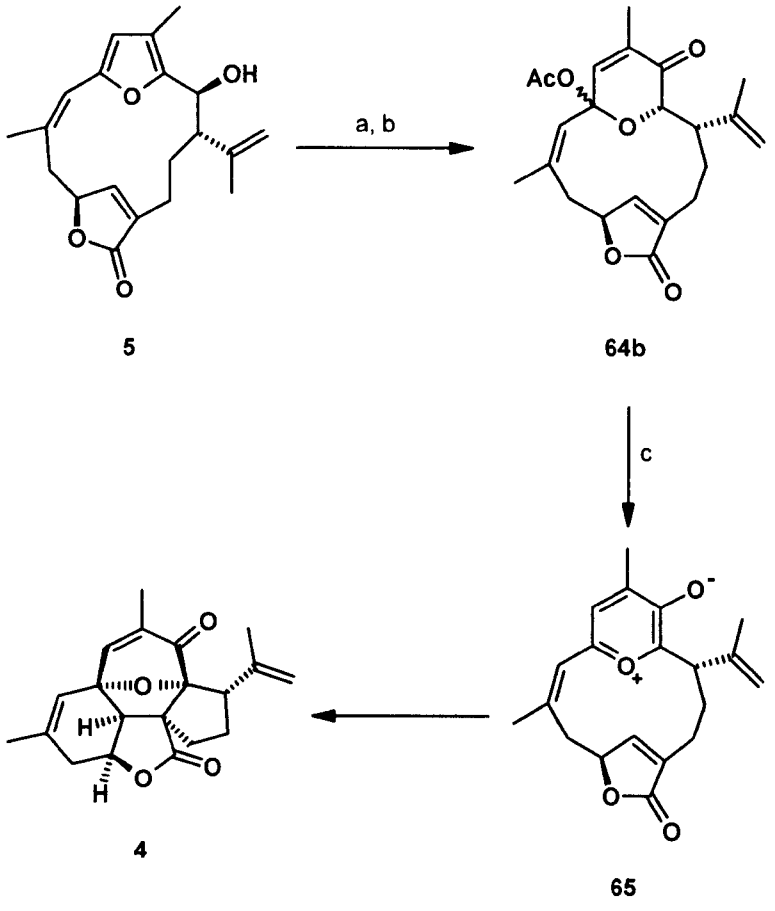
Scheme 3. Proposed formation of bielschowskysin **1**, verrillin **2** and plumarellide **3** from a furanobutenolide precursor.

biomimetic conversion into intricarene **4** could occur from the furanocembrane bipinnatin J (**5**) as shown in Scheme 4. If the furan ring of bipinnatin J (**5**) was oxidised to the corresponding dienedione **63**, this would be in equilibrium with the hydroxypyrone **64a**. This oxidative ring expansion of the furan unit in **5** now allows the oxidopyrylium ion **65** to be formed by elimination of the hydroxyl functionality or an alternative leaving group. The intermediate **65** can then undergo a transannular [5+2] cycloaddition between the oxidopyrylium ion and the alkene contained in the butenolide function. This novel [5+2] cycloaddition would then form intricarene **4** in a single transformation from the hydroxypyrone **64a**.



Scheme 4. Proposed chemical relationship between bipinnatin J (**5**) and intricarene **4**.

To investigate the biomimetic synthesis of (+)-intricarene **4** shown in Scheme 4, a collegue, Bencan Tang treated (–)-bipinnatin J (**5**) with $VO(acac)_2$ and ^tBuOOH (Scheme 5), which resulted in oxidative ring cleavage of the furan ring and led to the formation of the hydroxypyrone **64a** *via* the dienedione intermediate **63**.[112] Acetylation of the enedione-hydroxypyrone mixture **63** and **64a**, using Ac_2O and Et_3N, next gave the 6-acetoxypyranone **64b** as a 5:1 mixture of epimers at the C6 position. Treatment of the 6-acetoxypyranone **64b** with DBU in refluxing acetonitrile resulted in elimination of the acetoxy group and formation of the presumed oxidopyrylium ion **65**.[113,114] The intermediate ionic species **65** then underwent the [5+2] transannular cycloaddition leading to (+)-intricarene **4** in a yield of 10%.

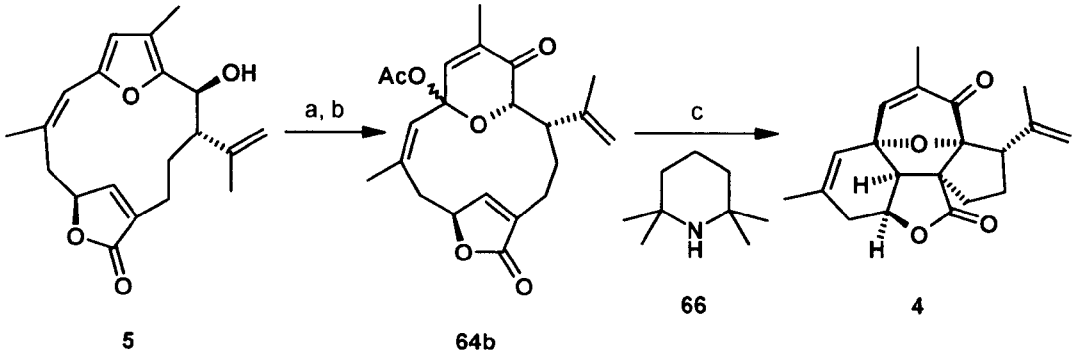


Scheme 5. *Reagents and conditions:* (a) $VO(acac)_2$, ^tBuOOH, CH_2Cl_2, -20 °C, 2 hrs; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t., 3 hrs, 30% (over 2 steps); (c) DBU, MeCN, reflux, 1 hr, 10%.

The same sequence was followed by Trauner *et al.* but utilising different reagents and conditions (Scheme 6). Thus, the furan ring in (–)-bipinnatin J (**5**) underwent oxidative cleavage using *m*CPBA in DCM to form the hydroxypyrone **64a**. Subsequent acetylation of intermediate **64a** next produced the 6-acetoxypyranone **64b**, which upon addition of the hindered secondary amine base, TMP **66**, in the polar solvent, DMSO, at 150 °C in a sealed tube formed (+)-intricarene **4**. These conditions produced (+)-intricarene **4** in yields of 10-26%.

The total synthesis of intricarene **4**, was first achieved by our own group in 2006 and then later by Trauner *et al.*[110,111] Buoyed by this success we hoped that a similar

transannular process could be applied to the synthesis of the polycyclic structures bielschowskysin **1**, verrillin **2** and plumarellide **3**.

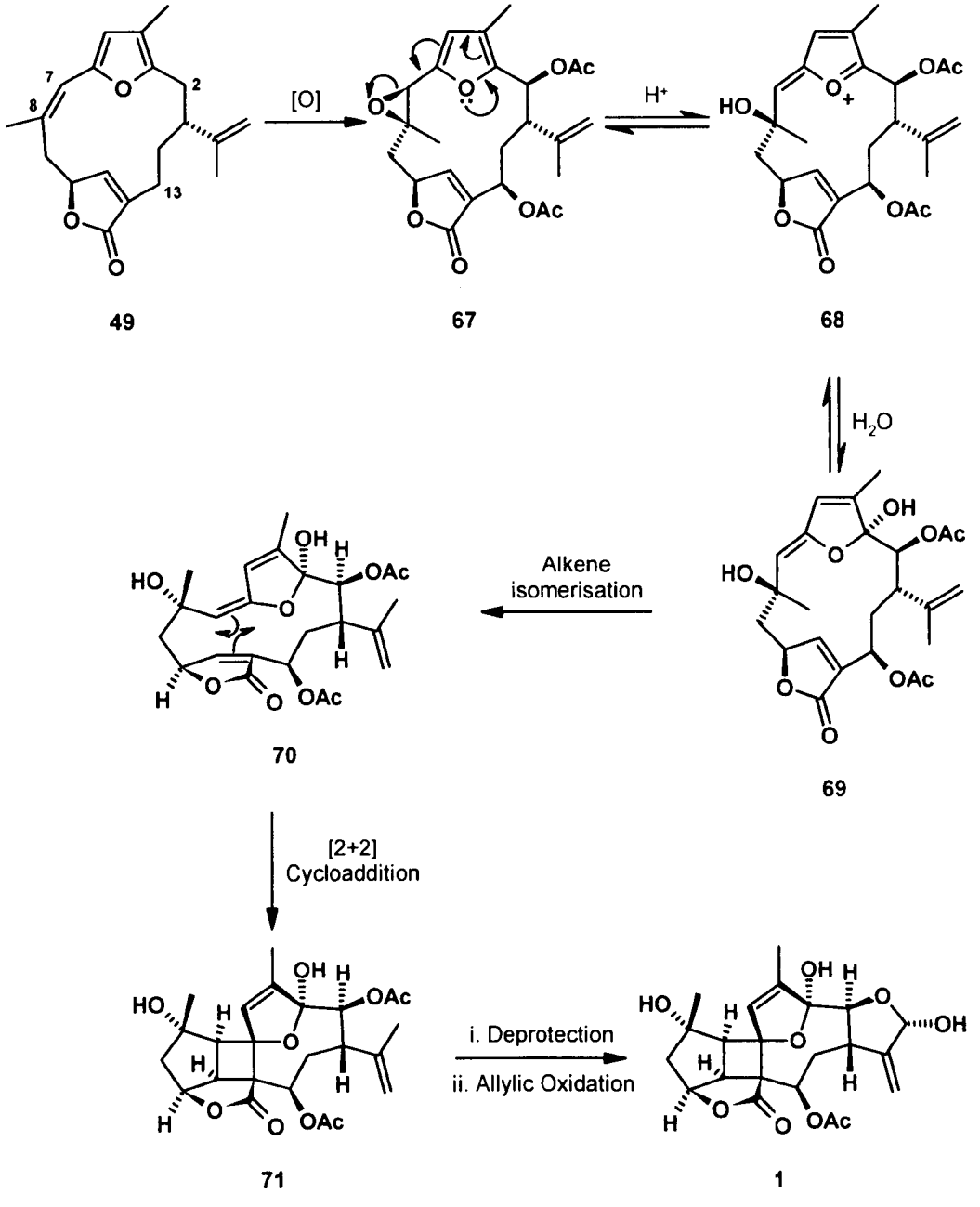


Scheme 6. *Reagents and conditions:* (a) *m*CPBA, CH_2Cl_2, 0 °C, 1 hr; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, r.t., 2 hrs, 81% (over 2 steps); (c) **66**, DMSO, 140 °C (sealed tube), 16 hrs, 26%.

Proposal for the origins of bielschowskysin 1, verrillin 2 and plumarellide 3 from furanobutenolide precursors

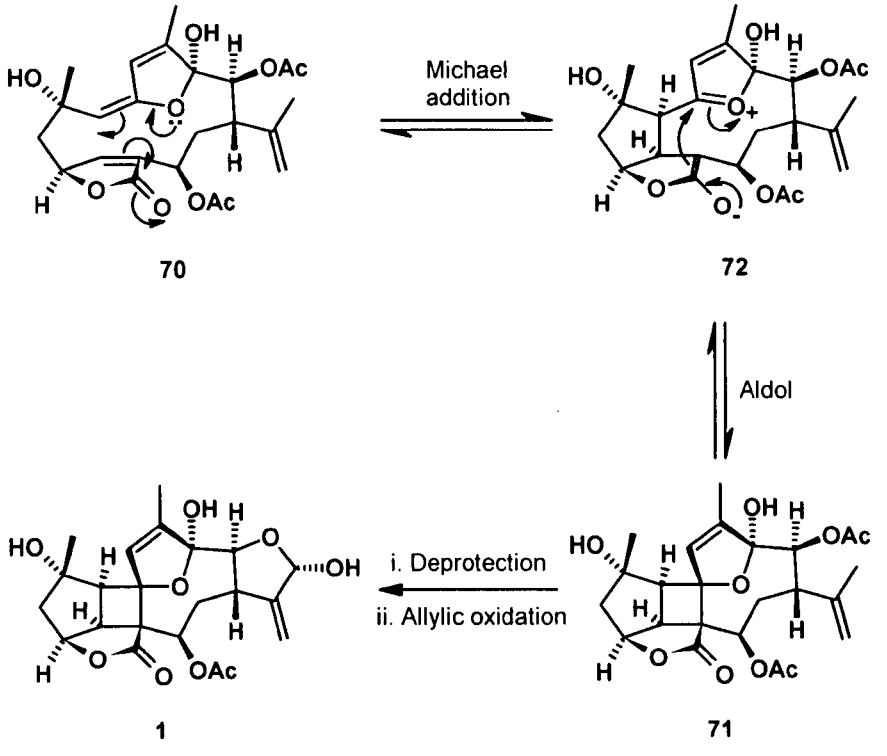
Our proposed biosynthetic route to bielschowskysin **1**,[1] verrillin **2**[2] and plumarellide **3**[3] starts from the simple furanobutenolide – based cembrane molecule, rubifolide **49**.[96] Selective enzymatic oxidations lead to the macrocyclic structure of *iso*-bipinnatin G (**67**), containing an epoxide function between the C7,C8 position and oxgenation at the C2 and C13 positions in the form of protected alcohols (Scheme 7). *iso*-Bipinnatin G (**67**) possesses the opposite $\Delta^{7,8}$-epoxide diastereoisomer to the natural product **6**. Bielschowskysin **1** could be formed from *iso*-bipinnatin G (**67**) *via* an intramolecular [2+2] cycloaddition process across the furanobutenolide – based cembrane macrocycle. An acid catalysed epoxide ring opening of **67** utilising the electron density located in the furan reveals the oxonium ion **68**. Quenching **68** with water leads to the enol ether **69** containing a *Z-exo*-alkene. For the [2+2] cycloaddition to occur the *exo*-cyclic alkene and the butenolide alkene must be held in close proximity. Isomerisation of the *Z-exo*-alkene **69** to the *E-exo*-alkene **70**, by acid

catalysis or exposure to light, draws the two alkenes functions into close vicinity. Utilising light allows the key [2+2] cycloaddition[115] to occur between the butenolide and the *exo*-cyclic alkene contained within the enol ether hemi-ketal functionality to produce the key cyclobutane tetracyclic core **71**.[116-119] Finally, acetyl deprotection and allylic oxidation of the isopropenyl side-chain would form the cyclic hemi-acetal and lock the macrocycle into position to produce bielschowskysin **1**.



Scheme 7. Proposed chemical relationship between *iso*-bipinnatin G (**67**) and bielschowskysin **1**.

An alternative formation of the key cyclobutane tetracyclic core **71** could occur under the acidic conditions which are used to open the epoxide function (Scheme 8). After the *exo*-cyclic alkene has been isomerised to form the intermediate **70**, the butenolide and the *exo*-cyclic alkene are close enough to undergo a simple Michael addition into the β-position of the butenolide facilitated by the enol ether functionality. The enolate generated **72** from the Michael addition can then add back into the oxonium ion *via* an aldol-type addition to generate the cyclobutane tetracyclic core **79**.[120-122] Finally cyclic hemi-acetal formation again leads to bielschowskysin **1**.

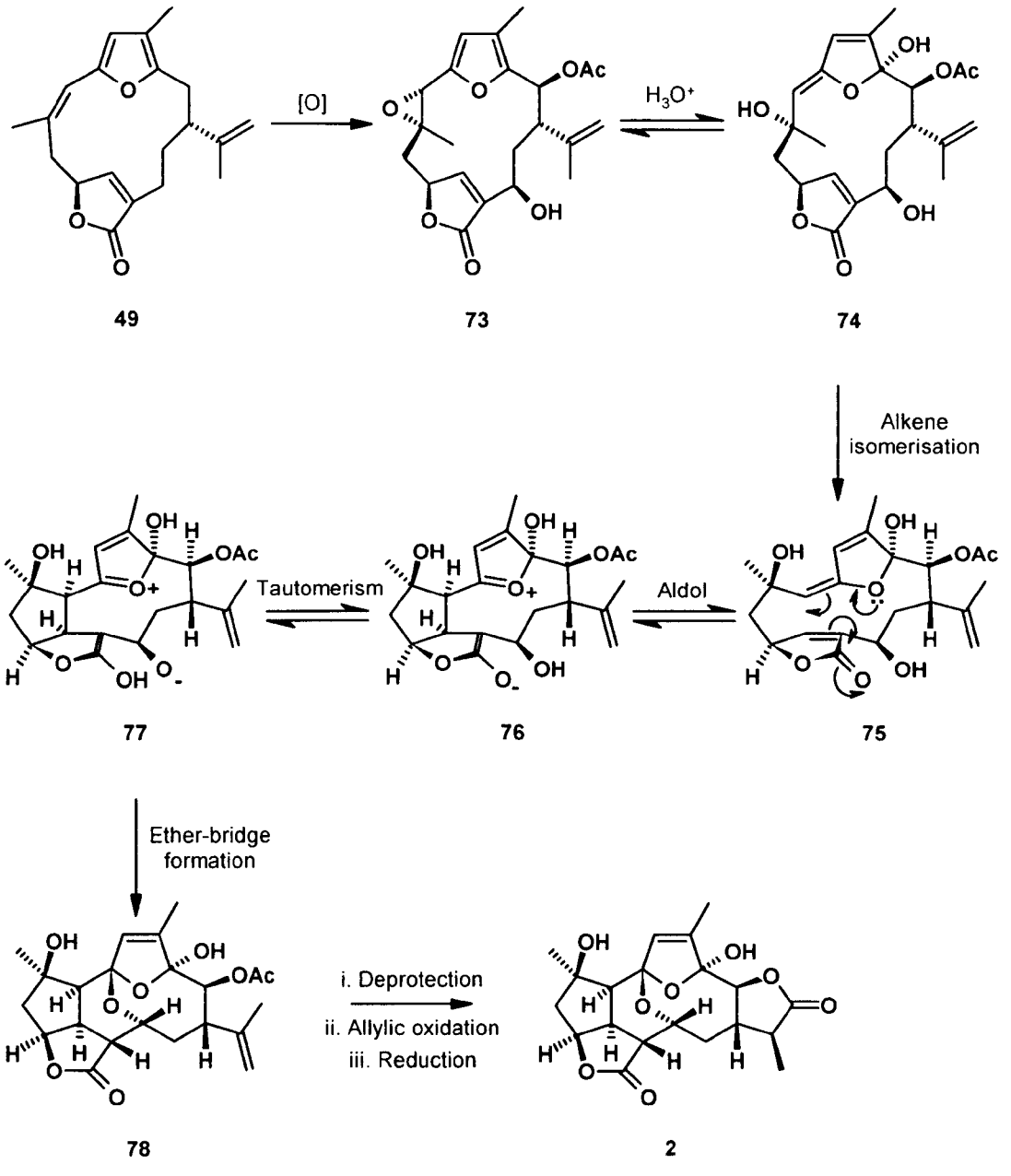


Scheme 8. Alternative biosynthesis of bielschowskysin **1**.

Verrillin **2** could be formed along a similar sequence to bielschowskysin **1** but using a Michael addition followed by formation of the ether-bridge (Scheme 9). Similar selective enzymatic oxidations of rubifolide **49** produce the macrocyclic structure of 13-deacetylbipinnatin G (**73**). Acid-catalysed epoxide opening of the furanobutenolide – based cembrane **73** followed by quench of the cationic furan species by water,

produces the enol ether intermediate **74**. Similar to bielschowskysin **1**, the *exo*-cyclic alkene of the enol ether hemi-ketal **74** undergoes isomerisation to produce the *E-exo*-alkene **75**. This again disposes the butenolide and the enol ether functional groups into close enough proximity for them to react. An acid-catalysed Michael addition into the β-position of the butenolide forms the enolate **76** in an identical manner to the alternative bielschowskysin **1** proposal. The enolate **76** produced from the Michael addition in then able to undergo proton exchange with the C13 secondary alcohol group to form the oxy anion species **77**. The enol group in **77** can undergo keto-enol tautomerism to reinstall the lactone functionality. The core structure of verrillin **78** is then elaborated upon ether bridge formation between the oxonium ion species and the butenolide oxy anion species. All that is now required to produce the natural product **2** is deprotection of the secondary alcohol functional group in **78**, allylic oxidation with *in-situ* lactonisation and finally a regiosepecific conjugate reduction of the *exo*-α,β-unsaturated lactone substituent. The reduction of the α-methylene lactone may be aided by the inherent conformation bias of the core macrocycle. This final transformation produces the natural product verrillin **2**.

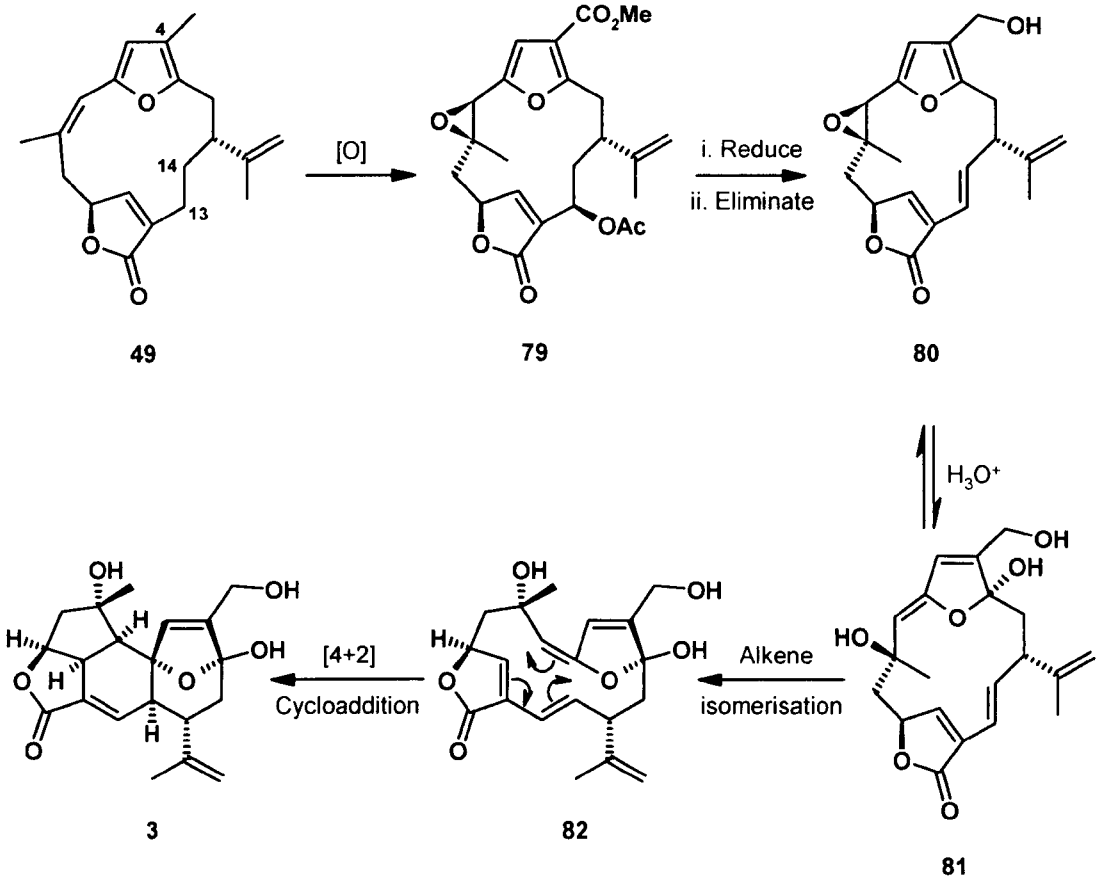
The proposed biosynthesis of plumarellide **3** would utilise the same structural motif as that shown previously in the biosynthesis of bielschowskysin **1** and verrillin **2**, namely the enol ether cyclic hemi-ketal **70** and **75**. The proposed biosynthesis is shown in Scheme 10 and starts from the furanobutenolide – based cembrane, *iso*-13-acetoxypukalide **79**[123] which could be produced *in vivo* by selective enzymatic oxidation of rubifolide **49**.[96] The furanocembrane intermediate **80** required for the biomimetic transformation contains an epoxy furan, substituted with a CH_2OH group



Scheme 9. Proposed chemical relationship between 13-deacetylbipinnatin G (**73**) and verrillin **2**.

at the C4 and an alkene unit at C13,C14 in conjugation with the butenolide functionality. This intermediate could be produced from *iso*-13-acetoxypukalide **79** upon reduction of the C4 ester functionality to form the hydroxymethyl furan substituent and elimination of the C13 acetyl-protected secondary alcohol could introduce the diene functionality. Treatment of intermediate **80** with acidic aqueous conditions should allow the same process to occur as that shown for both

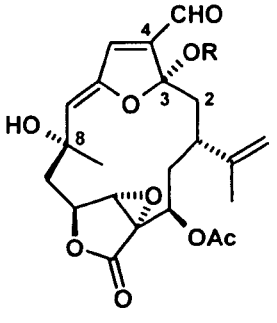
bielschowskysin **1** and verrillin **2**, to form the enol ether cyclic hemi-ketal **81**. It is this key motif which is again used for a transannular cyclisation, specifically the Diels-Alder process. Isomerisation of intermediate **81** places the alkene functionality of the *E*-enol ether **82** and the conjugated butenolide in close enough proximity to allow a [4+2] transannular cycloaddition process to occur.[124,125] The cyclohexene functionality produced from the Diels-Alder cycloaddition process forms the core structure of plumarellide **3**.



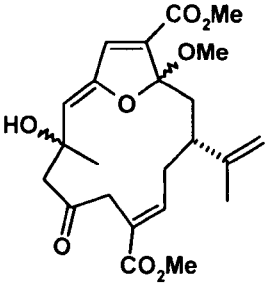
Scheme 10. Proposed conversion of rubifolide **49** into plumarellide **3** based on biomimetic speculation.

The initial stage in the biosynthesis of bielschowskysin **1**, verrillin **2** and plumarellide **3** is the acid catalysed ring opening of the C7,C8 epoxide to produce the enol ether cyclic hemi-ketal intermediates **69**, **74** and **81**. Four enol ether cyclic hemi-ketal natural products, *i.e.* **83a**, **83b**, **84** and **85**, have been isolated by Fenical *et al.*,[107] Abramson *et al.*,[105] Venkateswarlu *et al.*[126] and by Slattery *et al.*[127] The southern

portions in these structures, containing the butenolides, vary in oxidation pattern and functionality but the northern portions remain essentially unchanged. The structural features which remain constant throughout these enol ether natural products are: i) they contain a C3-methoxy group; ii) there is an unsubstituted *iso*-propyl side-chain; iii) the macrocycles are devoid of a hydroxyl group at the C2 position; iv) an electron-withdrawing substituent is present at the C4 position, namely a CO_2Me or CHO group; v) there is a tertiary alcohol substituent at the C8 position of the macrocyclic compounds. The isolation of **83a**, **83b**, **84** and **85** suggests that the proposed biosyntheses, *via* the enol ether hemi-ketal structural motif, has some creditability. We believe that more elaborate metabolites to further elucidate the biosynthesis of either bielschowskysin **1**, verrillin **2** or plumarellide **3** have still to be isolated.



R = Me **83a**
R = Et **83b**



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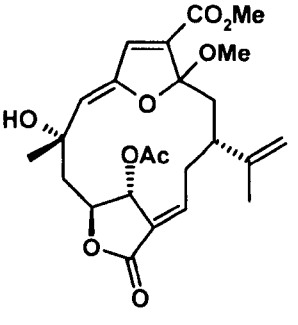


85

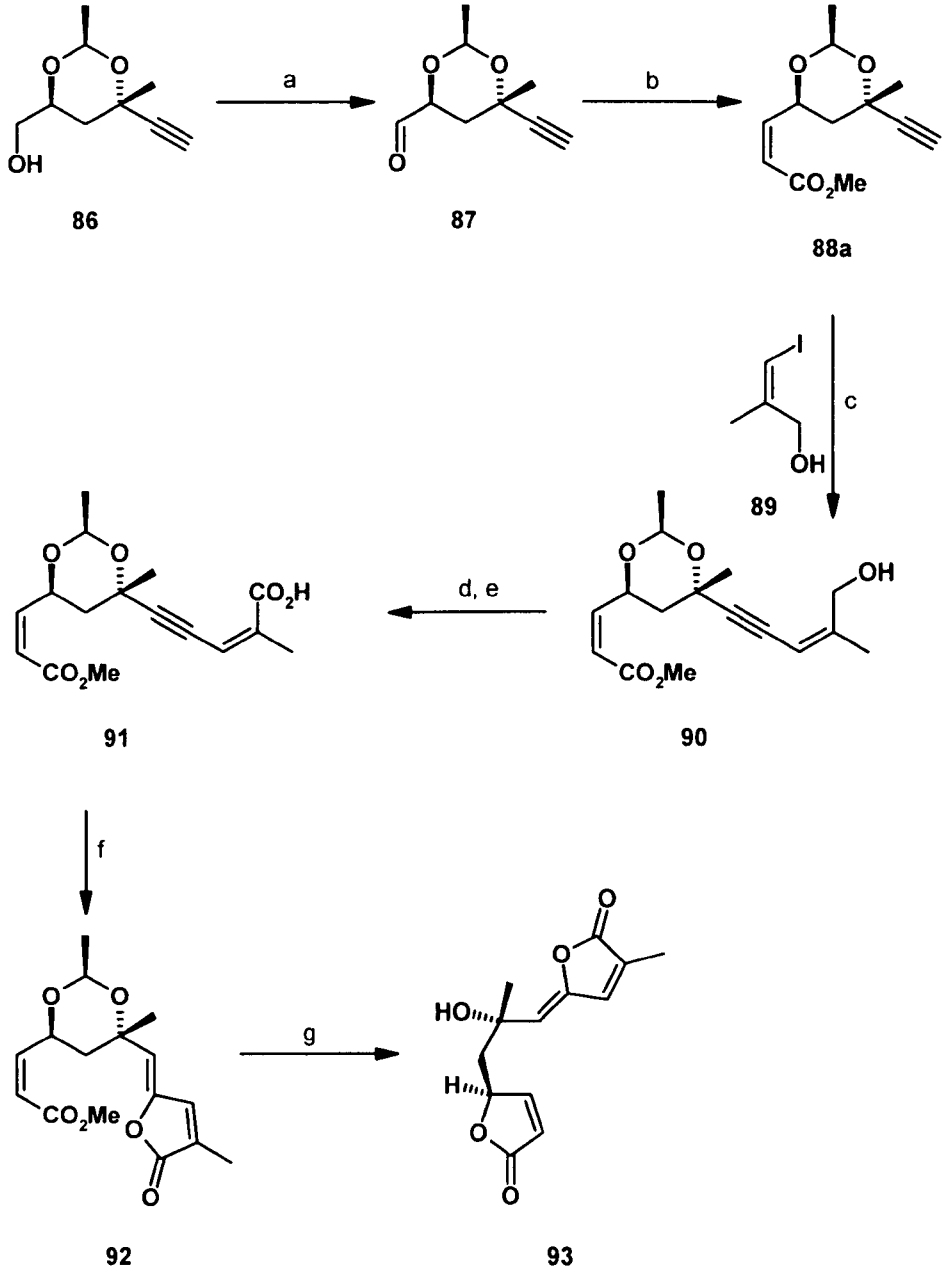
To date, there have been no syntheses of bielschowskysin **1**, verrillin **2** and plumarellide **3**. However, there have been publications which support the proposed biomimetic formation of the cyclobutane ring in bielschowskysin **1**. Thus, in 2006, Sulikowski *et al.* reported the formation of the cyclobutane – containing tetracyclic structure **98**,[128] *via* an intramolecular [2+2] cycloaddition process (Scheme 11). The synthesis started from malic acid, which was first converted over several steps to the 1,3-dioxane acetal compound **86**. Oxidation of the primary alcohol group in **86** using DMP next afforded the aldehyde **87** which was then used in a Still-Gennari

modified,[129] Wadworth-Emmons olefination[130] to produce the *Z*-enoate **88a**. A Sonogashira cross-coupling reaction[131] between the acetylene functionality in **88a** and the vinyl iodide **89** led to the allylic alcohol **90**, which was then transformed into the corresponding carboxylic acid **91** utilising sequential oxidation *via* the aldehyde functionality. The γ-alkylidene butenolide **92** was produced as a single geometric isomer by treatment of the carboxylic acid **91** with $AgNO_3$ in methanol under Negishi's conditions.[132] Finally, treatment of the γ-alkylidene butenolide **92** with aqueous acetic acid removed the acetal protecting group allowing the secondary alcohol functionality to cyclise on to the methyl ester substituent to form the butenolide **93**.

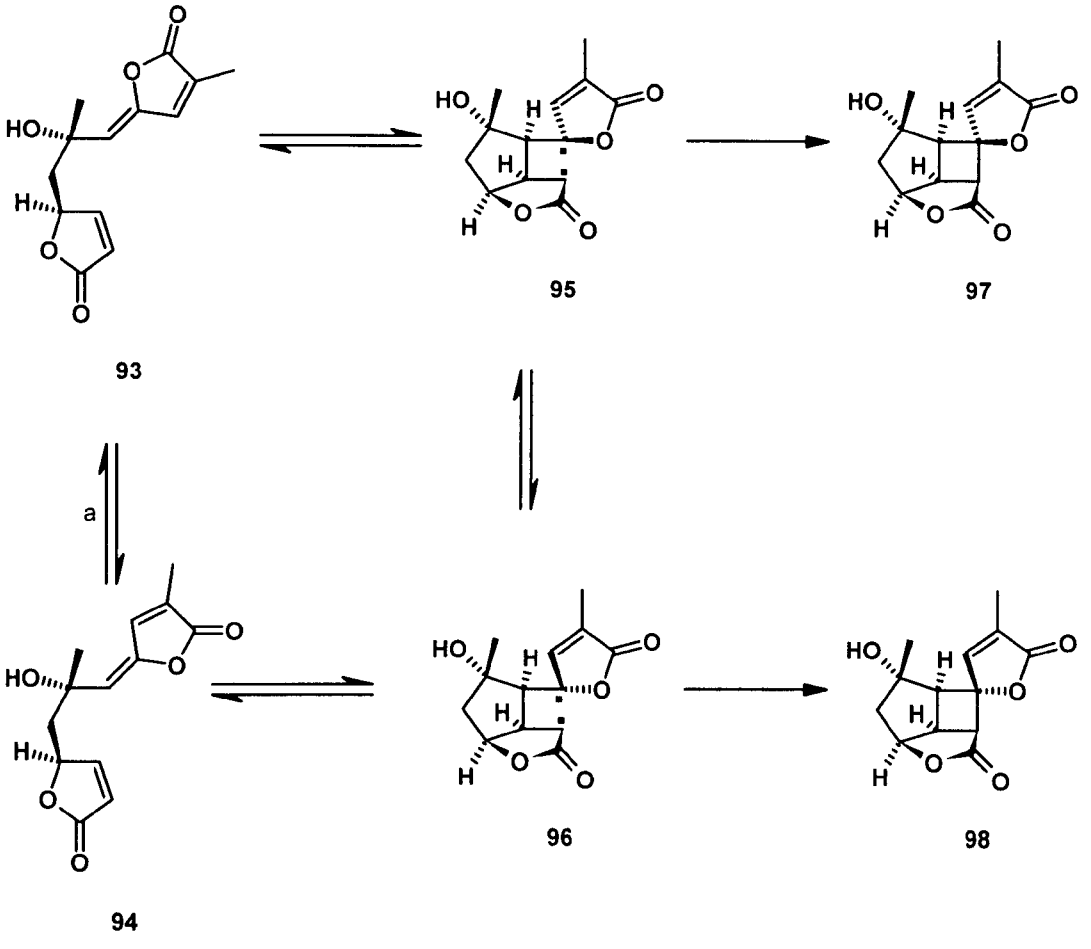
A solution of the butenolide **93** in acetone was irradiated with light through pyrex glass for 72 hours (Scheme 12),[115,116] which led initially to a photoequilibrium mixture of the geometric isomers **93** and **94**. However, upon prolonged exposure the butenolide and the alkylidene butenolide alkenes were excited and produced radical species, which cyclised following the "rule of five" to form the biradical intermediates **95** and **96**.[133,134] The intermediates **95** and **96**, could interchange *via* simple bond rotation or *via* re-formation of the precursor compounds **93** and **94**, which could interconvert *via* photoisomerisation. The final stage in this process was the formation of the cyclobutane ring structures **97** and **98** as a 1:5 mixture in 50% yield.

This study demonstrated that an intramolecular [2+2] cycloaddition process could potentially be applied to the *E*-enol ether **70** to produce the cyclobutane functionality in bielschowskysin **1**. The investigations by Sulikowski *et al.*[128] was complemented by a synthesis of the analogous tricyclic compound **101** published by Lear *et al.* in

2009.[135] The synthesis again utilised an intramolecular [2+2] cycloaddition process but this time involving an allene and a butenolide (Scheme 13). The synthesis initially followed a similar synthetic sequence to Sulkowski *et al.* in order to transform malic acid into the *Z*-enoate **88b** using several straightforward steps. Treatment of the *Z*-enoate **88b** with aqueous sulfuric acid in methanol deprotected the acetal functionality

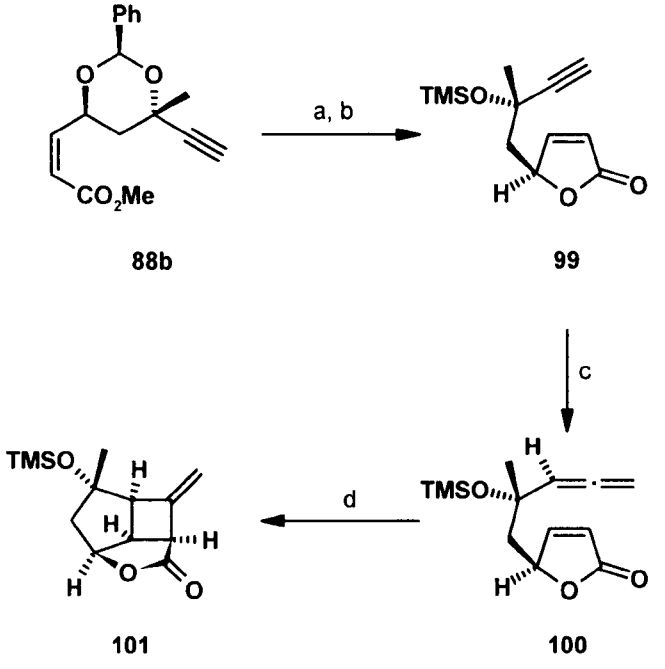


Scheme 11. *Reagents and conditions:* (a) DMP, CH_2Cl_2, r.t., 2 hrs, 85%; (b) KHMDS, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, -78 °C to r.t., 1 hrs, 71%; (c) **89**, $Pd(PPh_3)_4$, CuI, Et_3N, MeCN, r.t., 16 hrs, 75%; (d) DMP, CH_2Cl_2, r.t., 2 hrs; (e) $NaHPO_3.H_2O$, $NaClO_2$, H_2O, H_2O_2, MeCN, 0 °C, 90 mins, 59% (over 2 steps); (f) $AgNO_3$, MeOH, r.t., 1 hr, 75%; (g) AcOH, H_2O, r.t., 15 hrs, 43%.



Scheme 12. *Reagents and conditions:* (a) hν, Me_2CO, pyrex, r.t., 72 hrs, 50%.

allowing cyclisation to form a γ-butenolide, which upon protection of the tertiary alcohol functional group, produced the TMS-silyl ether **99**. The allene **100** was formed upon homologation of the acetylene unit in **99** by treatment with $(CH_2O)_n$, $^iPr_2NH$ and CuBr in refluxing dioxane. Initially the tricyclic precursor **100** was heated to investigate a thermal [2+2] cycloaddition, but this reaction did not result in the tricyclic core **101**. Instead, exposure of **100** to light in hexane/ DCM for 12 hours induced the intramolecular [2+2] cycloaddition process[115] leading to tricyclic compound **101** as a single diastereoisomer in a 70% yield.



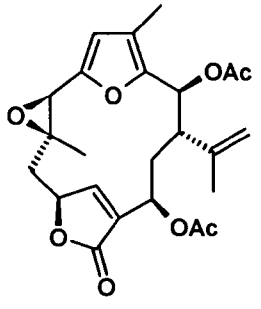
Scheme 13. *Reagents and conditions:* (a) H_2SO_4, MeOH, r.t., 15 hrs, 70%; (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to r.t., 2 hrs, 62%; (c) $(CH_2O)_n$, $^iPr_2NH$, CuBr, dioxane, reflux, 3 hrs, 68%; (d) hν, hexane, CH_2Cl_2, r.t., 12 hrs, 70%.

The syntheses of the cyclobutane containing ring systems **98** and **101** represent the most significant synthetic development towards the natural products bielschowskysin **1** published so far.

Planned model study with the simplified furanobutenolide – based structures 102 and 125

To achieve our proposed biomimetic synthesis of the natural products, bielschowskysin **1**,[1] verrillin **2**[2] and plumarellide **3**,[3] a furanobutenolide – based cembrane structure would have to be synthesised. The required epoxyfuran structures are represented by *iso*-bipinnatin G (**67**), 13-deacetylbipinnatin G (**73**) and the furanodiene **80**. Syntheses of any one of these structures with all the substituents present, is synthetically demanding. Therefore, it was considered more advantageous

to first undertake the synthesis of a more simple model substrate analogous to rubifolide **49**.[96]



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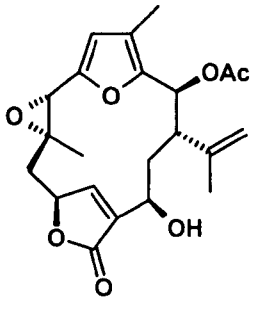

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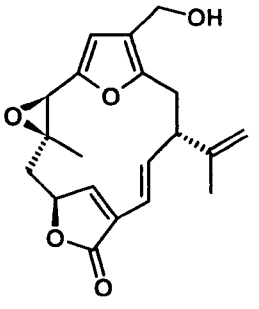
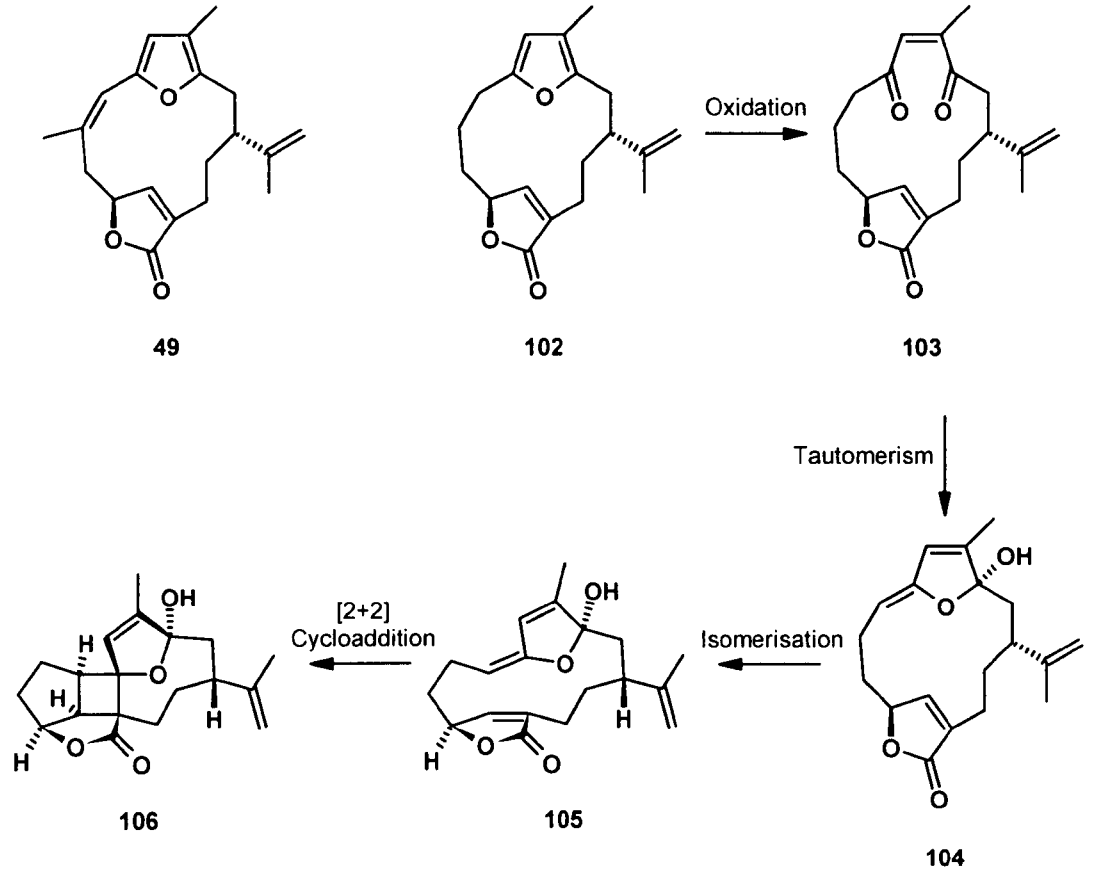


80

Initially, in order to examine the [2+2] cycloaddition process,[115-121] only a 14-membered macrocyclic structure with an α,β-unsaturated ester, in the form of a butenolide and an enol ether substituent is required. Simplification of rubifolide **49** led us to the macrocyclic furanobutenolide **102** (Scheme 14). Oxidative ring cleavage of the furan functionality in **102** would be expected to lead to the enedione **103**[136] which, following tautomerism forms the required enol ether hemi-ketal structure **104**. Isomerisation of the alkene bond in the *Z*-enol ether **104** to the *E*-enol ether **105** would then bring the butenolide into close enough proximity to allow the [2+2] cycloaddition[115,120] and generate the cyclobutane ring functionality in the bielschowskysin core **106**.

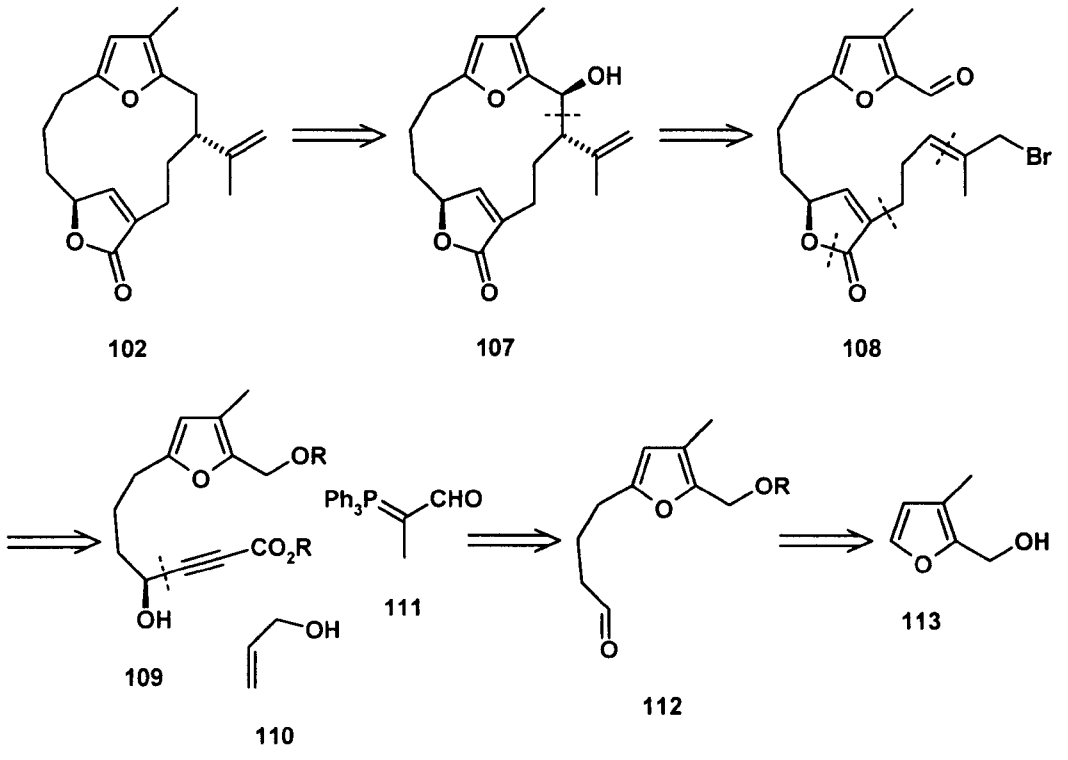
Thus, starting with the much more simple furanobutenolide structure **102**, retrosynthetic analysis reveals the intermediate **107** containing a C2 hydroxyl group and an isopropenyl substituent which would be elaborated *via* a Nozaki-Hiyama-Kishi (NHK) macrocyclisation process from the furan aldehyde **108** (Scheme 15). The furan aldehyde **108** could, in-turn, be produced *via* a Wittig olefination using the stabilised phosphorane **111**, and a Trost Alder-ene reaction between the propargylic



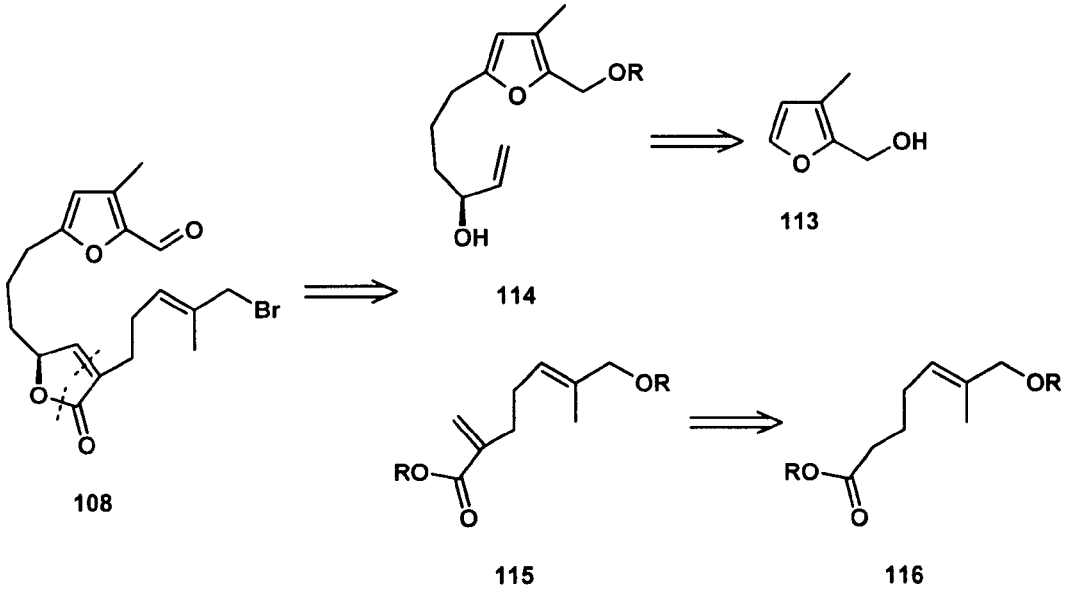
Scheme 14. Proposed transformation into the bielschowskysin core **106** from a rubifolide analogue **102** utilising a bioinspired sequence.

alcohol **109** and allyl alcohol **110**, would form the butenolide functionality. Removal of the propargylic alcohol substituent in **109** leads back to the aldehyde **112**, which ultimately could be derived from the known furanmethanol **113**.

Alternatively, the butenolide functionality of furan aldehyde **108** could be produced using an esterification reaction followed by a ring-closing metathesis (RCM) process between the allylic alcohol **114** and the α,β-unsaturated ester **115** fragments, as shown in Scheme 16. The allylic alcohol **114** could again be formed from the furan methanol **113** *via* the aldehyde **112**. Removal of the methylene group from the α,β-unsaturated ester **115** produces the ester **116**, which was used previously for our (–)-bipinnatin J (**5**)/ (+)-intricarene **4** synthesis.[110]



Scheme 15. Retrosynthesis of the bielschowskysin model precursor **102**.

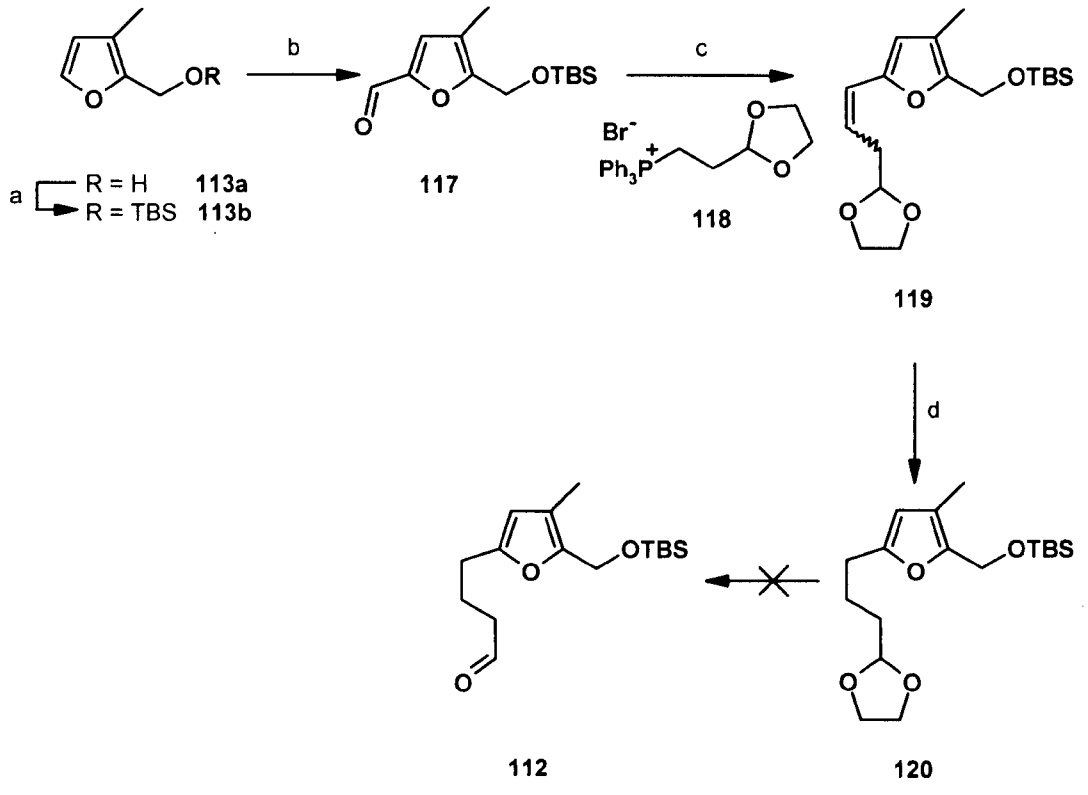


Scheme 16. Alternative retrosynthesis of the model furanobutenolide precursor **108**.

The synthesis of the model system **102** was initiated by forming the known furanmethanol **113a**[137] (Scheme 17) by straightforward reduction of commercially available methyl 3-methyl-2-furoate, using $LiAlH_4$. Protection of the alcohol **113a** as

its TBS-ether was then achieved using Corey's conditions,[138] *i.e.* TBS-Cl and imidazole in DMF, to produce the silyl ether **113b** in 96% yield. Addition of ^{n}BuLi to **113b** at 0 °C resulted in directed deprotonation at the C5 furan position which, on treatment with DMF, gave the furan aldehyde **117**.[139] Deprotonation of the commercially available phosphonium salt **118**, using ^{n}BuLi at -78 °C led to the corresponding ylide species which, on addition of the furan aldehyde **117**, gave a 3:2 mixture of the *E*:*Z*-alkene isomers of the alkenylfuran **119** in 75% yield.[140,141] The alkenylfuran **119** was reduced to **120**, using hydrogen in the presence of 5% palladium on carbon. To produce the aldehyde **112**, the acetal functional group in **120** had to be deprotected selectively in the presence of the silyl ether. A range of conditions were tried in order to achieve this selective deprotection, but none could be found. The conditions either, removed both protecting groups, decomposed the material or selectively deprotected the TBS-silyl ether to form the corresponding primary alcohol.

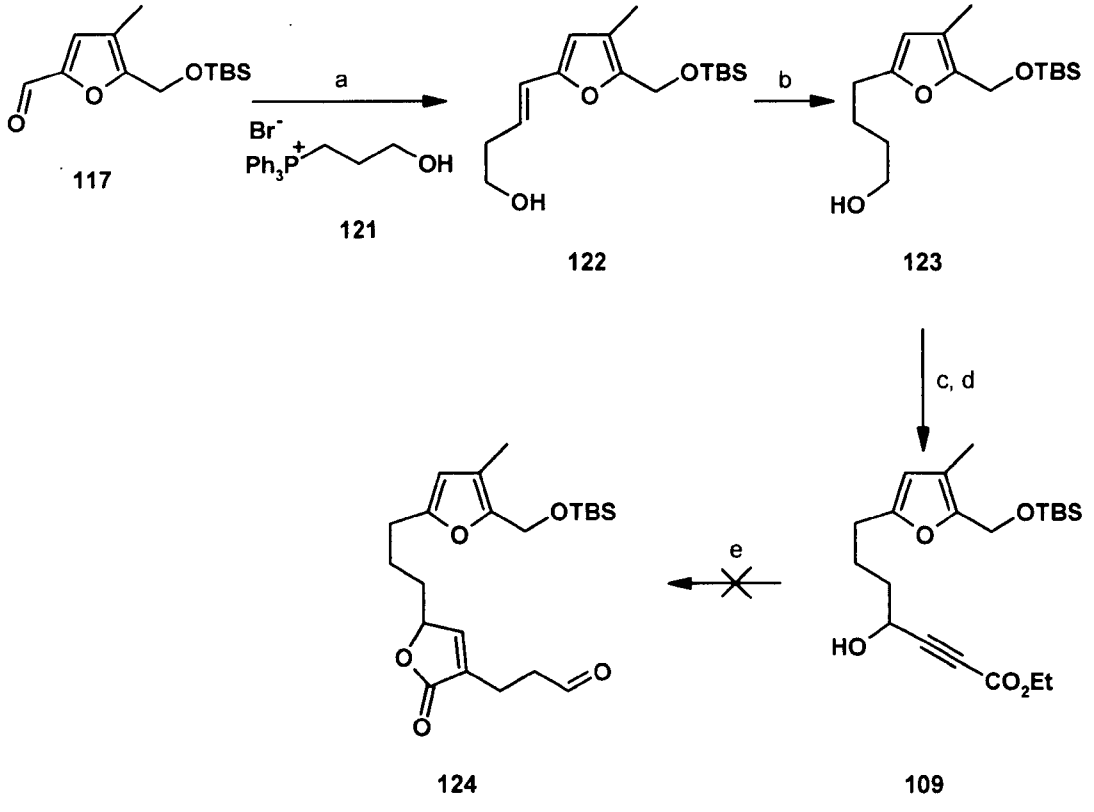
The aldehyde **112**, required to form the propargylic alcohol **109** and the allylic alcohol **114**, could still be formed potentially by altering the phosphonium salt used in the Wittig reaction (Scheme 18). Thus, the phosphonium salt **121**[142,143] was prepared by refluxing 3-bromo-1-propanol and Ph_3P in MeCN. Deprotonation of **121** using ^{n}BuLi at -20 °C produced the corresponding ylide intermediate which, on addition of the furan aldehyde **117** led to the *E*-alkenylfuran **122** in 60% yield, predominantly as the *E*-isomer; this followed from the magnitude of the vicinal coupling (*J* 15.8 Hz) between the olefinic hydrogens in the ^{1}H NMR spectrum. Unfortunately, the previous hydrogenation conditions only proceeded to decompose this substrate. The problem



Scheme 17. *Reagents and conditions:* (a) TBS-Cl, Im, DMF, 0 °C, 10 mins, 96%; (b) ^{n}BuLi, THF, -78 °C to 0 °C, 30 mins, then DMF, -78 °C to r.t., 4 hrs, 77%; (c) **118**, ^{n}BuLi, THF, -78 °C, 40 mins, then **117**, THF, -78 °C to r.t., 15 hrs, 75%; (d) 5% Pd/C, H_2, EtOAc, r.t., 3 hrs, 93%.

could be overcome be changing the solvent to THF and running the reaction in the presence of a base, *i.e.* Et_3N, in order to generate the furan **123**. Oxidation of the primary alcohol functional group in **123** using TPAP and NMO, cleanly afforded the aldehyde **112**, which upon addition of the lithiated ethyl propiolate species formed the propargylic alcohol **109**. With the propargylic alcohol **109** in-hand the Alder-ene reaction[144,145] could be examined. The highest yields and greatest regiochemical selectivity are obtained when the Trost Alder-ene reaction is preformed under acidic conditions,[146-148] but the substrate **109** has previously proven to be sensitive to acid. It was therefore hoped the reaction could be performed under neutral conditions so as to avoid decomposition of the substrate. Thus, the propargylic alcohol **109** was treated with $RuCp(MeCN)_3PF_6$ and allyl alcohol **110** in DMF at room temperature, but none of the required butenolide **124** was observed.[146] Unfortunately the reaction conditions

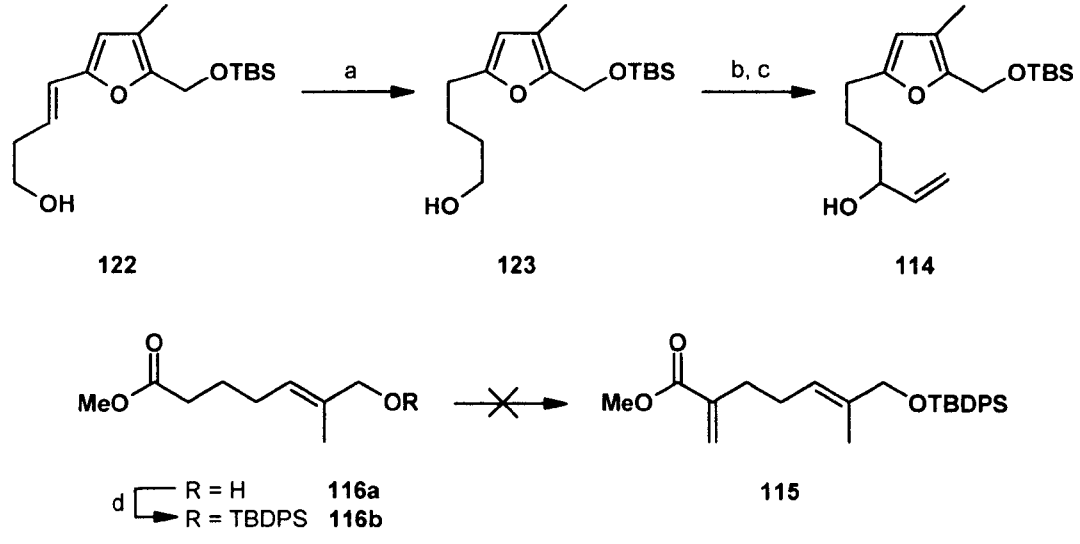
only proceeded to decompose the starting material. Addition of base to the reaction, *e.g.* K_2CO_3 and Et_3N, did not produce any of the butenolide **124** and returned only the starting materials. These results are unsurprising since the active catalyst is $CpRu^+$, a Lewis acid, which presumably causes the decomposition of the substrate; upon addition of base the catalyst was presumably deactivated and therefore the original substrate was returned.



Scheme 18. *Reagents and conditions:* (a) **121**, ^{n}BuLi, THF, -20 °C, 30 mins, then **117**, THF, -20 °C to r.t., 15 hrs, 60%; (b) 5% Pd/C, H_2, Et_3N, THF, r.t., 15 hrs; (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, r.t., 1 hr; (d) LDA, ethyl propiolate, THF, -78 °C, 2 hrs, 61% (over 3 steps); (e) allyl alcohol **110**, 10 mol% $RuCp(MeCN)_3PF_6$, DMF, r.t, 20 hrs.

The problem encountered during the Alder-ene process with **109** led us to examine the alternative RCM method, in order to form the butenolide functionality of **108** (Scheme 19). The *E*-alkenylfuran **122** produced from a Wittig reaction, again underwent hydrogenation, oxidation and upon treatment of the resulting aldehyde with vinylmagnesium bromide in THF at -78 °C produced the allylic alcohol fragment

114 in a combined 50% yield. The synthesis of the α,β-unsaturated ester fragment **115** commenced from the allylic alcohol **116a**,[110] which was first protected as the silyl ether **116b** using TBDPS-Cl and imidazole in DMF.[138] Unfortunately attempts to transform the silyl ether **116b** into the α,β-unsaturated ester **115** by deprotonation and addition of the enolate species into Eschenmoser's salt[149] failed.[150] This result was disappointing and abruptly interrupted the synthesis towards the furanobutenolide **102**.

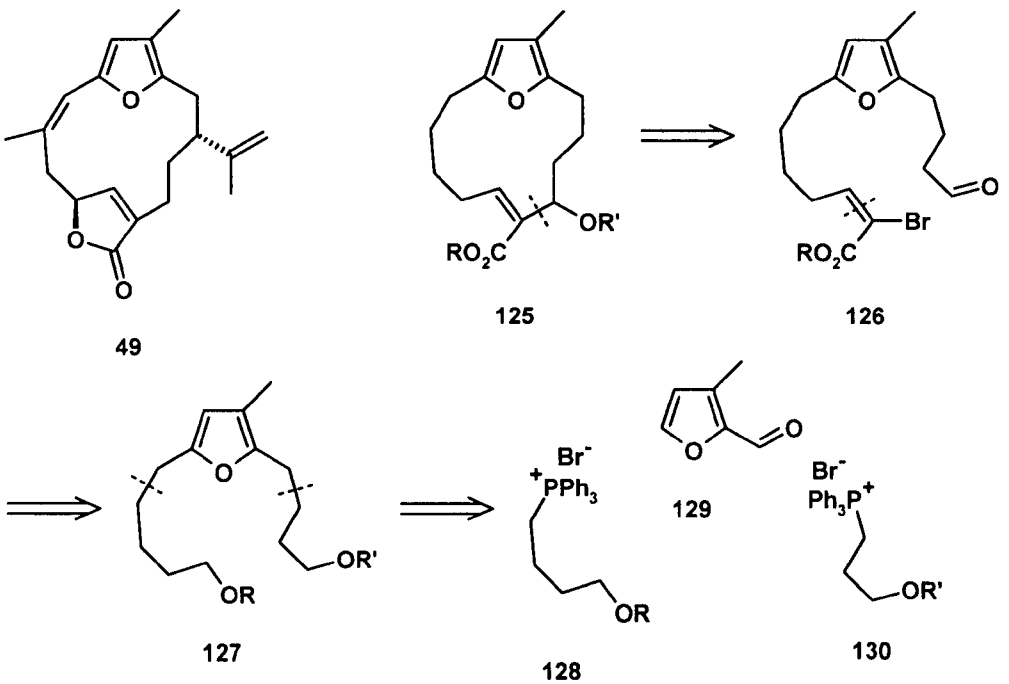


Scheme 19. *Reagents and conditions:* (a) 5% Pd/C, H_2, Et_3N, THF, r.t., 15 hrs; (b) TPAP, NMO, 4 Å MS, CH_2Cl_2, r.t., 1 hr; (c) vinylmagnesium bromide, THF, -78 °C, 1 hr, 50% (over 3 steps); (d) TBDPS-Cl, Im, DMF, 0 °C, 10 mins, 86%.

Due to the problems encountered during this model system it was decided to change the target structure in order to avoid the difficulties observed with stability and reactivity.

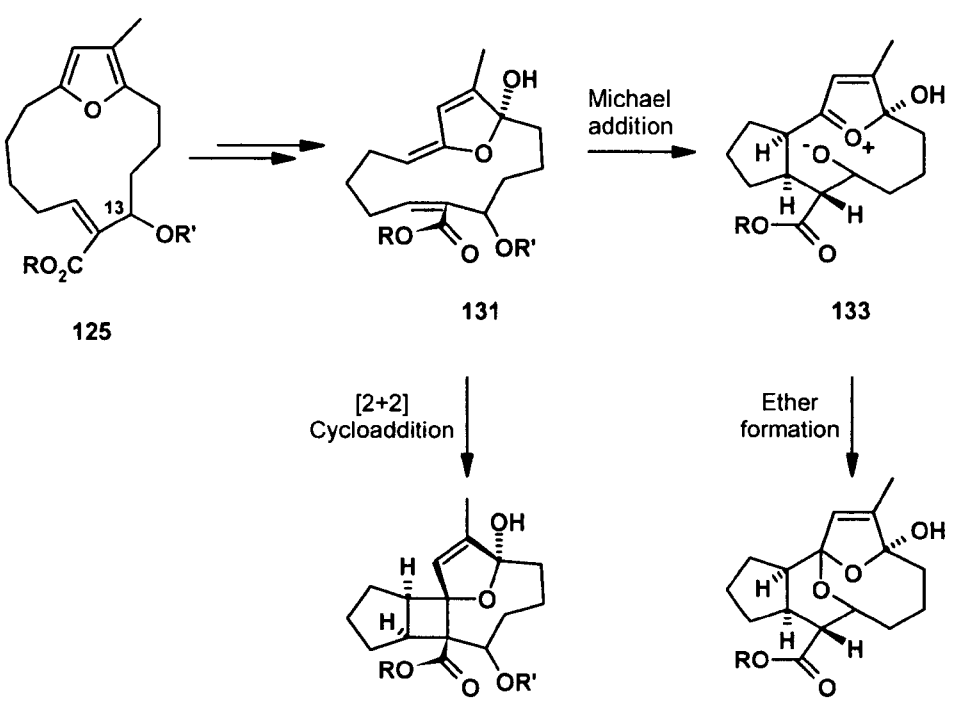
Simplification of rubifolide **49** led us to the intermediate **125** with a furan and an α,β-unsaturated ester substituent (Scheme 20). Construction of the macrocycle in the furanocembrane **125** could be achieved *via* a Reformatsky-type process within the compound **126**. A Wadsworth-Emmons olefination reaction would install the α-

bromoester functionality of aldehyde **126** from the protected diol **127**. Addition of both side-chains to the furan ring of intermediate **127** could be achieved utilising Wittig reactions between the furan aldehyde **129** and the two phosphonium salts **128** and **130**.



Scheme 20. Retrosynthesis of the alternative bielschowskysin model structure **125**.

Installation of the C13 hydroxyl group, not only provided a method for macrocyclisation but it also allowed access to both bielschowskysin and verrillin core structures, *i.e.* **132** and **134**, respectively, as shown in Scheme 21. Thus, transformation of the macrocyclic intermediate **125** into the enol ether **131** could be achieved along a similar sequence to that shown in the previous model system (Scheme 14) *via* oxidative ring cleavage,[112] tautomerism and isomerisation. A [2+2] transannular cycloaddition[115,120] on precursor **131** produces the bielschowskysin core **132**. Alternatively, the verrillin core **134** could be produced *via* a transannular Michael addition to form the oxonium intermediate **133** which upon ether-bridge formation secures the core structural motif.

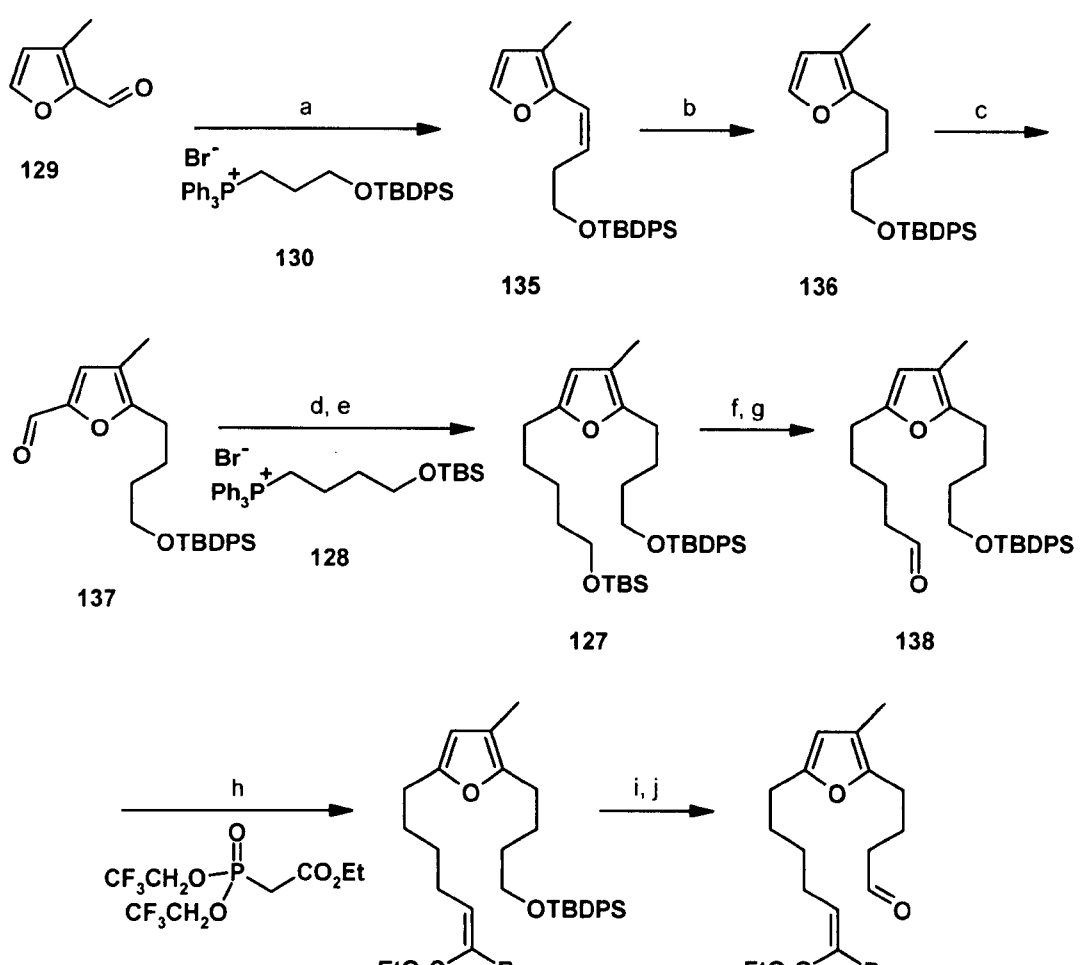


Scheme 21. Formation of the bielschowskysin and verrillin cores **132** and **134** from the furanocembrane **125**.

The starting point for the model structure **125** was the known furan aldehyde **129** (Scheme 22),[151] produced by treatment of the furanmethanol **113a** (used in the previous model system **102**) with MnO_2 in DCM. Deprotonation of the phosphonium salt **130**[152,153] using ^{n}BuLi gave the corresponding ylide which, on addition of the furan aldehyde **129** gave the *Z*-alkenylfuran **135**; this followed from the magnitude of the vicinal coupling (*J* 11.8 Hz) between the olefinic hydrogens in the ^{1}H NMR spectrum. Reduction of **135** under hydrogenation conditions, next gave the furan **136**. Directed deprotonation at the C5 furan position, followed by quenching of the intermediate lithiated species with DMF at -78 °C next produced the furan aldehyde **137**.[154] The Wittig reaction was used again by reacting the aldehyde **137** with the ylide derived from the phosphonium salt **128**.[155] Subsequent hydrogenation of the alkene bond, formed in the Wittig process, then produced the protected diol **127**. The protected diol **127** was next converted into the aldehyde **138** by selective cleavage of

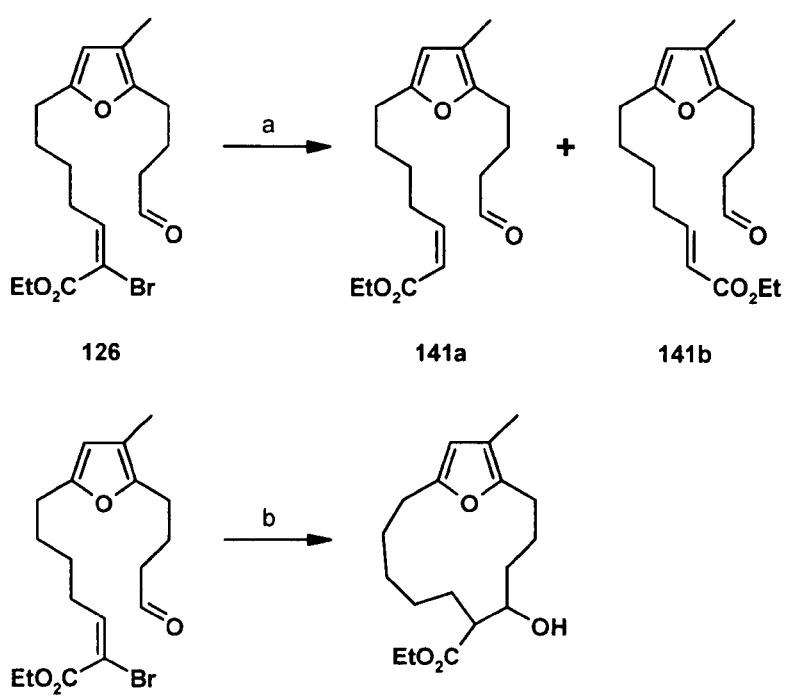
the primary TBS-ether under mildly acidic conditions, *i.e.* PPTS in MeOH and DCM, followed by Swern oxidation of the alcohol functional group. With the aldehyde functionality in place, a Wadsworth-Emmons reaction[130] using the fluorophosphonate reagent **139**, in a Still-Gennari modification[129] was performed on **138**. After work-up and chromatography the ^{1}H NMR spectroscopic data showed a signal at δ_H 6.65 ppm, which corresponded to the *E*-alkene isomer of the α-bromoester **140a** (*cf.* ^{1}H NMR spectroscopic data for ethyl 2-bromo-2-nonenoate: the *Z*-alkene isomer showed a signal at δ_H 7.23 ppm, whereas the *E*-alkene isomer showed a signal at δ_H 6.60 ppm).[156] Deprotection of the TBDPS-ether in **140a** was achieved with the HF.Py complex, and oxidation of the resulting alcohol using Dess-Martin periodinane produced the macrocycle precursor **126**, in a straightforward manner.

With the aldehyde **126** in hand the macrocyclisation process *via* a Reformatsky-type reaction was investigated (Scheme 23). Previous work by Nagamitsu *et al.*,[157] on the total synthesis of borrelidin, demonstrated that the Reformatsky reaction[158] was not as effective as a SmI_2 mediated[159] Reformatsky-type reaction[160,161] for the intramolecular macrocyclisation process. With this in mind, the macrocyclisation was examined with SmI_2.[159-161] Thus, the aldehyde **126** was treated with SmI_2 at -78 °C, but unfortunately the macrocyclic structure **125** was not produced. Instead, the α-bromoester substituent of intermediate **126** was reduced to the corresponding *Z*- and *E*-α,β-unsaturated esters **141a** and **141b**, in a combined 70% yield (*i.e.* *J* 11.6 Hz for the *Z*-isomer **141b** and *J* 15.6 Hz for the *E*-alkene isomer **141b**). Interestingly, the aldehyde functional group remained unaffected and was not reduced by SmI_2. The result was disappointing but it was thought that the macrocyclisation could be achieved by simply reversing the



Scheme 22. *Reagents and conditions:* (a) **130**, ^{n}BuLi, THF, -20 °C, 30 mins, then **129**, THF, -78 °C to r.t., 15 hrs, 99%; (b) 10% Pd/C, H_2, MeOH, r.t., 4 hrs, 85%; (c) ^{n}BuLi, THF, -78 °C to r.t., 45 mins, then DMF, -78 °C to r.t., 15 hrs, 50%; (d) **128**, ^{n}BuLi, THF, -20 °C, 30 mins, then **137**, THF, -78 °C to r.t., 15 hrs, 72%; (e) 5% Pd/C, H_2, MeOH, pentane, r.t., 4 hrs, 91%; (f) PPTS, CH_2Cl_2, MeOH, r.t., 24 hrs, 84%; (g) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, -78 °C, 2 hrs; (h) i: **139**, NaH, THF, -30 °C, 30 mins, then Br_2, -30 °C to r.t.; ii: NaH, -78 °C to ~ -30 °C, then **138**, THF, -78 °C to r.t., 15 hrs, 72% (over 2 steps); (i) HF.Py, Py, THF, r.t., 24 hrs, 92%; (j) DMP, CH_2Cl_2, r.t., 45 mins, 70%.

addition procedure. Thus, the aldehyde **126** was added to a solution of SmI_2 at -78 °C, and gratifyingly the Reformatsky-type process took place producing the macrocycle **142**. The macrocyclic alcohol **142** was unfortunately devoid of the unsaturation next to the ester functional group. The intramolecular Reformatsky-type process was induced by SmI_2 but the excess reagent used caused simultaneously reduction of the alkene bond post-macrocyclisation.

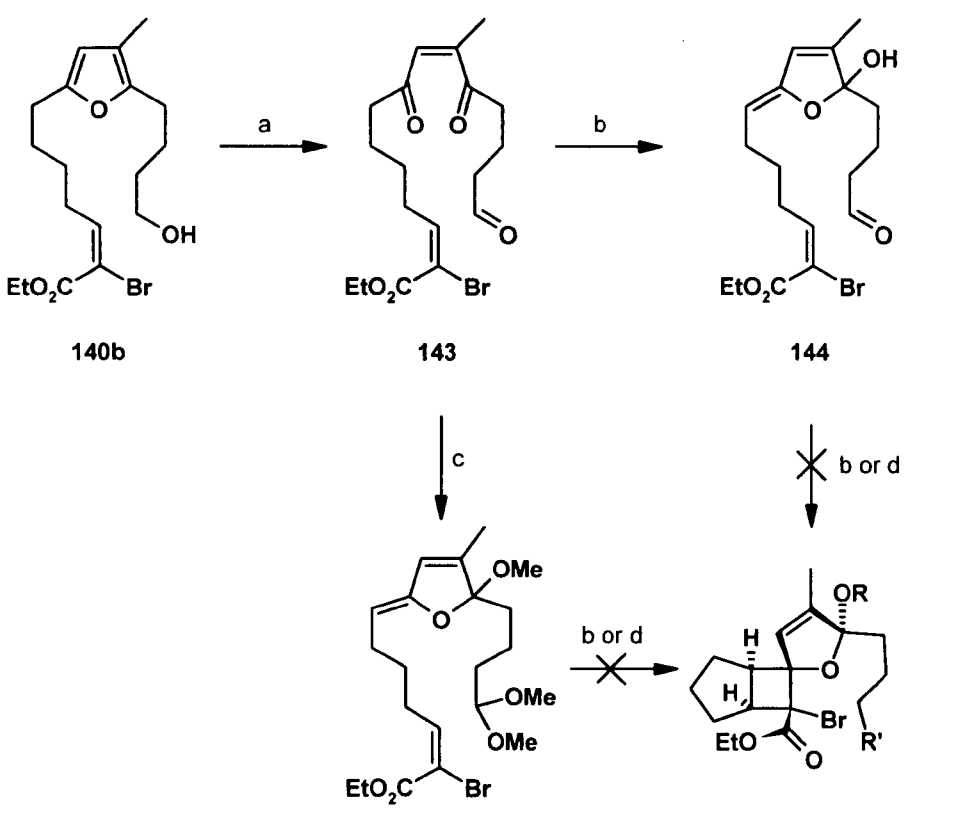


Scheme 23. *Reagents and conditions:* (a) SmI_2, THF, -78 °C, 30 mins, 25% (**141a**), 45% (**141b**); (b) SmI_2, THF, -78 °C, 30 mins, 33%.

The conjugate reduction of the α,β-unsaturated ester functional group in **126** seems inevitable. The $\Delta^{11,12}$-alkene bond could potentially be re-introduced by deprotonation, formation of a phenylselenium intermediate and upon oxidation, *syn*-elimination would occur, to re-introduce the α,β-unsaturated ester functionality. Unfortunately due to the dearth of alcohol **142**, this series of reactions could not be investigated.

It was noticed that when the alcohol **140b** was oxidised with a large excess of Dess-Martin periodinane, not only was the corresponding aldehyde produced, but the furan ring was also cleaved to the enedione **143** (Scheme 24).[136] The enedione intermediate **143** could potentially be transformed into the bielschowskysin core structure **132** but first tautomerisation must occur to form the enol ether cyclic ketal functionality **144**. Formation of the enol ether **144** would allow an intramolecular [2+2]

cycloaddition[115,120] process into the α-bromoester functional group to produce the cyclobutane motif. Finally, cyclisation of the α-bromoester substituent into the aldehyde functionality would produce the bielschowskysin core **132**. To investigate this transformation the enedione **143** was treated with *p*-TSA in THF-H_2O.[162,163] Under these conditions the ^1H NMR spectroscopic data showed a signal at δ_H 4.59 ppm. There were doubts that tautomerism of the enedione **143** had occurred to form the enol ether **144** but this result was supported by treatment of the enedione **143** with *p*-TSA in THF-MeOH which produced NMR spectroscopic data at δ_H 4.04 ppm, consistent with the methyl enol ether **145**. Under these reaction conditions there was simultaneous alteration of the aldehyde functional group of intermediate **143** into the corresponding acetal substituent. Both of the synthesised enol ether compounds, *i.e.* **144** and **145**, were re-subjected to the acidic conditions of *p*-TSA in THF-H_2O in order to induce the [2+2] cycloaddition *via* an acid catalysed Michael-aldol process[120-122] but unfortunately the cyclobutanes **146** and **147** were not produced. Irradiation of the enol ether intermediates **144** and **145** with light in acetone also did not produce the cyclobutane cores, *i.e.* **146** and **147**, *via* a photolytic process,[115-119] only decomposition was observed. Although it was disappointing not to produce either of the cyclobutanes **146** and **147**, the enol ether intermediates, *i.e.* **144** and **145**, are acyclic. Therefore, it was hoped that by forming the enol ether cyclic ketal functionality within a macrocyclic structure, the inherent conformational bias would force the [2+2] transannular cycloaddition process to occur. This would produce the cyclobutane functionality of the bielschowskysin core **132**.



Scheme 24. *Reagents and conditions:* (a) DMP, CH_2Cl_2, r.t., 45 mins, 50%; (b) *p*-TSA, THF, H_2O, r.t., 4 hrs, 80%; (c) *p*-TSA, THF, MeOH, r.t., 4 hrs, 80%, (d) hν, Me_2CO, r.t., 20hrs.

Although neither of the bielschowskysin core structures **106** and **132** could be synthesised, the key structural motif, *i.e.* the enol ether cyclic ketals **144** and **145**, was thought to have been produced *via* an acid catalysed tautomerism of the enedione **143**. Therefore, further investigation into the chemistry of alkenylfurans, and hence enol ethers, was deemed necessary in order to fully understand the reactivity and stability of these intriguing structural motifs.

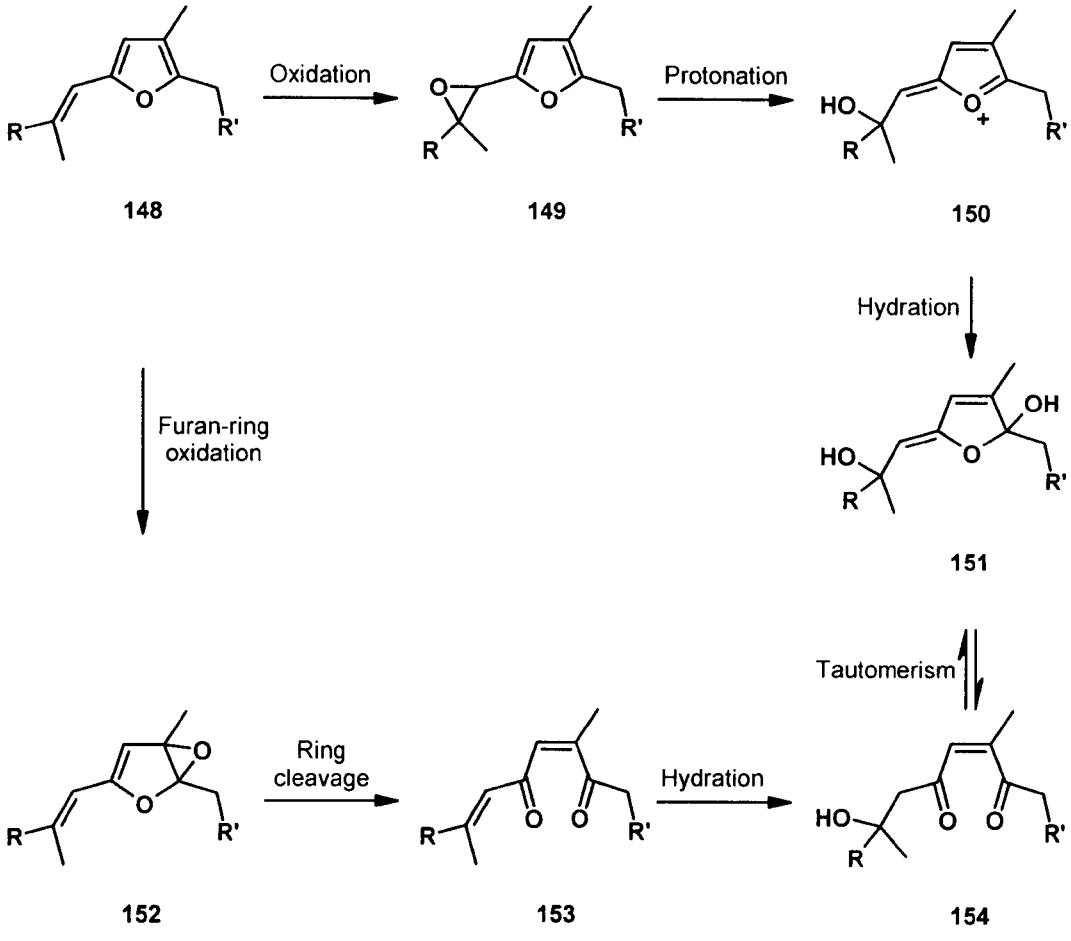
Studies of the oxidative cleavage of 2-alkenylfurans

The enol ether cyclic hemi-ketal structural motif is central to our proposed biosynthesis of the polycyclic natural products, **1**, **2** and **3**, (see Scheme 7, Scheme 9, and Scheme 10). There were doubts that tautomerism of the enedione **143** had

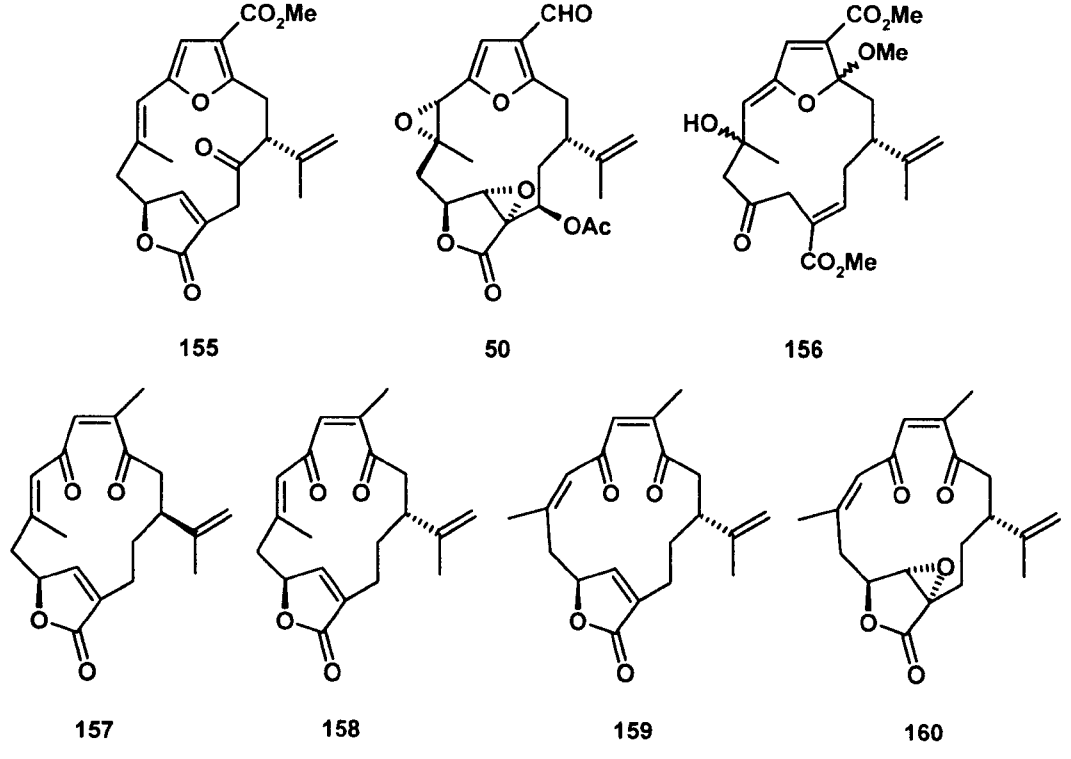
occurred in our model work to produce the enol ethers **144** and **145**. At this point in our research therefore we decided to study the synthesis of the most simple enol ether cyclic hemi-ketal structure we could imagine, *i.e.* **151**.

The enol ether cyclic hemi-ketal **151** could be produced from the epoxide **149** upon treatment with acid to catalyse the epoxide ring-opening and hydration of the subsequent oxonium species **150** (Scheme 25). Theoretically, there is also an alternative pathway to form the enol ether **151** from the alkenylfuran **148**. This sequence could be initiated by oxidative cleavage of the furan ring in **148** *via* rearrangement of the epoxide **152**, to form the dienedione moiety **153**. A regiospecific hydration of the $\Delta^{7,8}$-alkene bond in the dienedione **153** would then produce the β-hydroxyketone **154** which, *via* tautomerisation, forms the required enol ether structure **151**. Either of these routes are plausible.

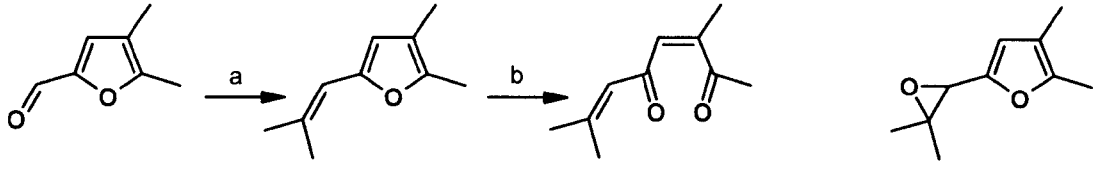
The alkenylfuran, epoxyfuran and enol ether structural units **148**, **149** and **151** are all contained within naturally occurring compounds, *e.g.* acerosolide **155**,[164] lophotoxin **50**[97] and sethukarailide **156**.[165] The dienedione functionality **153** is also present within several natural products, *i.e.* lophodione **157**,[166] epilophodione **158**,[96] isoepilophodione B (**159**)[167] and coralloidolide E (**160**).[168] These functional groups are likely to be inter-related but the sequence by which they are produced by the enzymes within the octocorals is unknown.



Scheme 25. Divergent formation of the enol ether **151** from the alkenylfuran **148**.



Bielschowskysin **1** and verrillin **2** both carry methyl substituents at C4. Hence, to effectively mirror the proposed biosynthesis the analogous model alkenylfuran **162** must also contain a methyl substituent at C3. Thus, the model alkenylfuran **162** was prepared by a Wittig reaction between isopropyltriphenylphosphoranylide and the commercially available 4,5-dimethylfuran-2-carbaldehyde **161** (Scheme 26).[169] Oxidation of the alkenylfuran **162** with a range of oxidising agents, *i.e.* *m*CPBA, dimethyldioxirane (DMDO), Dess-Martin periodinane, resulted in cleavage of the furan ring and formation of the *Z*-dienedione **163** as the sole product.[136] The epoxyfuran **164** was not produced under any of these reaction conditions. This result demonstrated that when the furan possesses a C3 methyl substituent, the furan becomes more nucleophilic towards the oxidising agents and is oxidised preferentially over the alkene functional group. Selective oxidation of the furan suggests that the second pathway, *via* the dienedione **153**, is the preferred route to the required enol ether intermediates **69**, **74** and **81**.

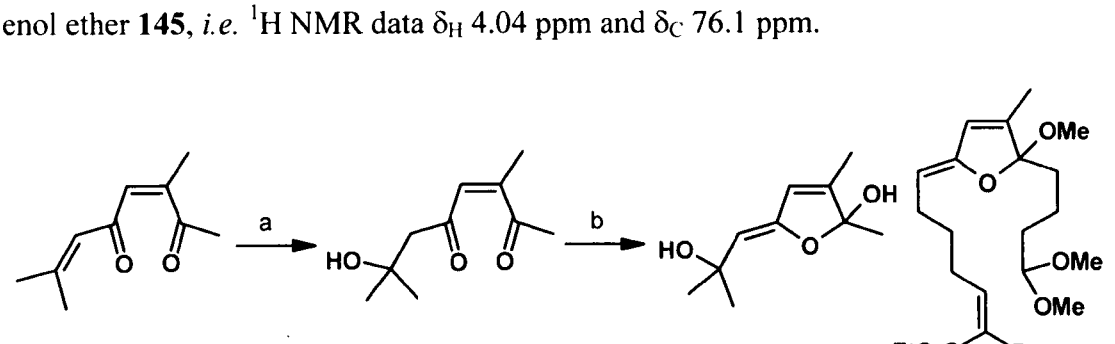


161 **162** **163** **164**

Scheme 26. *Reagents and conditions:* (a) isopropyltriphenylphosphonium iodide, ^{n}BuLi, THF, 0 °C, 30 mins; (b) *m*CPBA, CH_2Cl_2, 0 °C, 1 hr, 57% (over 2 steps).

To examine the transformation of the dienedione **163** into the enol ether intermediate **166** *via* hydration and tautomerisation, the substrate was treated with *p*-TSA in THF-H_2O, and the reaction was carefully monitored by t.l.c. and ^{1}H NMR spectroscopy. After a short period of time a new compound was present in the reaction mixture. Purification and characterisation, identified the product as the β-hydroxyketone **165**, formed by Michael addition of water into the enone functionality (Scheme 27). Upon

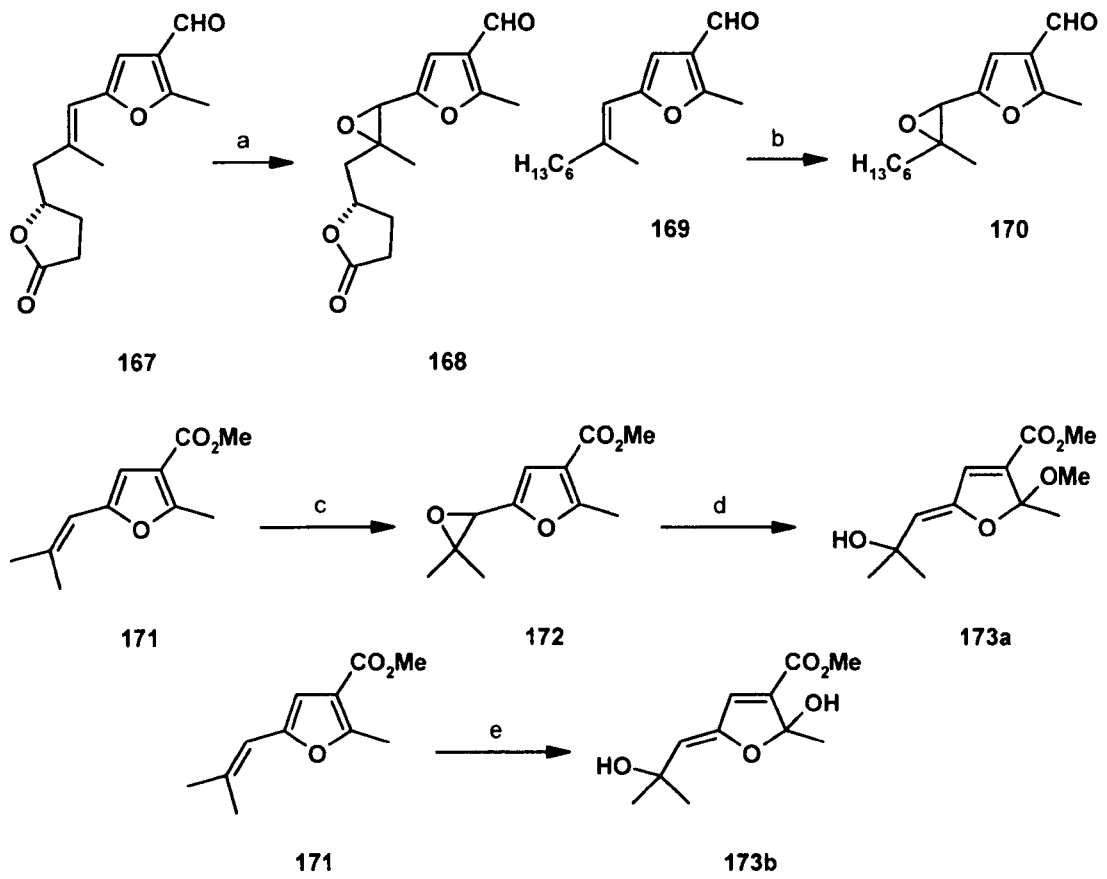
extended exposure of the dienedione **163** to the acidic conditions or by re-subjecting the β-hydroxyketone **164** to the reaction conditions, another compound was formed. After work-up and chromatography the compound showed ^{1}H NMR spectroscopic data, δ_H 4.38 ppm and δ_C 74.7 ppm, which we initially thought corresponded to the enol ether hemi-ketal **166**. By dissolving the dienedione **163** in d^8-THF and adding of one drop of water and a crystal of *p*-TSA, the reaction could be monitored efficiently by ^{1}H NMR spectroscopy. This study gave results similar to those obtained for the enol ether **145**, *i.e.* ^{1}H NMR data δ_H 4.04 ppm and δ_C 76.1 ppm.



Scheme 27. *Reagents and conditions:* (a) *p*-TSA (cat.), THF, H_2O, r.t., 20 hrs, 10%; (b) *p*-TSA, THF, H_2O, r.t., 20 hrs, 11%.

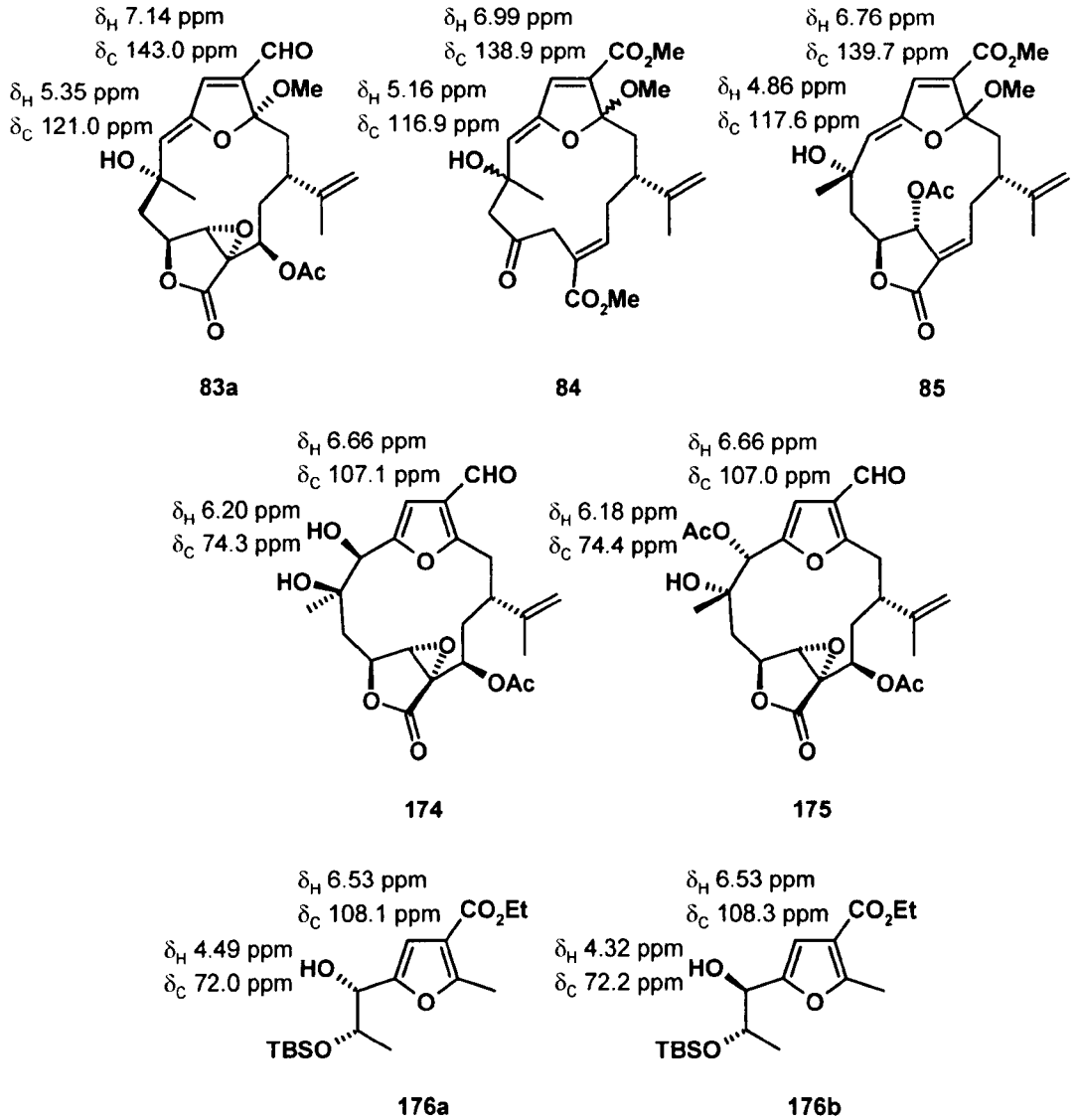
Studies by another colleague in our research group, attempted to produce the analogous C3-methoxycarbonyl substituted enol ether structural motif **173a** (Scheme 28) seen in the natural product sethukarailide **156**.[165] This work demonstrated that the alkenylfurans, *i.e.* **167**, **169** and **171**, bearing an electron-withdrawing substituent at the C3 furan position, *i.e.* CO_2Me or CHO, could be oxidised selectively with *m*CPBA or dimethyldioxirane (DMDO) to produce the corresponding epoxyfurans **168**, **170**[170] and **172**. The variation in the pattern of oxidation of the alkenylfurans **167**, **169** and **171** no doubt reflects the impact the ester/ aldehyde functional group has in deactivating the furan ring towards epoxidation in **171** relative to **162**, *i.e.* behaving as a vinylogous carbonate.[170] Attempts were made to form the enol ether fragment

173a from **172** *via* epoxide ring-opening and quenching the intermediate oxonium species using *p*-TSA in methanol. The product obtained after work-up and chromatography, showed ^{1}H NMR spectroscopic data, δ_H 6.59 ppm for the α,β-unsaturated carbonyl and δ_H 3.95 ppm for the enol ether, and the compound was assigned to the enol ether structure **173a**. This result was supported by the formation of the enol ether **173b** produced by running the oxidation reaction under different conditions. When the furan **171** was oxidised with DMDO at -40 °C and the reaction was warmed to room temperature the main product isolated was the enol ether **173b** having ^{1}H NMR spectroscopic data, δ_H 6.56 ppm and δ_C 108.7 ppm for the α,β-unsaturated ester and δ_H 4.43 ppm and δ_C 74.5 ppm for the enol ether substituent.



Scheme 28. *Reagents and conditions:* (a) *m*CPBA, CH_2Cl_2, r.t., 2 hrs, 85%; (b) *m*CPBA, CH_2Cl_2, r.t., 2 hrs, 43%; (c) DMDO, Me_2CO, -40 °C, 2.5 hr, 84%; (d) *p*-TSA (cat.), MeOH, r.t., 1 hr, 87%; (e) DMDO, Me_2CO, -40 °C to r.t., 15 hr, 70%.

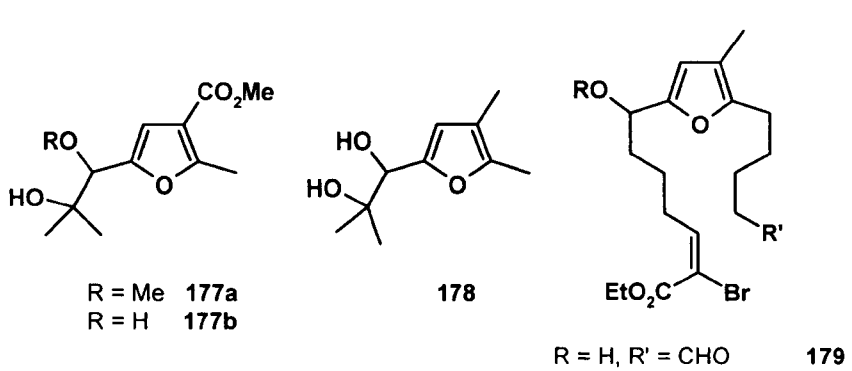
Comparison could now be made between the NMR spectroscopic data for the enol ether compounds **173a** and **173b** and the natural products, **83a**, **84** and **85** shown in Scheme 29.[107,126,127] The enol ether natural products have NMR spectroscopic data ranging from δ_H 6.8-7.1 ppm and δ_C 139-143 ppm for the C5 alkene, and δ_H 4.9-5.4 ppm and δ_C 117-121 ppm for the C7 alkene bond. This spectroscopic data differ with the observed data for the supposed synthetic enol ethers, *i.e.* **173a** and **173b**, by a minimum δ_H ~0.2 ppm and δ_C ~30 ppm for the C5 alkene but δ_H ~0.4 ppm and δ_C ~42 ppm for the C7 alkene. The differences in NMR spectroscopic data, especially the carbon data, between the synthetic and the natural enol ether substituents was worrying and confusing. A further examination of natural products which have been isolated from the gorgonian octocorals provided an answer. The spectropscopic data reported for lophodiol B (**174**)[171] and the acetyl analogue **175**[107] differ from the supposed synthetic enol ether structures by a minimum of δ_H ~0.1 ppm and δ_C ~2 ppm for the C5 alkene bond, and δ_H ~1.8 ppm and δ_C ~0 ppm for the C7 alkene functionality. The reason for the C7 alkene proton in the lophodiol natural products **174** and **175** being a lot more deshielded, and hence further downfield, in comparison to the model system **173a** and **173b** is unknown. Although, the rigidity enforced by the macrocycle may cause a deshielding effect on this proton by the furan ring and produce the large difference in ^{1}H NMR spectroscopic data. Therefore, comparison with the analogous models **176a** and **176b**[172] supports the alternative furanmethanol structure since the minimum differences in NMR spectroscopic data were, δ_H ~0.0 ppm and δ_C ~0 ppm for the furans, and δ_H ~0.1 ppm and δ_C ~2 ppm for the secondary alcohol functionalities. With both the proton and carbon NMR spectroscopic data for the intermediates **173a** and **173b** and lophodiol B (**174**), showing close similarity, we concluded that the enol ether functionality *i.e.* **166** was not formed in our reactions.



Scheme 29. Spectral data for a range of enol ether and furanmethanol natural products, *i.e.* **83a**, **84-85** and **174-175**.

Instead, the products of a presumed isomerisation, *i.e.* the furanmethanols **177a** and **177b**, were produced. This outcome also relayed back to the corresponding furan model substrates, **166**, **144** and **145** which, after analysis, also suggested that they had furanmethanol structures (*cf.* **178-180** shown in Scheme 30), and not the enol ether functionality as originally thought. These observations would also explain why difficulties were observed when trying to induce the [2+2] intramolecular cycloaddition of intermediates **179** and **180**. Therefore, it is probably unlikely that the enol ether natural products **83a**, **84** and **85** are produced from the corresponding

epoxyfuran substrates because acid-catalysed epoxide ring-opening produced the vicinal diol functionality seen in lophodiol B (**174**).



R = Me **177a**
R = H **177b**

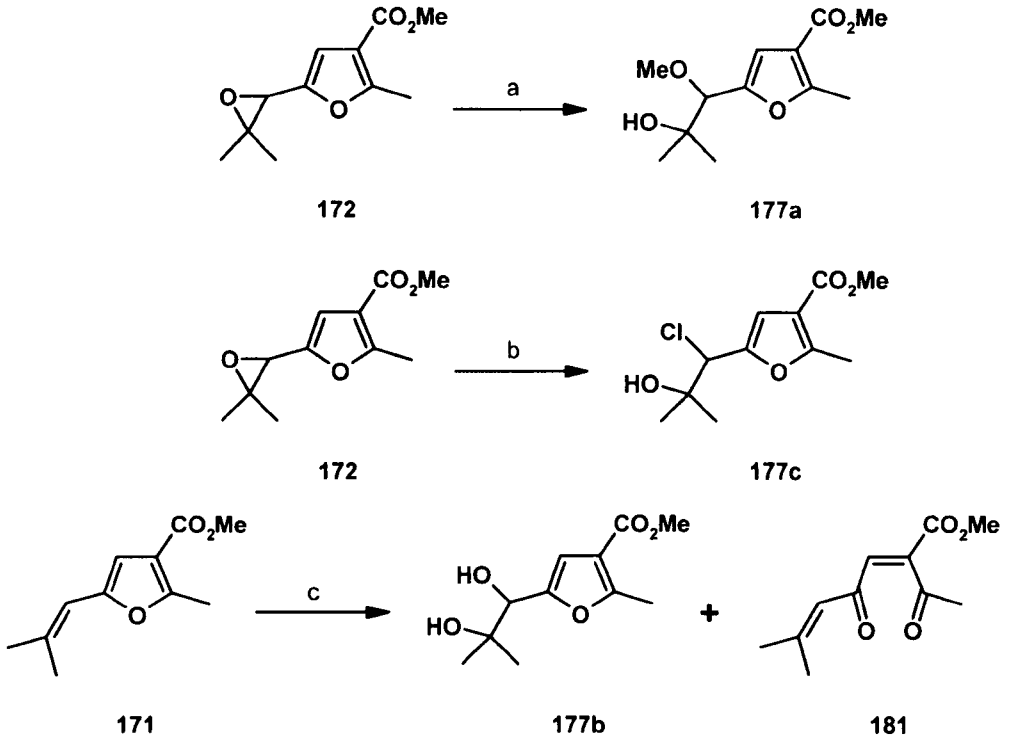
178

R = H, R' = CHO **179**
R = Me, R' = $C(OMe)_2$ **180**

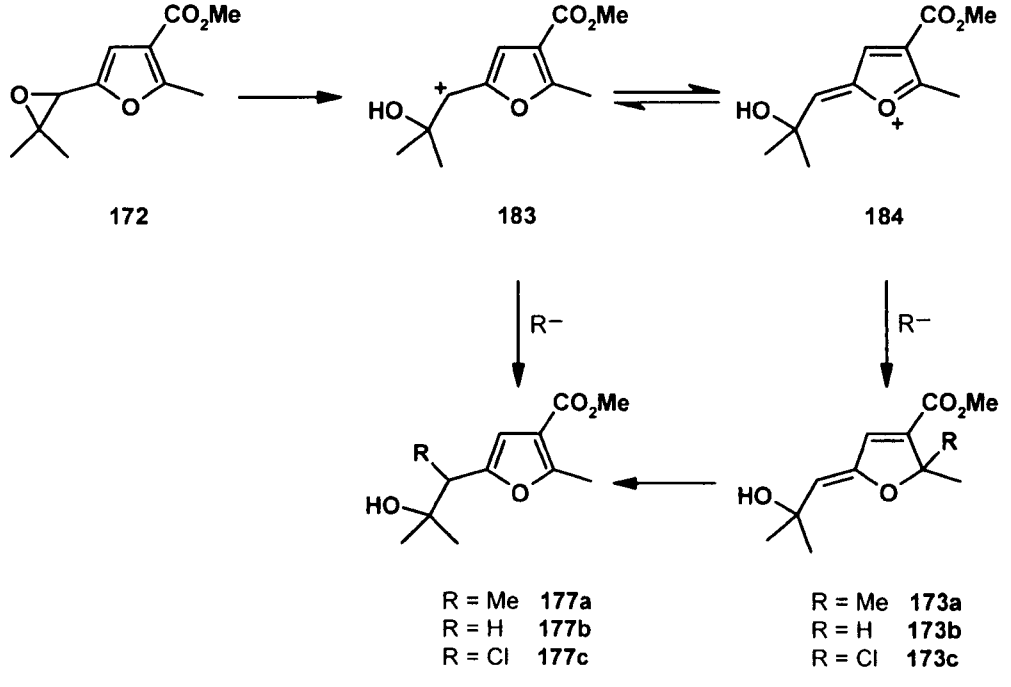
Scheme 30. Corrected structures for the furanmethanol intermediates **177-180**.

The vicinal diol methyl ether **177a** was formed upon treatment of the epoxyfuran **172** with *p*-TSA in methanol. This result was complemented by altering the conditions to aqueous 2M HCl in DCM in order to obtain the corresponding chlorohydrin **177c** (Scheme 31) with ^{1}H NMR spectroscopic data, δ_H 6.67 ppm and δ_C 110.7 ppm for the furan and δ_H 4.84 ppm and δ_C 64.8 ppm for the chloride functionality. A trace quantity (6%) of the dienedione **181**[173] was also observed on oxidation of the alkenylfuran **171** at room temperature alongside the major product, *i.e.* the vicinal diol **177b**.

The vicinal diol methyl ether **177a**, the vicinal diol **177b**, and the chlorohydrin **177c** are presumed to be formed *via* straightforward opening of the epoxide **172** (Scheme 32). This could occur by acid-catalysed ring-opening in a S_N2 process or *via* the stabilised carbocation intermediate **183**. Alternatively, nucleophilic quenching of the oxonium species **184**, an isomer of carbocation **183**, with subsequent allylic transposition of the enol ethers **173a**, **173b** and **173c**, would also result in the products **177a**, **177b** and **177c**, but no evidence for this pathway was obtained.



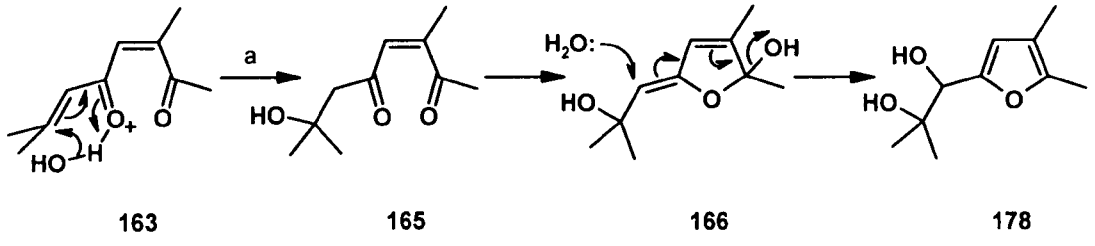
Scheme 31. *Reagents and conditions:* (a) *p*-TSA (cat.), MeOH, r.t., 1 hr, 87%; (b) 2M $HCl_{aq.}$, CH_2Cl_2, r.t., 12 hr, 57%; (c) DMDO, Me_2CO, -40 °C to r.t., 15 hr, 70% (**177b**), 6% (**181**).



Scheme 32. The proposed formation of the furanmethanol products, **177** from the epoxyfuran **172**.

The formation of the furanmethanol structures **177a**, **177b** and **177c** occurs *via* the epoxyfuran **172** but the vicinal diol **178** is produced *via* a different synthetic sequence

utilising the dienedione **163**. With the β-hydroxyketone **165** present in the reaction, it suggests that the enol ether cyclic hemi-ketal **166** is a transient species *en route* to the vicinal diol **178** (Scheme 33). Tautomerisation of the β-hydroxyketone **165** to the enol ether **166**, would then allow the vicinal diol **178** to be produced by either an intramolecular allylic transposition or intermolecular isomerisation facilitated by water. These results suggest that the enol ether functionalities seen in **83a**, **84** and **85** are not produced by epoxide ring-opening followed by quenching the oxonium species with water, even though epoxyfurans are prevalent in Nature. The labile enol ether functionality is probably produced in Nature *via* Michael addition of water into a dienedione substituent, with subsequently tautomerisation. All of the enol ether natural products isolated *i.e.* **83-85**, contain an electron withdrawing functionality at the C4 position. Therefore, isolation of an enol ether containing compound could be achieved if this same sequence is applied to the dienedione **181**.



163 **165** **166** **178**

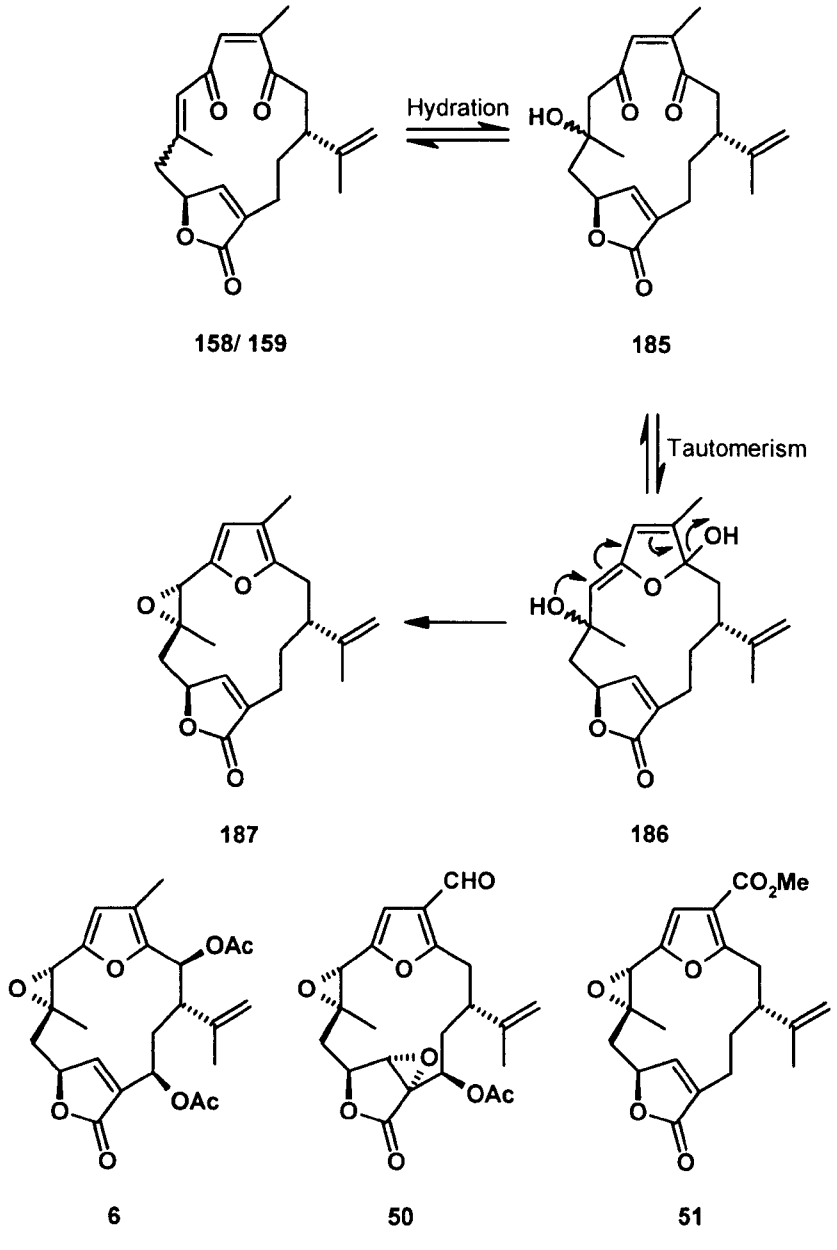
Scheme 33. The formation of the vicinal diol **178** from the dienedione **163**, *via* the enol ether **166**.

The epoxyfuran – based natural products, bipinnatin G (**6**),[6] lophotoxin **50**[97] and pukalide **51**,[98] could be produced from epilophodione **158**[96] or isoepilophodione B (**159**)[167] along a similar sequence to that shown in the model dienedione **163**. Thus, hydration of the $\Delta^{7,8}$-alkene bond could take place at either face of the enone functionality of epilophodione **158** or isoepilophodione B (**159**) leading to the mixed β-hydroxyketone functionality found within rubifol **185**[167] (Scheme 34). Tautomerisation of rubifol **185** would then lead to form the enol ether **186**, which

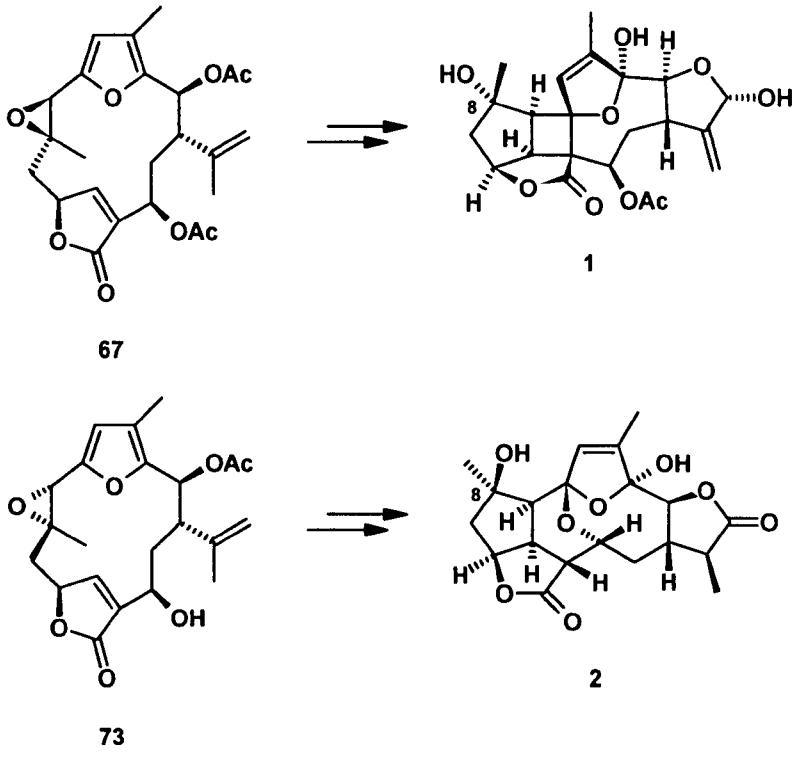
upon intramolecular nucleophilic addition of the tertiary alcohol into the enol ether cyclic hemi-ketal functionality would form the epoxyfuran product **187**, and release water. The hydration and tautomerism processes should be reversible, but upon production of the epoxyfuran **187**, derived form the corresponding *E*-$\Delta^{7,8}$-alkene, the furan and the epoxide functional groups would be orthogonal, rigidifying the macrocycle, and hence becoming an irreversible process. The epoxyfuran derived from the *Z*-$\Delta^{7,8}$-alkene would have more degrees of freedom and therefore the furan could destabilise the epoxide function to reverse the process back into the dienedione **158** or **159** *via* the enol ether **186**. The epoxide and the butenolide substituents in the epoxyfuran natural products, *e.g.* **6**, **50** and **51**, are always disposed *anti*-relative to each other. The reversibility of the hydration/ tautomerism sequence would allow the macrocycle to find the lowest energy conformation and hence consistently allow the epoxide functionality to be formed *anti* to the butenolide substituent.

Another indication that both bielschowskysin **1** and verrillin **2** are most likely produced from a dienedione functionality *via* a hydration/ tautomerism sequence, is the C8 tertiary hydroxyl functional groups. The two natural products, **1** and **2** have opposite hydroxyl group configurations at C8. Originally, this difference was thought to be derived from *iso*-bipinnatin G (**67**) and the bipinnatin G analogue **73** but if this were true there would be some epoxyfuran natural products which possess an epoxide functionality *syn* to a butenolide substituent, like intermediate **67**. This is not the case and all epoxyfuran natural products show the relative configuration displayed in intermediate **73** (Scheme 35). Therefore, the alcohol geometry shown within the two natural products could originate *via* hydration to either face of the $\Delta^{7,8}$-alkene bond of

the corresponding *E*- or *Z*-dienedione functionality leading to a rubifol **185**[167] analogue which possess a C8 hydroxyl group as a mixture of diastereoisomers.

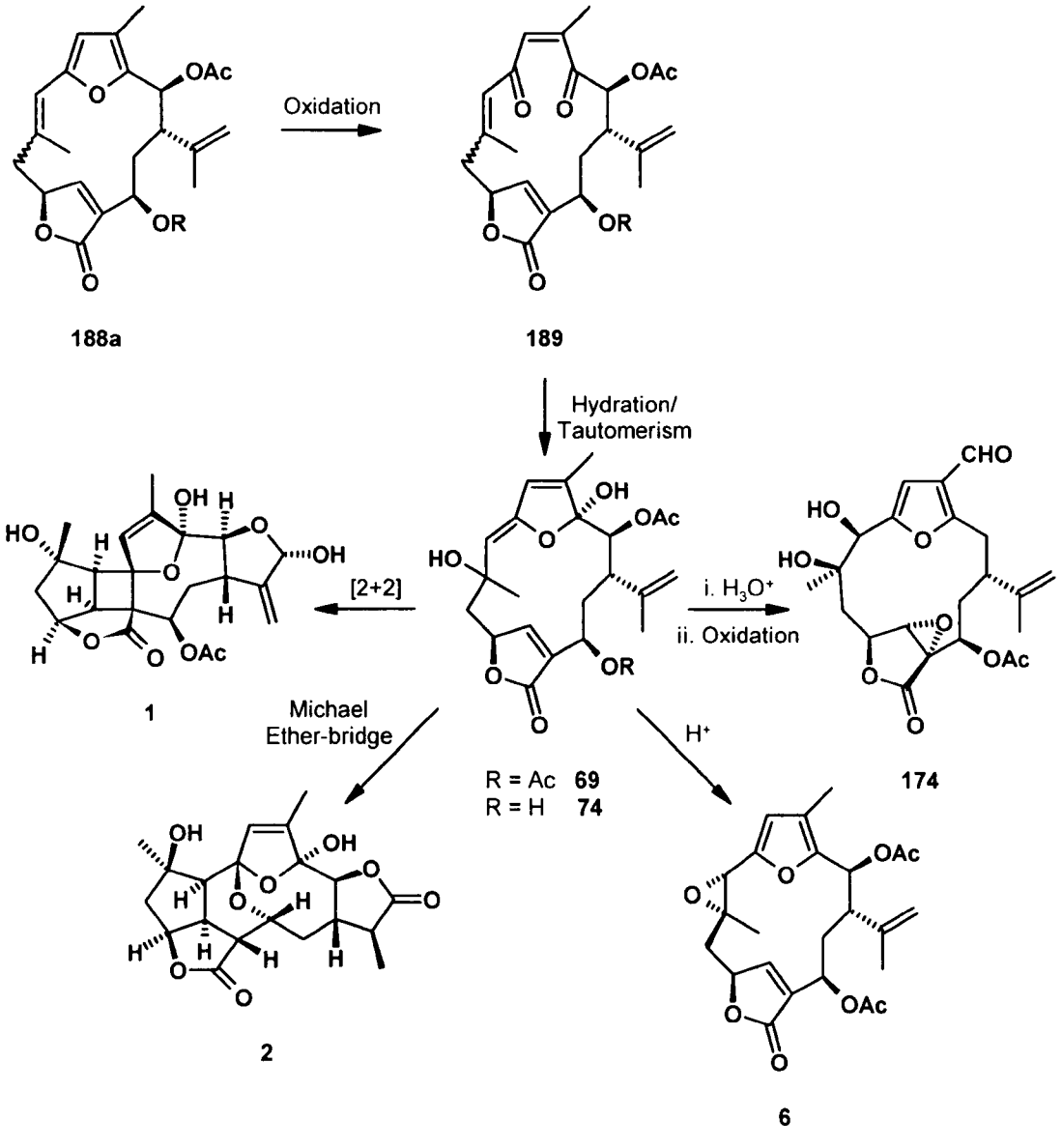


Scheme 34. Proposed formation of epoxyfurans, *e.g.* bipinnatin G (**6**), lophotoxin **50** and pukalide **51**, from dienediones, *e.g.* epilophodione **158** and isoepilophodione B (**159**).



Scheme 35. Proposed epoxyfuran intermediates **67** and **73** used to access bielschowskysin **1** and verrillin **2**.

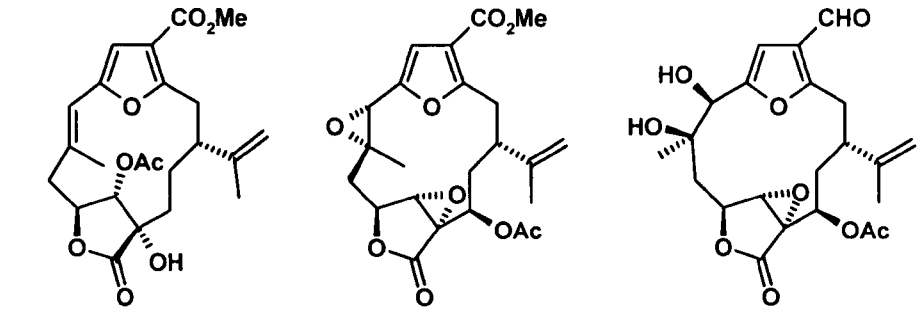
Our proposed biosynthesis of bielschowskysin **1** and verrillin **2** is still thought to occur *via* transannular processes involving the enol ether intermediates **69** and **74**. The enol ethers **69** and **74** are now thought to be derived from the alkenylfuran functionality **188a** which, upon oxidative ring cleavage of the furan ring, together with hydration of the $\Delta^{7,8}$-alkene bond in the dienedione product **189** and tautomerisation produce this key intermediate. Further manipulation of the enol ether functionality could then produce the epoxyfurans, **6**, **50** and **51**, the furanmethanols, **174** and **175**, and the polycyclic natural products, bielschowskysin **1** and verrillin **2**, as summarised in Scheme 36.



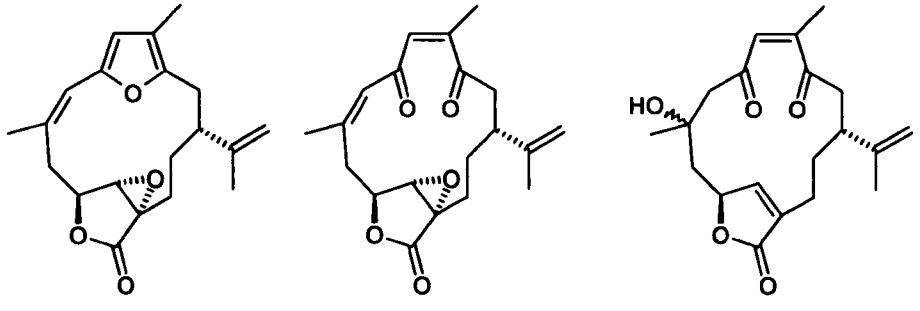
Scheme 36. Proposed transformation of the enol ethers **69** and **74** into a variety of natural products.

The functionalities seen in the model systems have all been observed previously within furanobutenolide – based cembrane natural products, except for the vicinal diol **178** containing a methyl group at C3 and the dienedione **181** possessing a methyl ester substituent at C3. The alkenylfuran functionalities are represented by the furanocembranes sethukarailin **190**[165] and coralloidolide A (**191**).[174] The epoxyfuran lopholide **192**[100] and the *Z*-dienedione coralloidolide E (**160**)[168] contain the functionalities observed when alkenylfurans are oxidised. Under acidic conditions

within an enzyme system in octocorals, lophodiol B (**174**)[171] and rubifol **185**[167] could potentially be produced.

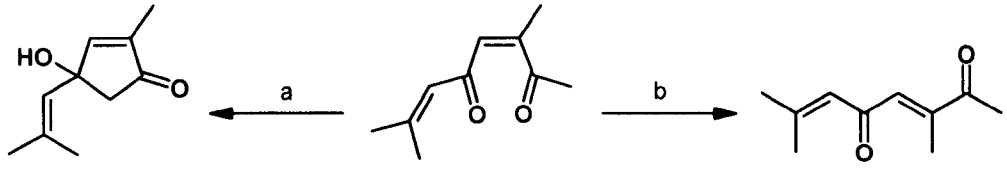


190 **192** **174**



191 **160** **185**

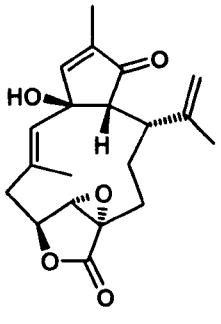
With the disappointment of not being able to isolate an enol ether cyclic ketal structures under acidic conditions, we questioned whether or not this functionality could be obtained under base catalysis. Thus, the dienedione **163** was treated with K_2CO_3 in THF-H_2O at room temperature, but again no evidence was obtained for formation of an enol ether structure. Instead the 4-hydroxycyclopent-2-enone **193** was isolated in 53% yield, resulting from intramolecular aldolisation (Scheme 37).



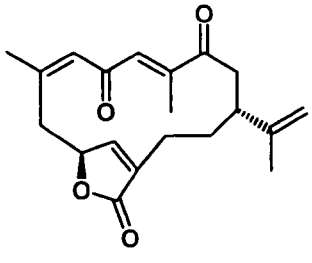
193 **163** **194**

Scheme 37. *Reagents and conditions:* (a) K_2CO_3, THF, H_2O, r.t., 20 hrs, 53%; (b) I_2, $CHCl_3$, r.t., 20 hrs, 90%.

Interestingly, some of the cembranoids isolated from the coral *Alcyonium coralloides*, also accommodate 4-hydroxycyclopentenone units within their macrocyclic structures, *e.g.* coralloidolide F (**195**).[175] It seems highly likely therefore that these compounds are produced *in vivo* by straightforward aldolisation of *Z*-dienedione – based cembranoids, similar in constitution to **160**. Also, in a separate study, and not surprisingly, when a solution of the *Z*-dienedione **163** in chloroform was stood in the presence of iodine overnight, it was isomerised to the corresponding *E*-isomer **194** in essentially quantitative yield (Scheme 37). Once again this observation could have significance in connection with the likely origin of macrocyclic *E*-dienediones, *e.g.* **196**, from furanocembrane precursors in corals, *i.e.* by oxidative cleavage of their furan rings followed by *Z*- to *E*-isomerisation of the resulting *Z*-dienediones.[166]



195

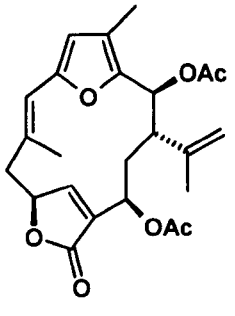


196

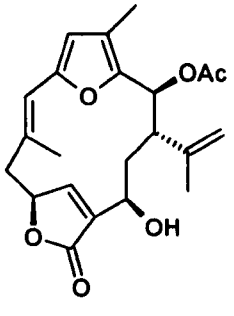
Although an enol ether functionality had not been isolated and characterised in our studies, we believe that it could have been produced as a transient species. Therefore, it was hoped that by forming an enol ether cyclic ketal functionality within a macrocyclic structure, *i.e.* structures **69** and **74**, conformational bias would allow the anticipated [2+2] transannular cycloaddition process to occur, leading to the natural products bielschowskysin **1** and verrillin **2**.

Ring-closing metathesis (RCM) approach to furanobutenolide – based cembranes 188b and 188c

The deceptively simple 14-membered macrocyclic furanobutenolide – based cembrane structures **188b** and **188c** are, in fact, very strained due to the furan and butenolide substitution patterns which are accommodated in the relatively small ring system. For this reason furanocembrane structures have been challenging synthetic targets. Since 1975, when pukalide **51** was isolated by Scheuer,[98] a great deal of work has been produced in this area of research in order to overcome the problems associated with the ring strain of the macrocycle and to gain perspective into the chemistry of furanobutenolide – based cembranes. Over the past 34 years several methods have been utilised to close the furanocembrane macrocyclic structure including, Nozaki-Hiyama-Kishi (NHK), Wadsworth-Emmons olefination, Stille cross-coupling and furan ring formation *via* a radical cascade. All of these processes produced the required macrocycle of a furanobutenolide – based cembrane compound, but with varying degrees of success.



188b

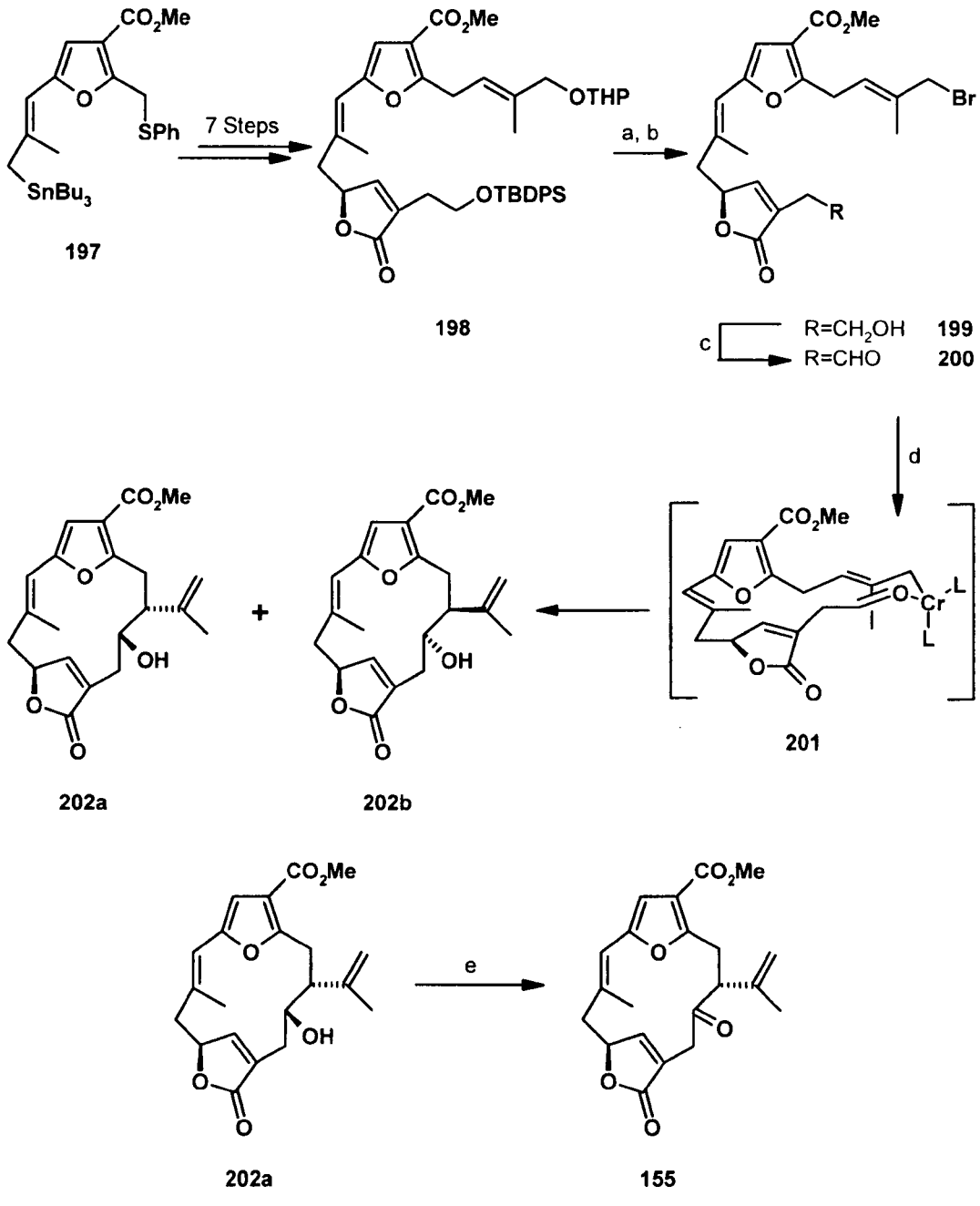


188c

Paquette *et. al.* have made large efforts in synthesising furanocembrane natural products.[176-179] Paquette's method to close the furanocembrane macrocycle was by the use of a chromium mediated Nozaki-Hiyama-Kishi (NHK) macrocyclisation reaction from an acyclic precursor. This key process was used in a concise and convergent

route to the natural product, acerosolide **155** (Scheme 38). The synthesis started with the allylic stannane **197**, which was converted over seven relatively simple steps to the vinyl furan **198**. Functional group conversion from the THP-protected allylic alcohol to the allylic bromide was achieved with bromine in the presence of di(phenylphosphine)ethane. Subsequent desilylation of this intermediate using hydrogen fluoride gave the alcohol **199**. The newly formed alcohol function was then oxidised to the aldehyde **200** using PDC in DCM. This produced the precursor for the macrocyclisation reaction containing both an aldehyde and an allylic bromide functional group. The key NHK macrocyclisation event[180-182] was achieved by treatment of the precursor **200** with $CrCl_2$ in THF at room temperature for 36 hours. During this period of time the allylic bromide **200** underwent transformation into an allylic chromate species which subsequently coordinated to the aldehyde function, forming a metal-mediated macrocycle. At the periphery of the macrocycle, a 6-membered ring transition state **201** is formed which exists in two chair conformations. Macrocyclisation gave rise to the two diastereomeric products **202a** and **202b** with the isopropenyl unit and the alcohol being transposed *anti* to each other, but unfortunately only a 20% yield was achieved.

The final stage was to oxidise the alcohol functionality formed during the NHK reaction to the corresponding ketone. Due to the nature of acerosolide **155**, only the product **202a** could be used in the final oxidation reaction. Thus, treatment of intermediate **202a** with PDC in DMF produced the natural product acerosolide **155** in a low 25% yield.

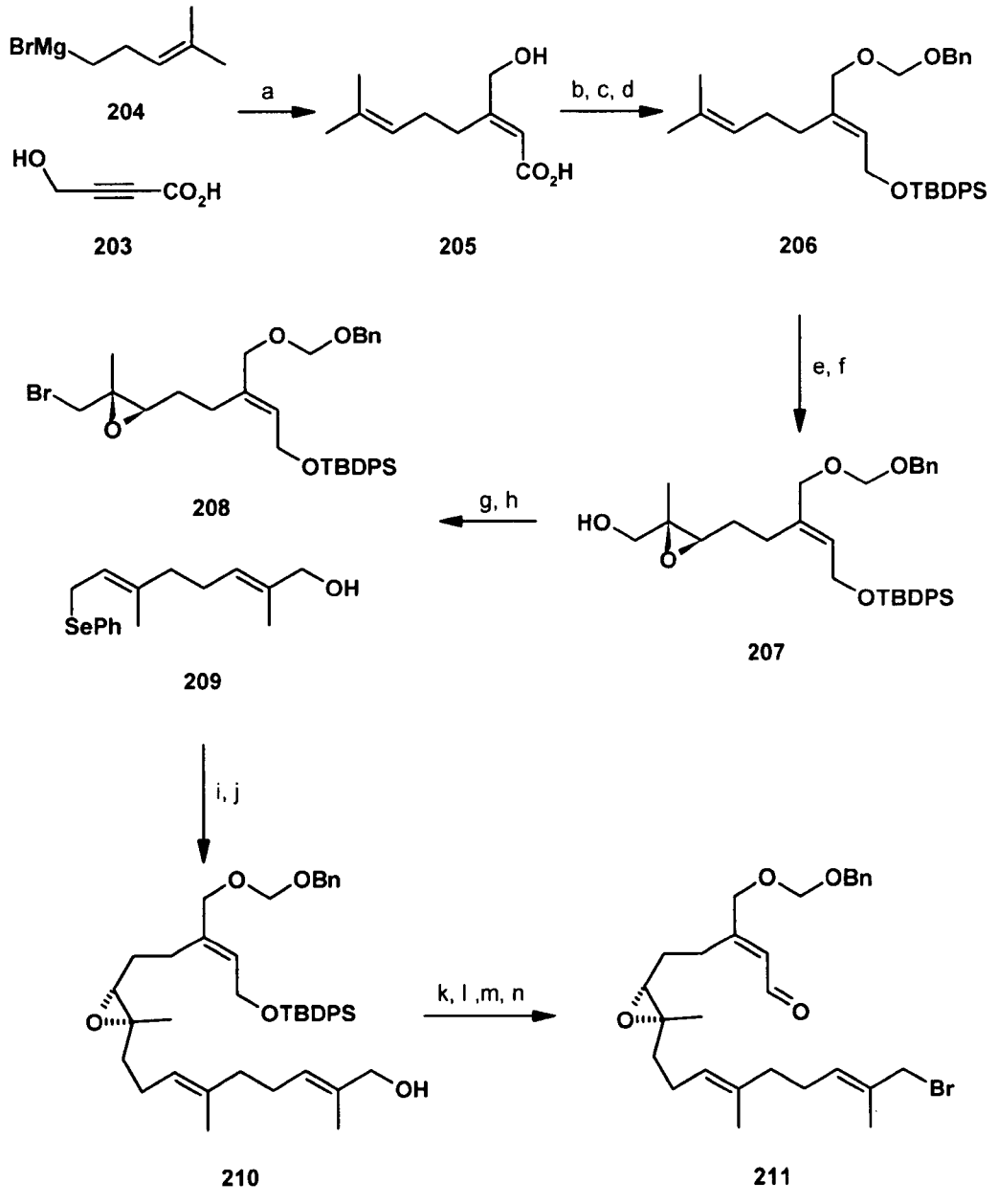


Scheme 38. *Reagents and conditions:* (a) dppe, Br_2, CH_2Cl_2, 0 °C, 2 hrs, 64%; (b) HF, MeCN, r.t., 3 hrs, 68%; (c) PDC, 4 Å MS, CH_2Cl_2, 0 °C, 3hrs, 46%; (d) $CrCl_2$, THF, 20 °C, 36 hrs, 20%; (e) PDC, 4 Å MS, DMF, r.t., 2 hrs, 25%.

The total synthesis of acerosolide **155** achieved by Paquette *et al.* was based on previous work reported by Still *et al.* in 1983,[183] which used the NHK macrocyclisation process to form the 14-membered cembranoid structure of asperdiol **215**. The synthesis started with *iso*-hexenylmagnesium bromide **204** (Scheme 39) which was added to the substituted tetrolic acid **203** at -78 °C in the presence of

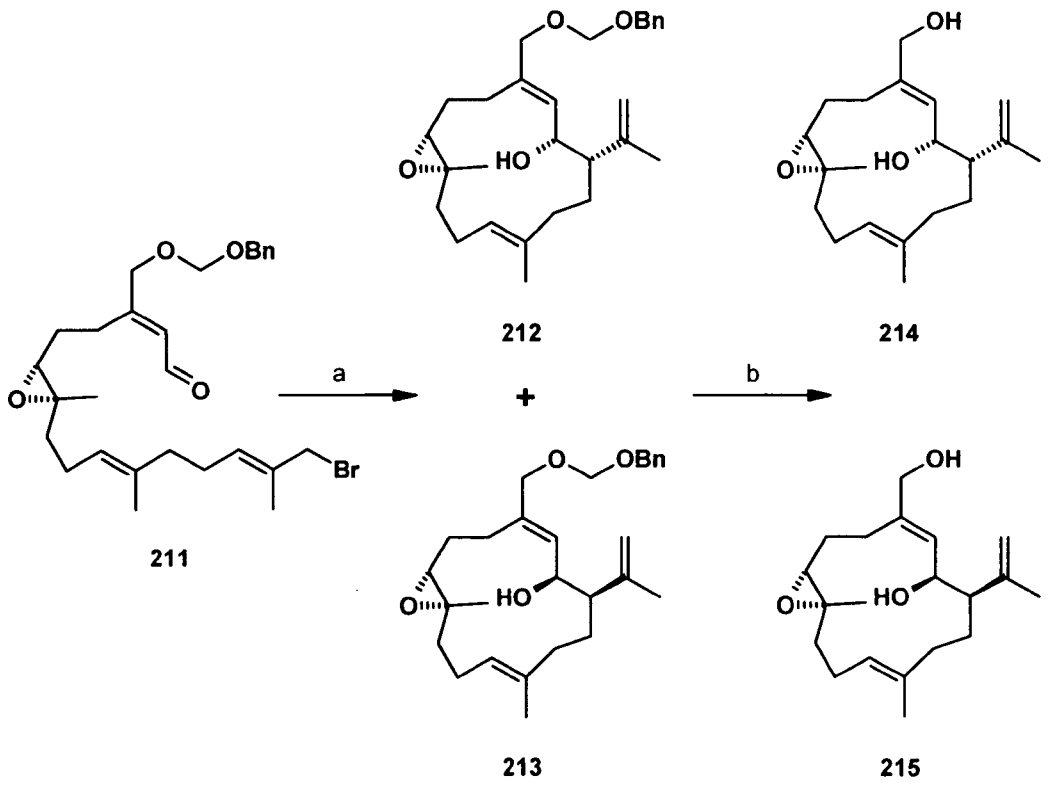
Li_2CuCl_4. This formed the corresponding organocuprate *in-situ* which, underwent conjugate addition into reagent **203** to form the corresponding *E*-hydroxy acid **205**. Protection of the hydroxyl group in **205** as the (benzyloxy)methyl derivative followed by reduction of the carboxylic acid with $LiAlH_4$ produced an allylic alcohol. The allylic alcohol was subsequently protected as the silyl-ether utilising TBDPS-Cl which formed intermediate **206**. The epoxy alcohol **207** was simply formed by an allylic oxidation using SeO_2 and ^tBuOOH which implemented the hydroxyl group to direct the stereoselective epoxidation. Mesylation of the epoxy alcohol **207** followed by displacement using LiBr in acetone generated the epoxy bromide **208**. The allylic selenide **209** produced from geranyl acetate, was doubly deprotonated with LDA, and the dianion was alkylated at low temperature on addition of the epoxy bromide **208**. The installed phenyl selenium functionality was then simply removed utilising Raney nickel in acetone, which upon chromatography over $AgNO_3$ impregnated silica gel, formed epoxide **210.** To produce the NHK precursor **211**, the allylic alcohol **210** was transformed to the corresponding allylic chloride and the TBDPS-silyl ether was subsequently deprotected with TBAF. Oxidation of the resulting alcohol to the aldehyde function was achieved using MnO_2 and transformation of the allylic chloride to the allylic bromide with LiBr in THF produced the NHK precursor **211**.

Exposure of intermediate **211** to $CrCl_2$ under high dilution efficiently affected the transformation to the two diastereomeric macrocyclic compounds **212** and **213** in 64% yield with a 4:1 ratio for the required intermediate **213**. Finally deprotection of the (benzyloxy)methyl group utilising sodium in ammonia at -78 °C produced the natural cembranoid asperdiol **215** and the diastereoisomer **214** shown in Scheme 40.



Scheme 39. *Reagents and conditions:* (a) **204**, Li_2CuCl_4, THF, -78 °C to r.t., 75%; (b) $BnOCH_2Cl$, $^iPr_2NEt$; (c) $LiAlH_4$, Et_2O; (d) TBDPS-Cl, Im, DMF, 60% (over 3 steps); (e) SeO_2, ^tBuOOH; (f) $VO(acac)_2$, ^tBuOOH; (g) MsCl, Et_3N; (h) LiBr, Me_2CO, 60% (over 4 steps); (i) **209**, LDA, THF, -55 °C, then **208**, -70 °C, 5 mins, 82%; (j) Raney-Ni, Me_2CO, 95%; (k) $(Me_2N)_3P$, CCl_4, THF, 87%; (l) 1M TBAF, THF, 94%; (m) MnO_2, CH_2Cl_2, 75%; (n) LiBr, THF, 95%.

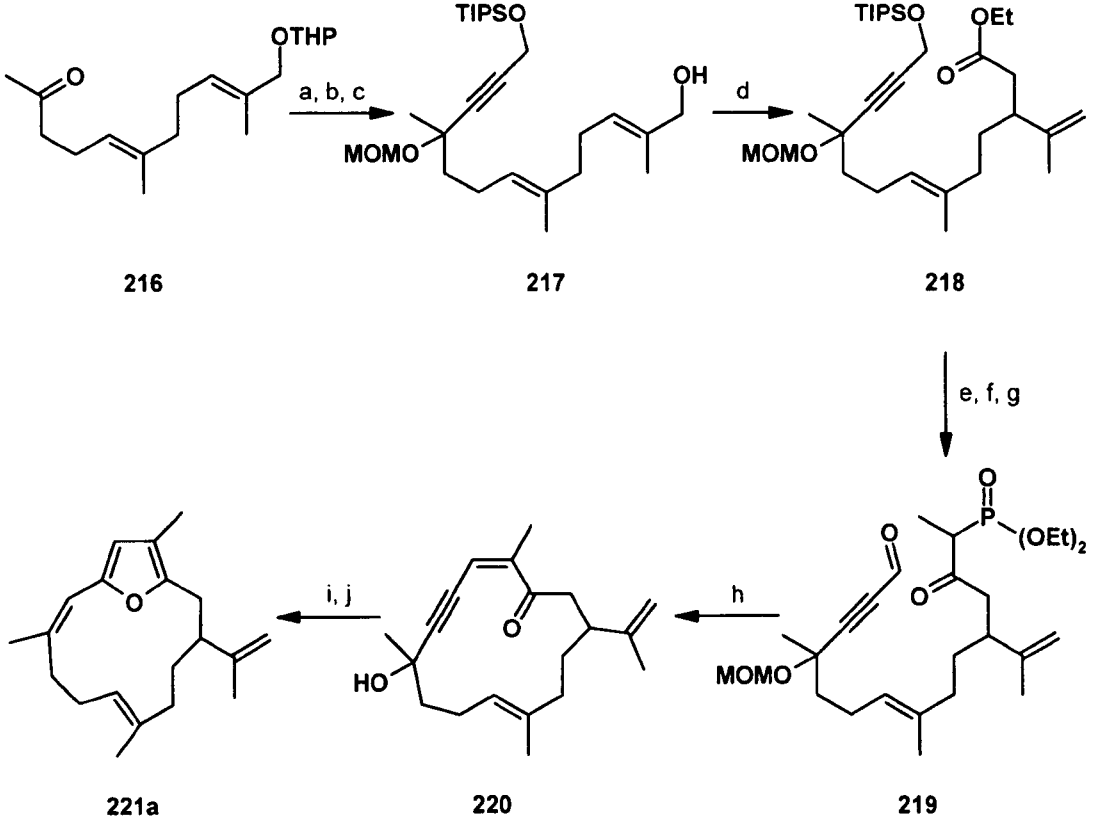
Work published by Marshall and DuBay in 1994[184] towards the rubifolide analogue **221a** demonstrated that a Wadsworth-Emmons olefination could be employed as a macrocyclisation process in order to construct the furan functionality (Scheme 41). The synthesis began from the THP-protected allylic alcohol **216**, formed by allylic



Scheme 40. *Reagents and conditions:* (a) $CrCl_2$, THF, r.t., 6 hrs, 64%; (b) Na/NH_3 -78 °C, 1 min, 51%.

oxidation of geranylacetone with SeO_2-^{t}BuOOH and protection of the resulting alcohol substituent. Deprotonation of TIPS-protected propargyl alcohol with ^{n}BuLi formed the lithiated species which underwent addition into the ketone functionality of intermediate **216** to form the tertiary alcohol substituent. The allylic alcohol **217** was produced by protection of the alcohol functionality as its MOM-ether followed by deprotection of the primary alcohol functional group with PPTS in MeOH. The isopropenyl substituent could now be introduced by a homologation procedure. Treatment of the allylic alcohol **217** with trimethylorthoacetate induced the Johnson orthoester rearrangement[185] to form the ester **218** in 97% yield as a 1:1 mixture of diastereoisomers. The aldehyde **219** was then formed from the intermediate **218** *via* addition of the lithiated diethyl ethylphosphonate species into the ester substituent, deprotection of the propargyl alcohol with TBAF-AcOH and finally oxidation utilising the Swern protocol. The Wadsworth-Emmons macrocyclisation process[130]

could now be examined. Thus, treatment of the aldehyde **219** with DBU and LiCl at room temperature induced the olefination process to form the macrocyclic enone **220** albeit in an unoptimised 42% yield. Reduction of the enone functionality with DIBAL-H and treatment of the corresponding allylic alcohol under basic conditions induced formation of the furan ring to produce the fuanocembrane rubifolide analogue **221a** in high yield.



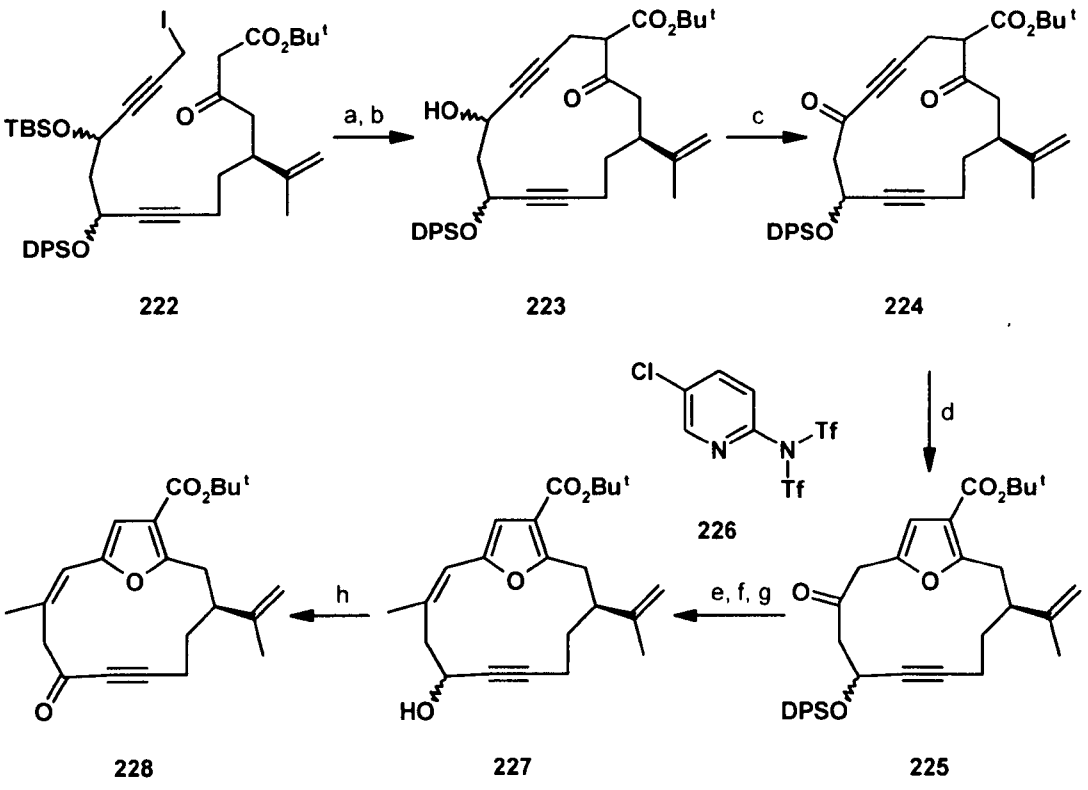
Scheme 41. *Reagents and conditions:* (a) 3-[(triisopropylsilyl)oxy]-1-propyne, ^{n}BuLi, THF, 0 °C, 15 mins, then **216**, THF, -78 °C to 0 °C, 2 hrs, 71%; (b) $^{i}Pr_2NH$, MOMCl, CH_2Cl_2, 0 °C, 6 hrs, 88%; (c) PPTS, MeOH, r.t., 24 hrs, 62%; (d) trimethylorthoacetate, propionic acid, 140 °C, 1 hr, 97%; (e) ethyl diethylphosphonate, ^{n}BuLi, THF, -78 °C, 15 mins, then **218**, -78 °C to 0 °C, 15 mins, 70%; (f) TBAF, $MeCO_2H$, THF, 0 °C to r.t., 2.5 hrs, 89%; (g) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t., 5 mins, 99%; (h) DBU, LiCl, MeCN, r.t., 2 hrs, 42%; (i) DIBAL-H, Et_2O, -78 °C, 15 mins, 93%; (j) ^{t}BuOK, 18-crown-6, ^{t}BuOH, THF, r.t., 1.5 hrs, 88%.

In 2007 Darias *et al.* isolated (+)-deoxypukalide from the Pacific octocoral *Leptogorgia* sp.,[186] originally in 2001 Marshall and Van Devender synthesised its (–)-enantiomer **232**.[187] The synthetic material correlated structurally and stereochemically to the natural substance but deviated in optical rotation, having an equal but opposite

value. This recently isolated furanobutenolide is similar structurally to pukalide **51**[98] except it is devoid of epoxy functionality at the C7,C8 position. This synthesis was achieved using a carbanion displacement of a propargylic iodide function to form the macrocycle in the initial stages, which was then later reacted with silver (I) nitrate to form the butenolide fragment in the final stages (Scheme 42 and Scheme 43). The synthesis started with the acyclic precursor **222**, which was subsequently deprotonated at the β-keto ester position to allow an S_N2 displacement of the iodide. Selective cleavage of the TBS-ether group in intermediate **222** was achieved slowly using PPTS in ethanol over a 10 day period to produce the α-hydroxyl alkyne macrocycle **223**. Oxidation of the alcohol function was simply achieved with Dess-Martin periodinane (DMP) to give the ketone **224**. Exposure of the ketone **224** to silica gel in hexanes produced the carboxy furan **225** in one, high yielding step. Reaction with Comins' pyridyl triflimide reagent **226**[188] gave a mixture of diastereomeric enol triflates, which rearranged through Pd-catalysed coupling with Me_2Zn to give the trisubstituted *Z*-alkene function. Removal of the DPS-protecting group using TBAF afforded the alcohol **227**. Oxidation, again using DMP, simply converted the alcohol **227** into the ketone **228** in high yield.

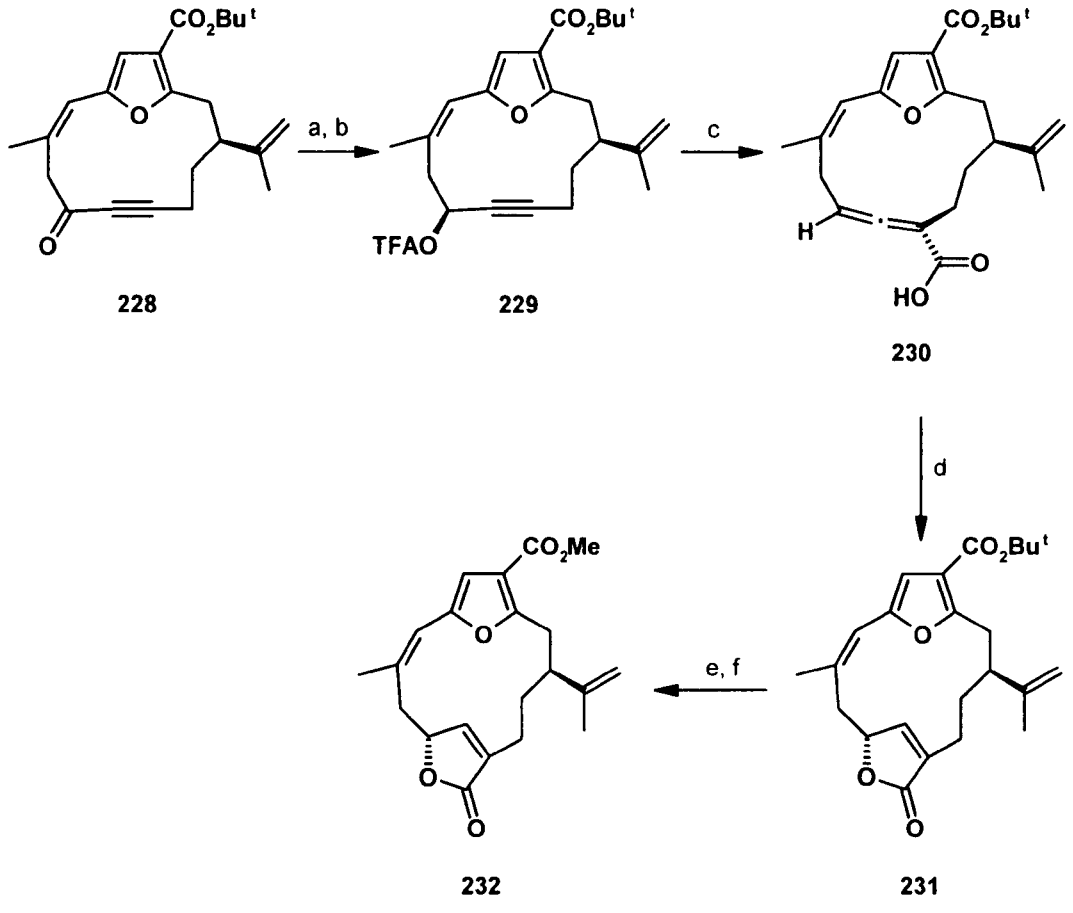
The completion of the (–)-deoxypukalide **232** synthesis is shown in Scheme 43. The ketone **228** was selectively reduced using K-selectride, which gave rise to the single diastereomeric, *cis*-propargylic alcohol and conversion to the trifluoroacetate functional group gave the intermediate **229**. Palladium catalysed carbohydroxylation produced the allenoic acid **230** which, without purification, was reacted in the presence of 10% $AgNO_3$ on silica gel in hexanes to produce the butenolide fragment **231**. Finally, functional group inter-conversion from the *tert*-butoxy ester to the

carboxylic acid using high temperature pyrolysis followed by conversion to the methoxy ester using TMS-diazomethane produced (–)-deoxypukalide **232**.



Scheme 42. *Reagents and conditions:* (a) KO'Bu, THF, -78 °C, 83%; (b) PPTS, EtOH, 10 days, 80%; (c) DMP, Et_3N; (d) silica gel, hexanes, 96% (over 2 steps); (e) **226**, LiHMDS, 75%; (f) Me_2Zn, $Pd(PPh_3)_4$, 91%; (g) TBAF, 85%; (h) DMP, Et_3N.

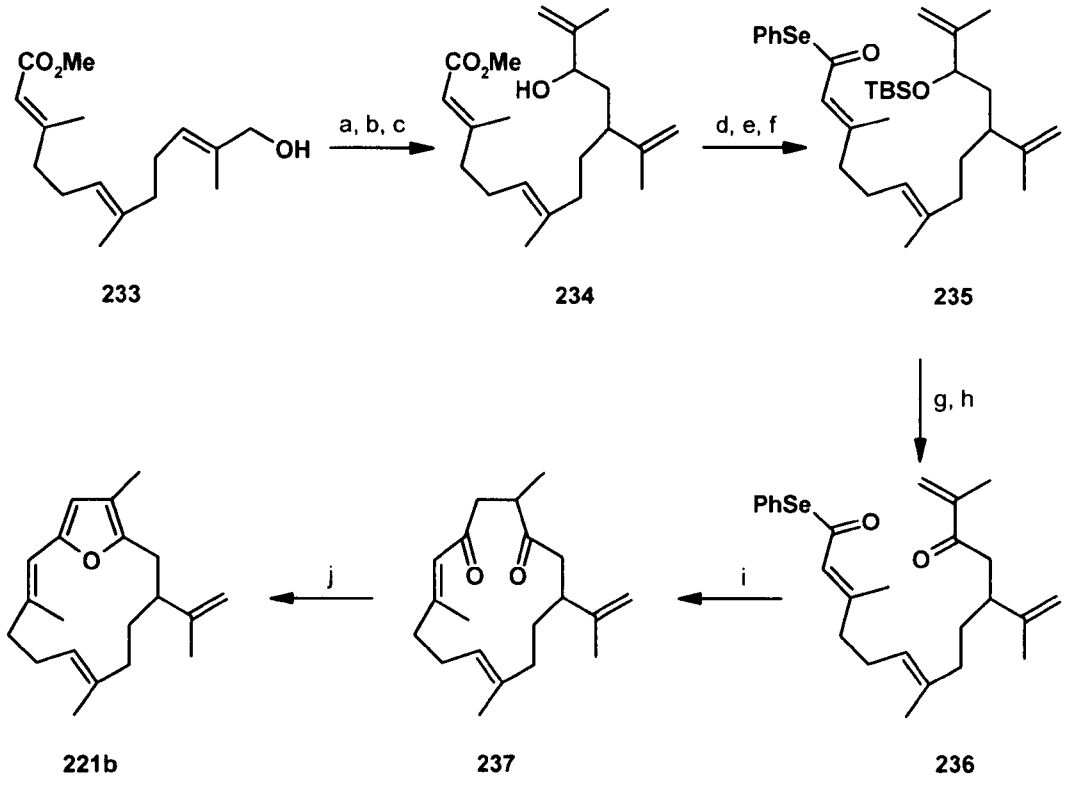
Earlier work from our own research group aimed to synthesise a furanocembranoid structure **221b** *via* a novel free-radical cascade approach (Scheme 44).[189] The synthesis utilised an acyl radical species[190,191] to induce a 14-*endo*-trig intramolecular macrocyclisation to produce the furan substituent of the rubifolide analogue **221b**. The synthesis commenced with the allylic alcohol **233**, produced by regiospecific allylic oxidation of methyl (*E,E*)-farnesoate on treatment with SeO_2 and ^tBuOOH. The alcohol functionality of the allylic alcohol **233** was converted into a vinyl ether, which upon heating induced a Claisen rearrangement[192] to form the corresponding γ,δ-unsaturated aldehyde. Treatment of the aldehyde with isopropenylmagnesium



Scheme 43. *Reagents and conditions:* (a) K-selectride; (b) TFAA; (c) $Pd(PPh_3)_4$, CO, 2,6-lutidine, TFA, 0 °C, THF, H_2O; (d) 10% $AgNO_3$, silica gel, hexanes, 58% (over 3 steps); (e) 210 °C; (f) $TMSCHN_2$, 92% (over 2 steps).

bromide at 0 °C next formed the carbinol **234** in good overall yield. The selenoester **235** was produced by protection of the secondary alcohol as its TBS-ether, sponification of the methyl ester to the corresponding carboxylic acid and treatment with phenylselenol in the presence of 1,1′-carbonyldiimidazole (CDI) to form the required selenide product. Deprotection of the intermediate **235** was achieved with TMS-OTf at -90 °C to form the secondary alcohol functionality, which upon treatment with PCC underwent oxidation leading to the enone radical precursor, **236**. Finally, a refluxing solution of the selenoester **236** was treated with tributyltin hydride and AIBN for 3 hours and upon work-up and chromatography the dione **237** was produced as a 1:1 mixture of diastereoisomers, in a combined 40% yield. The dione

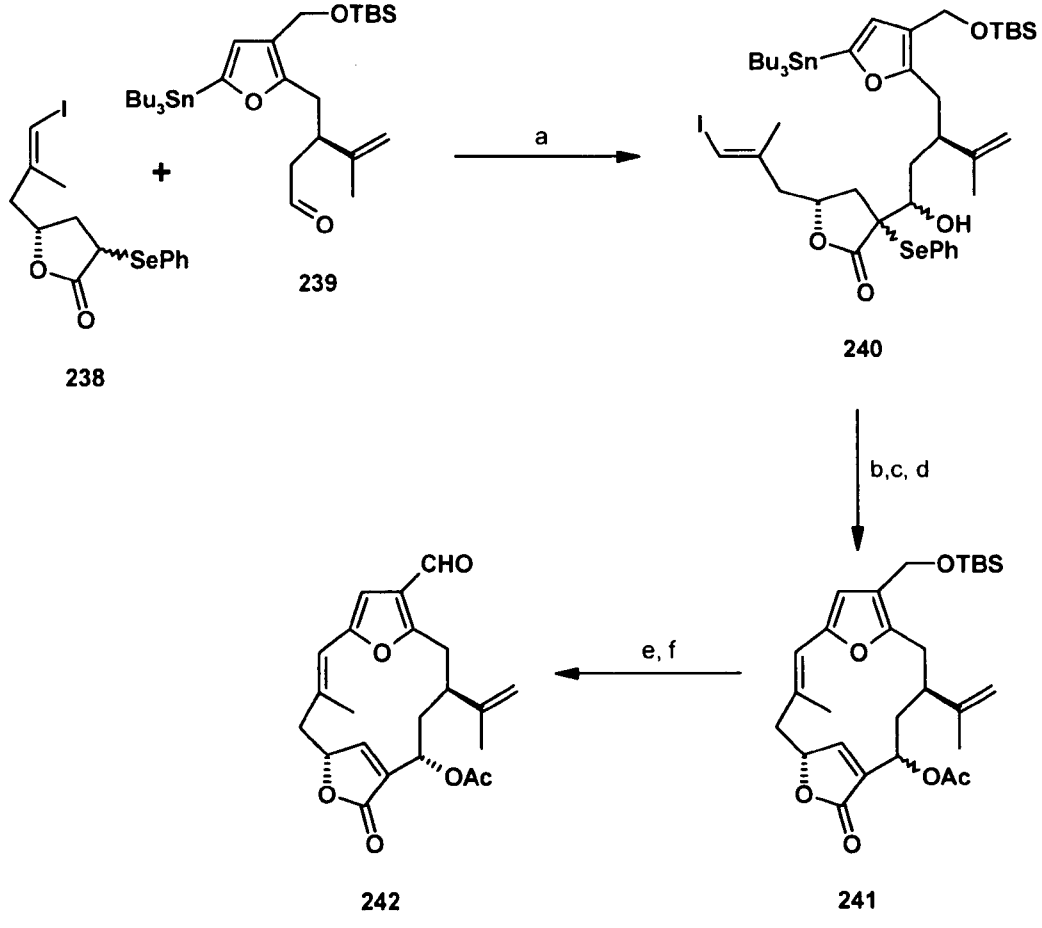
237 was then subjected to acidic conditions, *i.e.* TsOH in refluxing $CHCl_3$, and gave the furanocembrane macrocyclic structure **221b** in 50% yield.



Scheme 44. *Reagents and conditions:* (a) H_2C=CHOEt, Hg(OAc), reflux, 16 hrs, 79%; (b) 140 °C, 2 hrs, 97%; (c) isopropenylmagnesium bromide, THF, 0 °C, 30 mins, 82%; (d) TBSCl, Im, DMF, r.t., 18 hrs, 90%; (e) K_2CO_3, MeOH, reflux, 18 hrs, 49%; (f) PhSeH, Im_2CO, DMF, r.t., 2 hrs, 61%; (g) TMS-OTf, CH_2Cl_2, -90 °C, 25 mins, 95%; (h) PCC, CH_2Cl_2, -85 °C to r.t., 20 hrs, 41%; (i) Bu_3SnH, AIBN, PhH, reflux, 3 hrs, 40%; (j) TsOH, $CHCl_3$, reflux, 3.5 hrs, 50%.

Later, *bis*-deoxylophotoxin **242**[170,193] was synthesised in our group using a Pd-mediated Stille cross-coupling reaction[131] to form the furanocembrane macrocycle at the 5-position of the furan ring (Scheme 45). The synthesis started with (*R*)-epichlorohydrin and ethyl 2-bromomethyl-3-furoate to synthesise the α-phenylselenolactone **238** and the stannylfuran **239**, in 8 steps and 11 steps, respectively. These two fragments were then coupled together by deprotonation of the lactone ring **238** using LiHMDS followed by addition of the aldehyde **239**, which generated the alkylated product **240**. The phenylselenide residue was selectively eliminated into the lactone ring of **240** by oxidation using H_2O_2 to generate the

butenolide substituent. Macrocyclisation was then achieved by an intramolecular Stille cross-coupling reaction[194,195] to generate the trisubstituted alkenylfuran function, which was acetylated *in-situ* to give a mixture of acetyl protected, furanocembrane epimers **241**, but only in 20% yield. Subsequent removal of the TBS group on the furan using CSA in methanol revealed the alcohol, which allowed the acetyl protected diastereoisomers to be separated. Finally, the separated α-acetate epimer was oxidised using DMP in DCM to produce the furanocembrane *bis*-deoxylophotoxin **242**.

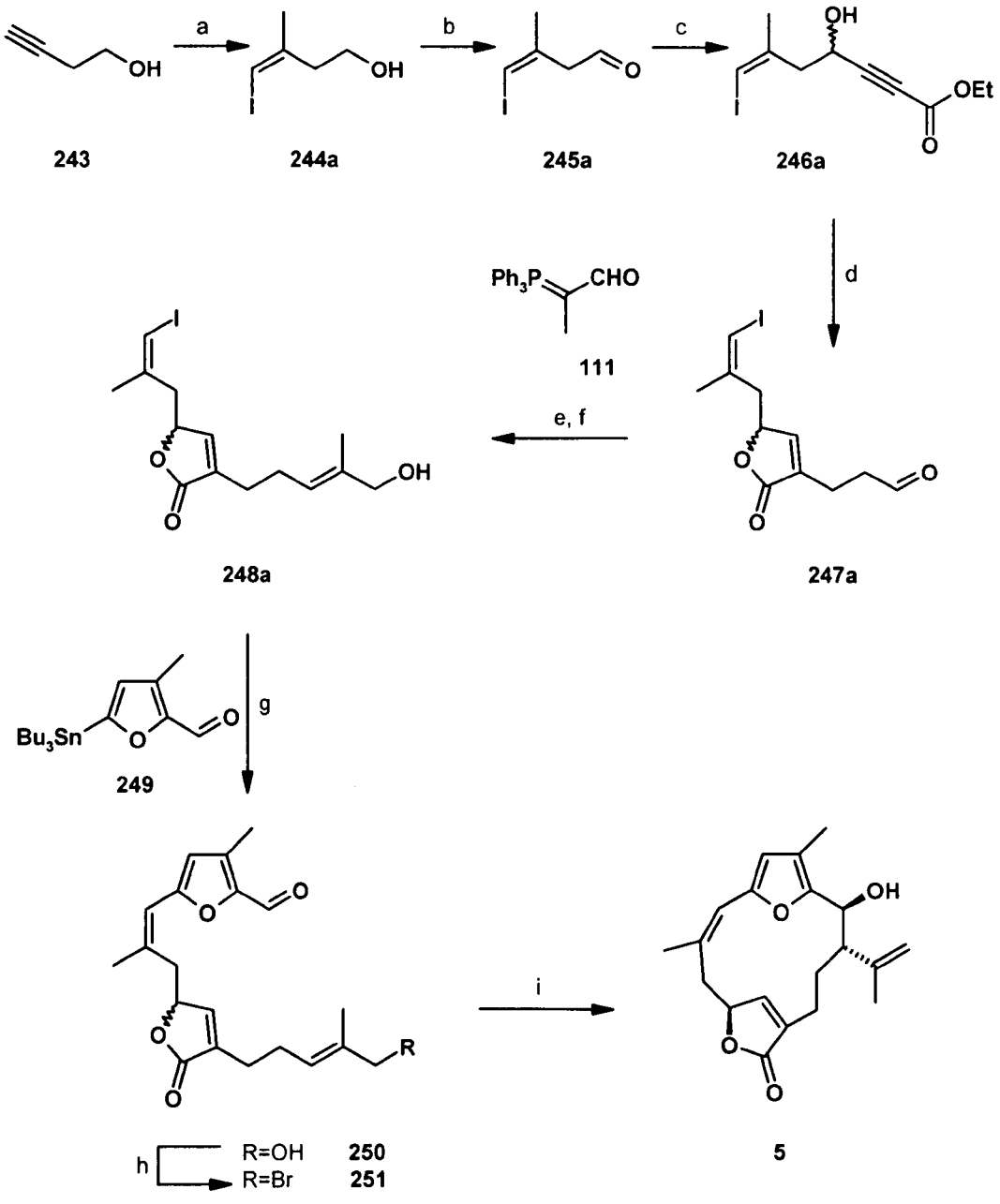


Scheme 45. *Reagents and conditions:* (a) **238**, LiHMDS, -78 °C, 10 mins; then **239**, 50 mins, 93%; (b) H_2O_2, CH_2Cl_2/ pyridine, 1 hr; (c) $AsPh_3$, Pd_2dba_3, 40 °C, 14 hrs, 20%; (d) Ac_2O, Et_3N, DMAP, r.t., 4 hrs, 54%; (e) CSA, MeOH, CH_2Cl_2, 3 hrs, 0 °C, 78%; (f) DMP, pyridine, CH_2Cl_2, 3 hrs, 0 °C, 61%.

A synthesis of racemic bipinnatin J (**5**) was first published by Trauner *et al.*[196] in 2006 using a nine step stereoselective sequence (Scheme 46). The synthesis utilised an Alder-ene reaction, a Stille cross coupling and NHK macrocyclisation to establish the

furanocembrane structure. The synthesis started with commercially available 3-butynol **243** which underwent zirconium-mediated carboalumination. Chelation controlled isomerisation at elevated temperature of the aluminium species followed by iodination produced the *Z*-vinyl iodide **244a**.[197] Oxidation of the alcohol function in **244a** was achieved using DMP in DCM to form the sensitive β,γ-unsaturated aldehyde **245a**. A lithiated ethyl propiolate species was then directly added to the reactive aldehyde **245a** leading to the propargylic alcohol **246a**. The next stage was a ruthenium (II)-catalysed enyne reaction, which was later described as a Trost Alder-ene reaction.[146] The alkyne function installed in intermediate **246a** was reacted with allyl alcohol **110** and under the reaction conditions the resulting enol tautomerised to the terminal aldehyde **247a** and the butenolide was formed from the γ-hydroxy α,β-unsaturated ester *via* intramolecular transesterification. A Wittig reaction on aldehyde **247a** with phosphorane **111**[198] produced an α,β-unsaturated aldehyde function which was subsequently reduced using $NaBH_4$ leading to the allylic alcohol **248a**. The previously installed vinyl iodide function was then used in an intermolecular Stille cross coupling reaction[131,194,195] with the stannylfuran aldehyde **249** to produce the alkenylfuran aldehyde **250** in high yield. Finally, conversion of the allylic alcohol **250** to the corresponding allylic bromide using NBS in the presence of PPh_3 produced the precursor **251** to (±)- bipinnatin J (**5**).

The final stage in the synthesis was the intramolecular NHK coupling[180-182] in the presence of $CrCl_2$ and $NiCl_2$ which produced bipinnatin J (**5**) in greater than 9:1 diastereomeric ratio and in 59% yield. This result suggested that one of the 6-membered chair transition states (similar to that shown in the synthesis of acerosolide **155**) was lower in energy and was hence formed preferentially.

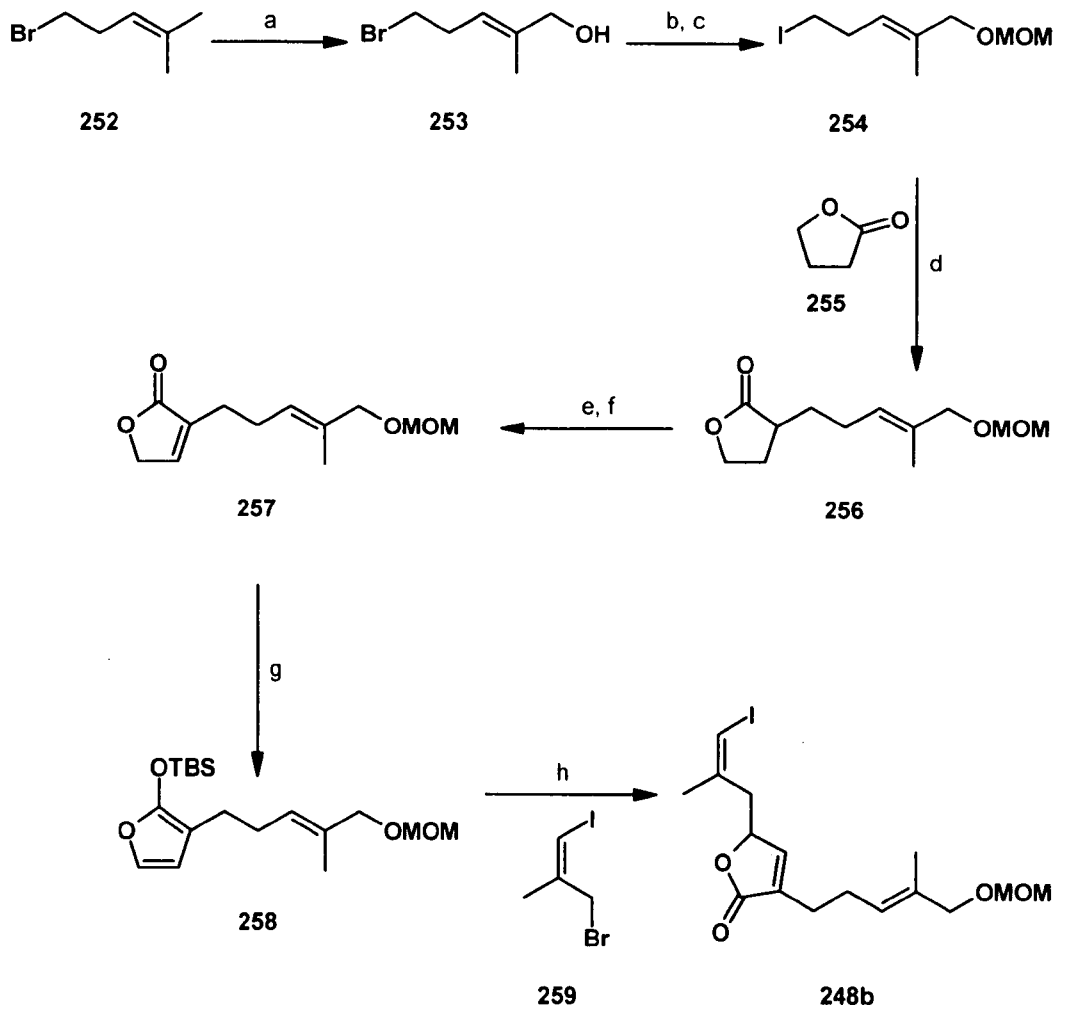


Scheme 46. *Reagents and conditions:* (a) $AlMe_3$, Cp_2ZrCl_2, CH_2Cl_2, r.t., 72 hrs, then I_2, -30 °C to r.t., 3 hrs, 60%; (b) DMP, CH_2Cl_2, $NaHCO_3$, r.t., 15 mins; (c) ethyl propiolate, LDA, THF, -78 °C, 30 mins, 66% (over 2 steps); (d) allyl alcohol, 5 mol% $RuCp(MeCN)_3PF_6$, CSA, THF, Me_2CO, 50 °C, 90 mins, 52%; (e) **111**, PhH, reflux, 12 hrs, 71%; (f) $NaBH_4$, MeOH, 20 mins, r.t., 99%; (g) **249**, $Pd(PPh_3)_4$, CuI, CsF DMF, 20 mins, r.t., 92% (h) PPh_3, NBS, CH_2Cl_2, -5 °C, 20 mins, 87%; (i) $CrCl_2$, $NiCl_2$·DME, 4 Å MS, THF, r.t., 12 hrs, 59%.

In a companion publication, Rawal *et al.* also reported a total synthesis of bipinnatin J (**5**).[199] The synthesis used similar chemistry to that previously shown Trauner *et al.* and also produced the natural product in racemic form. The total synthesis began with an allylic oxidation of 5-bromo-2-methyl-2-pentene **252** in the presence of SeO_2 and

^{t}BuOOH to produce the *E*-allylic alcohol **253** (Scheme 47). The allylic alcohol **253** was next protected as its MOM-ether, which then allowed the bromide function to be easily converted into the corresponding iodide **254** *via* a Finkelstein reaction. With the iodide **254** in place, γ-butyrolactone **255** was deprotonated using LDA-HMPA at -78 °C to produce the enolate species which, on addition of the iodide **254** led to the alkylated γ-butyrolactone **256**. At this stage the butenolide function was installed by deprotonation of the γ-butyrolactone **256**, and upon addition of PhSeCl the reaction was quenched to form a phenylselenide intermediate. Oxidation of the phenylselenium functionality by treatment with H_2O_2 allowed for a regioselective selenoxide elimination to occur to produce the butenolide **257**. Finally, the butenolide **257** was elaborated further by γ-alkylation. This transformation was achieved by trapping the enolate of intermediate **257** with TBSCl to produce a siloxyfuran species **258**. Addition of the allylic bromide **259** to the siloxyfuran **258** in the presence of $Ag(OCOCF_3)_2$ allowed γ-alkylation to occur successfully under S_N1 conditions to produce the γ-alkylation butenolide **248b**.

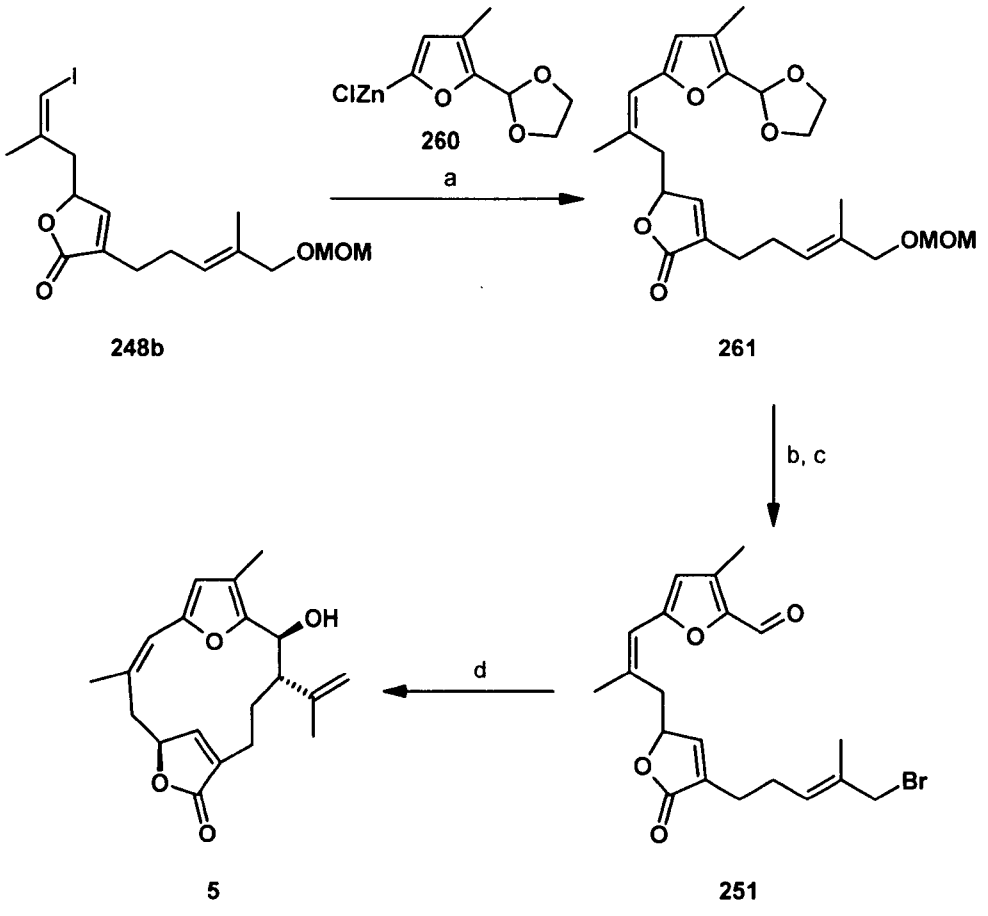
The butenolide **248b** was then reacted in an intermolecular Negishi cross-coupling reaction[200,201] with the dioxolane protected 3-methylfuran aldehyde species **260** (Scheme 48). The cross-coupling reaction produced the unstable alkenylfuran **261**, which upon treatment with the mild acid PPTS, removed both the MOM-ether and the dioxolane protecting groups to produce the allylic alcohol **250**. Addition of CBr_4 and Ph_3P transformed the allylic alcohol into the corresponding allylic bromide **251** which upon NHK macrocyclisation[180,181] produced racemic bipinnatin J (**5**), without incident, in a respectable 73% yield.



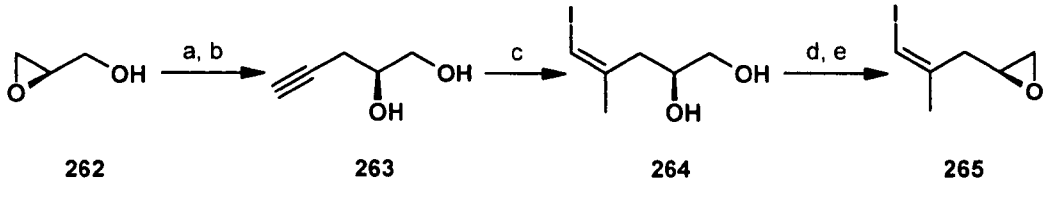
Scheme 47. *Reagents and conditions:* (a) SeO_2, ^tBuOOH, CH_2Cl_2, r.t., 12 hrs, 67%; (b) MOMCl, $^iPr_2NEt$, CH_2Cl_2, r.t., 3 hrs, 91%; (c) NaI, Me_2CO, r.t., 12 hrs, 100%; (d) **255**, LDA, THF, HMPA, -78 °C, then **254**, 90 mins, 72%; (e) LDA, THF, HMPA, -78 °C, then PhSeCl, 30 mins, 66%; (f) H_2O_2, THF, r.t., 12 mins, 82%; (g) LDA, THF, HMPA, -78 °C, then TBSCl, 20 mins, 100%; (h) **259**, CH_2Cl_2, $Ag(OCOCF_3)_2$, -40 °C to r.t., 4 hrs, 60%.

The first synthesis of (+)-intricarene **4** was achieved by our research group using an independent synthesis which started from chiral bipinnatin J (**5**).[110] The synthesis of (–)-bipinnatin J (**5**) starting from (+)-glycidol **262** which was first reacted with the anion of TMS-acetylene to generate an alkyne intermediate that upon treatment with K_2CO_3 removed the TMS group and formed the vicinal diol **263**. The vicinal diol **263** was next reacted under Negishi's *anti*-carboalumination conditions to form the *Z*-vinyl iodide **264**.[197] Selective tosylation of the primary alcohol in **264**, followed by

treatment with K_2CO_3 produced epoxide **265** (Scheme 49). The epoxide **265** generated was then used later in the synthesis.



Scheme 48. *Reagents and conditions:* (a) **260**, $PdCl_2dppf$, THF, r.t., 1 hr, 100%; (b) PPTS, ^tBuOH, 90 °C, 8 hrs, 81%; (c) CBr_4, CH_2Cl_2, PPh_3, 0 °C, 8 mins, 68%; (d) $CrCl_2$, 4 Å MS, THF, r.t., 16 hrs, 73%.

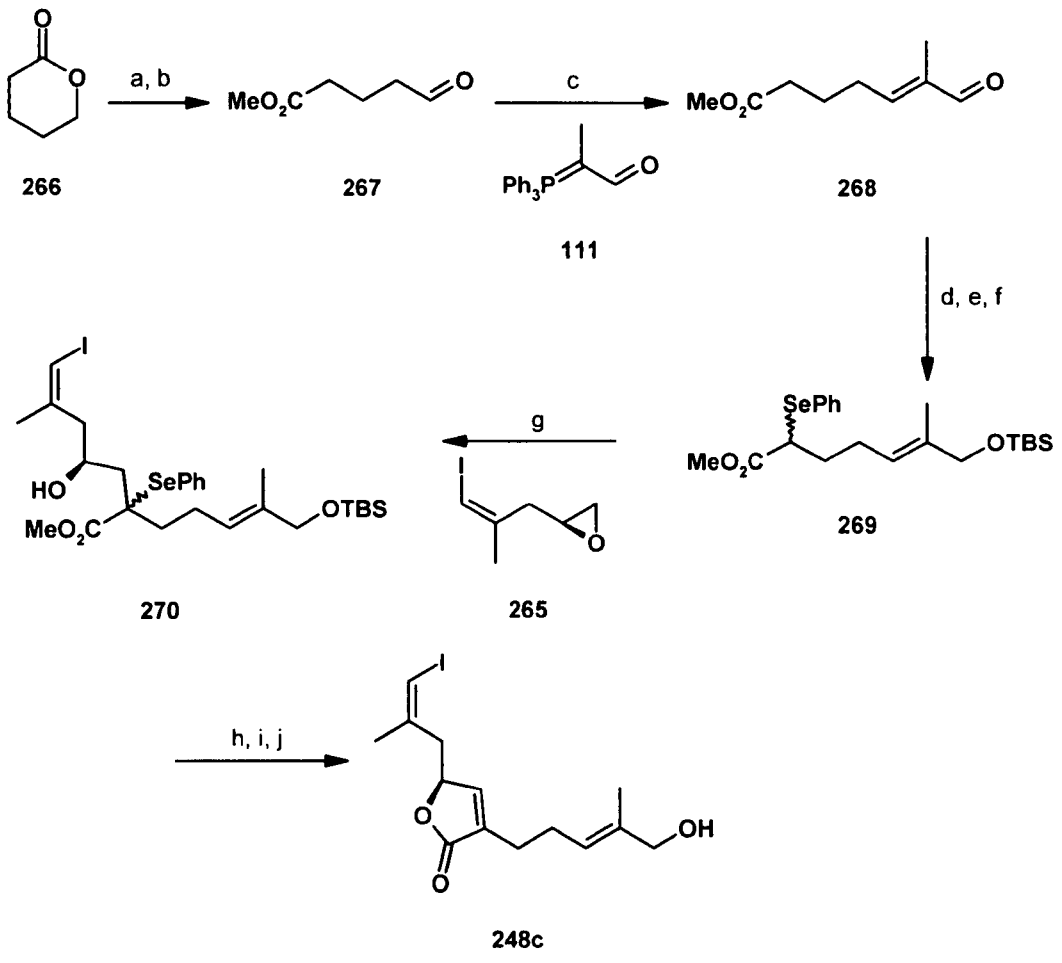


Scheme 49. *Reagents and conditions:* (a) TMS-actylene, ^nBuLi, $BF_3{\cdot}OEt_2$, -78 °C to -30 °C, 19 hrs, 97%; (b) K_2CO_3, MeOH, THF, r.t., 8 hrs, 92 %; (c) $AlMe_3$, Cp_2ZrCl_2, $(CH_2Cl)_2$, reflux, 72 hrs, then I_2, THF, -30 °C to 0 °C, 3 hrs; (d) TsCl, Pyridine, 0 °C, 3hrs, 48% (over 2 steps); (e) K_2CO_3, MeOH, r.t., 90 mins, 73%.

The synthesis of the second fragment started by acid catalysed addition of methanol into δ-velarolactone **266** (Scheme 50). The alcohol produced from this reaction was

then oxidised using PCC which gave aldehyde **267**. Wittig olefination of the aldehyde **267** using the formyl phosphorane **111**[198] in reflux benzene produced the α,β-unsaturated aldehyde **268**. The α-selenylester **269** was then easily produced by Luche reduction of the α,β-unsaturated aldehyde **268** to form the allylic alcohol which was subsequently protected in the form of a TBS-ether group. Finally, deprotonation of the ester formed the lithium enolate which, on addition of PhSeBr produced the α-selenylester **269**. A second deprotonation of the α-selenylester using NaHMDS followed by addition of the previously synthesised epoxide **265**, aided by $BF_3{\cdot}OEt_2$, gave alcohol **270**. Acid catalysed lactonisation between the alcohol and the methyl ester substituents produced the γ-lactone which was sequentially treated with H_2O_2 to induce a *syn*-elimination of PhSeOH and produce the key butenolide function. An acid catalysed deprotection of the TBS group using PPTS in MeOH-DCM produced vinyl iodide **248c**.

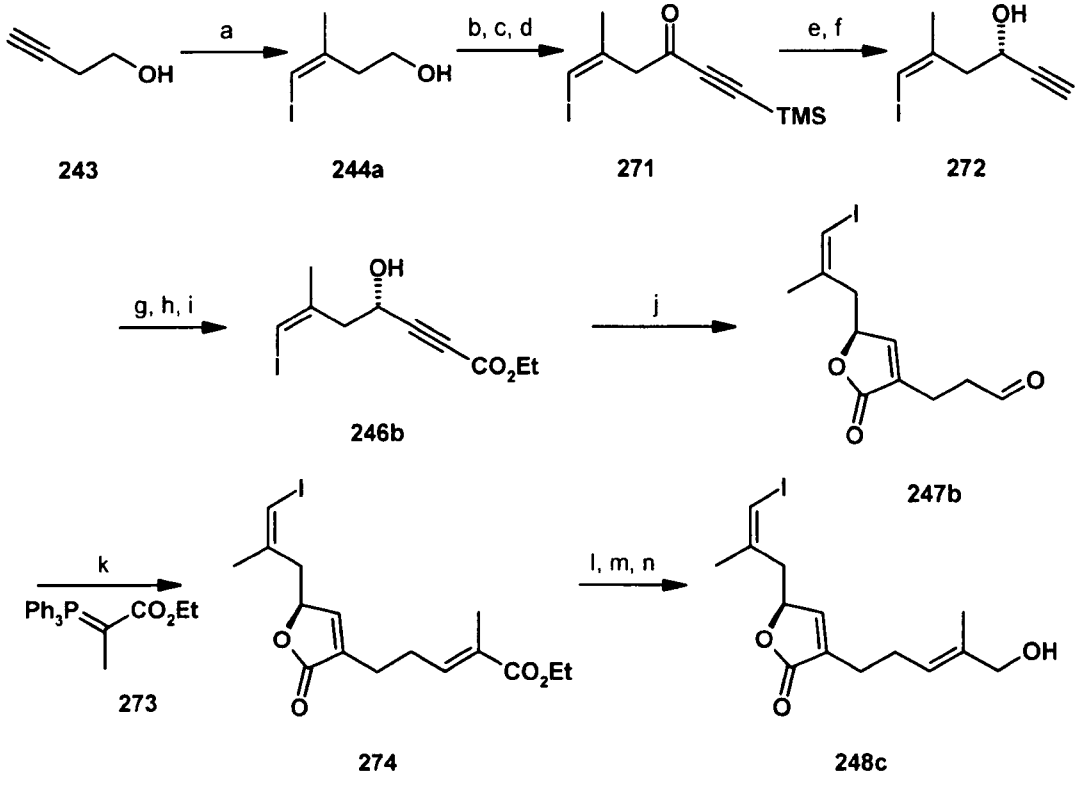
At around the same time, *i.e.* May 2006, Trauner *et al.* were also working towards an enantioselective synthesis of (+)-intricarene **4** *via* (–)-bipinnatin J (**5**).[111] Their synthesis is shown in Scheme 51 and produced the same vinyl iodide intermediate **248c** but utilising an Alder-ene process. The synthesis started from 3-butyne-1-ol **243** which was subjected to $AlMe_3$ and Cp_2ZrCl_2 in refluxing DCE to allow an *anti*-carboalumination to occur.[197] Subsequent *in situ* quenching with I_2 in THF at -30 °C produced the *Z*-vinyl iodide **244a**. Oxidation of the alcohol functional group in **244a** using DMP produced the unstable β,γ-unsaturated vinyl iodide, to which the lithium anion of TMS-acetylene was added to produce the propargylic alcohol. Further oxidation of the alcohol function again using DMP produced the ynone **271**. The



Scheme 50. *Reagents and conditions:* (a) MeOH, conc. H_2SO_4, reflux, 24 hrs, 77%; (b) PCC, CH_2Cl_2, r.t., 5 hrs, 76%; (c) **111**, PhH, reflux, 24 hrs, 79%; (d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C, 10 mins, 99%; (e) TBSCl, imidazole, DMF, 0 °C, 10 mins, 90%; (f) LDA, THF, -78 °C, 45 mins, then TMSCl, -78 °C, 30 mins, then PhSeBr, THF, -78 °C to r.t., 1 hr, 73%; (g) NaHMDS, THF, -78 °C, then $BF_3{\cdot}OEt_2$, **265**, -78 °C to r.t., 15 hrs, 60%; (h) *p*-TSA, CH_2Cl_2, r.t., 3 hrs; (i) H_2O_2, THF, 0 °C to r.t., 90 mins; (j) PPTS, CH_2Cl_2, MeOH, r.t., 15 hrs, 62% (over 3 steps).

ynone **271** was subjected to an asymmetric reduction using Midland's (*S*)-alpine borane complex[202,203] which re-introduced the propargylic alcohol functionality but in 92% ee. Removal of the TMS group from the acetylene using K_2CO_3 in MeOH gave vinyl iodide **272**. Protection of the propargylic alcohol of intermediate **272** as the TES-silyl ether followed by deprotonation of the acetylene and quenching with ethyl chloroformate produced a propargylic ester. Deprotection of the TES-group on the alcohol substituent using HF in MeCN gave the enantiomerically enriched propargylic alcohol **246b**. A Trost Alder-ene reaction between the propargylic alcohol **246b** and

allyl alcohol **110** in the presence of a ruthenium catalyst under acidic conditions generated,[146] in one step, the aldehyde-butenolide **247b**. A Wittig olefination on the aldehyde function in **247b** using the ester phosphorane **273** produced the α,β-unsaturated ester **274** but unfortunately the ee dropped to 88%. Treatment of intermediate **274** with DIBAL-H reduced both the α,β-unsaturated ester to the allylic alcohol and the butenolide to the lactol. The reactive lactol formed was then reoxidised to the corresponding butenolide using PDC, which simultaneously caused the allylic alcohol to be oxidised to an α,β-unsaturated aldehyde. Finally, selectively reduction of the aldehyde functionality to the allylic alcohol **248c** was achieved utilising $NaBH_4$ in MeOH.



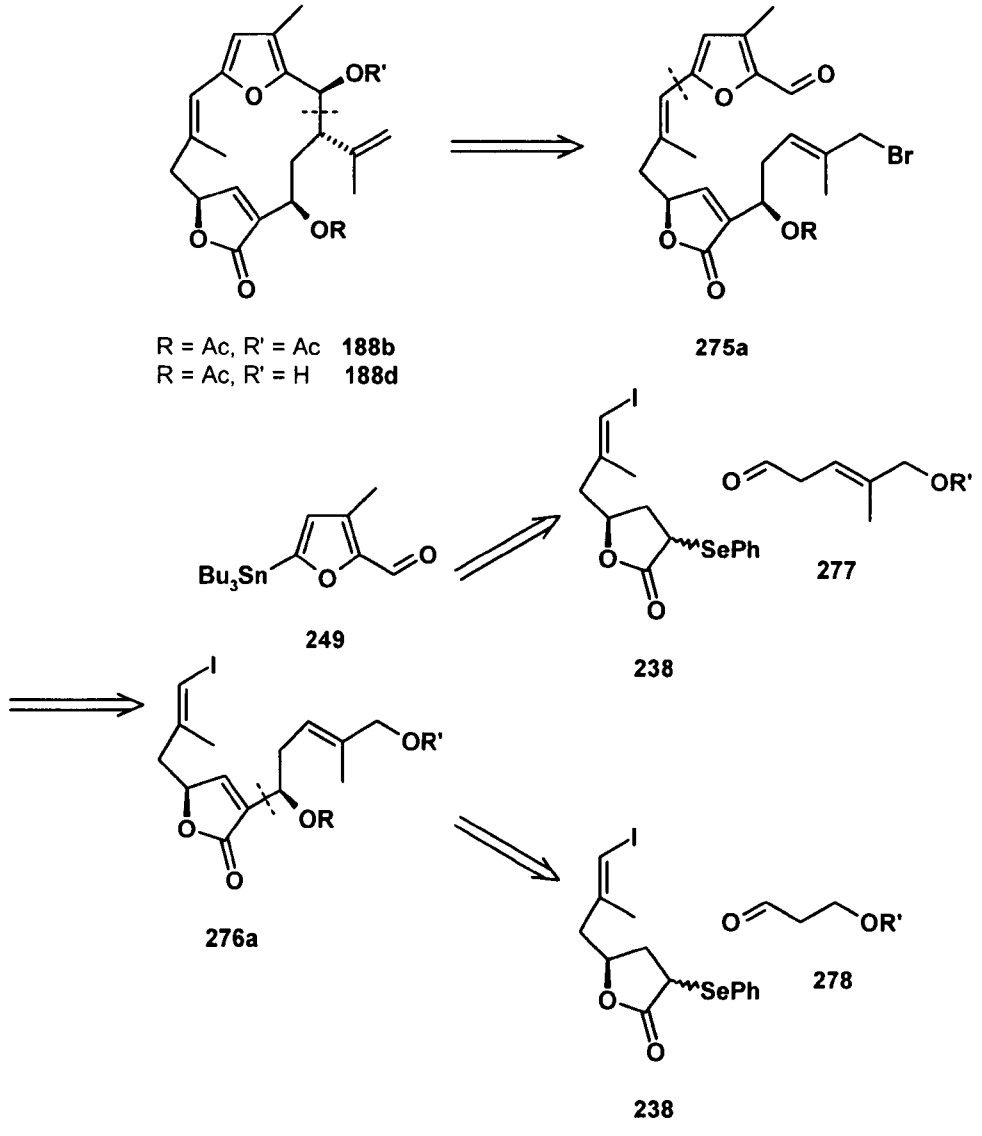
Scheme 51. *Reagents and conditions:* (a) $AlMe_3$, Cp_2ZrCl_2, $(CH_2Cl)_2$, reflux, 72 hrs, then I_2, THF, -30 °C to 0 °C, 1 hr, 60%; (b) DMP, CH_2Cl_2, $NaHCO_3$, r.t., 15 mins; (c) TMS-actylene, ^{n}BuLi, THF, 0 °C, 5 mins, then aldehyde, -78 °C, 15 mins, 60% (over 2 steps); (d) DMP, CH_2Cl_2, $NaHCO_3$, 0 °C, 25 mins; (e) (*S*)-alpine borane, r.t., 22 hrs, then propionaldehyde, 30 mins, then 3M NaOH, 30% H_2O_2, THF, r.t., 91% (over 2 steps); (f) K_2CO_3, MeOH, r.t., 45 mins, 99%; (g) TESOTf, 2,6-lutidine, THF, r.t., 20 mins, 93%; (h) LiHMDS, THF, -78 °C to -50 °C, 90 mins, then ethyl chloroformate, 15 mins, 97%; (i) HF, MeCN, r.t., 30 mins, 95%; (j) allyl alcohol, 5 mol% $RuCp(MeCN)_3PF_6$, CSA, THF, Me_2CO, 50 °C, 90 mins, 52%; (k) **273**, CH_2Cl_2, r.t., 5 hrs, 84%; (l) DIBAL-H, CH_2Cl_2, -78 °C, 20 mins; (m) PDC, CH_2Cl_2, r.t., 24 hrs, 70% (over 2 steps); (n) $NaBH_4$, MeOH, 20 mins, r.t., 99%.

The vinyl iodide **248c** synthesised by Trauner *et al.* contained the necessary functionality to be transformed to (–)-bipinnatin J (**5**). Thus, following the final three steps shown in Scheme 46, a Stille cross-coupling reaction[194,195] with 3-methyl-5-trimethylstannylfuran aldehyde **249**,[196] bromination of the allylic alcohol function and a diastereoselective NHK[180,181] macrocyclisation produced (–)-bipinnatin J (**5**) in a high 70% yield.

The syntheses by Paquette,[176-179] Still,[183] Trauner[196] and from our own group,[110] have shown that one of the most reliable methods to form furanobutenolide – based cembranes is *via* the NHK coupling reaction. Therefore, we aimed to implement a NHK macrocyclisation process in order to form *E*-deoxybipinnatin G (**188b**). Formation of *E*-deoxybipinnatin G (**188b**) will allow attempts to form the enol ethers **69** and **74** *via* an oxidation/ hydration sequence on the alkenylfuran motif embedded in **188b**. The structure of *E*-deoxybipinnatin G (**188b**) is similar to bipinnatin J (**5**) and hence there was only one alteration to the bipinnatin J (**5**) synthesis to consider, that was the presence of the C13 hydroxyl group.

A retrosynthetic analysis shows that starting from *E*-deoxybipinnatin G (**188b**), removal of the C2 acetyl protecting group gives the intermediate **188d** which, upon retro-NHK coupling reaction, leads back to the allylic bromide **275a** (Scheme 52). The allylic bromide **275a** is structurally similar to the intermediate **248** used during the synthesis (–)-bipinnatin J (**5**). The furan substituent in **275a** can be disconnected utilising an intermolecular Stille cross-coupling between the stannylfuran aldehyde **249** and the vinyl iodide intermediate **276a**. The intermediate vinyl iodide **276a** could then be synthesised *via* an alkylation reaction between either of the aldehydes, **277** or

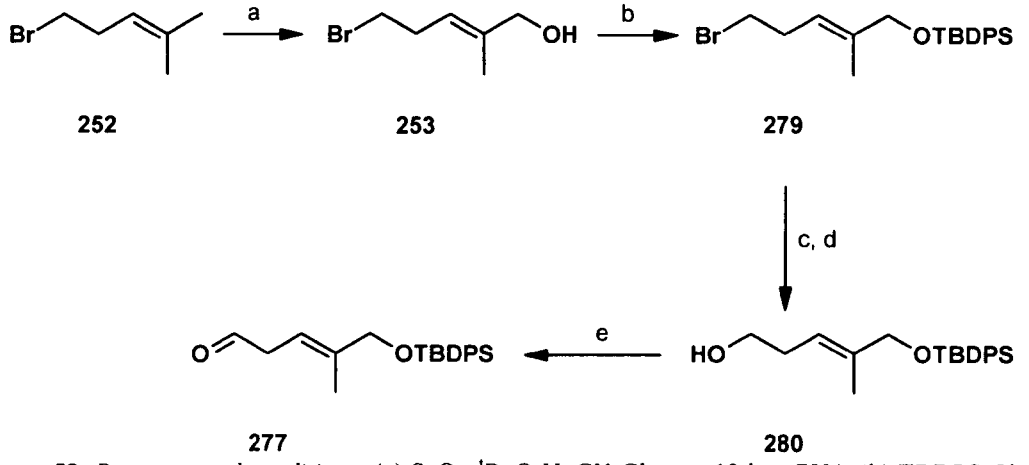
278, and the phenylselenium compound **238**, which had been synthesised previously within our group.[170,193]



Scheme 52. Proposed synthesis of the furanobutenolide – based cembrane macrocycle *E*-deoxybipinnatin G (**188b**).

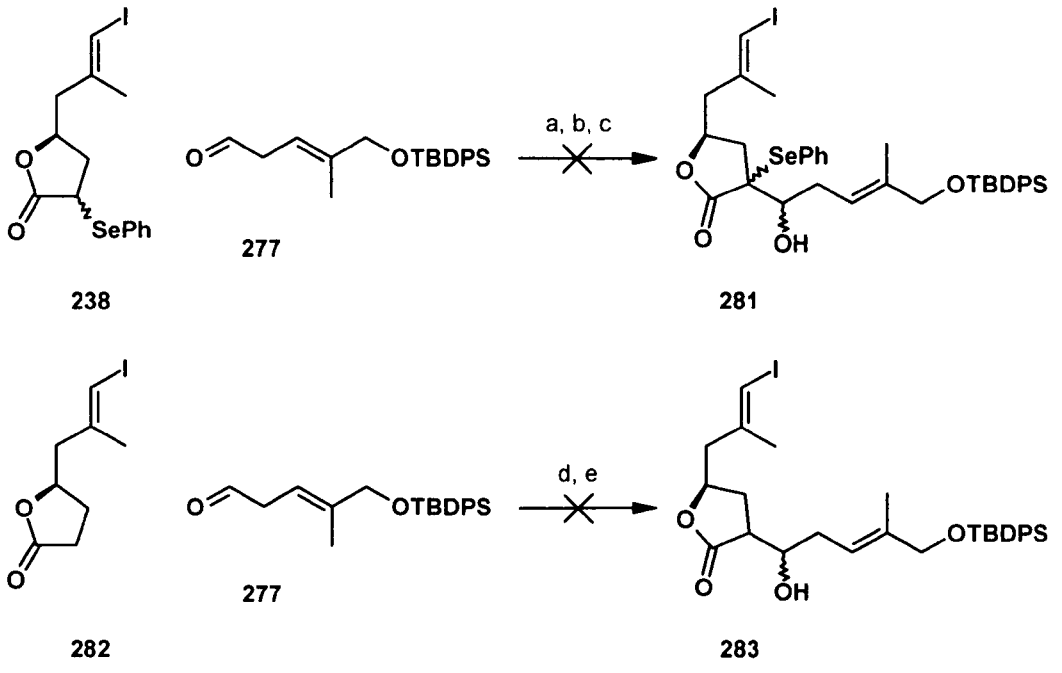
The synthesis towards the vinyl iodide **276a** commenced with commercially available 5-bromo-2-methyl-2-pentene **252** which, on treatment with SeO_2 and $^tBuO_2H$ induced a regioselective allylic oxidation process to produce the allylic alcohol **253**.[199] Protection of the alcohol functionality in **253** utilising TBDPS-Cl and imidazole in DMF at 0 °C, next gave the silyl-ether **279**. Treatment of the intermediate **279** with potassium acetate in DMF at 100 °C induced S_N2 nucleophilic displacement of the

alkyl bromide substituent, which on subsequent acetyl deprotection with K_2CO_3 in MeOH gave the alcohol **280**.[204] Finally, oxidation of the alcohol **280** using Dess-Martin periodinane produced the β,γ-unsaturated aldehyde **277** (Scheme 53).



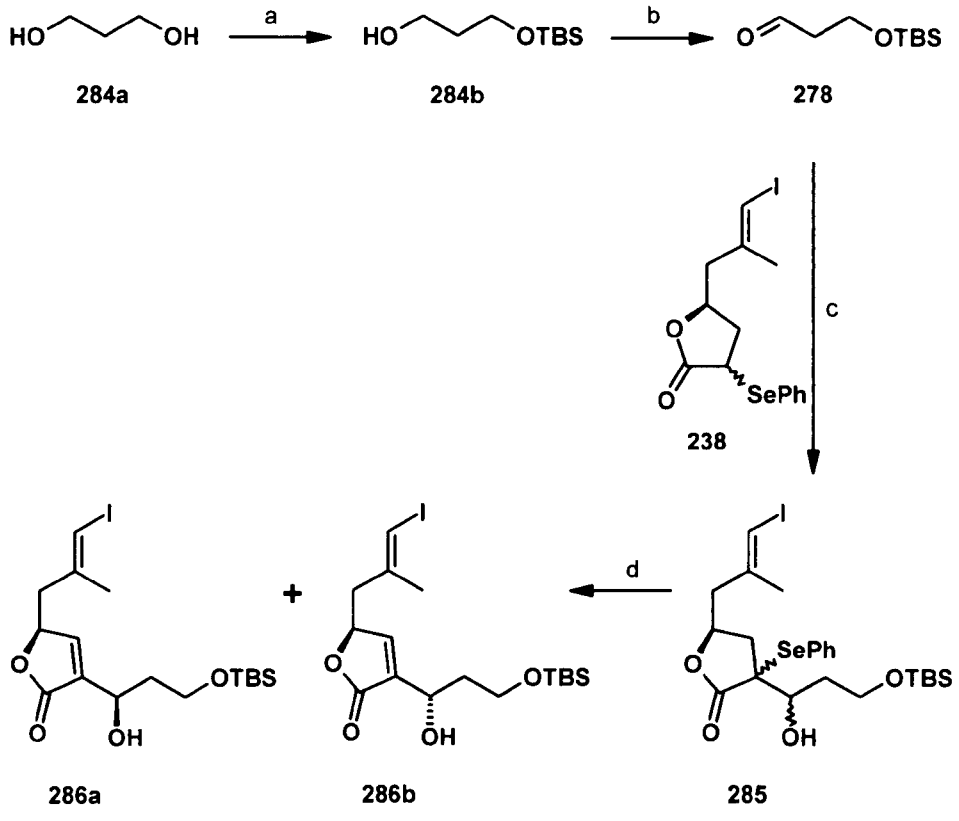
Scheme 53. *Reagents and conditions:* (a) SeO_2, $^tBuO_2H$, CH_2Cl_2, r.t., 12 hrs, 70%; (b) TBDPS-Cl, Im, DMF, 0 °C, 10 mins, 90%; (c) KOAc, DMF, 100 °C, 24 hrs; (d) K_2CO_3, MeOH, r.t., 90 mins, 84% (over 2 steps); (e) DMP, CH_2Cl_2, r.t., 30 mins, 100%.

With the β,γ-unsaturated aldehyde **277** in hand, the aldol process was tested under several conditions shown in Scheme 54. Deprotonation of the phenylselenyl lactone **238**[170,193] using several bases (LiHMDS, NaHMDS and LDA) followed by addition of the β,γ-unsaturated aldehyde **277** failed to produce the expected secondary alcohol **281**; only decomposition products were isolated. Unfortunately similar conditions on the lactone **282**, did not produce any of the required alcohol **283** and, again, only degradation was observed. Due to the instability of the β,γ-unsaturated aldehyde **277** this approach was abandoned in favour of the alternative aldol approach, which utilises the mono-protected 1,3-propanal **278** in order to form the vinyl iodide **276a**.



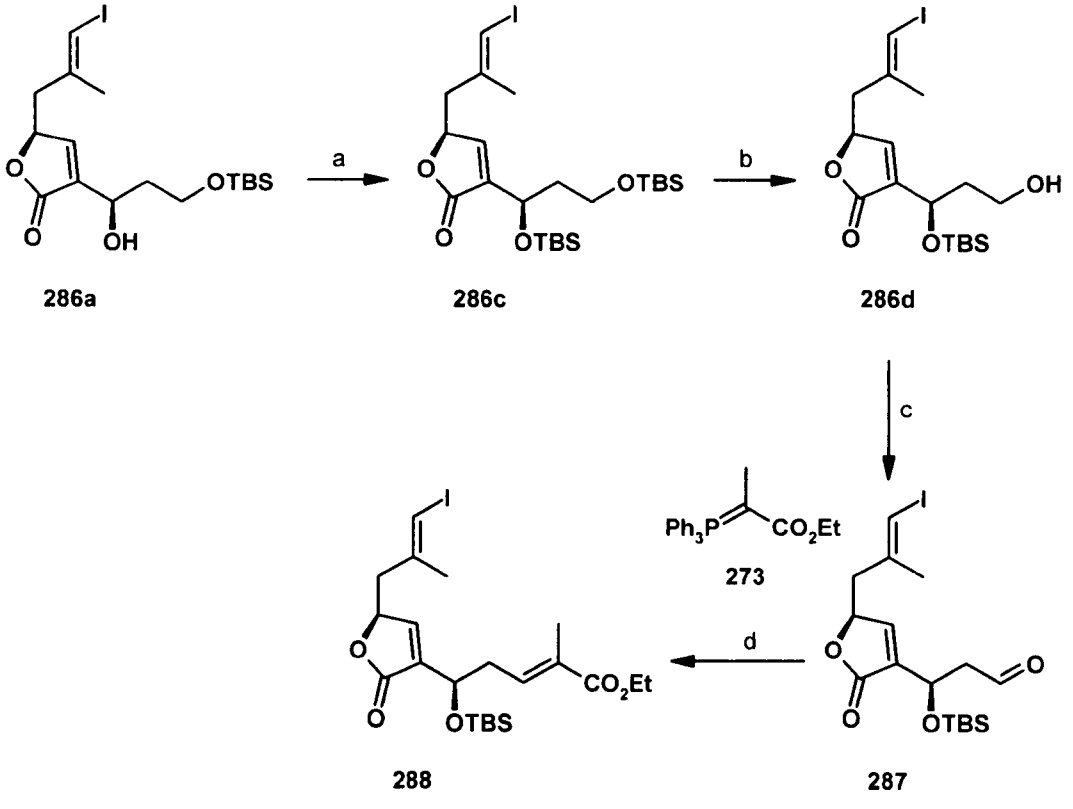
Scheme 54. *Reagents and conditions:* (a) **238**, LiHMDS, THF, -78 °C, 1 hr, then **277**, THF, 30 mins; (b) **238**, NaHMDS, THF, -78 °C, 1 hr, then **277**, THF, 30 mins; (c) **238**, LDA, THF, -78 °C, 1 hr, then **277**, THF, 30 mins; (d) **282**, LiHMDS, THF, -78 °C, 1 hr, then **277**, THF, 30 mins; (e) **282**, LiHMDS, TMSCl, THF, -78 °C, 1 hr, then **277**, THF, 30 mins.

The alternative aldol approach towards the vinyl iodide intermediate **276a** commenced with 1,3-propanediol **284a**. Several different protecting groups were investigated, but only the most reliable synthesis is described here (Scheme 55). The diol **284a** was first mono-protected utilising NaH and TBS-Cl to produce the TBS-protected propanol **284b**.[205] Oxidation of the primary alcohol group in **284b** was achieved using PDC in DCM and gave the aldehyde **278**.[206] Deprotonation of the phenyl selenium compound **238** using LiHMDS produced the corresponding lithium enolate which, on addition of the aldehyde **278**, produced the α-selenoester **285**. The aldol product was then oxidised directly with H_2O_2 in the presence of pyridine, which led to *syn*-elimination and formation of the epimeric secondary alcohol **286a** and **286b**.[170,193]



Scheme 55. *Reagents and conditions:* (a) NaH, TBSCl, THF, r.t., 90 mins, 82%; (b) PDC, CH_2Cl_2, r.t., 24 hrs, 38%; (c) **238**, LiHMDS, THF, -78 °C, then **278**, 1 hr; (d) $H_2O_2.H_2O$, pyridine, CH_2Cl_2, r.t., 1 hr, 59% (over 2 steps, for major diastereoisomer).

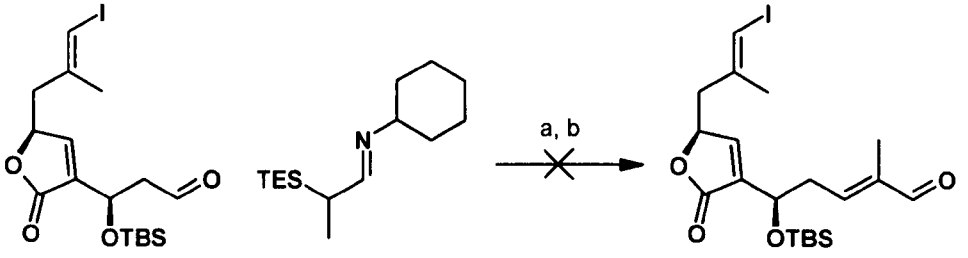
The relative configurations of the diastereoisomic alcohols was unknown. Hence, one of the butenolides was chosen arbitrarily and treated with TBS-OTf in the presence of 2,6-lutidine as base (Scheme 56). The doubly TBS-protected alcohol **286c** was then transformed into the primary alcohol **286d** *via* selective deprotection, under the mildly acidic conditions of PPTS in MeOH and DCM. With the primary alcohol accessible it could be easily oxidised to the aldehyde functionality with Dess-Martin periodinane. The aldehyde **287** could now be exposed to a variety of conditions with both stabilised phosphoranes **111**[198] and **273** to try to induce the Wittig reaction and form the α,β-unsaturated carbonyl compounds.



Scheme 56. *Reagents and conditions:* (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 90 mins, 87%; (b) PPTS, MeOH, CH_2Cl_2, r.t., 15 hrs, 86%; (c) DMP, CH_2Cl_2, r.t., 30 mins; (d) **273**, THF, r.t., 24 hrs, 95% (over 2 steps).

Initial results demonstrated that the Wittig reaction had to be run at room temperature since, on heating, the aldehyde intermediate **287** decomposed. The use of the formyl phosphorane **111**[198] caused decomposition of the aldehyde **287** even at this reduced temperature. Therefore, attention shifted to the more reactive ester phosphorane **273**, which gave more positive results when exposed to the aldehyde **287**. Treatment of the aldehyde **287** with the phosphorane **273** in THF produced the α,β-unsaturated ester **288** at room temperature, in a excellent 95% yield for both the oxidation and Wittig processes. This transformation was also quickly tested utilising a Peterson olefination reaction (Scheme 57). Deprotonation of the silyl imine **289** with *sec*-BuLi at -78 °C generated the lithium enamate which on addition into the aldehyde **287** forms the α,β-unsaturated imine. Addition of TFA caused the imine to hydrolyse to the corresponding α,β-unsaturated aldehyde **290**. Unsurprisingly the use of this highly

basic silyl imine **289** caused the aldehyde **287** to decompose and no product was observed.[207-209]



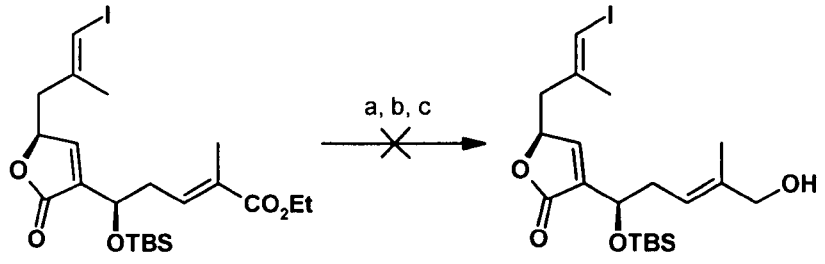
287 **289** **290**

Scheme 57. *Reagents and conditions:* (a) **289**, ^{s}BuLi, THF, -78 °C, 30 mins, then **287**, THF, -20 °C, 2 hrs; (b) TFA, THF, r.t., 2 hrs.

The formation of the α,β-unsaturated ester **288** had now been solved but this simultaneously introduced a new problem; the α,β-unsaturated ester function must be reduced selectively in the presence of the butenolide substituent, which itself possesses an α,β-unsaturated ester functionality. This reduction could prove difficult.

The final stage in the synthesis of the vinyl iodide **276a** was the transformation of the α,β-unsaturated ester **288** to the corresponding allylic alcohol. Several conditions were tried for this transformation (Scheme 58). Initially, $LiAlH_4$ and Super hydride were used, but these reducing agents were over-powering and caused decomposition. The α,β-unsaturated ester **288** was then treated with DIBAL-H. Initial results suggested that both the α,β-unsaturated ester and the lactone functional groups had been reduced to the corresponding allylic alcohol and the lactol respectively. Subsequent manipulation to try to form the vinyl iodide **276a** in a similar manner to Trauner *et al.*[111] produced unsatisfactory results. The reduction of the vinyl iodide **276a**, was unsuccessful, therefore, it was thought that the α,β-unsaturated ester **288**

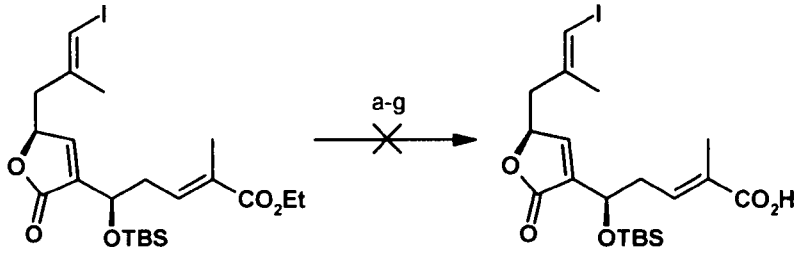
could be saponified to the α,β-unsaturated carboxylic acid **291**, which could in turn be selectively reduced to corresponding allylic alcohol substituent.



288 **276a**

Scheme 58. *Reagents and conditions:* (a) $LiAlH_4$, THF, 0 °C, 1 hr, 0%; (b) Super Hydride, THF, -78 °C, 1 hr, 0%; (c) DIBAL-H, DCM, -78 °C, 15 mins, 0%.

Saponification of the α,β-unsaturated ester **288** was tested under a variety of conditions shown in Scheme 59. All reagents which contained a hydroxyl group along with TMSOK, were too basic for the α,β-unsaturated ester **288**, and caused immediate decomposition. The reagents which did not use a hydroxyl group had varying effects but unfortunately none produced the required α,β-unsaturated carboxylic acid **291**. The $(Bu_3Sn)_2O$ reagent did not react and simply gave back the starting material. The only reagent to have a positive effect was when the α,β-unsaturated ester **288** was reacted with TMS-Cl and NaI to generate TMS-I *in-situ* and this removed the TBS-protecting group from the secondary alcohol.

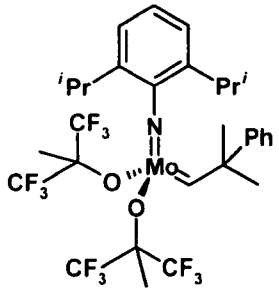


288 **291**

Scheme 59. *Reagents and conditions:* (a) 2M NaOH (aq.), THF, MeOH, r.t.; (b) NaOH, THF, MeOH, r.t.; (c) LiOH, THF, MeOH, r.t.; (d) $Ba(OH)_2.8H_2O$, MeOH, r.t.; (e) TMSOK, THF, r.t.; (f) TMSCl, NaI, MeCN, reflux, 15 hrs; (g) $(Bu_3Sn)_2O$, MeCN, reflux, 15 hrs.

All efforts to transform the α,β-unsaturated ester **288** into the vinyl iodide **276a** ending in failure, due to its highly sensitive nature towards basic reagents. Therefore, an alternative synthetic route towards the vinyl iodide **276a** was required.

An area of chemistry that has received a great deal of attention since its discovery is cross-metathesis (CM) and the ring closing metathesis (RCM) of alkenes.[210,211] Originally tungsten was used as the active metal for initiation of alkene metathesis,[212,213] but after development, the two processes were commonly facilitated by either a molybdenum catalyst, *i.e.* Schrock's catalyst **292**,[214] or a ruthenium based catalyst, *i.e.* Grubbs or Grubbs-Hoveyda catalysts (**293** – **296**).[215-220] The most commonly applied catalysts in this area are the Grubbs 1st generation **293**,[215,216] and 2nd generation **294** catalysts.[217]



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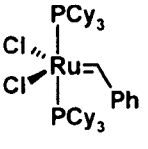

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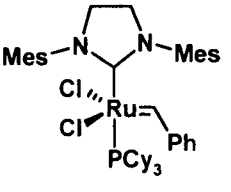

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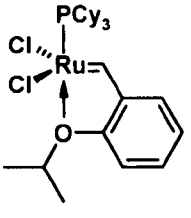

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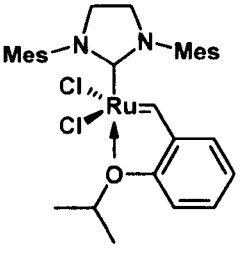

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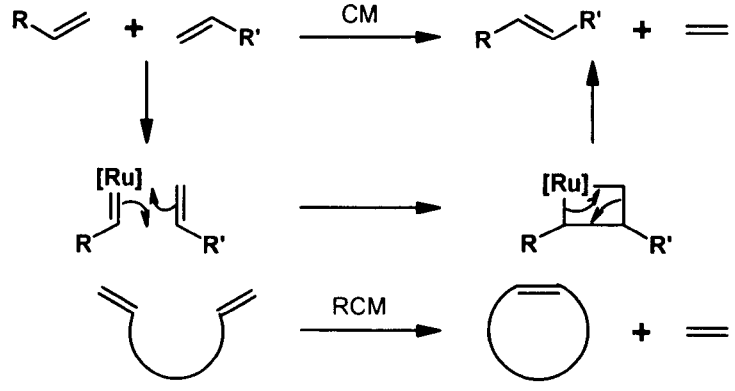
Both the CM and the RCM processes occur via a [2+2] cycloaddition between alkenes to form a ruthenium cyclobutane species, which upon a retro-[2+2] process, regenerates the olefinic function with the two new functional groups.[221] The basic CM

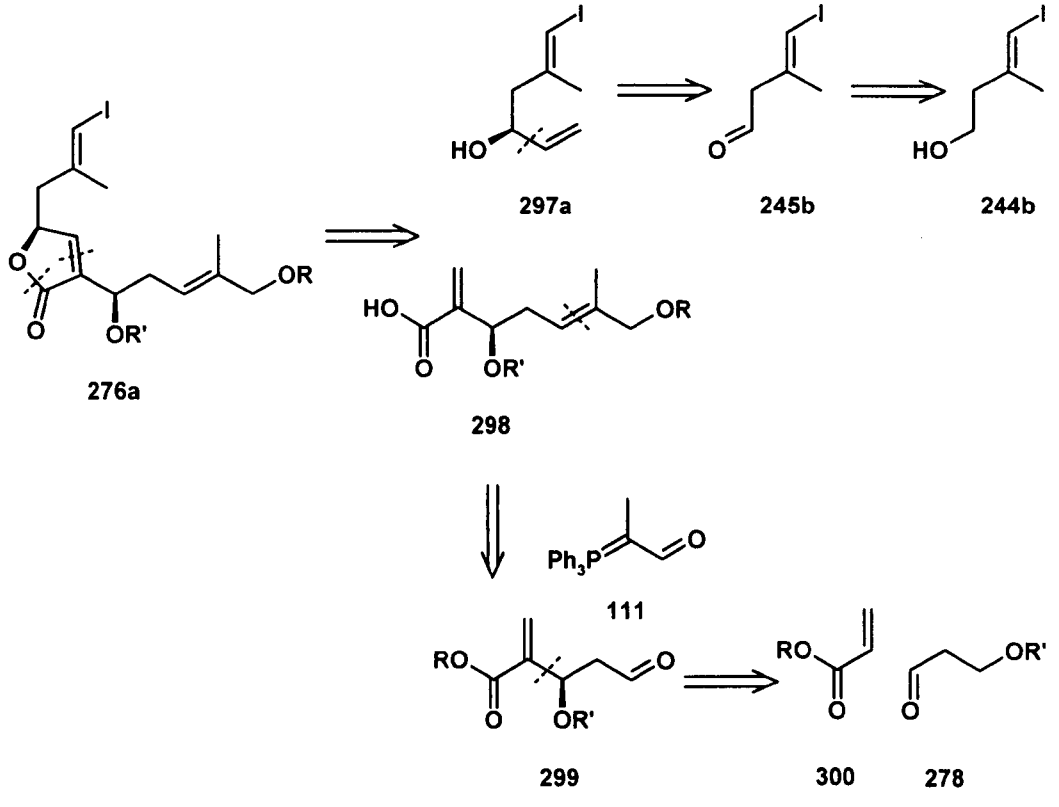
and RCM reactions using terminal alkenes are shown in Scheme 60. Both processes connect the alkene functionalities together in a single step, release ethane, and produce predominantly the more stable *E*-alkene within the product.



Scheme 60. Basic processes for cross-metathesis (CM) and ring closing metathesis (RCM).

The Grubbs catalysts have been tested extensively on most substrates and used to synthesise a wide array of natural products.[222-229] Both CM and RCM reactions are highly efficient processes and it was hoped that specifically, the RCM process could be applied successfully to the furanocembrane structure of *E*-deoxybipinnatin G (**188b**). Therefore, the aim was to implement this process in the formation of the butenolide functional group, which represents the most obvious point for disconnection.[230-233] Starting from the vinyl iodide **276a** (Scheme 61) a retro-RCM on the butenolide gives an allylic ester which can be disconnected further into the allylic alcohol **297a** and the 1,1-disubstituted alkene **298**. The allylic alcohol **297a** could be produced by addition of a nucleophile, *e.g.* vinylmagnesium halide or a lithiated acetylene, into the β,γ-unsaturated aldehyde **245b**, which upon oxidation and enantioselective reduction would produce the required product. Oxidation of the known alcohol intermediate **244b** will generate the β,γ-unsaturated aldehyde **245b**. The 1,1-disubstituted alkene **298** could be generated by saponification of the corresponding ester substituent, functional group manipulation and Wittig reaction

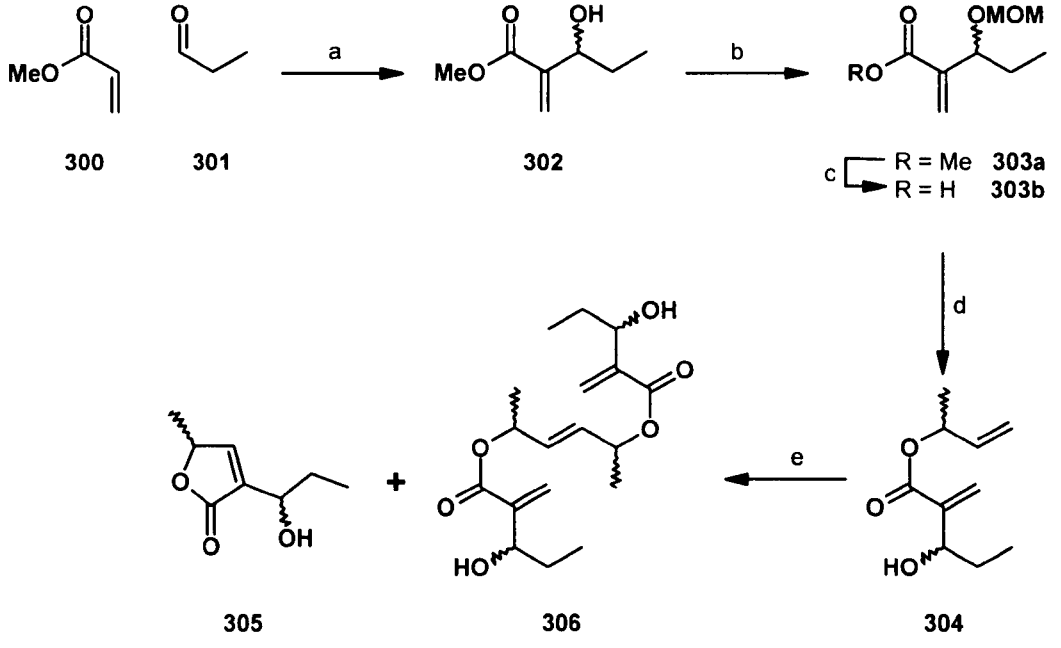
between the formyl phosphorane **111** and the aldehyde **299**. Simple functional group conversion and a retro-Baylis-Hillman reaction forms the two starting materials, methyl acrylate **300** and the aldehyde **278**. Coupling of the allylic alcohol **297a** with the 1,1-disubstituted alkene **298** will generate the vinyl iodide **276a** to allow access to *E*-deoxybipinnatin G (**188b**).



Scheme 61. Proposed retrosyntheis of vinyl iodide **276a**.

Before the synthesis of the vinyl iodide **276a** was initiated, the metathesis process was tested on a simple model system to ascertain if RCM could be achieved in order to form a butenolide substituent (Scheme 62). The model system synthesis was started with a Baylis-Hillman reaction[234-237] between methyl acrylate **300** and propionaldehyde **301** in the presence of DABCO.[235] The secondary alcohol function of the intermediate **302** produced during the Baylis-Hillman reaction, was subsequently protected using MOM-Cl and DIPEA to produce the MOM-ether **303a**.

Saponification of the ester functionality in **303a** gave the α,β-unsaturated carboxylic acid **303b**, which was directly coupled with 1-buten-3-ol utilising DCC, to produce the allylic ester **304**. The coupling reaction generated the required precursor to analyse the key RCM process. Fortunately, exposure of the allylic ester **304** to Grubbs 2nd generation catalyst **294** in refluxing DCM produced the butenolide **305** in a respectable 67% yield.[233]



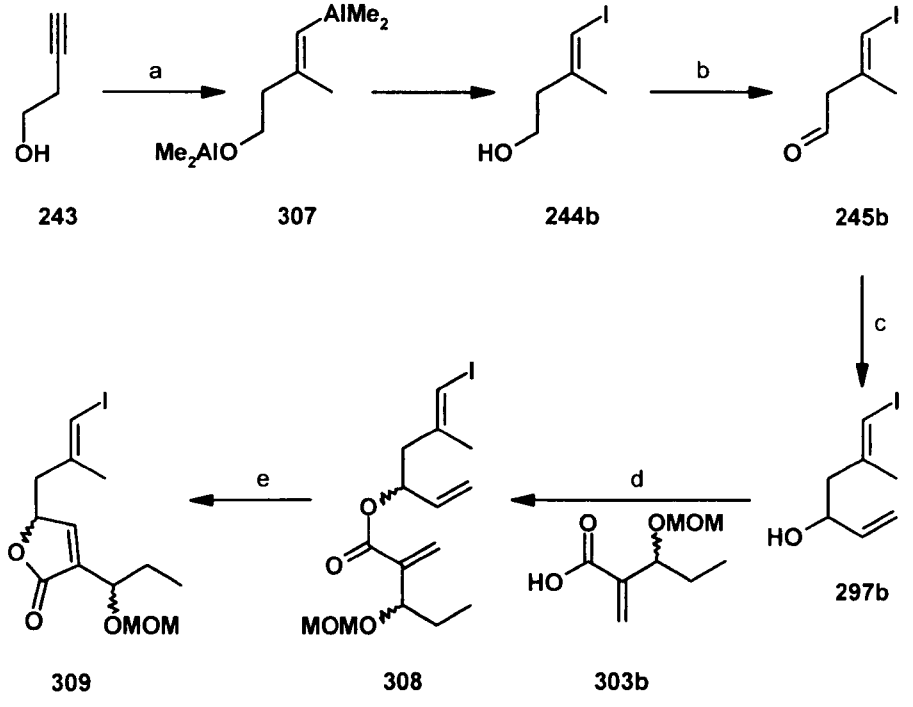
Scheme 62. *Reagents and conditions:* (a) DABCO, DMF, r.t., 4 days, 55%; (b) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, r.t., 24 hrs, 85%; (c) 1M LiOH, THF, H_2O, r.t., 20 hrs; (d) 1-buten-3-ol, DCC, DMAP, CH_2Cl_2, r.t., 24 hrs, 62% (over 2 steps); (e) Grubbs 2nd generation **294**, CH_2Cl_2, 40 °C, 24 hrs, 67% (**305**) and 23% (**306**).

The 67% yield produced from the RCM process was also supplemented by a 23% yield which was due to the dimer **306** formed when the mono-substituted alkene reacts intermolecularly. This result suggested that with higher dilution and slow addition of both the precursor **304** and the catalyst **294** that the butenolide could be potentially produced in a 90% yield.

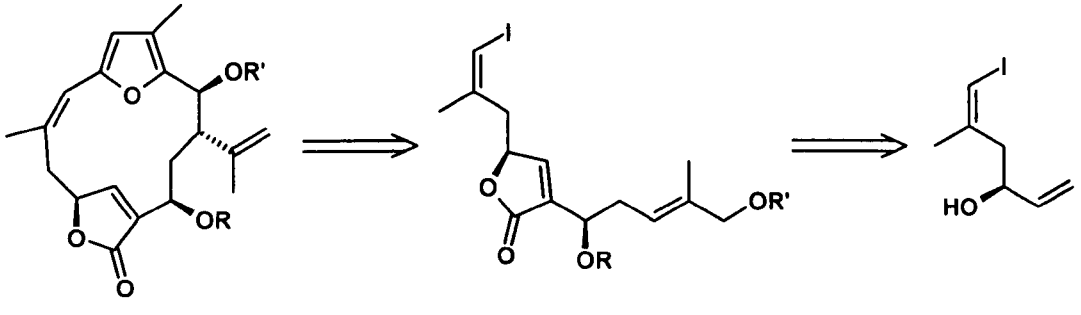
The next obvious progression towards the vinyl iodide intermediate **276a** was to produce a model system **308** containing a vinyl iodide to ensure that this functional group was stable to the Grubbs catalyst and to RCM conditions. The more complex model system (Scheme 63) began with commercially available 3-butyn-1-ol **243**, which was subjected to $AlMe_3$ and Cp_2ZrCl_2 in DCE to allow carboalumination to occur under Negishi's conditions.[238] The aluminium intermediate **307** formed *in-situ* was quenched utilising I_2 in THF at -30 °C to produce predominantly the *E*-vinyl iodide **244b**. Oxidation of the alcohol function in **244b** was achieved using DMP to produce the unstable β,γ-unsaturated aldehyde **245b** which was immediately treated with vinylmagnesium bromide at -78 °C to produce the allylic alcohol **297b**. The secondary alcohol substituent of intermediate **297b** could then be coupled with the previously synthesised α,β-unsaturated carboxylic acid **303b** again using DCC.[233] The allylic ester **308** produced from the coupling reaction serves as the precursor for the RCM process. Therefore, the precursor **308** was treated with Grubbs 2nd generation catalyst **294**[217] in refluxing DCM, under high dilution conditions with slow addition of both the substrate and the catalyst. Fortunately, after work-up and chromatography, the butenolide **309** was formed in 62% yield as predominantly two separable diastereoisomers. Limited formation of the dimer was observed. This result demonstrated that the vinyl iodide function was stable to the RCM conditions and could therefore be used to form the butenolide on the real vinyl iodide substrate **276a**.

At this point, we decided that the NHK macrocyclisation process would give us the greatest chance of success. To achieve this, simply altering the *E*-$\Delta^{7,8}$-alkene bond of intermediates **188b** and **188d** to the *Z*-$\Delta^{7,8}$-alkene macrocycle **188e** and **188f** (Scheme

64) will make the macrocycle less rigid and give more degrees of freedom to allow the NHK macrocyclisation to occur with maximum effect.



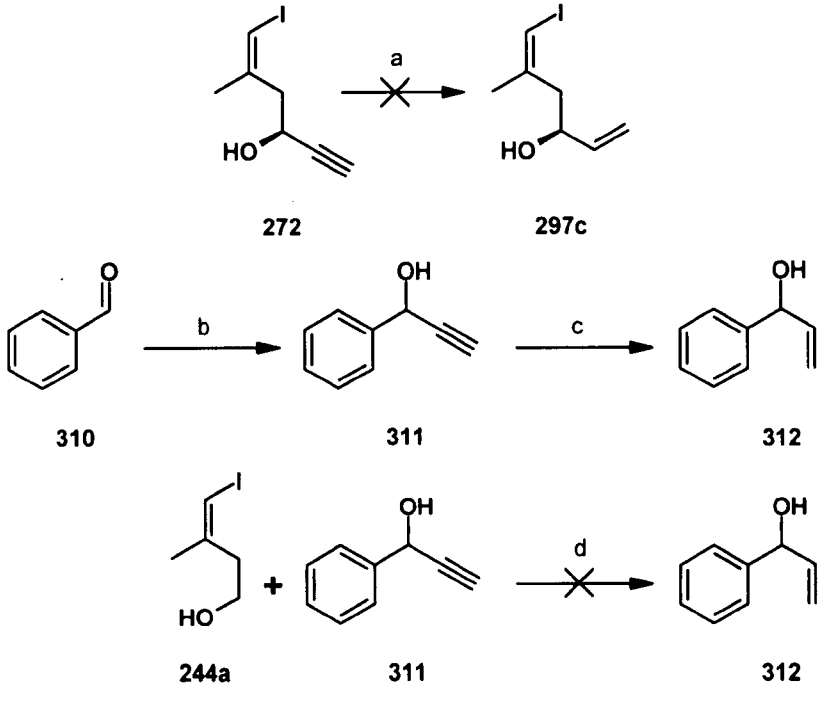
Scheme 63. *Reagents and conditions:* (a) $AlMe_3$, Cp_2ZrCl_2, $(CH_2Cl)_2$, reflux, 72 hrs, then I_2, THF, -30 °C to 0 °C, 1 hr, 81%; (b) DMP, CH_2Cl_2, $NaHCO_3$, r.t., 15 mins; (c) vinylmagnesium bromide, THF, -78 °C, 1 hr, 40% (over 2 steps); (d) **303b**, DCC, DMAP, CH_2Cl_2, r.t., 20 hrs, 59%; (e) Grubbs 2nd generation **294**, CH_2Cl_2, 40 °C, 24 hrs, 62%.



Scheme 64. Retrosynthesis of *Z*-deoxybipinnatin G (**188e**).

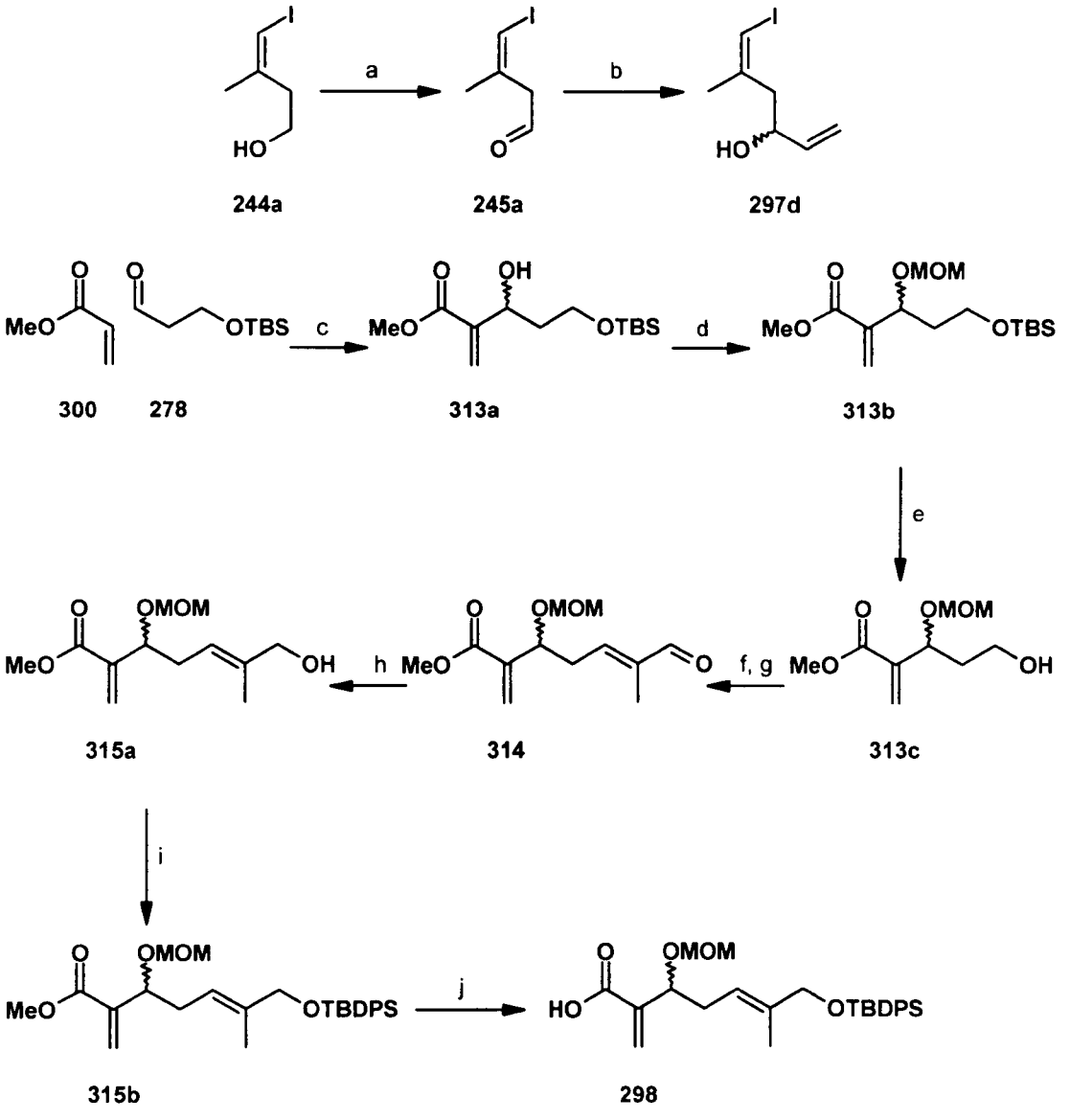
Conversion of the *Z*-macrocyclic structure of deoxybipinnatin G (**188e**) through the retrosynthesis produced the *Z*-vinyl iodide **276b**, which in-turn is produced from the allylic alcohol **297c**. Therefore, the synthesis of *Z*-deoxybipinnatin G (**188e**) was

initiated in an identical manner to the synthesis of (+)-intricarene **4** shown by Trauner *et al.* (Scheme 51),[111] and 3-butyn-1-ol **243** was converted into the propargylic alcohol **272** with 91% ee using (*S*)-alpine borane (*cf.* page 85). Attempts were made to reduce the alkyne functionality in **272** to the corresponding allylic alcohol **297c** with hydrogen in the presence of Lindlar's catalyst.[239] Unfortunately all attempts to induce this transformation failed independent of reaction temperature and time, and only the starting material was returned (Scheme 65). Further examination of the Lindlar reduction was undertaken using propargylic alcohol **311**,[240,241] produced by addition of ethynylmagnesium bromide to benzaldehyde **310** at -78 °C. Lindlar reduction on propargylic alcohol **311** produced the allylic alcohol **312** in 82% yield,[242,243] but in the presence of vinyl iodide **244a**, only starting materials were returned. This result demonstrated the vinyl iodide functionality in **272** was inhibiting the catalysts ability to reduce and form the allylic alcohol **297c**.



Scheme 65. *Reagents and conditions:* (a) H_2, Lindlar cat., quinoline, MeOH, 40 °C, 24 hrs, 0%; (b) ethynylmagnesium bromide, THF, -78 °C to r.t., 15 hrs, 100%; (c) H_2, Lindlar cat., quinoline, MeOH, 40 °C, 24 hrs, 82%; (d) H_2, Lindlar cat., quinoline, MeOH, 40 °C, 24 hrs, 0%.

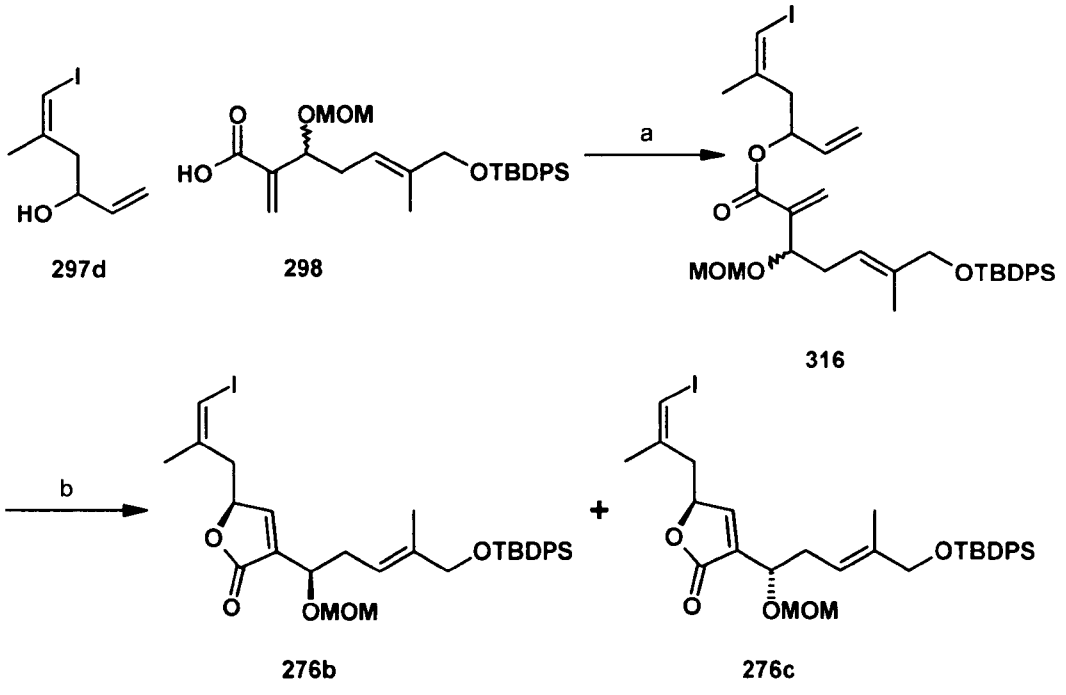
To eliminate this problem, the allylic alcohol **297d** was synthesised in racemic form following the same synthetic sequence shown in Scheme 63 for the corresponding *E*-vinyl iodide **297b**. The synthesis of the α,β-unsaturated carboxylic acid **298** portion is shown in Scheme 66 and commenced from the simple propanal **278**, produced by TBS-protection of commercially available 1,3-propanediol **284a** with oxidation of the alcohol function utilising the Swern reaction.[205,244] The TBS-protected propanal **278** could then be used in a Baylis-Hillman reaction[234] with methyl acrylate **300** in the presence of DABCO to form the alcohol **313a**. Protection of the secondary alcohol functionality in **313a** was achieved utilising MOM-Cl in the presence of DIPEA as a base, to produce the MOM-ether **313b**. Upon treatment of intermediate **313b** with the mildly acidic conditions of PPTS in MeOH and DCM, the TBS-protecting group was selectively removed to give the primary alcohol **313c**. Oxidation of the alcohol function was simply achieved using DMP which rapidly formed the aldehyde substituent. Direct treatment of the aldehyde functional group with the formyl phosphorane Wittig reagent **111**[198] produced the α,β-unsaturated aldehyde **314**. A regioselective $NaBH_4$ reduction at 0 °C upon the aldehyde functionality of intermediate **314** produced the allylic alcohol **315a**, albeit in a slightly disappointing 57% yield. Protection of the allylic alcohol **315a** as the TBDPS-silyl ether was achieved utilising the Corey conditions of, TBDPS-Cl and imidazole in DMF,[138] to produce the silyl-ether **315b**. The final step to produce the α,β-unsaturated carboxylic acid **298** was the saponification of the α,β-unsaturated ester **315b** using 1M LiOH in THF-H_2O.



Scheme 66. *Reagents and conditions:* (a) DMP, $NaHCO_3$, CH_2Cl_2, r.t., 30 mins; (b) vinylmagnesium bromide, THF, -78 °C, 1 hr, 45% (over 2 steps); (c) DABCO, r.t., 4 days, 51%; (d) MOM-Cl, DIPEA, CH_2Cl_2, 30 °C, 24 hrs, 89%; (e) PPTS, CH_2Cl_2, MeOH, r.t., 18 hrs, 85%; (f) DMP, CH_2Cl_2, r.t., 45 mins; (g) **111**, PhH, 80 °C, 24 hrs, 72% (over 2 steps); (h) $NaBH_4$, MeOH, 0 °C, 10 mins, 57%; (i) TBDPS-Cl, Im, DMF, 0 °C, 10 mins, 100%; (j) 1M LiOH, THF, H_2O (2:1), r.t., 24 hrs, 100%.

The carboxylic acid **298** could now be coupled with the previously synthesised allylic alcohol **297d** (Scheme 67). Therefore, the allylic alcohol **297d** and the α,β-unsaturated carboxylic acid **298** were treated with DCC in the presence of DMAP as a catalyst to form the allylic ester **316**.[233] This produced the metathesis precursor **316** which was subjected to Grubbs 2nd generation catalyst **294**[217] in refluxing DCM, under high dilution conditions (3 mM) and utilising a long addition period (8 hrs). Gratifyingly,

after a period of 48 hrs under the reaction conditions, the required butenolide functionality was furnished as separable diastereoisomers **276b** and **276c**, albeit in a slightly disappointing 33% yield.[230]

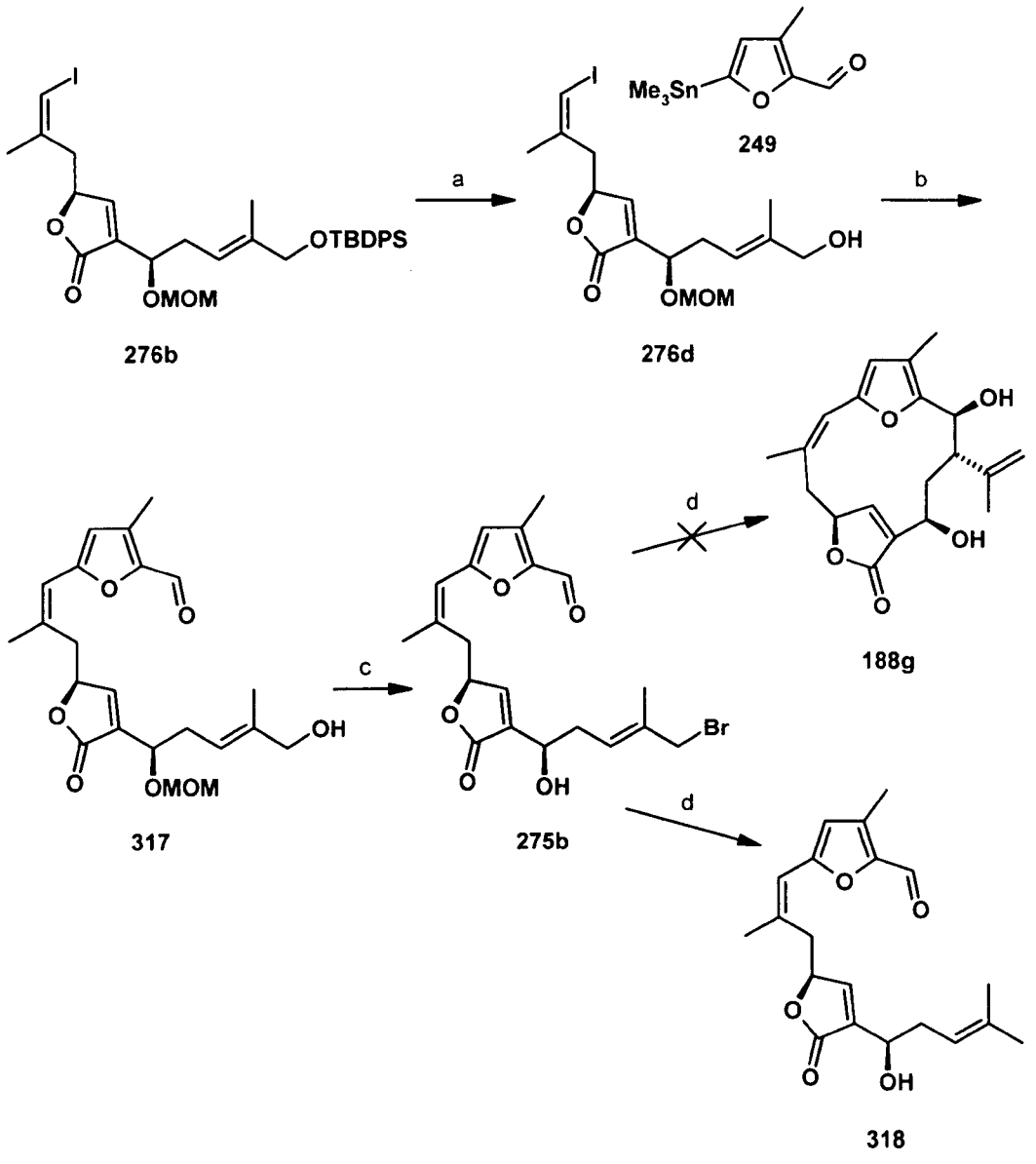


Scheme 67. *Reagents and conditions:* (a) DCC, DMAP, CH_2Cl_2, r.t., 24 hrs, 99%; (b) Grubbs 2nd generation catalyst **294**, CH_2Cl_2, 40 °C, 48 hrs, 33%.

Both diastereoisomers **276b** and **276c** have very similar spectral data and it is very difficult to ascertain which product is due to the *anti*- and *syn*-diastereoisomer. For this reason both the diastereoisomers were utilised in the attempted formation of the macrocyclic precursor **275b**. Thus, the butenolide **276b** was deprotected using the mild HF.Py complex in the presence of extra pyridine as a base to form the subsequent allylic alcohol **276d**. Stille cross-coupling[131,194,195] between the vinyl iodide functionality in **276d** and the stannylfuran aldehyde **249** using $Pd(Ph_3P)_4$ and CuI in DMF at room temperature, produced the alkenylfuran aldehyde **317** in 60% yield. Unlike the previous synthesis of bipinnatin J (**5**)[110,196] the Stille reaction had to be conducted without the use of CsF. With the additive present the allylic alcohol **276d** underwent rapid decomposition. The allylic alcohol substituent in **317** could be

transformed into the corresponding allylic bromide **275b** by exposure to CBr_4 and Ph_3P in THF. Disappointingly a low yield (40%) was obtained for this reaction and the material obtained was devoid of the MOM-ether protecting group. This unwanted side-reaction was presumably due to the formation of a small quantity of HBr during the reaction which subsequently deprotected the MOM-ether. Reprotection of the secondary alcohol was attempted with a range of functional groups but all were unsuccessful. Even though a low yield was obtained for the formation of the allylic bromide **275b**, enough material was generated to test the key NHK macrocyclisation process.[180-182] Exposure of the allylic bromide **275b** to $CrCl_2$ under high dilution conditions in the presence of 4 Å molecular sieves did unfortunately not produce any of the required macrocyclic compound **188g** or return any of the starting material **275b**. The only material isolated from the reaction was compound **318** produced *via* direct reduction of the allylic bromide functionality (Scheme 68). The reason the macrocycle **188g** was not observed is presumably due to the presence of the secondary alcohol functional group which provides the protic source for the reduction and simultaneously caused *in-situ* formation of the stable chromium-oxygen bond. Quenching the chromium allyl species in this manner stopped the required macrocyclisation process from occurring *via* the 6-membered transition state with the furan aldehyde substituent. Due to the dearth of material further analysis to fully investigate and alter the outcome of the NHK reaction to produce *Z*-deoxybipinnatin G (**188e**) was not possible.

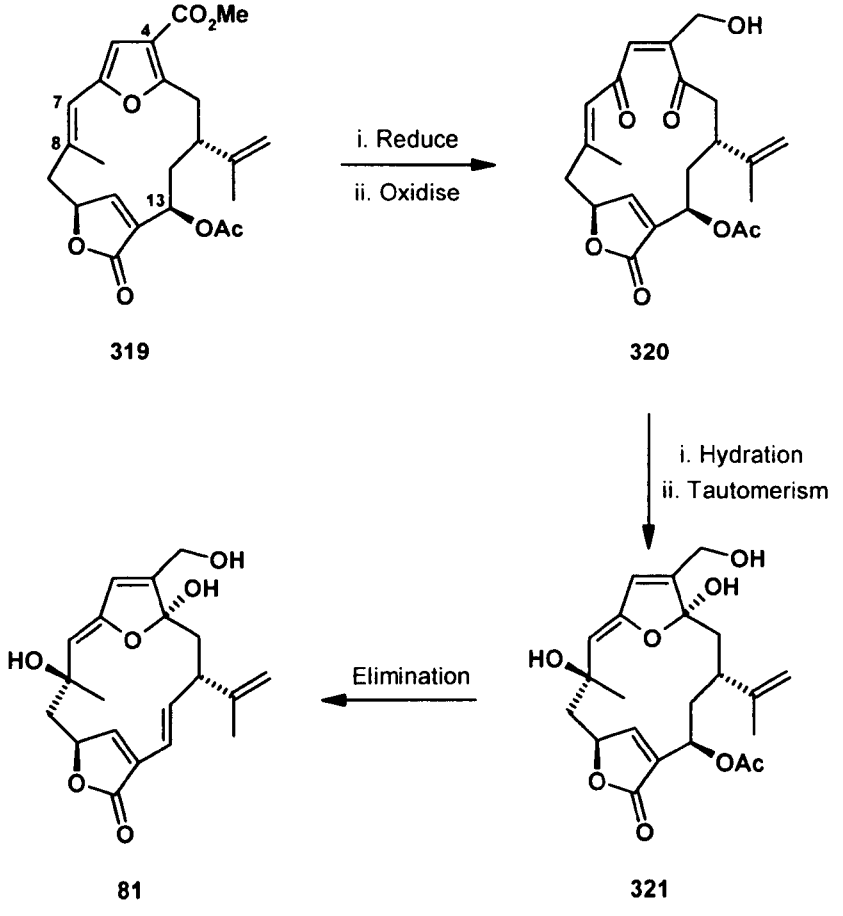
Unfortunately deoxybipinnatin G (**188b/ 188e**) could not be produced, which halted the chemistry to examine the proposed biomimetic transformation into bielschowskysin **1** and verrillin **2**.



Scheme 68. *Reagents and conditions:* (a) HF.Py, Py, THF, r.t., 24 hrs, 77%; (b) **249**, $Pd(PPh_3)_4$, CuI, DMF, r.t., 20 hrs, 60%; (c) CBr_4, Ph_3P, THF, 0 °C, 30 mins, 40%; (d) $CrCl_2$, 4 Å MS, THF, r.t., 16 hrs, 0%.

The results obtained utilising the RCM process in the formation of the butenolide functionality on both model systems, *i.e.* **305** and **309**, and the real substrate **276b** gave hope that it could also be applied as a macrocyclisation process. Therefore, an alternative synthetic study was run in parallel to the attempted formation of deoxybipinnatin G (**188b/ 188e**). The study attempted to form the furanocembrane

macrocyclic structure of *bis*-deoxylopholide **319**[123] utilising a RCM process *en route* to plumarellide **3** *via* the enol ether **81**.



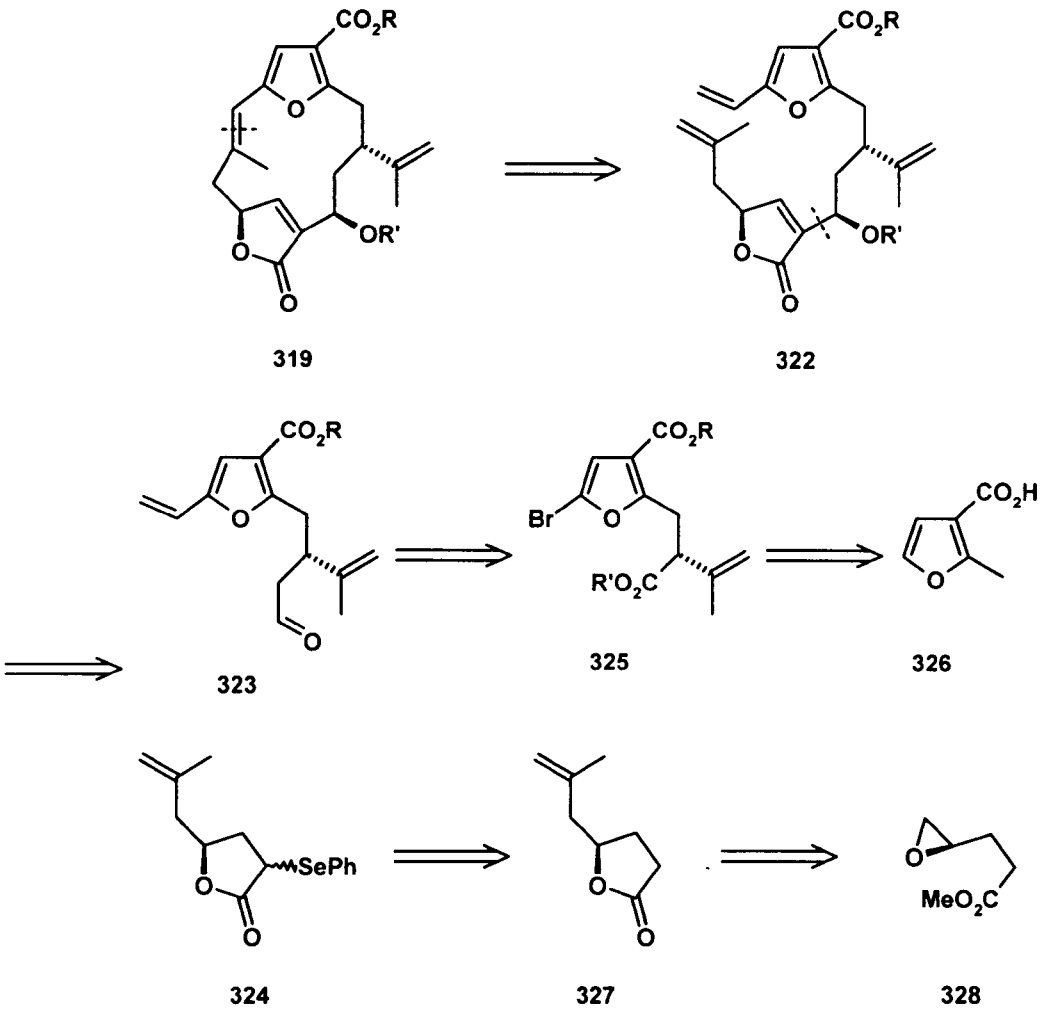
319 **320** **81** **321**

Scheme 69. Proposed formation of enol ether **81**, a precursor to verrillin **3**, from *bis*-deoxylopholide **319**.

As described earlier in the *Discussion* (Scheme 33), plumarellide **3**[3] could be produced from the enol ether **81** which, in-turn, could be formed from *bis*-deoxylopholide **319** (Scheme 69). Reduction of the C4 ester group in **319**, followed by directed oxidative cleavage of the furan ring leads to dienedione intermediate **320**. Hydration of the $\Delta^{7,8}$-alkene bond with subsequent tautomisation next produces enol ether **321**, which upon elimination of the C13 acetoxy functionality forms the conjugated butenolide **81**, a precursor to plumarellide **3**. The furanobutenolide *bis*-deoxylopholide **319** contains an *E*-$\Delta^{7,8}$-alkene bond to allow implementation a RCM process directly on the macrocycle. Disconnection of the alkenylfuran moiety in **319**,

as shown in Scheme 70, produces the vinylfuran **322**. It was hoped that the conformational bias inherent in the intramolecular RCM process would induce formation of the furanocembrane macrocycle **322**. Disconnection of vinylfuran **322** gives the aldehyde **323** and the phenylselenide **324**, which could be coupled together in a similar manner to that previously used within the research group during the synthesis of *bis*-deoxylophotoxin **242**.[170,193] The two components, *i.e.* **323** and **324**, could be produced from commercially available furan **326** and the known epoxide **328**,[193] respectively. The aldehyde intermediate **323** could be produced by homologation of the ester functionality and implementation of a sp^2-sp^2 coupling, *e.g.* a Stille cross-coupling reaction, on the bromofuran **325**. Elaboration of the simple furan, 2-methyl-3-furoic acid **326**, *via* selective bromination processes and a deconjugative addition should produce the bromofuran **325**. Removal of the phenylselenium substituent in **324** produces the corresponding lactone **327**. Nucleophilic addition of an isopropenyl functional group into the known epoxide **328**, followed by lactonisation should produce the lactone **327**. Coupling of the phenylselenide **324** with the aldehyde **323** would generate the vinylfuran **322** *en route* to *bis*-deoxylophodione **319**.

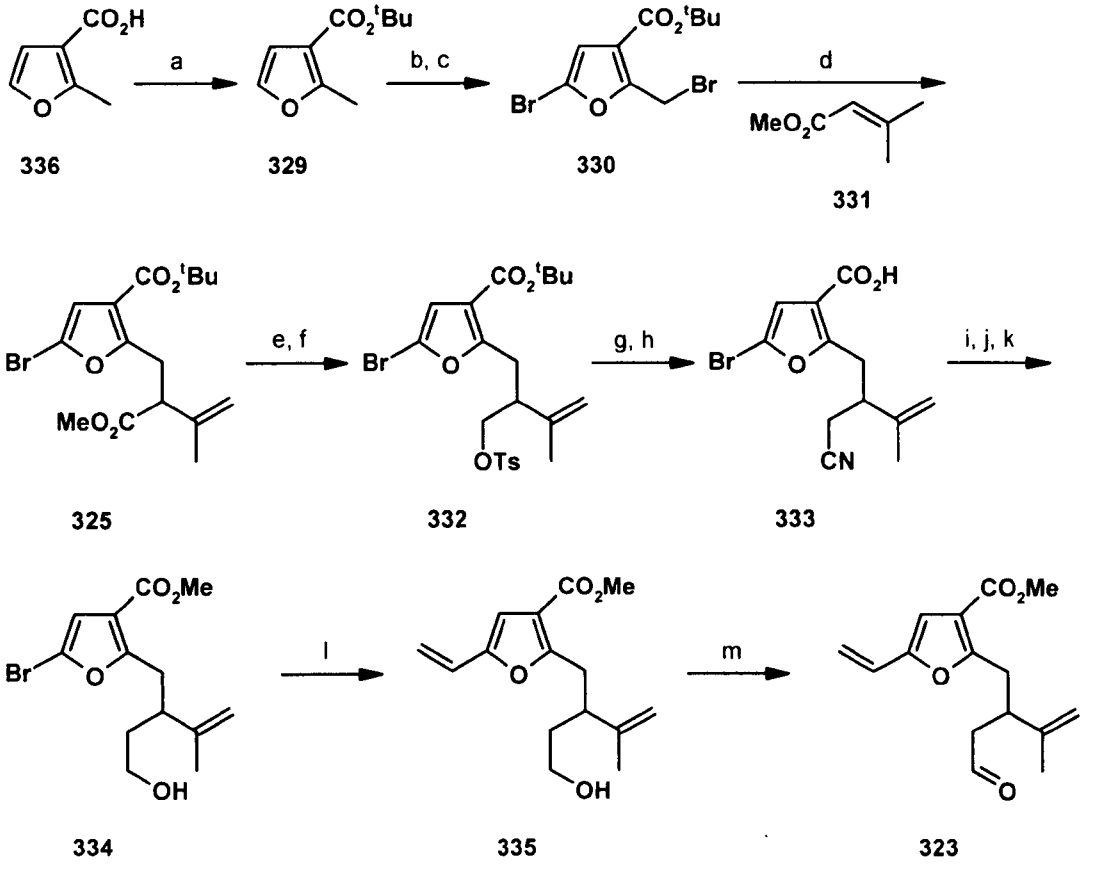
The synthesis of *bis*-deoxylopholide **319** started from commercially available 2-methyl-3-furoic acid **326** (Scheme 71). Treatment of **326** with 2-methylpropene catalysed by H_2SO_4 resulted in esterification of the carboxylic acid and formation of the ^{t}butyl ester **329**.[245] Addition of NBS to **329** in DMF next led to bromination at the 5-position of the furan ring which, upon allylic radical bromination with NBS and AIBN in refluxing CCl_4, gave the dibromofuran **330**.[246,247] Deprotonation of the



Scheme 70. Retrosynthesis of *bis*-deoxylopholide **319**.

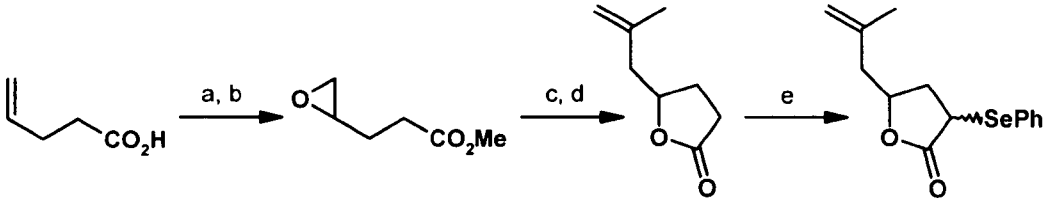
α,β-unsaturated ester **331** using LDA followed by addition of the dibromofuran **330**, allowed a deconjugative S_N2 displacement of the allylic bromide substituent, to form ester **325**.[193] The tosylate **332** was next produced by reduction of the ester functionality in **325** using $LiBH_4$ and treatment of the resulting alcohol with Ts-Cl, Et_3N and DMAP. The presence of the tosylate substituent set the stage for a one carbon homolygation of the side-chain. Thus, treatment of intermediate **332** with Et_4NCN, in DMSO at 60 °C led to displacement of the tosylate and formation of the nitrile functional group. Addition of TFA saponified the ^{t}butyl ester on the furan ring to produce the corresponding carboxylic acid **333**. Reduction of the nitrile functionality in the intermediate **333** to the corresponding alcohol **334** was achieved

over three relatively simple steps *i.e.* reduction of the nitrile **333** using DIBAL-H at -78 °C produced the aldehyde functionality, esterification of the carboxylic acid substituent with TMS-CHN_2 in methanol gave the ester and reduction of the aldehyde with $NaBH_4$ formed the alcohol **334**, in a combined 62% yield. The bromofuran moiety in the alcohol **334** could now be exploited in an intermolecular Stille cross-coupling reaction[194,195] using tributyl(vinyl)tin under Farina conditions, *i.e.* $Pd(OAc)_2$ and Ph_3As in DMF at 45 °C,[248] which produced the vinylfuran **335**. Finally, the alcohol functionality in **335** was oxidised to the corresponding aldehyde **323** using DMP. With the aldehyde **323** in hand, attention now turned to the synthesis of the phenylselenide intermediate **324**.



Scheme 71. *Reagents and conditions:* (a) 2-methylpropene, H_2SO_4, CH_2Cl_2, r.t., 24 hrs, 68%; (b) NBS, DMF, 0 °C, 10 mins, r.t., 20 mins, 50 °C, 30 mins, 92%; (c) NBS, AIBN, CCl_4, reflux, 12 hrs, 78%; (d) **331**, LDA, THF, -78 °C, 1 hr, then **330**, 1 hr, 58%; (e) $LiBH_4$, Et_2O, MeOH, 0 °C, 30 mins, 66%; (f) TsCl, Et_3N, DMAP, CH_2Cl_2, r.t., 16 hrs; (g) Et_4NCN, DMSO, 60 °C, 2 hrs, 78% (over 2 steps); (h) TFA, CH_2Cl_2, 0 °C to r.t., 90 mins; (i) DIBAL-H, PhMe, -78 °C, 15 mins; (j) TMS-CHN_2, MeOH, r.t., 10 mins; (k) $NaBH_4$, MeOH, r.t., 10 mins, 62% (over 4 steps); (l) tributyl(vinyl)tin, $Pd(OAc)_2$, Ph_3As, DMF, 45 °C, 17 hrs, 100%; (m) DMP, CH_2Cl_2, r.t., 75 mins, 93%.

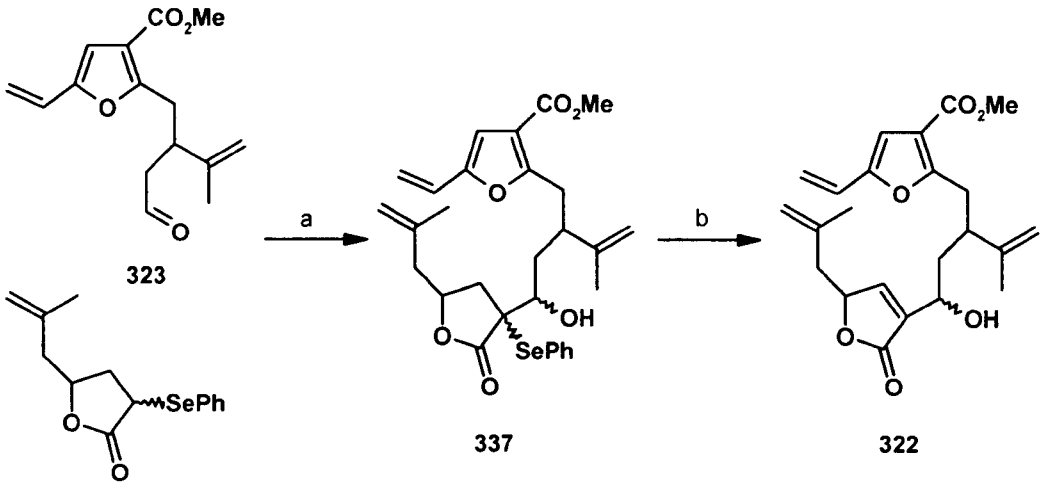
The synthesis of the phenylselenide intermediate **324** started from 5-pentenoic acid **336** (Scheme 72), which on treatment with thionyl chloride in methanol first gave the methyl ester.[249,250] Epoxidation of the terminal alkene in **336** was achieved using *m*CPBA in DCM leading to the epoxide **328** in a combined 75% yield.[251] The epoxide functionality in **328** then underwent Lewis acid catalysed ring opening upon treatment with $BF_3{\cdot}OEt_2$ and isopropenyl cuprate, generated *in-situ* from isopropenylmagnesium bromide and CuCN. This led to a secondary alcohol functionality which upon acid-catalysed lactonisation produced the lactone **327** in quantitative yield.[252] Deprotonation of the lactone **327**, utilising LiHMDS, generated the corresponding lithium enolate species which, on addition of PhSeBr, formed the phenylselenide intermediate **324**. This short synthesis provided the coupling partner to the aldehyde **323**.



336 **328** **327** **324**

Scheme 72. *Reagents and conditions:* (a) $SOCl_2$, MeOH, 0 °C, 25 mins; (b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, r.t., 15 hrs, 75% (over 2 steps); (c) isopropenylmagnesium bromide, CuCN, THF, -78 °C, 30 mins, then $BF_3{\cdot}OEt_2$, **328**, THF, 1 hr, 60%; (d) *p*-TSA, CH_2Cl_2, r.t., 30 mins, 100%; (e) LiHMDS, THF, -78 °C, 15 mins, then TMSCl, 30 mins, then PhSeBr, THF, -78 °C to r.t., 30 mins, 51%.

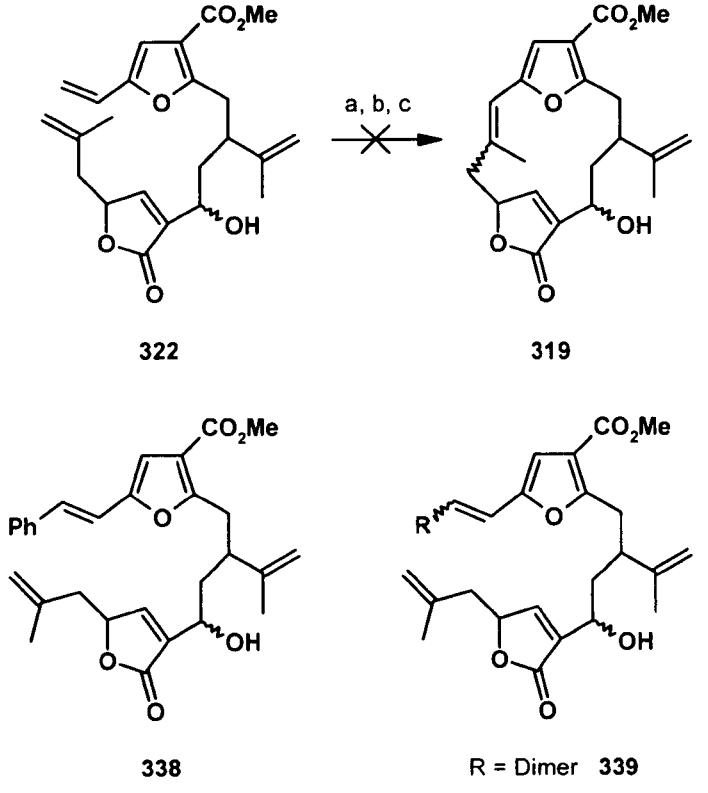
The next stage towards the RCM precursor **322** involved an aldol reaction (Scheme 73). Thus, deprotonation of the phenyl selenide **324** with LiHMDS at -78 °C produced the enolate species which, on addition of the aldehyde **323** led to the α-selenoester **337**. Oxidation of the phenylselenium unit in **337** with H_2O_2 and elimination of PhSeOH introduced the alkene bond in the butenolide intermediate **322**.[193] The synthesis of the vinylfuran **322** now allowed us to examine the RCM macrocyclisation process *en route* to *bis*-deoxylopholide **319**.



Scheme 73. *Reagents and conditions:* (a) **324**, LiHMDS, THF, -78 °C, then **323**, 1 hr; (b) H_2O_2, H_2O, CH_2Cl_2, pyridine, r.t., 1 hr, 48% (over 2 steps).

It was thought that the secondary alcohol substituent contained within the vinylfuran **322** was not in close enough proximity to the alkene functional groups to cause interference with the RCM process and hence, protection should not be required. To give the greatest chance for the RCM process to succeed the 2nd generation catalysts, *i.e.* **294** or **296**,[217,220] should be utilised. This is because the 1,1-disubstituted alkene substituent is less susceptible towards the metathesis process. Thus, the vinylfuran **322** was treated with Grubbs 2nd generation catalyst **294** in refluxing DCM, under high dilution, for 19 hrs but unfortunately the RCM reaction failed to produce the macrocyclic structure of *bis*-deoxylopholide **319**, shown in Scheme 74. Altering the solvent, temperature and catalyst loading had no desirable affect on the formation of the product **319**. After work-up and chromatography two 1, 2-disubstituted alkene compounds, *i.e.* **338** and **339**, were isolated from the reaction mixtures. The first compound was found to be the phenylvinylfuran **338**, which was produced when the catalyst reacts with the terminal alkene, was then unable to perform the RCM with the 1,1-disubstituted alkene and underwent a CM process with the styrene functionality of the pre-catalyst. The other compound formed was the dimer **339** of the intermediate

322 produced due to the catalysts' inability to react with the 1,1-disubstituted alkene, and undergo an intermolecular CM with another molecule of the vinylfuran **322**. The failure to produce the macrocycle **319** was solely due to the unreactive nature of the 1,1-disubstituted substituent towards all of the metathesis conditions examined.



Scheme 74. *Reagents and conditions:* (a) 5 mol% Grubbs 2nd generation catalyst **294**, CH_2Cl_2, 40 °C, 19 hrs; (b) 20 mol% Grubbs 2nd generation catalyst **294**, PhH, 40 °C, 2 hrs; (c) 20 mol% Grubbs 2nd generation catalyst **294**, PhH, 80 °C, 19 hrs.

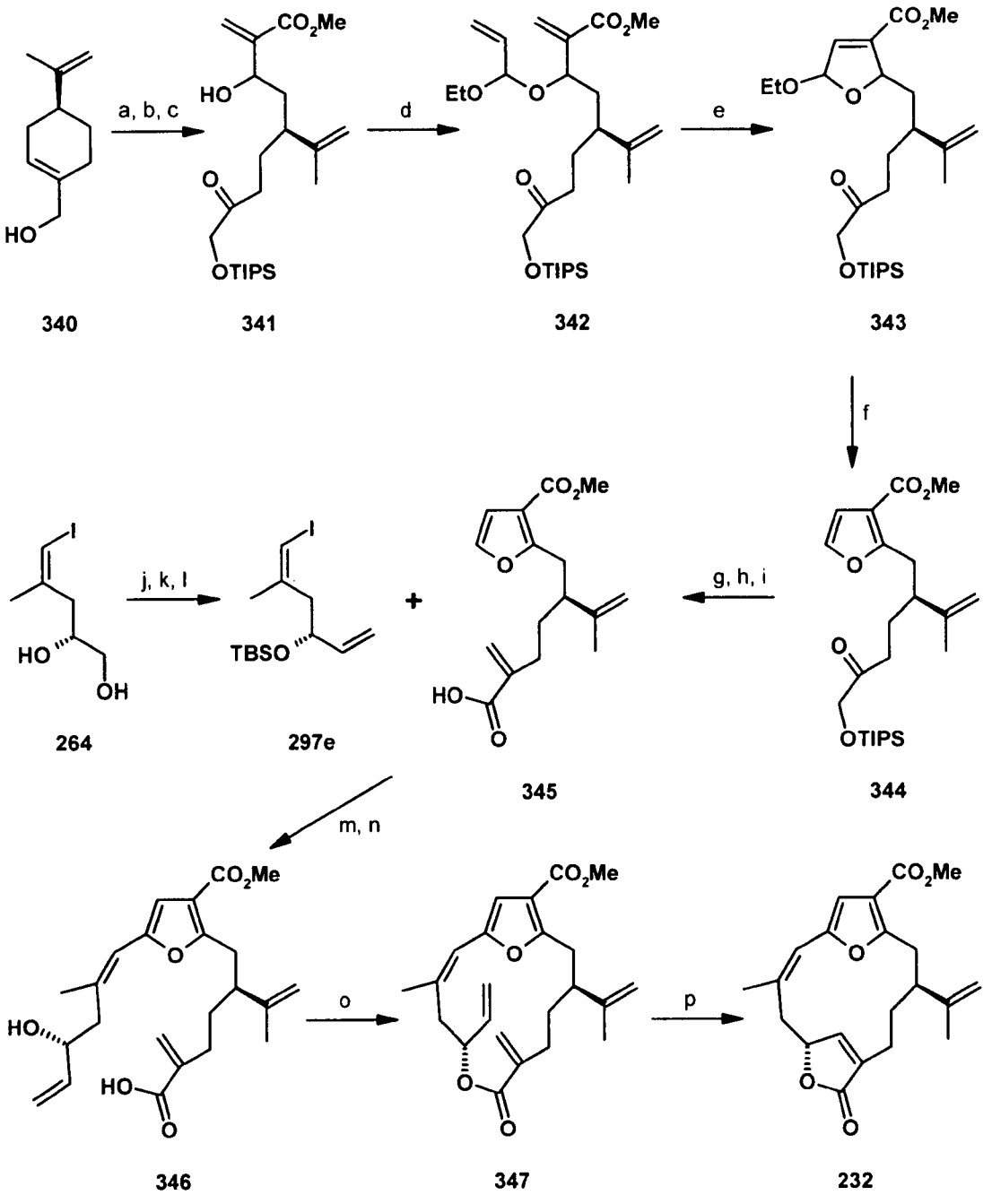
Unfortunately the attempted RCM did not lead to the furanocembrane macrocycle of *bis*-deoxylopholide **319**. With the metathesis strategy unsuccessful, another route towards a furanobutenolide – based cembranes will have to be pursued. Following the completion of our RCM studies Donohoe *et al.* published a synthesis of (–)-deoxypukalide **232** which used two RCM processes.[253]

The 2008 publication by Donohoe *et al.* complemented the earlier synthetic work of Marshall *et al.*[187] leading to (–)-deoxypukalide **232**.[253] Thus Donohoe *et al.*, utilised

two RCM processes and a Negishi cross coupling reaction, in a concise 12 steps synthesis of **232** (Scheme 75). The synthesis commenced from *S*-perillyl alcohol **340**, which had its primary alcohol functional group protected as the corresponding TIPS-ether. A regioselective ozonolysis of the trisubstituted alkene in the presence of pyridine and isoprene formed the aldehyde functionality, which upon treatment with a vinylalane intermediate, generated *in situ*, produced the secondary alcohol **341**. Formation of the mixed acetal **342** was achieved by treatment of the secondary alcohol **341** with acrolein diethylacetal under acidic conditions. Exposure of intermediate **342** to Grubbs 2nd generation catalyst **394**[217] in refluxing DCM followed by addition of the mildly acidic PPTS, induced aromatisation of cyclic hemi-acetal **343** next led to the furan **344** in a combined 85% yield. The carboxylic acid **345** was produced from the furan **344** upon Wittig olefination of the ketone functionality, deprotection of the primary alcohol with TBAF, and TEMPO oxidation in the presence of $NaClO_2$ and NaOCl. This fragment was then used in a cross-coupling process, but first the protected allylic alcohol **297e** had to be prepared. A regioselective sulfonylation was performed on the vicinal diol **264** (previously prepared in our synthesis of (+)-intricarene **4**)[110] using a hindered sulfur electrophile, which upon elimination produced an epoxide functionality. Ring opening of the epoxide, and alkene formation was achieved upon treatment with trimethylsulfonium iodide and ^{n}BuLi. Upon protection of the allylic alcohol as its TBS-silyl ether **297e**, by treatment with TBSCl and imidazole in DMF, the stage was now set to combine the two fragments. Thus, deprotonation at the C5-postion of the furan ring in the intermediate **345** which, on addition of $ZnBr_2$, quenched the lithiated species to produce the zincate *in situ*.[199] Directed treatment of the zincate with the vinyl iodide **297e** and $PdCl_2$(dppf) at 50 °C for 4 hours then gave the alkenylfuran

functionality,[200,201] which upon deprotection of the secondary alcohol produced the macrocyclic precursor, *i.e.* the allylic alcohol **346**. Macrolactonisation of the allylic alcohol **346** was achieved utilising the procedure developed by Shiina *et al.*[254] leading to the macrocyclic ester **347**. Upon exposure of **347** to Grubbs 2nd generation catalyst in refluxing toluene, the RCM process ensued to form the butenolide functionality and hence (–)-(*Z*)-deoxypukalide **232** in 72% yield.

Unfortunately, neither of the attempted NHK reactions and the RCM processes with intermediates **275b** and **322** led to macrocyclisation and the formation of deoxybipinnatin G (**188b**/ **188e**) and *bis*-deoxylopholide **319**, respectively. In order for us to evaluate the proposed biomimetic formation of bielschowskysin **1** *via* the enol ether cyclic hemi-ketal **69** we now decided that a furanobutenolide – based cembrane macrocycle must first be produced. This study is described below.



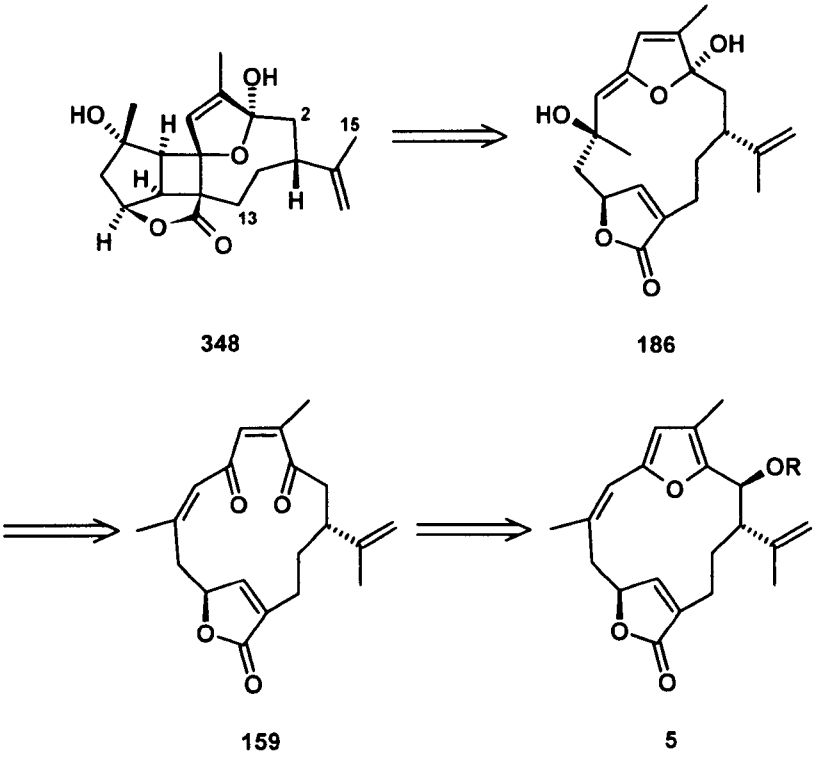
Scheme 75. *Reagents and conditions:* (a) TIPSCl, Im, DMF, r.t., 3 hrs, 98%; (b) O_3, Py, isoprene, MeOH, CH_2Cl_2, -78 °C, then Me_2S, -78 °C to r.t., 24 hrs; (c) methyl propiolate, DIBAL-H, HMPA, THF, 0 °C, 1.5 hrs, then 45 °C, 16 hrs, 49% (over 2 steps); (d) PPTS, acrolein diethylacetal, r.t., 1 hr; (e) Grubbs 2nd generation catalyst, CH_2Cl_2, reflux, 16 hrs; (f) PPTS, CH_2Cl_2, reflux, 2 hrs, 85% (over 3 steps); (g) $BrPh_3PMe$, ^nBuLi, THF, r.t., 30 mins, then **344**, THF, r.t., 2 hrs, 97%; (h) TBAF, THF, r.t., 2 hrs, 98%; (i) TEMPO, $NaClO_2$, NaOCl, MeCN, H_2O, 35 °C, 48 hrs, 95%; (j) Trisylimid, NaH, THF, r.t., 1 hr; (k) Me_3SI, ^nBuLi, THF, -10 °C, 3.5 hrs, 85% (over 2 steps); (l) TBSCl, Im, DMF, r.t., 2 hrs, 97%; (m) **345**, LDA, THF, -78 °C, 1 hr, then $ZnBr_2$, THF, 45 mins, then **297e**, $PdCl_2$(dppf), THF, 50 °C, 4 hrs; (n) TBAF, THF, 50 °C, 2 hrs, 78% (over 2 steps); (o) MNBA, Et_3N, DMAP, CH_2Cl_2, r.t., 19 hrs, 73%; (p) Grubbs 2nd generation catalyst **294**, PhMe, reflux, 16 hrs, 72%.

Formation of 19-hydroxyrubifolide 353 *via* oxidative cleavage of rubifolide 49

With the problems encountered thus far, it was decided to aim for a simpler furanobutenolide macrocyclic structure, containing all the relevant functionality in order to form the cyclobutane tetracyclic core of bielschowskysin **1**. Attention turned to the simplified bielschowskysin core structure **348** shown in Scheme 76, which was devoid of the C13-actoxy functionality and the 5-membered ring hemi-acetal between the C2,C15 positions. This target structure could be produced by cleavage of the cyclobutane core *via* a retro-[2+2] cycloaddition into the enol ether cyclic hemi-ketal **186**. As shown previously, oxidative cleavage of the furan ring of the alkenylfuran **5** would produce the *Z,Z*-dienedione of isoepilophodione B (**159**), which upon hydration and tautomerism could form the required bielschowskysin core precursor, *i.e.* the enol ether **186**. The simplified furanobutenolide – based cembrane starting material is the natural product, bipinnatin J (**5**) which has been synthesised previously and therefore, it should be possible to produce the bielschowskysin core **348** *via* this compound.

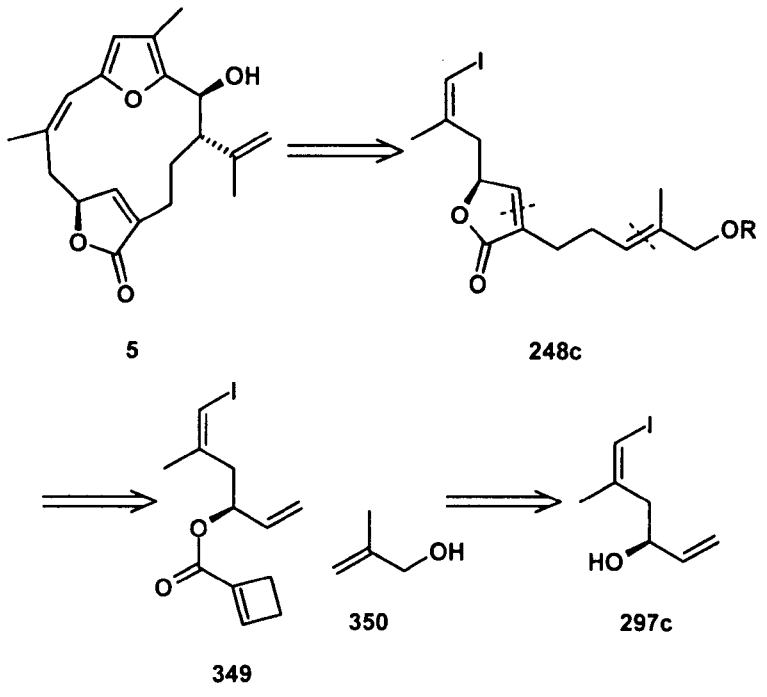
To date, the syntheses of bipinnatin J (**5**) have all been efficient and high yielding, *cf.* Trauner's 9 step synthesis,[196] however, following on from the work described earlier, it was thought that a metathesis process could be implemented to produce an even more expedient synthesis. The butenolide functionality was again selected as the focal point for this new metathesis chemistry (Scheme 77). As previously shown, bipinnatin J (**5**) can be disconnected back to the vinyl iodide **248c**, and our aim now was to form the butenolide and the allylic alcohol functionalities in a single metathesis process from the cyclobutene ester **349** and 2-methyl-2-propen-1-ol **350**. Esterification of the previously synthesised allylic alcohol **297c**, should form the cyclobutene ester **349**.

Production of bipinnatin J (**5**) will allow examination of the biomimetic conversion into the bielschowskysin core structure **348**.



Scheme 76. Retrosynthesis of the bielschowskysin core **348**.

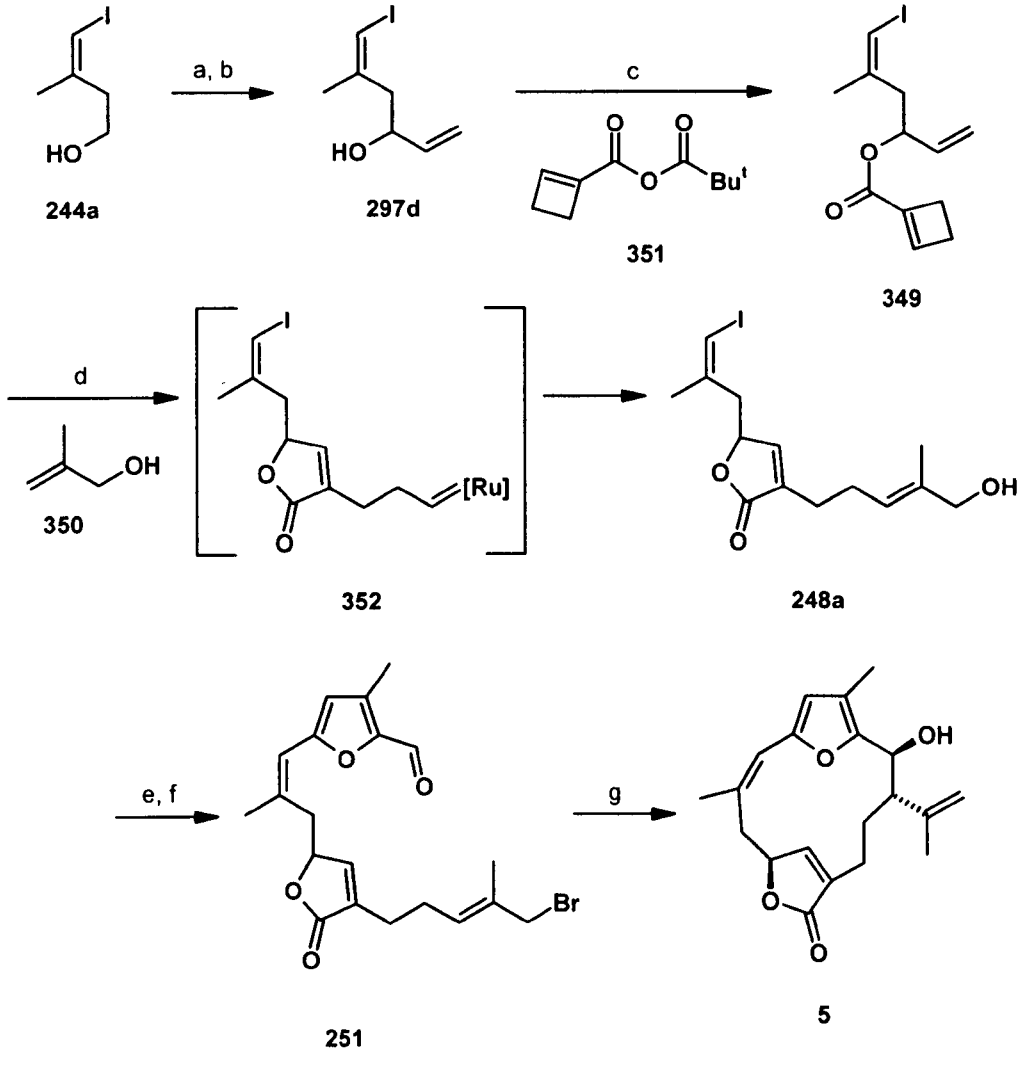
Our new approach to a synthesis of bipinnatin J (**5**) began with the vinyl iodide **244a**, which was produced from Negishi *anti*-carboalumination of commercially available 3-butyn-1-ol **243** (Scheme 78).[197] Oxidation of the primary alcohol group in **244a** followed by addition of vinylmagnesium bromide produced the allylic alcohol **297d** in a combined 45% yield. Treatment of 1-cyclobutene-1-carboxylic acid[255] with pivaloyl chloride in the presence of Et_3N next formed the mixed anhydride **351** *in-situ*, which was then added directly to the deprotonated alcohol functionality in **297d** to form the cyclobutene ester **349**.[256] Production of **349** allowed the key metathesis process to be



Scheme 77. Retrosynthesis of bipinnatin J (**5**) *via* the vinyl iodide **248c**.

analysed. Thus, treatment of the cyclobutene ester **349** with 2-methyl-2-propen-1-ol **350** in the presence of Grubbs 2nd generation catalyst **294**,[217] in refluxing DCM, under high dilution conditions and with slow addition of both the substrate and the catalyst produced the butenolide **248a** in a surprising 57% yield.[256] The butenolide was produced by addition of the catalyst to the terminal alkene functionality in the intermediate **349**. The catalyst was then able to trigger a simultaneous RCM/ ring-opening metathesis facilitated by the release of ring strain from the cyclobutene functional group, and form the butenolide substituent of the transient ruthenium species **352**. Finally, upon CM with 2-methyl-2-propen-1-ol **350** the required vinyl iodide **248a** was produced.[257-260] The substituted vinyl iodide has previously been shown to be an intermediate in the synthesis of bipinnatin J (**5**).[110,111,196] Therefore, we carried out a Stille cross-coupling between the vinyl iodide **248a** and the stannylfuran aldehyde **249** followed by immediate bromination of the resulting allylic alcohol functionality to give the macrocycle precursor **251**. Treatment of **251** under the

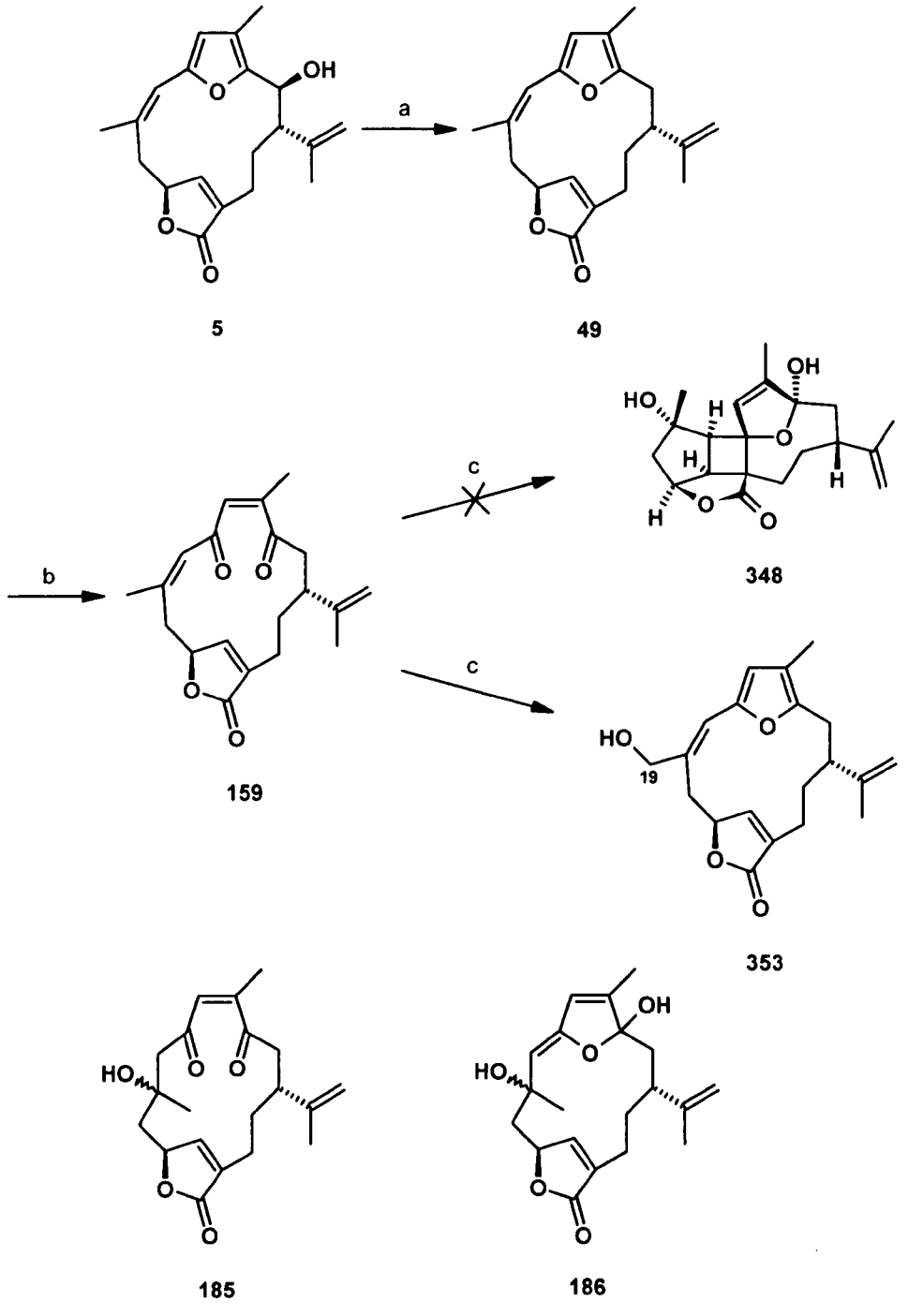
standard NHK reaction conditions then produced bipinnatin J (**5**), along with the *syn*-diastereoisomer at C1, in 70% yield. The formation of bipinnatin J (**5**) allowed the biomimetic transformation into the core structure of bielschowskysin **348** to be examined.



Scheme 78. *Reagents and conditions:* (a) DMP, $NaHCO_3$, CH_2Cl_2, r.t., 30 mins; (b) vinylmagnesium bromide, THF, -78 °C, 1 hr, 45% (over 2 steps); (c) LiHMDS, THF, -78 °C, 20 mins, then **351**, THF, 90 mins, 65%; (d) **350**, 10 mol% Grubbs 2nd generation catalyst **294**, CH_2Cl_2, reflux, 21 hrs, 57%; (e) 3-methyl-5-trimethylstannyl-2-furan aldehyde **249**, $Pd(PPh_3)_4$, CuI, DMF, r.t., 90 mins, 93%; (f) PPh_3, NBS, CH_2Cl_2, -5 °C, 20 mins, 83%; (g) $CrCl_2$, 4 Å MS, THF, r.t., 16 hrs, 70%.

The presence of the hydroxyl group next to the furan ring in **5** posed a problem since upon oxidative cleavage of the furan ring the dienedione product substituent would undergo cyclisation into the hydroxypyrone functionality, as shown during our

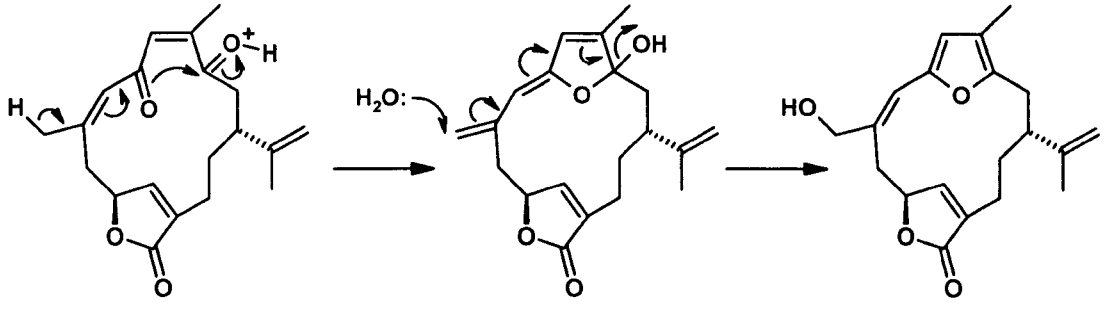
groups' synthesis of (+)-intricarene **4**.[110,111] Therefore, the hydroxyl functional group in **5**, along with the corresponding *syn*-diastereoisomer, was removed by treatment with TFA and Et_3SiH at 0 °C to induce an S_N1-deoxygenation process leading to rubifolide **49** as a single diastereoisomer (Scheme 79).[111] Oxidative cleavage of the furan ring in **49** was achieved upon addition of a peroxy reagent, *i.e. m*CPBA, which led to the dienedione functionality of isoepilophodione B (**159**). We had hoped that treatment of the dienedione **159** under the acidic conditions developed in the model system **163**, *i.e. p*-TSA in THF-H_2O would produce either rubifol **185**, the enol ether **186** or the bielschowskysin core **348**. Unfortunately however none of these structures were observed. The only compound to be isolated in 40% yield showed signals in the ^1H NMR spectroscopic data at δ_H 4.29 (d, *J* 16.9) ppm and 4.26 (d, *J* 16.9) ppm; ^{13}C DEPT NMR spectroscopic data showed the compound possessed one more CH_2 signal at δ_C 68.3 ppm and one less CH_3 signal from δ_C 22.9 ppm, on comparison to the dienedione **159**; ^1H-^1H COSY NMR spectroscopic data displayed a resonance at δ_H 6.14 ppm which correlated to δ_H 1.94 ppm, indicating that the furan ring had been re-introduced. Another resonance at δ_H 4.91 ppm correlated to δ_H 1.75 ppm, which indicated that the isopropenyl functionality was still present, and finally, a resonance at δ_H 6.33 ppm correlated to δ_H 4.29/ 4.26 ppm and δ_H 3.17 ppm, indicating that the there was a trisubstituted $\Delta^{7,8}$-alkene bond; mass spectroscopy showed the compound had a molecular formula of $C_{20}H_{24}O_4$, identical to isoepilophodione B (**159**). All the data corresponded to the unusual structure of 19-hydroxyrubifolide **353**, which on comparison to the natural product rubifolide **49**, displayed similar spectroscopic data. This assignment was confirmed from the ^1H-^{13}C HMQC and ^1H-^{13}C HMBC NMR spectroscopic data.



Scheme 79. *Reagents and conditions:* (a) TFA, Et_3SiH, CH_2Cl_2, 0 °C, 20 mins, 93%; (b) *m*CPBA, CH_2Cl_2, 0 °C, 90%; (c) *p*-TSA, THF, H_2O, r.t., 72 hrs, 40%.

19-Hydroxyrubifolide **353** was thought to have been produced from isoepilophodione B (**159**) by protonation of the C3 carbonyl functionality under the acidic conditions (Scheme 80). Instead of nucleophilic addition of water into the dienedione **159**, which was observed in the model system **163**, a tautomerisation processes occurred to

produce the conjugated enol ether **354**. Nucleophilic addition of water into the conjugated enol ether functionality in **354** facilitated by the acidic conditions, or intramolecular allylic transposition, simultaneously introduced the alkenylfuran substituent and the hydroxyl group at C19 of the rubifolide analogue **353**. Interestingly, this has not yet been described in Nature! Possibly more fascinating was the fact that this was the first furanobutenolide – based cembrane product to possess oxygenation at the C19 position!



159 **354** **353**

Scheme 80. Proposed formation of 19-hydroxyrubifolide **353**.

Concluding remarks and possible future work

In conclusion, the first model studies with the dienedione **163** set the foundations for the proposed biomimetic formation of bielschowskysin **1**. Initial results demonstrated that the *Z*-dienedione functionality in **163** could be transformed into the β-hydroxyketone **165** and the vicinal diol **178**, presumably *via* the transient enol ether species **166**, under acidic conditions. Utilising iodine induced isomerisation to the corresponding *E*-dienedione **194** and finally the 4-hydroxycyclopent-2-enone **193** was produced under basic conditions. These results highlighted the utility of the dienedione functionality and the wide array of products which can be obtained. It was thought these processes could be applied to a macrocyclic structure to gain access to a range of natural products, particularly, bielschowskysin **1** and verrillin **2**.

Two syntheses were attempted towards the simplified macrocycles **102** and **125**, from the furanmethanol **113a**. The route to the first model system **102** was abandoned due to the difficulties which were encountered with the stabilities of various substrates. The second synthesis towards the macrocycle **125** proceeded without incident until a SmI_2 mediated Reformatsky-type macrocyclisation process proved difficult, but a 14-membered macrocyclic structure **142** was obtained. Due to a dearth of material further manipulation of the substrate **142** could not be performed. The furan **140b** also underwent oxidative cleavage of the furan ring leading to the enedione **143**. Treatment of the intermediate **143** under aqueous acidic conditions led to the furanmethanols **179** and **180**, presumably *via* the transient enol ether species **144** and **145**. No products due to an intramolecular [2+2] cycloaddition process or Michael addition/ ether-bridge formation were observed.

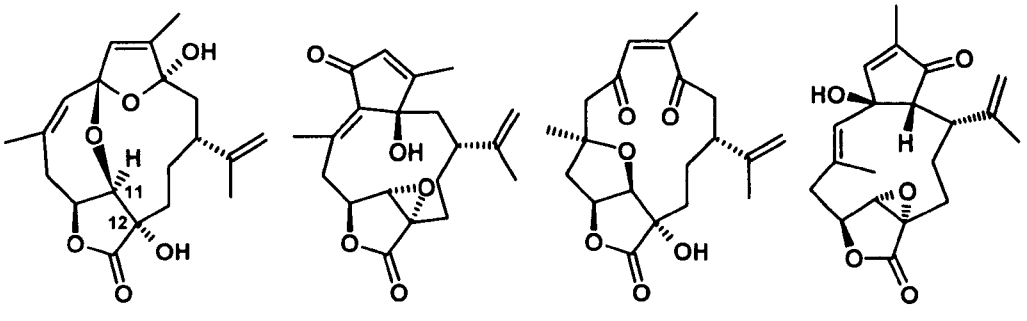
This result re-iterated that a macrocyclic structure was required to induce conformational bias and allow the anticipated [2+2] cycloaddition process between the enol ether and the butenolide substituent. Therefore, syntheses were attempted towards the highly oxygenated macrocyclic substrate of deoxybipinnatin G (**188b**/ **188e**). The study demonstrated that the presence of the C13 hydroxyl group makes the vinyl iodide intermediate **276** a lot more sensitive to basic reagents, in comparison to **248**. Initially, the aldol addition of a lithium enolate, *i.e.* **239** or **282**, into the β,γ-unsaturated aldehyde **277** proved problematic due to the extremely unstable nature of this intermediate. The next strategy utilised the mono-protected propanal **278** which successfully underwent the aldol addition and upon oxidation of the phenylselenium functionality, the α-hydroxyl butenolides **286a** and **286b** were produced as separable diastereoisomers. Unfortunately, further elaboration of the alcohol **286a** into the

allylic alcohol **276a** gave unsatisfactory results. This disappointing result led us to examine the use of the RCM process to form the butenolide substituent in **276b**. Initial results were promising as the model allylic esters **304** and **308** were transformed into the corresponding butenolide substituents **305** and **309** in 67% and 62% yields, respectively. Next, the RCM process was applied to the vinyl iodide **276b**. The metathesis precursor **316**, generated from 1,3-propanediol **284a** and 3-butyn-1-ol **243**, was exposed to Grubbs 2nd generation catalyst **294** in refluxing DCM and the butenolide functionality of intermediates **276b** and **276c** was produced in a disappointing 33% yield. Further elaboration of the butenolides **276b** and **276c** produced the macrocycle precursor **275b** but it lacked the protecting group on the C13-hydroxyl substituent. Unfortunately, the NHK macrocyclisation process failed to deliver the required macrocyclic furanocembrane **188g** and the acyclic structure **318** was observed instead. Further testing of the NHK process could not be achieved due to the dearth of material.

The route to deoxybipinnatin G (**188b/ 188e**) was run in parallel to a synthesis of *bis*-deoxylopholide **319** using a RCM macrocyclisation process. It was again hoped that the conformational bias inherent in the macrocyclic precursor **322** would allow the anticipated RCM process to occur. Thus, the macrocyclic precursor **322**, synthesised from the aldehyde **323** and the phenylselenium lactone **324**, was treated with Grubbs 2nd generation catalyst in refluxing DCM. Unfortunately, the RCM reaction failed to produce the required furanocembrane macrocycle **319** under all conditions tested, due to the lack of reactivity of 1,1-disubstituted alkene functional group in **322**.

Finally, we decided to form the more simple bielschowskysin structure **348** from a furanobutenolide precursor, *i.e.* bipinnatin J (**5**). An expedient synthesis of bipinnatin J (**5**) then ensued, which utilised a novel metathesis process to form the vinyl iodide **248a**. Further manipulation of **248a** produced bipinnatin J (**5**) which was converted into isoepilophodione B (**159**) *via* rubifolide **49**. Treatment of isoepilophodione B (**159**) under aqueous acidic conditions failed to form the bielschowskysin core **348** and instead produced the unusual rubifolide analogue **353** *via* a tautomerisation/ conjugate hydration sequence. The nucleophilic addition of water into the dienedione functionality in isoepilophodione B (**159**) could occur to produce rubifol **185**,[167] but conditions could not be found to induce this transformation.

The aim of the future work will be concerned with generating the natural product rubifol **185**.[167] This structure represents the key intermediate in the synthesis of multiple natural products, especially the bielschowskysin core **348**. The analogous structure which contains an epoxide functionality at the $\Delta^{11,12}$-butenolide alkene bond is reported to be the key intermediate in the biosynthesis of coralloidolide B (**355**),[174] C (**356**),[168] D (**357**)[168] and F (**195**).[175]

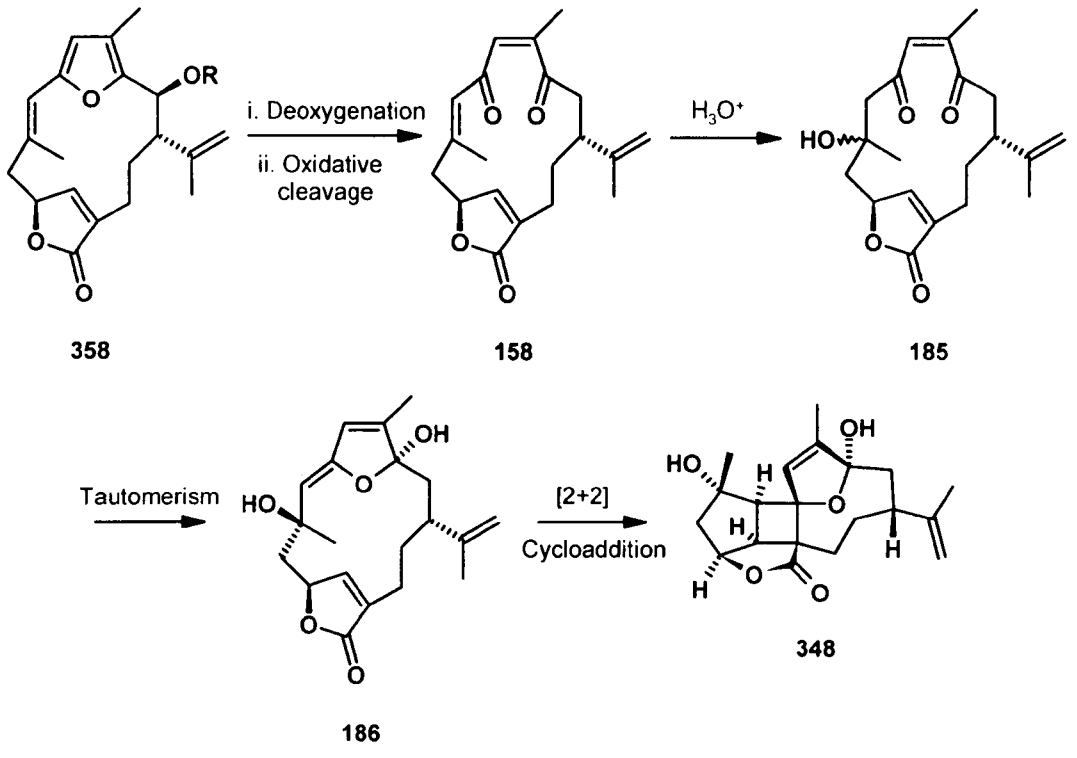


355 **356** **357** **195**

Rubifol **185** could be produced from the dienedione functionality in **159** by inhibiting the formation of the conjugated enol ether hemi-ketal structure **354**. Therefore, if the dienedione **159** were to increase the ring strain within the macrocycle, the extra

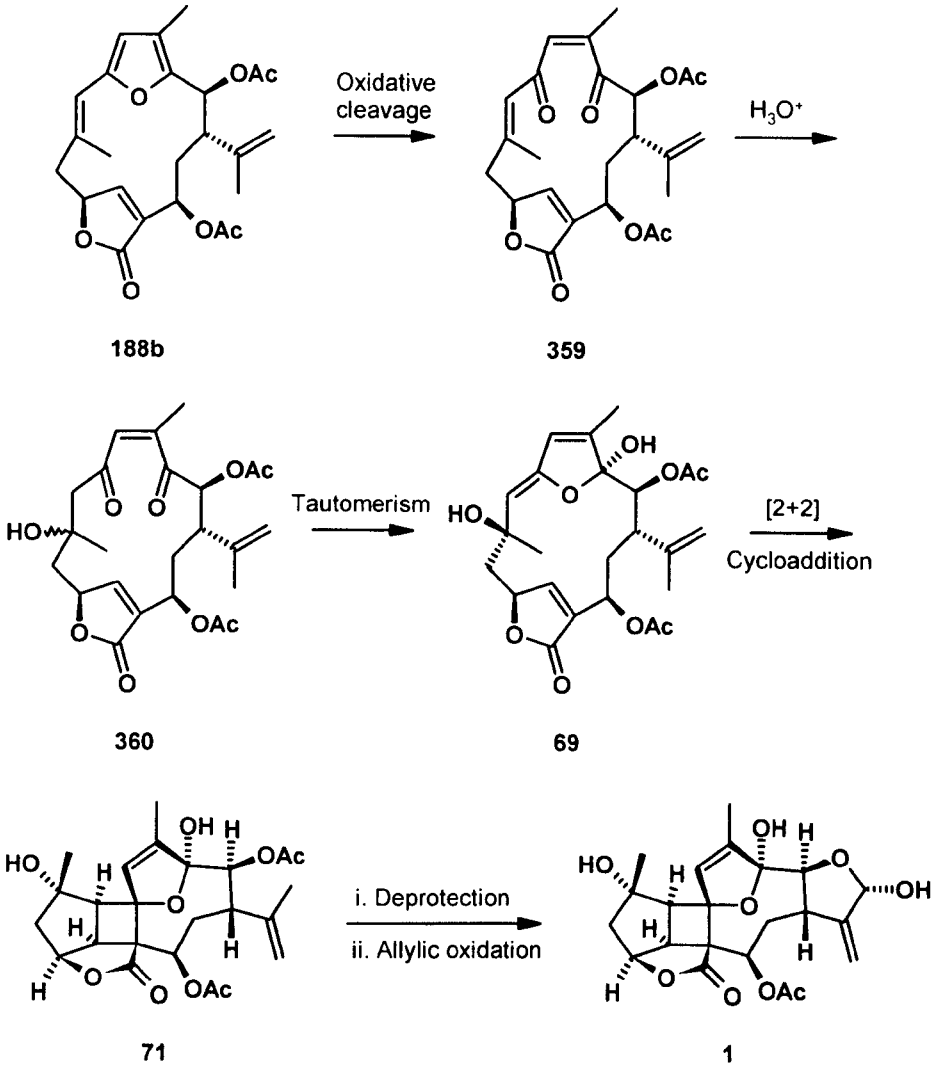
rigidity should reduce the production of the intermediate **354**. A more rigid macrocyclic dienedione can be achieved by simply altering the *Z,Z*-dienedione functionality in **159** to the corresponding *E,Z*-dienedione substituent **158**. This dienedione has also been isolated from natural sources, *i.e.* epilophodione **158**. The macrocyclic structure of epilophodione **158** could be produced from the corresponding *E*-$\Delta^{7,8}$-alkene isomer **358** of bipinnatin J (**5**), upon S_N1-deoxgenation and oxidative cleavage of the furan ring.[111] Alternatively, the previously synthesised isoepilophodione B (**159**) could undergo isomerisation in the presence of iodine, similar to that shown for the model dienedione **163**.[166] This process is less likely to be selective and could form a complex mixture of four isomeric products. Upon formation of epilophodione **158** its biomimetic transformation into the bielschowskysin core **348** could be examined (Scheme 81). Thus, treatment of the natural product **158** under the conditions developed in the model study, *i.e. p*-TSA in THF-H_2O, should form rubifol **185**[167] *via* acid catalysed nucleophilic addition of water into the C7,C8 alkene bond. Upon formation of rubifol **185**, tautomerisation, isomerisation and transannular [2+2] cycloaddition would produce the bielschowskysin core **348** *via* the enol ether cyclic hemi-ketal **186**.

Production of the cyclobutane containing structure **348** would then give precedence for the biomimetic conversion of a furanobutenolide structure into bielschowskysin **1**. Functionalisation of the furanobutenolide – based cembrane *E*-bipinnatin J (**358**) produces *E*-$\Delta^{7,8}$-deoxybipinnatin G (**188b**), which contains all the relevant functionality to obtain the polycyclic natural product **1**. Following the same sequence as Scheme 81, oxidative cleavage of the furan ring in **188b** would produce the



Scheme 81. Proposed future synthesis of the bielschowskysin core structure **348**.

dienedione **359**,[136] which upon hydration forms the β-hydroxyketone **360** (Scheme 82). Tautomerisation of the intermediate **360** would produce the transient enol ether **69** which *via* a [2+2] cycloaddition delivers the cyclobutane containing core of bielschowskysin **71**. Finally, selective deprotection of the C2 acetate protecting group and allylic oxidation of the isopropenyl substituent would form the hemi-acetal required for the natural product, *i.e.* **1**. Altering this procedure slightly could potentially deliver verrillin **2** *via* a Michael addition/ ether-bridge formation. These bioinspired transformations from *E*-deoxybipinnatin G (**188b**) should produce a wide array of natural products, specifically, bielschowskysin **1** and verrillin **2**.



Scheme 82. Proposed future synthesis of bielschowskysin **1** from *E*-deoxybipinnatin G (**188b**).

EXPERIMENTAL

Proton magnetic resonance chemical shifts (δ_H) are recorded in parts per million (ppm), are referenced to the residual solvent peak (δ_H = 7.27 for $CHCl_3$), and are recorded to two decimal places. Abbreviations used in the description of resonances are, s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad). Coupling constants (*J*), are reported to the nearest 0.1 Hz. Proton magnetic resonance spectra were recorded on a Bruker DPX300 (300.13 MHz), Bruker DPX360 (360.13 MHz), Bruker DPX400 (400.20 MHz), Bruker AV400 (400.13 MHz), Bruker AV(III)400 (400.07 MHz) or Bruker AV(III)500 (500.13 MHz) spectrometer, at ambient temperature, unless otherwise stated. All assignments are confirmed by ^1H-^1H COSY and ^1H-^{13}C HMQC correlations where necessary.

Carbon magnetic resonance chemical shifts (δ_C) are recorded in parts per million (ppm), are referenced to the residual solvent peak (δ_C = 77.0 for $CDCl_3$), and are recorded to one decimal places. Assignments were made on the basis of chemical shifts using the DEPT sequence with secondary pulses at 90° and 135°, where appropriate. In the spectroscopic data, C refers to quaternary carbon, CH to tertiary methine, CH_2 refers to secondary methylene and CH_3 to primary methyl. Carbon magnetic resonance spectra were recorded on a Bruker DPX300 (75.47 MHz), Bruker DPX360 (90.03 MHz), Bruker DPX400 (100.63 MHz), Bruker AV400 (100.61 MHz) or Bruker AV(III)500 (125.63 MHz) spectrometer, at ambient temperature, unless otherwise stated. All assignments are confirmed by ^1H-^{13}C HMQC correlations and DEPT analysis where necessary.

Infra-red spectra were recorded using a Perkin-Elmer FT 1600 spectrometer as dilute solutions in spectroscopic grade chloroform. Absorption maxima (ν_{max}) of the major peaks detected are reported in wavenumbers (cm^{-1}), quoted to the nearest integral wavenumber.

Mass spectra were recorded on a VG Autospec MM-701CF or Mircomass LCT spectrometer using electron ionisation (EI), fast atom bombardment (FAB), or electrospray (ESI) techniques. High-resolution mass spectra are calculated from the molecular formula corresponding to the observed signal using the most abundant isotopes of each element. Only molecular ions and other significant peaks/ fragments are reported and are quoted as a percentage of the base peak. Some mass spectra were recorded by the mass spectrometry service. These machines have a tolerance of ±5 ppm and only formulae within ±5 ppm are quoted. All mass spectrometry data is high resolution and quoted to four decimal places.

Optical rotations were recorded on a JASCO DIP 370 polarimeter and melting points were measured on a Bibby^{TM} Stuart Scientific SMP3 melting point apparatus. The melting points given are reported to the nearest °C and are uncorrected.

Thin Layer Chromatography (TLC) was carried out using Merck aluminium foil backed plates pre-coated with silica gel 60 F_{254} (1.05554.0001). Visualisation was effected *via* ultraviolet florescence quenching (λ_{max} = 254 nm) and then developed with either basic potassium permanganate solution or acidic alcoholic verrillin solution, followed by heating. Retention factors (R_f) are quoted to two decimal places. Flash column chromatography was performed using ICN silica 32-63, 60 Å.

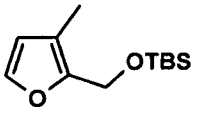
Unless stated otherwise, reactions requiring anhydrous conditions were conducted under an inert atmosphere of nitrogen in flame-dried or oven-dried apparatus. When necessary, solvents were dried prior to use. Anhydrous THF was obtained by distillation from sodium/ benzophenone, under a nitrogen atmosphere, or *via* filtration through a nitrogen pressurised, basic, activated, 58 Å aluminium oxide column. Anhydrous DCM was obtained by distillation over calcium hydride, under a nitrogen atmosphere. Anhydrous diethyl ether was obtained *via* filtration through a

nitrogen pressurised, basic, activated, 58 Å aluminium oxide column. Anhydrous *N*, *N*-dimethylformamide (DMF) was purchased from Aldrich. Petrol refers to the fraction of light petroleum ether boiling between 40 – 60 °C unless otherwise stated. Evaporation of solvents was achieved using a Büchi rotavapor R-200.

All reagents used were purified according to C. L. L. Chai and W. L. F. Armarego "Purification of Laboratory Chemicals" Elsevier Science Plc, fifth edition, 2003 or used as obtained from commercial sources. All chemical were handled and all procedures were carried out in accordance with the "Organic Chemistry Research General Safety Manual", Nottingham University, September 2005 booklet.

I thank Dr. C. D. Bray for supplying a sample of the bromofuran **334**, and Dr. Yi Li for the 2D NMR spectroscopic data of 19-hydroxyrubifolide **353**.

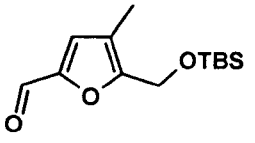
tert-Butyl-dimethyl-(3-methyl-furan-2-ylmethoxy)-silane 113b



tert-Butyldimethylsilyl chloride (6.96 g, 46.2 mmol) was added in one portion to a stirred solution of (3-methyl-furan-2-yl)-methanol **113a**[137] (4.71 g, 42.0 mmol) and imidazole (3.43 g, 50.4 mmol) in anhydrous DMF (11 mL) at 0 °C under a nitrogen atmosphere, and the mixture was then stirred at this temperature for 10 mins. Direct purification by chromatography on silica gel, using 2% diethyl ether in petroleum ether as eluent, gave the *TBS-protected alcohol* (9.13 g, 96%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2929, 2857, 1462, 1362, 1059; δ_H (400 MHz): 7.29 (d, 1H, *J* 1.8, C*H*(O)=CH), 6.20 (d, 1H, *J* 1.8, C=C*H*CMe), 4.62 (s, 2H, CH_2OTBS), 2.05 (s, 3H, C=CHC*Me*), 0.92 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.09 (s, 6H, Si(*Me*)$_2$^{t}Bu); δ_C (100

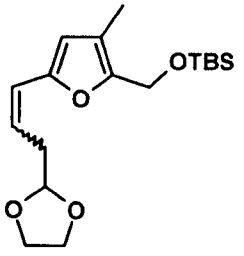
MHz): 149.2 (C), 141.0 (CH), 116.9 (C), 112.9 (CH), 56.0 (CH_2), 25.9 (3 x CH_3), 18.4 (C), 9.8 (CH_3), -5.3 (2 x CH_3); m/*z* (EI) found 169.0685 (M^+ - ^{t}Bu) (46%), $C_8H_{13}O_2Si$ requires 169.0679.

5-(tert-Butyl-dimethyl-silanyloxymethyl)-4-methyl-furan-2-carbaldehyde 117



A solution of *n*-butyllithium (8.9 mL, 22.1 mmol, 2.5 M in hexanes) was added dropwise over 10 mins to a stirred solution of the TBS-protected alcohol **113b** (5.01 g, 22.1 mmol) in THF (200 mL) at -78 °C under a nitrogen atmosphere. The mixture was warmed to 0 °C and allowed to stir at this temperature for 30 mins. The mixture was cooled to -78 °C and anhydrous DMF (3.4 mL, 44.3 mmol) was then added dropwise over 5 min. The mixture was warmed to room temperature over 4 hrs and then water (50 mL) and diethyl ether (50 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 10% diethyl ether in petroleum ether as eluent, gave the *furan aldehyde* (4.34 g, 77%) as a light yellow oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2930, 2858, 1682, 1462, 1363, 1079; δ_H (400 MHz): 9.55 (s, 1H, C*H*O), 7.05 (s, 1H, C(O)=C*H*CMe), 4.69 (s, 2H, CH_2OTBS), 2.11 (s, 3H, C(O)=CHC*Me*), 0.90 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.09 (s, 6H, Si(*Me*)$_2$^{t}Bu); δ_C (100 MHz): 177.7 (CH), 156.0 (C), 150.9 (C), 124.2 (br. C), 120.2 (CH), 56.6 (CH_2), 25.8 (3 x CH_3), 18.3 (C), 9.6 (CH_3), -5.4 (2 x CH_3); m/*z* (ESI) found 277.1232 ($M + Na^+$), $C_{13}H_{22}O_3SiNa$ requires 277.1230.

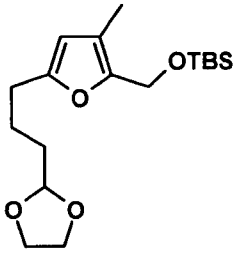
tert-Butyl-[5-(3-[1,3]dioxolan-2-yl-propenyl)-3-methyl-furan-2-ylmethoxy]-dimethyl-silane 119



A solution of *n*-butyllithium (4.1 mL, 10.2 mmol, 2.5 M in hexanes) was added dropwise over 5 mins to a stirred solution of the phosphonium salt **118** (4.52 g, 10.2 mmol) in THF (80 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 40 mins, and then a solution of the furan aldehyde **117** (1.73 g, 6.80 mmol) in THF (30 mL) was added dropwise over 15 mins. The mixture was warmed to room temperature over 15 hrs, and then water (50 mL) and diethyl ether (50 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Pentane (200 mL) was added to the residue which was then filtered and concentrated *in vacuo*. Purification by chromatography on silica gel, using 10% diethyl ether in petroleum ether as eluent, gave a 3:2 mixture of *E*:*Z*-isomers of the *alkenylfuran* (1.73 g, 75%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2929, 2858, 1620; δ_H (400 MHz): 6.29-6.20 (m, 1H, C*H*=CHCH$_2$), 6.12 (dt, 0.55H, *J* 15.9 and 7.1, CH=C*H*CH$_2$), 6.11 (s, 0.45H, C(O)=C*H*CMe), 5.99 (s, 0.55H, C(O)=C*H*CMe), 5.57 (dt, 0.45H, *J* 11.8 and 7.1, CH=C*H*CH$_2$), 5.02 (t, 0.45H, *J* 4.8, C*H*(O)$_2$), 4.97 (t, 0.55H, *J* 4.6, C*H*(O)$_2$), 4.60 (s, 0.90H, C*H*$_2$OTBS), 4.58 (s, 1.10H, C*H*$_2$OTBS), 4.04-3.96 (m, 2H, OC*H*$_2$CH$_2$O), 3.92-3.84 (m, 2H, OCH$_2$C*H*$_2$O), 2.87 (ddd, 0.90H, *J* 7.1, 4.8 and 1.8, C*H*$_2$CH=CH), 2.55 (ddd, 1.10H, *J* 7.1, 4.6 and 1.1, C*H*$_2$CH=CH), 2.02 (s, 1.35H, C(O)=CHC*Me*) and 1.99 (s, 1.65H, C(O)=CHC*Me*),

0.91 (2 x s, 9H, $Si(Me)_2C(\mathit{Me})_3$), 0.09 (2 x s, 6H, $Si(\mathit{Me})_2{}^tBu$); δ_C (100 MHz): 151.2 (C), 151.1 (C), 148.6 (C), 148.5 (C), 122.7 (CH), 122.2 (CH), 121.7 (CH), 119.7 (CH), 118.5 (2 x C), 113.1 (CH), 110.4 (CH), 103.8 (CH), 103.7 (CH), 65.0 (4 x CH_2), 56.2 (CH_2), 56.1 (CH_2), 37.7 (CH_2), 34.2 (CH_2), 25.9 (6 x CH_3), 18.4 (2 x C), 9.8 (2 x CH_3), -5.2 (2 x CH_3), -5.3 (2 x CH_3); m/z (ESI) found 361.1796 ($M + Na^+$), $C_{18}H_{30}O_4SiNa$ requires 361.1806.

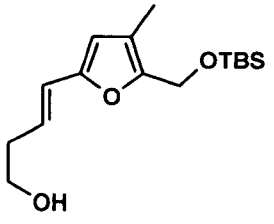
tert-Butyl-[5-(3-[1,3]dioxolan-2-yl-propyl)-3-methyl-furan-2-ylmethoxy]-dimethyl-silane 120



A suspension of the alkenylfuran **119** (1.79 g, 5.29 mmol) and 5% palladium on carbon (179 mg) in ethyl acetate (100 mL) was stirred under 1 atmosphere of hydrogen at room temperature for 3 hrs. The mixture was filtered through celite, eluting with diethyl ether, and the filtrate was then concentrated *in vacuo*. Purification by chromatography on silica gel, using 10% diethyl ether in petroleum ether as eluent, gave the *furan* (1.68 g, 93%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2928, 2858, 1678, 1570; δ_H (400 MHz): 5.80 (s, 1H, C(O)=C*H*CMe), 4.87 (t, 1H, *J* 4.4, $CH(O)_2$), 4.55 (s, 2H, CH_2OTBS), 3.98-3.93 (m, 2H, OCH_2CH_2O), 3.87-3.81 (m, 2H, OCH_2CH_2O), 2.61 (t, 2H, *J* 6.9, $CH_2C(O)$=CH), 1.97 (s, 3H, C(O)=CHC*Me*), 1.79-1.67 (m, 4H, $CH_2CH_2C(O)$=CH and $CH(O)_2CH_2CH_2$), 0.89 (s, 9H, $Si(Me)_2C(\mathit{Me})_3$), 0.06 (s, 6H, $Si(\mathit{Me})_2{}^tBu$); δ_C (100 MHz): 154.3 (C), 147.4 (C), 117.5 (C), 108.4 (CH), 104.3 (CH), 64.8 (2 x CH_2), 56.0 (CH_2), 33.2 (CH_2), 27.8 (CH_2), 25.9 (3 x CH_3), 22.4

(CH_2), 18.4 (C), 9.9 (CH_3), -5.2 (2 x CH_3); m/*z* (ESI) found 363.1961 ($M + Na^+$), $C_{18}H_{32}O_4SiNa$ requires 363.1962.

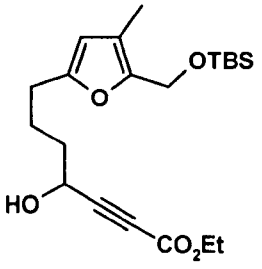
4-[5-(tert-Butyl-dimethyl-silanyloxymethyl)-4-methyl-furan-2-yl]-(*E*)-but-3-en-1-ol 122



A solution of *n*-butyllithium (3.8 mL, 9.43 mmol, 2.5 M in hexanes) was added dropwise over 5 mins to a stirred solution of the phosphonium salt **121**[142,143] (1.89 g, 4.72 mmol) in THF (30 mL) at -20 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 30 mins and then a solution of the furan aldehyde **117** (1.00 g, 3.93 mmol) in THF (20 mL) was added dropwise over 15 mins. The mixture was warmed to room temperature over 15 hrs, and then water (40 mL) and diethyl ether (40 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 40 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Pentane (200 mL) was added to the residue which was then filtered and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 30% to 40% diethyl ether in petroleum ether (product eluted at 40%) as eluent, gave the *alkenylfuran* (0.70 g, 60%) as predominantly the *E*-isomer. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3622, 2929, 2857, 1607; δ_H (400 MHz): 6.23 (dt, 1H, *J* 15.8 and 1.1, C*H*=CHCH$_2$), 6.09 (dt, 1H, *J* 15.8 and 7.2, CH=C*H*CH$_2$), 5.98 (s, 1H, C(O)=C*H*CMe), 4.59 (s, 2H, C*H*$_2$OTBS), 3.71 (br. td, 2H, *J* 6.5 and 4.0, C*H*$_2$OH), 2.43 (dtd, 1H, *J* 7.2, 6.5 and 1.1, C*H*$_2$CH=CH), 1.99 (s, 3H, C(O)=CHC*Me*), 1.80 (br.

t, 1H, *J* 4.0, CH_2OH), 0.91 (s, 9H, $Si(Me)_2C(Me)_3$), 0.09 (s, 6H, $Si(Me)_2{}^tBu$); δ_C (100 MHz): 151.1 (C), 148.4 (C), 124.8 (CH), 121.3 (CH), 118.6 (C), 110.3 (CH), 61.9 (CH_2), 56.0 (CH_2), 36.2 (CH_2), 25.9 (3 x CH_3), 18.4 (C), 9.8 (CH_3), -5.2 (2 x CH_3); m/*z* (ESI) found 319.1691 ($M + Na^+$), $C_{16}H_{28}O_3SiNa$ requires 319.1700.

7-[5-(tert-Butyl-dimethyl-silanyloxymethyl)-4-methyl-furan-2-yl]-4-hydroxy-hept-2-ynoic acid ethyl ester 109

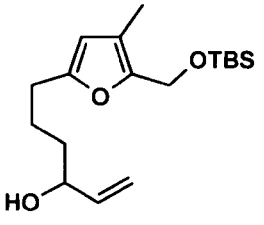


A suspension of the alkenylfuran **122** (370 mg, 1.25 mmol), triethylamine (0.87 mL, 6.24 mmol) and 5% palladium on carbon (37 mg) in THF (40 mL) was stirred under 1 atmosphere of hydrogen at room temperature for 15 hrs. The mixture was filtered through celite, eluting with diethyl ether, and the filtrate was then concentrated *in vacuo* to leave the *saturated alcohol* as a colourless oil that was used without further purification. δ_H (400 MHz): 5.80 (s, 1H, C(O)=C*H*CMe), 4.56 (s, 2H, CH_2OTBS), 3.65 (t, 2H, *J* 6.4, CH_2OH), 2.60 (t, 2H, *J* 7.1, CH_2C(O)=CH), 1.98 (s, 3H, C(O)=CHC*Me*), 1.73-1.58 (m, 4H, CH_2CH_2OH and CH_2CH_2C(O)=C), 1.49 (br. s, 1H, CH_2OH), 0.90 (s, 9H, $Si(Me)_2C(Me)_3$), 0.07 (s, 6H, $Si(Me)_2{}^tBu$). Tetrapropylammonium perruthenate (22 mg, 0.06 mmol) was added in one portion to a stirred solution of the crude saturated alcohol, *N*-methylmorpholine *N*-oxide (219 mg, 1.87 mmol) and 4 Å molecular sieves (670 mg) in DCM (20 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr and then filtered through celite, eluting with diethyl ether. The filtrate was

concentrated *in vacuo* to leave the *aldehyde* as a light brown oil that was used without further purification. δ_H (300 MHz): 9.76 (t, 1H, *J* 1.5, C*H*O), 5.82 (s, 1H, C(O)=C*H*CMe), 4.56 (s, 2H, CH_2OTBS), 2.62 (t, 2H, *J* 7.3, CH_2C(O)=CH), 2.48 (td, 1H, *J* 7.3 and 1.5, CH_2CHO), 2.01-1.90 (m, 2H, CH_2CH$_2$CHO), 1.98 (s, 3H, C(O)=CHC*Me*), 0.90 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.07 (s, 6H, Si(*Me*)$_2$^{t}Bu). A solution of *n*-butyllithium (1.5 mL, 3.74 mmol, 2.5 M in hexanes) was added dropwise over 2 mins to a stirred solution of diisopropylamine (0.52 mL, 3.74 mmol) in THF (20 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 20 mins and then cooled to -78 °C, and ethyl propiolate (0.38 mL, 3.74 mmol) was added dropwise over 5 mins. The mixture was stirred at this temperature for 1 hr and then a solution of the crude aldehyde in THF (10 mL) was added dropwise over 10 mins. The mixture was stirred at -78 °C for 1 hr and then water (30 mL) and diethyl ether (30 mL) were added and the mixture was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 20% to 30% diethyl ether in petroleum ether (product eluted at 30%) as eluent, gave the *propargylic alcohol* (301 mg, 61%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3599, 2929, 2858, 2237, 1709; δ_H (300 MHz): 5.81 (s, 1H, C(O)=C*H*CMe), 4.55 (s, 2H, CH_2OTBS), 4.51-4.40 (m, 1H, CH$_2$C*H*(OH)C≡C), 4.23 (q, 2H, *J* 7.1, CO$_2$CH_2Me), 2.71 (br. s, 1H, CH$_2$CH(O*H*)C≡C), 2.65-2.54 (m, 2H, CH_2C(O)=CHCMe), 1.97 (s, 3H, C(O)=CHC*Me*), 1.84-1.74 (m, 4H, CH(OH)CH_2CH$_2$ and CH_2CH$_2$C(O)=CH), 1.30 (t, 3H, *J* 7.1, CO$_2$CH$_2$*Me*), 0.89 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.06 (s, 6H, Si(*Me*)$_2$^{t}Bu); δ_C (75 MHz): 153.8 (C), 153.4 (C), 147.5 (C), 117.6 (C), 108.7 (CH), 87.7 (C), 76.4 (C), 62.1 (CH$_2$), 61.6 (CH), 56.0 (CH$_2$), 36.1 (CH$_2$), 27.4 (CH$_2$), 25.9 (3

x CH_3), 23.4 (CH_2), 18.4 (C), 13.9 (CH_3), 9.8 (CH_3), -5.2 (2 x CH_3); m/*z* (ESI) found 417.2071 ($M + Na^+$), $C_{21}H_{34}O_5SiNa$ requires 417.2068.

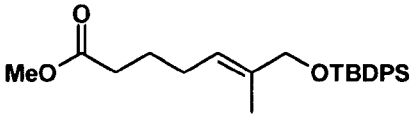
6-[5-(tert-Butyl-dimethyl-silanyloxymethyl)-4-methyl-furan-2-yl]-hex-1-en-3-ol 114



The aldehyde **112** was prepared in an identical manner to the procedure for propargylic alcohol **109**, from the alkenylfuran **122** (3.00 g, 10.1 mmol). A solution of the crude aldehyde in THF (20 mL) was added dropwise over 15 mins to a stirred solution of vinylmagnesium bromide (20.2 mL, 20.2 mmol, 1.0 M in THF) in THF (100 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr, then saturated aqueous NH_4Cl (50 mL), water (50 mL) and diethyl ether (50 mL) were added and the mixture was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 20% diethyl ether in petroleum ether as eluent, gave the *allylic alcohol* (1.63 g, 50%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3608, 2928, 2857, 1639, 1570; δ_H (400 MHz): 5.91-5.80 (m, 1H, C*H*=CH_2), 5.80 (s, 1H, C(O)=C*H*CMe), 5.22 (dm, 1H, *J* 17.0, CH=C*H*H), 5.10 (dm, 1H, *J* 10.4, CH=CH*H*), 4.56 (s, 2H, CH_2OTBS), 4.15-4.05 (m, 1H, C*H*(OH)CH=CH_2), 2.59 (t, 2H, *J* 7.3, CH_2C(O)=CHCMe), 1.98 (s, 3H, C(O)=CHC*Me*), 1.80-1.52 (m, 5H, CH(OH)C$H_2$$CH_2$, CH_2CH_2C(O)=CH and CH(O*H*)CH=CH_2), 0.90 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.07 (s, 6H, Si(*Me*)$_2$^{t}Bu); δ_C (100

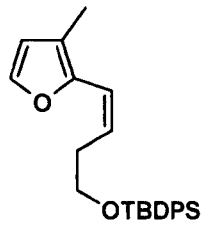
MHz): 154.5 (C), 147.4 (C), 141.1 (CH), 117.5 (C), 114.7 (CH_2), 108.4 (CH), 72.9 (CH), 56.0 (CH_2), 36.4 (CH_2), 27.8 (CH_2), 25.9 (3 x CH_3), 23.8 (CH_2), 18.4 (C), 9.9 (CH_3), -5.2 (2 x CH_3); m/*z* (ESI) found 347.2015 ($M + Na^+$), $C_{18}H_{32}O_3SiNa$ requires 347.2013.

7-(tert-Butyl-diphenyl-silanyloxy)-6-methyl-(*E*)-hept-5-enoic acid methyl ester 116b



tert-Butyldiphenylsilyl chloride (3.22 mL, 12.4 mmol) was added dropwise over 1 min to a stirred solution of the allylic alcohol **116a**[110] (1.94 g, 11.3 mmol) and imidazole (0.92 g, 13.5 mmol) in DMF (2.9 mL) at 0 °C under a nitrogen atmosphere, and the mixture was then stirred at this temperature for 10 mins. Direct purification by chromatography on silica gel, using 5% diethyl ether in petroleum ether as eluent, gave the *silyl ether* (3.99 g, 86%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2932, 2858, 1731, 1589; δ_H (360 MHz): 7.74-7.67 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.48-7.36 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 5.44 (t, 1H, *J* 7.3, C*H*=C(Me)CH_2O), 4.08 (br. s, 2H, C*H*$_2$OTBDPS), 3.70 (s, 3H, CO_2*Me*), 2.33 (t, 2H, *J* 7.5, C*H*$_2$$CO_2$Me), 2.10 (app. q, 2H, *J* 7.3, C*H*$_2$CH=C(Me)CH_2), 1.72 (app. quintet, 2H, *J* 7.4, C*H*$_2$$CH_2CO_2$Me), 1.62 (s, 3H, CH=C(*Me*)CH_2OSi), 1.09 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 174.1 (C), 135.5 (4 x CH), 135.0 (C), 133.8 (2 x C), 129.5 (2 x CH), 127.6 (4 x CH), 123.2 (CH), 68.8 (CH_2), 51.4 (CH_3), 33.5 (CH_2), 26.8 (3 x CH_3), 26.8 (CH_2), 24.8 (CH_2), 19.3 (C), 13.5 (CH_3); m/*z* (ESI) found 433.2163 ($M + Na^+$), $C_{25}H_{34}O_3SiNa$ requires 433.2169.

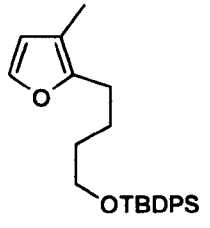
tert-Butyl-[4-(3-methyl-furan-2-yl)-but-3-enyloxy]-diphenyl-silane 135



A solution of *n*-butyllithium (8.60 mL, 21.5 mmol, 2.5 M in hexanes) was added dropwise over 5 mins to a stirred solution of the phosphonium salt **130**[152,153] (14.36 g, 22.5 mmol) in THF (100 mL) at -20 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 30 mins, and then cooled to -78 °C. A solution of 3-methyl-furan-2-carbaldehyde **129**[151] (2.06 g, 18.7 mmol) in THF (20 mL) was added dropwise over 10 min. The mixture was warmed to room temperature over 15 hrs and then water (60 mL) and diethyl ether (60 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 60 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Pentane (200 mL) was added to the residue which was then filtered and concentrated *in vacuo*. Purification by chromatography on silica gel, using 5% diethyl ether in petroleum ether as eluent, gave a 9:1 mixture of *Z*:*E*-isomers of the *alkenylfuran* (7.23 g, 99%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2930, 2859, 1650, 1589; δ_H (360 MHz): 7.77-7.70 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.49-7.35 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 7.30 (d, 0.85H, *J* 1.7, C*H*(O)=CH), 7.27 (d, 0.15H, *J* 1.7, C*H*(O)=CH), 6.31 (d, 0.15H, *J* 15.8, C(O)C*H*=CH), 6.25 (d, 0.85H, *J* 1.7, CH=C*H*CMe), 6.24 (d, 0.15H, *J* 1.7, CH=C*H*CMe), 6.20 (dt, 0.85H, *J* 11.8 and 1.4, C(O)C*H*=CH), 6.11 (dt, 0.15H, *J* 15.8 and 7.2, C(O)CH=C*H*CH$_2$), 5.61 (dt, 0.85H, *J* 11.8 and 7.5, C(O)CH=C*H*CH$_2$), 3.85 (t, 1.70H, *J* 6.7, C*H*$_2$OTBDPS), 3.82 (t, 0.30H, *J* 6.7, C*H*$_2$OSi), 2.90 (dtd, 1.70H, *J* 7.5, 6.7 and 1.4, C*H*$_2$CH$_2$OSi), 2.50 (dt, 0.30H, *J* 7.2 and 6.7, C*H*$_2$CH$_2$OSi), 2.07 (s, 2.55H, CH(O)=CHC*Me*), 2.06 (s, 0.45H, CH(O)=CHC*Me*), 1.12 (s, 1.35H, Si(Ph)$_2$C(*Me*)$_3$) and 1.11 (s, 7.65H,

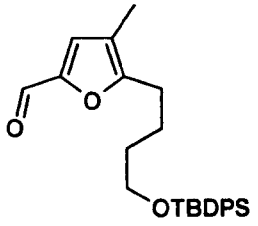
$Si(Ph)_2C(Me)_3$); δ_C (90 MHz): 149.3 (2 x C), 140.7 (CH), 140.5 (CH), 135.6 (8 x CH), 134.1 (2 x C), 133.9 (2 x C), 129.5 (4 x CH), 127.6 (8 x CH), 125.2 (CH), 124.5 (CH), 118.7 (CH), 118.3 (2 x C), 116.0 (CH), 113.7 (CH), 113.2 (CH), 63.8 (2 x CH_2), 36.4 (CH_2), 32.6 (CH_2), 26.9 (6 x CH_3), 19.3 (C), 19.2 (C), 10.1 (2 x CH_3); m/*z* (ESI) found 413.1917 ($M + Na^+$), $C_{25}H_{30}O_2SiNa$ requires 413.1907.

tert-Butyl-[4-(3-methyl-furan-2-yl)-butoxy]-diphenyl-silane 136



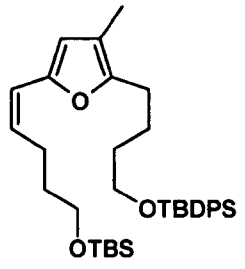
A suspension of the alkenylfuran **135** (1.57 g, 4.02 mmol) and 10% palladium on carbon (157 mg) in methanol (60 mL) was stirred under 1 atmosphere of hydrogen at room temperature for 4 hrs. The mixture was filtered through celite, eluting with diethyl ether, and the filtrate was concentrated *in vacuo*. Purification by chromatography on silica gel, using 5% diethyl ether in petroleum ether as eluent, gave the *furan* (1.35 g, 85%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2931, 2859, 1625, 1589; δ_H (360 MHz): 7.72-7.65 (m, 4H, $Si(Ph)_2{}^tBu$), 7.46-7.35 (m, 6H, $Si(Ph)_2{}^tBu$), 7.22 (d, 1H, *J* 1.8, C*H*(O)=CH), 6.16 (d, 1H, *J* 1.8, CH(O)=C*H*CMe), 3.68 (t, 2H, *J* 6.3, CH_2OTBDPS), 2.56 (t, 2H, *J* 7.3, C(O)CH_2CH_2), 1.94 (s, 3H, CH(O)=CHC*Me*), 1.76-1.66 (m, 2H, CH_2CH_2OSi), 1.63-1.53 (m, 2H, $C(O)CH_2CH_2CH_2$), 1.06 (s, 9H, $Si(Ph)_2C(Me)_3$); δ_C (90 MHz): 151.2 (C), 139.6 (CH), 135.6 (4 x CH), 134.1 (2 x C), 129.5 (2 x CH), 127.6 (4 x CH), 113.6 (C), 112.6 (CH), 63.6 (CH_2), 32.0 (CH_2), 26.9 (3 x CH_3), 25.6 (CH_2), 24.7 (CH_2), 19.2 (C), 9.8 (CH_3); m/*z* (ESI) found 415.2066 ($M + Na^+$), $C_{25}H_{32}O_2SiNa$ requires 415.2064.

5-[4-(tert-Butyl-diphenyl-silanyloxy)-butyl]-4-methyl-furan-2-carbaldehyde 137



A solution of *n*-butyllithium (0.72 mL, 1.78 mmol, 2.5 M in hexanes) was added dropwise over 5 mins to a stirred solution of the furan **136** (200 mg, 0.51 mmol) in THF (30 mL) at -78 °C under a nitrogen atmosphere. The mixture was warmed to room temperature for 45 mins and then cooled back to -78 °C. Once at this temperature anhydrous DMF (0.39 mL, 5.09 mmol) was added dropwise over 5 mins and the mixture was warmed to room temperature over 15 hrs and then water (30 mL) and diethyl ether (30 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 5%, 10% to 15% diethyl ether in petroleum ether (product eluted at 15%) as eluent, gave the *furan aldehyde* (107 mg, 50%) as a light yellow oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2932, 2859, 1674; δ_H (360 MHz): 9.48 (s, 1H, C*H*O), 7.71-7.65 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.47-7.36 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 7.04 (s, 1H, C(O)=C*H*CMe), 3.70 (t, 2H, *J* 6.3, C*H*$_2$OTBDPS), 2.68 (t, 2H, *J* 7.5, C(O)C*H*$_2$CH$_2$), 2.01 (s, 3H, C(O)=CHC*Me*), 1.86-1.75 (m, 2H, C*H*$_2$CH$_2$OSi), 1.65-1.55 (m, 2H, C(O)CH$_2$C*H*$_2$CH$_2$), 1.07 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 176.8 (CH), 159.5 (C), 150.6 (C), 135.5 (4 x CH), 133.8 (2 x C), 129.5 (2 x CH), 127.6 (4 x CH), 125.1 (br. C), 118.1 (CH), 63.3 (CH_2), 31.9 (CH_2), 26.8 (3 x CH_3), 26.1 (CH_2), 24.2 (CH_2), 19.1 (C), 9.6 (CH_3); m/*z* (ESI) found 459.1760 ($M + K^+$), $C_{26}H_{32}O_3SiK$ requires 459.1752.

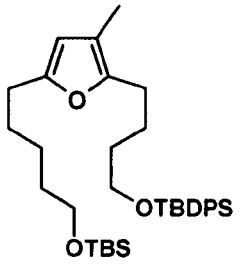
5-[5-(tert-Butyl-dimethyl-silanyloxy)-pent-1-enyl]-2-[4-(tert-butyl-diphenyl-silanyloxy)-butyl]-3-methyl-furan 361



A solution of *n*-butyllithium (4.00 mL, 10.1 mmol, 2.5 M in hexanes) was added dropwise over 5 mins to a stirred solution of the phosphonium salt **128**[155] (5.82 g, 10.1 mmol) in THF (120 mL) at -20 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 30 mins and then cooled to -78 °C. A solution of the furan aldehyde **137** (2.83 g, 6.73 mmol) in THF (30 mL) was added dropwise over 10 min. The mixture was warmed to room temperature over 15 hrs and then water (60 mL) and diethyl ether (60 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 60 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Pentane (250 mL) was added to the residue which was then filtered and concentrated *in vacuo*. Purification by chromatography on silica gel, using 5% diethyl ether in petroleum ether as eluent, gave a 4:1 mixture of *Z*:*E*-isomers of the *alkenylfuran* (2.85 g, 72%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2929, 2858, 1621; δ_H (360 MHz): 7.70-7.64 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.46-7.33 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 6.15-6.01 (m, 1H, CH=C*H*CO and 0.2H, C*H*=CHCO), 6.08 (s, 0.80H, C(O)=C*H*CMe), and 5.91 (s, 0.20H, C(O)=C*H*CMe), 5.45 (dt, 0.80H, *J* 11.7 and 7.3, C*H*=CHCO), 3.71-3.63 (m, 4H, CH_2OTBS and CH_2OTBDPS), 2.56 (t, 1.60H, *J* 7.3, C(O)CH_2CH$_2$), 2.54 (t, 0.40H, *J* 7.3, C(O)CH_2CH$_2$), 2.45 (dtd, 1.60H, *J* 7.6, 7.3 and 1.6, CH_2CH=CH), 2.22 (app. q, 0.40H, *J* 7.1, CH_2CH=CH), 1.92 (s, 2.40H, C(O)=CHC*Me*), 1.89 (s, 0.60H, C(O)=CHC*Me*), 1.77-1.65 (m, 4H,

CH_2CH_2OTBS and $CH_2CH_2OTBDPS$), 1.65-1.54 (m, 2H, $C(O)CH_2CH_2CH_2$), 1.06 (s, 9H, $Si(Ph)_2C(Me)_3$), 0.91 (s, 9H, $Si(Me)_2C(Me)_3$), 0.06 (s, 6H, $Si(Me)_2{}^tBu$); δ_C (90 MHz): 150.4 (2 x C), 150.3 (2 x C), 135.5 (8 x CH), 134.0 (4 x C), 129.5 (4 x CH), 128.7 (2 x CH), 127.6 (8 x CH), 119.0 (CH), 117.9 (CH), 115.5 (C), 115.3 (C), 112.3 (CH), 109.5 (CH), 63.6 (2 x CH_2), 62.9 (CH_2), 62.5 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 32.0 (2 x CH_2), 26.9 (6 x CH_3), 26.0 (6 x CH_3), 25.8 (2 x CH_2), 25.7 (2 x CH_2), 24.9 (CH_2), 24.7 (CH_2), 19.2 (2 x C), 18.3 (2 x C), 9.8 (2 x CH_3), -5.3 (4 x CH_3); m/*z* (ESI) found 613.3502 ($M + Na^+$), $C_{36}H_{54}O_3Si_2Na$ requires 613.3504.

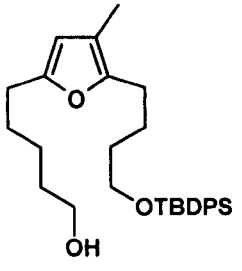
5-[5-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-2-[4-(tert-butyl-diphenyl-silanyloxy)-butyl]-3-methyl-furan 127



A suspension of the alkenylfuran **361** (2.85 g, 4.82 mmol) and 5% palladium on carbon (285 mg) in methanol (120 mL) and pentane (50 mL) was stirred under 1 atmosphere of hydrogen at room temperature for 4 hrs. The mixture was filtered through celite, eluting with diethyl ether, and the filtrate was concentrated *in vacuo*. Purification by chromatography on silica gel, using 2% diethyl ether in petroleum ether as eluent, gave the *furan* (2.60 g, 91%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2931, 2859, 1462, 1389, 1361, 1104; δ_H (360 MHz): 7.71-7.64 (m, 4H, $Si(Ph)_2{}^tBu$), 7.46-7.34 (m, 6H, $Si(Ph)_2{}^tBu$), 5.74 (s, 1H, C(O)=C*H*CMe), 3.68 (t, 2H, *J* 6.3, $CH_2OTBDPS$), 3.61 (t, 2H, *J* 6.6, CH_2OTBS), 2.53 (t, 2H, *J* 7.2, $C(O)CH_2CH_2$), 2.51 (t, 2H, *J* 7.2, $CH_2C(O)=CH$), 1.89 (s, 3H, C(O)=CHC*Me*), 1.74-1.49 (m, 8H,

CH_2CH_2OTBS, $CH_2CH_2OTBDPS$, $C(O)CH_2CH_2CH_2$ and $CH_2CH_2C(O)=CH$), 1.43-1.33 (m, 2H, $CH_2CH_2CH_2CO$), 1.06 (s, 9H, $Si(Ph)_2C(Me)_3$), 0.90 (s, 9H, $Si(Me)_2C(Me)_3$), 0.05 (s, 6H, $Si(Me)_2{}^tBu$); δ_C (90 MHz): 153.3 (C), 149.1 (C), 135.6 (4 x CH), 134.1 (2 x C), 129.5 (2 x CH), 127.6 (4 x CH), 114.0 (C), 107.7 (CH), 63.6 (CH_2), 63.1 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 28.0 (2 x CH_2), 26.9 (3 x CH_3), 26.0 (3 x CH_3), 25.6 (CH_2), 25.5 (CH_2), 25.0 (CH_2), 19.2 (C), 18.4 (C), 9.9 (CH_3), -5.3 (2 x CH_3); m/*z* (ESI) found 615.3670 ($M + Na^+$), $C_{36}H_{56}O_3Si_2Na$ requires 615.3660.

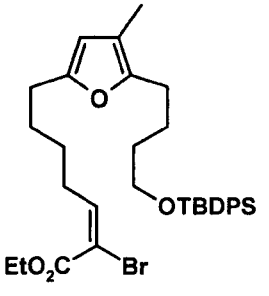
5-{5-[4-(tert-Butyl-diphenyl-silanyloxy)-butyl]-4-methyl-furan-2-yl}-pentan-1-ol 362



Pyridinium *para*-toluenesulfonate (1.09 g, 4.33 mmol) was added in one portion to a stirred solution of the furan **127** (2.57 g, 4.33 mol) in DCM (50 mL) and methanol (50 mL) at room temperature. The mixture was stirred at this temperature for 24 hrs and then concentrated *in vacuo*. Diethyl ether (50 mL) and water (50 mL) were added and the separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 20% to 30% diethyl ether in petroleum ether (product eluted at 30%) as eluent, gave the *alcohol* (1.73 g, 84%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3626, 2932, 2860, 1574; δ_H (360 MHz): 7.72-7.67 (m, 4H, $Si(Ph)_2{}^tBu$), 7.47-7.36 (m, 6H, $Si(Ph)_2{}^tBu$), 5.76 (s, 1H, $C(O)=CHCMe$), 3.69 (t, 2H, *J* 6.2, $CH_2OTBDPS$), 3.65 (t, 2H, *J* 6.6, CH_2OH), 2.56

(t, 2H, *J* 7.5, C(O)CH_2CH$_2$), 2.53 (t, 2H, *J* 7.3, CH_2C(O)=CH), 1.90 (s, 3H, C(O)=CHC*Me*), 1.75-1.55 (m, 8H, CH_2CH$_2$OH, CH_2CH$_2$OTBDPS, C(O)CH$_2$CH_2CH$_2$ and CH_2CH$_2$C(O)=CH), 1.47-1.37 (m, 2H, CH_2CH$_2$CH$_2$CO), 1.32 (br. s, 1H, CH$_2$O*H*), 1.07 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 153.0 (C), 149.0 (C), 135.4 (4 x CH), 133.9 (2 x C), 129.4 (2 x CH), 127.5 (4 x CH), 113.9 (C), 107.8 (CH), 63.5 (CH$_2$), 62.6 (CH$_2$), 32.3 (CH$_2$), 31.9 (CH$_2$), 27.8 (2 x CH$_2$), 26.8 (3 x CH$_3$), 25.5 (CH$_2$), 25.2 (CH$_2$), 24.9 (CH$_2$), 19.1 (C), 9.8 (CH$_3$); m/*z* (ESI) found 479.2972 (M + H$^+$), $C_{30}H_{43}O_3Si$ requires 479.2976.

(*E*)-2-Bromo-7-{5-[4-(tert-butyl-diphenyl-silanyloxy)-butyl]-4-methyl-furan-2-yl}-hept-2-enoic acid ethyl ester 140a

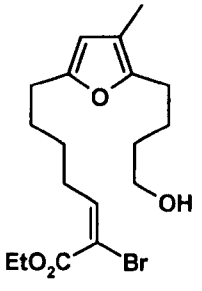


Dimethylsulphoxide (33 µl, 0.46 mmol) was added dropwise over 5 mins to a stirred solution of oxalyl chloride (24 µl, 0.27 mmol) in DCM (20 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 10 mins and then a solution of the alcohol **362** (100 mg, 0.21 mmol) in DCM (5 mL) was added dropwise over 5 mins, immediately followed by dropwise addition of triethylamine (0.15 mL, 1.04 mmol) over 1 min. The mixture was stirred at -78 °C for 2 hrs and then warmed to 0 °C and then water (20 mL) and diethyl ether (20mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *aldehyde* as a colourless oil that was used without further purification. The

phosphonate **139** (0.11 mL, 0.76 mmol) was added dropwise over 5 mins to a stirred solution of sodium hydride (18 mg, 0.76 mmol, 60% dispersed in mineral oil) suspended in THF (10 mL) at -30 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 30 mins and then bromine (24 μl, 0.76 mmol) was added dropwise over 5 mins. The cloudy, yellow mixture was briefly warmed to room temperature and then cooled to -78 °C where sodium hydride (18 mg, 0.76 mmol, 60% dispersed in mineral oil) was added in one portion. The mixture was warmed up until gas evolved from the mixture. The resulting cloudy, colourless solution was held at this temperature (~ -30 °C) for 5 mins and then cooled to -78 °C where the mixture was stirred for 25 mins. A solution of the crude aldehyde in THF (10 mL) was added dropwise over 10 mins to the mixture and then warmed to room temperature over 15 hrs. Water (20 mL) and diethyl ether (20 mL) were added and the separated aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 2% to 5% diethyl ether in petroleum ether (product eluted at 5%) as eluent, gave the *α-bromoester* (95 mg, 72%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2932, 2860, 1714, 1614; δ_H (360 MHz): 7.71-7.65 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.45-7.34 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 6.65 (t, 1H, *J* 7.8, C*H*=C(Br)CO_2Et), 5.74 (s, 1H, C(O)=C*H*CMe), 4.27 (q, 2H, *J* 7.1, CO_2CH_2Me), 3.68 (t, 2H, *J* 6.2, CH_2OTBDPS), 2.61-2.41 (m, 6H, C(O)CH_2CH_2, CH_2C(O)=CH and CH_2CH=C), 1.88 (s, 3H, C(O)=CHC*Me*), 1.73-1.45 (m, 8H, CH_2CH_2CH=C, CH_2CH_2OTBDPS, C(O)$CH_2CH_2CH_2$ and CH_2CH_2C(O)=CH), 1.33 (t, 3H, *J* 7.1, CO_2CH_2*Me*), 1.05 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 162.8 (C), 152.7 (C), 149.3 (C), 148.2 (CH), 135.5 (4 x CH), 134.0 (2 x C), 129.4 (2 x CH), 127.5 (4 x CH), 114.0 (C), 111.3 (C), 108.0 (CH), 63.6 (CH_2), 62.0 (CH_2), 32.0 (CH_2), 31.1 (CH_2), 28.2 (CH_2), 27.6 (2 x CH_2),

26.8 (3 x CH_3), 25.6 (CH_2), 24.9 (CH_2), 19.2 (C), 14.1 (CH_3), 9.8 (CH_3); m/*z* (ESI) found 647.2162 ($M + Na^+$), $C_{34}H_{45}O_4SiBrNa$ requires 647.2163.

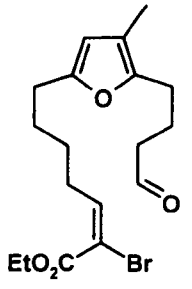
(*E*)-2-Bromo-7-[5-(4-hydroxy-butyl)-4-methyl-furan-2-yl]-hept-2-enoic acid ethyl ester 140b



70% Hydrogen fluoride-pyridine complex (0.50 mL, 19.2 mmol) was added to a stirred solution of the α-bromoester **140a** (169 mg, 0.27 mmol) and pyridine (0.25 mL, 3.09 mmol) in THF (5 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at this temperature for 24 hrs, and then saturated aqueous $NaHCO_3$ (5 mL) and diethyl ether (5 mL) were added. The resulting biphasic mixture was dried ($MgSO_4$) and then filtered through a short plug of silica gel, eluting with diethyl ether, and the filtrate was then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 20% to 40% diethyl ether in petroleum ether (product eluted at 40%) as eluent, gave the *alcohol* (97 mg, 92%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3624, 2939, 2864, 1716, 1613; δ_H (360 MHz): 6.66 (t, 1H, *J* 7.8, C*H*=C(Br)CO_2Et), 5.74 (s, 1H, C(O)=C*H*CMe), 4.27 (q, 2H, *J* 7.1, CO_2CH_2Me), 3.65 (t, 2H, *J* 6.3, CH_2OH), 2.61-2.41 (m, 6H, C(O)CH_2CH_2, CH_2C(O)=CH and CH_2CH=C), 1.90 (s, 3H, C(O)=CHC*Me*), 1.73-1.45 (m, 8H, CH_2CH_2CH=C, CH_2CH_2OH, C(O)$CH_2CH_2CH_2$ and CH_2CH_2C(O)=CH), 1.41 (br. s, 1H, CH_2OH), 1.34 (t, 3H, *J* 7.1, CO_2CH_2*Me*); δ_C (90 MHz): 162.6 (C), 152.5 (C), 148.8 (C), 148.0 (CH), 113.8 (C), 111.0 (C), 107.8 (CH), 62.1 (CH_2), 61.8 (CH_2),

31.9 (CH_2), 30.9 (CH_2), 27.9 (CH_2), 27.4 (2 x CH_2), 25.3 (CH_2), 24.7 (CH_2), 13.8 (CH_3), 9.6 (CH_3); m/*z* (ESI) found 411.0963 ($M + Na^+$), $C_{18}H_{27}O_4{}^{81}BrNa$ requires 411.0964.

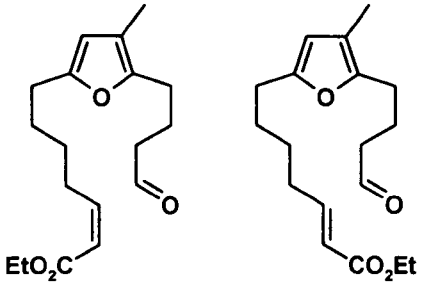
(*E*)-2-Bromo-7-[4-methyl-5-(4-oxo-butyl)-furan-2-yl]-hept-2-enoic acid ethyl ester 126



Dess-Martin periodinane (93 mg, 0.22 mmol) was added in three portions over a 1 hr period to a stirred solution of the alcohol **140b** (50 mg, 0.13 mmol) in DCM (15 mL) at room temperature. The mixture was stirred at this temperature for 45 mins, and then saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (15 mL, 1:1) were added and the resulting biphasic mixture was stirred vigorously for 45 mins. The separated aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 5% to 10% ethyl acetate in petroleum ether (product eluted at 10%) as eluent, gave the *aldehyde* (35 mg, 70%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2932, 2863, 1716, 1614; δ_H (360 MHz): 9.71 (t, 1H, *J* 1.6, C*H*O), 6.66 (t, 1H, *J* 7.8, C*H*=C(Br)CO_2Et), 5.75 (s, 1H, C(O)=C*H*CMe), 4.27 (q, 2H, *J* 7.1, CO_2CH_2Me), 2.62-2.47 (m, 6H, C(O)CH_2CH_2, CH_2C(O)=CH and CH_2CH=C), 2.43 (td, 2H, *J* 7.2 and 1.6, CH_2CHO), 1.94 (app. quintet, 2H, *J* 7.2, C(O)$CH_2CH_2CH_2$), 1.89 (s, 3H, C(O)=CHC*Me*), 1.69-1.56 (m, 2H, CH_2CH_2C(O)=CH), 1.56-1.45 (m, 2H, CH_2CH_2CH=C), 1.34 (t, 3H, *J* 7.1,

CO_2CH_2*Me*); δ_C (90 MHz): 202.2 (CH), 162.9 (C), 153.2 (C), 148.2 (CH), 147.9 (C), 115.0 (C), 111.3 (C), 108.1 (CH), 62.0 (CH_2), 43.0 (CH_2), 31.1 (CH_2), 28.2 (CH_2), 27.6 (2 x CH_2), 24.9 (CH_2), 21.2 (CH_2), 14.1 (CH_3), 9.8 (CH_3); m/*z* (ESI) found 407.0829 ($M + Na^+$), $C_{18}H_{25}O_4BrNa$ requires 407.0828.

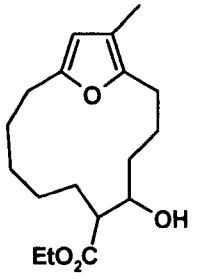
7-[4-Methyl-5-(4-oxo-butyl)-furan-2-yl]-(*Z*)-hept-2-enoic acid ethyl ester 141a and 7-[4-Methyl-5-(4-oxo-butyl)-furan-2-yl]-(*E*)-hept-2-enoic acid ethyl ester 141b



A solution of samarium iodide (2.6 mL, 0.26 mmol, 0.1 M in THF) was added dropwise over 30 mins to a stirred, degassed solution of the aldehyde **126** (25 mg, 0.06 mmol) in THF (100 mL) at -78 °C under an argon atmosphere. The mixture was stirred at this temperature for 30 mins and then opened to the atmosphere. Silica gel (20 g) and pentane (50 mL) were added and the mixture was warmed to room temperature and then stirred vigorously for 30 mins. The mixture was filtered through a short plug of silica gel, eluting with diethyl ether, and the filtrate was then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 5%, 10% to 20% ethyl acetate in petroleum ether (product eluted at 20%) as eluent, gave the *Z-α,β-unsaturated ester* (5 mg, 25%) and the *E-α,β-unsaturated ester* (9 mg, 45%) as separable isomers. *Z-isomer:* ν_{max}/cm^{-1} ($CHCl_3$ solution): 2926, 2857, 1716, 1644; δ_H (360 MHz): 9.71 (t, 1H, *J* 1.6, C*H*O), 6.21 (dt, 1H, *J* 11.6 and 7.5, C*H*=CHCO$_2$Et), 5.77 (dt, 1H, *J* 11.6 and 1.6, CH=C*H*CO$_2$Et), 5.75 (s, 1H,

C(O)=C*H*CMe), 4.17 (q, 2H, *J* 7.1, CO_2CH_2Me), 2.73-2.64 (m, 2H, CH_2CH=CH), 2.61-2.51 (m, 4H, $C(O)CH_2CH_2$, $CH_2C(O)$=CH), 2.43 (td, 2H, *J* 7.2 and 1.6, CH_2CHO), 1.94 (app. quintet, 2H, *J* 7.2, $C(O)CH_2CH_2CH_2$), 1.89 (s, 3H, C(O)=CHC*Me*), 1.70-1.57 (m, 2H, $CH_2CH_2C(O)$=CH), 1.57-1.46 (m, 2H, CH_2CH_2CH=CH), 1.30 (t, 3H, *J* 7.1, CO_2CH_2Me); δ_C (90 MHz): 202.3 (CH), 166.4 (C), 153.6 (C), 150.1 (CH), 147.8 (C), 119.9 (CH), 115.1 (C), 108.0 (CH), 59.8 (CH_2), 43.0 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 27.7 (CH_2), 25.0 (CH_2), 21.3 (CH_2), 14.3 (CH_3), 9.8 (CH_3); m/*z* (ESI) found 329.1723 ($M + Na^+$), $C_{18}H_{26}O_4Na$ requires 329.1723; *E-isomer:* ν_{max}/cm^{-1} ($CHCl_3$ solution): 2930, 2862, 1716, 1653; δ_H (360 MHz): 9.70 (t, 1H, *J* 1.6, C*H*O), 6.96 (dt, 1H, *J* 15.6 and 6.9, C*H*=$CHCO_2Et$), 5.82 (dt, 1H, *J* 15.6 and 1.5, CH=C*H*CO_2Et), 5.75 (s, 1H, C(O)=C*H*CMe), 4.19 (q, 2H, *J* 7.1, CO_2CH_2Me), 2.58 (t, 2H, *J* 7.2, $C(O)CH_2CH_2$), 2.54 (t, 2H, *J* 7.0, $CH_2C(O)$=CH), 2.43 (td, 2H, *J* 7.2 and 1.6, CH_2CHO), 2.27-2.18 (m, 2H, CH_2CH=CH), 1.94 (app. quintet, 2H, *J* 7.2, $C(O)CH_2CH_2CH_2$), 1.89 (s, 3H, C(O)=CHC*Me*), 1.68-1.57 (m, 2H, $CH_2CH_2C(O)$=CH), 1.56-1.45 (m, 2H, CH_2CH_2CH=CH), 1.29 (t, 3H, *J* 7.1, CO_2CH_2Me); δ_C (90 MHz): 202.3 (CH), 166.7 (C), 153.3 (C), 148.9 (CH), 147.9 (C), 121.5 (CH), 115.1 (C), 108.1 (CH), 60.1 (CH_2), 43.0 (CH_2), 31.9 (CH_2), 27.7 (CH_2), 27.6 (CH_2), 27.5 (CH_2), 25.0 (CH_2), 21.3 (CH_2), 14.3 (CH_3), 9.8 (CH_3); m/*z* (ESI) found 307.1910 ($M + H^+$), $C_{18}H_{27}O_4$ requires 307.1904.

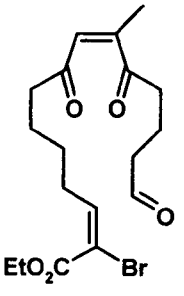
5-Hydroxy-14-methyl-15-oxa-bicyclo[10.2.1]pentadeca-1(14),12-diene-6-carboxylic acid ethyl ester 142



A degassed solution of the aldehyde **126** (35 mg, 0.09 mmol) in THF (100 mL) was added dropwise over 1 hr to a stirred solution of samarium iodide (18 mL, 1.80 mmol, 0.1 M in THF) at -78 °C under an argon atmosphere. The mixture was stirred at this temperature for 30 mins and then opened to the atmosphere. Silica gel (20 g) and pentane (50 mL) were added and the mixture was warmed to room temperature where it was stirred vigorously for 30 mins. The mixture was filtered through a short plug of silica gel, eluting with diethyl ether, and the filtrate was then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 5%, 10% to 20% ethyl acetate in petroleum ether (product eluted at 20%) as eluent, gave the *alcohol* (9 mg, 33%) as a mixture of diastereoisomers. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3524, 2927, 2864, 1713; δ_H (360 MHz): 5.76 (s, 1H, C(O)=C*H*CMe), 4.17 (2 x q, 2H, *J* 7.1, CO_2CH_2Me), 3.81 (br. s, 1H, C*H*(OH)CH_2), 2.78-2.67 (m, 3H, C(O)C*H*$_2CH_2$ and CH(O*H*)CH_2), 2.51-2.37 (m, 3H, C*H*$_2$C(O)=CH and C*H*(CO_2Et)CH), 1.90 (s, 3H, C(O)=CHC*Me*), 1.81-1.53 (m, 8H, C*H*$_2CH_2$C(O)=CH, C*H*$_2$CH(CO_2Et)CH, C(O)CH_2C*H*$_2CH_2$ and CH(OH)C*H*$_2CH_2$), 1.53-1.34 (m, 4H, C*H*$_2CH_2$CHCO_2Et and C*H*$_2CH_2CH_2$CO), 1.28 (t, 3H, *J* 7.1, CO_2CH_2*Me*); δ_C (90 MHz): 176.7 (2 x C), 153.6 (2 x C), 148.9 (2 x C), 114.9 (2 x C), 108.7 (2 x CH), 71.2 (2 x CH), 60.6 (2 x CH_2), 47.3 (2 x CH), 31.1 (2 x CH_2), 27.4 (2 x CH_2), 27.1 (2 x CH_2), 26.3 (2 x CH_2), 25.4 (2

x CH_2), 24.4 (2 x CH_2), 24.1 (2 x CH_2), 23.7 (2 x CH_2), 14.3 (2 x CH_3), 9.7 (2 x CH_3); m/*z* (ESI) found 331.1874 ($M + Na^+$), $C_{18}H_{28}O_4Na$ requires 331.1880.

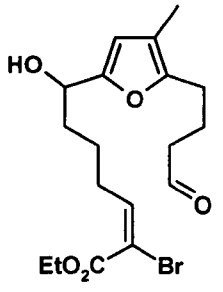
(*E*)-2-Bromo-10-methyl-8,11,15-trioxo-(*Z*)-pentadeca-2,9-dienoic acid ethyl ester 143



Dess-Martin periodinane (164 mg, 0.39 mmol) was added in one portion to a stirred solution of the alcohol **140b** (50 mg, 0.13 mmol) in DCM (15 mL) at room temperature. The mixture was stirred at this temperature for 45 mins, and then saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (15 mL, 1:1) were added and the resulting biphasic mixture was stirred vigorously for 45 mins. The separated aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 5%, 10% to 30% ethyl acetate in petroleum ether (product eluted at 30%) as eluent, gave the *enedione* (26 mg, 50%) as a light yellow oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2981, 2938, 1732, 1616; δ_H (360 MHz): 9.81 (t, 1H, *J* 1.2, C*H*O), 6.64 (t, 1H, *J* 7.8, C*H*=C(Br)CO_2Et), 6.06 (q, 1H, *J* 1.5, C(O)=C*H*CMe), 4.26 (q, 2H, *J* 7.1, CO_2CH_2Me), 2.64 (td, 2H, *J* 7.0 and 1.2, CH_2CHO), 2.56 (t, 2H, *J* 7.0, C(O)CH_2CH_2), 2.55-2.43 (m, 4H, CH_2C(O)=CH and CH_2CH=C), 2.02 (app. quintet, 2H, *J* 7.0, C(O)$CH_2CH_2CH_2$), 1.97 (d, 3H, *J* 1.5, C(O)=CHC*Me*), 1.67-1.54 (m, 2H, CH_2CH_2C(O)=CH), 1.54-1.40 (m, 2H, CH_2CH_2CH=C), 1.34 (t, 3H, *J* 7.1, CO_2CH_2*Me*); δ_C (90 MHz): 208.2 (C), 202.3 (CH),

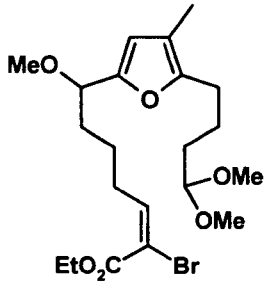
198.7 (C), 162.8 (C), 155.9 (C), 147.9 (CH), 124.1 (CH), 111.5 (C), 62.1 (CH_2), 42.5 (CH_2), 42.4 (CH_2), 38.8 (CH_2), 31.1 (CH_2), 28.1 (CH_2), 23.1 (CH_2), 20.6 (CH_3), 15.5 (CH_2), 14.1 (CH_3); m/*z* (ESI) found 423.0779 ($M + Na^+$), $C_{18}H_{25}O_5BrNa$ requires 423.0778.

(*E*)-2-Bromo-7-hydroxy-7-[4-methyl-5-(4-oxo-butyl)-furan-2-yl]-hept-2-enoic acid ethyl ester 179



A solution of the enedione **143** (5 mg, 0.01 mmol) and *para*-toluenesulfonic acid (2 mg, 0.01 mmol) in THF (2 mL) and water (1 mL) were stirred at room temperature for 4 hrs and then water (5 mL) and ethyl acetate (5 mL) were added. The separated aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10% to 50% ethyl acetate in petroleum ether (product eluted at 50%) as eluent, gave the *furan methanol* (4 mg, 80%) as a light yellow oil. δ_H (360 MHz): 9.69 (t, 1H, *J* 1.6, C*H*O), 6.66 (t, 1H, *J* 7.8, C*H*=C(Br)CO_2Et), 6.01 (s, 1H, C(O)=C*H*CMe), 4.59 (t, 1H, *J* 6.7, C*H*(OH)CO), 4.27 (q, 2H, *J* 7.1, CO_2CH_2Me), 2.64-2.50 (m, 4H, C(O)CH_2CH_2 and CH_2CH=C), 2.44 (td, 2H, *J* 7.1 and 1.6, CH_2CHO), 1.97 (app. quintet, 2H, *J* 7.1, C(O)$CH_2CH_2CH_2$), 1.92 (s, 3H, C(O)=CHC*Me*), 1.89-1.79 (m, 2H, CH_2CH(OH)CO), 1.70-1.47 (m, 2H, CH_2CH_2CH=C), 1.35 (t, 3H, *J* 7.1, CO_2CH_2*Me*).

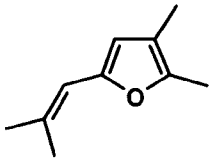
(*E*)-2-Bromo-7-[5-(4,4-dimethoxy-butyl)-4-methyl-furan-2-yl]-7-methoxy-hept-2-enoic acid ethyl ester 180



A solution of the enedione **143** (5 mg, 0.01 mmol) and *para*-toluenesulfonic acid (2 mg, 0.01 mmol) in THF (2 mL) and methanol (1 mL) were stirred at room temperature for 4 hrs and then water (5 mL) and ethyl acetate (5 mL) were added. The separated aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 5%, 10% to 20% ethyl acetate in petroleum ether (product eluted at 20%) as eluent, gave the *methyl furanmethanol* (4 mg, 80%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2929, 2859, 1715, 1614; δ_H (500 MHz): 6.65 (t, 1H, *J* 7.7, C*H*=C(Br)CO_2Et), 6.03 (s, 1H, C(O)=C*H*CMe), 4.37 (t, 1H, *J* 5.5, C*H*$(OMe)_2$), 4.27 (q, 2H, *J* 7.1, CO_2CH_2Me), 4.04 (t, 1H, *J* 7.0, C*H*(OMe)CO), 3.30 (s, 6H, CH(O*Me*)$_2$), 3.23 (s, 3H, CH(O*Me*)CO), 2.57 (t, 2H, *J* 7.1, C(O)C$H_2CH_2CH_2$), 2.52 (app. q, 2H, *J* 7.7, CH_2CH=C), 1.93 (s, 3H, C(O)=CHC*Me*), 1.92-1.84 (m, 1H, C*H*HCH(OMe)CO), 1.83-1.74 (m, 1H, CH*H*CH(OMe)CO), 1.70-1.62 (m, 2H, CH_2CH_2CH=C), 1.62-1.55 (m, 2H, C(O)$CH_2CH_2CH_2$), 1.55-1.48 (m, 1H, C*H*HCH$(OMe)_2$), 1.48-1.38 (m, 1H, CH*H*CH$(OMe)_2$), 1.34 (t, 3H, *J* 7.1, CO_2CH_2*Me*); δ_C (125 MHz): 162.9 (C), 150.9 (C), 150.7 (C), 148.2 (CH), 114.3 (C), 111.4 (C), 111.3 (CH), 104.3 (CH), 76.1 (CH), 62.1 (CH_2), 56.2 (CH_3), 52.6 (2 x CH_3), 33.4 (CH_2), 31.8 (CH_2), 31.1 (CH_2), 25.6

(CH_2), 24.9 (CH_2), 23.6 (CH_2), 14.1 (CH_3), 9.8 (CH_3); m/*z* (ESI) found 483.1351 (M + Na^+), $C_{21}H_{33}O_6BrNa$ requires 483.1353.

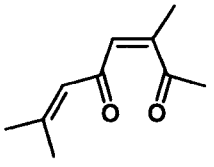
2, 3-Dimethyl-5-(2-methylpropenyl)-furan 162



A solution of *n*-butyllithium (5.25 mL, 13.1 mmol, 2.5 M in hexanes) was added dropwise over 5 mins to a stirred suspension of isopropyltriphenylphosphonium iodide (5.70 g, 13.1 mmol) in THF (30 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 40 mins and then 4, 5-dimethylfuran-2-carbaldehyde **161** (0.74 g, 5.96 mmol) was added dropwise over 10 min. The mixture was stirred at 0 °C for 30 mins and then saturated aqueous NH_4Cl (20 mL), water (10 mL) and diethyl ether (30 mL) were added. The mixture was warmed to room temperature and the separated aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Pentane (50 mL) was added to the residue which was then filtrated and concentration *in vacuo* to leave the *alkenylfuran* as a light yellow oil that was used without further purification. A small portion was purified in order to obtain the spectroscopic data by chromatography on silica gel, using light petroleum as eluent, which gave the *alkenylfuran* as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2920, 1626, 1442; δ_H (400 MHz): 5.98 (br. s, 1H, $(Me)_2C=CH$), 5.97 (s, 1H, C(O)=C*H*CMe), 2.21 (s, 3H, C(O)*Me*), 1.96 (s, 3H, C(O)=CHC*Me*), 1.94 (s, 3H, *Me*MeC=CH), 1.89 (s, 3H, Me*Me*C=CH); δ_C (100 MHz): 150.7 (C), 145.4 (C), 133.2

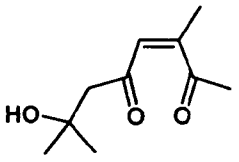
(C), 115.3 (C), 114.4 (CH), 110.5 (CH), 26.9 (CH_3), 20.0 (CH_3), 11.3 (CH_3), 9.8 (CH_3); m/*z* (EI) found 150.1037 (M^+) (12%), $C_{10}H_{14}O$ requires 150.1045.

(*Z*)-3, 7-Dimethyl-octa-3, 6-diene-2, 5-dione 163



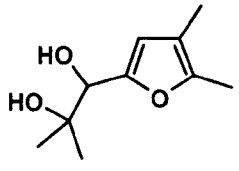
meta-Chloroperbenzoic acid (1.37 g, 5.96 mmol, 70-75 % weight balance) was added in one portion to a stirred solution of the alkenylfuran **162** (895 mg, 5.96 mmol) in DCM (50 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr and then water (30 mL) was added. The separated organic phase was washed with saturated aqueous $NaHCO_3$ (30 mL) and then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 20% diethyl ether in pentane as eluent, gave the *dienedione* (564 mg, 57% over 2 steps) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2914, 1699, 1672, 1627; δ_H (400 MHz): 6.09 (app. heptet, 1H, *J* 1.1, $(Me)_2C=CH$), 6.03 (q, 1H, *J* 1.6, CH=CMe), 2.33 (s, 3H, C(O)*Me*), 2.17 (d, 3H, *J* 1.1, *Me*MeC=CH), 1.98 (d, 3H, *J* 1.6, CH=C*Me*), 1.93 (d, 3H, *J* 1.1, Me*Me*C=CH); δ_C (100 MHz): 207.7 (C), 188.3 (C), 158.7 (C), 155.4 (C), 126.3 (CH), 123.7 (CH), 28.3 (CH_3), 28.0 (CH_3), 21.0 (CH_3), 20.2 (CH_3); m/*z* (ESI) found 189.0876 ($M + Na^+$), $C_{10}H_{14}O_2Na$ requires 189.0886.

(*Z*)-7-Hydroxy-3,7-dimethyl-oct-3-ene-2,5-dione 165



A solution of the dienedione **163** (25 mg, 0.15 mmol) and *para*-toluenesulfonic acid (2.9 mg, 0.02 mmol) in THF (10 mL) and water (5 mL) were stirred at room temperature for 20 hrs and then water (5 mL) and ethyl acetate (5 mL) were added. The separated aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 60% to 80% ethyl acetate in petroleum ether (product eluted at 80%) as eluent, gave the *tertiary alcohol* (3 mg, 10%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3642, 3516, 2927, 1704, 1614; δ_H (400 MHz): 6.03 (q, 1H, *J* 1.6, C*H*=CMe), 3.53 (br. s, 1H, $(Me)_2C(OH)CH_2$), 2.67 (s, 2H, $C(OH)CH_2$), 2.32 (s, 3H, C(O)*Me*), 2.00 (d, 3H, *J* 1.6, CH=C*Me*), 1.27 (s, 6H, $(Me)_2C(OH)CH_2$); δ_C (100 MHz): 206.6 (C), 200.2 (C), 156.7 (C), 124.6 (CH), 69.8 (C), 53.3 (CH_2), 29.4 (2 x CH_3), 28.0 (CH_3), 20.3 (CH_3); m/*z* (ESI) found 207.0989 ($M + Na^+$), $C_{10}H_{16}O_3Na$ requires 207.0992.

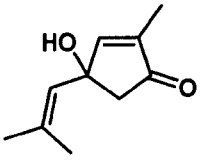
5-(2-Hydroxy-2-methyl-propylidene)-2,3-dimethyl-2,5-dihydro-furan-2-ol 178



A solution of the dienedione **163** (100 mg, 0.60 mmol) and *para*-toluenesulfonic acid (114 mg, 0.60 mmol) in THF (10 mL) and water (5 mL) were stirred at room temperature for 20 hrs and then water (5 mL) and ethyl acetate (5 mL) were added. The separated aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the

combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 40% to 50% ethyl acetate in petroleum ether (product eluted at 50%) as eluent, gave the *vicinal diol* (12 mg, 11%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3578, 2927, 1704, 1672; δ_H (300 MHz): 6.08 (s, 1H, C(O)=C*H*CMe), 4.38 (br. s, 1H, C*H*(OH)C), 2.19 (s, 3H, C(O)*Me*), 1.92 (s, 3H, C(O)=CHC*Me*), 1.28 (s, 3H, *Me*MeC(OH)CH), 1.26 (br. s, 2H, $(Me)_2C(OH)CH$ and CH(O*H*)C), 1.19 (s, 3H, Me*Me*C(OH)CH); δ_C (75 MHz): 150.7 (C), 147.0 (C), 114.5 (C), 111.3 (CH), 74.7 (CH), 73.1 (C), 26.0 (CH_3), 25.0 (CH_3), 11.4 (CH_3), 9.8 (CH_3); m/*z* (ESI) found 207.0988 ($M + Na^+$), $C_{10}H_{16}O_3Na$ requires 207.0992.

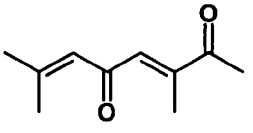
4-Hydroxy-2-methyl-4-(2-methyl-propenyl)-cyclopent-2-enone 193



A solution of the dienedione **163** (100 mg, 0.60 mmol) and potassium carbonate (83 mg, 0.60 mmol) in THF (50 mL) and water (25 mL) were stirred at room temperature for 20 hrs and then water (30 mL) and diethyl ether (30 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 40% to 50% diethyl ether in pentane (product eluted at 50%) as eluent, gave the *tertiary alcohol* (53 mg, 53%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3592, 2922, 2253, 1709, 1663; δ_H (400 MHz): 7.11 (q, 1H, *J* 1.4, C*H*=CMe), 5.46 (app. heptet, 1H, *J* 1.4, $(Me)_2C=CH$), 2.70 (s, 2H, $CH_2C=O$), 2.32 (br. s, 1H, C(O*H*)CH_2), 1.80 (d, 3H, *J* 1.4, *Me*MeC=CH),

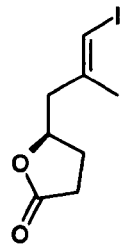
1.77 (d, 3H, *J* 1.4, CH=C*Me*), 1.73 (d, 3H, *J* 1.4, Me*Me*C=CH); δ_C (100 MHz): 207.4 (C), 159.5 (CH), 140.6 (C), 138.4 (C), 127.7 (CH), 75.4 (C), 51.8 (CH_2), 26.6 (CH_3), 19.3 (CH_3), 9.7 (CH_3); m/*z* (ESI) found 189.0880 ($M + Na^+$), $C_{10}H_{14}O_2Na$ requires 189.0886.

(*E*)-3,7-Dimethyl-octa-3,6-diene-2,5-dione 194



A solution of the *Z*-dienedione **163** (5 mg, 0.03 mmol) and iodine (2 drops of a solution formed by dissolving 1 crystal of iodine in 5 mL of $CDCl_3$) in $CDCl_3$ (0.60 mL) were allowed to stand at room temperature, exposed to laboratory light, for 20 hrs and then the mixture was concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10% to 15% diethyl ether in pentane (product eluted at 15%) as eluent, gave the *E-dienedione* (5 mg, 90%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2926, 2854, 1674, 1623; δ_H (400 MHz): 6.86 (q, 1H, *J* 1.4, C*H*=CMe), 6.22 (app. hept, 1H, *J* 1.2, $(Me)_2C=CH$), 2.39 (s, 3H, C(O)*Me*), 2.23 (d, 3H, *J* 1.2, *Me*MeC=CH), 2.15 (d, 3H, *J* 1.4, CH=C*Me*), 1.97 (d, 3H, *J* 1.2, Me*Me*C=CH); δ_C (100 MHz): 200.8 (C), 191.9 (C), 158.4 (C), 146.2 (C), 134.9 (CH), 125.2 (CH), 28.0 (CH_3), 26.2 (CH_3), 21.1 (CH_3), 13.1 (CH_3); m/*z* (ESI) found 189.0879 ($M + Na^+$), $C_{10}H_{14}O_2Na$ requires 189.0886.

(*R*)-5-((*E*)-3-Iodo-2-methyl-allyl)-dihydro-furan-2-one 282

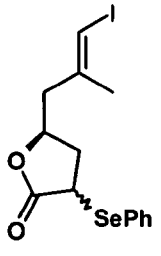


The lactone **282** was prepared according to the procedures described for the opposite enantiomer.[170,193] Commercially available (*S*)-epichlorohydrin was used.

A solution of *n*-butyllithium (2.70 mL, 6.70 mmol, 2.5 M in hexanes) was added dropwise over 5 mins to a stirred solution of ethoxyacetylene (1.60 mL, 8.03 mmol, 50% w/w in hexanes) in THF (9 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 20 mins and then boron trifluoride diethyletherate (0.85 mL, 6.70 mmol) was added dropwise over 1 min. The mixture was stirred at -78 °C for 2 mins and then a solution of (*R*)-2-((*E*)-3-iodo-2-methylallyl)-oxirane[170,193] (0.60 g, 2.68 mmol) in THF (5 mL) was added dropwise over 5 mins. The final mixture was stirred at -78 °C for 2 hrs, and then saturated aqueous $NaHCO_3$ (50 mL), water (50 mL) and diethyl ether (50 mL) were added and the mixture was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3 x 80 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *secondary alcohol* as a light yellow oil that was used without further purification. *p*-Toluenesulfonic acid (51 mg, 0.27 mmol) was added in one portion to a stirred solution of the crude secondary alcohol in ethanol (12 mL). The mixture was stirred at room temperature for 2 hrs and then concentrated *in vacuo* and again directly dissolved in chloroform (25 mL). The mixture was heated to reflux for 15 hrs, cooled to room temperature and then

saturated aqueous $NaHCO_3$ (20 mL) was added. The separated aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 20%, 30% to 50% diethyl ether in petroleum ether (product eluted at 50%) as eluent, gave the *lactone* (545 mg, 77%) as a colourless oil. $[\alpha]_D^{21}$ -41.3 (*c* 3.5 in CH_2Cl_2), *lit.*[170,193] $[\alpha]_D^{22}$ +41.8 (*c* 3.5 in CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$ solution): 2947, 1770; δ_H (360 MHz): 6.08 (q, 1H, *J* 1.0 , IC*H*=C), 4.66-4.56 (m, 1H, C*H*(O)CH_2), 2.63 (ddd, 1H, *J* 14.4, 7.4 and 0.8, C=C(Me)C*H*H), 2.52 (dd, 2H, *J* 9.6 and 6.9, CH_2C=O), 2.49 (ddd, 1H, *J* 14.4, 5.5 and 0.8, C=C(Me)CH*H*), 2.36-2.26 (m, 1H, C*H*HCH_2C=O), 1.93-1.80 (m, 1H, CH*H*CH_2C=O), 1.88 (d, 3H, *J* 1.0, C=C(*Me*)CH_2); δ_C (90 MHz): 176.6 (C), 142.7 (C), 78.5 (CH), 78.3 (CH), 44.8 (CH_2), 28.4 (CH_2), 27.5 (CH_2), 24.3 (CH_3); m/*z* (ESI) found 288.9695 (M + Na^+), $C_8H_{11}O_2INa$ requires 288.9696.

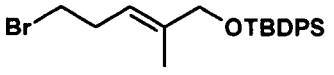
(*S*)-5-((*E*)-3-Iodo-2-methyl-allyl)-3-phenylselanyl-dihydro-furan-2-one 238



A solution of the lactone **282** (545 mg, 2.05 mmol) in THF (4 mL) was added dropwise over 10 mins to a stirred solution of LiHMDS (2.25 mL, 2.25 mmol, 1.0 M in THF) in THF (4 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 15 mins and then trimethylchlorosilane (0.29 mL, 2.25 mmol) was added dropwise over 1 min. The mixture was stirred at -78 °C for 30 mins and then a solution of phenylselenium bromide (531 mg, 2.25 mmol) in THF (4 mL)

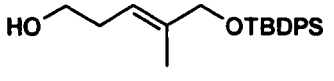
was added dropwise over 10 mins. The final mixture was stirred at -78 °C for 30 mins and then warmed to room temperature and stirred for 30 mins. Saturated aqueous NH_4Cl (15 mL), water (40 mL) and diethyl ether (80 mL) were added to the mixture and the separated aqueous phase was extracted with diethyl ether (3 x 80 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10%, 20%, to 30% diethyl ether in petroleum ether (product eluted at 30%) as eluent, gave the *seleno-lactone* (691 mg, 80%) as a mixture of diastereoisomers. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2920, 1770; δ_H (360 MHz): 7.69-7.62 (m, 2H, Se*Ph*), 7.42-7.30 (m, 3H, Se*Ph*), 6.03 (q, 0.60H, *J* 1.0, IC*H*=C), 5.97 (q, 0.40H, *J* 1.0, IC*H*=C), 4.57-4.48 (m, 0.40H, C*H*(O)CH_2), 4.40-4.31 (m, 0.60H, C*H*(O)CH_2), 4.01 (app. t, 0.40H, *J* 9.4, C*H*SePh), 3.93 (dd, 0.60H, *J* 6.1 and 4.8, C*H*SePh), 2.72 (ddd, 0.40H, *J* 13.7, 9.4 and 6.8, C*H*HCHSePh), 2.58 (dd, 0.60H, *J* 14.4 and 7.5, C=C(Me)C*H*H), 2.47-2.37 (m, 0.40H, C=C(Me)C*H*H and 0.60H, C=C(Me)CH*H*), 2.35-2.25 (m, 0.40H, C=C(Me)CH*H*, 0.60H, C*H*HCHSePh and 0.60H, CH*H*CHSePh), 1.97-1.87 (m, 0.40H, CH*H*CHSePh), 1.82 (d, 1.80H, *J* 1.0, C=C(*Me*)CH_2), 1.80 (d, 1.20H, *J* 1.0, C=C(*Me*)CH_2); δ_C (90 MHz): 175.3 (C), 175.2 (C), 142.3 (2 x C), 135.8 (2 x CH), 135.7 (2 x CH), 129.4 (2 x CH), 129.3 (2 x CH), 129.2 (CH), 129.0 (CH), 126.7 (C), 126.4 (C), 78.8 (CH), 78.7 (CH), 76.8 (CH), 76.5 (CH), 44.7 (CH_2), 44.3 (CH_2), 36.9 (CH), 36.5 (CH), 36.2 (CH_2), 35.0 (CH_2), 24.1 (2 x CH_3); m/*z* (ESI) found 422.9355 ($M + H^+$), $C_{14}H_{16}O_2ISe$ requires 422.9355.

(5-Bromo-2-methyl-(*E*)-pent-2-enyloxy)-*tert*-butyl-diphenyl-silane 279



tert-Butyldiphenylsilyl chloride (0.34 g, 0.32 mL, 1.23 mmol) was added in dropwise over 10 mins to a stirred solution of the allylic alcohol **253**[199] (0.20 g, 1.12 mmol) and imidazole (91 mg, 1.34 mmol) in anhydrous DMF (0.6 mL) at 0 °C under a nitrogen atmosphere. After 10 mins of stirring at 0 °C, diethyl ether (20 mL) and silica gel (~2 g) were added and the resulting suspension was concentrated *in vacuo*. Direct purification by Purification by chromatography on silica gel (anhydrous loading) with 5% diethyl ether in petroleum ether as eluent, gave the *bromide* (0.42 g, 90%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2932, 2859, 1590, 643; δ_H (360 MHz): 7.75-7.69 (m, 4H, Si^{t}Bu(*Ph*)$_2$), 7.49-7.37 (m, 6H, Si^{t}Bu(*Ph*)$_2$), 5.53 (tq, 1H, *J* 7.2 and 1.4, C*H*=C(Me)CH_2), 4.10 (s, 2H, CH_2OTBDPS), 3.39 (t, 2H, *J* 7.2, CH_2Br), 2.66 (app. q, 2H, *J* 7.2, CH_2CH_2Br), 1.64 (d, 3H, *J* 1.4, CH=C(*Me*)CH_2), 1.11 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 137.1 (C), 135.5 (4 x CH), 133.7 (2 x C), 129.6 (2 x CH), 127.6 (4 x CH), 120.4 (CH) 68.4 (CH_2), 32.6 (CH_2), 31.1 (CH_2), 26.8 (3 x CH_3), 19.3 (C), 13.7 (CH_3); m/*z* (ESI) found 439.1041 (M + Na^+), $C_{22}H_{29}OBrSiNa$ requires 439.1063.

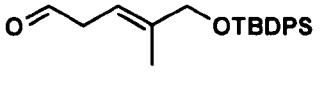
5-(*tert*-Butyl-diphenyl-silanyloxy)-4-methyl-(*E*)-pent-3-en-1-ol 280



Potassium acetate (0.30 g, 3.03 mmol) was added in one portion to a stirred solution of the bromide **279** (0.42 g, 1.01 mmol) in anhydrous DMF (3.5 mL) at room temperature under a nitrogen atmosphere. The resulting mixture was heated to 100 °C for 17 hrs, cooled to room temperature and then diethyl ether (30 mL) and water (20

mL) were added. The separated aqueous phase was extracted with diethyl ether (2 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *acetyl alcohol* as a light yellow oil that was used without further purification. Potassium carbonate (0.49 g, 3.53 mmol) was added in one portion to a stirred solution of the crude acetyl alcohol in methanol (14 mL) at room temperature. The mixture was stirred at this temperature for 90 mins and then diethyl ether (30 mL) and water (20 mL) were added. The separated aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 40% diethyl ether in petroleum ether as eluent, gave the *alcohol* (0.30 g, 83%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3625, 2932, 2859, 1589; δ_H (360 MHz): 7.76-7.68 (m, 4H, Si^{t}Bu(*Ph*)$_2$), 7.49-7.36 (m, 6H, Si^{t}Bu(*Ph*)$_2$), 5.47 (tq, 1H, *J* 7.4 and 1.4, C*H*=C(Me)CH_2), 4.12 (s, 2H, CH_2OTBDPS), 3.65 (t, 2H, *J* 6.6, CH_2OH), 2.35 (dt, 2H, *J* 7.4 and 6.6, CH_2CH_2OH), 1.67 (d, 3H, *J* 1.4, CH=C(*Me*)CH_2), 1.66 (br. s, 1H, CH_2O*H*), 1.11 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 137.3 (C), 135.5 (4 x CH), 133.7 (2 x C), 129.6 (2 x CH), 127.6 (4 x CH), 119.7 (CH) 68.7 (CH_2), 62.3 (CH_2), 31.0 (CH_2), 26.8 (3 x CH_3), 19.2 (C), 13.6 (CH_3); m/*z* (ESI) found 377.1904 (M + Na^+), $C_{22}H_{30}O_2SiNa$ requires 377.1907.

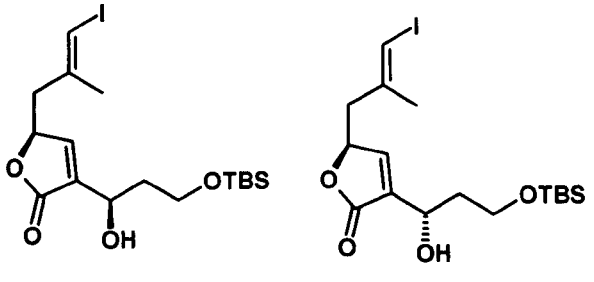
5-(*tert*-Butyl-diphenyl-silanyloxy)-4-methyl-(*E*)-pent-3-enal 277



Dess-Martin periodinane (168 mg, 0.40 mmol) was added in one portion to a stirred solution of the alcohol **280** (94 mg, 0.26 mmol) in DCM (10 mL) at room temperature. The mixture was stirred at this temperature for 30 mins, and then saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (30 mL, 1:1) were added

and the resulting biphasic mixture was stirred vigorously for 45 mins. The separated aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude mixture by filtration through a short plug of silica gel, using diethyl ether as eluent, gave the *aldehyde* (93 mg, 100%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2932, 2859, 1724, 1693, 1590; δ_H (360 MHz): 9.66 (t, 1H, *J* 2.1, C*H*O), 7.76-7.65 (m, 4H, Si^{t}Bu(*Ph*)$_2$), 7.50-7.36 (m, 6H, Si^{t}Bu(*Ph*)$_2$), 5.73 (tq, 1H, *J* 7.3 and 1.5, C*H*=C(Me)CH_2), 4.15 (s, 2H, CH_2OTBDPS), 3.20 (dd, 2H, *J* 7.3 and 2.1, CH_2CHO), 1.64 (d, 3H, *J* 1.5, CH=C(*Me*)CH_2), 1.11 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 199.8 (CH), 139.7 (C), 135.5 (4 x CH), 133.5 (2 x C), 129.6 (2 x CH), 127.6 (4 x CH), 112.5 (CH), 68.2 (CH_2), 42.8 (CH_2), 26.8 (3 x CH_3), 19.2 (C), 13.8 (CH_3); m/*z* (ESI) found 353.1915 ($M + H^+$), $C_{22}H_{29}O_2Si$ requires 353.1931.

3-[3-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy-propyl]-(*R*)-5-((*E*)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one 286a and 286b

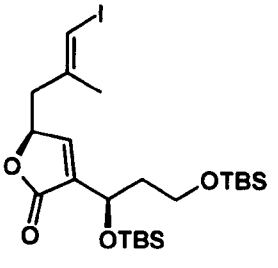


A solution of the seleno-lactone **238** (192 mg, 0.46 mmol) in THF (10 mL) was added dropwise over 20 mins to a stirred solution of LiHMDS (0.50 mL, 0.50 mmol, 1.0 M in THF) in THF (10 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 50 mins and then a solution of 3-(*tert*-butyl-dimethyl-silanyloxy)-propionaldehyde **278**[205,244] (172 mg, 0.91 mmol) in THF (10 mL) was added dropwise over 20 mins. The final mixture was stirred at -78 °C for 1 hr and

then saturated aqueous NH_4Cl (50 mL), water (50 mL) and diethyl ether (50 mL) were added and the biphasic solution was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *seleno-alcohol* as a yellow oil that was used without further purification. A solution of hydrogen peroxide (0.20 mL, 30% w/w in water) was added dropwise over 1 min to a stirred solution of the crude seleno-alcohol and pyridine (12 mL) in DCM (12 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr, and then saturated aqueous $NaHCO_3$ (30 mL), water (30 mL) and DCM (40 mL) were added. The separated aqueous phase was extracted with DCM (3 x 40 mL) and the combined organic extracts were then concentrated *in vacuo*. The crude mixture was dissolved in DCM (100 mL), washed with saturated aqueous $CuSO_4$ (3 x 50 mL) and then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 30% to 40% diethyl ether in petroleum ether (product eluted at 40%) as eluent, gave the *alcohol* (182 mg, 99%) as separable diastereoisomers. *1st isomer (minor):* $[\alpha]_D^{22}$ +16.2 (*c* 2.0 in CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$ solution): 3444, 2930, 2858, 1755, 1618; δ_H (360 MHz): 7.32 (app. t, 1H, *J* 1.7, C*H*=CCH), 6.14 (q, 1H, *J* 1.0, IC*H*=C(Me)CH_2), 5.08-5.02 (m, 1H, C*H*(O)CH), 4.71 (ddd, 1H, *J* 8.6, 4.0 and 1.7, C*H*(OH)CH_2), 4.37 (br. s, 1H, CH(O*H*)CH_2), 3.96-3.86 (m, 2H, CH_2OTBS), 2.62-2.54 (m, 2H, C=C(Me)CH_2), 2.17-2.08 (m, 1H, C*H*HCH_2OTBS), 1.93 (d, 3H, *J* 1.0, ICH=C(*Me*)CH_2), 1.85-1.74 (m, 1H, CH*H*CH_2OTBS), 0.91 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.10 (s, 3H, Si^{t}Bu*Me*Me), 0.09 (s, 3H, Si^{t}BuMe*Me*); δ_C (90 MHz): 171.5 (C), 148.0 (CH), 141.8 (C), 137.3 (C), 79.4 (2 x CH), 68.5 (CH), 62.7 (CH_2), 42.8 (CH_2), 36.0 (CH_2), 25.8 (3 x CH_3), 24.5 (CH_3), 18.0 (C), -5.6 (2 x CH_3); m/*z* (ESI) found 453.0950 (M + H^+), $C_{17}H_{30}O_4ISi$ requires

453.0953. *2nd isomer (major):* $[\alpha]_D^{21}$ -13.5 (*c* 2.0 in CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$ solution): 3449, 2930, 2858, 1756, 1618; δ_H (360 MHz): 7.31 (app. t, 1H, *J* 1.7, C*H*=CCH), 6.13 (q, 1H, *J* 1.0, IC*H*=C(Me)CH_2), 5.11-5.04 (m, 1H, C*H*(O)CH), 4.72 (br. d, 1H, *J* 8.3, C*H*(OH)CH_2), 4.34 (br. s, 1H, CH(O*H*)CH_2), 3.96-3.85 (m, 2H, CH_2OTBS), 2.69-2.52 (m, 2H, C=C(Me)CH_2), 2.17-2.08 (m, 1H, C*H*HCH_2OTBS), 1.93 (d, 3H, *J* 1.0, ICH=C(*Me*)CH_2), 1.86-1.74 (m, 1H, CH*H*CH_2OTBS), 0.92 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.11 (s, 3H, Si^{t}Bu*Me*Me), 0.10 (s, 3H, Si^{t}BuMe*Me*); δ_C (90 MHz): 171.5 (C), 147.9 (CH), 141.7 (C), 137.5 (C), 79.4 (2 x CH), 68.4 (CH), 62.8 (CH_2), 42.7 (CH_2), 36.2 (CH_2), 25.8 (3 x CH_3), 24.7 (CH_3), 18.0 (C), -5.5 (CH_3), -5.6 (CH_3); m/*z* (ESI) found 453.0939 ($M + H^+$), $C_{17}H_{30}O_4ISi$ requires 453.0953.

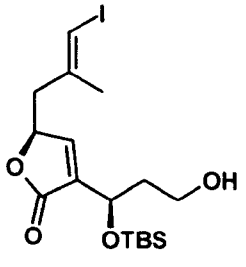
3-[1,3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-(*R*)-1-propyl]-(*R*)-5-((*E*)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one 286c



tert-Butyldimethylsilyl trifluoromethanesulfonate (0.13 mL, 0.56 mmol) was added dropwise over 2 mins to a stirred solution of the alcohol (–)-**286a** (85 mg, 0.19 mmol) and 2,6-lutidine (0.54 mL, 4.67 mmol) in DCM (10 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 90 mins, and then methanol (5 mL) was added and the mixture was then warmed to room temperature. Diethyl ether (25 mL) was added to the mixture and the organic phase was sequentially washed with saturated aqueous $CuSO_4$ (25 mL), water (25 mL) and brine (25 mL) and then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by

chromatography on silica gel, using a gradient of 10% to 20% diethyl ether in petroleum ether (product eluted at 10%) as eluent, gave the *silyl ether* (92 mg, 87%) as a colourless oil. $[\alpha]_D^{22}$ -41.3 (*c* 2.0 in CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$ solution): 2929, 2857, 1757, 1618; δ_H (360 MHz): 7.16 (app. t, 1H, *J* 1.5, C*H*=CCH), 6.13 (q, 1H, *J* 1.0, IC*H*=C(Me)CH_2), 5.06-4.97 (m, 1H, C*H*(O)CH), 4.70-4.61 (m, 1H, C*H*(OTBS)CH_2), 3.78-3.62 (m, 2H, C*H*$_2$OTBS), 2.63 (dd, 1H, *J* 14.3 and 5.0, C=C(Me)C*H*H), 2.51 (dd, 1H, *J* 14.3 and 7.7, C=C(Me)CH*H*), 2.02-1.89 (m, 1H, C*H*HCH_2OTBS), 1.93 (d, 3H, *J* 1.0, ICH=C(*Me*)CH_2), 1.79-1.69 (m, 1H, CH*H*CH_2OTBS), 0.91 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.90 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.09 (s, 3H, Si^{t}Bu*Me*Me), 0.06 (s, 3H, Si^{t}Bu*Me*Me), 0.05 (s, 3H, Si^{t}BuMe*Me*), 0.00 (s, 3H, Si^{t}BuMe*Me*); δ_C (90 MHz): 171.1 (C), 147.5 (CH), 141.9 (C), 139.2 (C), 79.3 (CH), 79.1 (CH), 64.7 (CH), 58.9 (CH_2), 42.8 (CH_2), 39.9 (CH_2), 25.9 (3 x CH_3), 25.8 (3 x CH_3), 24.6 (CH_3), 18.3 (C), 18.1 (C), -4.7 (CH_3), -5.1 (CH_3), -5.2 (CH_3), -5.3 (CH_3); m/*z* (ESI) found 567.1820 ($M + H^+$), $C_{23}H_{44}O_4ISi_2$ requires 567.1817.

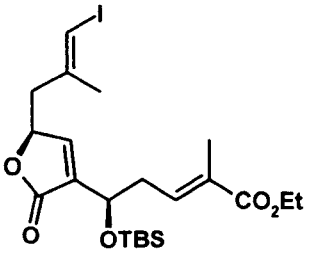
3-[(*R*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-3-hydroxy-propyl]-(*R*)-5-((*E*)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one 286d



A solution of the silyl ether (–)-**286c** (336 mg, 0.59 mmol) and pyridinium *para*-toluenesulfonate (149 mg, 0.59 mmol) in methanol (15 mL) and DCM (15 mL) was stirred at room temperature for 15 hrs and then the mixture was concentrated *in vacuo*. Water (25 mL) and diethyl ether (25 mL) were added to the residue and the separated

aqueous phase was extracted with diethyl ether (3 x 25 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 50% diethyl ether in petroleum ether to 100% ethyl acetate (product eluted at 100% ethyl acetate) as eluent, gave the *alcohol* (231 mg, 86%) as a colourless oil. $[\alpha]_D^{23}$ -49.8 (*c* 2.1 in CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$ solution): 3526, 2931, 2858, 1755, 1618; δ_H (360 MHz): 7.23 (app. t, 1H, *J* 1.5, C*H*=CCH), 6.12 (q, 1H, *J* 1.0, IC*H*=C(Me)CH_2), 5.11-5.03 (m, 1H, C*H*(O)CH), 4.79-4.72 (m, 1H, C*H*(OTBS)CH_2), 3.74-3.62 (m, 2H, C*H*$_2$OH), 2.68 (dd, 1H, *J* 14.4 and 4.9, C=C(Me)C*H*H), 2.52 (dd, 1H, *J* 14.4 and 7.5, C=C(Me)CH*H*), 2.44 (br. s, 1H, CH_2OH), 2.05-1.85 (m, 2H, C*H*$_2$$CH_2$OH), 1.90 (d, 3H, *J* 1.0, ICH=C(*Me*)CH_2), 0.90 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.10 (s, 3H, Si^{t}Bu*Me*Me), 0.02 (s, 3H, Si^{t}BuMe*Me*); δ_C (90 MHz): 171.4 (C), 148.4 (CH), 141.6 (C), 138.2 (C), 79.5 (2 x CH), 66.7 (CH), 59.1 (CH_2), 42.4 (CH_2), 38.3 (CH_2), 25.7 (3 x CH_3), 24.7 (CH_3), 17.9 (C), -4.9 (CH_3), -5.2 (CH_3); m/*z* (ESI) found 453.0962 ($M + H^+$), $C_{17}H_{30}O_4ISi$ requires 453.0953.

(*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-5-[(*R*)-5-((*E*)-3-iodo-2-methyl-allyl)-2-oxo-2,5-dihydro-furan-3-yl]-(*E*)-2-methyl-pent-2-enoic acid ethyl ester 288

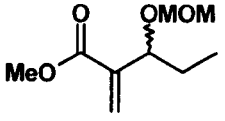


Dess-Martin periodinane (397 mg, 0.94 mmol) was added in one portion to a stirred solution of the alcohol (–)-**286d** (212 mg, 0.47 mmol) in DCM (25 mL) at room temperature. The mixture was stirred at this temperature for 45 mins and then saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (20 mL, 1:1) were added

and the resulting biphasic mixture was stirred vigorously for 45 mins. The separated aqueous phase was extracted with DCM (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *aldehyde* as a colourless oil that was used without further purification. δ_H (360 MHz): 9.73 (dd, 1H, *J* 2.5 and 1.9, C*H*O), 7.24 (app. t, 1H, *J* 1.6, C*H*=CCH), 6.12 (q, 1H, *J* 1.0, IC*H*=C(Me)CH_2), 5.12-5.03 (m, 1H, C*H*(O)CH), 5.03-4.95 (m, 1H, C*H*(OTBS)CH_2), 2.81 (ddd, 1H, *J* 16.0, 4.1 and 1.9, C*H*HCHO), 2.75-2.61 (m, 2H, CH*H*CHO and C=C(Me)C*H*H), 2.57-2.46 (m, 1H, C=C(Me)C*HH*), 1.90 (d, 3H, *J* 1.0, ICH=C(*Me*)CH_2), 0.88 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.09 (s, 3H, Si^{t}Bu*Me*Me), 0.03 (s, 3H, Si^{t}BuMe*Me*). Phosphorane **273** (339 mg, 0.94 mmol) was added in one portion to a stirred solution of the crude aldehyde in THF (25 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 hrs and then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 5%, 10% to 20% diethyl ether in petroleum ether (product eluted at 20%) as eluent, gave the *α,β-unsaturated ester* (238 mg, 95%) as a colourless oil. $[\alpha]_D^{24}$ -40.5 (*c* 2.0 in CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$ solution): 2930, 2858, 1755, 1704, 1651; δ_H (360 MHz): 7.19 (app. t, 1H, *J* 1.5, C*H*=CCH), 6.75 (ddq, 1H, *J* 8.4, 6.5 and 1.3, C*H*=C(Me)CO_2Et), 6.10 (q, 1H, *J* 1.0, IC*H*=C(Me)CH_2), 5.08-5.01 (m, 1H, C*H*(O)CH), 4.67-4.60 (m, 1H, C*H*(OTBS)CH_2), 4.16 (q, 2H, *J* 7.1, CO_2CH_2Me), 2.66-2.54 (m, 2H, C=C(Me)CH_2), 2.53-2.42 (m, 2H, CH(OTBS)CH_2), 1.89 (d, 3H, *J* 1.0, ICH=C(*Me*)CH_2), 1.80 (d, 3H, *J* 1.3, CH=C(*Me*)CO_2Et), 1.26 (t, 3H, *J* 7.1, CO_2CH_2*Me*), 0.88 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.05 (s, 3H, Si^{t}Bu*Me*Me), -0.01 (s, 3H, Si^{t}BuMe*Me*); δ_C (90 MHz): 171.0 (C), 167.6 (C), 148.4 (CH), 141.6 (C), 137.9 (C), 136.6 (CH), 130.1 (C), 79.4 (CH), 79.2 (CH), 66.8 (CH), 60.3 (CH_2), 42.7 (CH_2), 35.5

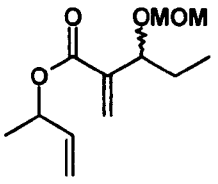
(CH_2), 25.6 (3 x CH_3), 24.5 (CH_3), 18.0 (C), 14.2 (CH_3), 12.6 (CH_3), -4.9 (CH_3), -5.1 (CH_3); m/*z* (ESI) found 552.1646 ($M + NH_4^+$), $C_{22}H_{39}O_5NISi$ requires 552.1642.

3-Methoxymethoxy-2-methylene-pentanoic acid methyl ester 303a



MOM-Cl (1.19 mL, 15.6 mmol) was added over 2 mins to a stirred solution of 3-hydroxy-2-methylene-pentanoic acid methyl ester **302** (500 mg, 3.12 mmol) and DIPEA (5.4 mL, 31.2 mmol) in DCM (20 mL) at 30 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 24 hrs and then DCM (100 mL) and water (50 mL) were added. The separated aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10% to 20% diethyl ether in petroleum ether (product eluted at 20%) as eluent, gave the *MOM-ether* (497 mg, 85%) as a colourless oil. (Found C, 57.5; H, 8.5, $C_9H_{16}O_4$ requires C, 57.4; H, 8.6); ν_{max}/cm^{-1} ($CHCl_3$ solution): 2936, 2891, 1715, 1629; δ_H (360 MHz): 6.26 (d, 1H, *J* 1.5, C=C*H*H), 5.80 (dd, 1H, *J* 1.5 and 0.8, C=CH*H*), 4.56 (d, 1H, *J* 6.7, OC*H*HOMe), 4.53 (d, 1H, *J* 6.7, OCH*H*OMe), 4.41 (ddd, 1H, *J* 7.3, 4.6 and 0.8, C*H*(OMOM)CH_2), 3.72 (s, 3H, CO_2*Me*), 3.34 (s, 3H, OCH_2O*Me*), 1.78-1.65 (m, 1H, C*H*HMe), 1.63-1.49 (m, 1H, CH*H*Me), 0.90 (t, 3H, *J* 7.4, CH_2*Me*); δ_C (90 MHz): 166.5 (C), 140.9 (C), 125.2 (CH_2), 94.7 (CH_2), 75.6 (CH), 55.5 (CH_3), 51.6 (CH_3), 28.4 (CH_2), 9.7 (CH_3); m/*z* (ESI) found 211.0931 ($M + Na^+$), $C_9H_{16}O_4Na$ requires 211.0946.

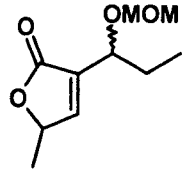
3-Methoxymethoxy-2-methylene-pentanoic acid 1-methyl-allyl ester 304



A solution of lithium hydroxide (13.3 mL, 13.3 mmol, 1.0 M in water) was added to a stirred solution of the MOM-ether **303a** (250 mg, 1.33 mmol) in THF (10 mL) and water (5 mL) at room temperature. The mixture was stirred at this temperature for 24 hrs and then acidified to pH 3 using 0.5 M aqueous hydrochloric acid. Diethyl ether (30 mL) was added to the mixture and the separated aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *carboxylic acid* as a yellow oil that was used without further purification. 1-Buten-3-ol (0.23 mL, 2.66 mmol) in DCM (10 mL) was added over 5 mins to a stirred solution of the crude carboxylic acid and DMAP (16 mg, 0.13 mmol) in DCM (10 mL) at 0 °C under a nitrogen atmosphere. DCC (288 mg, 1.39 mmol) was added in one portion and the mixture was warmed to room temperature and then stirred for 24 hrs. The mixture was filtered, eluting with DCM, and the filtrate was then concentrated *in vacuo*. Purification by chromatography on silica gel, using 10% diethyl ether in petroleum ether as eluent, gave the *allylic ester* (188 mg, 62%) as a mixture of diastereoisomers. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2934, 2890, 1714, 1628; δ_H (360 MHz): 6.30 (d, 1H, *J* 1.5, C=C*H*H), 5.87 (ddd, 0.50H, *J* 17.2, 10.6 and 5.8, C*H*=CH_2), 5.86 (ddd, 0.50H, *J* 17.2, 10.6 and 5.8, C*H*=CH_2), 5.82 (2 x dd, 1H, *J* 1.5 and 0.8, C=CH*H*), 5.46-5.37 (m, 1H, C*H*(O)CH), 5.26 (ddd, 0.50H, *J* 17.2, 1.4 and 1.4, CH=C*H*H), 5.25 (ddd, 0.50H, *J* 17.2, 1.4 and 1.4, CH=C*H*H), 5.15 (dd, 0.50H, *J* 10.6 and 1.4, CH=CH*H*), 5.14 (dd, 0.50H, *J* 10.6 and 1.4, CH=CH*H*), 4.61 (d, 0.50H, *J* 6.7, OC*H*HOMe), 4.60 (d, 0.50H, *J* 6.7, OC*H*HOMe), 4.57 (d, 1H, *J*

6.7, OCH*H*OMe), 4.48-4.41 (m, 1H, C*H*(OMOM)CH_2), 3.38 (s, 3H, OCH_2O*Me*), 1.82-1.69 (m, 1H, C*H*HMe), 1.67-1.53 (m, 1H, CH*H*Me), 1.36 (d, 1.50H, *J* 0.9, *Me*CH(O)CH), 1.34 (d, 1.50H, *J* 0.9, *Me*CH(O)CH), 0.94 (t, 3H, *J* 7.4, CH_2*Me*); δ_C (90 MHz): 165.3 (2 x C), 141.4 (2 x C), 137.5 (2 x CH), 125.0 (CH_2), 124.9 (CH_2), 115.8 (CH_2), 115.7 (CH_2), 94.9 (2 x CH_2), 75.8 (CH), 75.7 (CH), 71.3 (2 x CH), 55.6 (2 x CH_3), 28.5 (2 x CH_2), 19.9 (2 x CH_3), 9.9 (2 x CH_3); m/*z* (ESI) found 251.1246 ($M + Na^+$), $C_{12}H_{20}O_4Na$ requires 251.1259.

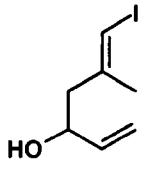
3-(1-Methoxymethoxy-propyl)-5-methyl-5*H*-furan-2-one 305



A solution of the allylic ester **304** (40 mg, 0.20 mmol) in DCM (10 mL) was added over 1 min to a stirred solution of Grubbs second generation catalyst (50 mg, 0.06 mmol) in DCM (10 mL) at room temperature under a nitrogen atmosphere. The mixture was heated to reflux for 24 hrs, cooled to room temperature and then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10%, 20%, 30%, 50% to 100% diethyl ether in petroleum ether (product eluted at 100%) as eluent, gave the *butenolide* (47 mg, 67%) as a mixture of diastereoisomers. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2935, 2891, 1747, 1650; δ_H (360 MHz): 7.25-7.22 (m, 1H, C*H*=CCH), 5.09-5.01 (m, 1H, C*H*(O)CH), 4.63 (s, 2H, OCH_2OMe), 4.42-4.36 (m, 1H, C*H*(OMOM)CH_2), 3.37 (s, 3H, OCH_2O*Me*), 1.90-1.68 (m, 2H, CH_2Me), 1.44 (d, 1.50H, *J* 2.0, *Me*CH(O)CH), 1.42 (d, 1.50H, *J* 2.0, *Me*CH(O)CH), 0.93 (2 x t, 3H, *J* 7.4, CH_2*Me*); δ_C (90 MHz): 171.9 (C), 171.8 (C), 150.8 (CH), 150.7 (CH), 134.7 (2 x C), 95.2 (2 x CH_2), 77.6 (2 x CH), 72.5 (CH), 72.4 (CH), 55.7 (2 x CH_3), 26.9

(CH_2), 26.8 (CH_2), 19.1 (2 x CH_3), 9.3 (CH_3), 9.2 (CH_3); m/*z* (ESI) found 223.0931 ($M + Na^+$), $C_{10}H_{16}O_4Na$ requires 223.0946.

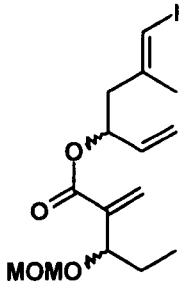
(*E*)-6-Iodo-5-methyl-hexa-1,5-dien-3-ol 297b



Dess-Martin periodinane (1.50 g, 3.54 mmol) was added in one portion to a stirred solution of (*E*)-4-iodo-3-methyl-but-3-en-1-ol **244b**[238] (500 mg, 2.36 mmol) and $NaHCO_3$ (1.00 g, 11.8 mmol) in DCM (10 mL) at room temperature. The mixture was stirred at this temperature for 45 mins, and then saturated aqueous $Na_2S_2O_3$, water and saturated aqueous $NaHCO_3$ (30 mL, 1:1:1) were added and the resulting biphasic mixture was stirred vigorously for 45 mins. The separated aqueous phase was extracted with DCM (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *aldehyde* as a colourless oil that was used without further purification. Vinylmagnesium bromide (2.8 mL, 2.83 mmol, 1.0 M in THF) was added dropwise over 15 mins to a stirred solution of the crude aldehyde in THF (15 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr, then water (10 mL) and diethyl ether (10 mL) were added and the mixture was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 20% to 30% diethyl ether in petroleum ether (product eluted at 30%) as eluent, gave the *allylic alcohol* (226 mg, 40%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3603, 2915, 1710, 1614; δ_H (360 MHz): 6.02 (q, 1H, *J*

0.9, IC*H*=C(Me)CH_2), 5.84 (ddd, 1H, *J* 17.2, 10.4 and 5.9, C*H*=CH_2), 5.26 (ddd, 1H, *J* 17.2, 1.3 and 1.3, CH=C*H*H), 5.13 (dd, 1H, *J* 10.4 and 1.3, CH=CH*H*), 4.29-4.21 (m, 1H, C*H*(OH)CH), 2.42 (d, 2H, *J* 6.9, C=C(Me)CH_2), 1.88 (d, 3H, *J* 0.9, ICH=C(*Me*)CH_2) 1.88 (br. s, 1H, CH(O*H*)CH); δ_C (90 MHz): 144.2 (C), 139.8 (CH), 115.1 (CH_2), 77.8 (CH), 70.3 (CH), 47.1 (CH_2), 24.1 (CH_3); m/*z* (EI) found 220.9826 (M^+ - OH) (97%), $C_7H_{10}I$ requires 220.9827.

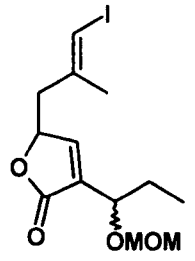
3-Methoxymethoxy-2-methylene-pentanoic acid (*E*)-4-iodo-3-methyl-1-vinyl-but-3-enyl ester 308



A solution of lithium hydroxide (10.6 mL, 10.6 mmol, 1.0 M in water) was added to a stirred solution of the MOM-ether **303a** (200 mg, 1.06 mmol) in THF (10 mL) and water (5 mL) at room temperature. The mixture was stirred at this temperature for 24 hrs and then acidified to pH 3 using 0.5 M aqueous hydrochloric acid. Diethyl ether (30 mL) was added to the mixture and the separated aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *carboxylic acid* as a yellow oil that was used without further purification. A solution of the vinyl iodide **297b** (226 mg, 0.95 mmol) in DCM (10 mL) was added over 5 mins to a stirred solution of the crude carboxylic acid and DMAP (13 mg, 0.11 mmol) in DCM (10 mL) at 0 °C under a nitrogen atmosphere. DCC (230 mg, 1.12 mmol) was added in one portion and the mixture was warmed to room temperature and then stirred for 24 hrs. The mixture was filtered,

eluting with DCM, and the filtrate was then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10% to 20% diethyl ether in petroleum ether (product eluted at 20%) as eluent, gave the *allylic ester* (232 mg, 59%) as a mixture of diastereoisomers. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2935, 2891, 1714, 1628; δ_H (360 MHz): 6.27 (d, 1H, *J* 1.5, C=C*H*H), 5.99 (q, 0.50H, *J* 1.0, IC*H*=C(Me)CH_2), 5.98 (q, 0.50H, *J* 1.0, IC*H*=C(Me)CH_2), 5.82 (dd, 1H, *J* 1.5 and 0.8, C=CH*H*), 5.79 (2 x ddd, 1H, *J* 17.2, 10.5 and 6.1, C*H*=CH_2), 5.51-5.42 (m, 1H, C*H*(O)CH), 5.27 (ddd, 0.50H, *J* 17.2, 1.2 and 1.2, CH=C*H*H), 5.25 (ddd, 0.50H, *J* 17.2, 1.2 and 1.2, CH=C*H*H), 5.19 (dd, 0.50H, *J* 10.5 and 1.2, CH=CH*H*), 5.18 (dd, 0.50H, *J* 10.5 and 1.2, CH=CH*H*), 4.58 (2 x d, 1H, *J* 6.7, OC*H*HOMe), 4.55 (2 x d, 1H, *J* 6.7, OCH*H*OMe), 4.41 (ddd, 1H, *J* 8.2, 5.1 and 1.2, C*H*(OMOM)CH_2), 3.36 (2 x s, 3H, OCH_2O*Me*), 2.61 (dd, 0.50H, *J* 14.0 and 8.2, ICH=C(Me)C*H*H), 2.59 (dd, 0.50H, *J* 14.0 and 8.2, ICH=C(Me)C*H*H), 2.48 (dd, 1H, *J* 14.0 and 5.1, ICH=C(Me)CH*H*), 1.86 (d, 3H, *J* 1.0, ICH=C(*Me*)CH_2), 1.78-1.66 (m, 1H, C*H*HMe), 1.63-1.52 (m, 1H, CH*H*Me), 0.92 (t, 3H, *J* 7.4, CH_2*Me*); δ_C (90 MHz): 165.0 (C), 164.9 (C), 143.0 (2 x C), 141.1 (C), 141.0 (C), 135.4 (2 x CH), 125.3 (2 x CH_2), 117.1 (CH_2), 117.0 (CH_2), 94.8 (2 x CH_2), 78.2 (2 x CH), 75.6 (CH), 75.5 (CH), 72.0 (2 x CH), 55.6 (2 x CH_3), 44.2 (CH_2), 44.1 (CH_2), 28.4 (2 x CH_2), 24.0 (CH_3), 23.9 (CH_3), 9.9 (CH_3), 9.8 (CH_3); m/*z* (ESI) found 417.0552 ($M + Na^+$), $C_{15}H_{23}O_4INa$ requires 417.0533.

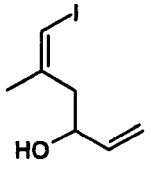
5-((*E*)-3-Iodo-2-methyl-allyl)-3-(1-methoxymethoxy-propyl)-5*H*-furan-2-one 309



A solution of Grubbs second generation catalyst (65 mg, 0.08 mmol) in DCM (8 mL) and a solution of the allylic ester **308** (100 mg, 0.25 mmol) in DCM (8 mL) were added simultaneously over 8 hrs to a refluxing solution of DCM (120 mL) under a nitrogen atmosphere. The mixture was stirred under reflux for 24 hrs, cooled to room temperature and then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 30% to 50% diethyl ether in petroleum ether (product eluted at 50%) as eluent, gave the *butenolide* (57 mg, 62%) as separable diastereoisomers. *1st isomer:* ν_{max}/cm^{-1} ($CHCl_3$ solution): 2930, 2853, 1749, 1651, 1617; δ_H (360 MHz): 7.22 (app. t, 1H, *J* 1.4, C*H*=CCH), 6.13 (q, 1H, *J* 1.0, IC*H*=C(Me)CH_2), 5.10-5.04 (m, 1H, C*H*(O)CH), 4.64 (s, 2H, OCH_2OMe), 4.44-4.38 (m, 1H, C*H*(OMOM)CH_2), 3.39 (s, 3H, OCH_2OMe), 2.61 (d, 2H, *J* 6.6, ICH=C(Me)CH_2), 1.93 (d, 3H, *J* 1.0, ICH=C(*Me*)CH_2), 1.89-1.67 (m, 2H, CH_2Me), 0.94 (t, 3H, *J* 7.4, CH_2Me); δ_C (90 MHz): 171.4 (C), 148.6 (CH), 141.9 (C), 135.8 (C), 95.3 (CH_2), 79.3 (CH), 79.2 (CH), 72.6 (CH), 55.8 (CH_3), 42.8 (CH_2), 26.8 (CH_2), 24.6 (CH_3), 9.3 (CH_3); m/*z* (ESI) found 389.0230 ($M + Na^+$), $C_{13}H_{19}O_4INa$ requires 389.0226; *2nd isomer:* ν_{max}/cm^{-1} ($CHCl_3$ solution): 2934, 2854, 1759, 1616; δ_H (360 MHz): 7.22 (app. t, 1H, *J* 1.4, C*H*=CCH), 6.13 (q, 1H, *J* 1.0, IC*H*=C(Me)CH_2), 5.07 (dddd, 1H, *J* 7.0, 5.8, 1.6 and 1.4, C*H*(O)CH), 4.64 (s, 2H, OCH_2OMe), 4.42 (dddd, 1H, *J* 6.6, 5.1, 1.6 and 1.4, C*H*(OMOM)CH_2), 3.38 (s, 3H, OCH_2OMe), 2.65 (dd, 1H, *J* 14.4 and 5.8, ICH=C(Me)C*H*H), 2.59 (dd, 1H, *J* 14.4 and 7.0, ICH=C(Me)CH*H*), 1.92 (d, 3H, *J*

1.0, ICH=C(*Me*)CH_2), 1.90-1.67 (m, 2H, CH_2Me), 0.94 (t, 3H, *J* 7.4, CH_2*Me*); δ_C (90 MHz): 171.3 (C), 148.4 (CH), 141.7 (C), 135.9 (C), 95.3 (CH_2), 79.5 (CH), 79.2 (CH), 72.5 (CH), 55.8 (CH_3), 42.7 (CH_2), 26.9 (CH_2), 24.8 (CH_3), 9.3 (CH_3); m/*z* (ESI) found 389.0228 ($M + Na^+$), $C_{13}H_{19}O_4INa$ requires 389.0226.

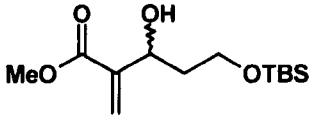
(*Z*)-6-Iodo-5-methyl-hexa-1,5-dien-3-ol 297d



Dess-Martin periodinane (7.50 g, 17.7 mmol) was added in one portion to a stirred solution of (*Z*)-4-iodo-3-methyl-but-3-en-1-ol **244a**[197] (2.50 g, 11.8 mmol) and $NaHCO_3$ (4.95 g, 59.0 mmol) in DCM (60 mL) at room temperature. The mixture was stirred at this temperature for 45 mins and then saturated aqueous $Na_2S_2O_3$, water and saturated aqueous $NaHCO_3$ (45 mL, 1:1:1) were added and the resulting biphasic mixture was stirred vigorously for 45 mins. The separated aqueous phase was extracted with DCM (3 x 60 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *aldehyde* as a colourless oil that was used without further purification. Vinylmagnesium bromide (35.4 mL, 35.4 mmol, 1.0 M in THF) was added dropwise over 15 mins to a stirred solution of the crude aldehyde in THF (150 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr, then water (60 mL) and diethyl ether (60 mL) were added and the mixture was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3 x 60 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 20% to 30% diethyl ether in petroleum ether (product

eluted at 30%) as eluent, gave the *allylic alcohol* (1.27 g, 45%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3605, 2945, 2915, 1645, 1614; δ_H (360 MHz): 6.00 (q, 1H, *J* 1.4, IC*H*=C(Me)CH_2), 5.92 (ddd, 1H, *J* 17.1, 10.4 and 6.1, C*H*=CH_2), 5.27 (ddd, 1H, *J* 17.1, 1.3 and 1.3, CH=C*H*H), 5.12 (dd, 1H, *J* 10.4 and 1.3, CH=CH*H*), 4.39-4.31 (m, 1H, C*H*(OH)CH), 2.52 (dd, 1H, *J* 13.5 and 8.2, C=C(Me)C*H*H), 2.42 (dd, 1H, *J* 13.5 and 5.6, C=C(Me)CH*H*), 1.95 (d, 3H, *J* 1.4, ICH=C(*Me*)CH_2), 1.93 (br. s, 1H, CH(O*H*)CH); δ_C (90 MHz): 144.3 (C), 140.2 (CH), 114.9 (CH_2), 76.9 (CH), 71.2 (CH), 45.8 (CH_2), 24.5 (CH_3); m/*z* (EI) found 209.9520 (M^+ - C_2H_4) (100%), C_5H_7OI requires 209.9542.

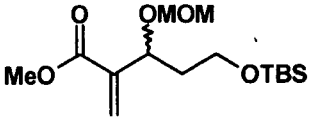
5-(*tert*-Butyl-dimethyl-silanyloxy)-3-hydroxy-2-methylene-pentanoic acid methyl ester 313a



3-(*tert*-Butyl-dimethyl-silanyloxy)-propionaldehyde **278**[205,244] (2.36 g, 12.5 mmol), methyl acrylate (1.35 mL, 15.0 mmol) and DABCO (1.41 g, 12.5 mmol) in DMF (0.73 mL) were stirred at room temperature under a nitrogen atmosphere for 4 days and then diethyl ether (50 mL) and water (50 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 5%, 10%, 20% to 40% diethyl ether in petroleum ether (product eluted at 20%) as eluent, gave the *alcohol* (1.75 g, 51%) as a colourless oil. (Found C, 56.9; H, 9.8, $C_{13}H_{26}O_4Si$ requires C, 56.9; H, 9.6); ν_{max}/cm^{-1} ($CHCl_3$ solution): 3461, 2930, 2858, 1714, 1631; δ_H (360 MHz): 6.24 (dd, 1H, *J* 1.5 and 0.8, C=C*H*H), 5.92 (app. t, 1H, *J* 1.5, C=CH*H*), 4.68-4.61 (m, 1H, C*H*(OH)CH_2), 3.95 (d,

1H, *J* 4.1, CH(O*H*)CH_2), 3.83-3.75 (m, 2H, C*H*$_2$OTBS), 3.70 (s, 3H, CO_2*Me*), 1.97-1.87 (m, 1H, C*H*HCH_2O), 1.74-1.63 (m, 1H, CH*H*CH_2O), 0.86 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.03 (s, 3H, Si^{t}Bu*Me*Me), 0.03 (s, 3H, Si^{t}BuMe*Me*); δ_C (90 MHz): 166.5 (C), 142.3 (C), 124.7 (CH_2), 70.2 (CH), 61.8 (CH_2), 51.5 (CH_3), 37.6 (CH_2), 25.7 (3 x CH_3), 18.0 (C), -5.7 (CH_3), -5.7 (CH_3); m/*z* (ESI) found 297.1488 (M + Na^+), $C_{13}H_{26}O_4SiNa$ requires 297.1498.

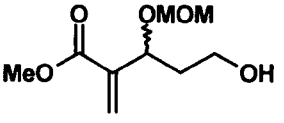
5-(*tert*-Butyl-dimethyl-silanyloxy)-3-methoxymethoxy-2-methylene-pentanoic acid methyl ester 313b



MOM-Cl (0.97 mL, 12.8 mmol) was added over 2 mins to a stirred solution of the alcohol **313a** (1.75 g, 6.38 mmol) and DIPEA (5.6 mL, 31.9 mmol) in DCM (30 mL) at 30 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 24 hrs and then DCM (50 mL) and water (50 mL) were added. The separated aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10% to 20% diethyl ether in petroleum ether (product eluted at 20%) as eluent, gave the *MOM-ether* (1.80 g, 89%) as a colourless oil. (Found C, 56.7; H, 9.6, $C_{15}H_{30}O_5Si$ requires C, 56.6; H, 9.5); ν_{max}/cm^{-1} ($CHCl_3$ solution): 2929, 2856, 1714, 1631; δ_H (360 MHz): 6.26 (d, 1H, *J* 1.5, C=C*H*H), 5.81 (dd, 1H, *J* 1.5 and 0.8, C=CH*H*), 4.61 (ddd, 1H, *J* 8.6, 4.0 and 0.8, C*H*(OMOM)CH_2), 4.57 (d, 1H, *J* 6.7, OC*H*HOMe), 4.54 (d, 1H, *J* 6.7, OCH*H*OMe), 3.77-3.62 (m, 2H, C*H*$_2$OTBS), 3.72 (s, 3H, CO_2*Me*), 3.33 (s, 3H, OCH_2O*Me*), 1.95-1.85 (m, 1H, C*H*HCH_2O), 1.82-1.71 (m, 1H, CH*H*CH_2O), 0.86 (s, 9H, Si(Me)$_2$C(*Me*)$_3$), 0.01 (s,

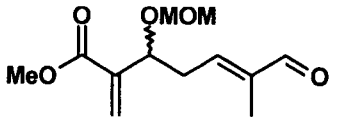
6H, Si^{t}Bu(*Me*)$_2$); δ_C (90 MHz): 166.2 (C), 141.2 (C), 125.4 (CH_2), 94.9 (CH_2), 71.9 (CH), 59.3 (CH_2), 55.6 (CH_3), 51.6 (CH_3), 38.7 (CH_2), 25.8 (3 x CH_3), 18.1 (C), -5.4 (CH_3), -5.5 (CH_3); m/*z* (ESI) found 341.1756 (M + Na^+), $C_{15}H_{30}O_5SiNa$ requires 341.1760.

5-Hydroxy-3-methoxymethoxy-2-methylene-pentanoic acid methyl ester 313c



Pyridinium *para*-toluenesulfonate (1.03 g, 4.08 mmol) was added in one portion to a stirred solution of the MOM-ether **313b** (1.30 g, 4.08 mol) in DCM (30 mL) and methanol (30 mL) at room temperature. The mixture was stirred at this temperature for 18 hrs and then concentrated *in vacuo*. Diethyl ether (50 mL) and water (50 mL) were added and the separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 80% ethyl acetate in petroleum ether as eluent, gave the *alcohol* (706 mg, 85%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3626, 3541, 2953, 2891, 1715, 1630; δ_H (360 MHz): 6.31 (d, 1H, *J* 1.3, C=C*H*H), 5.87 (app. t, 1H, *J* 1.3, C=CH*H*), 4.68 (ddd, 1H, *J* 8.1, 4.3 and 1.3, C*H*(OMOM)CH_2), 4.56 (d, 1H, *J* 6.7, OC*H*HOMe), 4.54 (d, 1H, *J* 6.7, OCH*H*OMe), 3.78-3.63 (m, 2H, CH_2OH), 3.73 (s, 3H, CO_2*Me*), 3.35 (s, 3H, OCH_2O*Me*), 2.61 (br. s, 1H, CH_2O*H*), 2.00-1.88 (m, 1H, C*H*HCH_2O), 1.87-1.76 (m, 1H, CH*H*CH_2O); δ_C (90 MHz): 166.3 (C), 140.5 (C), 125.7 (CH_2), 94.9 (CH_2), 73.1 (CH), 59.6 (CH_2), 55.8 (CH_3), 51.8 (CH_3), 38.0 (CH_2); m/*z* (ESI) found 227.0883 (M + Na^+), $C_9H_{16}O_5Na$ requires 227.0895.

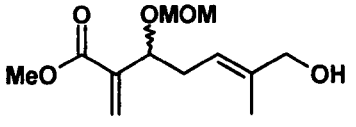
3-Methoxymethoxy-6-methyl-2-methylene-7-oxo-(*E*)-hept-5-enoic acid methyl ester 314



Dess-Martin periodinane (2.20 g, 5.18 mmol) was added in one portion to a stirred solution of the alcohol **313c** (706 mg, 3.46 mmol) in DCM (20 mL) at room temperature. The mixture was stirred at this temperature for 45 mins and then saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (20 mL, 1:1) were added and the resulting biphasic mixture was stirred vigorously for 45 mins. The separated aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *aldehyde* as a colourless oil that was used without further purification. δ_H (360 MHz): 9.77 (dd, 1H, *J* 2.7 and 1.6, C*H*O), 6.37 (d, 1H, *J* 1.3, C=C*H*H), 5.95 (app. t, 1H, *J* 1.3, C=CH*H*), 5.02 (ddd, 1H, *J* 7.8, 4.3 and 1.3, C*H*(OMOM)CH_2), 4.61 (d, 1H, *J* 6.8, OC*H*HOMe), 4.58 (d, 1H, *J* 6.8, OCH*H*OMe), 3.76 (s, 3H, CO_2*Me*), 3.34 (s, 3H, OCH_2O*Me*), 2.80-2.65 (m, 2H, CH_2CHO). Phosphorane **111** (2.20 g, 6.91 mmol) was added in one portion to a stirred solution of the crude aldehyde in benzene (50 mL) at room temperature under a nitrogen atmosphere, and the mixture was stirred under reflux for 24 hrs and then cooled to room temperature. Saturated aqueous NH_4Cl (50 mL) and diethyl ether (50 mL) were added and the separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 30% to 40% diethyl ether in petroleum ether (product eluted at 40%) as eluent, gave the *α,β-unsaturated aldehyde* (600 mg, 72%) as a light yellow oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2953, 2893, 2826, 1715, 1682, 1644; δ_H (360 MHz):

9.35 (s, 1H, C*H*O), 6.52 (ddq, 1H, *J* 7.6, 6.8 and 1.3, C*H*=C(Me)CHO), 6.31 (d, 1H, *J* 1.5, C=C*H*H), 5.87 (dd, 1H, *J* 1.5 and 0.8, C=CH*H*), 4.66 (ddd, 1H, *J* 7.0, 4.4 and 0.8, C*H*(OMOM)CH_2), 4.55 (d, 1H, *J* 6.8, OC*H*HOMe), 4.51 (d, 1H, *J* 6.8, OCH*H*OMe), 3.71 (s, 3H, CO_2*Me*), 3.29 (s, 3H, OCH_2O*Me*), 2.75 (ddd, 1H, *J* 15.6, 6.8 and 4.4, C*H*HCH=C), 2.62 (ddd, 1H, *J* 15.6, 7.6 and 7.0, CH*H*CH=C), 1.68 (d, 3H, *J* 1.3, CH=C(*Me*)CHO); δ_C (90 MHz): 194.7 (CH), 165.9 (C), 149.5 (CH), 140.8 (C), 139.7 (C), 126.1 (CH_2), 94.7 (CH_2), 73.0 (CH), 55.6 (CH_3), 51.8 (CH_3), 34.6 (CH_2), 9.2 (CH_3); m/*z* (ESI) found 265.1049 ($M + Na^+$), $C_{12}H_{18}O_5Na$ requires 265.1052.

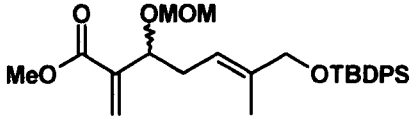
7-Hydroxy-3-methoxymethoxy-6-methyl-2-methylene-(*E*)-hept-5-enoic acid methyl ester 315a



Sodium borohydride (103 mg, 2.72 mmol) was added in one portion to a stirred solution of the α,β-unsaturated aldehyde **314** (600 mg, 2.48 mmol) in methanol (15 mL) at 0 °C. The mixture was stirred at this temperature for 10 mins and then saturated aqueous NH_4Cl (25 mL) was slowly added followed by diethyl ether (50 mL). The separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 40% to 50% diethyl ether in petroleum ether and finally 50% ethyl acetate in petroleum ether (product eluted at 50% ethyl acetate) as eluent, gave the *allylic alcohol* (345 mg, 57%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3616, 3484, 2951, 2892, 1716, 1630; δ_H (360 MHz): 6.30 (d, 1H, *J* 1.3, C=C*H*H), 5.85 (app. t, 1H, *J* 1.3, C=CH*H*), 5.46 (ddq, 1H, *J* 7.2, 7.2 and 1.2, C*H*=C(Me)CH_2), 4.60-4.51 (m, 3H, C*H*(OMOM)CH_2 and

OCH_2OMe), 3.97 (br. s, 2H, CH_2OH), 3.74 (s, 3H, CO_2*Me*), 3.34 (s, 3H, OCH_2O*Me*), 2.48 (ddd, 1H, *J* 14.8, 7.2 and 4.7, C*H*HCH=C), 2.33 (ddd, 1H, *J* 14.8, 7.2 and 7.2, CH*H*CH=C), 1.82 (br. s, 1H, CH_2O*H*), 1.64 (d, 3H, *J* 1.2, CH=C(*Me*)CH_2); δ_C (90 MHz): 166.4 (C), 140.6 (C), 137.2 (C), 125.6 (CH_2), 121.1 (CH), 94.8 (CH_2), 74.2 (CH), 68.6 (CH_2), 55.6 (CH_3), 51.8 (CH_3), 33.6 (CH_2), 13.8 (CH_3); m/*z* (ESI) found 267.1195 ($M + Na^+$), $C_{12}H_{20}O_5Na$ requires 267.1208.

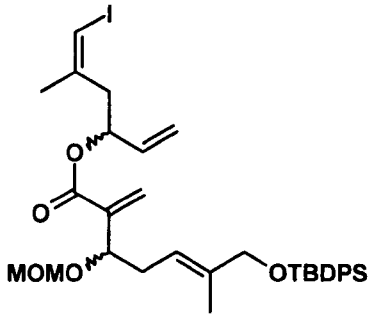
7-(*tert*-Butyl-diphenyl-silanyloxy)-3-methoxymethoxy-6-methyl-2-methylene-(*E*)-hept-5-enoic acid methyl ester 315b



tert-Butyldiphenylsilyl chloride (0.37 mL, 1.44 mmol) was added in dropwise over 1 min to a stirred solution of the allylic alcohol **315a** (319 mg, 1.31 mmol) and imidazole (107 mg, 1.57 mmol) in DMF (0.66 mL) at 0 °C under a nitrogen atmosphere. After 10 mins of stirring at 0 °C, diethyl ether (20 mL) and silica gel (~2 g) were added and the resulting suspension was concentrated *in vacuo*. Direct purification by Purification by chromatography on silica gel (anhydrous loading) eluting with a gradient of 10% to 20% diethyl ether in petroleum ether (product eluted at 20%) as eluent, gave the *α,β-unsaturated ester* (630 mg, 100%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2931, 2893, 2858, 1716, 1630, 1589; δ_H (360 MHz): 7.74-7.68 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.49-7.36 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 6.37 (d, 1H, *J* 1.3, C=C*H*H), 5.91 (app. t, 1H, *J* 1.3, C=CH*H*), 5.64 (ddq, 1H, *J* 7.2, 7.2 and 1.3, C*H*=C(Me)CH_2), 4.66-4.60 (m, 3H, C*H*(OMOM)CH_2 and OCH_2OMe), 4.11 (br. s, 2H, CH_2OTBDPS), 3.80 (s, 3H, CO_2*Me*), 3.38 (s, 3H, OCH_2O*Me*), 2.59 (ddd, 1H, *J* 14.7, 7.2 and 4.7, C*H*HCH=C), 2.42 (ddd, 1H, *J* 14.7, 7.2 and 7.2, CH*H*CH=C), 1.66

(d, 3H, *J* 1.3, CH=C(*Me*)CH_2), 1.12 (s, 9H, $Si(Ph)_2C(Me)_3$); δ_C (90 MHz): 166.4 (C), 140.7 (C), 136.3 (C), 135.5 (4 x CH), 133.7 (2 x C), 129.5 (2 x CH), 127.6 (4 x CH), 125.7 (CH_2), 119.4 (CH), 94.7 (CH_2), 74.4 (CH), 68.6 (CH_2), 55.6 (CH_3), 51.7 (CH_3), 33.5 (CH_2), 26.8 (3 x CH_3), 19.2 (C), 13.7 (CH_3); m/*z* (ESI) found 505.2397 (M + Na^+), $C_{28}H_{38}O_5SiNa$ requires 505.2386.

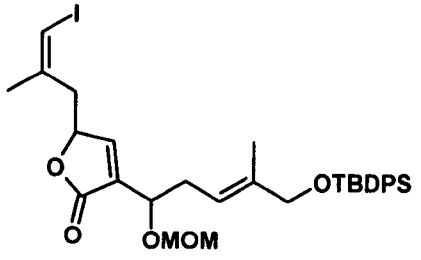
7-(*tert*-Butyl-diphenyl-silanyloxy)-3-methoxymethoxy-6-methyl-2-methylene-(*E*)-hept-5-enoic acid (*Z*)-4-iodo-3-methyl-1-vinyl-but-3-enyl ester 316



A solution of lithium hydroxide (27 mL, 26.9 mmol, 1.0 M in water) was added to a stirred solution of the α,β-unsaturated ester **315b** (1.30 g, 2.69 mmol) in THF (80 mL) and water (40 mL) at room temperature. The mixture was stirred at this temperature for 24 hrs and then acidified to pH 3 using 0.5 M aqueous hydrochloric acid. Diethyl ether (50 mL) was added to the mixture and the separated aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *carboxylic acid* as a yellow oil that was used without further purification. Vinyl iodide **297d** (962 mg, 4.04 mmol) in DCM (20 mL) was added over 5 mins to a stirred solution of the crude carboxylic acid and DMAP (494 mg, 4.04 mmol) in DCM (50 mL) at 0 °C under a nitrogen atmosphere. DCC (667 mg, 3.23 mmol) was added in one portion and the mixture was then warmed to room temperature and stirred for 24 hrs. The mixture was filtered,

eluting with DCM, and the filtrate was then concentrated *in vacuo*. Purification by chromatography on silica gel, using 20% ethyl acetate in petroleum ether as eluent, gave the *allylic ester* (1.82 g, 99%) as a mixture of diastereoisomers. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2931, 2858, 1713, 1628, 1589; δ_H (360 MHz): 7.75-7.68 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.49-7.37 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 6.43 (d, 1H, *J* 1.3, C=C*H*H), 6.05 (q, 0.50H, *J* 1.4, IC*H*=C(Me)CH_2), 6.03 (q, 0.50H, *J* 1.4, IC*H*=C(Me)CH_2), 5.94 (d, 1H, *J* 1.3, C=CH*H*), 5.92 (2 x ddd, 1H, *J* 17.2, 10.5 and 6.3, C*H*=CH_2), 5.68-5.58 (m, 2H, C*H*=C(Me)CH_2 and C*H*(O)CH), 5.37 (ddd, 0.50H, *J* 17.2, 1.1 and 1.1, CH=C*H*H), 5.34 (ddd, 0.50H, *J* 17.2, 1.1 and 1.1, CH=C*H*H), 5.25 (ddd, 0.50H, *J* 10.5, 1.1 and 1.1, CH=CH*H*), 5.23 (ddd, 0.50H, *J* 10.5, 1.1 and 1.1, CH=CH*H*), 4.67-4.59 (m, 3H, C*H*(OMOM)CH_2 and OC*H*$_2$OMe), 4.10 (br. s, 2H, C*H*$_2$OTBDPS), 3.38 (2 x s, 3H, OCH_2O*Me*), 2.79 (2 x dd, 1H, *J* 13.7 and 8.5, ICH=C(Me)C*H*H), 2.63-2.52 (m, 1H, C*H*HCH=C), 2.55 (2 x dd, 1H, *J* 13.7 and 5.5, ICH=C(Me)CH*H*), 2.48-2.37 (m, 1H, CH*H*CH=C), 1.97 (d, 1.50H, *J* 1.4, ICH=C(*Me*)CH_2), 1.95 (d, 1.50H, *J* 1.4, ICH=C(*Me*)CH_2), 1.65 (s, 3H, CH=C(*Me*)CH_2), 1.11 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 164.9 (2 x C), 142.9 (2 x C), 140.7 (C), 140.6 (C), 136.2 (2 x C), 135.4 (8 x CH), 134.7 (2 x CH), 133.7 (4 x C), 129.5 (4 x CH), 127.5 (8 x CH), 125.9 (CH_2), 125.8 (CH_2), 119.5 (CH), 119.4 (CH), 117.2 (CH_2), 117.0 (CH_2), 94.8 (CH_2), 94.7 (CH_2), 77.7 (2 x CH), 74.4 (CH), 74.3 (CH), 72.6 (CH), 72.5 (CH), 68.6 (2 x CH_2), 55.5 (2 x CH_3), 43.2 (2 x CH_2), 33.5 (CH_2), 33.4 (CH_2), 26.8 (6 x CH_3), 23.9 (2 x CH_3), 19.2 (2 x C), 13.7 (2 x CH_3); m/*z* (ESI) found 711.1970 (M + Na^+), $C_{34}H_{45}O_5ISiNa$ requires 711.1973.

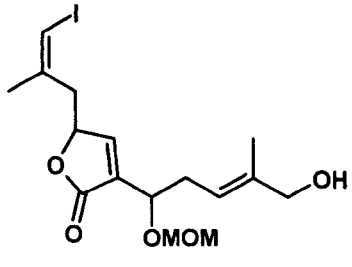
3-[5-(*tert*-Butyl-diphenyl-silanyloxy)-1-methoxymethoxy-4-methyl-(*E*)-pent-3-enyl]-5-((*Z*)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one 276b and 276c



A solution of Grubbs second generation catalyst (108 mg, 0.13 mmol) in DCM (15 mL) and a solution of the allylic ester **316** (292 mg, 0.42 mmol) in DCM (15 mL) were added simultaneously over 8 hrs to a refluxing solution of DCM (250 mL) under a nitrogen atmosphere. The mixture was stirred under reflux for 24 hrs, cooled to room temperature and then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10%, 20%, 30% to 50% diethyl ether in petroleum ether (product eluted at 50%) as eluent, gave the *butenolide* (85 mg, 33%) as separable diastereoisomers. *1st isomer:* ν_{max}/cm^{-1} ($CHCl_3$ solution): 2931, 2857, 1756, 1698, 1652; δ_H (360 MHz): 7.69-7.64 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.46-7.35 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 7.29 (app. t, 1H, *J* 1.3, C*H*=CCH), 6.12 (q, 1H, *J* 1.4, IC*H*=C(Me)CH_2), 5.54 (app. tq, 1H, *J* 7.0 and 1.3, C*H*=C(Me)CH_2), 5.07-5.01 (m, 1H, C*H*(O)CH), 4.66 (s, 2H, OCH_2OMe), 4.61-4.55 (m, 1H, C*H*(OMOM)CH_2), 4.06 (br. s, 2H, CH_2OTBDPS), 3.37 (s, 3H, OCH_2O*Me*), 2.68 (dd, 1H, *J* 13.7 and 6.2, ICH=C(Me)C*H*H), 2.58 (dd, 1H, *J* 13.7 and 7.3, ICH=C(Me)CH*H*), 2.72-2.46 (m, 2H, CH(OMOM)CH_2), 1.97 (d, 3H, *J* 1.4, ICH=C(*Me*)CH_2), 1.60 (d, 3H, *J* 1.3, CH=C(*Me*)CH_2), 1.06 (s, 9H, Si(Ph)$_2$C(*Me*)$_3$); δ_C (90 MHz): 171.4 (C), 149.1 (CH), 142.2 (C), 137.1 (C), 135.5 (4 x CH), 135.0 (C), 133.7 (2 x C), 129.6 (2 x CH), 127.6 (4 x CH), 118.2 (CH), 95.1 (CH_2), 79.6 (CH), 78.6 (CH), 70.9 (CH), 68.5 (CH_2), 55.7 (CH_3), 42.3 (CH_2), 31.6 (CH_2), 26.8 (3 x CH_3), 24.8 (CH_3), 19.3 (C), 13.8 (CH_3); m/*z* (ESI) found 683.1667

($M + Na^+$), $C_{32}H_{41}O_5ISiNa$ requires 683.1660; *2nd isomer:* ν_{max}/cm^{-1} ($CHCl_3$ solution): 2932, 2857, 1757, 1652; δ_H (360 MHz): 7.69-7.64 (m, 4H, Si(*Ph*)$_2$^{t}Bu), 7.46-7.35 (m, 6H, Si(*Ph*)$_2$^{t}Bu), 7.30 (app. t, 1H, *J* 1.4, C*H*=CCH), 6.10 (q, 1H, *J* 1.5, IC*H*=C(Me)CH_2), 5.53 (app. tq, 1H, *J* 7.3 and 1.3, C*H*=C(Me)CH_2), 5.11-5.05 (m, 1H, C*H*(O)CH), 4.65 (s, 2H, OC*H*$_2$OMe), 4.57-4.51 (m, 1H, C*H*(OMOM)CH_2), 4.06 (br. s, 2H, C*H*$_2$OTBDPS), 3.36 (s, 3H, OCH_2O*Me*), 2.63 (dd, 1H, *J* 13.7 and 5.9, ICH=C(Me)C*H*H), 2.50 (dd, 1H, *J* 13.7 and 7.7, ICH=C(Me)CH*H*), 2.68-2.46 (m, 2H, C*H*$_2$CH=C), 1.96 (d, 3H, *J* 1.5, ICH=C(*Me*)CH_2), 1.62 (d, 3H, *J* 1.3, CH=C(*Me*)CH_2), 1.06 (s, 9H, $Si(Ph)_2C(Me)_3$); δ_C (90 MHz): 171.4 (C), 149.2 (CH), 142.2 (C), 137.2 (C), 135.5 (4 x CH), 135.0 (C), 133.7 (2 x C), 129.6 (2 x CH), 127.6 (4 x CH), 118.4 (CH), 95.2 (CH_2), 79.6 (CH), 78.6 (CH), 71.1 (CH), 68.7 (CH_2), 55.7 (CH_3), 42.4 (CH_2), 31.8 (CH_2), 26.8 (3 x CH_3), 24.8 (CH_3), 19.3 (C), 13.8 (CH_3); m/*z* (ESI) found 683.1655 ($M + Na^+$), $C_{32}H_{41}O_5ISiNa$ requires 683.1660.

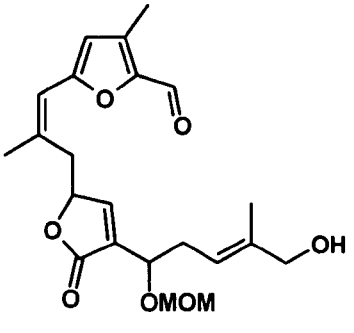
3-[5-Hydroxy-1-methoxymethoxy-4-methyl-(*E*)-pent-3-enyl]-5-((*Z*)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one 276d



70% Hydrogen fluoride-pyridine complex (0.50 mL, 19.2 mmol) was added to a stirred solution of the butenolide **276b** (36 mg, 0.06 mmol) and pyridine (0.25 mL, 3.09 mmol) in THF (5 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at this temperature for 24 hrs, and then saturated aqueous $NaHCO_3$ (5 mL) and diethyl ether (10 mL) were added. The resulting biphasic

mixture was dried ($MgSO_4$) and then filtration through a short plug of silica gel using a gradient of 50% to 80% diethyl ether in petroleum ether and finally 100% ethyl acetate (product eluted at 100% ethyl acetate) as eluent, gave the *allylic alcohol* (18 mg, 77%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3616, 2926, 2855, 1756; δ_H (400 MHz): 7.35 (app. t, 1H, *J* 1.4, C*H*=CCH), 6.15 (q, 1H, *J* 1.5, IC*H*=C(Me)CH_2), 5.46 (app. tq, 1H, *J* 7.2 and 1.3, C*H*=C(Me)CH_2), 5.15-5.09 (m, 1H, C*H*(O)CH), 4.65 (s, 2H, OCH_2OMe), 4.58-4.52 (m, 1H, C*H*(OMOM)CH_2), 4.01 (br. s, 2H, CH_2OH), 3.37 (s, 3H, OCH_2OMe), 2.68 (dd, 1H, *J* 13.7 and 6.1, ICH=C(Me)C*H*H), 2.59 (dd, 1H, *J* 13.7 and 7.3, ICH=C(Me)CH*H*), 2.63-2.54 (m, 2H, CH_2CH=C), 2.00 (d, 3H, *J* 1.5, ICH=C(*Me*)CH_2), 1.68 (d, 3H, *J* 1.3, CH=C(*Me*)CH_2), 1.66 (br. s, 1H, CH_2OH); δ_C (100 MHz): 171.4 (C), 149.2 (CH), 142.1 (C), 137.9 (C), 135.1 (C), 119.9 (CH), 95.2 (CH_2), 79.6 (CH), 78.8 (CH), 71.0 (CH), 68.6 (CH_2), 55.7 (CH_3), 42.3 (CH_2), 32.0 (CH_2), 24.8 (CH_3), 14.0 (CH_3); m/*z* (ESI) found 445.0490 ($M + Na^+$), $C_{16}H_{23}O_5INa$ requires 445.0482.

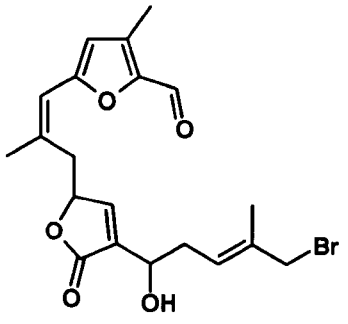
(*Z*)-5-{3-[4-(5-Hydroxy-1-methoxymethoxy-4-methyl-(*E*)-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-3-methyl-furan-2-carbaldehyde 317



Tetrakis(triphenylphosphine)palladium(0) (53 mg, 0.05 mmol) and CuI (18 mg, 0.09 mmol) were added in one portion to a stirred, degassed solution of the allylic alcohol **276d** (49 mg, 0.12 mmol) and 3-methyl-5-trimethylstannanyl-furan-2-carbaldehyde

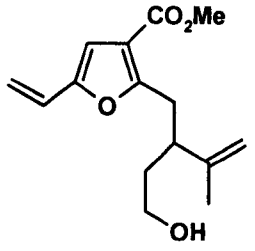
249[196] (50 mg, 0.14 mmol) in DMF (5 mL) at room temperature under an argon atmosphere. The mixture was degassed again then stirred at room temperature for 20 hrs, and then ethyl acetate (20 mL) and water (20 mL) were added. The separated organic phase was washed with water (4 x 20 mL) and then dried ($MgSO_4$). The organic phase was filtered through a short plug of celite, eluting with ethyl acetate, and the filtrate was then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 70%, 90% to 100% ethyl acetate in petroleum ether (product eluted at 100%) as eluent, gave the *alkenylfuran* (28 mg, 60%) as a light yellow oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3450, 2983, 2932, 1732, 1661, 1579; δ_H (400 MHz): 9.64 (s, 1H, C*H*O), 7.53 (br. s, 1H, C*H*=CCH), 6.20 (s, 1H, C(O)=C*H*CMe), 6.19 (s, 1H, C(O)C*H*=C(Me)CH_2), 5.47 (app. tq, 1H, *J* 7.2 and 1.2, C*H*=C(Me)CH_2), 5.23-5.17 (m, 1H, C*H*(OMOM)CH_2), 4.65 (s, 2H, OCH_2OMe), 4.56-4.51 (m, 1H, C*H*(OMOM)CH_2), 4.00 (br. s, 2H, CH_2OH), 3.37 (s, 3H, OCH_2O*Me*), 3.19 (dd, 1H, *J* 13.8 and 3.6, C(O)CH=C(Me)C*H*H), 2.65-2.46 (m, 3H, C(O)CH=C(Me)CH*H* and CH(OMOM)CH_2), 2.36 (s, 3H, C(O)=CHC*Me*), 2.06 (s, 3H, C(O)CH=C(*Me*)CH_2), 1.75 (br. s, 1H, CH_2O*H*), 1.67 (d, 3H, *J* 1.2, CH=C(*Me*)CH_2); δ_C (100 MHz): 175.6 (br. CH), 171.8 (C), 156.8 (C), 150.5 (CH), 147.5 (C), 141.8 (br. C), 138.0 (2 x C), 134.6 (C), 119.9 (CH), 115.7 (CH), 114.1 (CH), 95.3 (CH_2), 81.5 (CH), 70.9 (CH), 68.6 (CH_2), 55.7 (CH_3), 38.0 (CH_2), 32.0 (CH_2), 26.7 (CH_3), 14.0 (CH_3), 10.1 (CH_3); m/*z* (ESI) found 427.1727 ($M + Na^+$), $C_{22}H_{28}O_7Na$ requires 427.1727.

(*Z*)-5-{3-[4-(5-Bromo-1-methoxymethoxy-4-methyl-(*E*)-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]- 2-methyl-propenyl}-3-methyl-furan-2-carbaldehyde 275b



Carbon tetrabromide (13 mg, 0.04 mmol) was added in one portion to a stirred solution of the alkenylfuran **317** (5 mg, 0.01 mmol) and triphenylphosphine (10 mg, 0.04 mmol) in DCM (5 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr, heated to 40 °C for 30 mins, cooled to room temperature and then concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 50% to 70% ethyl acetate in petroleum ether (product eluted at 70%) as eluent, gave the *allylic bromide* (2 mg, 40%) as a light yellow oil. δ_H (360 MHz): 9.65 (s, 1H, C*H*O), 7.48 (br. s, 1H, C*H*=CCH), 6.21 (s, 2H, C(O)=C*H*CCMe and C(O)C*H*=C(Me)CH_2), 5.66 (app. tq, 1H, *J* 7.2 and 1.3, C*H*=C(Me)CH_2), 5.24-5.18 (m, 1H, C*H*(O)CH), 4.61-4.55 (m, 1H, C*H*(OMOM)CH_2), 3.97 (br. s, 2H, CH_2Br), 3.21 (dd, 1H, *J* 13.8 and 4.6, C(O)CH=C(Me)C*H*H), 2.68-2.44 (m, 3H, C(O)CH=C(Me)CH*H* and CH_2CH=C), 2.37 (s, 3H, C(O)=CHC*Me*), 2.06 (s, 3H, C(O)CH=C(*Me*)CH_2), 1.79 (d, 3H, *J* 1.3, CH=C(*Me*)CH_2); m/*z* (ESI) found 445.0623 ($M + Na^+$), $C_{20}H_{23}O_5BrNa$ requires 445.0621.

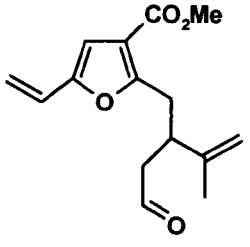
2-[2-(2-Hydroxy-ethyl)-3-methyl-but-3-enyl]-5-vinyl-furan-3-carboxylic acid methyl ester 335



Palladium acetate (35 mg, 0.16 mmol) and triphenyl arsene (193 mg, 0.63 mmol) were added in one portion to a stirred, degassed solution of the bromofuran **334** (0.25 g, 0.79 mmol) and tributyl(vinyl)tin (0.35 mL, 1.18 mmol) in anhydrous DMF (6 mL) at room temperature under an argon atmosphere. The mixture was heated to 45 °C for 17 hrs and then cooled to room temperature where diethyl ether (20 mL) and water (20 mL) were added. The separated organic phase was washed with water (5 x 10 mL) and brine (5 x 10 mL) and then filtered through celite, eluting with diethyl ether. The filtrate was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 40% diethyl ether in petroleum ether as eluent, gave the *vinylfuran* (236 mg, 100%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3623, 3526, 2951, 1725, 1697, 1645, 1594; δ_H (360 MHz): 6.44 (s, 1H, C(O)=C*H*CCO$_2$Me), 6.39 (dd, 1H, *J* 17.5 and 11.3, C*H*=CH$_2$), 5.62 (dd, 1H, *J* 17.5 and 1.1, CH=C*H*H), 5.17 (dd, 1H, *J* 11.3 and 1.1, CH=CH*H*), 4.73-4.68 (m, 2H, C*H*$_2$=C(Me)CH), 3.80 (s, 3H, CO$_2$*Me*), 3.70-3.53 (m, 2H, C*H*$_2$OH), 3.08 (d, 1H, *J* 7.4, C(O)C*H*HCH), 3.08 (d, 1H, *J* 8.0, C(O)CH*H*CH), 2.81-2.70 (m, 1H, C*H*(C)CH$_2$), 1.92 (br. s, 1H, CH$_2$O*H*), 1.78-1.60 (m, 2H, C*H*$_2$CH$_2$OH), 1.70 (br. s, 3H, CH$_2$=C(*Me*)CH); δ_C (90 MHz): 164.3 (C), 161.1 (C), 151.1 (C), 146.3 (C), 124.3 (CH), 114.9 (C), 113.0 (CH$_2$), 112.4 (CH$_2$), 108.1 (CH), 60.9 (CH$_2$), 51.3 (CH$_3$), 43.4

(CH), 35.2 (CH_2), 31.8 (CH_2), 18.1 (CH_3); m/*z* (ESI) found 287.1235 ($M + Na^+$), $C_{15}H_{20}O_4Na$ requires 287.1254.

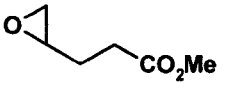
2-[3-Methyl-2-(2-oxo-ethyl)-but-3-enyl]-5-vinyl-furan-3-carboxylic acid methyl ester 323



Dess-Martin periodinane (0.48 g, 1.13 mmol) was added in one portion to a stirred solution of the vinylfuran **335** (0.22 g, 0.76 mmol) in DCM (10 mL) at room temperature. The mixture was stirred at this temperature for 75 mins and then saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (40 mL, 1:1) were added and the resulting biphasic mixture was stirred vigorously for 30 mins. The separated aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 30% diethyl ether in petroleum ether as eluent, gave the *aldehyde* (199 mg, 93%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2953, 2922, 2856, 1714, 1646, 1597; δ_H (360 MHz): 9.63 (dd, 1H, *J* 2.6 and 1.7, C*H*O), 6.46 (s, 1H, C(O)=C*H*CCO_2Me), 6.41 (dd, 1H, *J* 17.5 and 11.3, C*H*=CH_2), 5.65 (dd, 1H, *J* 17.5 and 1.0, CH=C*H*H), 5.20 (dd, 1H, *J* 11.3 and 1.0, CH=CH*H*), 4.80-4.74 (m, 2H, CH_2=C(Me)CH), 3.82 (s, 3H, CO_2*Me*), 3.24-3.04 (m, 3H, C(O)CH_2CH and C*H*(C)CH_2), 2.58 (ddd, 1H, *J* 16.6, 8.0 and 2.6, C*H*HCHO), 2.48 (ddd, 1H, *J* 16.6, 5.7 and 1.7, CH*H*CHO), 1.76 (br. s, 3H, CH_2=C(*Me*)CH); δ_C (90 MHz): 201.5 (CH), 164.0 (C), 159.6 (C), 151.4 (C), 145.2

(C), 124.2 (CH), 115.6 (C), 113.4 (CH_2), 112.5 (CH_2), 108.1 (CH), 51.4 (CH_3), 46.3 (CH_2), 40.5 (CH), 31.6 (CH_2), 19.4 (CH_3); m/*z* (ESI) found 285.1083 ($M + Na^+$), $C_{15}H_{18}O_4Na$ requires 285.1097.

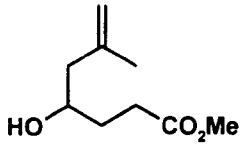
3-Oxiranyl-propionic acid methyl ester 328[249-251]



Thionyl chloride (0.80 mL, 11.0 mmol) was added dropwise over 10 mins to a stirred solution of 4-pentenoic acid **336** (1.00g, 1.02 mL, 10.0 mmol) in methanol (11 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 25 mins and then basified to pH 9 using saturated aqueous $NaHCO_3$. Diethyl ether (50 mL) and water (50 mL) were added to the mixture and the separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were then filtered through a short plug of silica gel, eluting with diethyl ether. The filtrate was dried (Na_2SO_4) and concentrated *in vacuo* to leave the *ester* as a colourless oil that was used without further purification. A solution of *meta*-chloroperbenzoic acid (4.92g, 20.0 mmol, 70-75% weight balance) in DCM (10 mL) was added dropwise over 10 mins to a stirred solution of the crude ester and $NaHCO_3$ (4.19 g, 50.0 mmol) in DCM (33 mL) at 0 °C under a nitrogen atmosphere. The mixture was warmed to room temperature and stirred for 15 hrs and then filtered, eluting with DCM. Saturated aqueous $Na_2S_2O_3$ (50 mL) was added to the filtrate and the resulting biphasic mixture was stirred vigorously for 20 mins and then water (100 mL) and DCM (100 mL) were added. The separated aqueous phase was extracted with DCM (3 x 75 mL) and the combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 30%

diethyl ether in petroleum ether as eluent, gave the *epoxide* (0.98 g, 75%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2954, 2929, 1732; δ_H (360 MHz): 3.66 (s, 3H, CO_2Me), 2.99-2.92 (m, 1H, $CH(O)CH_2$), 2.74 (dd, 1H, *J* 4.9 and 4.0, $CHH(O)CH$), 2.48 (dd, 1H, *J* 4.9 and 2.7, $CHH(O)CH$), 2.44 (t, 2H, *J* 7.4, CH_2CO_2Me), 2.01-1.89 (m, 1H, $CHHCH_2CO_2Me$), 1.80-1.69 (m, 1H, $CHHCH_2CO_2Me$); δ_C (90 MHz): 173.2 (C), 51.6 (CH_3), 51.1 (CH), 46.9 (CH_2), 30.0 (CH_2), 27.5 (CH_2); m/*z* (ESI) found 153.0534 ($M + Na^+$), $C_6H_{10}O_3Na$ requires 153.0522.

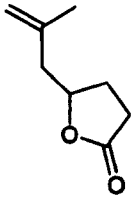
4-Hydroxy-6-methyl-hept-6-enoic acid methyl ester 363



A solution of isopropenylmagnesium bromide (6.1 mL, 3.02 mmol, 0.5 M in THF) was added dropwise over 10 mins to a stirred solution of CuCN (68 mg, 0.75 mmol) in THF (10 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 30 mins and then boron trifluoride diethyl etherate (0.40 mL, 3.02 mmol) was added dropwise over 2 mins. The mixture was stirred at -78 °C for 2 mins and then a solution of the epoxide **328** (196 mg, 1.51 mmol) in THF (5 mL) was added dropwise over 10 mins. The final mixture was stirred at this temperature for 1 hr and then saturated aqueous NH_4OH and saturated aqueous NH_4Cl (20 mL, 1:9), diethyl ether (50 mL) and water (50 mL) were added. The mixture was warmed to room temperature and the separated aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 45% diethyl ether in

petroleum ether as eluent, gave the *alcohol* (156 mg, 60%) as a colourless oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3584, 2937, 1732, 1647; δ_H (360 MHz): 4.84-4.79 (m, 1H, C*H*H=C(Me)CH_2), 4.76-4.71 (m, 1H, CH*H*=C(Me)CH_2), 3.76-3.67 (m, 1H, C*H*(OH)CH_2), 3.63 (s, 3H, CO_2*Me*), 2.52-2.36 (m, 2H, C*H*$_2CO_2$Me), 2.22 (br. s, 1H, CH(O*H*)CH_2), 2.18-2.06 (m, 2H, CH_2=C(Me)C*H*$_2$), 1.85-1.75 (m, 1H, C*H*HCH$_2CO_2$Me), 1.74-1.59 (m, 1H, CH*H*CH$_2CO_2$Me), 1.70 (br. s, 3H, CH_2=C(*Me*)CH_2); δ_C (90 MHz): 174.3 (C), 142.2 (C), 113.4 (CH_2), 67.8 (CH), 51.1 (CH_3), 46.0 (CH_2), 31.7 (CH_2), 30.3 (CH_2), 22.2 (CH_3); m/*z* (ESI) found 195.1006 (M + Na^+), $C_9H_{16}O_3Na$ requires 195.0992.

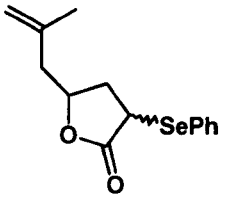
5-(2-Methyl-allyl)-dihydro-furan-2-one 327



A solution of the alcohol **363** (70 mg, 0.41 mmol) and *para*-toluenesulfonic acid (16 mg, 0.08 mmol) in DCM (2 mL) were stirred at room temperature for 30 mins under a nitrogen atmosphere, and then saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and DCM (10 mL) were added. The separated aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave the *lactone* (57 mg, 100%) as a colourless oil that was used without further purification. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2940, 1770, 1651; δ_H (360 MHz): 4.84-4.80 (m, 1H, C*H*H=C(Me)CH_2), 4.77-4.72 (m, 1H, CH*H*=C(Me)CH_2), 4.66-4.57 (m, 1H, C*H*(O)CH_2), 2.49 (dd, 2H, *J* 9.3 and 6.9, C*H*$_2$C=O), 2.44 (br. dd, 1H, *J* 14.4 and 6.9, CH_2=C(Me)C*H*H), 2.34-2.20 (m, 2H, CH_2=C(Me)CH*H* and C*H*HCH$_2$C=O), 1.93-1.77 (m, 1H, CH*H*CH$_2$C=O), 1.73 (br. s,

3H, CH_2=C(*Me*)CH_2); δ_C (90 MHz): 177.0 (C), 140.3 (C), 113.5 (CH_2), 79.0 (CH), 43.2 (CH_2), 28.4 (CH_2), 27.5 (CH_2), 22.6 (CH_3); m/*z* (ESI) found 163.0732 (M + Na^+), $C_8H_{12}O_2Na$ requires 163.0730.

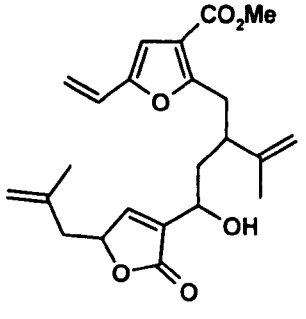
5-(2-Methyl-allyl)-3-phenylselanyl-dihydro-furan-2-one 324



A solution of the lactone **327** (200 mg, 1.43 mmol) in THF (3 mL) was added dropwise over 10 mins to a stirred solution of LiHMDS (1.6 mL, 1.57 mmol, 1.0 M in THF) in THF (3 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 15 mins and then trimethylchlorosilane (0.20 mL, 1.57 mmol) was added dropwise over 1 min. The mixture was stirred at -78 °C for 30 mins and then a solution of phenylselenium bromide (370 mg, 1.57 mmol) in THF (3 mL) was added dropwise over 10 mins. The final mixture was stirred at -78 °C for 30 mins, warmed to room temperature and then stirred for 30 mins. Saturated aqueous NH_4Cl (15 mL), water (40 mL) and diethyl ether (80 mL) were added and the separated aqueous phase was extracted with diethyl ether (3 x 80 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 10%, 20%, to 30% diethyl ether in petroleum ether (product eluted at 30%) as eluent, gave the *seleno-lactone* (215 mg, 51%) as a mixture of diastereoisomers. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2938, 1770, 1651; δ_H (360 MHz): 7.71-7.60 (m, 2H, Se*Ph*), 7.40-7.26 (m, 3H, Se*Ph*), 4.84-4.78 (m, 1H, C*H*H=C(Me)CH_2), 4.73-4.65 (m, 1H, CH*H*=C(Me)CH_2), 4.60-4.50 (m, 0.40H, C*H*(O)CH_2), 4.42-4.32 (m, 0.60H, C*H*(O)CH_2), 4.01 (app. t, 0.40H, *J* 9.5, C*H*SePh),

3.93 (dd, 0.60H, *J* 6.8 and 4.2, C*H*SePh), 2.71 (ddd, 0.40H, *J* 13.7, 9.5 and 6.6, C*H*HCHSePh), 2.41 (br. dd, 0.60H, *J* 14.5 and 7.1, CH_2=C(Me)C*H*H), 2.41-2.24 (m, 0.60H, C*H*HCHSePh, 0.60H, CH*H*CHSePh, and 0.40H, CH_2=C(Me)C*H*H), 2.20 (br. dd, 0.60H, *J* 14.5 and 6.3, CH_2=C(Me)CH*H*), 2.07 (br. dd, 0.40H, *J* 14.5 and 6.5, CH_2=C(Me)CH*H*), 1.95 (ddd, 0.40H, *J* 13.7, 9.5 and 8.2, CH*H*CHSePh), 1.68 (2 x br. s, 3H, CH_2=C(*Me*)CH_2); δ_C (90 MHz): 175.6 (C), 175.5 (C), 139.9 (2 x C), 135.7 (2 x CH), 135.5 (2 x CH), 129.2 (4 x CH), 129.0 (CH), 128.7 (CH), 126.8 (C), 126.5 (C), 113.7 (CH_2), 113.6 (CH_2), 77.4 (CH), 77.2 (CH), 43.2 (CH_2), 42.9 (CH_2), 37.2 (CH), 36.7 (CH), 36.2 (CH_2), 35.2 (CH_2), 22.5 (2 x CH_3); m/*z* (ESI) found 297.0379 ($M + H^+$), $C_{14}H_{17}O_2Se$ requires 297.0388.

2-(2-{2-Hydroxy-2-[5-(2-methyl-allyl)-2-oxo-2,5-dihydro-furan-3-yl]-ethyl}-3-methyl-but-3-enyl)-5-vinyl-furan-3-carboxylic acid methyl ester 322

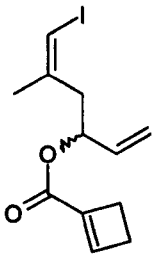


A solution of the seleno-lactone **324** (218 mg, 0.74 mmol) in THF (4 mL) was added dropwise over 10 mins to a stirred solution of LiHMDS (0.81 mL, 0.81 mmol, 1.0 M in THF) in THF (5 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 50 mins and then a solution of the aldehyde **323** (193 mg, 0.74 mmol) in THF (4 mL) was added dropwise over 10 mins. The final mixture was stirred at -78 °C for 1 hr and then saturated aqueous NH_4Cl (20 mL), water (50 mL) and diethyl ether (50 mL) were added. The mixture was warmed to room temperature and the separated aqueous phase was extracted with diethyl ether (3 x 50

mL). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave the *seleno-alcohol* as a yellow oil that was used without further purification. A solution of hydrogen peroxide (0.24 mL, 30% w/w in water) was added dropwise over 1 min to a stirred solution of the crude seleno-alcohol and pyridine (20 mL) in DCM (20 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr and then saturated aqueous $NaHCO_3$ (30 mL), water (30 mL) and DCM (40 mL) were added. The separated aqueous phase was extracted with DCM (3 x 75 mL) and the combined organic extracts were then concentrated *in vacuo*. The residue was dissolved in DCM (100 mL) then washed with saturated aqueous $CuSO_4$ (3 x 50 mL) and then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 30%, 40% to 50% diethyl ether in petroleum ether (1^{st} isomer eluted at 40% and the 2^{nd} isomer was eluted at 50%) as eluent, gave the *secondary alcohol* (141 mg, 48%) as separable diastereoisomers. *1^{st} isomer:* ν_{max}/cm^{-1} ($CHCl_3$ solution): 3491, 2952, 1749, 1716, 1646, 1605; δ_H (360 MHz): 7.26-7.21 (m, 1H, C*H*=CCH), 6.45 (s, 1H, C(O)=C*H*CCO$_2$Me), 6.40 (dd, 1H, *J* 17.5 and 11.3, C*H*=CH$_2$), 5.63 (dd, 1H, *J* 17.5 and 1.0, CH=C*H*H), 5.18 (dd, 1H, *J* 11.3 and 1.0, CH=CH*H*), 5.11-5.04 (m, 1H, C*H*(O)CH), 4.92 (br. s, 1H, C*H*H=C(Me)CH$_2$), 4.82 (br. s, 1H, CH*H*=C(Me)CH$_2$), 4.81-4.74 (m, 2H, C*H*$_2$=C(Me)CH), 4.61-4.55 (m, 0.35H, C*H*(OH)CH$_2$), 4.47-4.40 (m, 0.65H, C*H*(OH)CH$_2$), 3.81 (s, 1.05H, CO$_2$*Me*), 3.80 (s, 1.95H, CO$_2$*Me*), 3.23-2.93 (m, 4H, C(O)C*H*$_2$CH, C*H*(C)CH$_2$ and CH(O*H*)CH$_2$), 2.44 (br. dd, 1H, *J* 14.4 and 7.0, CH$_2$=C(Me)C*H*H), 2.34 (br. dd, 1H, *J* 14.4 and 6.7, CH$_2$=C(Me)CH*H*), 2.04-1.95 (m, 1H, CH(OH)C*H*H), 1.80 (br. s, 3H, CH$_2$=C(*Me*)CH$_2$), 1.75 (br. s, 1.95H, CH$_2$=C(*Me*)CH), 1.73 (br. s, 1.05H, CH$_2$=C(*Me*)CH), 1.68-1.59 (m, 1H, CH(OH)CH*H*); δ_C (90 MHz): 172.2 (C), 172.1 (C), 164.4 (C), 164.2 (C), 161.1 (C),

160.6 (C), 151.2 (2 x C), 148.6 (CH), 147.9 (CH), 146.5 (C), 145.4 (C), 139.6 (2 x C), 137.0 (2 x C), 124.3 (CH), 124.2 (CH), 115.1 (2 x C), 114.3 (2 x CH_2), 113.6 (2 x CH_2), 113.1 (2 x CH_2), 108.1 (CH), 108.0 (CH), 80.2 (CH), 80.1 (CH), 65.6 (CH), 65.1 (CH), 51.5 (CH_3), 51.4 (CH_3), 43.5 (CH), 43.0 (CH), 41.4 (CH_2), 41.3 (CH_2), 38.5 (CH_2), 37.9 (CH_2), 32.2 (2 x CH_2), 22.9 (2 x CH_3), 17.9 (2 x CH_3); m/*z* (ESI) found 423.1776 (M + Na^+), $C_{23}H_{28}O_6Na$ requires 423.1778; *2nd isomer:* ν_{max}/cm^{-1} ($CHCl_3$ solution): 3489, 2952, 1750, 1715, 1647, 1604; δ_H (360 MHz): 7.26 (app. t, 0.30H, *J* 1.5, C*H*=CCH), 7.24 (app. t, 0.70H, *J* 1.5, C*H*=CCH), 6.44 (s, 1H, C(O)=C*H*CCO_2Me), 6.39 (dd, 1H, *J* 17.5 and 11.3, C*H*=CH_2), 5.62 (dd, 0.70H, *J* 17.5 and 1.0, CH=C*H*H), 5.61 (dd, 0.30H, *J* 17.5 and 1.0, CH=C*H*H), 5.17 (dd, 1H, *J* 11.3 and 1.0, CH=CH*H*), 5.10-5.03 (m, 1H, C*H*(O)CH), 4.91 (s, 1H, C*H*H=C(Me)CH_2), 4.81 (s, 1H, CH*H*=C(Me)CH_2), 4.79-4.74 (m, 2H, CH_2=C(Me)CH), 4.47-4.39 (m, 1H, C*H*(OH)CH_2), 3.80 (s, 0.90H, CO_2*Me*), 3.79 (s, 2.10H, CO_2*Me*), 3.23-2.91 (m, 4H, C(O)CH_2CH, C*H*(C)CH_2 and CH(O*H*)CH_2), 2.43 (br. dd, 1H, *J* 14.4 and 7.2, CH_2=C(Me)C*H*H), 2.35 (br. dd, 1H, *J* 14.4 and 6.5, CH_2=C(Me)CH*H*), 2.02-1.92 (m, 1H, CH(OH)C*H*H), 1.79 (br. s, 3H, CH_2=C(*Me*)CH_2), 1.74 (br. s, 2.10H, CH_2=C(*Me*)CH), 1.72 (br. s, 0.90H, CH_2=C(*Me*)CH), 1.69-1.58 (m, 1H, CH(OH)CH*H*); δ_C (90 MHz): 172.2 (C), 172.1 (C), 164.4 (C), 164.2 (C), 161.1 (C), 160.5 (C), 151.1 (2 x C), 148.5 (CH), 147.9 (CH), 146.5 (C), 145.3 (C), 139.5 (2 x C), 137.0 (2 x C), 124.2 (2 x CH), 115.0 (2 x C), 114.4 (2 x CH_2), 113.5 (2 x CH_2), 113.0 (2 x CH_2), 108.1 (CH), 108.0 (CH), 80.1 (CH), 80.0 (CH), 65.4 (CH), 65.0 (CH), 51.4 (CH_3), 51.3 (CH_3), 43.4 (CH), 42.9 (CH), 41.2 (2 x CH_2), 38.6 (CH_2), 38.0 (CH_2), 32.2 (2 x CH_2), 22.9 (2 x CH_3), 17.8 (2 x CH_3); m/*z* (ESI) found 423.1772 (M + Na^+), $C_{23}H_{28}O_6Na$ requires 423.1778.

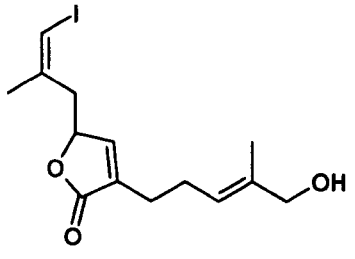
Cyclobut-1-enecarboxylic acid (*Z*)-4-iodo-3-methyl-1-vinyl-but-3-enyl ester 349



Triethylamine (2.12 mL, 15.2 mmol) was added dropwise over 2 mins to a stirred solution of 1-cyclobutene-1-carboxylic acid[255] (1.49 g, 15.2 mmol) and pivaloyl chloride (1.87 mL, 15.2 mmol) in THF (30 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at this temperature for 30 mins. Meanwhile, a solution of LiHMDS (7.61 mL, 7.61 mol, 1.0 M in THF) was added dropwise over 2 mins to a stirred solution of the allylic alcohol **297d** (1.51 g, 6.34 mmol) in THF (75 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 20 mins. The mixed anhydride solution was quickly filtered and then added dropwise over 15 mins to the stirred solution of the allylic alcohol at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 90 mins, and then water (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and diethyl ether (50 mL) were added and the mixture was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3 x 75 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 100% petroleum ether, 5% to 10% diethyl ether in petroleum ether (product eluted at 10%) as eluent, gave the *allylic ester* (1.32 g, 65%) as a light yellow oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2928, 2852, 2254, 1712, 1647, 1610; δ_H (400 MHz): 6.82 (t, 1H, *J* 1.2, C=C*H*CH_2), 6.02 (q, 1H, *J* 1.4, IC*H*=C(Me)CH_2), 5.88 (ddd, 1H, *J* 17.2, 10.5 and 6.3, C*H*=CH_2), 5.57-5.50 (m, 1H, C*H*(O)CH), 5.32 (ddd, 1H, *J* 17.2, 1.2 and 1.2, CH=C*H*H), 5.20

(ddd, 1H, *J* 10.5, 1.2 and 1.2, CH=CH*H*), 2.77-2.66 (m, 3H, C*H*$_2$CH$_2$CH=C and ICH=C(Me)C*H*H), 2.54-2.45 (m, 3H, CH$_2$C*H*$_2$CH=C and ICH=C(Me)CH*H*), 1.94 (d, 3H, *J* 1.4, ICH=C(*Me*)CH$_2$); δ_C (100 MHz): 161.2 (C), 147.0 (CH), 143.2 (C), 138.5 (C), 135.7 (CH), 117.0 (CH$_2$), 77.5 (CH), 72.1 (CH), 43.2 (CH$_2$), 29.1 (CH$_2$), 27.1 (CH$_2$), 24.2 (CH$_3$); m/*z* (ESI) found 341.0017 (M + Na$^+$), $C_{12}H_{15}O_2INa$ requires 341.0009.

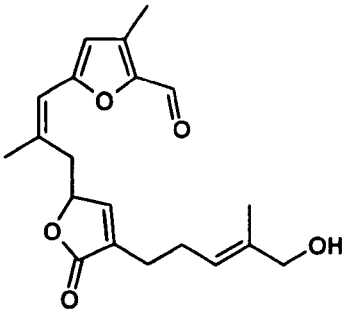
3-(5-Hydroxy-4-methyl-(*E*)-pent-3-enyl)-5-((*Z*)-3-iodo-2-methyl-allyl)-5H-furan-2-one 248a



A solution of Grubbs second generation catalyst (467 mg, 0.55 mmol) in DCM (10 mL) and a solution of the allylic ester **349** (1.75 g, 5.50 mmol) with 2–methyl-2-propen-1-ol (0.93 mL, 11.0 mmol) in DCM (10 mL) were added simultaneously over 8 hrs to a refluxing solution of DCM (1.75 lts) under a nitrogen atmosphere. 2–Methyl-2-propen-1-ol (3.70 mL, 44.0 mmol) was added dropwise over 1 hr and the mixture was stirred under reflux for 12 hrs. The mixture was cooled to room temperature and then concentrated *in vacuo*. Purification by chromatography on silica gel, using 50% ethyl acetate in petroleum ether as eluent, gave a 7:1 mixture of *E*:*Z*-isomers of the *allylic alcohol* (1.13 g, 57%) as a yellow oil. δ_H (400 MHz): 7.11 (app. q, 1H, *J* 1.4, C*H*=CCH$_2$), 6.11 (q, 1H, *J* 1.4, IC*H*=C(Me)CH$_2$), 5.44-5.34 (m, 1H, C*H*=C(Me)CH$_2$), 5.05 (ddd, 1H, *J* 7.4, 6.1 and 1.4, C*H*(O)CH), 3.99 (br. s, 2H, C*H*$_2$OH), 2.66 (dd, 1H, *J* 13.6 and 6.1, ICH=C(Me)C*H*H), 2.54 (dd, 1H, *J* 13.6 and

7.4, ICH=C(Me)CH*H*), 2.41-2.25 (m, 4H, C*H*$_2$CH=C and C*H*$_2$CH$_2$CH=C), 1.98 (d, 3H, *J* 1.4, ICH=C(*Me*)CH$_2$), 1.77 (br. s, 1H, CH$_2$O*H*), 1.66 (br. s, 3H, CH=C(*Me*)CH$_2$); δ_C (100 MHz): 173.4 (C), 147.8 (CH), 142.3 (C), 136.2 (C), 133.9 (C), 123.8 (CH), 79.4 (CH), 78.5 (CH), 68.4 (CH_2), 42.4 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 24.8 (CH_3), 13.7 (CH_3). The spectroscopic data were identical to those published previously by Trauner *et. al.*[196]

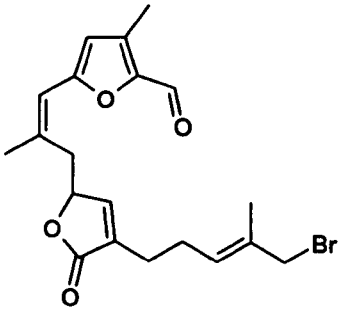
(*Z*)-5-{3-[4-(5-Hydroxy-4-methyl-(*E*)-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-3-methyl-furan-2-carbaldehyde 250



Tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.06 mmol) and CuI (21 mg, 0.11 mmol) were added in one portion to a stirred, degassed solution of the allylic alcohol **248a** (500 mg, 1.38 mmol) and 3-methyl-5-trimethylstannanyl-furan-2-carbaldehyde **249**[196] (753 mg, 2.76 mmol) in DMF (10 mL) at room temperature under an argon atmosphere. The mixture was degassed again then stirred at room temperature for 90 mins, and then diethyl ether (20 mL) and saturated aqueous NH_4Cl (20 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using a gradient of 65% ethyl acetate in petroleum ether as eluent, gave the *alkenylfuran* (443 mg, 93%) as a light yellow oil. δ_H (400 MHz): 9.61 (s, 1H, C*H*O), 7.35 (br. s, 1H,

C*H*=CCH$_2$), 6.19 (s, 1H, C(O)=C*H*CMe), 6.18 (s, 1H, C(O)C*H*=C(Me)CH$_2$), 5.45-5.37 (m, 1H, C*H*=C(Me)CH$_2$), 5.17-5.10 (m, 1H, C*H*(O)CH), 4.00 (br. s, 2H, C*H*$_2$OH), 3.30-3.20 (m, 1H, C(O)CH=C(Me)C*H*H), 2.48-2.26 (m, 6H, C(O)CH=C(Me)CH*H*, C*H*$_2$CH=C, C*H*$_2$CH$_2$CH=C and CH$_2$O*H*), 2.36 (s, 3H, C(O)=CHC*Me*), 2.07 (s, 3H, C(O)CH=C(*Me*)CH$_2$), 1.66 (br. s, 3H, CH=C(*Me*)CH$_2$); δ_C (100 MHz): 175.3 (br. CH), 173.9 (C), 157.0 (C), 149.2 (CH), 147.5 (C), 142.2 (br. C), 136.5 (2 x C), 133.4 (C), 123.9 (CH), 115.2 (CH), 113.9 (CH), 81.7 (CH), 68.6 (CH$_2$), 38.3 (CH$_2$), 26.8 (CH$_3$), 25.3 (CH$_2$), 24.8 (CH$_2$), 13.8 (CH$_3$), 10.1 (CH$_3$). The spectroscopic data were identical to those published previously by Trauner *et. al.*[196]

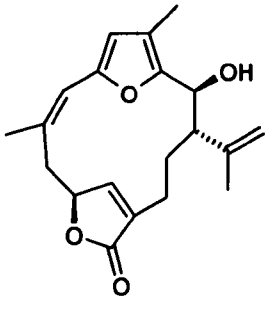
(*Z*)-5-{3-[4-(5-Bromo-4-methyl-(*E*)-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-3-methyl-furan-2-carbaldehyde 251



N-Bromosuccinimide (249 mg, 1.40 mmol) was added in one portion to a stirred solution of the alkenylfuran **250** (437 mg, 1.27 mmol) and triphenylphosphine (366 mg, 1.40 mmol) in DCM (10 mL) at -5 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 20 mins and then water (20 mL) was added. The separated aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 35% ethyl acetate in petroleum ether as eluent, gave the *allylic bromide* (430 mg, 83%) as a light yellow oil. δ_H (400 MHz): 9.67 (s,

1H, C*H*O), 7.27 (br. s, 1H, C*H*=CCH$_2$), 6.20 (s, 1H, C(O)=C*H*CMe), 6.19 (s, 1H, C(O)C*H*=C(Me)CH$_2$), 5.60-5.53 (m, 1H, C*H*=C(Me)CH$_2$), 5.18-5.11 (m, 1H, C*H*(O)CH), 3.96 (br. s, 2H, C*H*$_2$Br), 3.20 (dd, 1H, *J* 13.8 and 4.1, C(O)CH=C(Me)C*H*H), 2.55 (dd, 1H, *J* 13.8 and 8.3, C(O)CH=C(Me)CH*H*), 2.42-2.26 (m, 4H, C*H*$_2$CH=C and C*H*$_2$CH$_2$CH=C), 2.37 (s, 3H, C(O)=CHC*Me*), 2.06 (s, 3H, C(O)CH=C(*Me*)CH$_2$), 1.76 (br. s, 3H, CH=C(*Me*)CH$_2$); δ_C (100 MHz): 175.5 (br. CH), 173.4 (C), 156.5 (C), 148.9 (CH), 147.3 (C), 141.0 (br. C), 135.8 (br. C), 133.4 (C), 133.0 (C), 129.2 (CH), 115.6 (CH), 113.9 (CH), 81.1 (CH), 41.1 (CH$_2$), 38.0 (CH$_2$), 26.6 (CH$_3$), 25.8 (CH$_2$), 24.5 (CH$_2$), 14.6 (CH$_3$), 10.0 (CH$_3$). The spectroscopic data were identical to those published previously by Trauner *et. al.*[196]

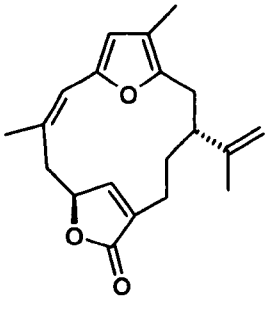
12-Hydroxy-11-isopropenyl-3,14-dimethyl-6,16-dioxa-tricyclo[11.2.1.1^{5,8}]heptadeca-(*Z*)-1(15),2,8(17),13-tetraen-7-one (bipinnatin J) 5



A solution of the allylic bromide **251** (254 mg, 0.62 mmol) in THF (260 mL) was added over 1 hr to a stirred mixture of $CrCl_2$ (1.54 g, 12.5 mmol) and 4 Å molecular sieves (2.90 g) at room temperature under an argon atmosphere. The mixture was stirred at this temperature for 16 hrs and then filtered through celite, eluting with diethyl ether, and the filtrate was concentrated *in vacuo*. Diethyl ether (150 mL) was added to the residue which was washed with water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 30% ethyl acetate in petroleum ether as eluent, gave *bipinnatin J* (143 mg,

70%) as a colourless crystalline solid. δ_H (400 MHz): 6.86 (app. t, 1H, *J* 1.6, C*H*=CCH$_2$), 6.12 (br. s, 1H, C*H*=C(Me)CH$_2$), 6.04 (s, 1H, C(O)=C*H*CMe), 5.18 (br. s, 1H, C=C*H*H), 5.07 (br. s, 1H, C=CH*H*), 5.03-4.95 (m, 1H, C*H*(O)CH), 4.51 (dd, 1H, *J* 10.9 and 3.0, C*H*(CH)OH), 3.21 (dd, 1H, *J* 11.8 and 11.8, CH=C(Me)C*H*H), 2.74 (dd, 1H, *J* 11.8 and 4.4, CH=C(Me)CH*H*), 2.47-2.33 (m, 2H, C*H*C(Me)=CH$_2$ and CH=CC*H*H), 2.15-2.06 (m, 1H, CH=CCH*H*), 2.06 (s, 3H, C(O)=CHC*Me*), 2.01 (br. s, 3H, CH=C(*Me*)CH$_2$), 1.86 (d, 1H, *J* 3.0, CH(CH)O*H*), 1.81 (br. s, 3H, CHC(*Me*)=CH$_2$), 1.68 (dtd, 1H, *J* 14.0, 10.9 and 3.3, CH$_2$C*H*HCH), 0.91 (dt, 1H, *J* 14.0 and 3.7, CH$_2$CH*H*CH); δ_C (100 MHz): 174.3 (C), 152.3 (CH), 151.0 (C), 149.2 (C), 142.1 (C), 132.6 (C), 129.0 (C), 121.1 (C), 118.8 (CH$_2$), 117.4 (CH), 113.9 (CH), 78.7 (CH), 65.0 (CH), 51.2 (CH), 39.7 (CH$_2$), 30.1 (CH$_2$), 25.9 (CH$_3$), 19.7 (CH$_2$), 17.5 (CH$_3$), 9.5 (CH$_3$). The spectroscopic data were identical to those published previously by Trauner *et. al.*[196]

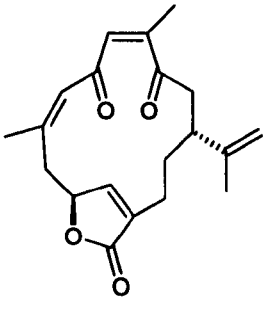
11-Isopropenyl-3,14-dimethyl-6,16-dioxa-tricyclo[11.2.1.1^{5,8}]heptadeca-(*Z*)-1(15),2,8(17),13-tetraen-7-one (rubifolide) 49



Trifluoroacetic acid (11 μL, 0.14 mmol) was added dropwise over 1 min to a stirred solution of bipinnatin J **5** (43 mg, 0.13 mmol) and triethylsilane (46 μL, 0.29 mmol) in DCM (10 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 20 mins and then saturated aqueous NaHCO$_3$ (10 mL) was added. The

separated aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 12% ethyl acetate in petroleum ether as eluent, gave *rubifolide* (38 mg, 93%) as a colourless crystalline solid. δ_H (400 MHz): 6.91 (app. t, 1H, *J* 1.6, C*H*=CCH_2), 6.07 (br. s, 1H, C*H*=C(Me)CH_2), 6.00 (s, 1H, C(O)=C*H*CMe), 5.00-4.93 (m, 1H, C*H*(O)CH), 4.93-4.86 (m, 2H, C=CH_2), 3.24 (dd, 1H, *J* 11.8 and 11.8, CH=C(Me)C*H*H), 2.70 (dd, 1H, *J* 11.8 and 4.2, CH=C(Me)CH*H*), 2.61-2.31 (m, 4H, C(O)CH_2CH, C*H*C(Me)=CH_2 and CH=CC*H*H), 2.14-2.04 (m, 1H, CH=CCH*H*), 1.99 (br. s, 3H, C(O)=CHC*Me*), 1.93 (br. s, 3H, CH=C(*Me*)CH_2), 1.75 (br. s, 3H, CHC(*Me*)=CH_2), 1.65 (dtd, 1H, *J* 14.0, 10.8 and 3.4, CH_2C*H*HCH), 1.18 (dtd, 1H, *J* 14.0, 3.5 and 1.0, CH_2CH*H*CH). The spectroscopic data were identical to those published previously by Trauner *et. al.*[111]

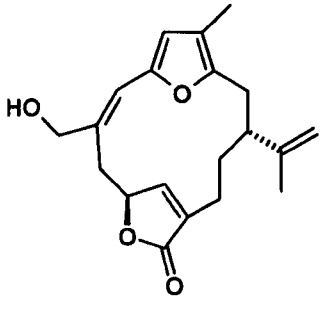
4-Isopropenyl-7,11-dimethyl-14-oxa-bicyclo[11.2.1]-(*Z*,*Z*)-hexadeca-1(16),7,10-triene-6,9,15-trione (isoepilophodione B) 159



meta-Chloroperbenzoic acid (7 mg, 0.03 mmol, 70-75 % weight balance) was added in one portion to a stirred solution of rubifolide **49** (9 mg, 0.03 mmol) in DCM (10 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr and then saturated aqueous Na_2SO_3 (5 mL) was added. The separated aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on

silica gel, using a gradient of 35% to 40% ethyl acetate in petroleum ether (product eluted at 40%) as eluent, gave *isoepilophodione B* (8 mg, 90%) as a colourless crystalline solid. δ_H (400 MHz): 7.16 (br. s, 1H, C*H*=CCH_2), 6.25 (br. s, 1H, C*H*=C(Me)CH_2), 6.21 (q, 1H, *J* 1.4, C(O)C*H*=CMe), 5.27 (br. s, 1H, C*H*(O)CH), 4.83 (br. s, 1H, C=C*H*H), 4.64 (br. s, 1H, C=CH*H*), 4.03 (br. s, 1H, CH=C(Me)C*H*H), 2.93-2.61 (m, 2H, CH=C(Me)CH*H* and C(O)C*H*HCH), 2.61-2.19 (m, 4H, C(O)CH*H*CH, C*H*C(Me)=CH_2 and CH=CCH_2), 2.07 (d, 3H, *J* 1.4, C(O)CH=C*Me*), 2.03-1.85 (m, 1H, CH_2C*H*HCH), 1.88 (br. s, 3H, CH=C(*Me*)CH_2), 1.69 (br. s, 3H, CHC(*Me*)=CH_2), 1.47-1.35 (m, 1H, CH_2CH*H*CH). The spectroscopic data were identical to those published previously by Trauner *et. al.* [111]

3-Hydroxymethyl-11-isopropenyl-14-methyl-6,16-dioxa-tricyclo[11.2.1.1^{5,8}]heptadeca-(*Z*)-1(15),2,8(17),13-tetraen-7-one (19-hydroxyrubifolide) 353



A solution of isoepilophodione B (**159**) (19 mg, 0.06 mmol) and *para*-toluenesulfonic acid (11 mg, 0.06 mmol) in THF (12 mL) and water (6 mL) were stirred at room temperature for 72 hrs and then saturated aqueous $NaHCO_3$ (5 mL) and ethyl acetate (5 mL) were added. The separated aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica gel, using 40% ethyl acetate in

petroleum ether as eluent, gave *19-hydroxyrubifolide* (8 mg, 40%) as a colourless crystalline solid. ν_{max}/cm^{-1} ($CHCl_3$ solution): 3452, 2930, 2868, 1748, 1646, 1628, 1452, 1366, 1068; δ_H (400 MHz): 6.90 (app. t, 1H, *J* 1.5, C*H*=CCH_2), 6.33 (br. s, 1H, C*H*=$C(CH_2OH)CH_2$), 6.14 (br. s, 1H, C(O)=C*H*CMe), 5.10-5.03 (m, 1H, C*H*(O)CH), 4.94-4.87 (m, 2H, C=CH_2), 4.29 (d, 1H, *J* 16.9, CH=C(C*H*HOH)CH_2), 4.26 (d, 1H, *J* 16.9, CH=C(CH*H*OH)CH_2), 3.17 (dd, 1H, *J* 12.1 and 12.1, CH=$C(CH_2OH)$C*H*H), 2.87 (dd, 1H, *J* 12.1 and 4.4, CH=$C(CH_2OH)$CH*H*), 2.64-2.33 (m, 4H, C(O)CH_2CH, C*H*C(Me)=CH_2 and CH=CC*H*H), 2.14-2.05 (m, 1H, CH=CCH*H*), 1.94 (br. s, 3H, C(O)=CHC*Me*), 1.75 (br. s, 3H, CHC(*Me*)=CH_2), 1.70-1.58 (m, 2H, CH_2C*H*HCH and CH_2O*H*), 1.17 (dtd, 1H, *J* 13.8, 3.3 and 0.8, CH_2CH*H*CH); δ_C (100 MHz): 174.5 (C), 151.9 (CH), 150.6 (C), 149.3 (C), 145.4 (C), 132.9 (C), 129.1 (C), 117.6 (C), 117.6 (CH), 116.0 (CH), 113.1 (CH_2), 79.6 (CH), 68.3 (CH_2), 43.4 (CH), 35.9 (CH_2), 31.2 (CH_2), 30.6 (CH_2), 20.1 (CH_2), 19.2 (CH_3), 9.6 (CH_3); m/*z* (ESI) found 351.1566 (M + Na^+), $C_{20}H_{24}O_4Na$ requires 351.1567.

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