Development of an Assay for a Diels-Alderase Enzyme

A Thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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Dedicated to my family

"Do they give Nobel prizes for attempted chemistry? Do they!?"

from 'The Simpsons'
by Matt Groening

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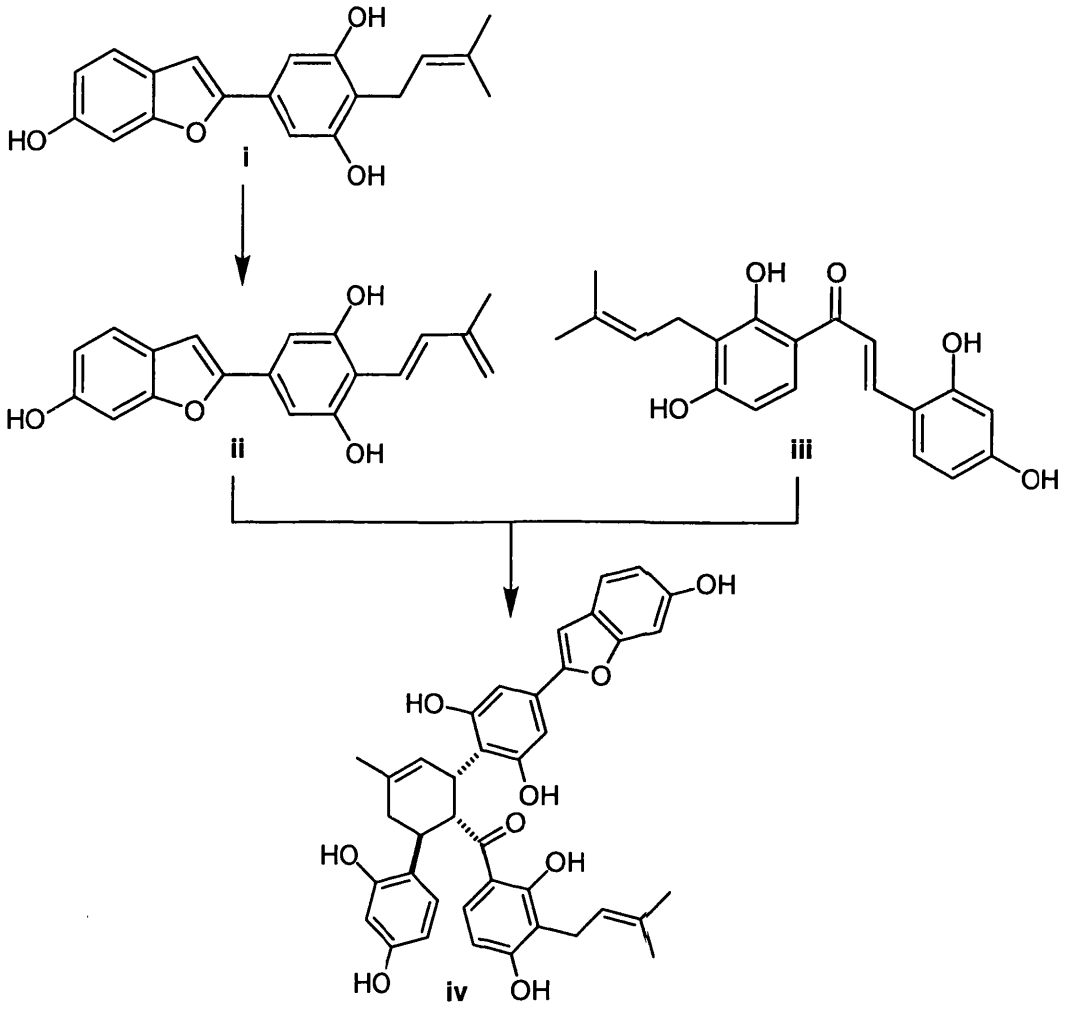
Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aromatic
Bn	benzyl
br	broad
BuLi	butyllithium
°C	degrees centigrade
CI	chemical ionisation
d	doublet (NMR spectroscopy)
d	day(s)
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	dicyclohexylurea
de	distereomeric excess
DEPT	distortionless enhancement through polarisation transfer
DIBAL-H	diisobutylaluminium hydride
DMAP	*N*,*N*-dimethylaminopyridine
DMF	dimethylformamide
DMPU	*N*,*N'*-dimethylpropyleneurea
DMSO	dimethylsulfoxide
ee	enantiomeric excess
FT	Fourier Transform
h	hour(s)
HOMO	highest occupied molecular orbital
HMDS	hexamethyldisilazane
Hz	hertz
HRMS	high resolution mass spectrum
IR	infra red
LDA	lithium diisopropylamide
LUMO	lowest occupied molecular orbital
LRMS	low resolution mass spectrum
m	multiplet (NMR spectroscopy)
m	medium (IR spectroscopy)
Me	methyl
min	minute(s)
mol	mole(s)

MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
q	quartet (NMR spectroscopy)
RT	room temperature
s	singlet (NMR spectroscopy)
SEM	(trimethylsilyl)ethoxymethyl
t	triplet (NMR spectroscopy)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TIPS	triisopropylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylenediamine
TMS	trimethylsilyl

Summary

We have been developing an assay for a Diels-Alderase enzyme. The assay is based on the proposed biosynthesis of chalcomoracin **iv**, a natural antifungal compound from the white mulberry *Morus alba*, which is thought to be formed by an enzyme-mediated Diels-Alder reaction between diene **ii** and morachalcone A **iii**. Diene **ii** has never been isolated, but an analogue of **ii**, moracin C **i** has been isolated from *M. alba* and is thought to be a biological precursor to diene **ii**.



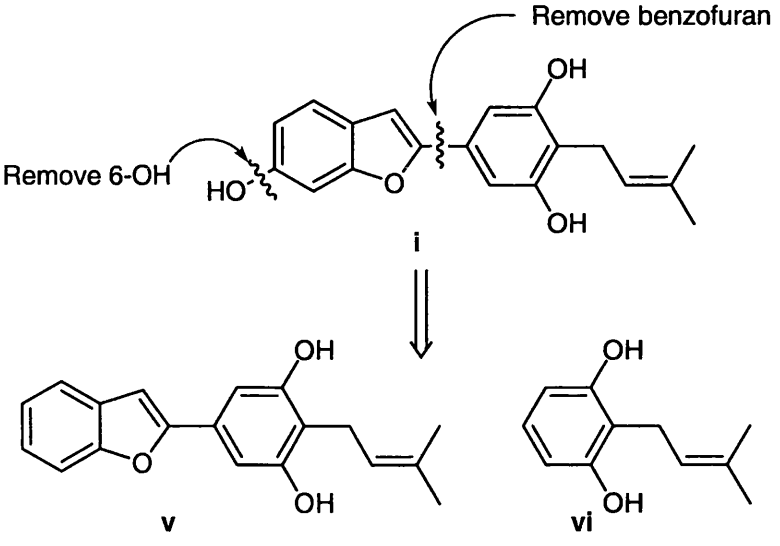
We have developed the most efficient synthesis of moracin C **i** to date (10 steps, 12.3% overall), involving a 'one-pot' ester formation/intramolecular Wittig reaction, regioselective *ortho*-lithiation, and an unexpected but advantageous acid-induced acyl migration. Our route provides a general method for the synthesis of polyphenolic benzofurans.

We have synthesised a sample of diene **ii** using a route similar to that of moracin C (12 steps). This synthesis included a regioselective carboxylation and an *E*-

selective modified Julia olefination. The small sample of **ii** obtained was not fully characterised, due to instability during chromatography, but the structure was unequivocally confirmed by ^{1}H NMR spectroscopy.

We have prepared a series of protected morachalcone A **iii** precursors. These are easily prepared (3 steps), and while suitable deprotection conditions have not yet been found, this route can provide suitable intermediates for a biomimetic or total synthesis of chalcomoracin.

Structural modifications were made to moracin C (see below), and in an attempt to probe the substrate specificity of the Diels-Alderase enzyme, two potential substrates **v** and **vi**, were fed to suspensions of *M. alba* cells. Initial analysis suggested that one of these compounds (**v**) was incorporated.



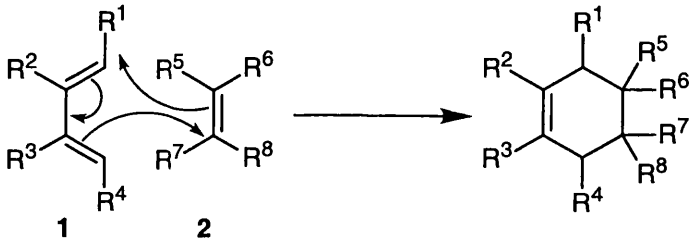
1

The Enzymatic Diels-Alder Reaction

1.1 The Diels-Alder Reaction: A Brief History

In 1928, Otto Diels and Kurt Alder made a discovery which was to become one of the great milestones in the history of organic chemistry.[1] This discovery, which earned them a Nobel prize in 1950, was the [4+2] cycloaddition, or Diels-Alder reaction as it was later known. This proved to be one of the most useful carbon-carbon bond-forming reactions ever discovered.

The Diels-Alder reaction is the formation of a new 6-membered ring through reaction of a 1,3-diene **1** with an olefin (or dienophile) **2**. In a single step, 2 new carbon-carbon bonds and up to 4 chiral centres are formed in a controlled manner (*Scheme 1*).



Scheme 1

Bond formation arises through overlap of the molecular orbitals on one face of the diene component with the molecular orbitals on one face of the dienophile. The main interaction is between the **H**ighest **O**ccupied **M**olecular **O**rbital (HOMO) of the diene with the **L**owest **U**noccupied **M**olecular **O**rbital (LUMO) of the dienophile (*Figure 1*).

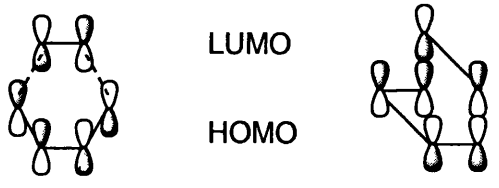


Figure 1

Decreasing the energy difference between the HOMO and LUMO improves the efficiency of the Diels-Alder reaction. This can be done by varying the substituents

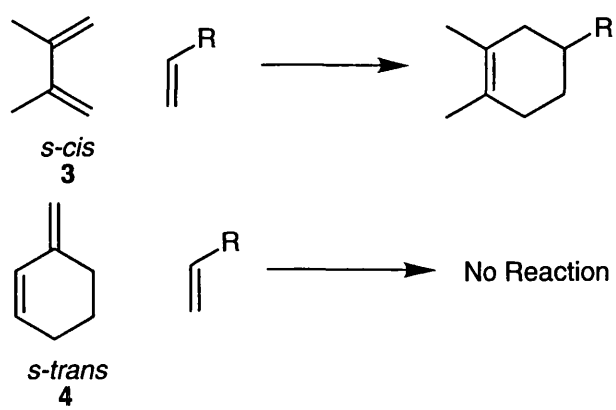
on the two reactants. Electron-donating groups (e.g. aromatics) raise the HOMO of the diene. Electron-withdrawing groups (e.g. C=O, CN, CO_2R, etc.) remove electron-density from the dienophile, thus lowering the LUMO.

1.2 Control in the Diels-Alder Reaction

The Diels-Alder reaction mechanism is concerted (i.e. bonds break at the same time as new bonds form), and as a result, the reaction is stereospecific with respect to the diene and the dienophile geometries. The reaction may also exhibit *endo-exo* diastereoselectivity, regioselectivity and face-selectivity. These types of control will be dealt with in turn.

1.2.1 Geometry of the Diene[2]

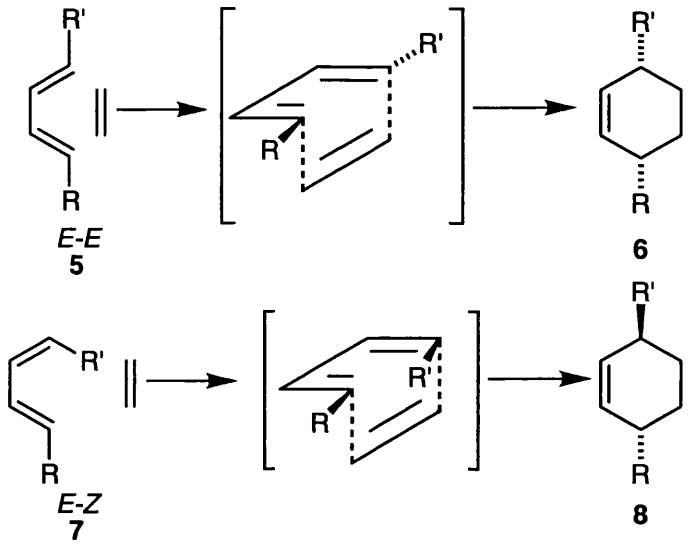
The first, and most important feature of the diene is that is must be able to adopt the *s-cis* (cisoid) conformation **3** (*Scheme 2*). Cycloaddition is not possible in the *s-trans* (transoid) form **4**.



Scheme 2

The geometry of each of the double bonds in the diene has a bearing on the reaction product. Feasibly, there are 4 types of diene geometry: *E-E*, *E-Z*, *Z-E* and *Z-Z*.

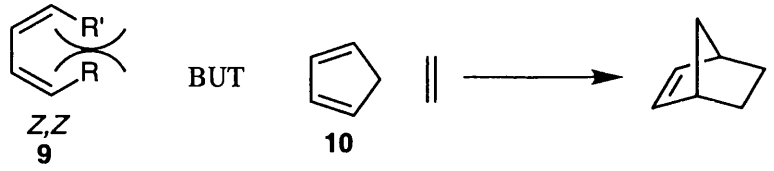
Cycloadditions involving *E-E* dienes **5** always give rise stereospecifically to products **6** with a *syn*-R/R' relationship. Conversely, *E-Z* dienes **7** give products **8** with *anti*-R/R' stereochemistry (*Scheme 3*). In each case, reaction of the dienophile on the opposite face of the diene gives the opposite enantiomer.



[Note: in all diagrams, ---- denotes where a new σ-bond will form]

Scheme 3

Note that, with the exception of cyclic dienes e.g. **10**,, reactions of *Z*-*Z* dienes **9** are often disfavoured due to steric crowding of the substituents, but when they do occur, they give *syn* products. (*Scheme 4*).



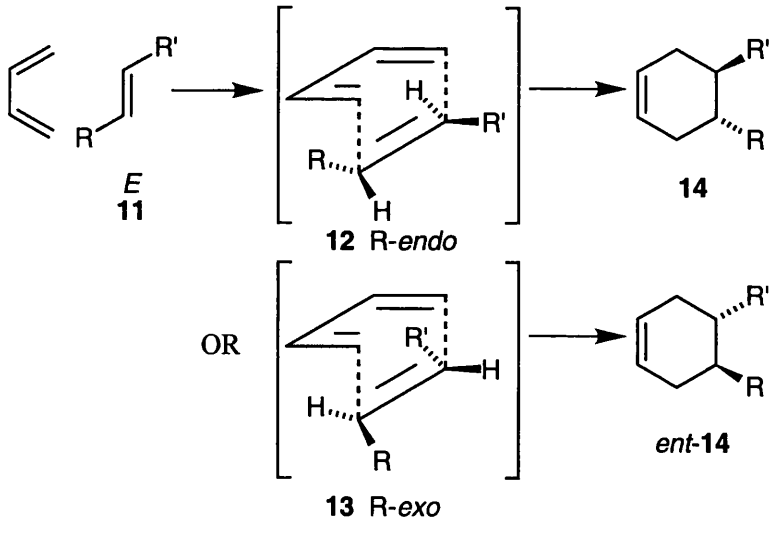
Scheme 4

1.2.2 Geometry of the Dienophile[2]

An alkene can have either a *Z*- or *E*-geometry. As with the diene, this geometry influences the outcome of the reaction, and is retained in the product.

E-Dienophiles

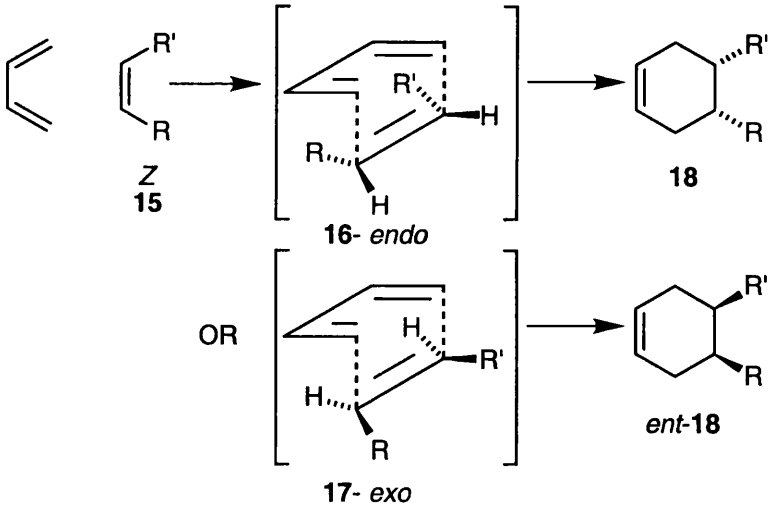
As shown in *Scheme 5*, the reaction of *E*-alkenes **11** always results in a 1,2-*anti* relationship in the cyclohexene **14** and *ent*-**14**. There are two modes of reaction: the R-*endo* mode **12**, where R lies 'underneath' the diene (*endo*: Greek 'within'), and the R-*exo* mode **13**, where the diene does not 'cover' R (*exo*: Greek 'outside'). For each mode of reaction, the diene could approach the dienophile from the opposite face to that illustrated. This would form the opposite enantiomer in each case.



Scheme 5

Z-Dienophiles

Reaction of Z-dienophiles **15** also gives rise to *exo*- and *endo*-products **18** and *ent*-**18**, that have their substitutents R and R' in a *syn* relationship (*Scheme 6*).



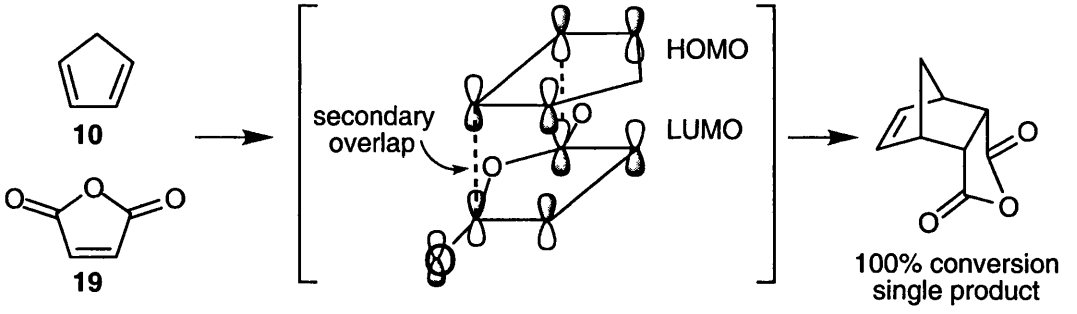
Scheme 6

1.2.3 *Endo-Exo* Diastereoselectivity[2,3]

As discussed, the Diels-Alder reaction proceeds with retention of diene and dienophile geometry. We have also seen how the two reaction modes (*endo* and *exo*) can alter the stereochemistry of the product.

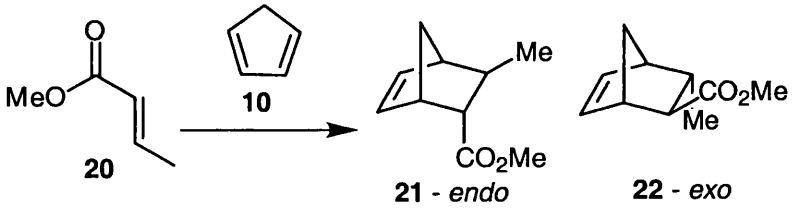
In the simple examples used above, the *endo* and *exo* products were enantiomeric. Normally however, the *endo* and *exo* modes of addition give diastereomeric products.

In general, *endo*-products tend to be favoured, due to the secondary orbital overlap between the HOMO of the diene and the LUMO of the dienophile. This effect is greatest in the reactions of cyclic dienes (e.g. cyclopentadiene **10**) with cyclic dienophiles (e.g. maleic anhydride **19**) (*Scheme 7*).



Scheme 7

Consider the reaction between cyclopentadiene **10** and methyl crotonate **20** (*Scheme 8*).[4] At 30 °C, we see formation of both products with a very low preference for the *endo* product **21** (*Table 1*, entry 1) Again, this slight preference can be attributed to the secondary orbital overlap between **10** and **20** (*Figure 2a*). An ideal reaction would produce exclusively the *endo* or *exo* product, so how do we influence the outcome of the reaction? When 0.9 equivalents of $AlCl_3$ was added, the ratio of products changed drastically (*Table 1*, entry 2). Not only was there a massive selectivity for the *endo*-product **21** (*endo-exo*, 94:6), but the reaction was complete in 30 minutes (*cf.* 24 hours for the uncatalysed reaction). What was causing this?



Scheme 8

	Reaction conditions	*%endo*	*% exo*
1	PhH, 30 °C, 24 h	54	46
2	PhH, 30 °C, 30 min, 0.9 mol eq $AlCl_3$	94	6

Table 1

The Lewis acid has an effect on the rate of the reaction, and on the *endo-exo* selectivity.

(i) Rate Enhancement

With methyl crotonate **20**,[5] the Lewis acid coordinates with the carbonyl resulting in an metal-acid complex **23** (*Figure 2b*). The allylic cation quality of this complex lowers the energy of the LUMO of the dienophile. This brings the HOMO and LUMO closer together, resulting in an increased rate.

(ii) Endo-exo selectivity

Complexation results in the carbonyl carbon having a greater LUMO coefficient. This makes the secondary orbital overlap greater, and hence favours formation of the *endo* product **21** (*Figure 2b*).

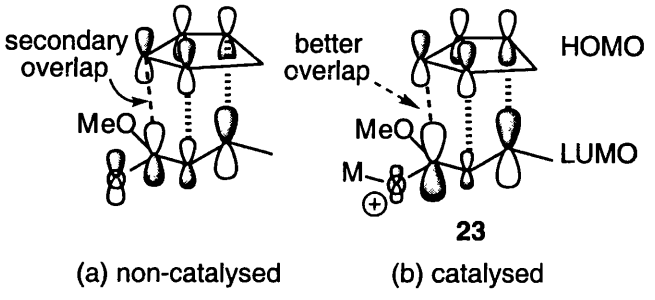
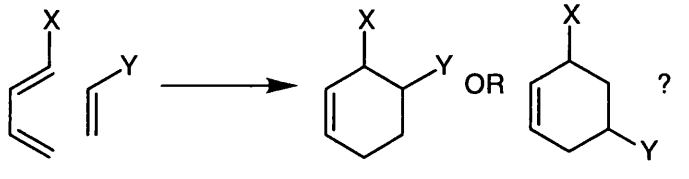


Figure 2

In addition, use of Lewis acids enables the reaction to be carried out at a much lower temperature. This decreases the extent of retro-Diels-Alder reaction which can occur at higher temperatures.

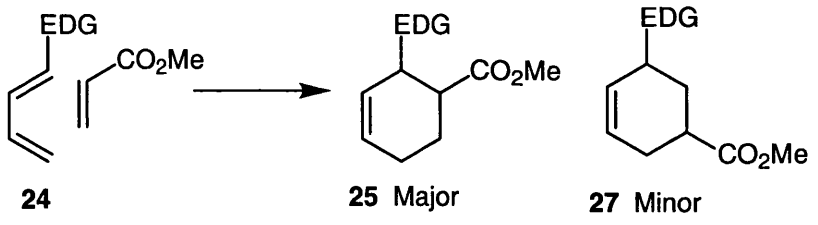
1.2.4 Regioselectivity[2,3]

Up to now, all the examples we have covered have involved simple symmetrical dienes. The next aspect of Diels-Alder control we must consider is when both diene and dienophile are unsymmetrical (*Scheme 9*). What control do we have over the product now?



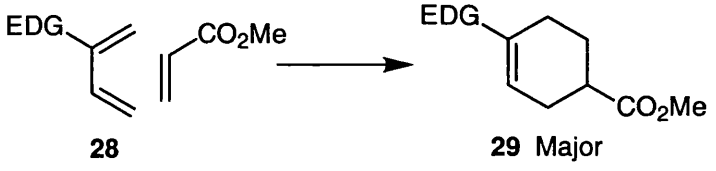
Scheme 9

The regioselectivity depends on the nature of any substitutents, and their position on the diene. Electron-donating groups (EDG) at C-1 of the diene **24** favour '*ortho*' products **25** over '*meta*' products **26** (*Scheme 10*). If the EDG is at C-2 of the diene **28** however, the '*para*' product **29** is preferred (*Scheme 11*).



24 **25** Major **27** Minor

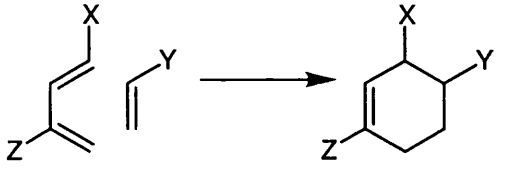
Scheme 10



28 **29** Major

Scheme 11

This *ortho-para* preference is beneficial to 1,3-substituted dienes **30**, where the two 'directing effects' favour a single product (*Scheme 12*). In many substituted dienes however, there can be some ambiguity over which product is preferred. In cases such as this, the nature of the substituent, and its position on the diene are most important in determining the outcome of the reaction.



30

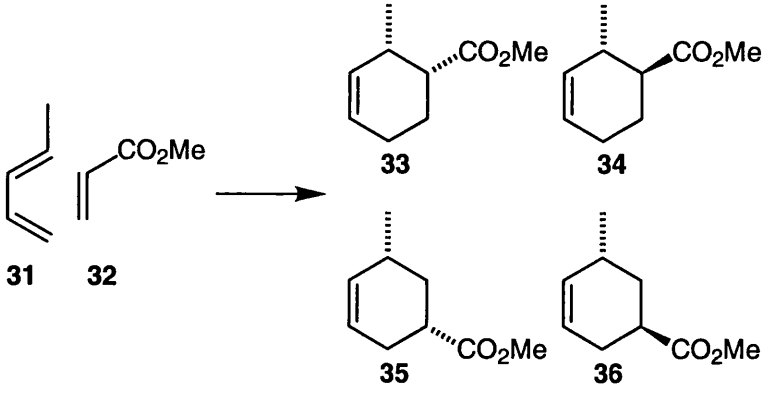
only product
Y is both *ortho* and *para*

Scheme 12

Consider the reaction between *E*-1,3-pentadiene **31** with methyl acrylate **32** (*Scheme 13*).[3] There are potentially four products (and their enantiomers). Products **33** and **35** are the *endo*-products and products **34** and **36** are the *exo*-products. When the two components were heated together at 120 °C, all 4 possible products were isolated with very poor selectivity (*Table 2*, entry 1).

This result demonstrates two points:

- *Endo*-products **33** and **35** predominate, but they are by no means exclusive (the approximate *endo-exo* ratio is 56:44).
- '*Ortho*'-products **33** and **34** are favoured over '*meta*'-products **35** and **36** (*ortho-meta*, 84:16).



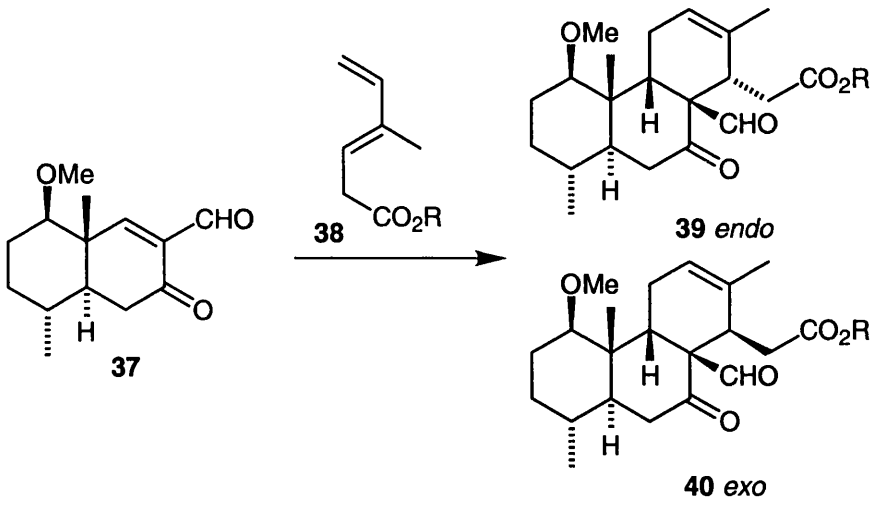
Scheme 13

		33	34	35	36
1	120 °C, 6 h	45	39	11	5
2	10-20 °C, $AlCl_3$, 3 h	93	5	2	0

Table 2

When 0.15 equivalents of $AlCl_3$ was added (*Table 2*, entry 2), the reaction could be carried out at room temperature rather than at reflux in benzene. Furthermore, the *endo-exo* selectivity increased from 56:44 to 95:5 and the *ortho-meta* regioselectivity improved from 84:16 to 98:2.

Another method of improving the reactivity and selectivity of the Diels-Alder reaction is to carry out the reaction in water. The hydrophobicity of the organic reagents cause them to be 'driven together' thus forcing the reaction. During the study of the quassinoids,[6] Grieco *et al* used this 'hydrophobic effect' to enhance the outcome of a poorly-selective reaction (*Scheme 14*). Simply by changing the diene from an ester to a carboxylate salt **38** (R=Na, *Table 3*), and running the reaction in water, the ratio of desired product was improved by a factor of 3.5, and the reaction time was reduced from 12 days to a mere 5 hours. As well as regioselectivity and *exo-endo* selectivity, this reaction shows face-selectivity due to blocking of the upper face by the axial methyl group of the ring function in **37**.



Scheme 14

R	Solvent	Time (h)	Yield (%)	*endo-exo*
Et	PhH	288	52	0.85:1
Na	H_2O	5	100	3:1

Table 3

1.2.5 Face-selectivity

The final element of control required in the Diels-Alder reaction is the control of absolute stereochemistry. How do we achieve an enantioselective reaction? Not only do we have to control *endo-exo* selectivity, we also have to differentiate between faces of the diene or dienophile. We need to have the reaction take place solely on one face of either component. This can be done in two ways:

- Covalently-bound chiral auxiliaries;
- Chiral (Lewis Acid) Catalysts.

1.2.5.1 Covalently-Bound Chiral Auxiliary

Chiral auxiliaries work by blocking one face of the dienophile (*Figure 3a*) or diene (*Figure 3b*), thereby restricting reaction to the opposite face.

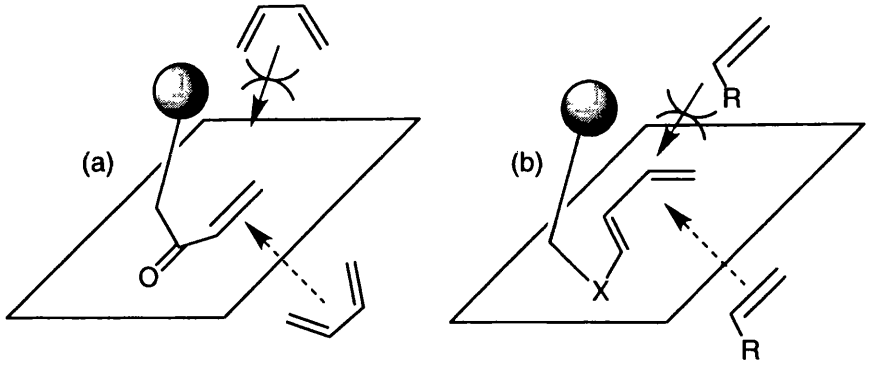
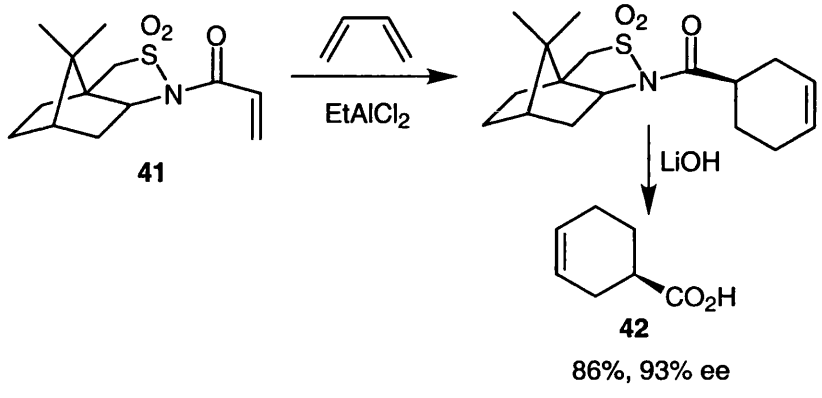


Figure 3

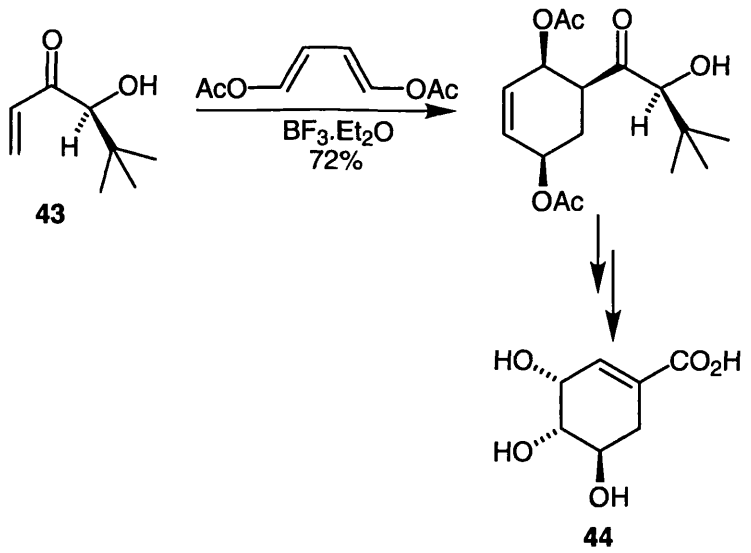
Auxiliaries bound to the dienophile (*Figure 3a*)**:**

- Camphorsultam **41** (*Scheme 15*) - used by Smith III *et al* in the synthesis of acid **42**, an intermediate in the synthesis of immunosuppressant FK-506.[7]



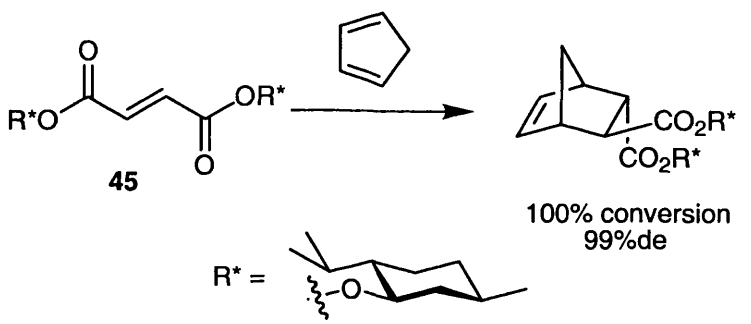
Scheme 15

- α,β-unsaturated hydroxyketones **43** (*Scheme 16*) - used in the synthesis of optically active shikimic acid **44**.[8]



Scheme 16

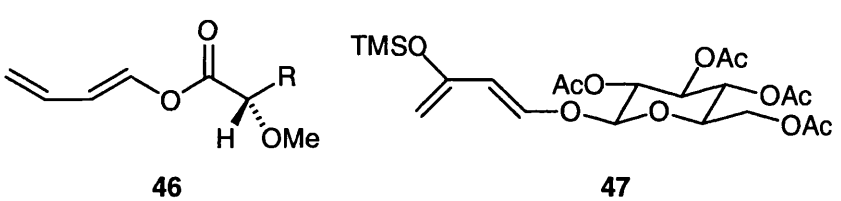
- Menthyl ester (*Scheme 17*) - Yamamoto and co-workers have shown that the di-menthyl ester of fumaric acid **45** can undergo Diels-Alder reactions with remarkable diastereoselctivity.[9]



Scheme 17

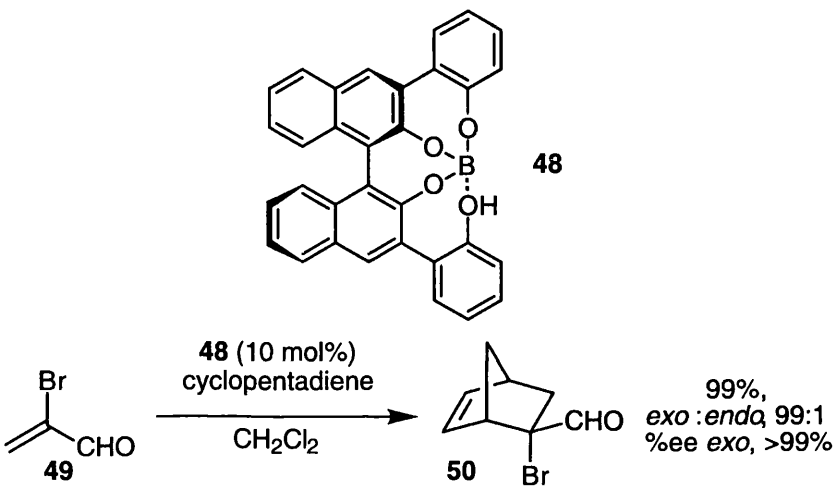
Chiral auxiliaries bound to the diene (*Figure 3b*):

These are less common, but examples include 1-(*O*-methylmandeloxy)dienes **46**,[10] and dienylglucopyranosides **47**.[11]



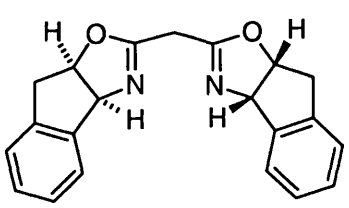
1.2.5.2 Chiral (Lewis Acid) Catalysts

Since Lewis Acids have proved to be most effective at catalysing and controlling Diels-Alder reactions, the logical step was to use a enantiopure Lewis acid to induce enantioselectivity. Recently, Yamamoto and co-workers[12] have developed a Brønsted acid-assisted chiral Lewis acid catalyst **48**, combining intramolecular hydrogen-bonding with attractive π-π donor-acceptor interactions. This catalyses the Diels-Alder reaction of a variety of α,β-unsaturated aldehydes with cyclopentadiene with excellent yield and enantioselectivity (*Scheme 18*). (Bromoacrolein **49** gives the *exo*-product **50**, whereas α-unsubstituted aldehydes give predominately *endo*-products, but with less selectivity.)



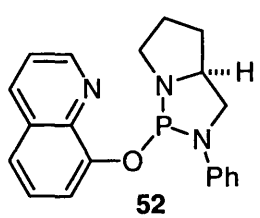
Scheme 18

Two recent examples of chiral ligands used in Lewis acid catalysts are **51**[13] and **52**.[14] Copper complexes of these ligands catalyse the Diels-Alder reaction of cyclopentadiene and two point-binding dienophiles **53** (so called due to the presence of two Lewis acid binding sites, e.g. C=O). All give high diastereo- and enantioselectivity (*Scheme 19*).



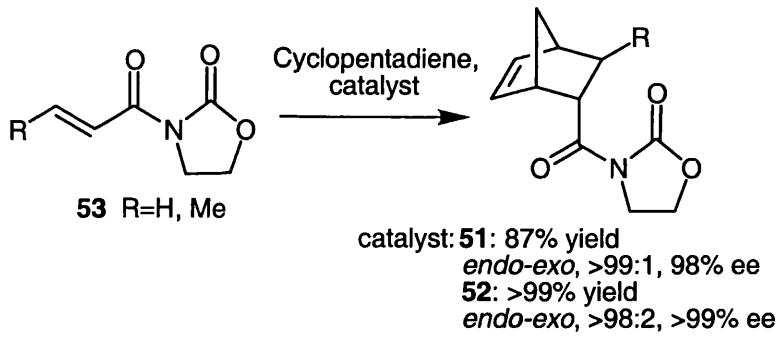
51

10 mol% $Cu(ClO_4)_2.6H_2O$



52

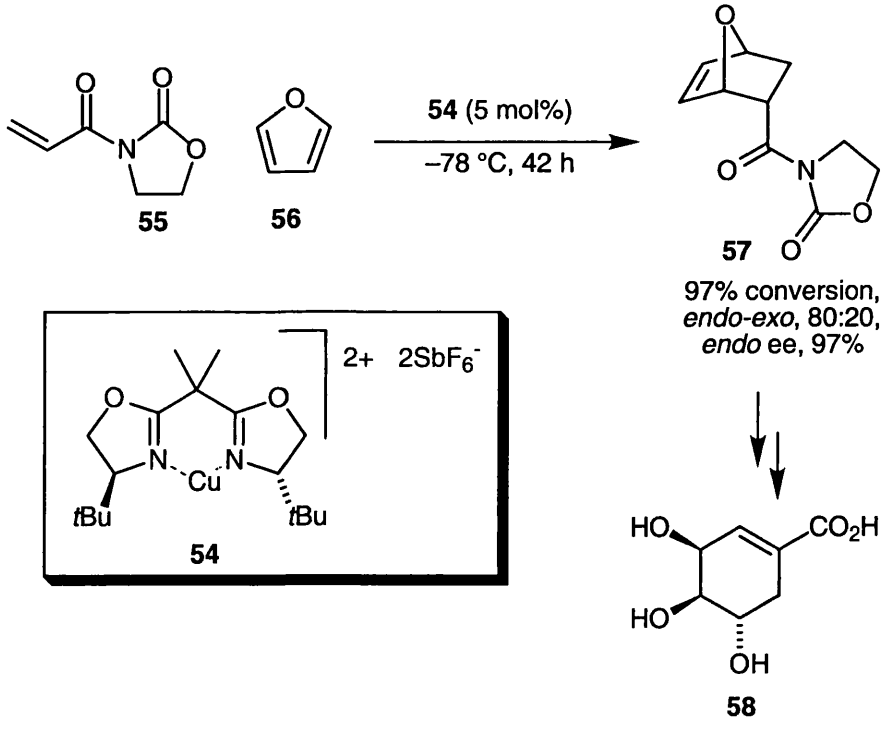
10 mol% $Cu(OTf)_2$



Scheme 19

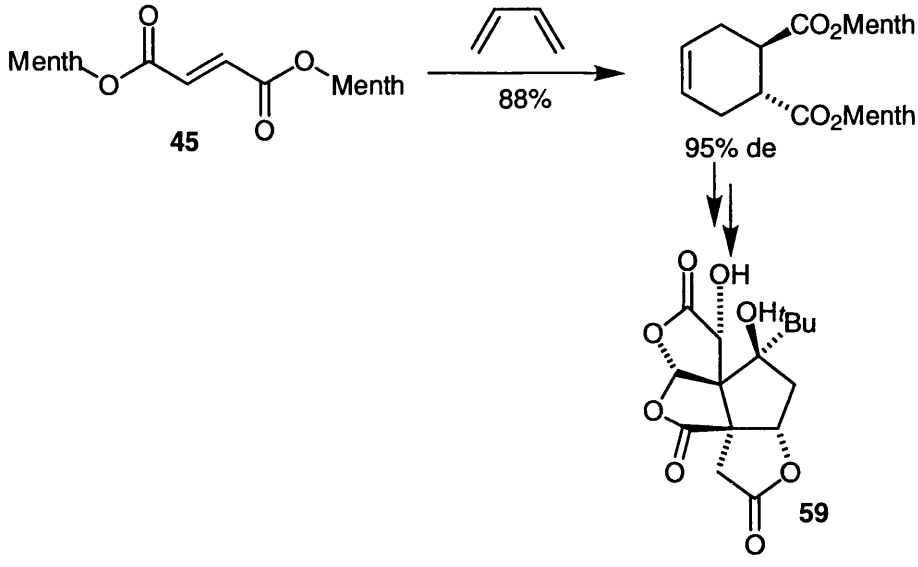
1.3 Further Examples in Target-Orientated Synthesis

As we have seen, the Diels-Alder reaction is 'one of the most common and powerful transforms'[15] in organic synthesis. The importance of this reaction in modern organic chemistry is evident from its involvement in many complicated and stylish syntheses. These include the synthesis of (-)-shikimic acid **58** by Evans *et al* (*Scheme 20*).[16] This used an enantiomerically pure ligand complex **54**. The cycloaddition between oxazolidinone **55** and furan **56** in the presence of **54** gave adduct **57** with high *endo-exo* selectivity and excellent enantioselectivity. This was also used by Evans in the synthesis of *ent*-tetrahydrocannabinol.[17]



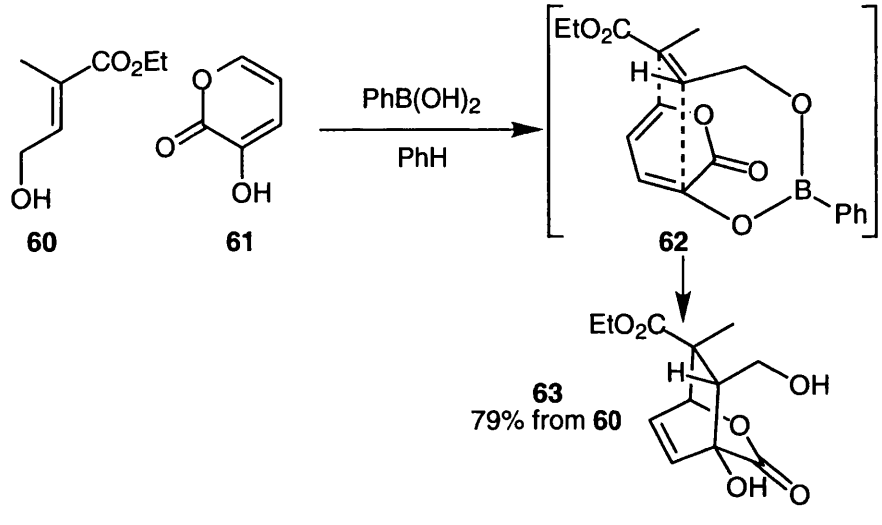
Scheme 20

The menthyl chiral auxiliary developed by Yamamoto and co-workers[9] has also been of great use in the field of natural product synthesis. Corey *et al* used the dimenthyl fumarate **45** to great effect in the synthesis of bilobalide **59**, a tetracyclic macrolide isolated from the ginkgo tree *Ginkgo biloba* (*Scheme 21*).[18]



Scheme 21

Finally, in one of the most famous total syntheses in organic chemistry, the total synthesis of Taxol®, Nicolaou *et al*[19] used phenylboronic acid to achieve total selectivity for one diastereomer in the reaction of allylic alcohol **60** with lactone **61** to give adduct **63**. In the absence of the boronic acid, the wrong regiochemistry resulted. However, complete regiocontrol can be induced by tethering the dienophile **60** to the diene **61** as a boronate ester **62**. The resulting intramolecular Diels-Alder reaction proceeds with complete endo selectivity (*Scheme 22*).



Scheme 22

1.4 Why Do We Need a Diels-Alderase Enzyme?

Despite being such a common reaction, the Diels-Alder reaction has several major disadvantages. The main drawbacks to this reaction are that it often requires harsh conditions - namely high temperature and pressure, and the use of environmentally-unfriendly reagents such as chlorinated solvents and transition metal-based Lewis-acids.

Enzymes are exceptionally good catalysts that can be used in very low stoichiometric amounts, and can perform in very mild conditions (neutral pH, room temperature, aqueous solution, etc.).[20] They can increase the rate of a reaction by a magnitude of 10^6-10^{14}. In addition, an enzyme can control the outcome of the reaction it catalyses. Use of a chemo- and regioselective enzyme may eliminate the need for any protecting groups within the substrate. A Diels-Alderase enzyme could influence the diastereoselectivity of the Diels-Alder reaction, thus giving control over the *endo*:*exo* ratio. Finally, as with all enzymes, a Diels-Alderase would perform its function to give an enantiomerically enriched/pure product.

In these days of environmental-friendliness, the 'cleaning-up' of chemistry is always an issue, and enzymes have proved themselves to be leaders in the field of clean technology. Enzymes can be produced very efficiently in water using only biodegradable materials (e.g. by over-expression in bacteria), and the enzymes themselves, being proteins, are also biodegradable. Many biological molecules are only soluble in water, therefore a catalyst that would survive (and excel!) in an aqueous system would be of great synthetic benefit. Also, from a chemists point of view, understanding enzyme mechanisms can allow us to design better chemical catalysts.[21]

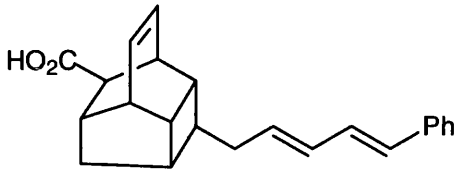
There are examples of antibodies being used to catalyse the Diels-Alder reaction,[22] but no natural Diels-Alderase enzyme has ever been isolated (as a single band by SDS gel electrophoresis). Indeed, there has been only one unambiguous demonstration of the involvement of a Diels-Alderase in biosynthesis[23] and this enzyme, in this case, catalysed the intramolecular Diels-Alder reaction (See section 1.8.1). An enzyme that catalyses an intermolecular Diels-Alder reaction is potentially much more useful to synthetic organic chemists.

1.4.1 Choice of Biological System[24]

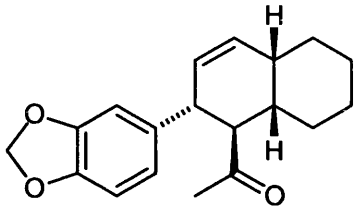
Many natural products are claimed to be formed by enzymatic Diels-Alder reactions.[24] However, when selecting a biological system from which to isolate a Diels-Alderase enzyme there are several types of evidence for the existence of this enzyme that should be considered.

(i) Evidence from the structure of the natural product

The product of the putative enzymatic Diels-Alder reaction must contain a cyclohexene ring, and have stereochemistry consistent with a concerted [4+2] cycloaddition. The natural product must also be enantiomerically enriched/pure. Several possible Diels-Alder natural products have been isolated as racemates (e.g. endiandric acid C **64**[25] and brombins II **65**[26]). This indicates a non-enzymatic biosynthesis.

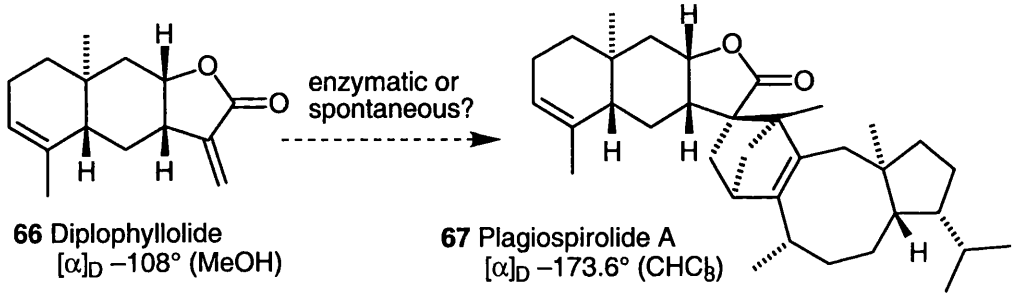


64 Endiandric acid C
from *Endiandra introsa*(*Lauraceae*)



65 Brombins II
from *Brombya platynema*

Enantiomeric purity is not sufficient evidence of an enzymatic reaction, however. We have seen how using water as a solvent can improve Diels-Alder reactions, as shown by Breslow and Rizzo, who demonstrated a 70-fold increase in reaction rate when using water over isooctane.[27] An enantiomerically pure/enriched Diels-Alder adduct could arise by spontaneous cycloaddition if the diene and/or dienophile were themselves enantiomerically pure [e.g. Plagiospirolide A **67** derived from diplophyllolide **66** (*Scheme 23*)].[28]



66 Diplophyllolide
$[\alpha]_D$ −108° (MeOH)

67 Plagiospirolide A
$[\alpha]_D$ −173.6° ($CHCl_3$)

Scheme 23

Therefore, the proposed diene and dienophile must both be achiral, and the natural product must be optically active.

(ii) Evidence of biosynthesis

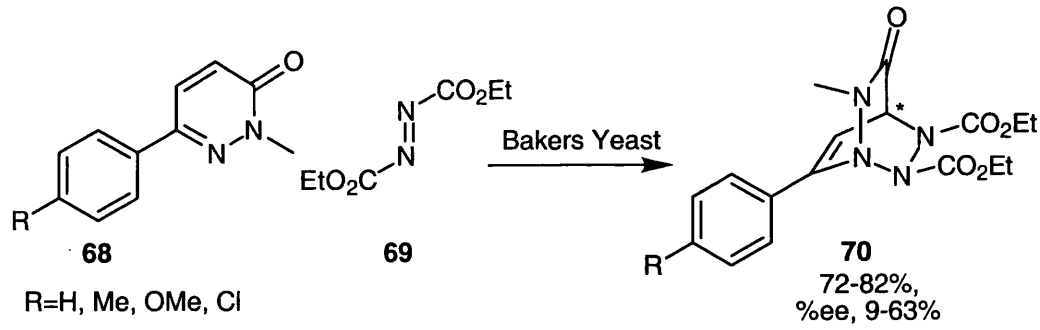
It must be possible to propose a reasonable biosynthesis for the natural product, involving the Diels-Alder reaction and precursors that have already been isolated from the same system. Feeding studies must primarily show incorporation of natural and unnatural substrates, but also the viability of the Diels-Alder biosynthesis (i.e. the substrates fed should be dienes or dienophiles).

(iii) Chemical evidence

A biomimetic synthesis would confirm that a Diels-Alder reaction is possible between the proposed precursors.

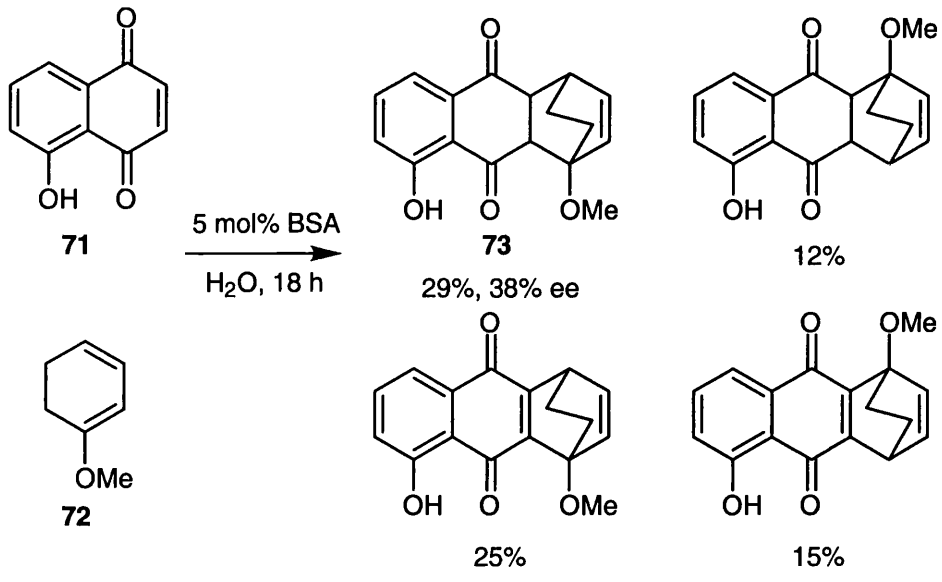
1.4.2 What about Biocatalysis?

Is it possible that natural, enantioselective Diels-Alder reactions are being catalysed, but not by a specific enzyme? Kakulapati *et al*[29] have shown that Bakers yeast acts as an efficient biocatalyst in the Diels-Alder reaction between a range of oxo-arylpyridazines **68** and azodicarboxylates such as **69** (*Scheme 24*). No cycloaddition occurred in the absence of yeast, or in the presence of boiled yeast. Likewise, experiments to resolve racemic **70** using yeast were unsuccessful.



Scheme 24

Common proteins have also been used as biocatalysts. Colonna *et al*[30] used Bovine Serum Albumin (BSA) in the reaction of naphthoquinone **71** with cyclohexadiene **72** (*Scheme 25*). Enantiomeric enrichment of cycloadduct **73** was very low (<38% ee) and the reaction was very slow.



Scheme 25

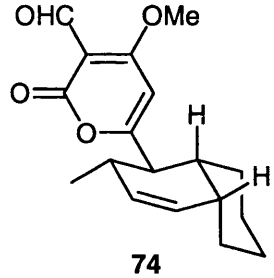
These studies indicate that biocatalysis without a specific Diels-Alderase enzyme may have a role in the biosynthesis of Diels-Alder adducts. However, low enantiomeric enrichment and (especially in the case of the BSA-catalysed reactions) poor product selectivity suggest that enantiomerically pure Diels-Alder adducts must be produced by something more specific, i.e. an enzyme.

1.5 The Intramolecular Enzymatic Diels-Alder Reaction

As mentioned, there are several natural products which are claimed to be formed by an enzymatic Diels-Alder reaction. In this section we shall discuss only those examples with the strongest evidence.

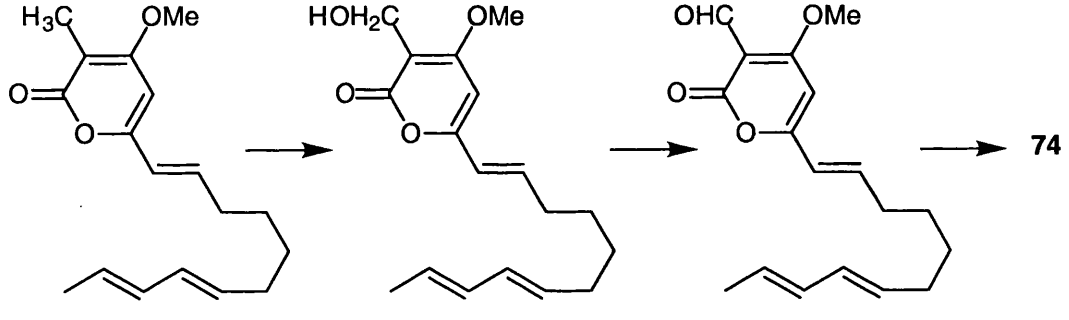
1.5.1 The Solanapyrone A System

All previous work into the enzymatic Diels-Alder reaction have focused on the intramolecular reaction. For several years Oikawa *et al*[31,32] has been studying the biosynthesis of (-)-solanapyrone A **74**, a phytoalexin from the pathogenic fungus *Alternaria solani.*



74

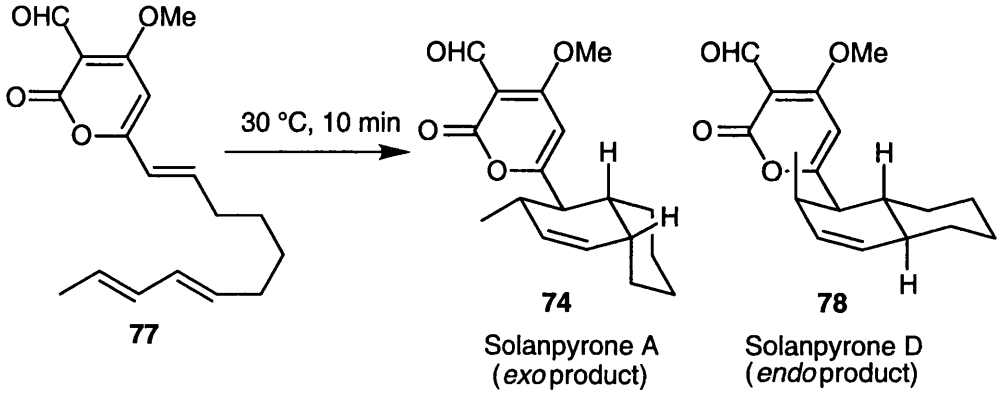
(-)-Solanapyrone A is biosynthesised by an *exo* Diels-Alder reaction from prosolanapyrone III **77** which, in turn is produced by sequential oxidation from prosolanapyrones II **76** and I **75** (*Scheme 26*).



Scheme 26

The most conclusive experiments used cell-free extracts.[32] When prosolanapyrone III **77** was incubated in enzyme-free aqueous solution under standard conditions (30 °C, 10 min), 10% was converted into Diels-Alder adducts, solanapyrones A **74** and D **78**, the product of the *endo* Diels-Alder (*Scheme 27*, *Table 4*, entry 1). The ratio of *exo-endo* was 3:97. When carried out in cell-free extract, 25%

of **77** was consumed giving **74** and **78** in a ratio of 53:47 (entry 2). By comparison of these results, Oikawa concluded that the consumption of **77** by the enzyme was 15%, giving products with an overall *exo* selectivity of 87:13 (entry 3). The enantiomeric purity of **74** was 92±8% [determined by CD absorption compared to natural (–) solanapyrone A].



Scheme 27

		Conditions	Conversion	*%Exo*	*%Endo*
1.	Control	Aqueous	10%	3	97
2.	Test	Cell-free extract	25%	53	47
3.	Difference	Enzyme	15%	87	13

Table 4

The cell-free extract experiment was repeated with prosolanapyrone II **76** as the fed substrate. Under an inert atmosphere, no cyclisation took place. When the experiment was carried out in air, three products of note were isolated: prosolanapyrone III **77**, and solanapyrones A **74** and D **78**. Once again, there was a noted *exo* selectivity (83:17) and a very high enantioselectivity (%ee *exo*, 99±4% ee).

The following points were noted from the first set of experiments:

- Solanapyrone A was produced in optically active form from an achiral precursor.
- There was a difference in diastereoselectivity between spontaneous cyclisation and cyclisation in a cell-free extract. Solanapyrone D **78** is produced by spontaneous cyclisation in water (and in chemical synthesis),[33] but levels of solanapyrone A **74** rise markedly in the cell-free extract experiments.
- A small rate-enhancement was observed. When four times the concentration of extract was used, the reaction proceeded 4.1 times faster than the control.

The prosolanapyrone II-feeding experiment showed that:

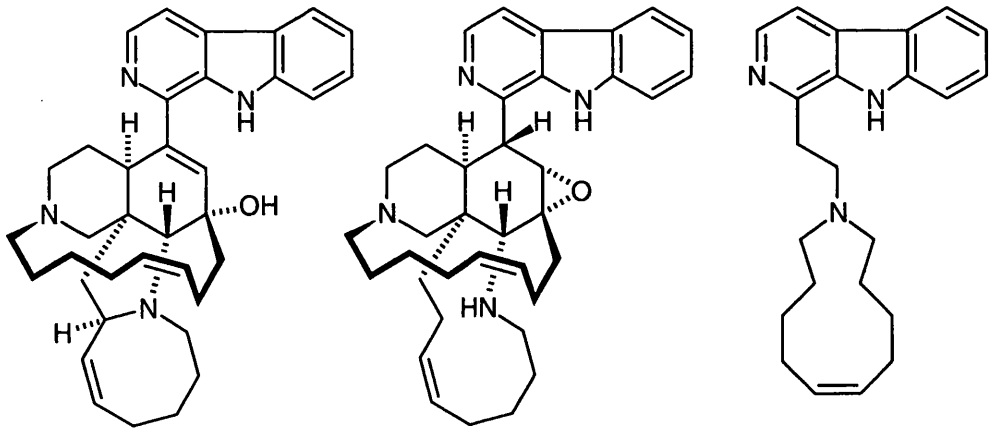
- Under no circumstances do unoxidised cycloadducts form (i.e. cycloadducts of **77** and **76**).
- No cycloaddition occurs without oxygen.
- Prosolanapyrone III **77** is formed in the presence of oxygen.
- Diastereo- and enantioselectivities were better when prosolanapyrone II **76** was the fed substrate.

From these results, Oikawa concluded that the Diels-Alder reaction is enzyme controlled. The enzyme's main function is as an oxidase, but it does have a small catalytic influence on the diene cyclisation, and a substantial effect on the *exo-endo* ratio. Recently, Oikawa *et al* managed to partially purify the Diels-Alderase from *A. solani*,[23] but they have yet to obtain a sample of the enzyme that is a single band by SDS gel electrophoresis.[34]

1.5.2 The Manzamine System

The other major contributors to the investigation of intramolecular enzymatic Diels-Alder reactions have been Baldwin and Whitehead in their study of the biosynthesis of manzamine alkaloids.

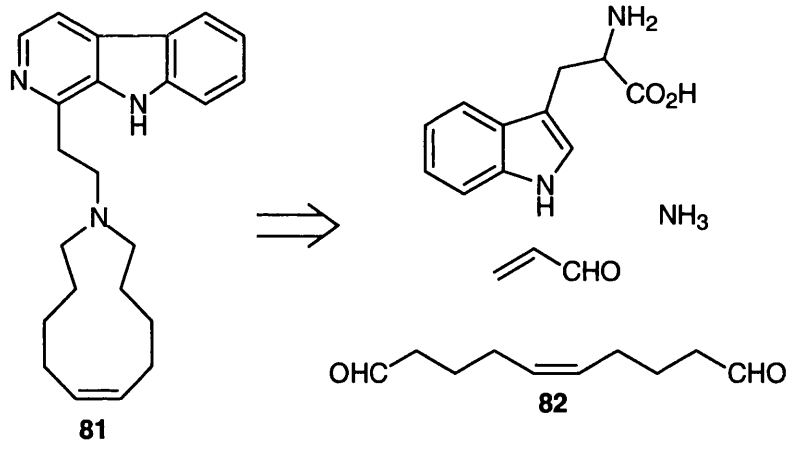
Manzamine A **79** was first isolated in 1986 by Higa and co-workers from the sponge *Haliclona* sp.[35] This was closely followed by the isolation of manzamines B **80** and C **81** from the same sponge.[36] Their complicated structural formulae led Higa to state that "there appears no obvious biogenetic pathway."



79 **80** **81**

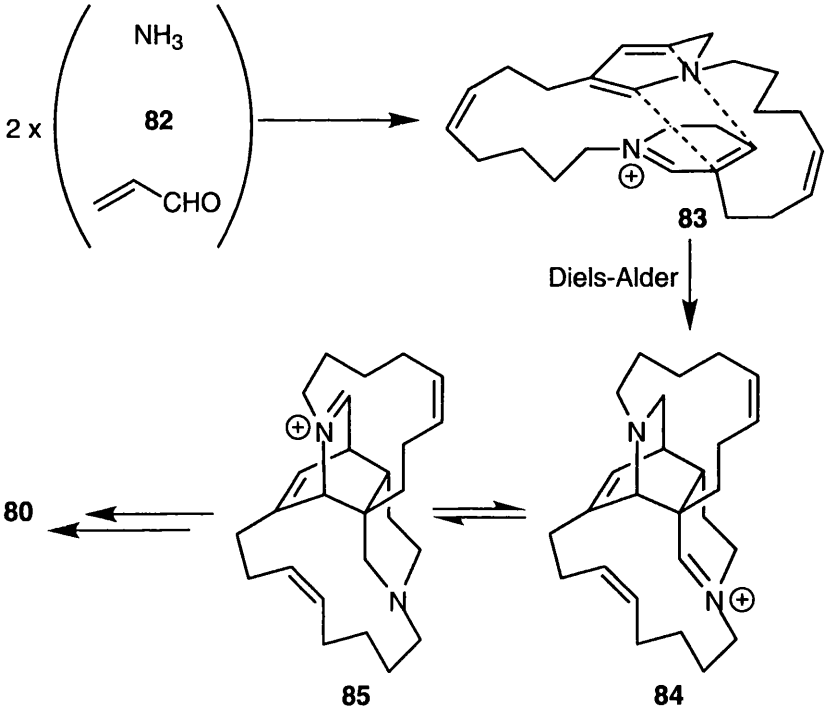
In 1992, Baldwin and Whitehead proposed a common biosynthetic path to these compounds.[37] Manzamine C **81** could be traced to three precursors, tryptophan,

acrolein and a symmetrical C_{10} dialdehyde **82** (*Scheme 28*). Reductive coupling with ammonia would give **81**.



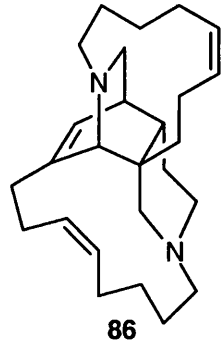
Scheme 28

Baldwin and Whitehead then proposed an analogous biosynthetic pathway for the more complicated manzamines A **79** and B **80** (*Scheme 29*). Two molecules each of ammonia, acrolein and **82** could be coupled to give hydropyridinium **83**. This undergoes an *endo* Diels-Alder reaction to give adduct **84** (in redox equilibrium with **85**). Ring-opening, incorporation of tryptophan and oxidation would then give manzamine B **80**. Minor changes after tryptophan incorporation would give manzamine A **79** by the same path.



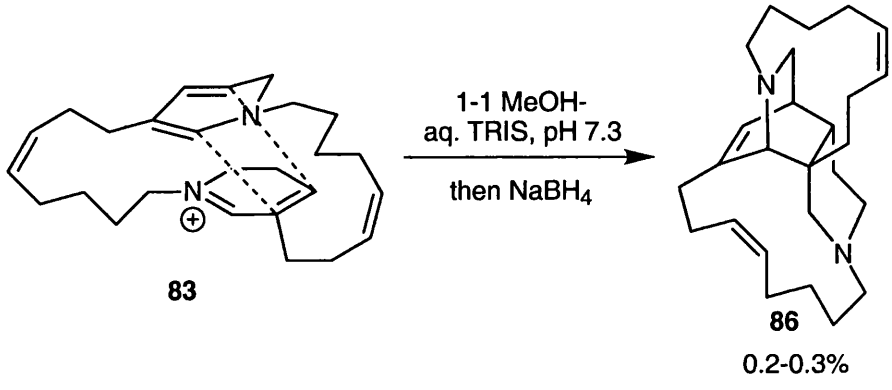
Scheme 29

The only evidence to suggest the involvement of a Diels-Alderase was the proposal that optically active manzamines were derived from an achiral precursor. In 1994, Kobayashi *et al* isolated keramaphidin B **86** from the marine sponge *Amphimedon* sp..[38] Keramaphidin B is a pentacyclic alkaloid, and is a reduced form of iminium **84** in Baldwin and Whiteheads' proposed biosynthesis.



86

The discovery of a compound similar to a proposed intermediate should be further evidence of a Diels-Alderase. However Kobayashi discovered that crystals of natural keramaphidin B **86**, which has 4 chiral centres, were racemic. If a Diels-Alderase were involved, keramaphidin B **86** should have been isolated in an optically active form. Kobayashi then looked at the isolated sample of **86** in more detail.[39] Chiral HPLC analysis of both crystals and mother liquors showed that the ratio of (+):(-) enantiomers was 1:1 and 20:1, respectively. Keramiphidin B was being produced enantiomerically enriched, but was crystallising as a racemate. This observation proved crucial to the acceptance of Baldwin and Whiteheads' biosynthesis. In order to provide more evidence of a Diels-Alderase, a biomimetic synthesis of keramaphidin B **86** was attempted (*Scheme 30*).[40] In a methanol-water solution buffered at pH 7.3, pyridinium ion **83** underwent an *endo* cycloaddition giving an adduct which was immediately reduced. Exhaustive chromatography gave a sample of pure **86** in low yield.



83 **86**

0.2-0.3%

Scheme 30

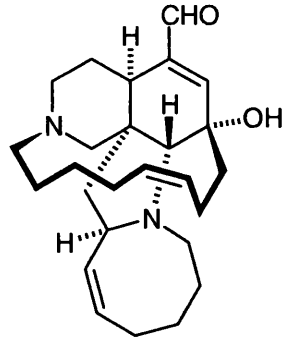
The following points can be made about this study:

- The structure of the manzamines A and B, **79** and **80** is consistent with a biological Diels-Alder reaction as proposed by Baldwin and Whitehead.
- Biomimetic synthesis has shown that keramaphidin B **86** can be formed by an intramolecular cycloaddition.
- Keramaphidin B is produced in optically active form, however the putative precursor is achiral.

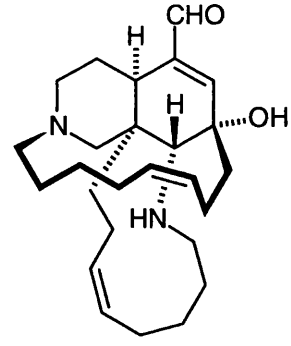
Baldwin concluded that the involvement of a Diels-Alderase enzyme in this system was very likely.

1.5.3 Other Natural Products from this Intramolecular Enzymatic Diels-Alder Reaction

Several natural products, mainly derived from keramaphidin B **86**, can also be described as being 'Diels-Alderase' adducts. Two of these are the ircinals A **87** and B **88**.[41] Both have been isolated from the sponge *Ircinia* sp.. These have the same keramaphidin-derived skeleton as the manzamines A and B and may be converted into the latter by condensation with tryptophan as proposed by Baldwin and Whitehead.

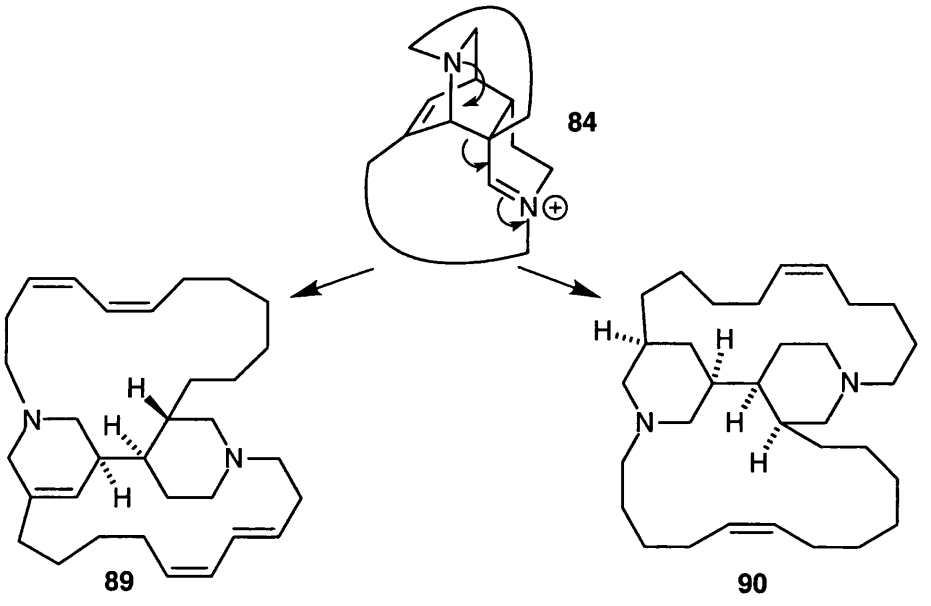


87



88

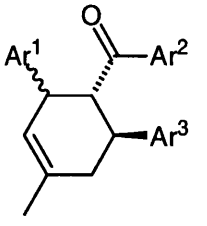
As well as the (+)-ircinals **87** and **88**,[41] (-)-halicyclamine A **89**,[42] and haliclonacyclamine A **90**,[43] (from *Haliclona* sp.) are thought to be formed by a retro-aza-aldol opening of keramaphidin B-precursor **84** (*Scheme 31*).[44]



Scheme 31

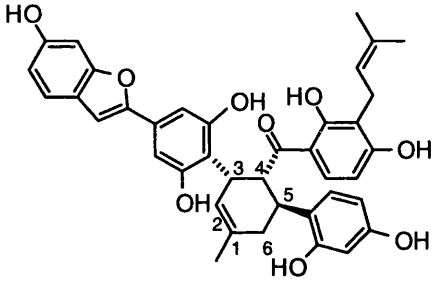
1.6 The Intermolecular Enzymatic Diels-Alder Reaction

Many polyphenolic compounds isolated from moraceous plants show evidence of Diels-Alderase involvement. These all have the same basic skeleton (*Figure 4*) and include chalcomoracin **91**,[45] kuwanon G **92**,[46] dorstenone **93**,[47] and artonin I **94**.[48]

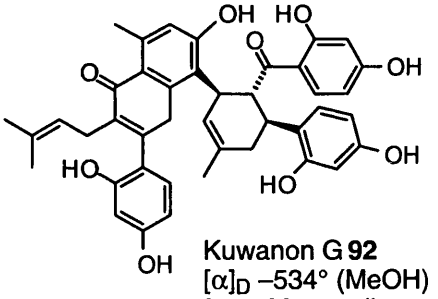


Ar^1 = a flavone, flavonoid, chalcone or biaryl
Ar^2 = a phenol
Ar^3 = a phenol

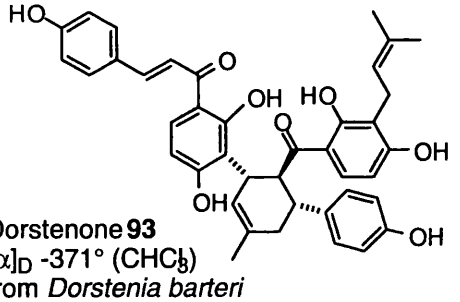
Figure 4



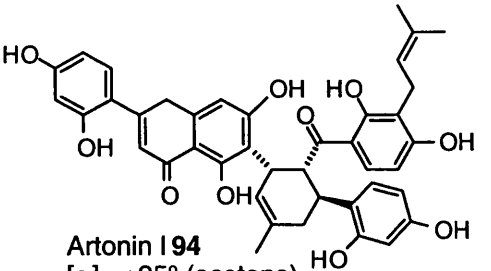
Chalcomoracin **91**
$[\alpha]_D$ +194° (acetone)
from *Morus alba*



Kuwanon G **92**
$[\alpha]_D$ –534° (MeOH)
from *Morus alba*



Dorstenone **93**
$[\alpha]_D$ -371° ($CHCl_3$)
from *Dorstenia barteri*



Artonin I **94**
$[\alpha]_D$ +95° (acetone)
from *Artcarpus heterophyllus*

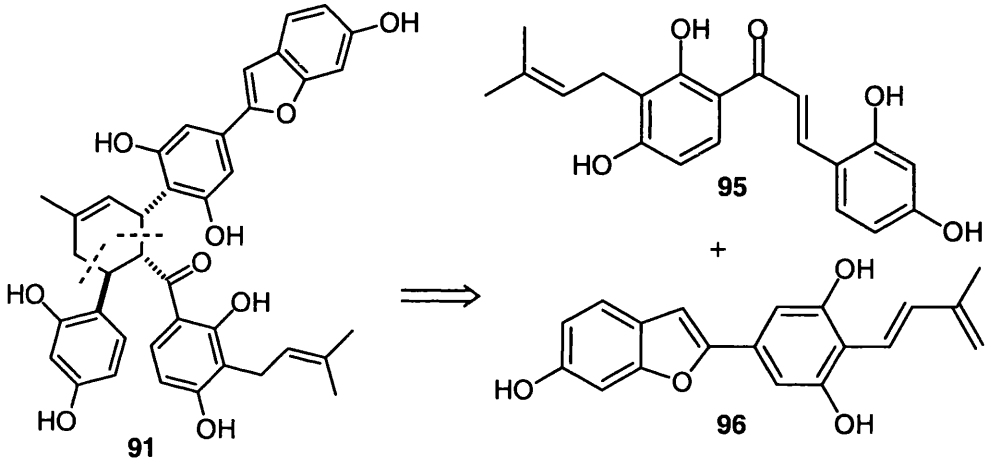
Evidence for Diels-Alderase Involvement:

- All of these compounds are optically active and are derived from achiral diene and dienophiles.
- The 4,5-relationship in the cyclohexene ring is consistent with a Diels-Alder reaction on an *E*-chalcone.
- In cases where the absolute stereochemistry has been determined (by X-ray crystallography and CD spectroscopy), it is always 4*R*, 5*S*.
- There are examples of both *endo* and *exo* adducts, but in all cases addition occurs on the same face of the diene.

1.6.1 The Chalcomoracin System

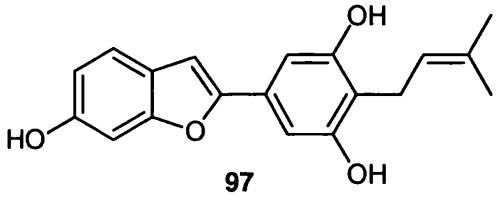
Of all the Diels-Alder adducts produced, the chalcomoracin system was of most interest to us.

In 1980, Takasugi *et al* isolated and elucidated the structure of chalcomoracin **91**.[45] Chalcomoracin is a naturally-occurring antifungal compound found in the diseased shoots of the white mulberry *Morus alba*. It consists of several polyphenolic aromatic moieties and a methylcyclohexene ring, which has stereochemistry consistent with an *endo* Diels-Alder reaction of an *E*-dienophile. It was proposed that chalcomoracin was derived from dienophile morachalcone A **95** and diene **96** (*Scheme 32*).[49,50] The production of an optically active adduct from achiral precursors suggested the involvement of an enzyme.



Scheme 32

Of the two precursors, only morachalcone A **95** has ever been isolated from *M. alba*. Although the existence of the diene **96** has never been proven, the antifungal compound moracin C **97** has been found in *M. alba*. It has been proposed that moracin C is a biological precursor to **96** which, once formed, undergoes cycloaddition with morachalcone A **95**.



Much of the biosynthetic work in this area has been carried out by Nomura and co-workers,[50] investigating Diels-Alderase activity in moraceous plants. They

performed a series of feeding experiments with *M. alba*, using ^{13}C-labelled acetates; modified substrates; and unnatural substrates.

1.6.1.1 ^{13}C-Labelled Substrates

Sodium [1-^{13}C]-, [2-^{13}C]- and [1,2-$^{13}C_2$]-acetates were fed to *M. alba* cells and the suspensions shaken for 7 days at room temperature.[50] After work-up, it was found that, in all 3 experiments incorporation of the labelled acetates had occurred (*Figure 5*).

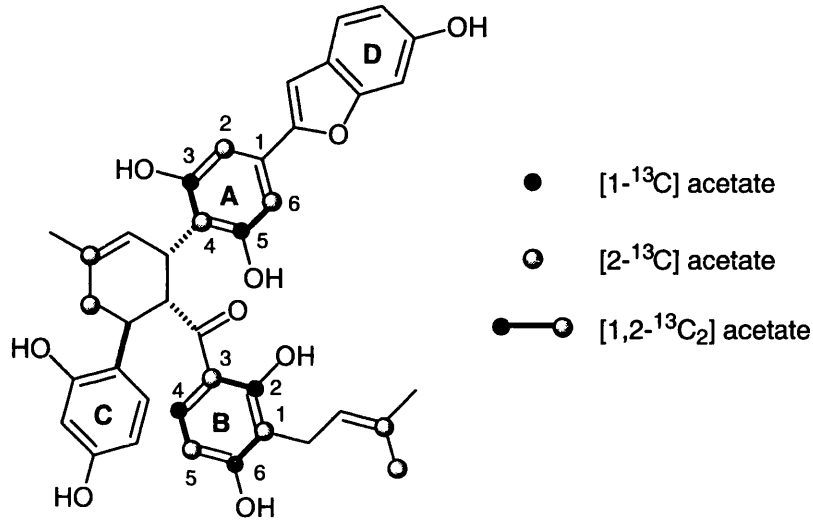
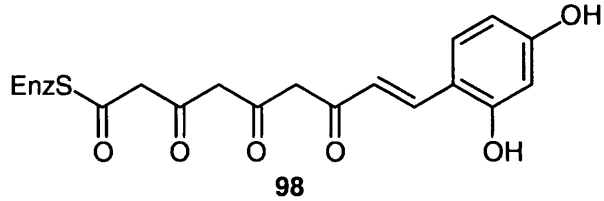


Figure 5

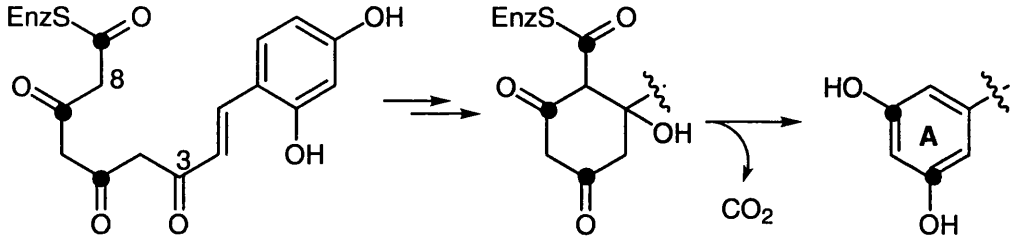
The labelling pattern from the experiments with [1-^{13}C]- and [2-^{13}C]-acetate indicate several things:

- If chalcomoracin is formed by the suggested Diels-Alder reaction, then the chalcone is derived from a cinnamoyl polyketide skeleton **98**. This is shown, both by the incorporation of [2-^{13}C]-acetate into positions 2, 4 and 6 of ring B, and the lack of labelling in ring C.
- Ring A has a labelling pattern similar to ring B, while no labels were incorporated into ring D. This suggests that the arylbenzofuran is also derived from polyketide **98**.

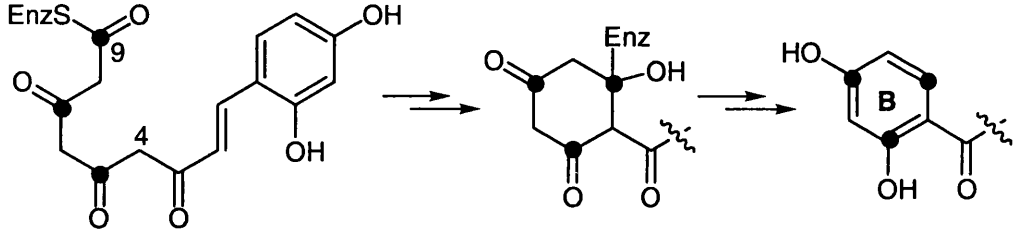


98

- [1-^{13}C]-Acetate incorporation into the arylbenzofuran was only noted in positions 3'-and 5'- of ring A, suggesting cyclisation occurs between carbons 3 and 8 of the polyketide, followed by decarboxylation (*Scheme 33*). On the other hand, [1-^{13}C]-acetate incorporation into ring B suggests cyclisation between C-4 and C-9 of **98** (*Scheme 34*).

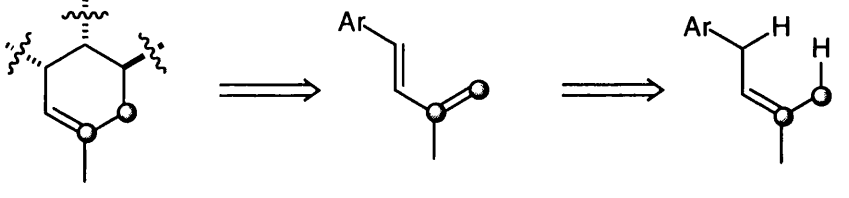


Scheme 33



Scheme 34

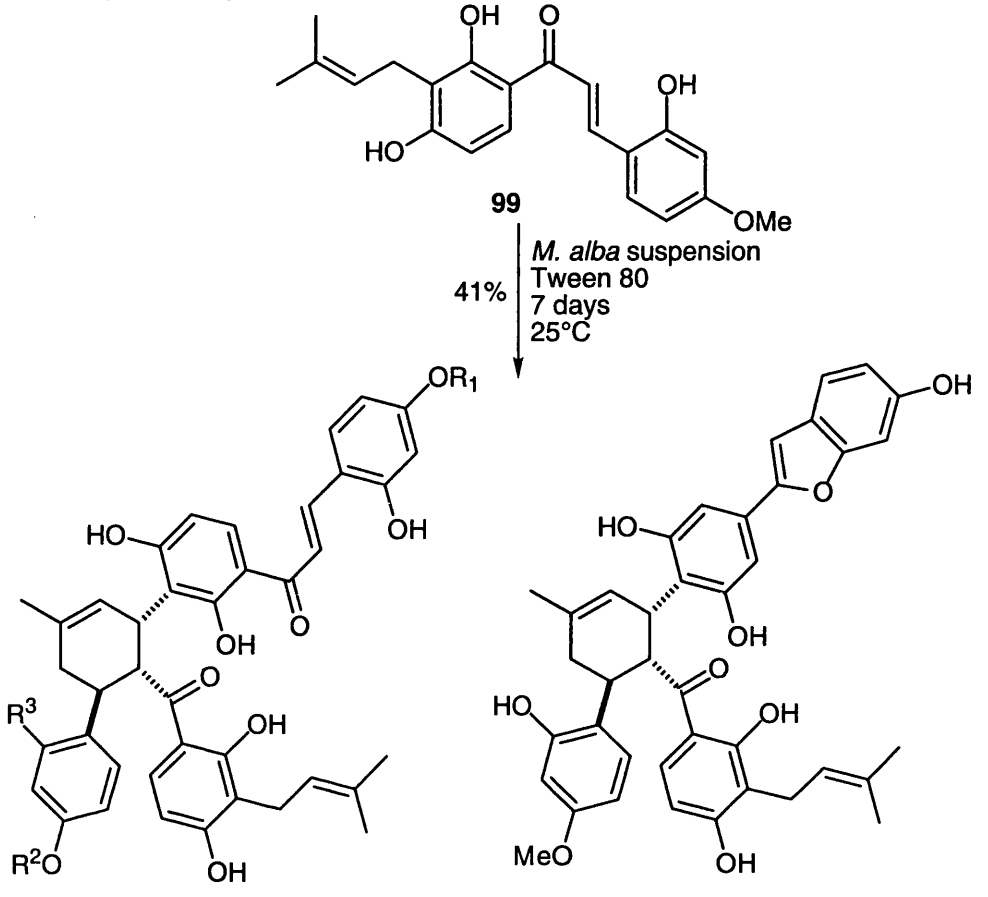
Examination of the labelled products showed that there were differing levels of isotope incorporation. The aromatic sections showed 17% uptake, while the prenyl groups had only a 0.4% incorporation. This difference in labelling suggests that these portions are biosynthesised in a different way. The cyclohexene ring has a labelling pattern consistent with a diene formed by elimination of H_2 from the methylene and the *cis*-methyl groups of the prenyl group of moracin C **97**. The prenyl group in moracin C is labelled in a similar manner to the prenyl group in the chalcone (*Scheme 35*).



Scheme 35

1.6.1.2 Modified Substrates

In a later study by Nomura and co-workers,[51] 4-*O*-methylmorachalcone **99** was fed to a suspension of *M. alba* cells. After 7 days, standard extractive work-up gave a 41% yield of optically active Diels-Alder adducts (*Scheme 37* and *Table 5*).



Scheme 36

	Isolated Yield	$R^1/R^2/R^3$	$[\alpha]_D$
100 (methylkuwanon J)	1.9%	R^1=Me, R^2=H, R^3=OH	+26 (0.16, EtOH)
101 (methylkuwanon Q)	2.6%	R^1=Me, R^2=R^3=H	+133(0.075, EtOH)
102 (dimethylkuwanon J)	27.7%	R^1=R^2=Me, R^3=OH	+28 (0.085, EtOH)
103	8.7%	—	+152(0.088, EtOH)

Table 5

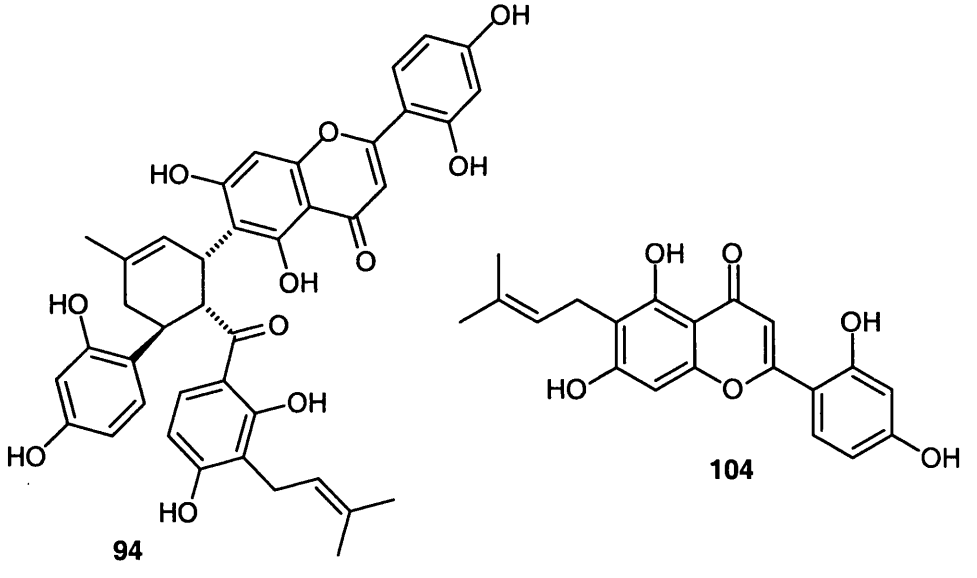
All adducts were isolated in optically active form. Three of the four adducts (**100**, **101** and **102**) were of the kuwanon family and are believed to be formed by

cycloaddition between the double bond of the chalcone and a morachalcone-derived diene. The other adduct was 18"-*O*-methylchalcomoracin **103**.

The results of these feeding studies prove that chalcomoracin and the members of the kuwanon family are synthesised from morachalcone A **95** in a manner consistent with an enzymatic Diels-Alder reaction.

1.6.1.3 Unnatural Substrates

Labelled moracin C has never been fed to cell cultures to confirm that it is the natural precursor to chalcomoracin. However, studies on artonin I **94** support this hypothesis. Artonin I **94** is an optically active natural product isolated from the Indonesian moraceous plant *Artocarpus heterophyllus* (*Figure 6*).[48] Examination of its structure shows that it too is a plausible Diels-Alderase adduct. Artocarpesin **104** is a natural flavone also from *A. heterophyllus*, and is presumed to be the precursor to the diene required in artonin I biosynthesis. While prevalent in *A. heterophyllus*, neither compound has ever been isolated from *M. alba*.



$[\alpha]_D$ +95 (0.05, acetone)
from *A. heterophyllus*

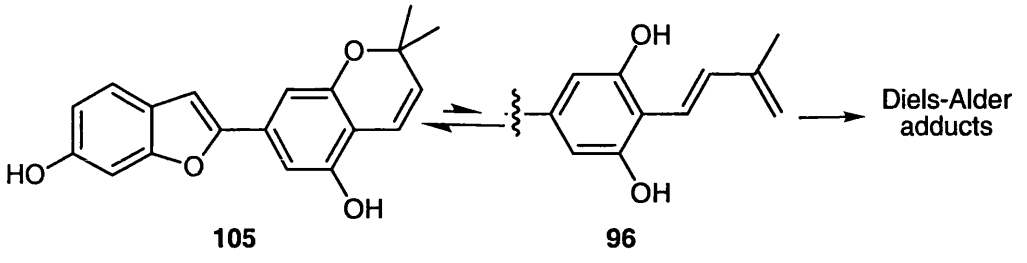
Figure 6

The obvious structural similarities between **104** and the prenylated compounds from *M. alba* led Nomura and co-workers to believe that it may be a suitable unnatural substrate to use in their feeding studies. Artocarpesin was fed to *M. alba* cell cultures under standard conditions.[48] After work-up, several naturally-occurring Diels-Alder adducts were isolated including a significant amount (8%) of artonin I **94**. The artonin

I from these experiments was of comparable optical purity to the naturally-occurring compound {$[\alpha]_D$ +91 (0.0075, acetone) from *M. alba*}.

1.6.2 Will the Diene Really Exist?

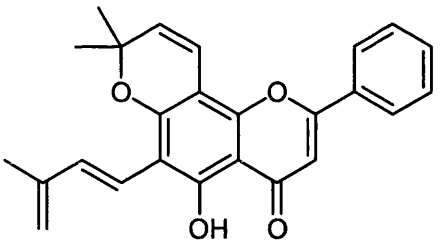
As mentioned, although moracin C **95** is known, diene **96** has never been isolated (*Scheme 33*, p27). Possibly the diene moiety is not stable in water and cyclises onto one of the neighbouring hydroxyls. Such a cyclisation would form another member of the moracin family, moracin D **105**. This natural chromene has been isolated from *M. alba*.[52] However, moracin D may also be a precursor to diene **96**. The chromene ring in moracin D **105** is in the same oxidation state as the diene group, and it is possible that the chromene ring is 'opened' by the Diels-Alderase (or another) enzyme to give diene **96** (*Scheme 37*). To date, no investigation of this has been made.



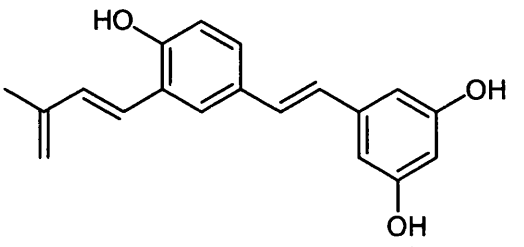
105 **96**

Scheme 37

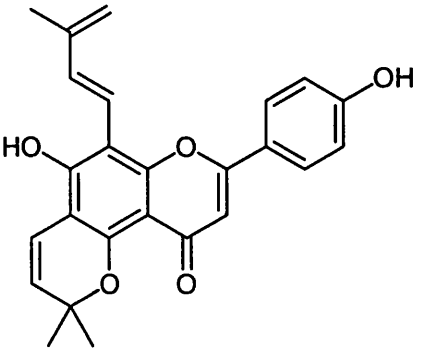
Several phenolic dienes have been isolated from natural sources (*Figure 7*), and so diene **96** is a plausible intermediate.



From *Tephrosia fulvinervis*[53]



From Groundnut kernels[54]



From *Ormosia monosperma*[55]

Figure 7

1.7 Primary Aims

We have chosen the chalcomoracin system for the following reasons:

- The stereochemistry of the cyclohexene ring in chalcomoracin is consistent with a concerted [4+2] cycloaddition on an *E*-chalcone.
- Chalcomoracin is optically active and derived from achiral precursors. These precursors (or derivatives of them) have been found in the same organism.
- The Diels-Alder reaction is intermolecular.
- Chalcomoracin is an *endo* Diels-Alder adduct. The corresponding *exo*-product has never been isolated from *M. alba*, indicating that the reaction is diastereoselective.
- There have been a range of Diels-Alder adducts found in *M. alba*. This, together with the incorporation of an unnatural substrate, suggests that the enzyme has a reasonably broad substrate-specificity.

The aim of this project is to develop an assay for the Diels-Alderase enzyme. This assay will be based on the biosynthesis of chalcomoracin proposed by Nomura and co-workers.[40] For this assay we require to synthesise both dienophile **95** and diene **96**. These can be used in a biomimetic study to establish the involvement of a Diels-Alder reaction. The synthesis of **95** and **96** will also provide relevant intermediates for the total synthesis of chalcomoracin. Our initial efforts will be directed towards the total synthesis of moracin C **97**. Due to the obvious structural similarities, we hope that a synthesis of **97** will provide a straightforward route to diene **96**.

2

Benzofuran Synthesis

2.1 Previous Syntheses of Moracin C

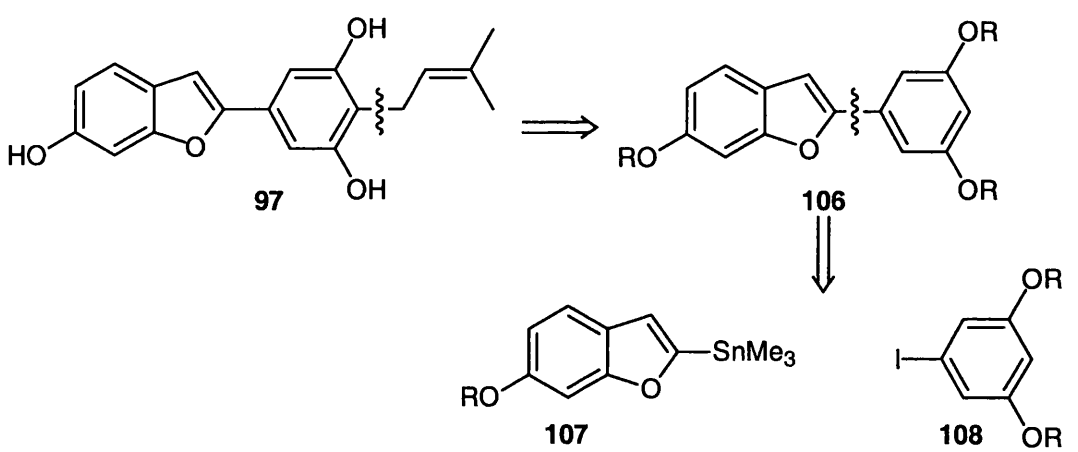
2.1.1 What is moracin C?

As well as being a powerful antifungal compound,[56] moracin C **97** is also an oviposition stimulant for the lesser mulberry pyralid moth *Glyphodes pyloalis*.[57] To show this, Nakamura and co-workers inoculated mulberry leaves with samples of natural and synthetic moracin C in concentrations as low as 0.01 gram leaf equivalents (18μg per leaf), and found that egg-laying on those leaves was greatly stimulated.

These interesting biological properties, as well as moracin C's involvement in chalcomoracin biosynthesis have made it a popular synthetic target.

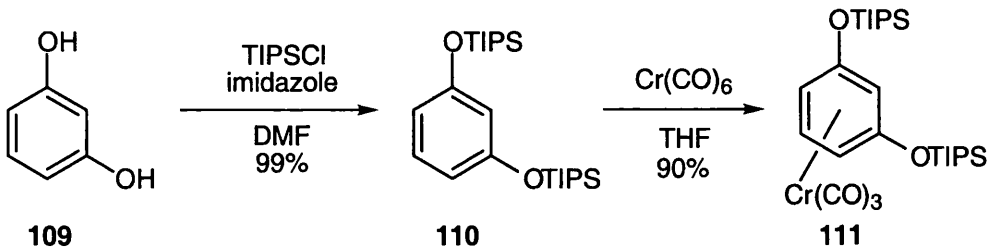
2.1.2 Mann and Widdowson's Synthesis

The first of the two previous syntheses of moracin C was by Mann and Widdowson in 1991.[58] The primary disconnection in their route involved regioselective prenylation of an aromatic ring, and a Stille coupling to form the arylbenzofuran nucleus **106** (*Scheme 38*).[59] This required the establishment of a 1,3,5-substitution pattern in the aryl iodide **108** - a notoriously difficult relationship to set up.



Scheme 38

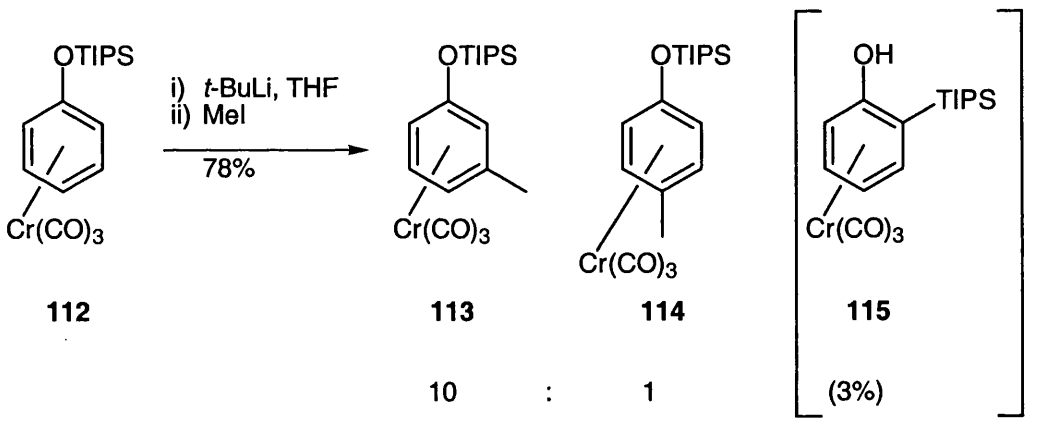
The starting material for the synthesis was resorcinol **109**. The iodine could be introduced by remote lithiation of an aryl-chromium complex using a method already pioneered by Masters and Widdowson.[59,60] *Scheme 39* outlines the initial preparation of the chromium complex **111** from resorcinol.



109 **110** **111**

Scheme 39

In a previous study[59] Masters and Widdowson had used the bulky triisopropylsilyl group to direct to the *meta* position. Treatment of (η^6-triisopropylsilyloxybenzene)tricarbonylchromium(0) **112** with *tert*-butyllithium and quenching with methyl iodide gave two monomethylated products **113** and **114** in a combined total of 78% yield (*Scheme 40*). These were the *meta*- and *para*- derivatives, respectively and were isolated in a ratio of 10:1 (by ^{1}H NMR spectroscopy). There was also a small amount (3%) of *o*-triisopropylsilyl phenol **115**, a result of *ortho*-lithiation followed by silicon migration.



112 **113** **114** **115**

10 : 1 (3%)

Scheme 40

There are two possible explanations for this regioselectivity. The first concerns the conformation of the chromium complex. The normal arrangement of an arenetricarbonylchromium(0) complex is where the substituent is eclipsed by one of the carbonyl groups. This has been shown to be the most stable conformation (*Figure 8*),[61] and causes an electron-deficiency at the eclipsed carbons, making them more susceptible to either nucleophilic attack or deprotonation.

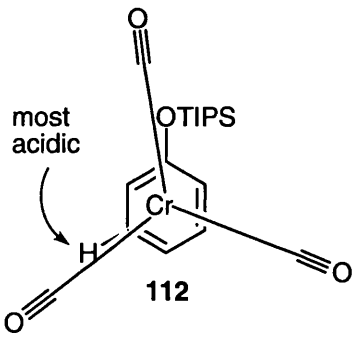
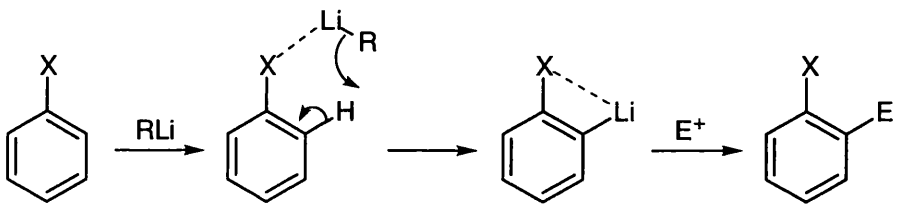


Figure 8

The second explanation concerns a property common to aromatic rings substituted with electronegative groups. *Ortho*-Lithiation is a method of aromatic substitution which involves initial chelation of an alkyllithium to a heteroatom, followed by deprotonation in the *ortho*-position. Addition of an electrophile leads to highly regioselective substitution of the aromatic ring (*Scheme 41*).[62]



Scheme 41

The most common groups *ortho* to which lithiation is possible are *O*-alkyl (methyl and benzyl especially), *N*-alkyl, and *S*-alkyl, although other groups may also direct lithiation (e.g. Se, F, -CONHR', -CN, and oxazolines).[62] In complex **111** however, it is possible that the bulkiness of the triisopropylsilyl groups makes the *ortho* proton inaccessible (*Figure 9*).

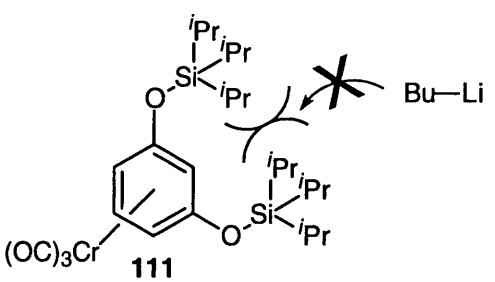
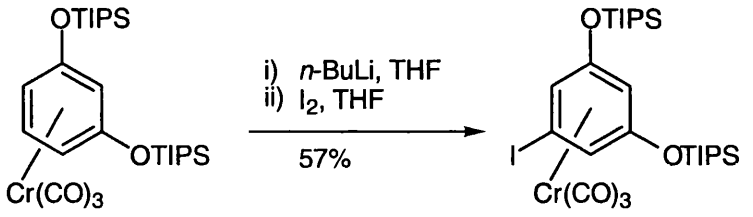


Figure 9

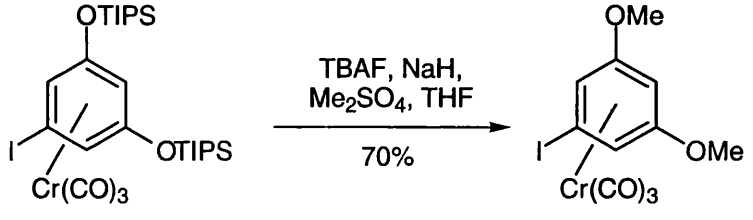
Treatment of complex **111** with *n*-butyllithium followed by quenching with iodine resulted in isolation of a single regioisomer **116** in moderate yield (*Scheme 42*).



111 **116**

Scheme 42

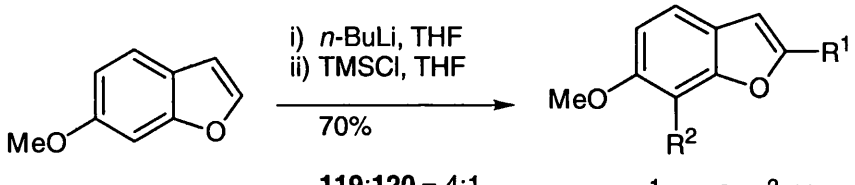
The prenyl unit in moracin C was to be inserted by *o*-lithiation later in the synthesis, and this required a change in the protecting group. Of all the functionality that directs lithiation, the methoxy group is one of the most efficient. It is a very strong *ortho*-director, and its relatively small size means that it does not sterically hinder the reaction process. The protecting groups on complex **116** were changed using a convenient 'one-pot' sequence of desilylation with tetrabutylammonium fluoride (TBAF) and methylation. This gave dimethoxy complex **117** in good yield (*Scheme 43*), and completed the first fragment for the Stille coupling.



116 **117**

Scheme 43

The desired stannane fragment was to be constructed by lithiation at C-2 of a benzofuran having an oxygen substitutent at C-6. Previously however, Mann and Widdowson had discovered that lithiation of 6-methoxybenzofuran **118** gave a 4:1 mixture of benzofurans **119** and **120**, substituted in the 2- and 7- positions, respectively (*Scheme 44*).[63] The side-product **120** arises as a result of co-ordination of the lithium atom to the oxygen atom of the methoxy group and the benzofuran (*Figure 10*).



118

119:**120** = 4:1

119: R^1=TMS, R^2=H
120: R^1=H, R^2=TMS

Scheme 44

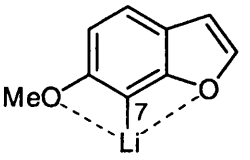
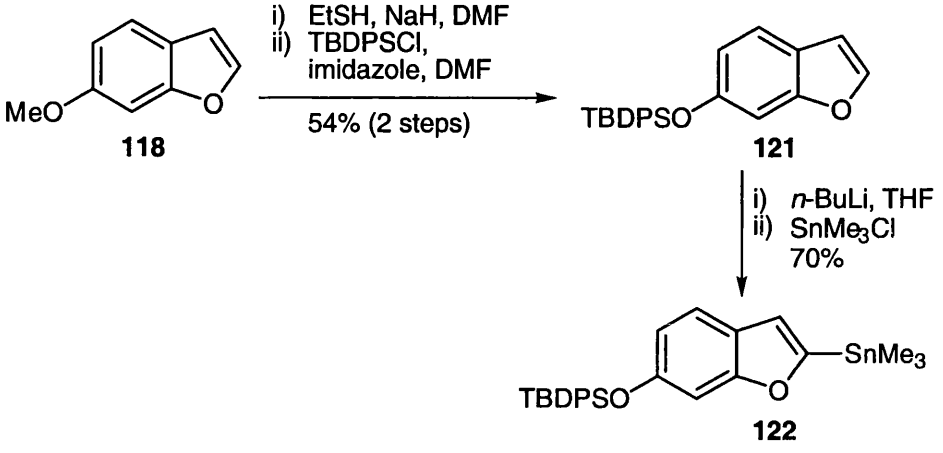


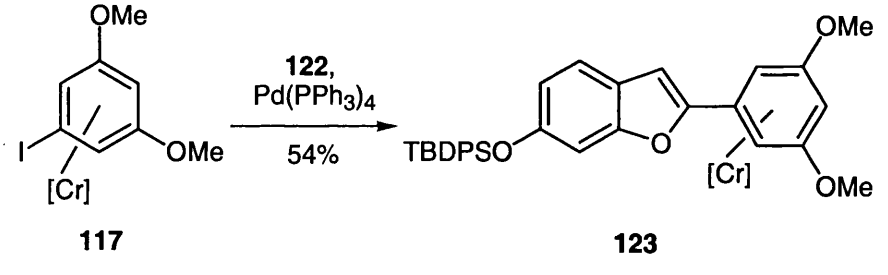
Figure 10

When the protecting group was changed from methyl to the *tert*-butyldiphenylsilyl group (which is relatively bulky and does not direct lithiation) alkylation occurred solely in the 2-position. This finished the synthesis of stannane **122**, the second fragment for the Stille coupling reaction (*Scheme 45*).



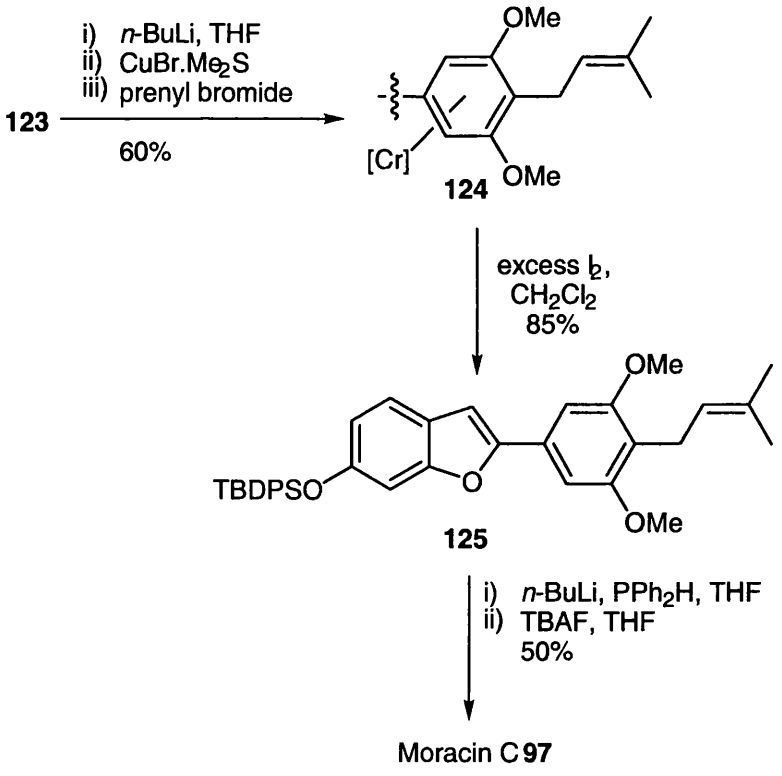
Scheme 45

Coupling of the two fragments under standard Stille conditions gave the aryl benzofuran complex **123** in moderate yield (*Scheme 46*).



Scheme 46

Prenylation of the aromatic ring of **123** to give complex **124**, proceeded cleanly *via* regioselective lithiation, transmetallation to copper and alkylation with prenyl bromide (*Scheme 47*). Decomplexation with iodine, followed by demethylation (Ph_2PLi) and desilylation (TBAF) gave moracin C in 12 steps (longest linear sequence = 9 steps from resorcinol, overall yield = 4.9%).

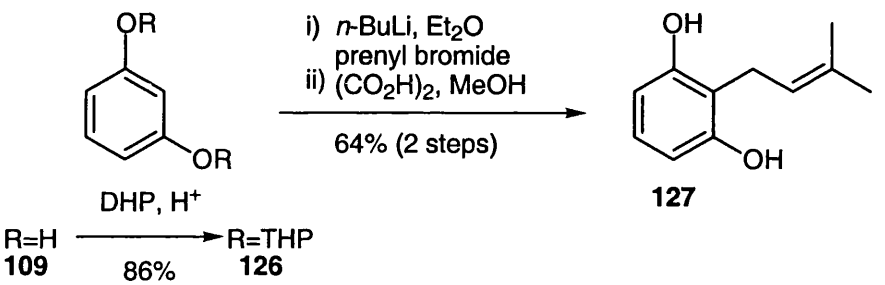

i) n-BuLi, THF
ii) CuBr.Me2S
iii) prenyl bromide
123
60%
OMe
[Cr]
OMe
124
excess I2,
CH2Cl2
85%
OMe
TBDPSO
O
OMe
125
i) n-BuLi, PPh2H, THF
ii) TBAF, THF
50%
Moracin C 97

Scheme 47

2.1.3 Nakamura and co-worker's Synthesis

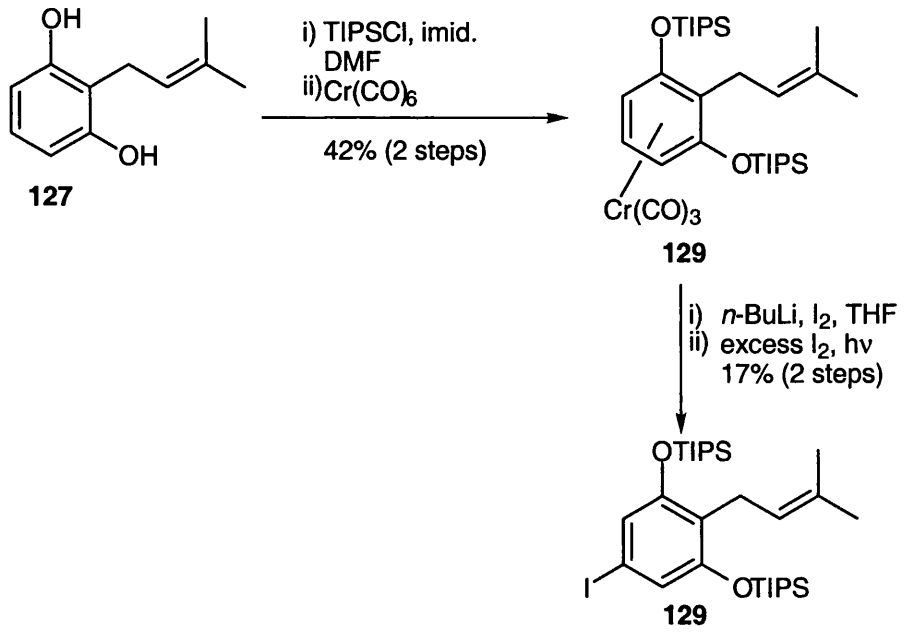
The second synthesis of moracin C was also in 1991, by Nakamura and co-workers.[57] Like Mann and Widdowson, they opted to form the 2-arylbenzofuran nucleus by a Stille coupling and to install the prenyl group by *ortho*-lithiation.

Once again, the starting material for the aryl iodide fragment was resorcinol. This time however, the prenyl group was installed early in the synthesis. Resorcinol **109** was converted into the *bis*-tetrahydropyranyl (THP) ether **126**, as the THP group is a good *ortho*-director, and is easier to remove than a methyl group. Ether **126** was treated with *n*-butyllithium and prenyl bromide to afford alkylation in the desired position. The THP groups were then removed under weakly acidic conditions to give prenylated resorcinol **127** (*Scheme 48*).



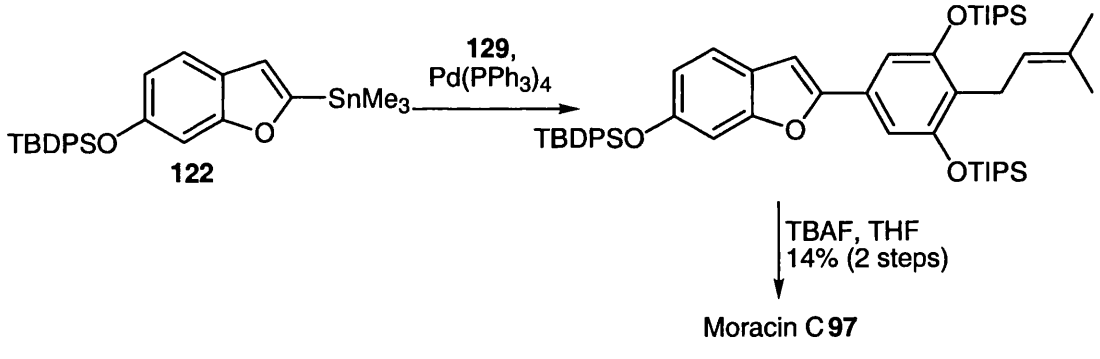
Scheme 48

Iodination of the inaccessible 5-position of the ring was done using Masters and Widdowson's protocol of remote lithiation of an arenetricarbonylchromium(0) complex.[59,60] This required protection of the free hydroxyls in **127** as bulky triisopropylsilyl ethers and complexation to chromium (*Scheme 49*). Remote lithiation and iodination of complex **128** followed by decomplexation gave aryl iodide **129**, the first fragment of moracin C, in very poor yield (*Scheme 49*).



Scheme 49

The stannylated benzofuran **122** was prepared from 6-hydroxybenzofuran, by the same method as Widdowson and Mann (*Scheme 45*).[63] The two fragments were then coupled together in the presence of palladium and desilylated to give moracin C **97** (*Scheme 50*).



Scheme 50

Unfortunately, the Stille coupling and deprotection were again very low yielding. This meant that, although the synthesis was the same length as Mann and Widdowson's (12 steps with 9 steps in the longest linear sequence from resorcinol), the overall yield was substantially lower (<1% overall).

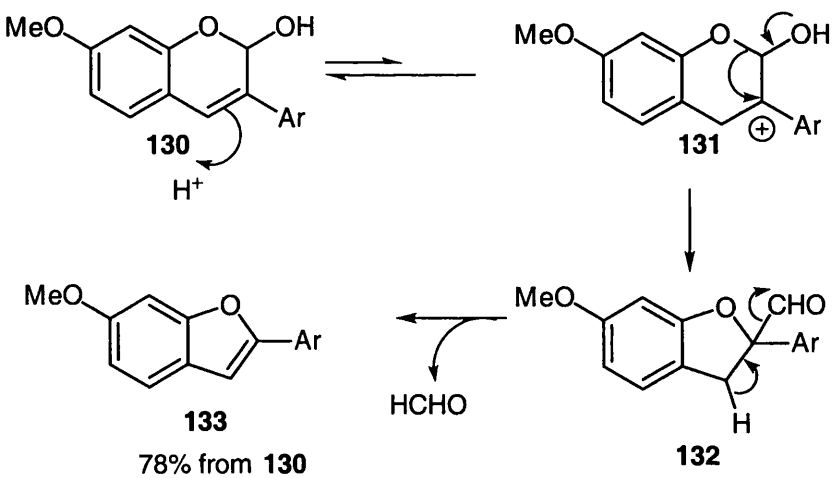
2.2 Synthetic Approaches to Benzofurans

Over the years, chemists have used a vast number of methods to synthesise 2-arylbenzofurans. This chapter shall highlight specific examples of the various ways of constructing these often biologically important compounds. As well as the cross-coupling methods used by Widdowson and Nakamura, routes to these compounds fall into 3 major categories:

- rearrangements;
- alkyne cyclisations; and
- non-alkyne cyclisations.

2.2.1 Rearrangements

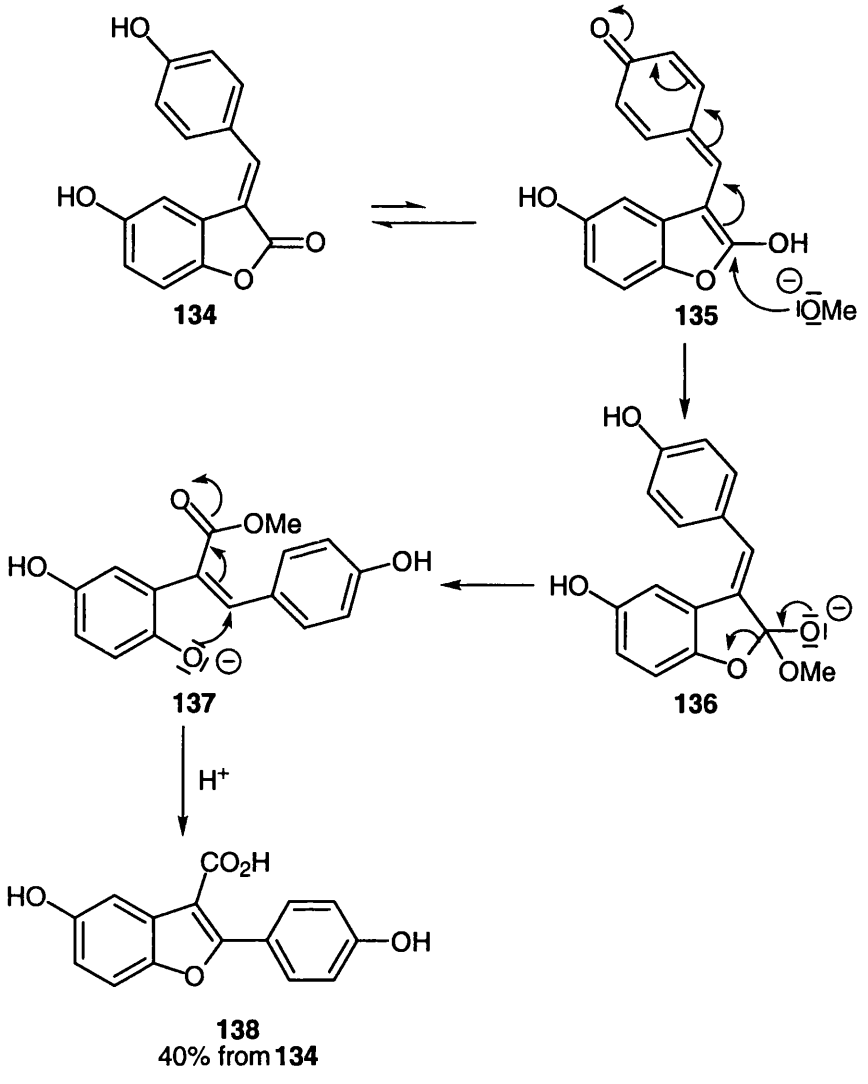
The first of the three categories concerns the rearrangement of a precursor (sometimes cyclic, often acyclic) into the desired benzofuran. Whilst exploring the biosynthesis of 2-arylbenzofurans derived from isoflavonoids, Kinoshita discovered an acid-induced ring contraction that conveniently converted a 2-hydroxy-isoflav-3-ene **130** into a benzofuran **133** in 78% yield.[64] Treatment of **130** with acid gave an intermediate tertiary cation **131**, which spontaneously underwent ring contraction to the dihydrobenzofuran **132**. Loss of formaldehyde gave the fully aromatic system. This was used in the synthesis of vignafuran **133** (Ar=4-hydroxy-2-methoxyphenyl), a potent antimicrobial phytoalexin isolated from cowpea leaves infected with the microorganism *Vigna unguiculata* (*Scheme 51*).



Scheme 51

In contrast to the above acid-induced reaction, Barbier demonstrated the synthesis of 2-phenylbenzofurans by base-catalysed rearrangement.[65] Treatment of

marginalin **134**, a natural benzofuranone from the water beetle *Dytiscus marginalis* (Coleoptera), with sodium methoxide in methanol gave moderate rearrangement to benzofuran **138** (*Scheme 52*).

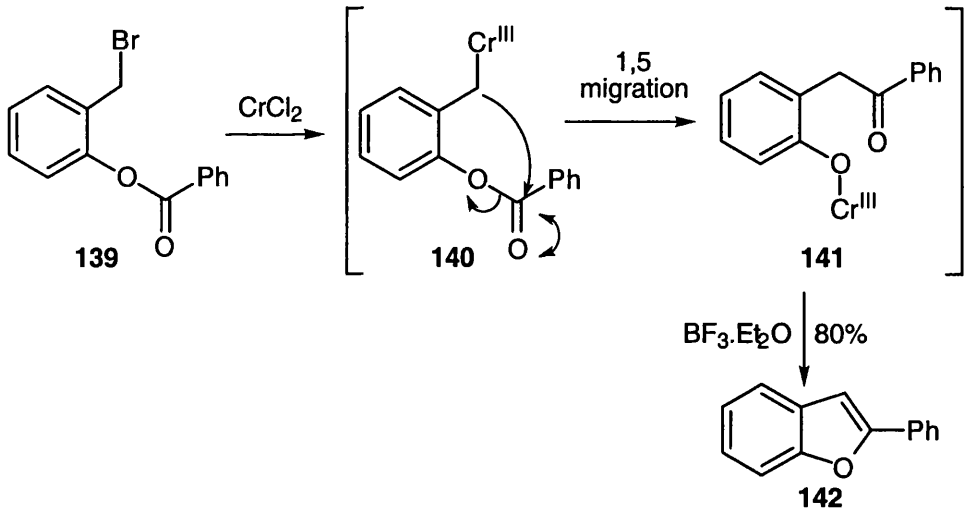


Scheme 52

Barbier proposed that this proceeded *via* conjugate addition of methoxide onto a *p*-quinomethide **135** formed *in situ*. Ring-opening of addition product **136** gave phenoxide **137**. Intramolecular Michael addition followed by treatment with acid gave the arylbenzofuran **138**.

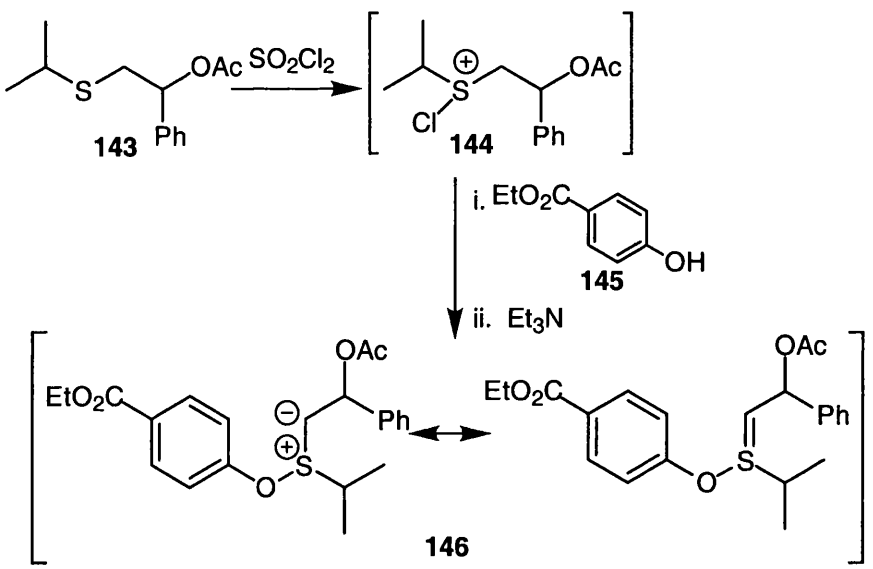
Both of these above examples have involved the rearrangement of cyclic intermediates. There are however, several cases where an acyclic precursor has undergone rearrangement prior to cyclisation. Ledoussal *et al*,[66] found that treatment of an *ortho-O*-acyl benzylic bromide **139** with chromium(II) chloride gave a σ-bonded chromium complex **140**. This complex underwent a 1,5-acyl migration yielding

benzylic ketone **141**. Treatment of this ketone with a Lewis-acid resulted in benzofuran **142** formation (*Scheme 53*).



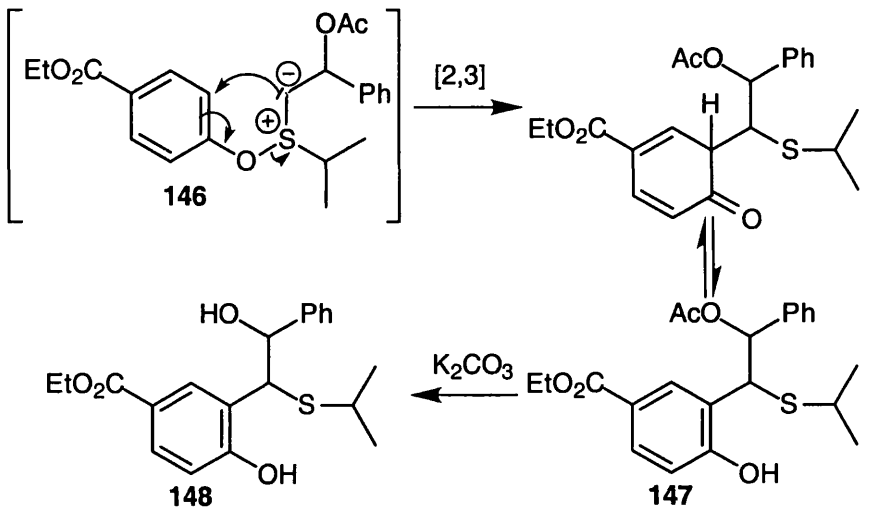
Scheme 53

A somewhat unusual approach was taken by Sato and co-workers,[67] who utilised a [2,3]-sigmatropic rearrangement of phenoxysulfonium ylides to give a range of 2-substituted benzofurans. The reaction of dialkyl sulfide **143** with sulfuryl chloride gave cation intermediate **144**. This reacts with a phenol such as **145** giving sulfonium ylide **146** (*Scheme 54*).



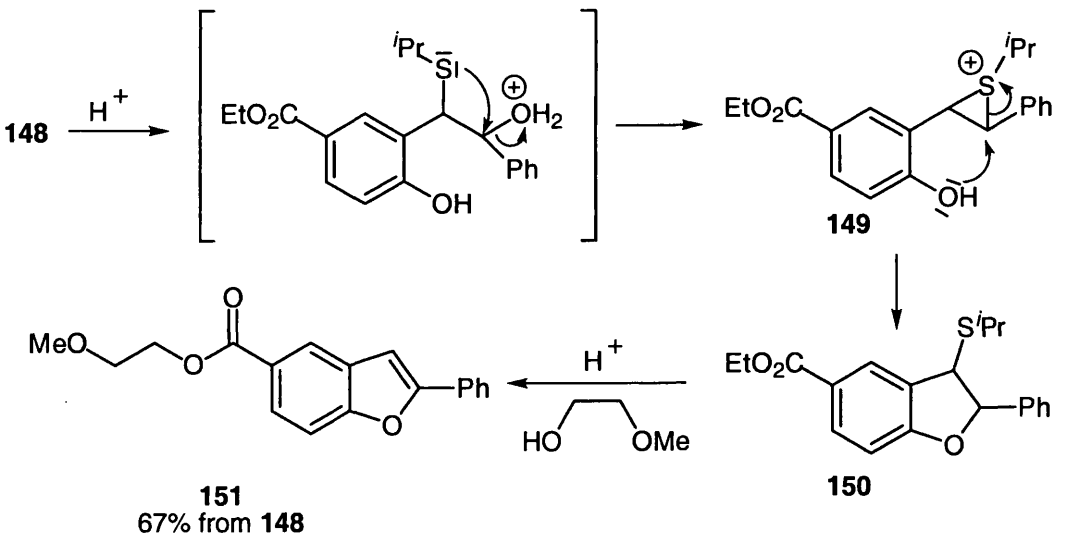
Scheme 54

[2,3]-Sigmatropic rearrangement of ylide **146** followed by tautomerism and acetate removal gave *o*-alkylated phenol **148** (*Scheme 55*).



Scheme 55

Treatment of phenol **148** with acid resulted in formation of episulfide intermediate **149** which immediately underwent cyclisation to dihydrobenzofuran **150**. Loss of thiol gave the 2-phenylbenzofuran **151** (*Scheme 56*).

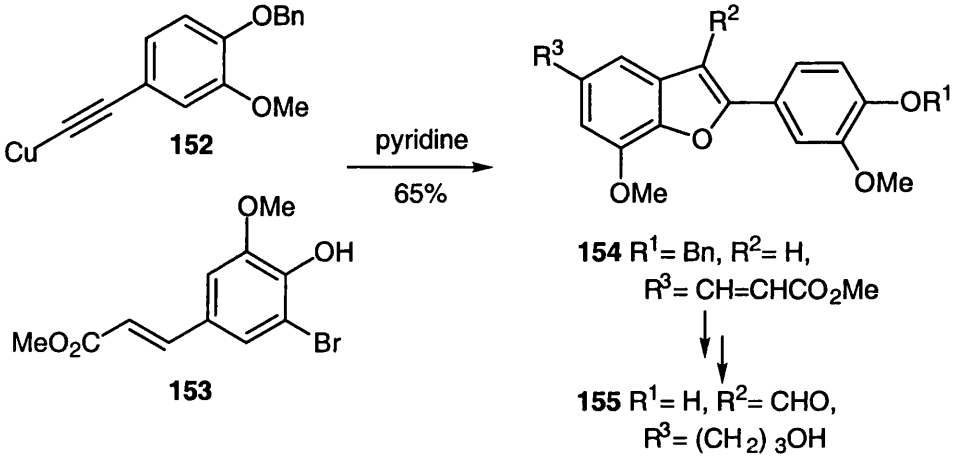


Scheme 56

2.2.2 Alkyne Cyclisations

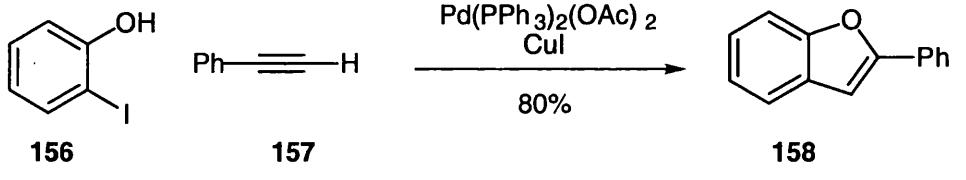
One of the commonest, and easiest ways of forming substituted benzofurans is through reaction of a phenol with an alkyne.

In the synthesis of an A^1-selective adenosine antagonist **155** (isolated from *Salvia miltorrhizia* Bunge),[68] Wong and co-workers constructed the central benzofuran nucleus through coupling of cuprous acetylide **152** with bromophenol **153**, using the method of Castro and Stephens (*Scheme 57*).[69]



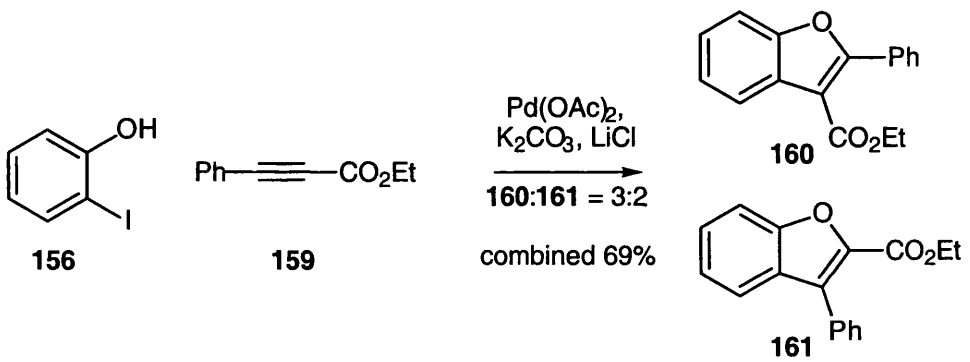
Scheme 57

Palladium-catalysed cyclisations onto alkynes are also common. Arcadi *et al* demonstrated the synthesis of 2-substituted benzofurans with complete regiocontrol.[70] A palladium/copper iodide mixture was used under Sonogashira coupling conditions (*Scheme 58*). This resulted in isolation of a single regioisomer **158**.



Scheme 58

Controlling the regioselectivity of these Pd-mediated reactions can sometimes be problematic. This was demonstrated by Larock *et al* who investigated the palladium-catalysed annulation of alkynes.[71] Coupling of iodophenol **156** with alkyne **159** in the presence of palladium diacetate gave a 3:2 mixture of 2,3-disubstituted benzofurans **160** and **161** (*Scheme 59*).

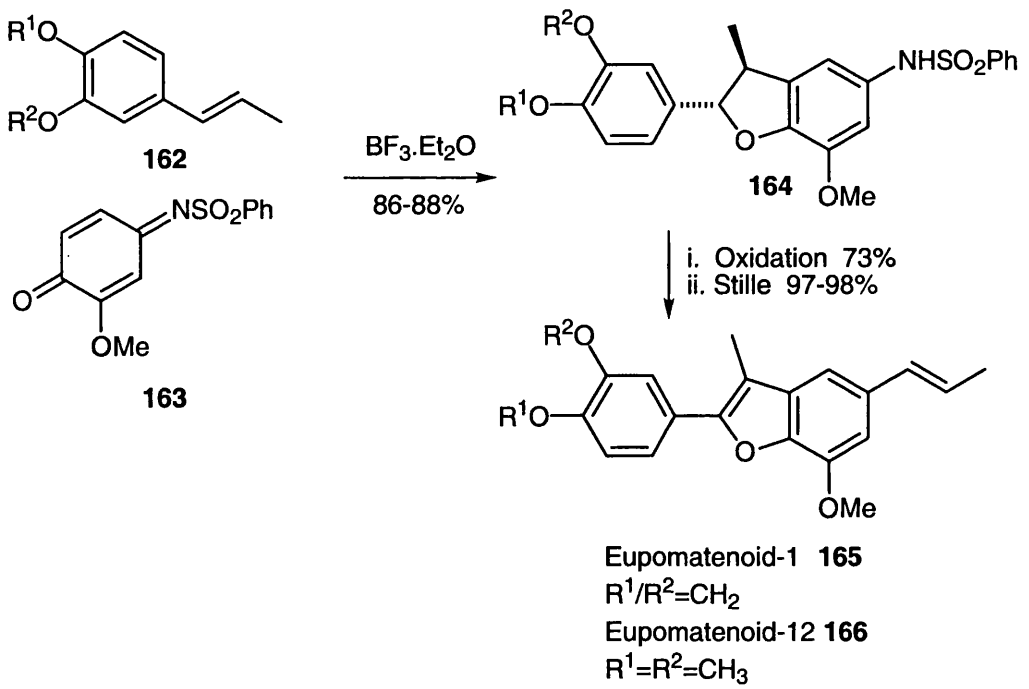


Scheme 59

2.2.3 Non-Alkyne Cyclisations

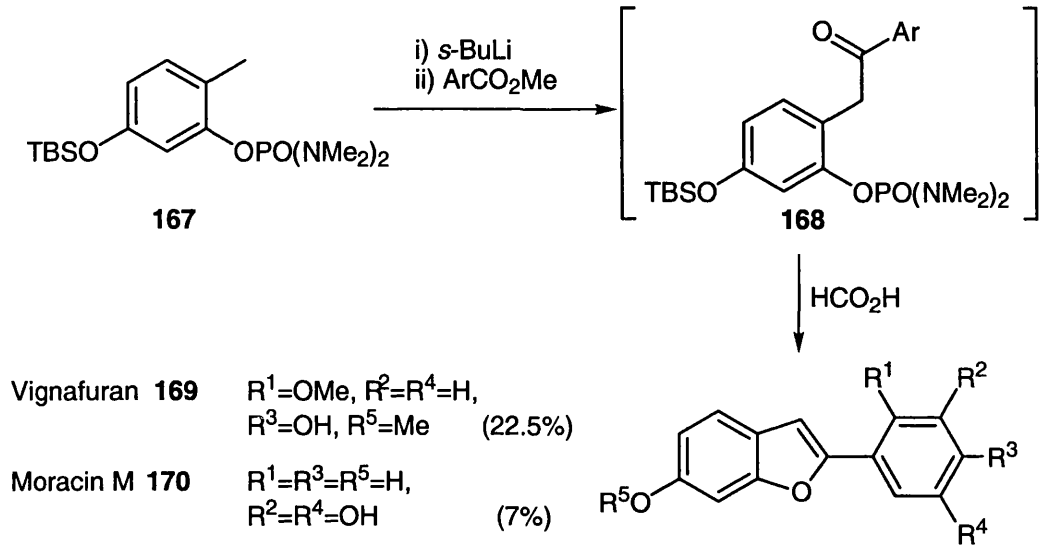
The final, and largest, category concerns the formation of benzofurans by either inter- or intramolecular cyclisation. Once again, this approach has been used in the synthesis of several natural products.

The first example demonstrates a Lewis acid-promoted cycloaddition of styrene **162** to quinone monoimide **163**, and was the approach taken by Engler *et al* (*Scheme 60*).[72] The resulting dihydrobenzofuran **164** was oxidised to give the target system. This method was used in the synthesis of eupomatenoids-1 **165** and -12 **166**, which are natural neolignan compounds with potent antibacterial and immunosuppressant properties.



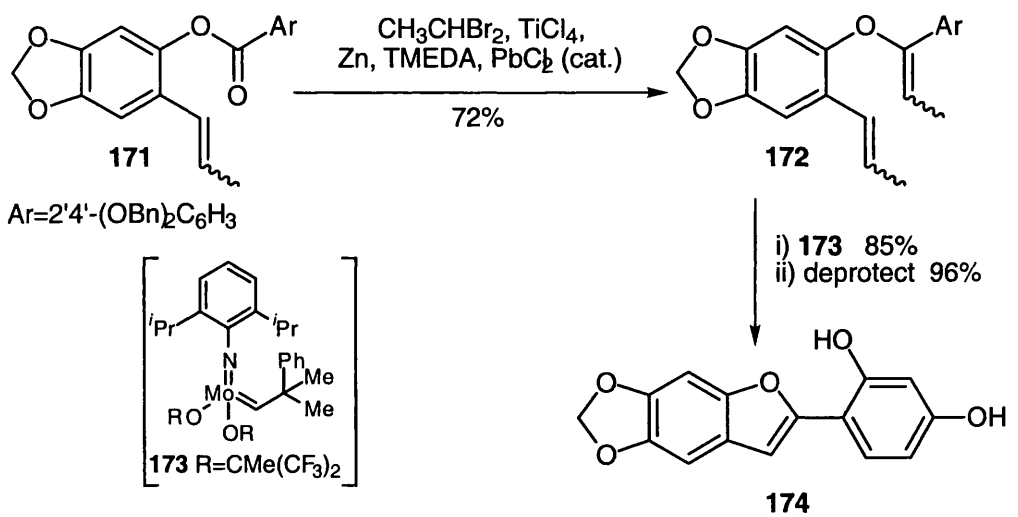
Scheme 60

In the synthesis of the phytoalexin vignafuran **169**, and another member of the moracin family, moracin M **170**, Watanabe *et al* used a convenient cyclisation of deoxybenzoin derivatives to make the benzofuran core.[73] Lithiation of phosphoramidate **167** with *sec*-butyllithium followed by quenching with a variety of methyl benzoate esters gave the deoxybenzoin derivatives **168**. Immediate treatment with formic acid resulted in cyclisation (*Scheme 61*).



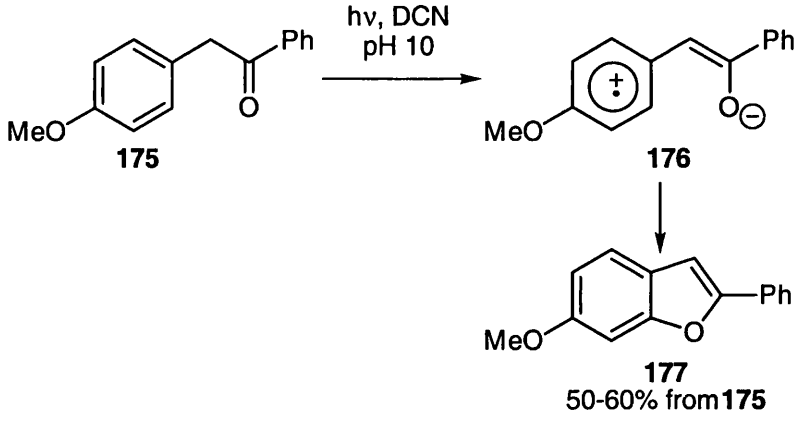
Scheme 61

A more unusual approach was taken by Grubbs and co-workers in the synthesis of a phytoalexin **174** isolated from *Sophora tomentosa* L.[74] A combination of olefination followed by ring-closing metathesis gave a short, easy route to this target. Olefination of ester **171** (using the procedure developed by Takai and co-workers)[75] gave the acyclic enol ether **172**. Ring-closing metathesis catalysed by molybdenum complex **173**[76] gave the natural product in high yield (*Scheme 62*).



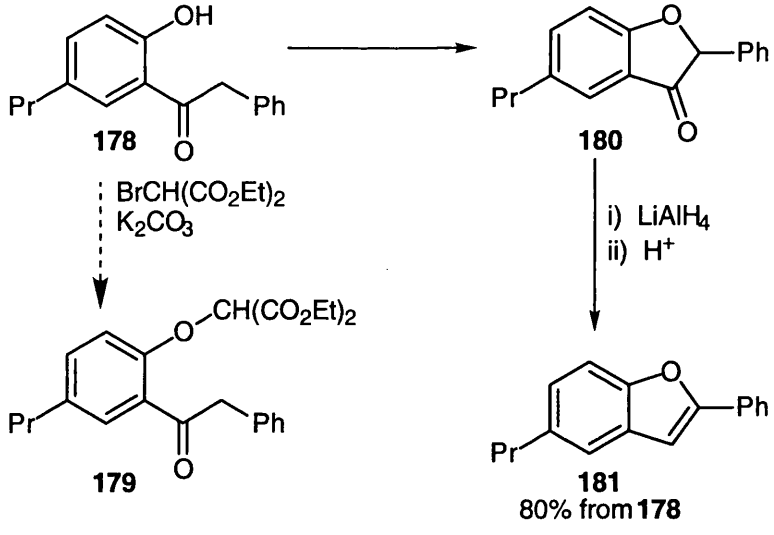
Scheme 62

Pandey *et al* effectively demonstrated the use of photochemistry in their approach.[77] Irradiation of a range of substituted acetone derivatives such as **175**, in the presence of 1,4-dicyanonaphthalene (DCN), caused single electron transfer (SET) and formation of an intermediate arene radical cation **176**. Intramolecular cyclisation yielded the benzofuran **177** (*Scheme 63*).



Scheme 63

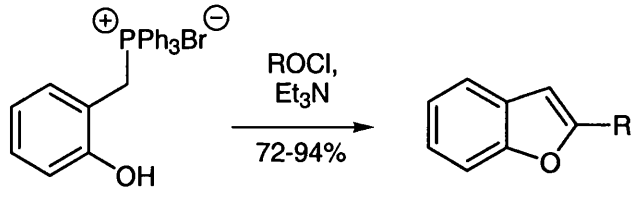
A more traditional approach to benzofurans is cyclodehydration, as adopted by Kavinde *et al.*[78] Unexpectedly, reaction of *o*-hydroxyketone **178** with diethyl bromomalonate in the presence of potassium carbonate did not give the corresponding diester **179**. Instead, benzofuranone **180** was isolated. Subsequent reduction and elimination gave the 2-arylbenzofuran **181** (*Scheme 64*). It was proposed that the diethyl bromomalonate brominated the activated methylene group of ketone **178**.



Scheme 64

The final examples represent the type of cyclisation which was of most interest to us. Hercouet and Le Corre had shown that it was possible to form benzofurans by a

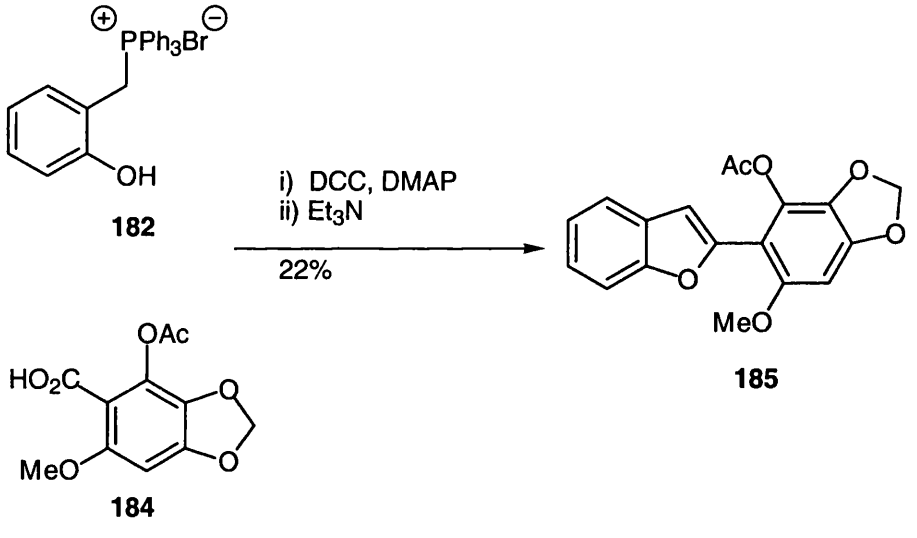
'one-pot, two-stage' process.[79] Reaction of *o*-hydroxybenzyltriphenylphosphonium bromide **182** with an acid chloride in the presence of triethylamine resulted in formation of an intermediate ester. This ester cyclised by an intermolecular Wittig reaction to give benzofuran **183** (*Scheme 65*).



z182 **183**

Scheme 65

McKittrick and Stevenson used an adaptation of this procedure in their synthesis of the benzofuran **185**, which is an oxidant in yeast.[80] Esterification of the free hydroxyl of phosphonium salt **182** with carboxylic acid **184** was done using standard DCC-coupling conditions. The intramolecular Wittig reaction was done as before to give the natural product **185** (*Scheme 66*).



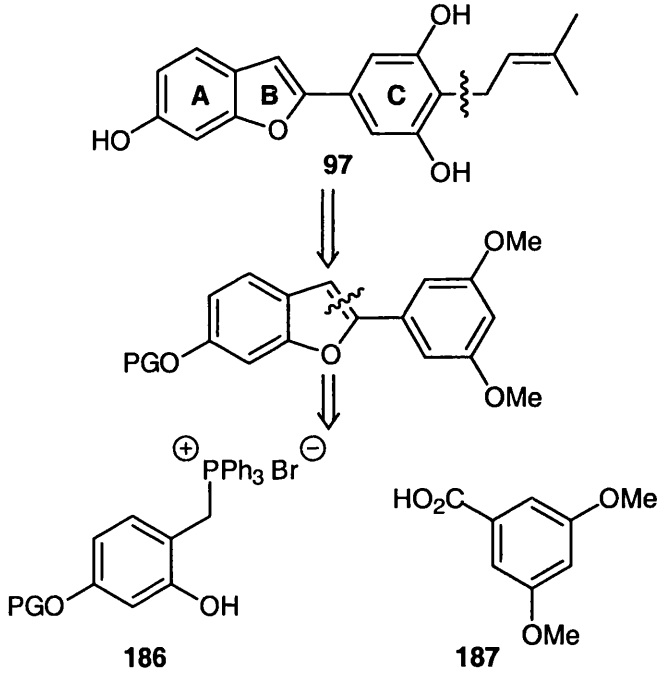
Scheme 66

3

The Synthesis of Moracin C

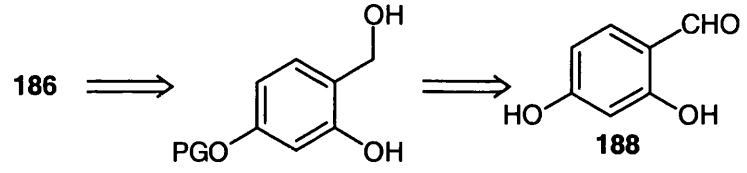
3.1 Initial Strategy

Our retrosynthesis of moracin C **97** featured two main disconnections. The prenyl group was to be installed by a regioselective *ortho*-lithiation, in a manner similar to that used by Mann and Widdowson.[58] We planned to construct the arylbenzofuran nucleus using the intramolecular Wittig reaction used by Hercouet and Le Corre (*Scheme 67*).[79] This would require synthesis of a suitably protected phosphonium salt **186**, which would be coupled with commercially available 3,5-dimethoxybenzoic acid **187**. Our approach avoids having to set up the difficult 1',3',5' relationship in the C-ring of moracin C



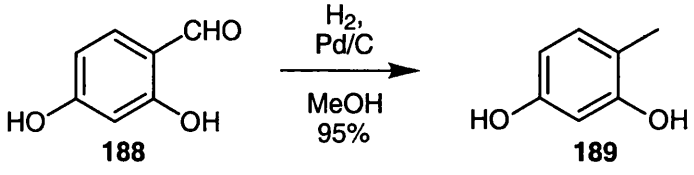
Scheme 67

Hercouet and Le Corre had demonstrated that benzylic phosphonium salts could easily be prepared from the corresponding benzylic alcohols, simply by reaction with triphenylphosphine hydrobromide.[79] The phenol **186** that we require should be accessible from 2,4-dihydroxybenzaldehyde **188** (*Scheme 68*).



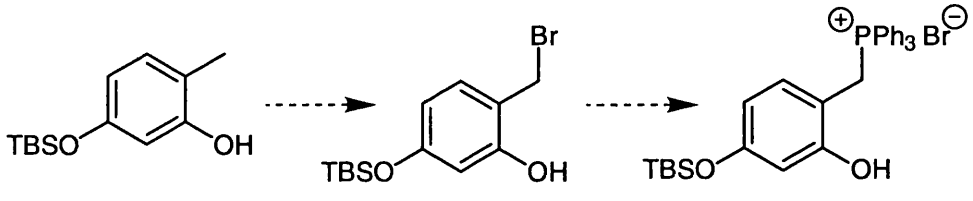
Scheme 68

Reduction of 2,4-dihydroxybenzaldehyde **188** to the corresponding alcohol proved difficult. Standard reduction methods (sodium borohydride, lithium aluminium hydride) were unsuccessful. However, catalytic hydrogenation resulted in a near quantitative yield of 4-methylresorcinol **189** (*Scheme 69*).



Scheme 69

Since the alcohol was not accessible, we decided to brominate in the benzylic position. Treatment of the benzylic bromide with triphenylphosphine would then give the salt we required (*Scheme 70*). This required the protection of the 4-hydroxyl of **189**. We decided to protect this hydroxyl as a *tert*-butyldimethylsilyl (TBS) ether which would be stable throughout the bromination, but would be easy to remove.



Scheme 70

However, attempts to silylate selectively in the 4-position of **189** were unsuccessful, giving a complex mixture of products. We felt that since the TBS group would be stable to hydrogenation, selective protection of 2,4-dihydroxybenzaldehyde **188** would be easier. The internal chelation between the carbonyl and the 2-hydroxyl should make the 4-hydroxyl slightly more reactive, enabling selective protection (*Figure 11*).

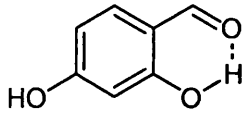
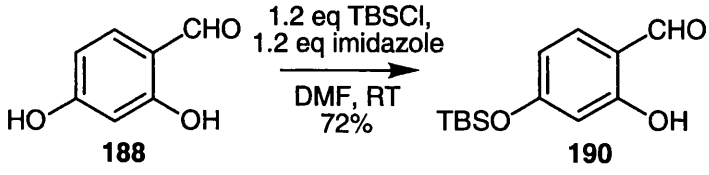


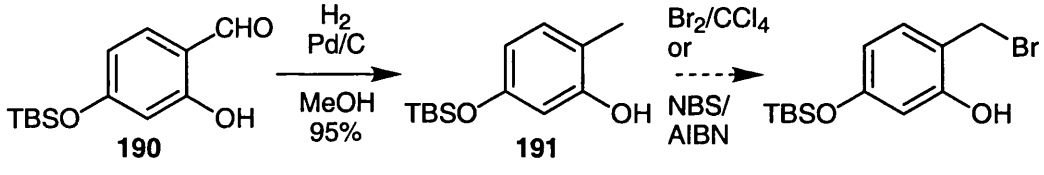
Figure 11

By adapting the conditions described by Ronald *et al*,[81] we were able to protect the 4-hydroxyl as the TBS ether: 1.2 equivalents each of imidazole and *tert*-butyldimethylsilyl chloride in DMF at room temperature gave a 72% yield of mono-TBS ether **190** (plus approximately 15% bis-TBS product) (*Scheme 71*).



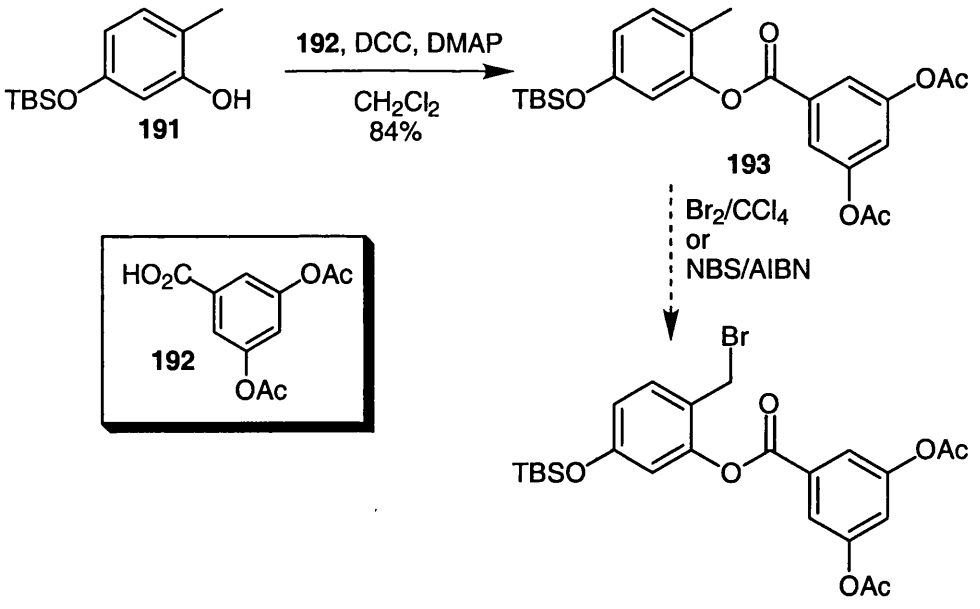
Scheme 71

Catalytic hydrogenation of aldehyde **190** went as expected in high yield to give phenol **191** (*Scheme 72*). Hercouet and Le Corre has described a method of benzylic bromination using bromine in CCl_4, seemingly avoiding aromatic substitution.[79] This method, and one by Zhang *et al* using NBS/AIBN[82] were both tried with **191**, but resulted in complex mixtures of products (*Scheme 72*).



Scheme 72

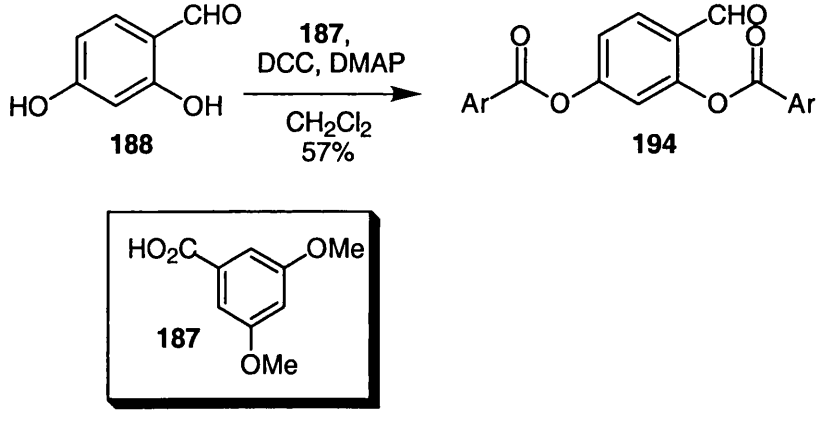
This lack of selectivity may be because the aromatic ring is too electron-rich. The presence of an electron-withdrawing group may deactivate the ring sufficiently to favour aliphatic bromination. Consequently, we decided to esterify phenol **191** with 3,5-diacetoxybenzoic acid **192** under DCC conditions to give ester **193** (*Scheme 73*). It was hoped that the two acetoxy groups would further deactivate the system. Bromination of ester **193**, under several conditions, gave a complex mixture of products. In view of this, a different method was sought.



Scheme 73

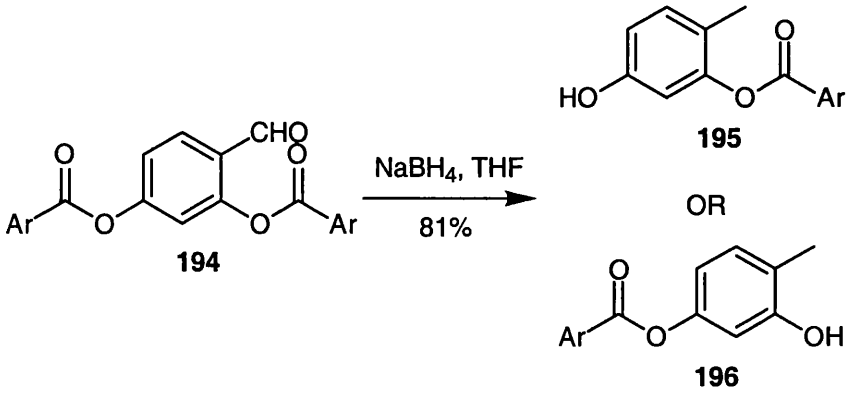
3.2 Second Approach

For our alternative approach, we considered the question of protecting group selectivity. Did we need to differentiate between the two hydroxyls of the starting material? As shown in *Scheme 67*, the first step in benzofuran formation is the coupling of salt **186** with 3,5-dimethoxybenzoic acid **187**. What if this was done at the start of the synthesis? Esterification of both hydroxyl groups of aldehyde **188** would avoid the problem of of differentiating between them, and the extra ester could be hydrolysed after benzofuran formation. To investigate this, aldehyde **194** was prepared under standard DCC conditions (*Scheme 74*).



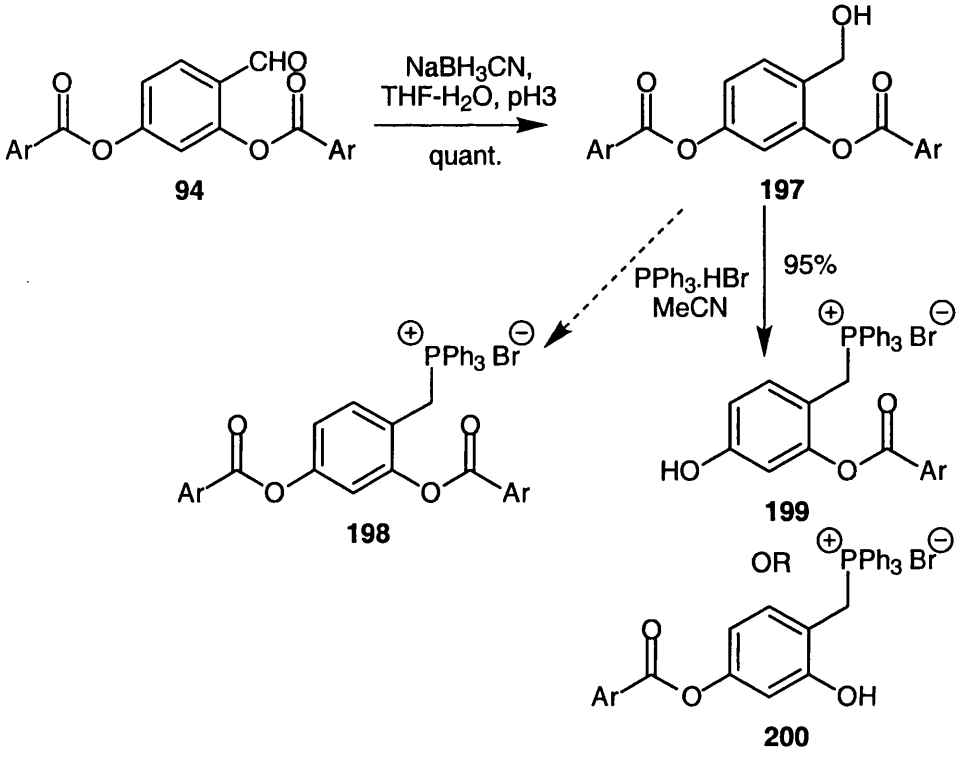
Scheme 74

Reduction of aldehyde **194** in the presence of two esters was not considered a problem. Use of a mild reducing agent should furnish the alcohol leaving the esters untouched. However, on treatment with sodium borohydride, ^{1}H NMR spectroscopy of the product showed that, not only had the carbonyl been 'over-reduced' to the methyl group, but one of the esters had hydrolysed (*Scheme 75*). At this stage it was not clear which ester had been cleaved, so the product was characterised as **195** or **196**.



Scheme 75

Further attempts at reduction were made, this time using sodium cyanoborohydride. It was found that, although no reaction took place at pH 7, reduction occurred at pH 3 to give the benzylic alcohol **197** in quantitative yield (*Scheme 76*).

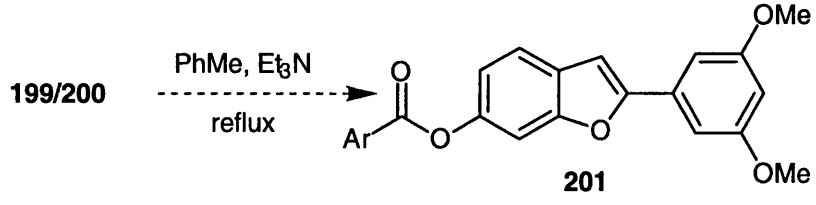


Scheme 76

When alcohol **197** was heated with triphenylphosphine hydrobromide (*Scheme 76*), instead of isolating salt **198** as anticipated, we once again saw selective hydrolysis of one of the esters. As before it was not clear which ester had cleaved, although ^{1}H and ^{31}P NMR spectroscopy confirmed the presence of a single product, salt **199** or **200**. In order to determine the structure of the product, a series of trial reactions were performed.

(i) The salt **199** or **200** was heated in toluene with triethylamine (*Scheme 77*).

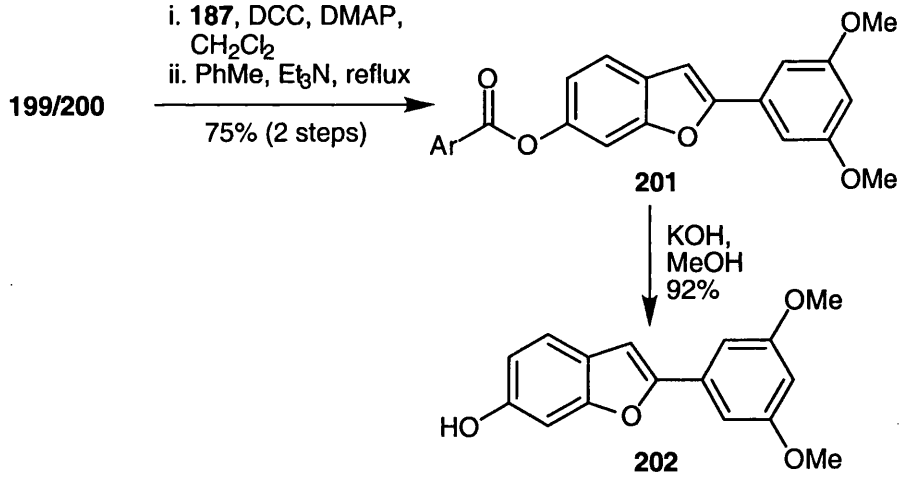
Result: no benzofuran **201** was produced.



Scheme 77

(ii) The salt **199** or **200** was esterified with acid **187**, and was then heated in toluene with triethylamine (*Scheme 78*).

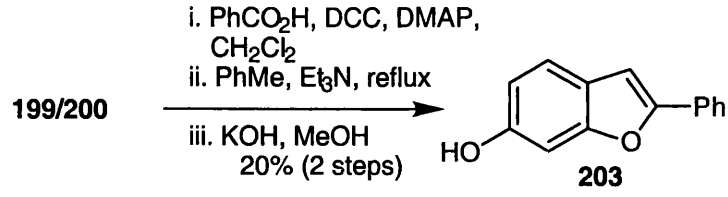
Result: benzofuran **201** was isolated. Treatment with potassium hydroxide hydrolysed the ester group and gave benzofuran **202**, which is the synthetic precursor of moracin C.



Scheme 78

(iii) The salt **199** or **200** was esterified with benzoic acid, and was then heated in toluene with triethylamine (*Scheme 79*).

Result: benzofuran **203** was the only benzofuran product isolated.

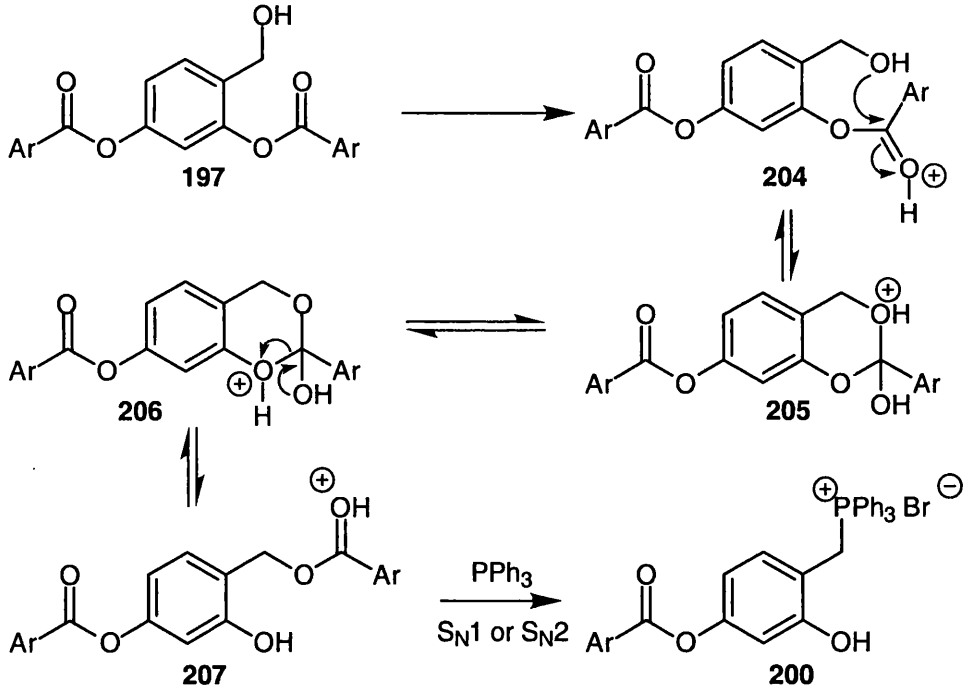


Scheme 79

These tests confirm that the ester group in the 2-position of alcohol **197** is hydrolysing and salt **200** is being produced.

Why is there Regioselective Hydrolysis?

We believe we are witnessing an intramolecular acyl migration, an example of neighbouring-group participation. *Scheme 80* outlines a possible mechanism. Protonation of the ester at C-2 of alcohol **197** results in intramolecular attack from the neighbouring hydroxyl. This gives cyclic intermediate **205** which, after a series of proton transfers, collapses to give protonated benzylic ester **207**. From here, salt **200** is produced by either S_N1 or S_N2 reaction with triphenylphosphine.



Scheme 80

Migration occurs because benzylic ester **208** (*Figure 12*) is thermodynamically favoured over benzylic alcohol **197**: the lone pairs on the benzylic oxygen are conjugated with a carbonyl group in the benzylic ester **208** but are isolated in benzylic alcohol **197** (*Figure 12*). This more than compensates for the loss of conjugation when

the cross-conjugated ester group of aryl ester **197** is converted into a phenol. Put another way, a phenol is a better leaving group than an alcohol, so intermediate **206** is converted into phenol **207** more readily than intermediate **205** is converted into alcohol **204**.

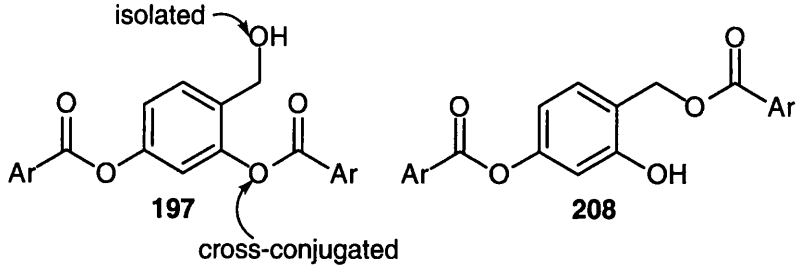
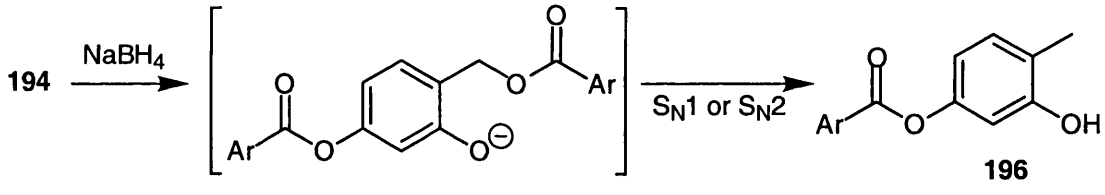


Figure 12

Further evidence of this mechanism arose during a routine cyanoborohydride reduction of aldehyde **194**. The reaction was left for longer than usual, and migration occurred under low pH conditions to give phenol **208** in 90% yield.

We can assume that in the sodium borohydride reduction of aldehyde **194** as discussed above, we see a related base-induced migration resulting in phenol **196** being formed (*Scheme 81*).

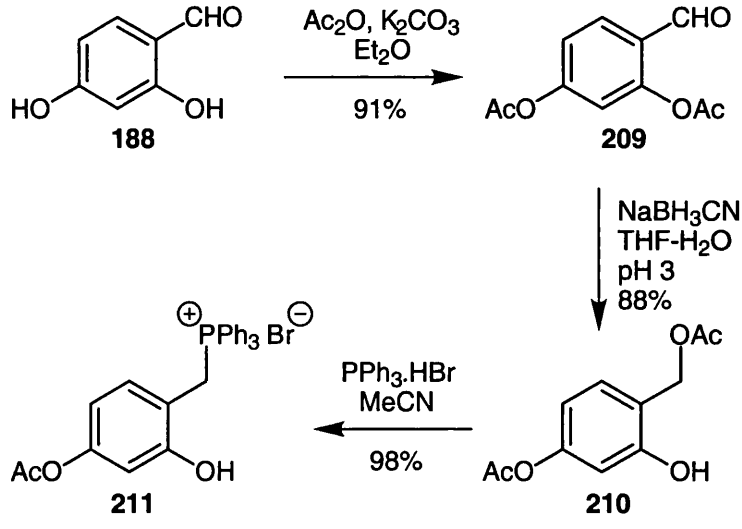


Scheme 81

There have been other examples of migrations from phenolic to benzylic hydroxyls which support our proposed mechanism.[83]

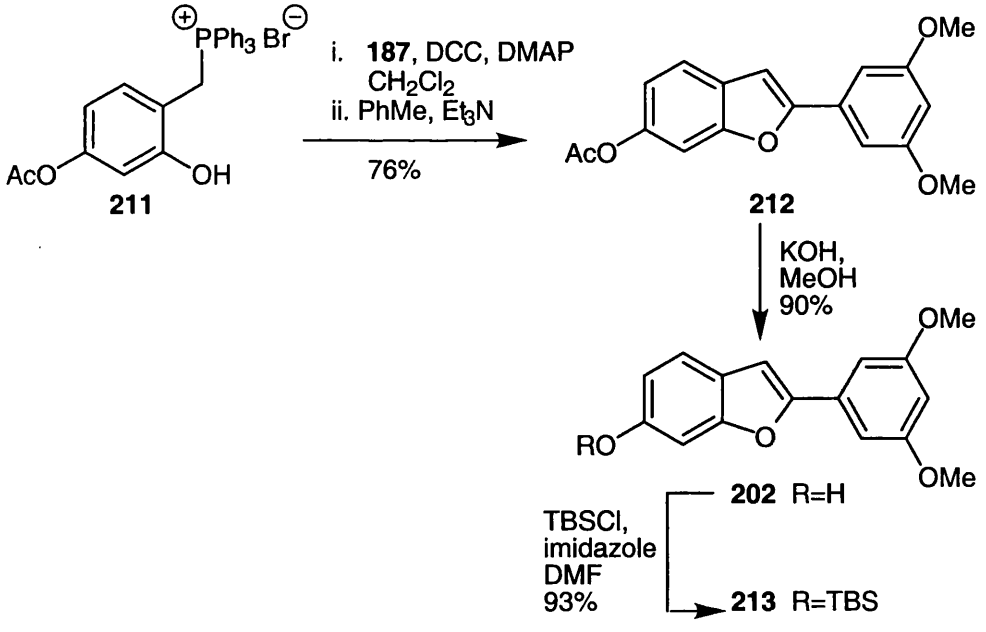
Having proved the structure of salt **200**, and having shown that the benzofuran **201** can be constructed from it, we turned our attention to the efficiency of the synthesis. Neither of the ester groups in alcohol **197** are retained in benzofuran **201**. The ester in the 2-position is lost during the migration, and that at the 4-position (essentially a protecting group) is removed by hydrolysis after cyclisation. We decided to investigate whether this migration/selective hydrolysis occurred with simple esters. If successful, this would not only make our synthesis more efficient, but would also provide a general route to 2-arylbenzofurans. 2,4-Diacetoxybenzaldehyde **209** was prepared in high yield by modifying the procedure of Malkin and Nierenstein (*Scheme*

82).[84] Reduction of aldehyde **209**, at pH 3 led to acyl migration and the formation of phenol **210**. This was then converted into phosphonium salt **211** without difficulty (*Scheme 82*).



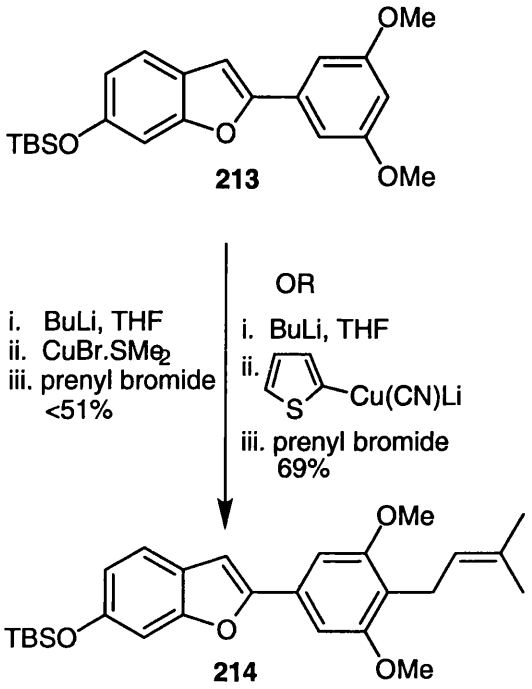
Scheme 82

After forming benzofuran **212** (*Scheme 83*), we needed to change the protecting group at the 6-position. As discussed in Section 2.1.2, a bulky protecting group is required to prevent lithiation at C-7 of the benzofuran. We opted for the TBS group. The acetate in **212** was removed, and the free hydroxyl of **202** silylated to give benzofuran **213** in good overall yield (*Scheme 83*).



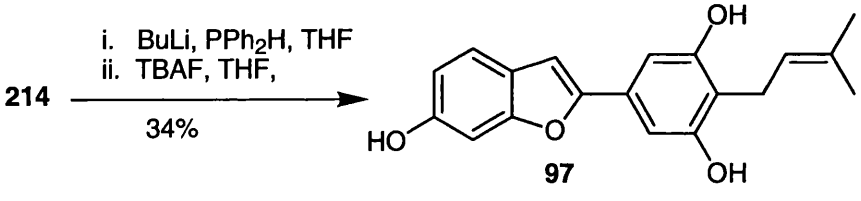
Scheme 83

For the prenylation of **213**, we originally followed Mann and Widdowson's method,[58] involving lithiation, transmetallation using copper(II) bromide-dimethyl sulfide complex, then alkylation (*Scheme 84*). Although successful, this was low yielding (maximum 51%). In an attempt to improve the yield, we used the lithium thienylcyanocuprate reagent.[85] After lithiation, transmetallation to this reagent forms an organocopper species which should be more reactive towards electrophiles. This proved successful with prenylation taking place in 69% yield (*Scheme 84*).



Scheme 84

All that remained now was to deprotect **214**. Demethylation often requires very harsh conditions. The presence of the prenyl group increases the problem, as it is prone to cyclisation when *ortho* to free hydroxyls. Mann and Widdowson used lithium diphenylphosphide (prepared *in situ* from diphenylphosphine and butyllithium) to demethylate,[58] and we followed this protocol. Treatment of **214** with an excess of this reagent followed by immediate desilylation with TBAF gave the target, albeit in a low yield (*Scheme 85*).



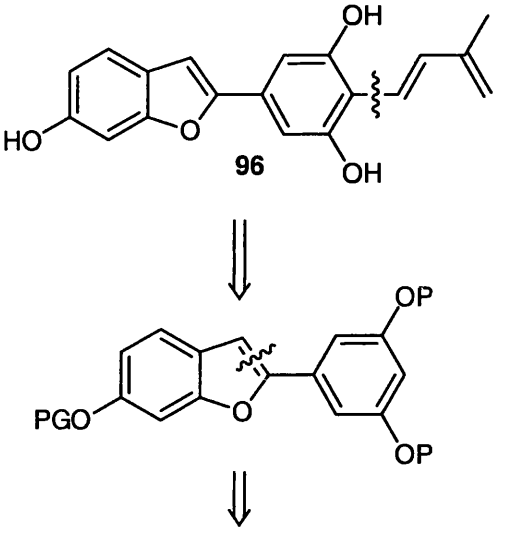
Scheme 85

This concluded our total synthesis of moracin C.[86] Although a completely linear synthesis, our route is by far the most efficient to date (10 steps, 12.3% overall yield).

4

Diene Synthesis

We required diene **96** for our assay of Diels-Alder activity. We wanted to use a similar retrosynthetic strategy to that used in the synthesis of moracin C **97**, namely intramolecular Wittig reaction, form the benzofuran and *ortho*-lithiation to install the diene side-chain (*Scheme 86*). The major question was how to make the *E*-diene?

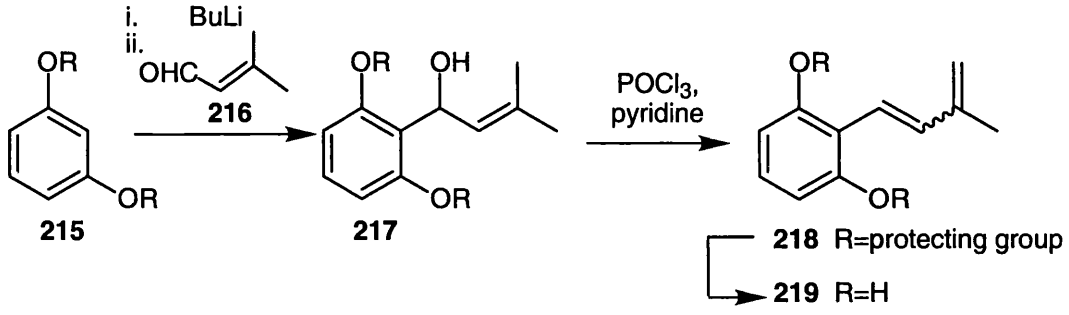


Scheme 86

4.1 Preliminary Studies

There were two important aspects of this synthesis that had to be considered: (i) How do we *ortho*-lithiate to give an *E*-diene? (ii) How can we deprotect to give the free hydroxyl, without causing cyclisation?

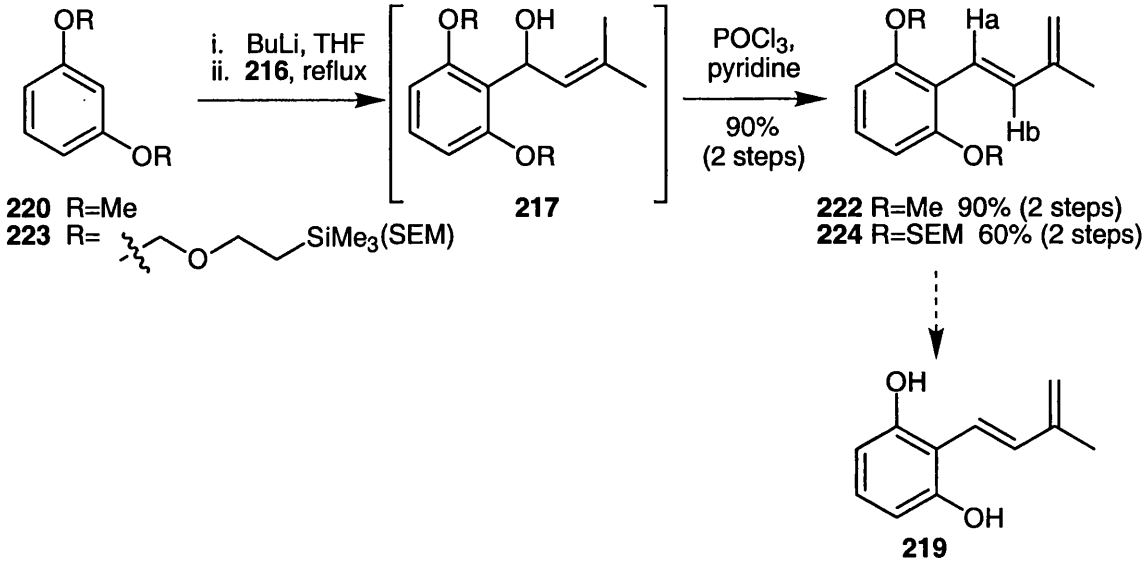
For our initial experiments, we used a series of protected resorcinols **215** as a model system. We planned to *ortho*-lithiate then quench with 3-methylbutenal **216**. Dehydration of intermediate alcohol **217** using conditions outlined by Runk *et al*[87] would give a diene (hopefully with the requisite *E*-geometry), which could then be deprotected (*Scheme 87*). The most important aspect of this route was the choice of protecting group. How resilient would the diene be to the deprotection conditions?



Scheme 87

We planned to use three different protecting groups, all with *ortho*-lithiating ability. The most simple was the methyl group, and we also studied the THP group (as well as being *ortho*-directing, it is relatively simple to removal),[48] and the (trimethylsilyl)ethoxymethyl (SEM) group since it can be removed in acid-free conditions.[88]

We first tried commercially available 1,3-dimethoxybenzene **220**. This was easily lithiated at low temperature (*Scheme 88*). Quenching with aldehyde **216** gave us intermediate alcohol **221**. We found that it was easier to proceed with the dehydration rather than purify and characterise at this stage. Dehydration using phosphorus oxychloride and pyridine went smoothly giving diene **222** in high yield. ^{1}H NMR spectroscopy showed that only the *E*-isomer had been produced ($J_{Ha\text{-}Hb}$ 16.5 Hz). Problems arose however, when deprotection was attempted. Lithium diphenylphosphide, used in the synthesis of moracin C, was unsuccessful, as were more traditional methods of demethylating using boron tribromide or trimethylsilyl iodide.[89]

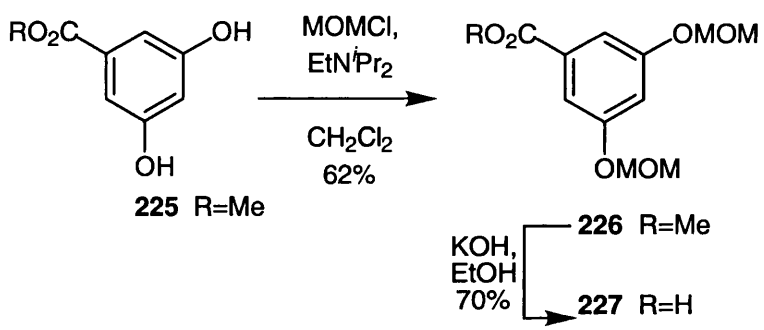


Scheme 88

Use of the THP group in diene formation was unsuccessful. It was assumed that lithiation proceeded cleanly, but there was not enough spectroscopic evidence to prove the formation of any diene product. The *bis*-SEM ether **223** was more successful, with isolation of diene **224** at the end of the sequence (*Scheme 88*). Once again however, deprotection was difficult. Treatment with TBAF at room temperature, or with TBAF and *N,N*-dimethyl propyleneurea (DMPU) at reflux both proved unsuccessful.

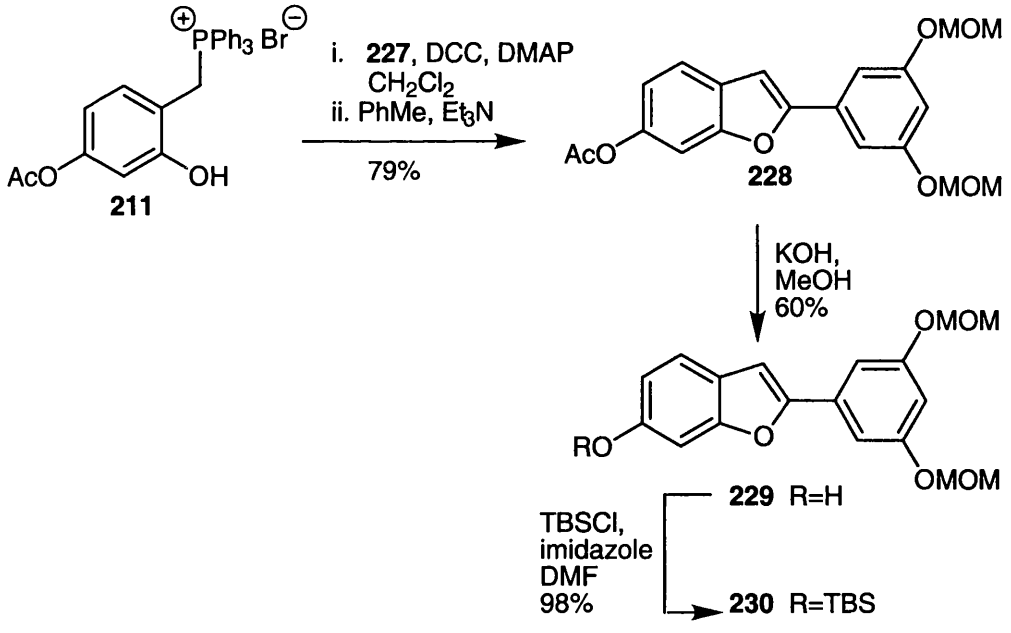
4.2 Synthesis of a Protected Diene

As well as requiring diene **96** for our Diels-Alderase assay, we also wanted to synthesise chalcomoracin to prove that it can be made by a Diels-Alder reaction. Due to the problems encountered when trying to deprotect our model dienes, we decided to postpone deprotection until after the Diels-Alder reaction. The model studies had shown that the methyl protecting group would be too difficult to remove. We hoped that the methoxymethyl (MOM) group would have the same *ortho*-directing ability, but would be much more labile. Methyl 3,5-dihydroxybenzoate **225** was protected to give ester **226**. Hydrolysis then gave free acid **227** in moderate overall yield (*Scheme 89*).



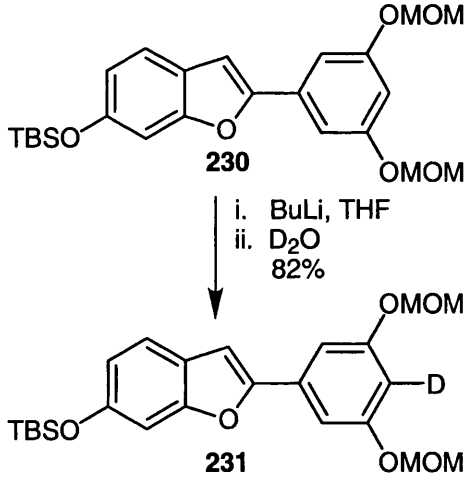
Scheme 89

Carboxylic acid **227** and phosphonium salt **211** were coupled under the same conditions used in the synthesis of moracin C, to give benzofuran **228** (*Scheme 90*). The acetate was removed and replaced with the bulky TBS group.



Scheme 90

Initial attempts to lithiate **230** were unsuccessful. Only starting material was recovered, even after forcing conditions (4 hours at reflux). In order to make sure that lithiation was taking place, we performed a labelling experiment, lithiating as normal, then quenching with D_2O (*Scheme 91*) to give benzofuran **231**. ^1H and ^{13}C NMR spectroscopy showed that incorporation of the deuterium label to give benzofuran **231** was complete, confirming that lithiation had occurred.



Scheme 91

Although easily formed, the organolithium intermediate is clearly not reactive towards the electrophilic aldehyde. It is possible that the two MOM groups are completely blocking access to the nucleophilic carbon atom (*Figure 13*), or that aggregates between molecules of lithiated species are formed.

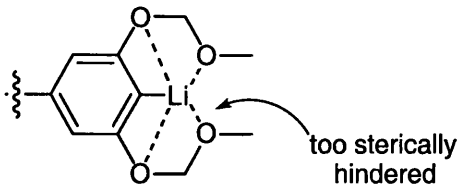
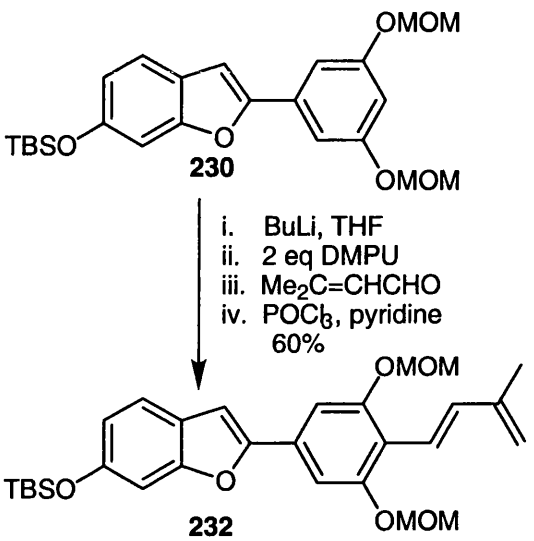


Figure 13

The problem we faced was how to 'expose' the organolithium to the aldehyde. We required a reagent which would compete for co-ordination to the lithium, making it more easily accessible. Lithiation was carried out as before, but this time two equivalents of DMPU were added prior to the aldehyde (*Scheme 92*). The resulting alcohol was immediately dehydrated to give the diene **232** in moderate yield over two steps. ^{1}H NMR spectroscopy of diene **232** confirmed the double bond geometry as exclusively *E* (*J* 16.5 Hz).



Scheme 92

It is thought that the addition of DMPU would have two main effects.

- Co-ordination of DMPU to the lithium 'pushes' the MOM groups away, and so exposes the carbanion (*Figure 14*).

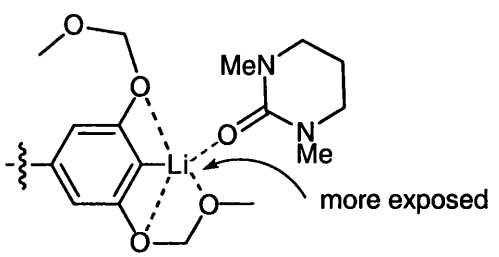


Figure 14

- Co-ordination to lithium makes the carbon-lithium bond longer and hence more reactive (*Figure 15*).

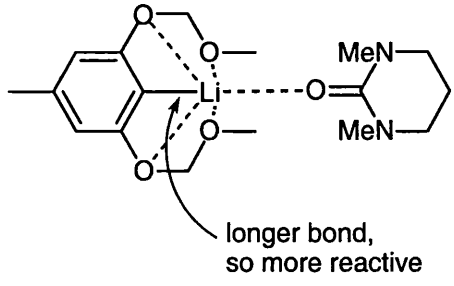


Figure 15

4.3 Synthesis of Phenolic Dienes

Synthetic routes to phenolic dienes are rare. These routes have many disadvantages, including low yield and selectivity. Typical examples include:

- Base-induced elimination of HCl or HBr from allylic halides.[90] Although *E*-selective, these are usually low yielding (<10%).
- Grignard opening of coumarins.[91] Once again, these are low yielding (20-25%), but do give exclusively *Z*-products.
- Irradiative opening of chromenes.[92] Reactions of this type are often poorly selective.
- Acid-induced dehydration of complex naturally-occurring alcohols.[93]

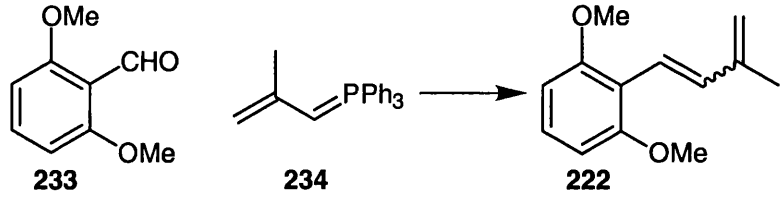
A more general, connective method of synthesising compounds such as these is by an alkenation reaction. Reactions of this sort have been used to make dienes of protected phenols, and in one case, a free phenol. Alkenation reactions fall into three classes:

- Phosphorus-based (Wittig, Horner-Wittig, Horner-Wadsworth-Emmons);
- Silicon-based (Peterson); and
- Sulfur-based reactions (Julia).

4.3.1 Phosphorus-based Reactions

The olefination reaction most commonly used to make dienes is the Wittig reaction. The main disadvantage with this reaction is the lack of geometrical control.

In a continuing study on mulberry phytoalexins,[94] Takasugi and co-workers attempted a Wittig reaction between 2,6-dimethoxybenzaldehyde **233** and the ylide **234**, derived from methallyltriphenylphosphonium chloride (*Scheme 93*). Diene **222** was produced but with very low selectivity (*E/Z*, 3:2).

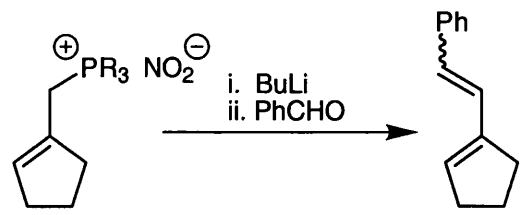


233 **234** **222**

E/Z, 3:2

Scheme 93

In a later study,[95] Tamura *et al* investigated the geometrical effect of changing the group on phosphorus. Treatment of phosphonium nitrite **235** with butyllithium followed by benzaldehyde gave diene **236** in moderate yield (63%) but with poor selectivity (*Scheme 94*). However, when the reaction was repeated using the tributylphosphonium salt **237**, not only was the yield higher (82%), but the selectivity was dramatically increased (*E* >95%).

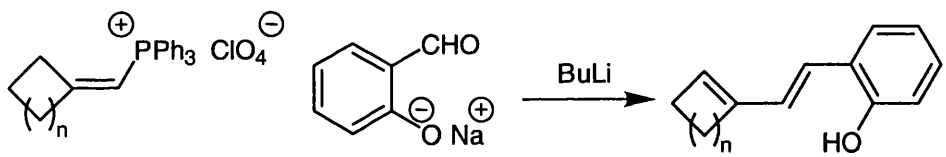


235 R=Ph
237 R=^{n}Bu

236 R=Ph, 63%, *E/Z*, 45:55
238 R=^{n}Bu,82%, *E/Z*, >95%

Scheme 94

An example which was of particular interest to us was the synthesis of a phenolic diene, produced without protection of the hydroxyl.[96] Minami *et al* reported the synthesis of dienes **243-245** by Wittig reaction between phosphonium salts **239-241** and the sodium salt of salicylaldehyde **242** (*Scheme 95*). All dienes were isolated in good yield, with ^{1}H NMR spectroscopy showing that only *E*-isomers were formed.



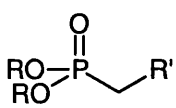
239 n=1
240 n=2
241 n=3

242

243 n=1, 64%
244 n=2, 54%
245 n=3, 72%

Scheme 95

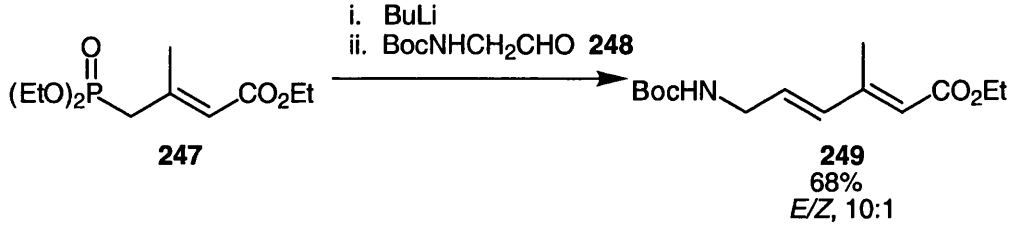
A common variant of the Wittig reaction is the Horner-Wadsworth-Emmons reaction.[97] This uses anions derived from dialkylphosphonates **246**.



246
R=Et, iPr

The main advantages are that the anions are generally more nucleophilic than standard Wittig-type ylides, and by changing the phosphonate ester size, greater selectivity can be achieved. The Horner-Wadsworth-Emmons reaction is of particular

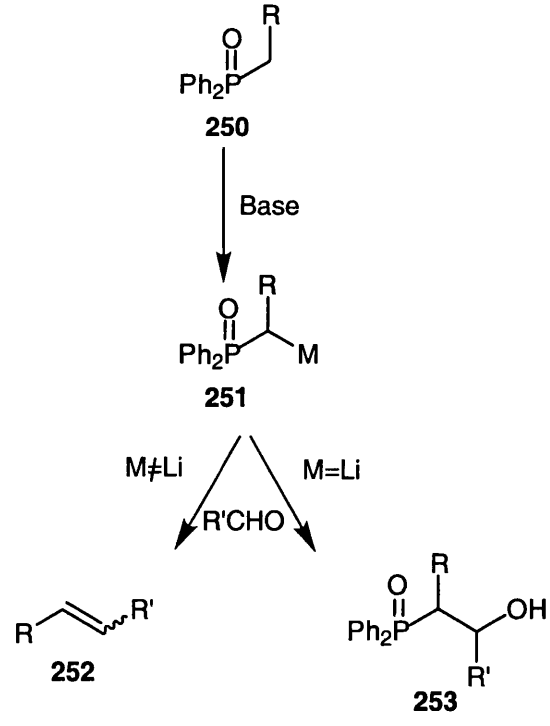
use in the synthesis of α,β- or α,β,γ,δ-unsaturated carbonyl compounds (often esters). This was demonstrated in the synthesis of the C_9-C_{23} fragment of streptogramin antibiotics, by Helquist *et al* (*Scheme 96*).[98] Good selectivity was achieved in the reaction of phosphonate **247** with N-protected glycinal **248**.



247 **249** 68% *E/Z*, 10:1

Scheme 96

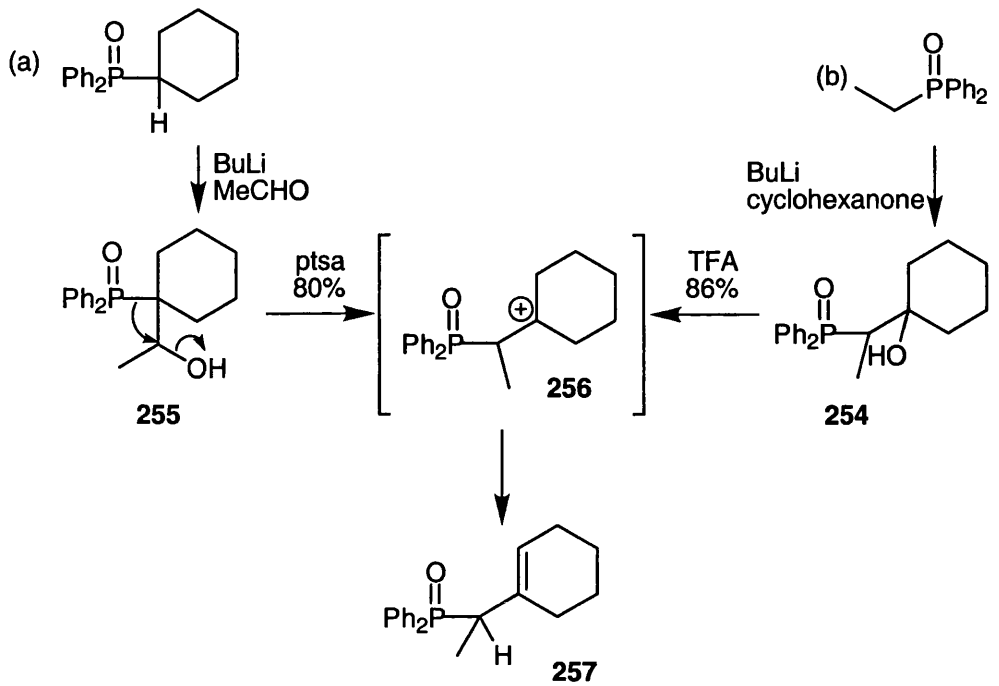
The final example of phosphorus-based olefination is the Horner-Wittig reaction.[99] This involves deprotonation of a phosphine oxide **250**, followed by reaction with a carbonyl compound to give alkene **252** (*Scheme 97*). If a lithium base is used, the reaction can be 'stopped' at the α-hydroxyphosphine oxide intermediate **253** and it is this property that was exploited by Warren and Davidson in a stereocontrolled synthesis of dienes.[100]



Scheme 97

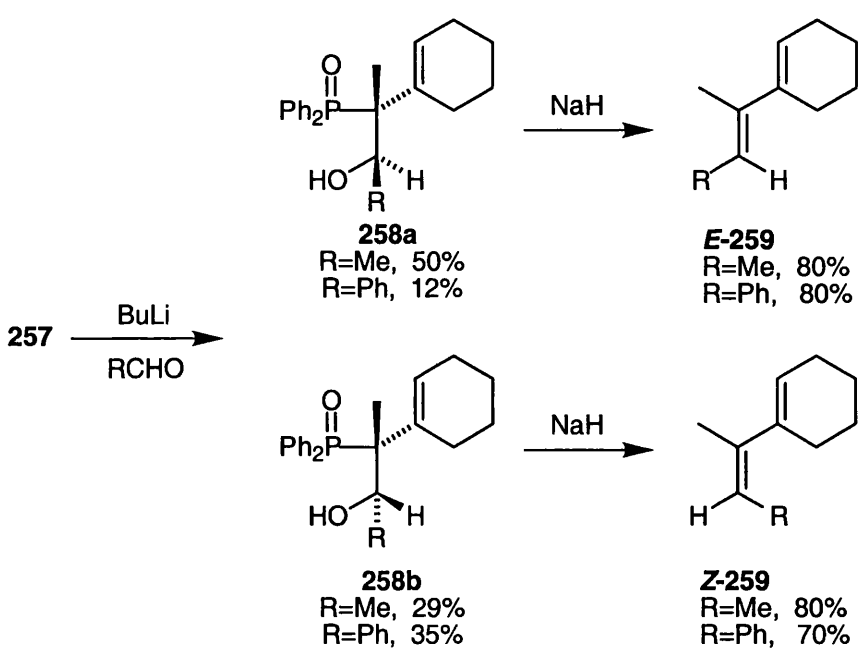
Warren and Davidson prepared allylic phosphine oxide **257** by acid-induced dehydration of a tertiary alcohol **254**, and by rearrangement/dehydration of a

secondary alcohol **255** *via* cation **256** (*Scheme 98*). The overall yields of **257** were comparable in each case.



Scheme 98

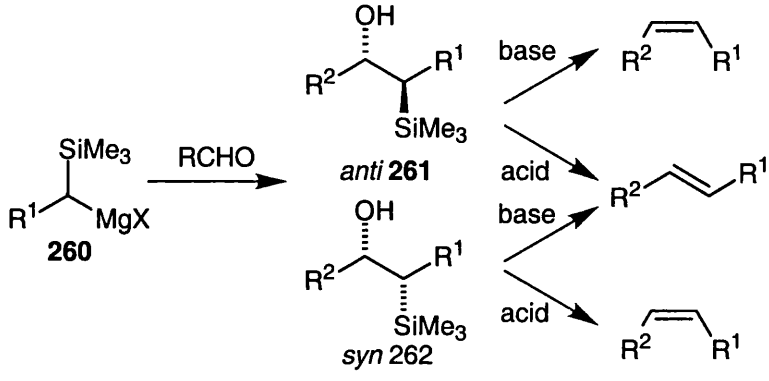
Further treatment of **257** with butyllithium and either acetaldehyde or benzaldehyde, gave diastereomeric alcohols **258a** and **258b** (*Scheme 99*). These were easily separated and, upon reaction with sodium hydride were converted stereospecifically into dienes ***Z*-259** and ***E*-259**.



Scheme 99

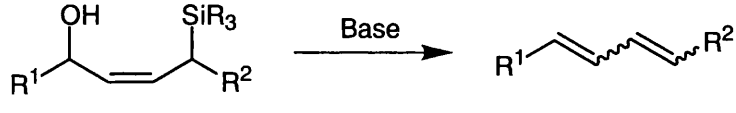
4.3.2 Silicon-based Reactions

The use of silicon in olefination reactions is best demonstrated in the Peterson reaction.[101] This involves either acid or base-catalysed elimination of β-hydroxysilanes. The geometrical outcome of the elimination depends on both the configuration of the silane, and the reaction conditions used. The most common method of preparing β-hydroxysilanes is by addition of an α-silyl anion (e.g. Grignard **260**) to a carbonyl compound (*Scheme 100*), producing two diastereomers, *anti* **261** and *syn* **262**. At this stage, both geometrical isomers are accessible from either diastereomer. Treatment of the *syn* isomer with base gives the *Z*-alkene, while the *anti* gives rise to the *E*-alkene. Conversely, acid-catalysed elimination results in *syn* producing *E*- and *anti* producing *Z*-alkenes.



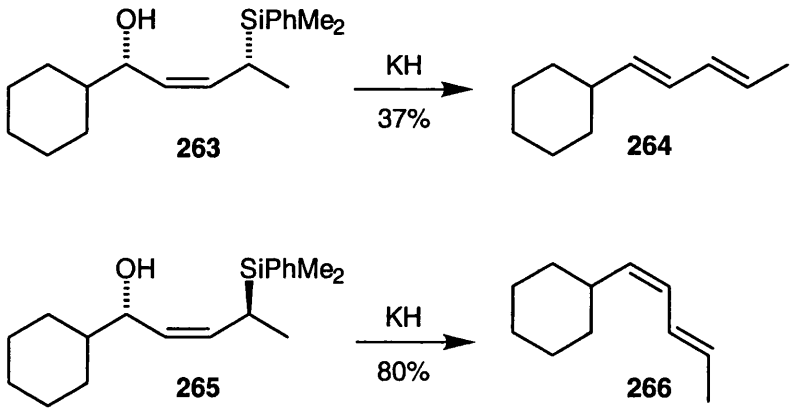
Scheme 100

A similar method can be employed in the synthesis of dienes. In a recent report,[102] Fleming *et al* investigated the stereochemical control that can be achieved in the vinylogous Peterson reaction (*Scheme 101*).



Scheme 101

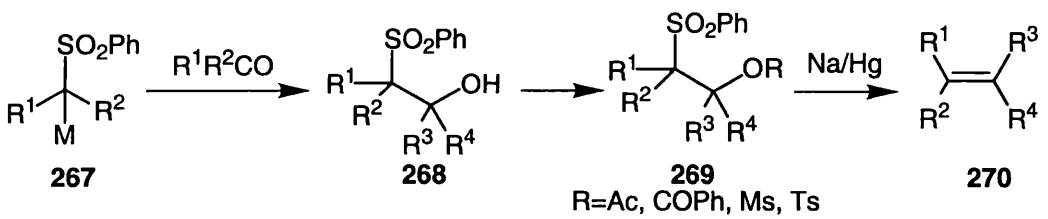
The substrates for this reaction were prepared by addition of the anions of propargylsilanes to aldehydes, followed by hydrogenation of the triple bonds to the *Z*-double bonds. Base-catalysed elimination of the *syn*-hydroxysilane **263** gave an exclusively *E-E* diene **264**. Similarly, the *anti*-isomer **265** gave the *Z-E* diene **266** (*Scheme 102*).



Scheme 102

4.3.3 Sulfur-based Reactions

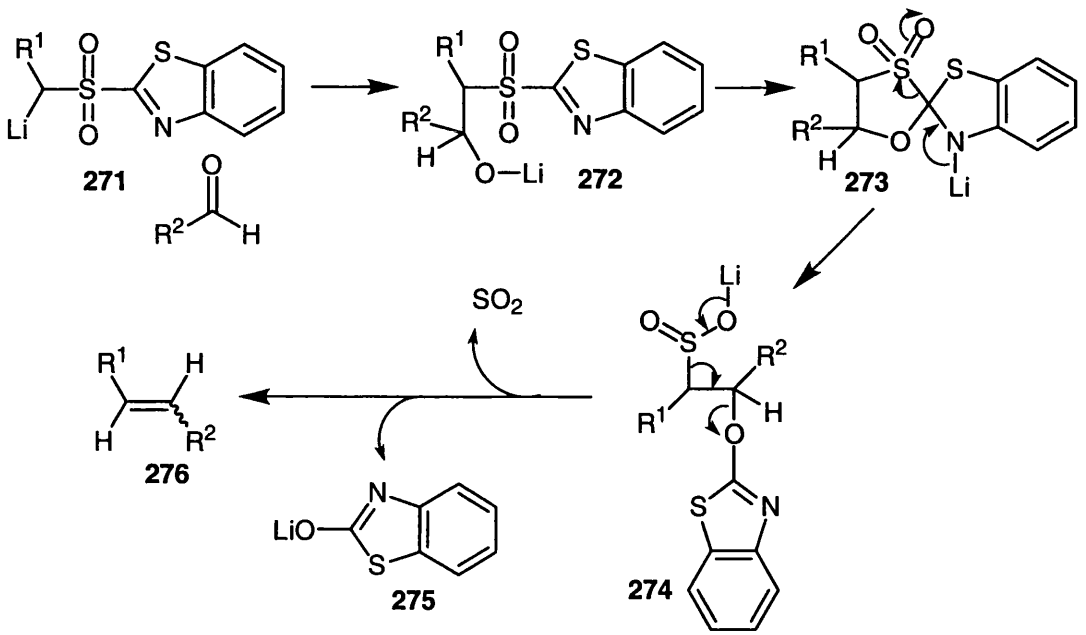
The most famous example of a sulfur-based olefination is the Julia coupling (*Scheme 103*).[103] This involves addition of metallated sulfone **267** to a carbonyl compound. The β-hydroxysulfone **268** is then functionalised (usually as an ester, mesylate or tosylate), and reductive elimination with sodium amalgam gives the alkene **270**.



Scheme 103

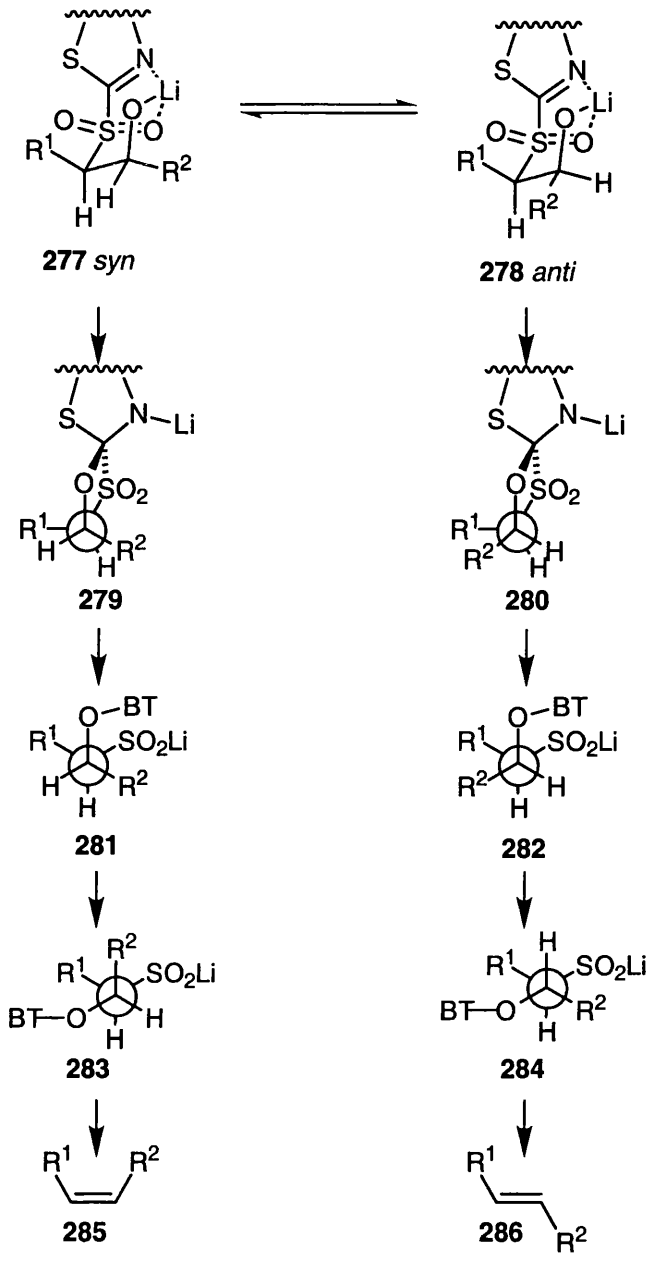
The Julia reaction has been widely used in the synthesis of complex natural products, and has proved to be a very selective method of forming *E,E*-dienes.[104] The main disadvantages are that it is a two-step process, and harsh conditions are required for reductive elimination.

In 1991, S. A. Julia (brother of M. Julia who discovered the original reaction) and co-workers reported the direct olefination from carbonyl compounds and lithiated sulfones.[105] This 'one-pot Julia reaction' uses a lithiated alkyl (or alkenyl-benzyl-, etc.) sulfonyl benzothiazole **271** (*Scheme 104*). Reaction with a carbonyl compound gives a β-alkoxysulfone **272** which immediately forms a spirocyclic intermediate **273**. The benzothiazole moiety is then transferred from sulfur to oxygen giving **274**. Finally, elimination of sulfur dioxide and lithiated benzothiazolone **275** yields the alkene **276**.



Scheme 104

The main question concerned the geometry of the products. In an extensive study of the reaction,[106] Julia and co-workers noted that use of aromatic, alkenyl or alkynyl carbonyl compounds gave predominately *E*-alkenes, while alkyl carbonyls gave predominately *Z*-alkenes (but with less selectivity). In an attempt to rationalise these results, Julia proposed the following process (*Scheme 105*). Upon reaction of a lithiated sulfone with an aldehyde, two diastereomeric intermediates **277** and **278** are formed. Both have a chair-like conformation, where the lithium is chelated to the neighbouring nitrogen of the benzothiazole and one of the oxygens of the sulfone. These alkoxides add to the C=N of the benzothiazole to give spirocyclic intermediates **279** and **280**. After transfer of the benzothiazole from S to O, giving **281** and **282**, rotation positions the benzothiazole antiperiplanar to the sulfonyl group, enabling *anti* elimination of **283** and **284** to give the appropriate alkenes.

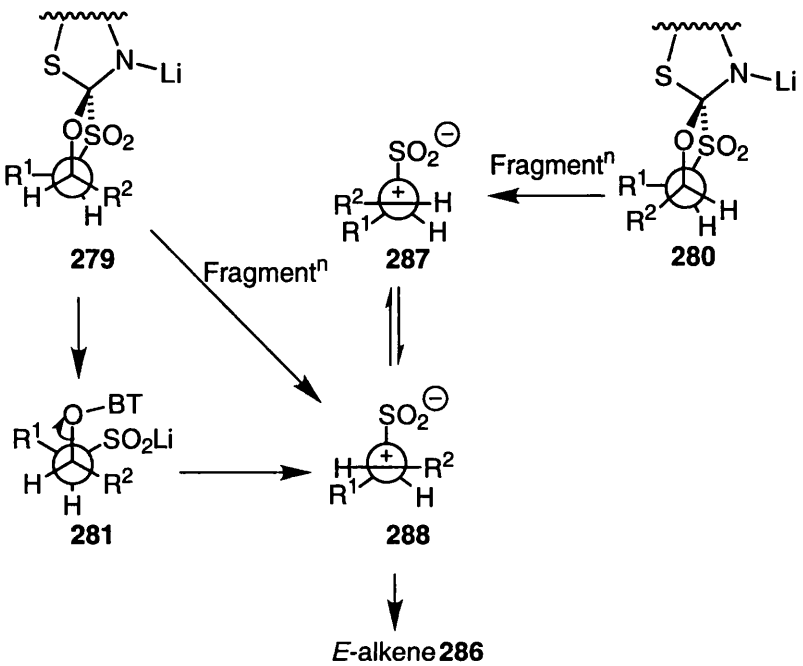


Scheme 105

The *anti* isomer **278** (which becomes the *E*-alkene), would be expected to be disfavoured due to the proximity of the R^1 and R^2 groups, leading to an overall preference for *Z*-alkene **285** by this route. The *Z*-isomer does indeed predominate when R^1 is alkyl, but an alternative pathway has to be used to explain the preferential formation of the *E*-alkene when R^2 is aromatic, alkenyl or alkynyl (*Scheme 106*). Fragmentation of spirocycle **280** to give zwitterion **287** would be encouraged by stabilisation of the carbocation by conjugation with aromatic or other electron-rich R^2-groups. Rotation to relieve steric congestion would give zwitterion **288**, then elimination of sulfur dioxide would give the *E*-alkene **286**. More importantly, it is also

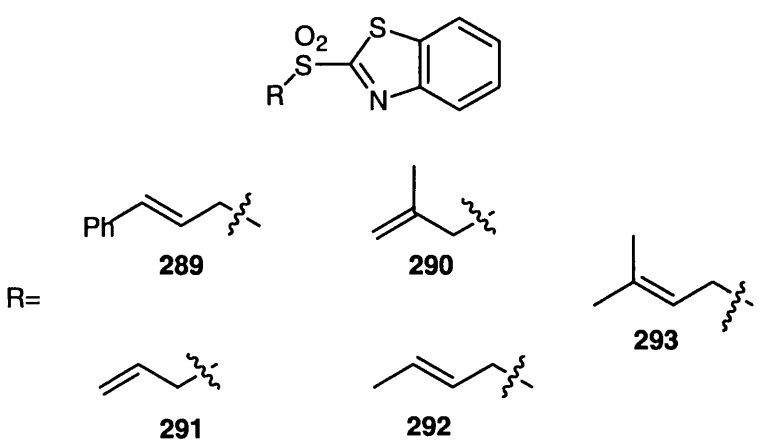
possible to form zwitterion **288** from the *syn*-alkoxide **277**, either by fragmentation of spirocycle **279**, or by loss of lithiated benzothaizolone from sulfinate **281**.

The modified Julia reaction provides some of the best selectivity in the synthesis of conjugated *E*-olefins. In most cases, the required sulfone is easily prepared, and the coupling step is quick (2-4 hours) and gives products that can easily purified.



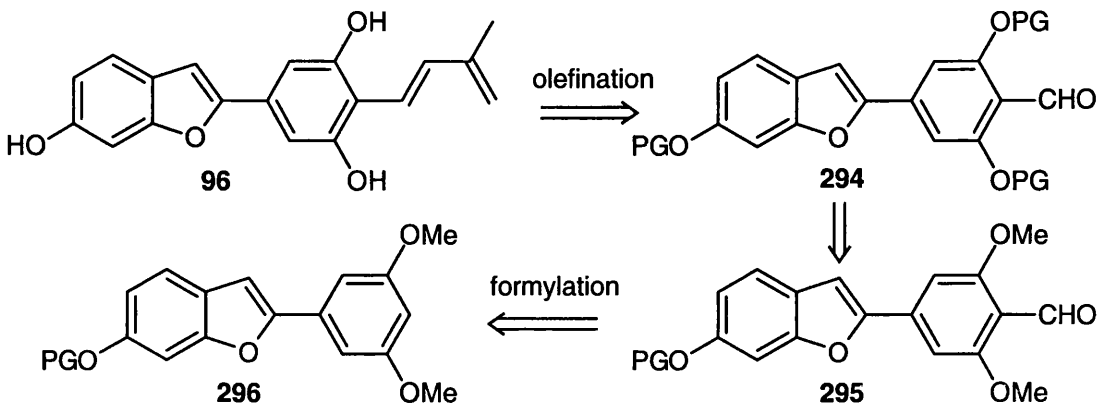
Scheme 106

Julia prepared several dienes from the range of sulfones below. In each case, the diene was isolated in good-excellent yield (40-93%) and high selectivity (*E*/*Z*, 66:34-95:5).



4.4 Synthesis of Diene 96

We required the fully deprotected diene **96** for our assay. We were not able to deprotect diene **232** (see page 66) without destroying the diene side-chain, so we considered the alternative retrosynthesis outlined below (*Scheme 107*).

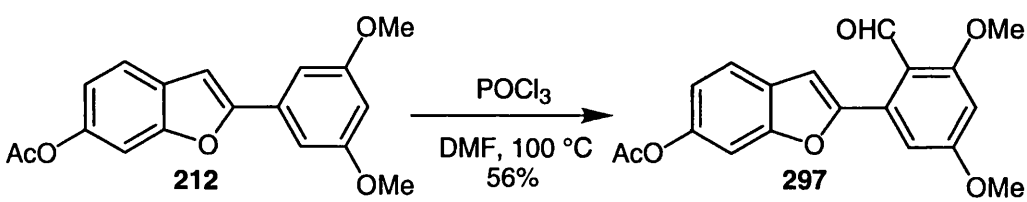


Scheme 107

Compounds like benzofuran **296** are intermediates in our synthesis of moracin C, so their synthesis has already been well developed. Regiospecific introduction of a formyl group might be achieved by *ortho*-lithiation, or alternatively under Vilsmeier-Haack conditions. The aldehyde should be stable to demethylation conditions, so the two methyl groups could be removed and replaced with a more labile protecting group (e.g. silyl ether) that could be removed after olefination without affecting the acid-sensitive diene functionality. Wittig reaction followed by deprotection would give **96**.

4.3.1 Vilsmeier-Haack Route

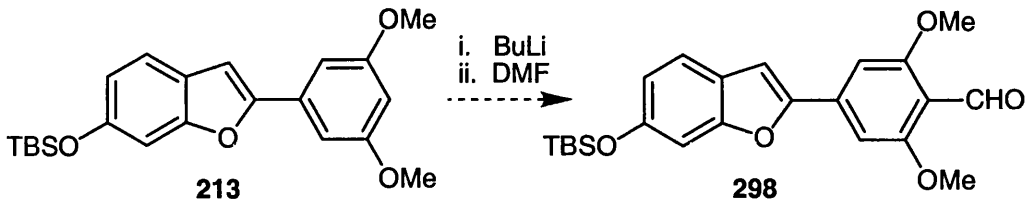
We first attempted aldehyde formation by Vilsmeier-Haack formylation of benzofuran **212**. Using the method of Godfrey and Sargent,[107] we treated **212** with phosphorus oxychloride in hot DMF (*Scheme 108*). After 1 hour, it was found that the aldehyde isolated was not the desired 4'-formylated product, but a regioisomer **297** where the aldehyde had been introduced in the 2'-position.



Scheme 108

4.4.2 *Ortho*-Lithiation Route

The introduction of a formyl group by reaction of an organolithium with DMF (or equivalent formamide) has been well documented in the literature.[108] Using the lithiation procedure already established, we attempted the synthesis of aldehyde **298** from benzofuran **213** (*Scheme 109*). All efforts were unsuccessful, with mainly starting material recovered (plus a small amount of desilylated compound). A range of conditions were tried, as outlined in *Table 6*. As well as using DMF as an aldehyde equivalent, we also used boronate ester **299** unsuccessfully.[109] The use of similar boronate esters had been reported by Rathke *et al.*[110]



Scheme 109

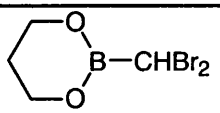
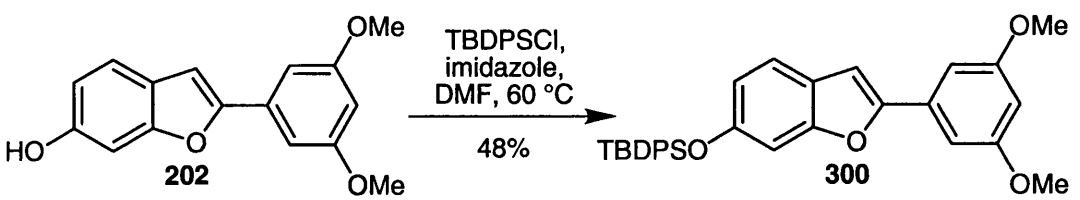
Aldehyde Equivalent	Temperature
DMF	–78 °C
DMF	–35 °C
DMF	0 °C
 **299**	–35 °C

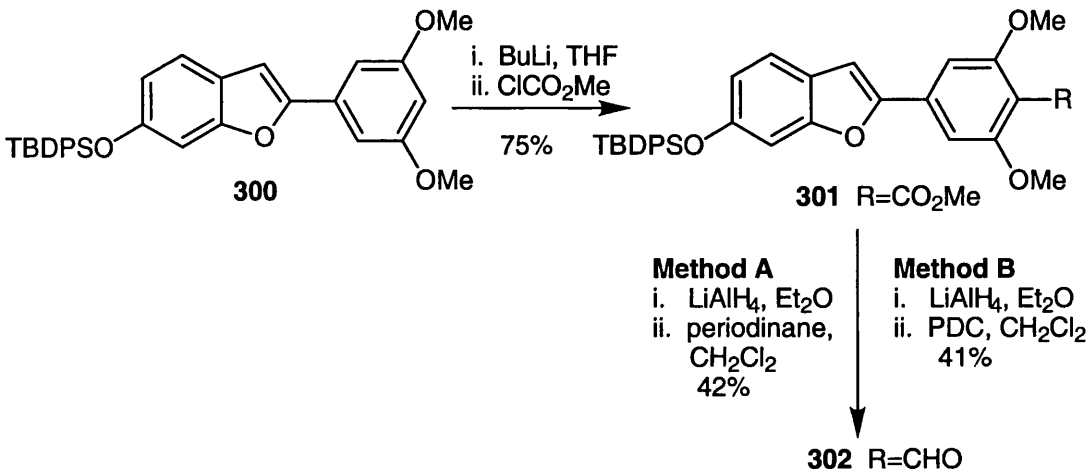
Table 6

Our next approach proved more successful. Since it was problematic to get the organolithium to react with DMF, we decided to prepare an ester from which the aldehyde would be easily accessible. We changed the silyl protecting group from the *tert*-butyldimethylsilyl (TBS) to the *tert*-butyldiphenylsilyl (TBDPS) group (*Scheme 110*), as we hoped that the increased bulk would provide more stability and so avoid desilylation.



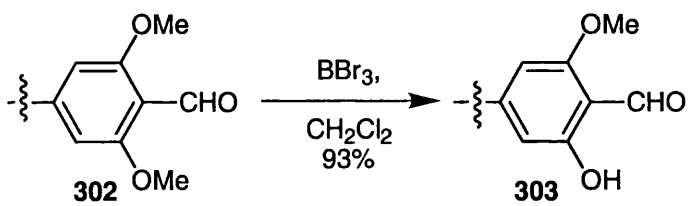
Scheme 110

Lithiation of **300** proceeded cleanly and, after reaction with methyl chloroformate, gave ester **301** in good yield (*Scheme 111*). Our original plan was to reduce this directly to the aldehyde with DIBAL-H, but this resulted in a complex mixture of compounds, including 'over-reduced' alcohol. More success was found by treating with an excess of lithium aluminium hydride, followed by oxidation using either Dess-Martin periodinane,[111] or pyridinium dichromate. Both methods gave aldehyde **302** in moderate yield over two steps.



Scheme 111

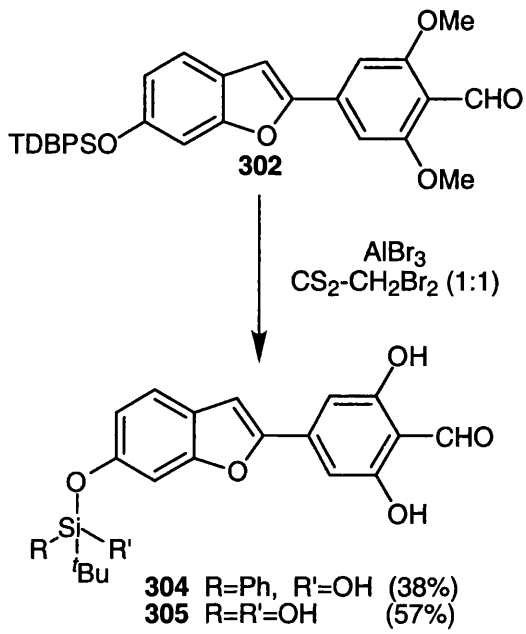
At this stage, we expected demethylation to be straightforward, but when aldehyde **302** was treated with an excess of boron tribromide it was converted to the monomethylated aldehyde **303**, albeit in high yield (*Scheme 112*). It was found that a greater excess of boron tribromide, or a longer reaction time only resulted in decomposition of **303**.



Scheme 112

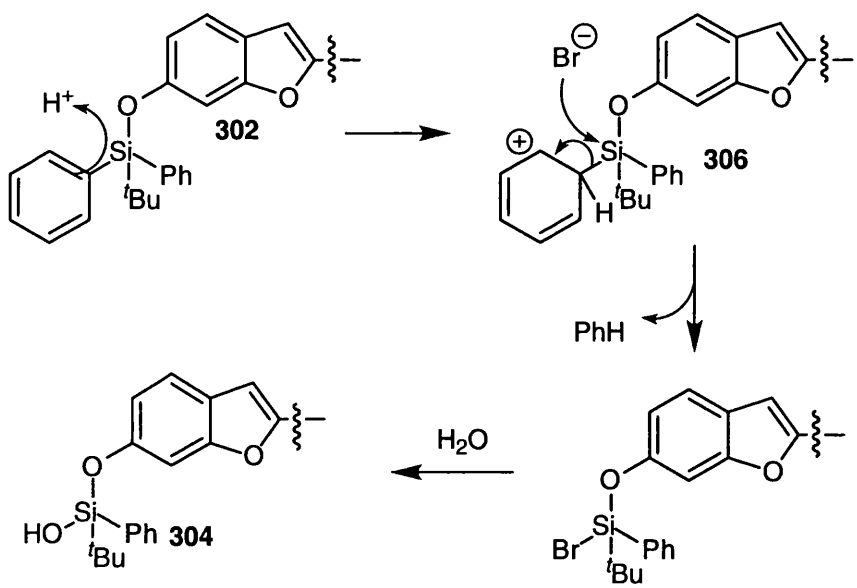
Since the demethylation of **302** with boron tribromide was not successful, we tried a different method. Wagner *et al* reported the complete demethylation of 2,6-dimethoxybenzaldehyde using aluminium tribromide in a mixture of carbon disulfide and dibromomethane.[112] We tried this procedure with aldehyde **302**, and isolated two products (*Scheme 113*). Both products were aldehydes and ^{1}H NMR spectroscopy showed no trace of methoxyl groups, but both seemed to be lacking a complete TBDPS group. Structural analysis eventually showed them to be aldehydes **304**

(where one phenyl group had been replaced with a hydroxyl), and **305** (where both had been replaced).



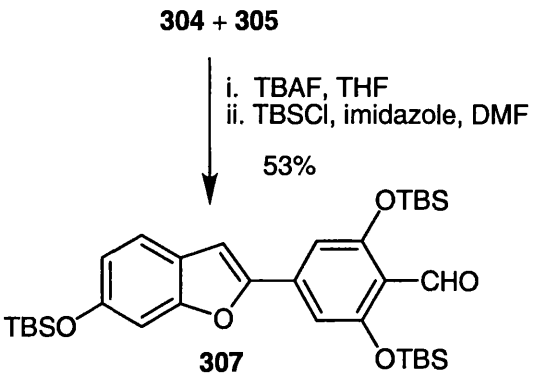
Scheme 113

A possible explanation for the formation of silanols **304** and **305** is outlined in *Scheme 114*. The presence of residual water in the system, either from the Lewis acid or from the solvents, could produce HBr in solution. Protonation of a phenyl ring would generate cation **306**, which would be stabilised due to its position β- to the silicon. Attack in a S_N2 fashion by bromide followed by water during the work-up, would eliminate benzene giving the silanol **304**. Repetition of this procedure would result in the loss of the second phenyl group, giving **305**.



Scheme 114

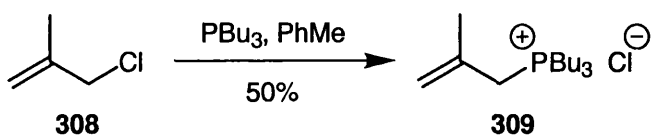
As well as the unforeseen reaction with aluminium tribromide, demethylation occurred cleanly. We felt however, that the presence of free hydroxyls, (both *ortho-* to the aldehyde and on the silicon), would prevent olefination, so we removed the hydroxysilyl groups from **304** and **305**, and reprotected the hydroxyls to give the *tris*-TBS ether **307** (*Scheme 115*).



Scheme 115

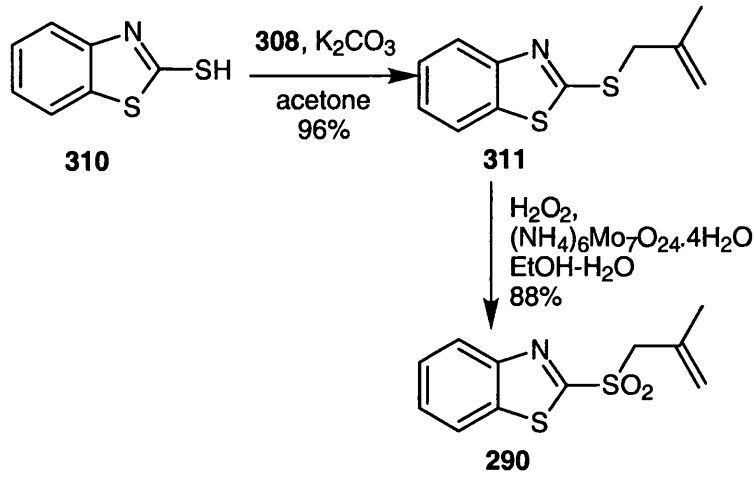
At this stage, we were dealing with very low quantities of substrate, and since the chromatographic stability of these compounds was in question, they were carried through subsequent steps without full characterisation (although ^{1}H NMR spectroscopy confirmed the structures as those shown).

We had originally planned to construct the diene by a Wittig reaction. As mentioned earlier, it had been shown by Tamura *et al*[95] that tributylphosphonium salts provided better geometrical selectivity in reactions of allylic ylides, so we prepared phosphonium salt **309** for our olefination reaction (*Scheme 116*). Although easy to prepare, the salt **309** was hygroscopic and difficult to handle, and the Wittig reaction was unsuccessful.



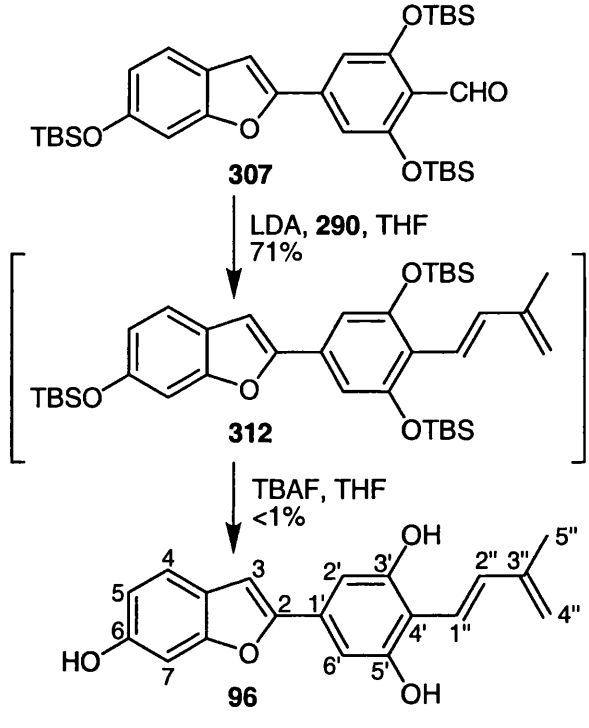
Scheme 116

Given the excellent results shown by Julia and co-workers in the synthesis of *E*-dienes from allylic sulfones,[106] we opted for the modified Julia reaction to construct our diene. The required sulfone **290** was easily prepared by reaction of 2-mercaptobenzothiazole **310** and methallyl chloride **308**, followed by oxidation of sulfide **311** (*Scheme 117*).



Scheme 117

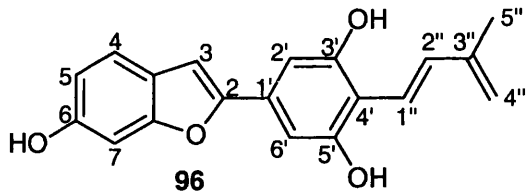
Julia reaction between aldehyde **307** and sulfone **290** was carried out using the method outlined by Julia and co-workers,[106] and gave diene **312** in good yield (*Scheme 118*). As with the starting aldehyde **307**, diene **312** was not completely characterised, but ^{1}H NMR spectroscopy confirmed exclusive formation of the *E*-diene ($J_{H1''\text{-}H2''}$ 16.4 Hz). Immediate desilylation with TBAF gave diene **96** in low yield after repeated attempts at chromatography.



Scheme 118

Purification (specifically the removal of excess TBAF) was difficult due to the instability of the diene **96** on both silica and deactivated, neutral alumina gels. However, ^{1}H NMR spectroscopy showed that only the *E*-isomer was present (*Figure 16*).

Section of 400 MHz ^{1}H NMR of diene 96



96

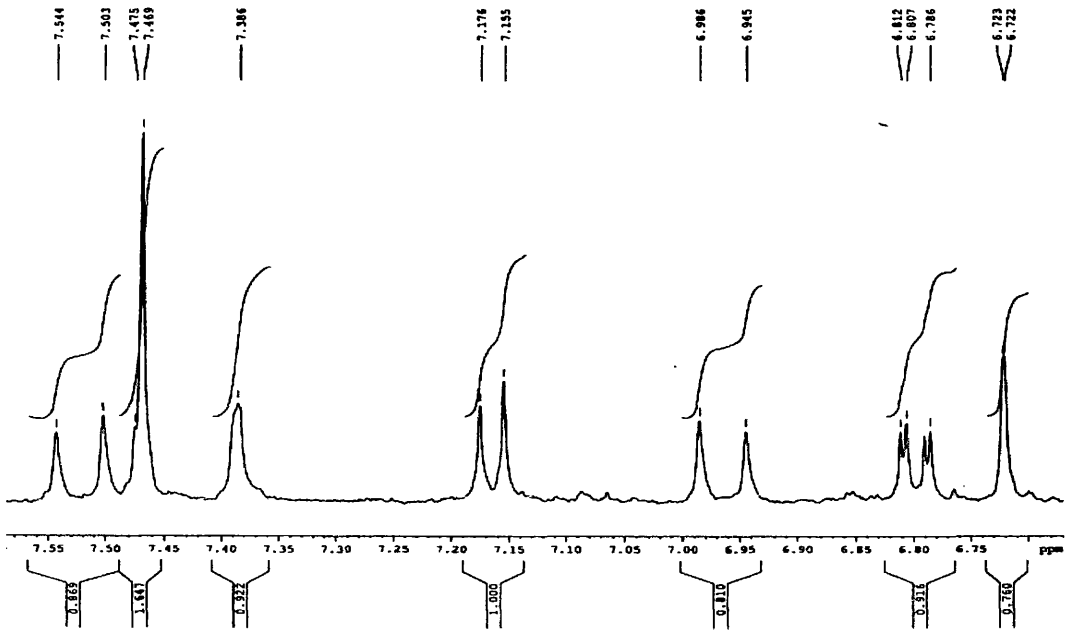


Figure 16

The ^{1}H NMR spectrum shows that only one benzofuran product is present. A singlet for H-3 is present at δ7.39, while H-4, H-5 and H-7 are identified by signals at δ7.16 (*ortho*-coupled doublet, *J* 8.4 Hz), δ6.80 (*ortho*-and *meta*-coupled double-doublet, *J* 8.4 and 2.0 Hz), and δ6.72 (*meta*-coupled doublet, *J* 2.0 Hz), respectively. The *E*- geometry is confirmed by the presence of two doublets at δ7.52 and 6.96 with coupling constants of 16.4 Hz. The 2H singlet at δ7.47 shows that the aryl ring is completely symmetrical, i.e. no cyclisation has taken place. This is also confirmed by the presence of both a terminal methylene group, which can be seen as two broad singlets at δ4.82 and 4.76, and the hydroxyl signals at δ11.18 and 11.03 in the ratio of 2:1 (*Figure 17*).

Section of 400 MHz ^{1}H NMR of diene 96

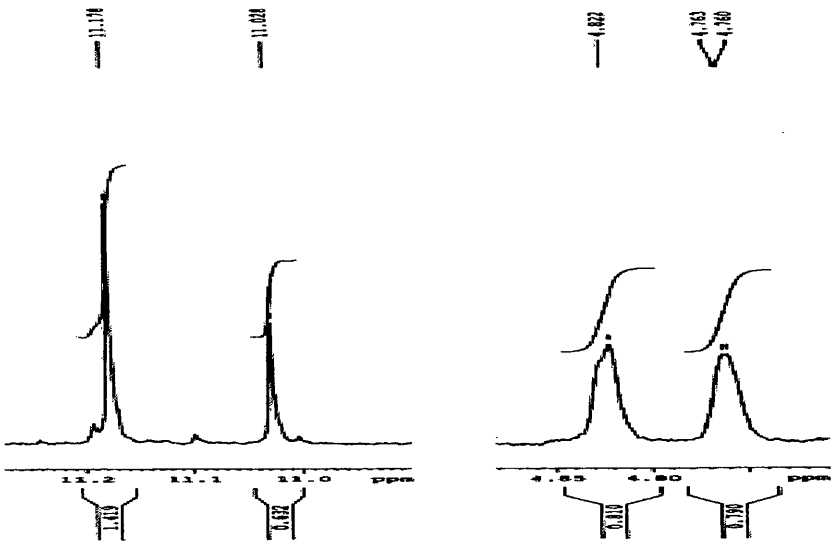
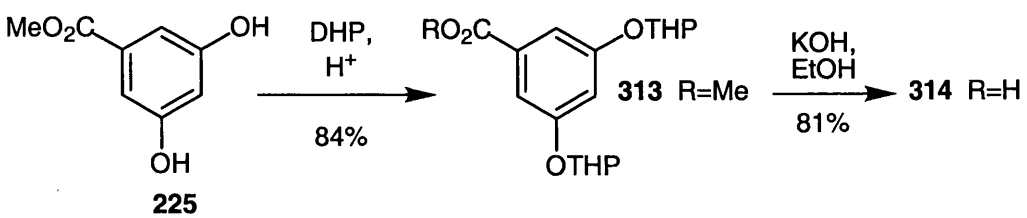


Figure 17

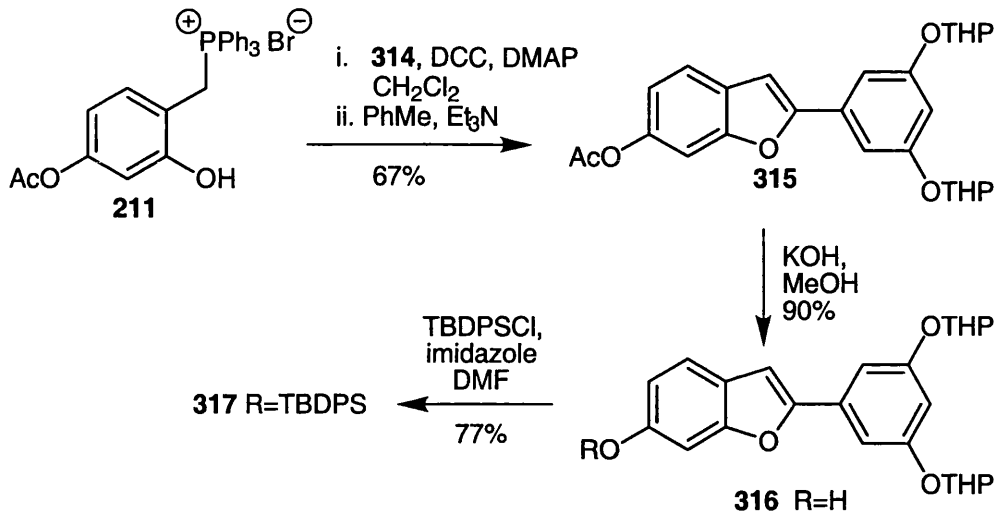
Although successful in our synthesis of diene **96**, we felt that the route could be improved. One of the main flaws was the reaction of the TBDPS group with aluminium tribromide, leading to a rather uneconomical deprotect-reprotect sequence (*Scheme 115*).

The synthesis of moracin C by Nakamura and co-workers had shown the *ortho*-directing ability of the THP group.[48] We felt that the use of this protecting group instead of methyl might be advantageous, since it should be much easier to remove under mild conditions.



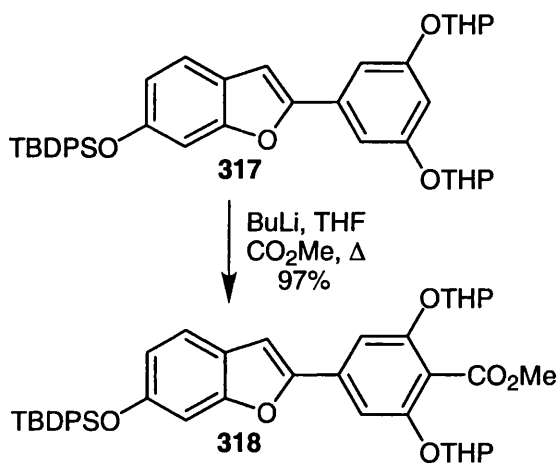
Scheme 119

We prepared the fully THP-protected acid **314** by protection of methyl 3,5-dihydroxybenzoate **225**, followed by hydrolysis of ester **313** (*Scheme 119*). Acid **314** was coupled with phosphonium salt **211** under standard cyclisation conditions, giving benzofuran **315** (*Scheme 120*). Once again, the acetate was removed and replaced with the bulky TBDPS group.



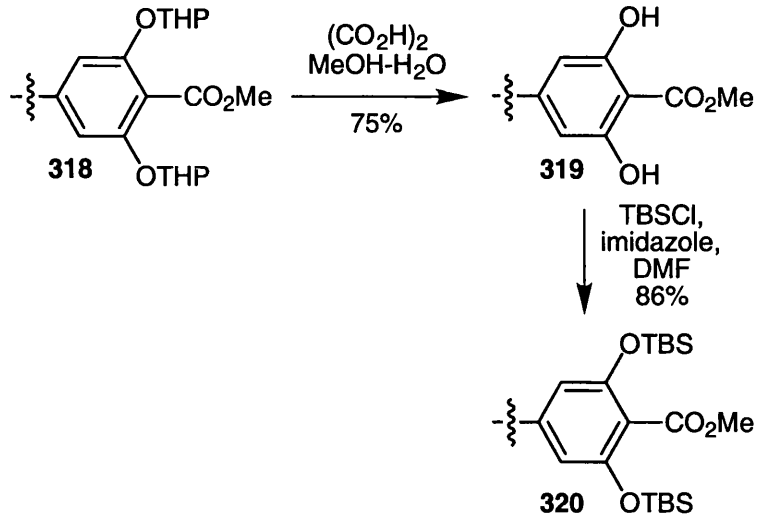
Scheme 120

Lithiation of benzofuran **317** to give ester **318** proceeded cleanly, although more forcing conditions were required (*Scheme 121*). Reduction and oxidation of ester **318** proved difficult, with no aldehyde recovered after a number of attempts.



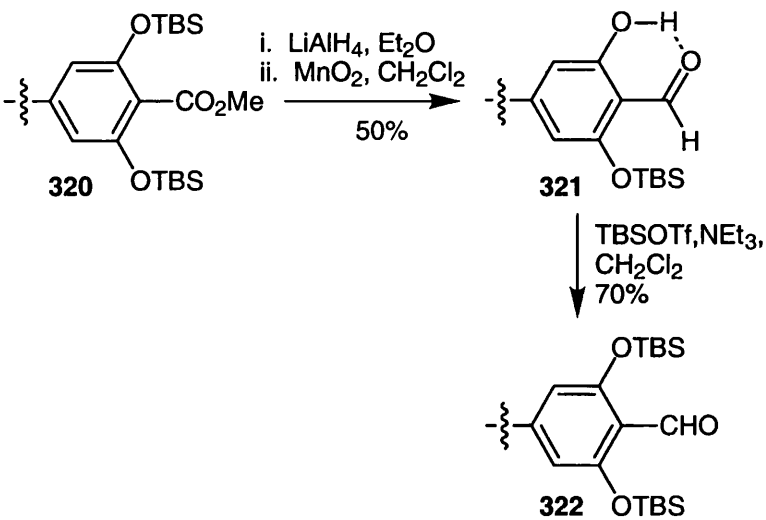
Scheme 121

In the hope that the TBS group would be more stable to the reduction/oxidation conditions, the THP groups were replaced at this stage (*Scheme 122*). The procedure outlined by Nakamura and co-workers using methanol and aqueous oxalic acid[48] gave ester **319** in good yield. Ester **319** was then reprotected as the *bis*-TBS ether **320**.



Scheme 122

Reduction and oxidation of ester **320** was more successful although, despite using manganese dioxide as a milder oxidant, one of the TBS groups was lost during the reaction (*Scheme 123*). This was attributed to the strong internal chelation between the carbonyl and the hydroxyl of aldehyde **321**. This aldehyde was resilylated but a more reactive silylating agent was required. We were now dealing with such low quantities that the structure of aldehyde **322** was confirmed by ^{1}H NMR spectroscopy and mass spectrometry alone.



Scheme 123

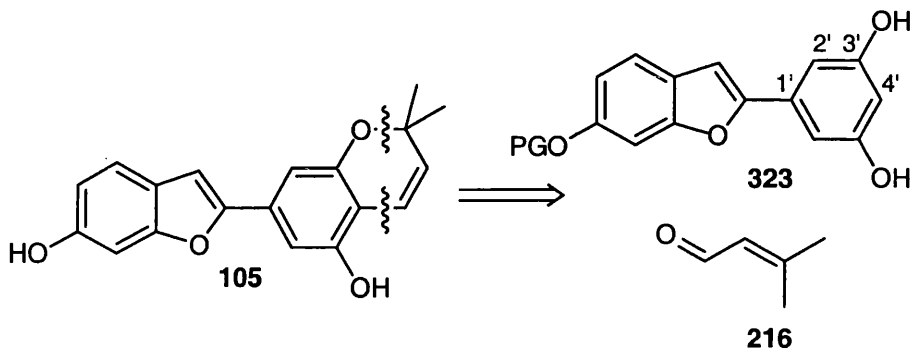
We attempted the Julia reaction between aldehyde **322** and sulfone **290**, with immediate desilylation of the product. However, we encountered difficulties with removal of excess TBAF and *tert*-butyldiphenylsilanol and the material was destroyed during several attempts at preparative thin layer chromatography. We believe the first route to be superior.

In summary, we synthesised and characterised by ^{1}H NMR spectroscopy, a small quantity of the desired diene **96**. However, a more satisfactory method of purifying the final product is required.

4.5 Studies Towards the Synthesis of Moracin D

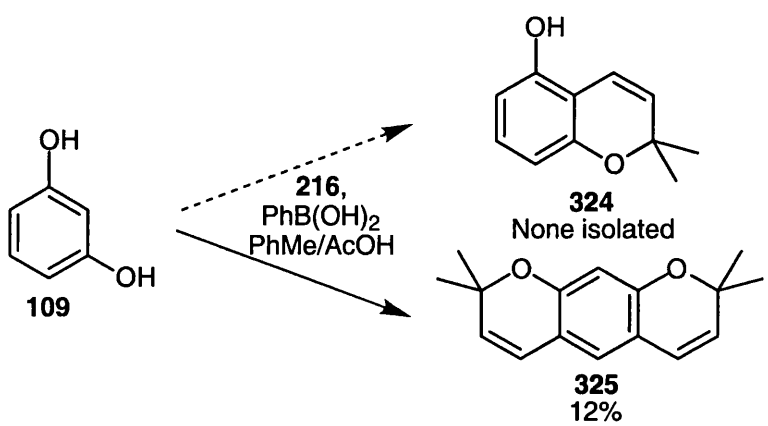
The natural occurence of diene **96** in *M. alba* has never been confirmed (See Section 1.9.2). We had already developed a synthesis of one of its proposed biosynthetic precursors, moracin C **97**, so we decided to devote some attention to the other possible precursor, moracin D **105**.

Scheme 124 shows our retrosynthetic strategy. Benzofuran **323** would be formed in a manner similar to that used in the synthesis of moracin C and diene **96**. We aimed to make the chromene ring by the reaction of benzofuran **323** with 2-methylbutenal **216**. Lopes and co-workers had shown that the condensation of phenols with unsaturated aldehydes, including **216**, in the presence of phenylboronic acid gave chromenes in good-excellent yield.[113]



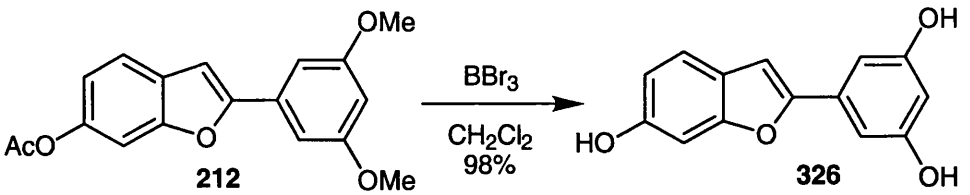
Scheme 124

We first tried the phenylboronic acid cyclisation on a model system (*Scheme 125*). Reaction of resorcinol **109** with 2-methylbutenal **216** did not give phenol **324**, but instead produced chromene **325** (the result of double cyclisation), in low yield. Although the regiochemistry of the cyclisation was wrong in this example, we decided to attempt the reaction on an arylbenzofuran **323**.



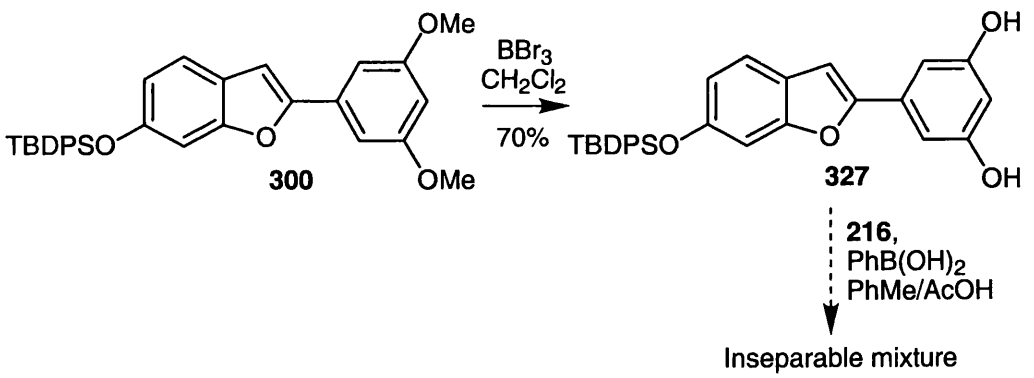
Scheme 125

A suitable arylbenzofuran for the phenylboronic acid cyclisation would need the hydroxyl in the 6-position protected. Treatment of benzofuran **212**, an intermediate in the synthesis of moracin C **97**, with boron tribromide resulted in efficient demethylation, but the acetate protecting group was also hydrolysed. The product another member of the moracin family of natural products, moracin M **326**.



Scheme 126

We needed a more robust protecting group. Our synthesis of diene **97** had shown that the TBDPS group was stable to certain demethylation conditions. Benzofuran **300**, an intermediate in the synthesis of diene **232**, was treated with boron tribromide (*Scheme 127*). Demethylation occurred cleanly, but more importantly the TBDPS group remained intact. Unfortunately, reaction of benzofuran **327** with 2-methylbutenal **216** resulted in a mixture of products which were inseparable by chromatography.



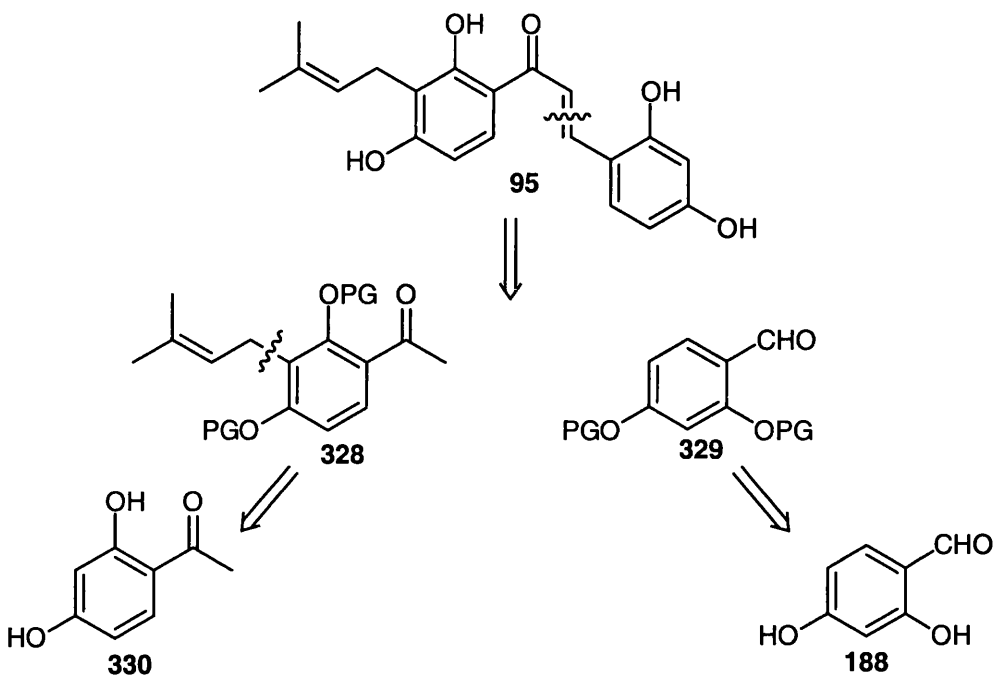
Scheme 127

5

Approaches to the Synthesis of Morachalcone A

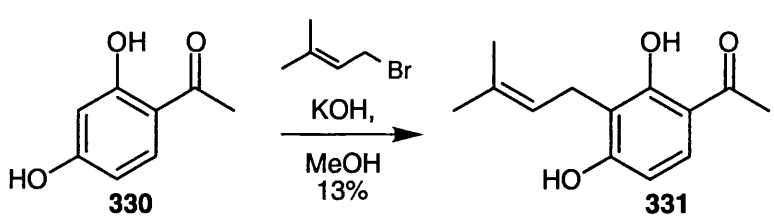
5.1 Aldol Approach

To complete our enzyme assay, we required the dienophile morachalcone A **95**. The easiest disconnection is in the α,β-unsaturated section of the molecule (*Scheme 128*). Ketone **328** and aldehyde **329** are readily prepared from commercial starting materials, and can be coupled together in an aldol condensation to form the chalcone.



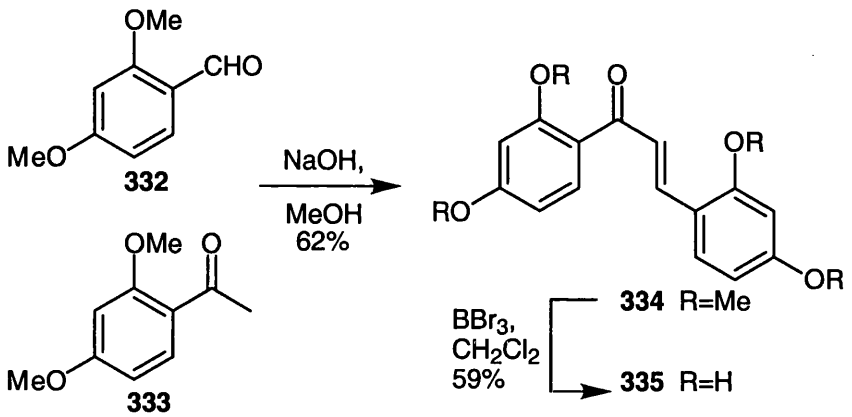
Scheme 128

Jain *et al* outlined a procedure for the preparation of ketone **331** involving reaction of 2,4-dihydroxyacetophenone **330** with prenyl bromide and potassium hydroxide (*Scheme 129*).[114] Although low yielding, this route had the advantage that it could be done on a large scale and, by slight adaptation of the work-up outlined by Jain, pure ketone **331** could be isolated without the need for chromatography.



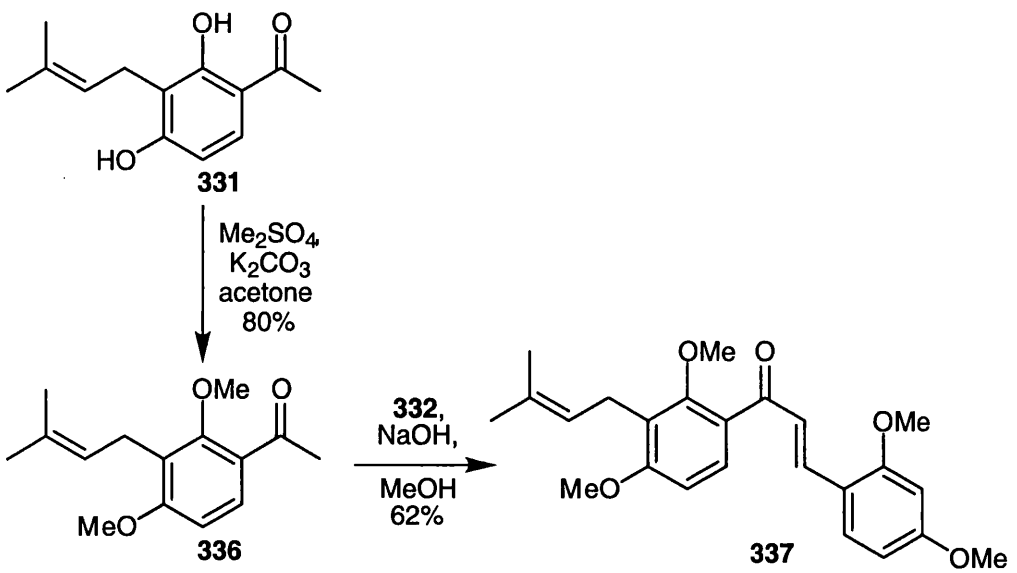
Scheme 129

The main consideration when planning the aldol condensation was the choice of protecting group. We first looked at the most simple, the methyl group. Following the method of Wattanasin and Murphy,[115] we prepared chalcone **334** in good yield by simple condensation of 2,4-dimethoxybenzaldehyde **332** with 2,4-dimethoxyacetophenone **333** (*Scheme 130*). Demethylation with boron tribromide gave chalcone **335**.



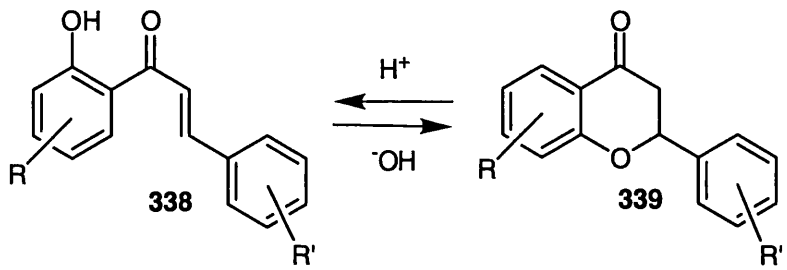
Scheme 130

These aldol conditions were then repeated using the prenylated ketone **331**, protected as the *bis*-methyl ether **336**. Once again, condensation with aldehyde **332** proceeded in good yield with ^{1}H NMR spectroscopy of the chalcone **337** showing exclusively *E*-double bond geometry (*J* 15.9 Hz) (*Scheme 131*). Unfortunately, treatment with boron tribromide gave only a complicated mixture of products, with no trace of the desired product.



Scheme 131

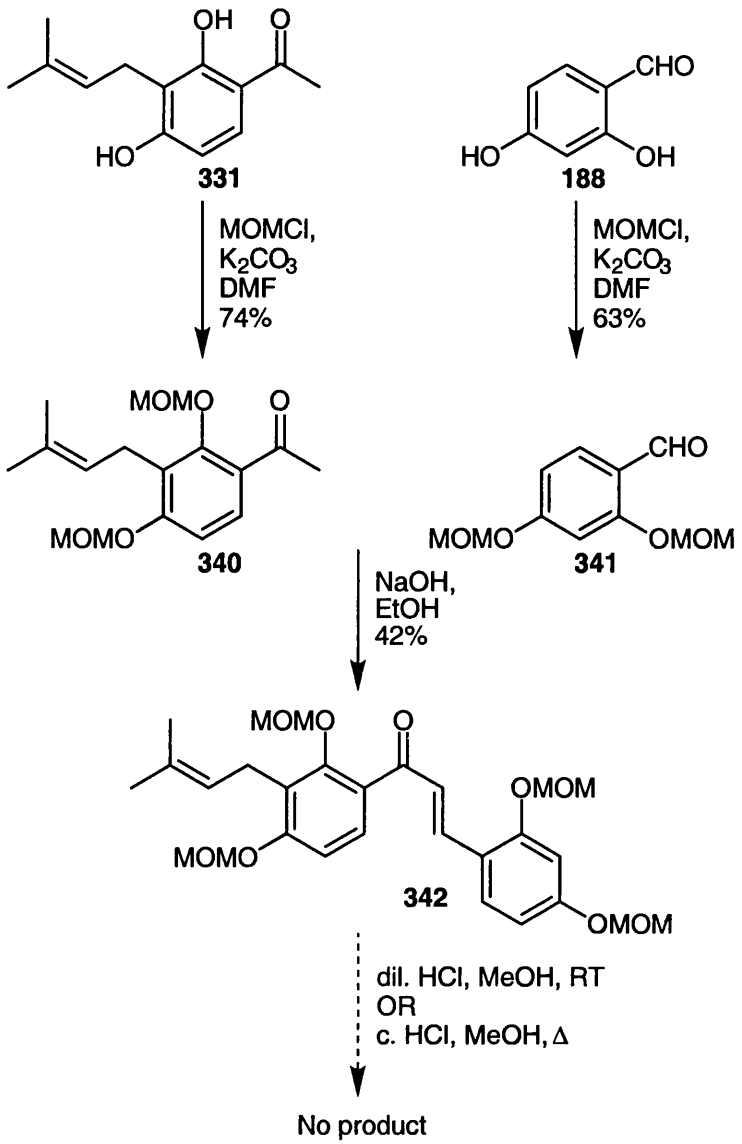
One of the main problems encountered when dealing with chalcones such as **338**, having a free hydroxyl in the 2-position, is the potential for cyclisation in acid conditions, forming the isoflavanone **339** (*Scheme 132*). It is possible however, to open isoflavanones and reform the chalcone in basic conditions.[116]



Scheme 132

Our next attempt at the synthesis of morachalcone A **95** used the MOM protecting group. We expected that this would be easy to remove under mildly acidic conditions, and if cyclisation were to occur, we would be able to generate morachalcone A by treatment with base. *Scheme 133* shows the synthesis of chalcone **342**. Again, protection of aldehyde **188** and ketone **331** followed by condensation, using the procedure of Wattanasin and Murphy[115] gave the *E*-chalcone.

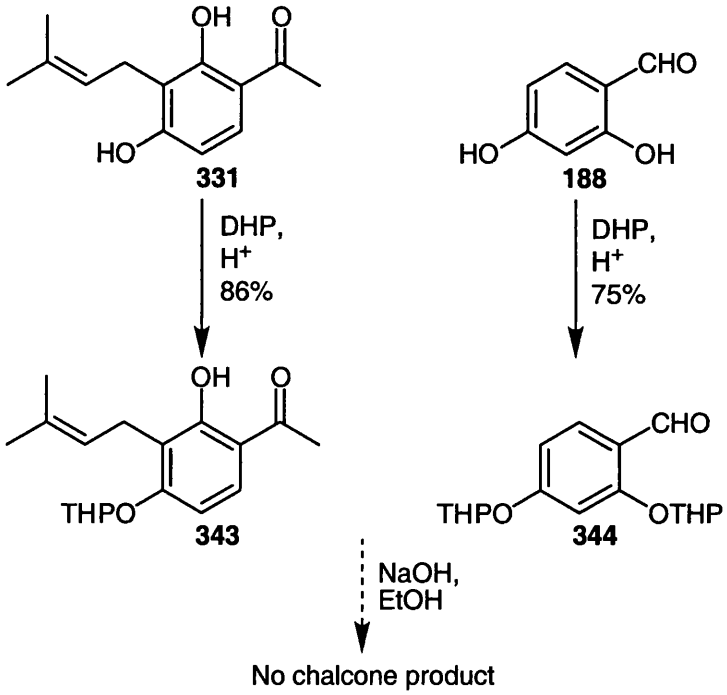
Once again we encountered difficulties when trying to deprotect (*Scheme 133*). Treatment with dilute HCl gave only recovered starting material, while more forcing conditions (conc. HCl, reflux) only resulted in degradation of the substrate.



Scheme 133

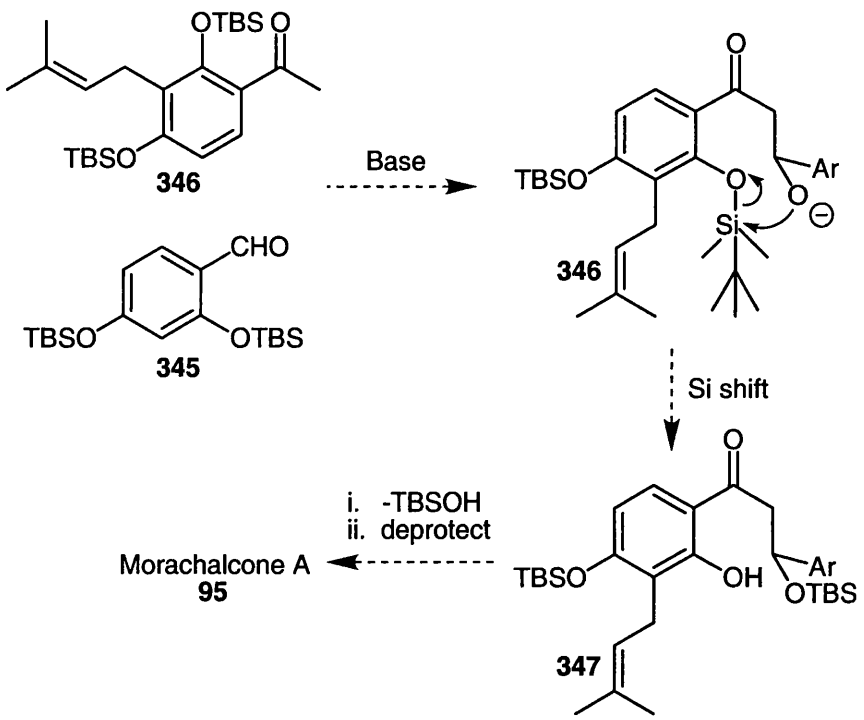
Other Protecting Groups Tried:

We also used the THP group in the hope that it would be even easier to remove than the MOM group (*Scheme 134*). We were only able to protect the hydroxyl at C-4 of ketone **331**, presumably due to steric crowding of the hydroxyl at C-2. Deprotonation of the free phenolic hydroxyl in ketone **343** will inhibit enolisation of the ketone and so prevent aldol condensation. The ^1H NMR spectrum of the crude mixture from the aldol condensation showed no sign of chalcone formation.



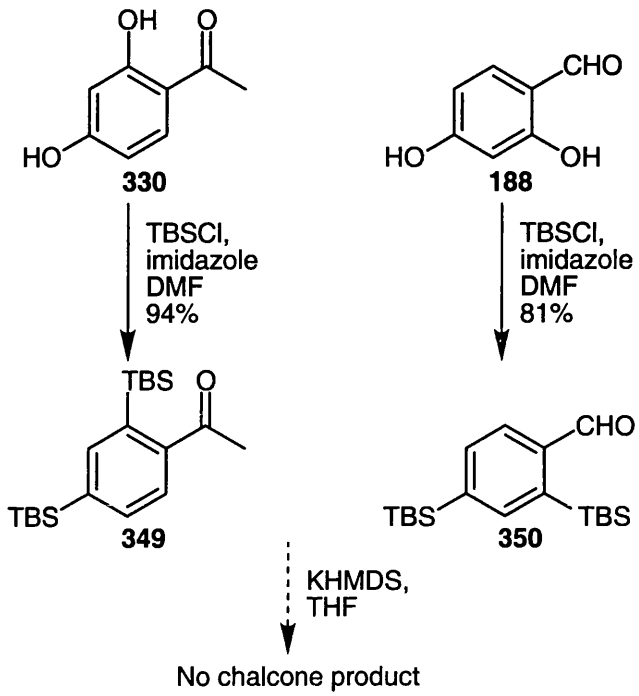
Scheme 134

In a move away from carbon-based protecting groups, we tried the TBS group. In the presence of a strong base, reaction of aldehyde **345** and ketone **346** would give intermediate **347**. The lability of the silyl group may result in silicon migration onto the adjacent oxygen giving phenol **348**. Loss of silanol followed by desilylation would give morachalcone A **95** (*Scheme 135*).



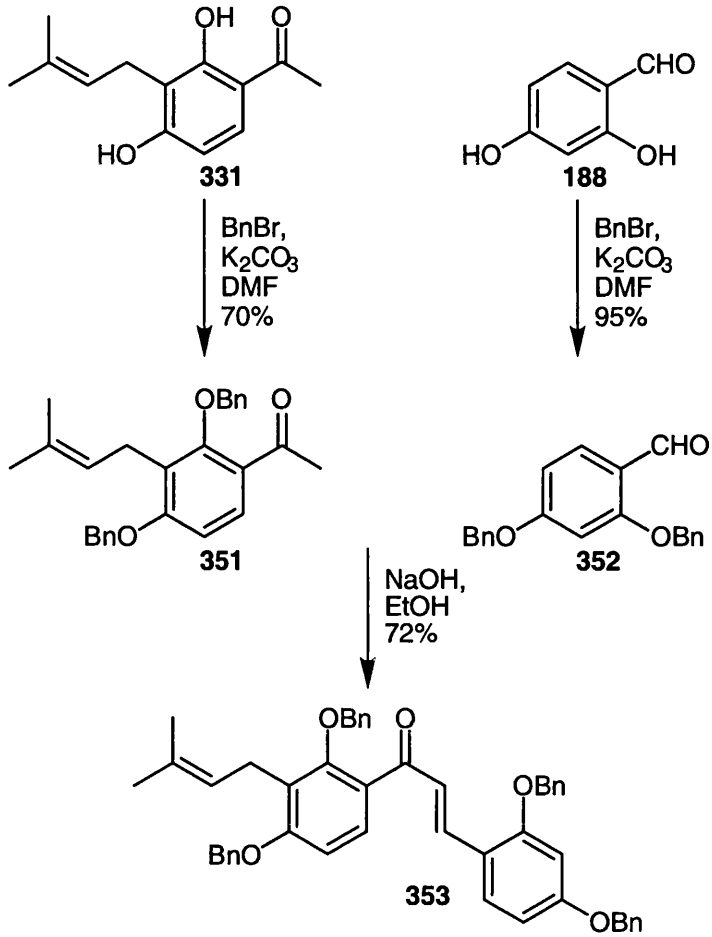
Scheme 135

We tested the silyl protecting group using non-prenylated ketone **330**, since prenylation was very low yielding. After silylation of aldehyde **188** and ketone **330** , we attempted the coupling step using potassium hexamethyldisilazide as base (*Scheme 136*). Thin layer chromatography and ^{1}H NMR spectroscopy of the crude reaction showed a complex mixture, including starting aldehyde and ketone and some desilylated starting material. This route was not pursued further.



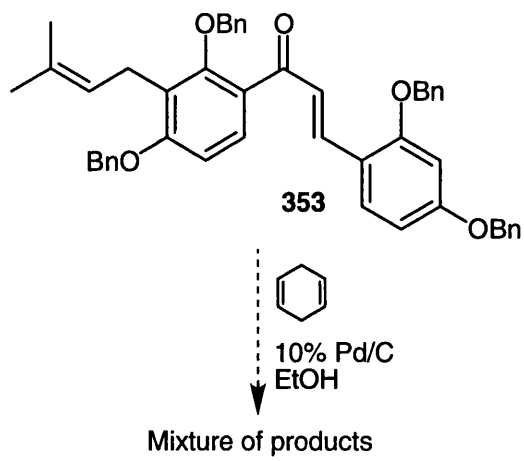
Scheme 136

Monache *et al* report the synthesis of phenolic chalcones where the benzyl group was used to protect free hydroxyls.[117] Here debenzylation was carried out using boron trichloride. We felt that, while the use of boron trichloride would be unsuccessful given our results with boron tribromide, it might be possible to debenzylate using other methods. To this end, we prepared chalcone **353**, by protection of aldehyde **188** and ketone **331**, then condensation of **351** and **352** (*Scheme 137*).



Scheme 137

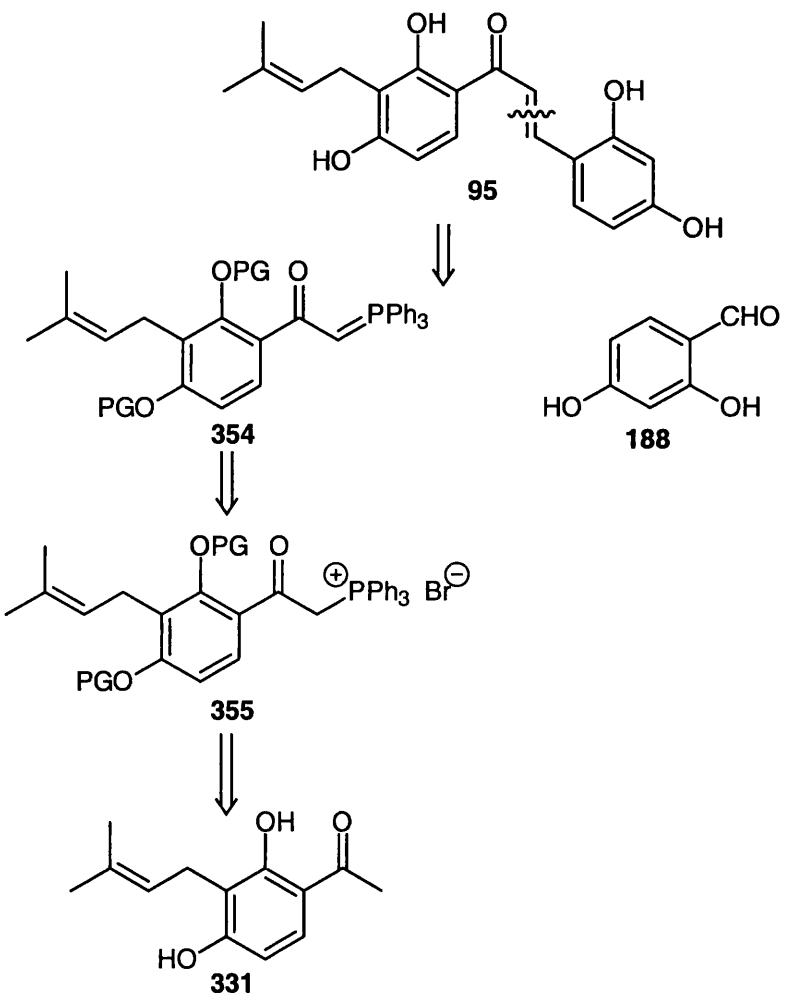
Jung et al reported that transfer hydrogenation using 1,4-cyclohexadiene with a palladium on charcoal catalyst allowed debenzylation of secondary alcohols in the presence of a trisubstituted double bond.[118] When we tried this method with chalcone **353** (*Scheme 138*) we found that, although ^1H NMR spectroscopy showed some debenzylation, thin layer chromatography showed the presence of several products as well as starting material.



Scheme 138

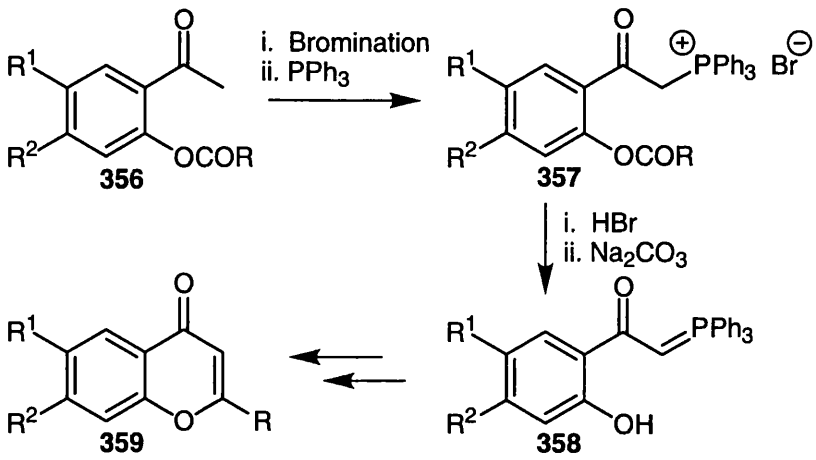
5.2 Wittig Approach

An alternative approach to morachalcone A **95** would be to form the chalcone by a Wittig reaction between ylide **354** and aldehyde **188** (*Scheme 139*). Ylide **354** can be formed by deprotonation of phosphonium salt **355**, which is easily prepared from ketone **331** by protection, α-bromination and bromide displacement by triphenylphosphine.



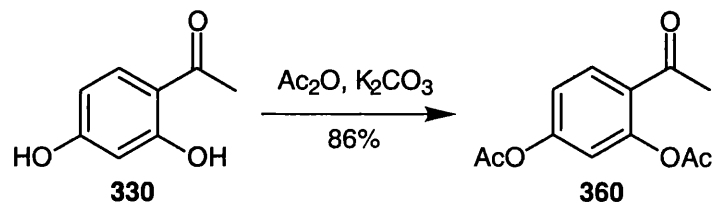
Scheme 139

Hercouet and Le Corre[119] and later Le Floc'h and Lefeuvre[120] reported the synthesis of ylides similar to **354** as part of the synthesis of chromenones **359** (*Scheme 140*). Bromination of ketones **356**, followed by displacement of the bromide by triphenylphosphine gave salt **357**. Ester hydrolysis then deprotonation gave ylide **358** in good yield.



Scheme 140

We decided to follow this protocol. Again, our initial attempts were carried out using the non-prenylated ketone **330**. We protected the free hydroxyls as acetates using the method of Malkin and Nierenstein (*Scheme 141*)[84] to give ketone **360** in good yield.

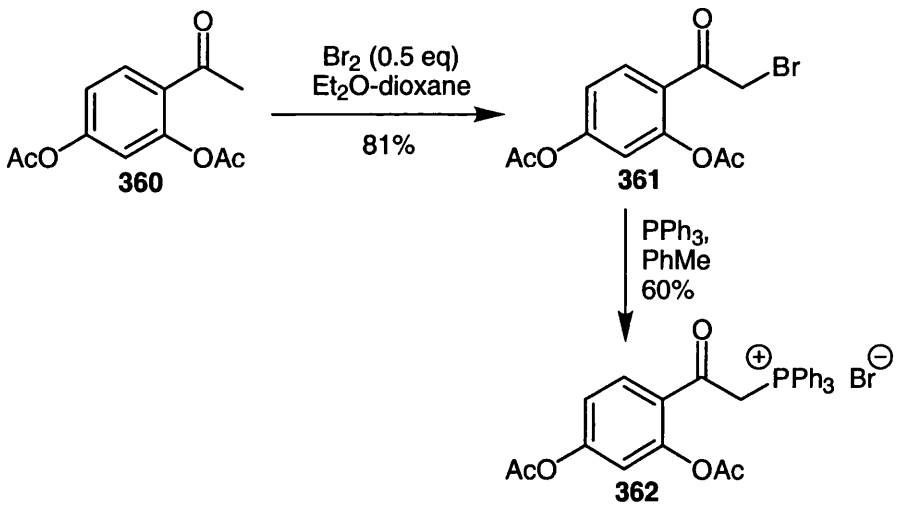


Scheme 141

Several methods of α-bromination were tried (*Scheme 142*, *Table 8*), including the method mentioned by Le Floc'h and Lefeuvre using bromine and carbon tetrachloride.[120] The best results came from addition of 0.5 equivalents of ethereal bromine to an open solution of ketone **360** in ether-dioxane exposed to air (*Table 8*, entry 5). Bromoketone **361** was isolated in good yield, with ^{1}H NMR spectroscopy showing no signs of over-bromination. Reaction of bromoketone **361** with triphenylphosphine in toluene gave salt **362**.

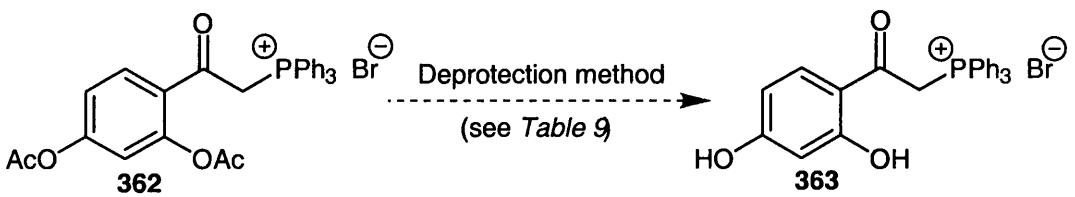
	Reaction Conditions	Result
1	$Br_2/CHCl_3$	Starting Material
2	Br_2/CCl_4/reflux	Complex Mixture
3	$Br_2/CHCl_3/AlCl_3$	Starting Material
4	Br_2/AcOH	Starting Material
5	Br_2/Et_2O/dioxane	Bromoketone **361**

Table 8



Scheme 142

The next step was to deacetylate **362** prior to ylide formation. Le Floc'h and Lefeuvre had achieved this by heating the ester at reflux with conc. HBr.[120] This, and other methods of deprotection (*Scheme 143*, *Table 9*) were unsuccessful, resulting in substrate degradation, with no characterisable material isolated.

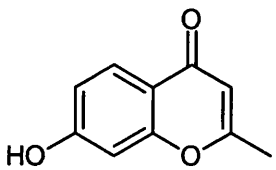


Scheme 143

	Reaction Conditions	Temperature	Result
1	HBr	Reflux	Complex Mixture
2	HBr/EtOH	Reflux	Complex Mixture
3	HBr/EtOH	RT	Complex Mixture
4	MeOH/HCl	RT	Complex Mixture
5	Zn/MeOH	RT	Complex Mixture
6	K_2CO_3/MeOH	RT	Cyclisation?

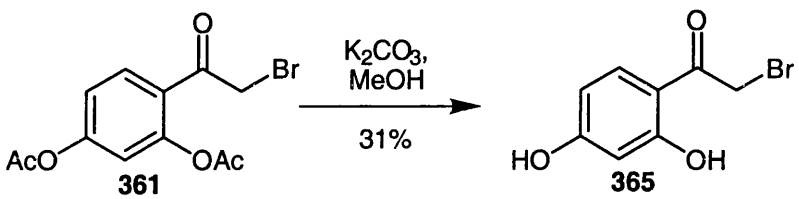
Table 9

Direct treatment of salt **362** with potassium carbonate in methanol (*Table 9*, entry 6) gave, amongst other compounds, a highly UV active product. It is possible that this was chromenone **364**, the result of an intramolecular Wittig reaction with the acetate in the 2-position of **362**.



364

An alternative approach was to deacetylate bromoketone **361** prior to bromide displacement by triphenylphosphine. Deacetylation was carried out using potassium carbonate in methanol (*Scheme 144*) giving bromoketone **365** in low yield. Further reaction of this compound was difficult due to its low solubility in even very polar organic solvents. All attempts to increase solubility (e.g. by silylation), or to form the chalcone by 'one-pot' bromide displacement-Wittig reaction were unsuccessful.



361 **365**

Scheme 144

To summarise, we have completed the synthesis of protected morachalcone A. These protected precursors may be useful in a synthesis of chalcomoracin. Of all the protecting groups tried, the benzyl group looks most promising, although exact conditions for complete debenzylation have yet to be found.

6

Substrate Specificity and Feeding Studies

6.1 Substrate Specificity

It has not yet been conclusively proven that chalcomoracin **91** is produced by an enzymatic Diels-Alder reaction (see Section 1.9.1). Although all existing evidence suggests that this is the case, there has been no demonstration of a diene being incorporated into chalcomoracin. We wished to prove that a diene is involved in chalcomoracin biosynthesis (this shall be discussed later), and to develop an assay for enzyme activity. We also wanted to probe the specificity of the enzyme. At present, the synthesis of diene **96** is long and low yielding. If the enzyme were able to accept a simpler substrate, this would make the development of the assay much easier.

We looked at the synthesis of moracin C **97** to see if we could synthesise simpler structures that would be accepted by the enzyme. The two main simplifications are shown in *Scheme 145*. These simplifications led us to two target compounds for study, 2-prenylresorcinol **366**, and 6-deoxymoracin C **367**.

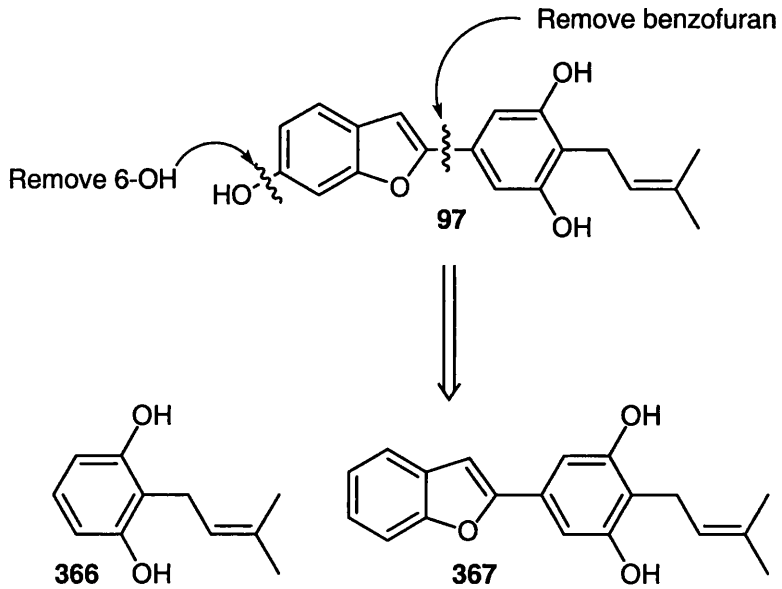
2-Prenylresorcinol **366** is the simplest possible moracin C analogue. Incorporation of **366** into a Diels-Alder adduct would show that the benzofuran moiety was not needed in enzyme binding, and this would mean that simple substrates for the enzyme could be made very easily.

If 6-deoxymoracin C **367** was converted into a Diels-Alder adduct in cell culture, it would show that the 6-hydroxyl was not required for binding to the enzyme. This would be valuable information for three reasons:

i. Synthesis of 6-deoxymoracin C and related substrates would be much quicker.

ii. Any Diels-Alder adducts would be easily distinguishable from natural adducts.

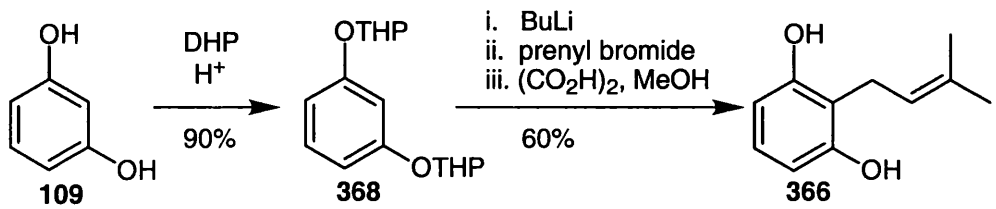
iii. When trying to isolate the enzyme, the 6-hydroxyl could be used to 'tether' diene **96** to an affinity column.



Scheme 145

2-Prenylresorcinol 366

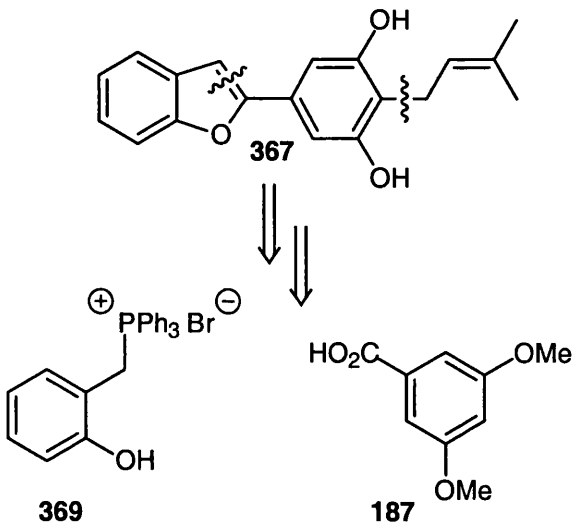
We prepared 2-prenylresorcinol **366** following the method of Nakamura and co-workers (*Scheme 146*).[57] *ortho*-Lithiation of THP-protected resorcinol **368**, followed by immediate deprotection gave the target compound **366** in moderate overall yield.



Scheme 146

6-Deoxymoracin C 367

6-Deoxymoracin C **367** can be made in the same way as moracin C (*Scheme 147*), except that we start from commercially available phosphonium salt **369**, thus shortening the synthesis considerably.

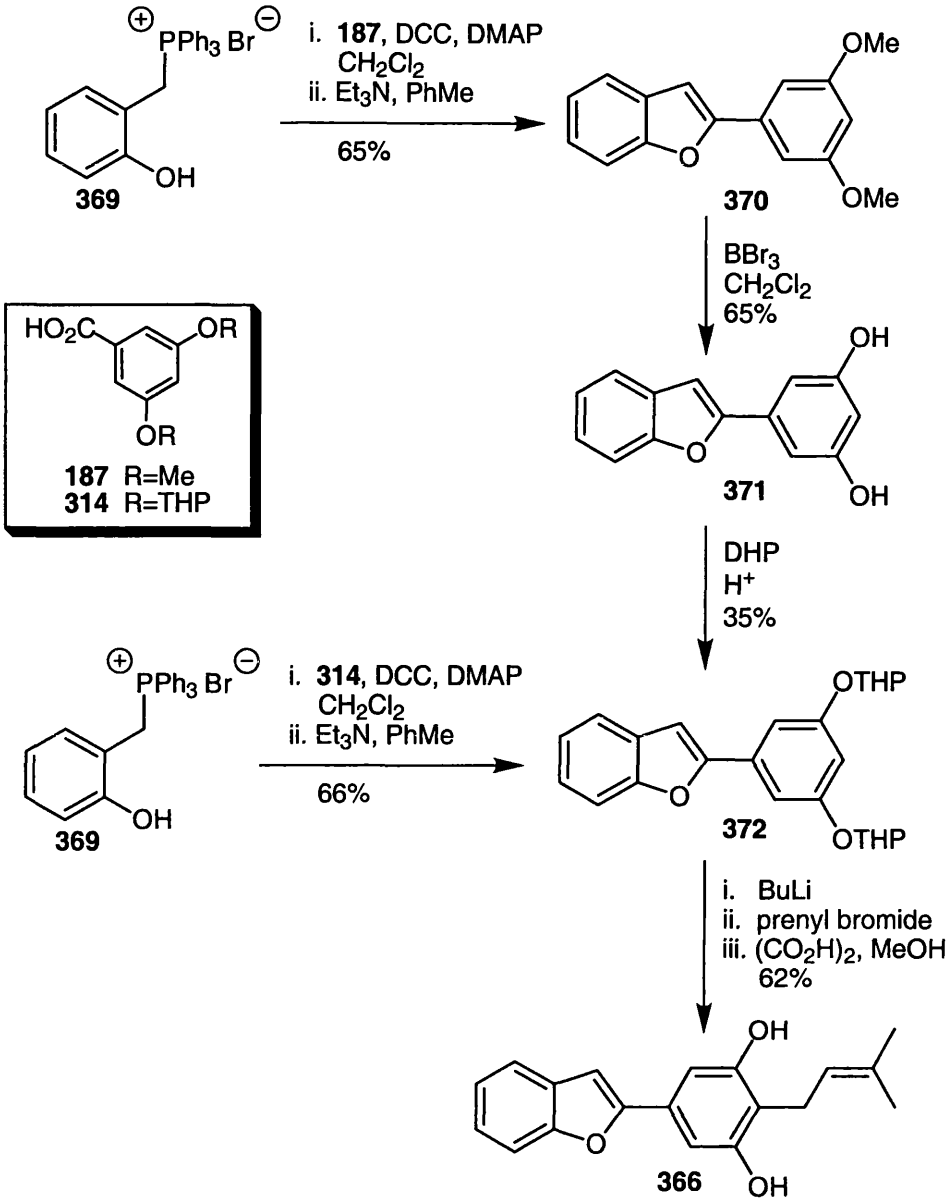


Scheme 147

The synthesis of 6-deoxymoracin C is outlined in *Scheme 148*. Benzofuran **370**, made by standard coupling of phosphonium salt **369** with 3,5-dimethoxybenzoic acid **187**, was demethylated and the product, benzofuran **371**, reprotected with the THP group to give benzofuran **372**.

Demethylation after introducing the prenyl group would require lithium diphenylphosphide. Although such demethylation was successful in our synthesis of moracin C, it was low yielding and required a large excess of the lithium reagent. Removal of THP is generally more efficient.

We later prepared benzofuran **372** by direct coupling of salt **369** and acid **314** (prepared by the THP protection of methyl 3,5-dihydroxybenzoate **225**, followed by alkaline hydrolysis), thus reducing the number of steps. The synthesis was completed by *ortho*-lithiation and prenylation, followed by deprotection. This gave 6-deoxymoracin C in low to moderate yield (9% from acid **187**, 42% from acid **314**).


PPh3 Br
OH
369
i. 187, DCC, DMAP
CH2Cl2
ii. Et3N, PhMe
65%
OMe
OMe
370
BBr3
CH2Cl2
65%
OH
OH
371
DHP
H+
35%
HO2C
OR
OR
187 R=Me
314 R=THP
PPh3 Br
OH
369
i. 314, DCC, DMAP
CH2Cl2
ii. Et3N, PhMe
66%
OTHP
OTHP
372
i. BuLi
ii. prenyl bromide
iii. (CO2H)2, MeOH
62%
OH
OH
366

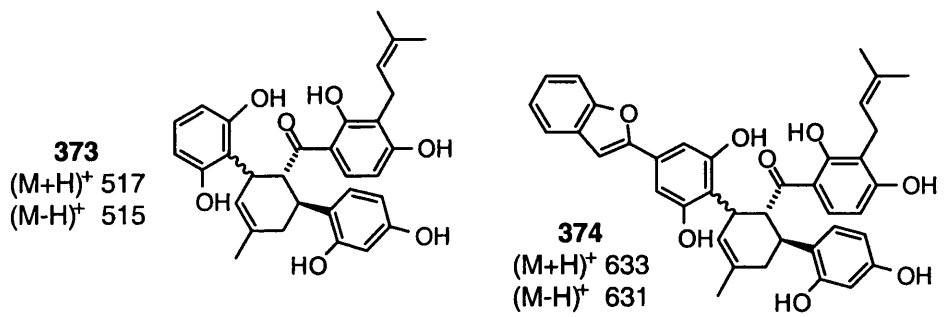
Scheme 148

6.2 Feeding Experiments

We now had the modified substrates we required to probe the specificity of the Diels-Alderase enzyme, and we had a substantial amount of *M. alba* cell cultures (grown by Dr Chris Brett of the University of Glasgow, and Mrs Jyoti Vithlani of GlaxoWellcome). We devised a series of feeding experiments using 2-prenylresorcinol **366** and 6-deoxymoracin C **367**. These substrates were fed to suspensions of *M. alba* cells (approximately 5 mg of substrate per 30 cm^3 of cell suspension) under the conditions outlined in *Table 11*. There were six experiments in all, 3 experiments per substrate. Sampling of the experiments was carried out after 2, 6 and 9 days (see Chapter 10). Analysis was carried out by LCMS by scanning for specific molecular ions [$(M+H)^+$ and $(M-H)^+$] of the desired adducts, **373** and **374**.

	Suspension Solvent	Substrate Addition Solvent
Control	H_2O	No Substrate Added
1.	H_2O	DMSO
2.	H_2O/MS4 Growth Medium	DMSO
3.	H_2O	Aqueous Tween 80

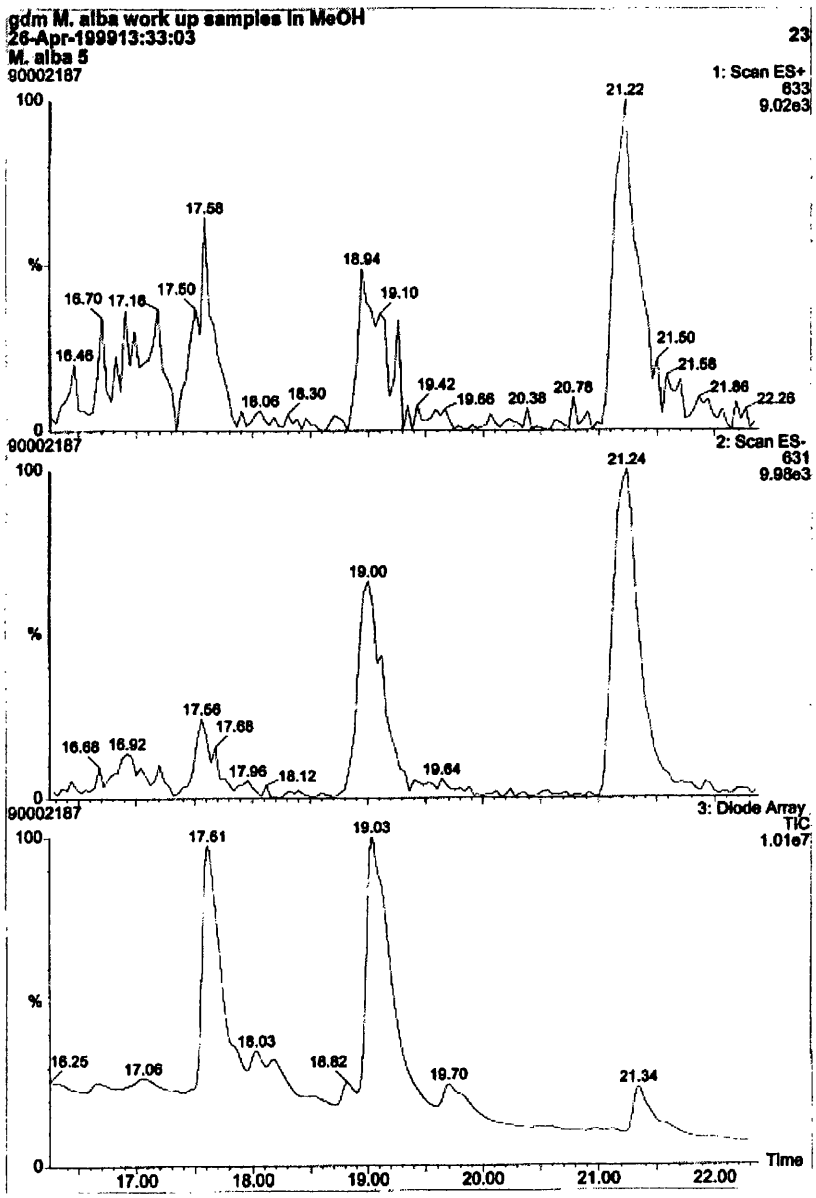
Table 11



The experiments with 2-prenylresorcinol **366** showed little success. This was attributed to the 'over-simplicity' of **366** as a substrate.

The most conclusive results came from two of the 6-deoxymoracin C experiments. After nine days, the experiments using Tween 80 showed the presence of only natural chalcomoracin (by comparison with a substrate-free control experiment), however the other experiments showed the presence of two compounds with the desired molecular ion for deoxychalcomoracin **374**. The LCMS spectrum is shown in *Figure 18.*

Section of the LCMS of Deoxymoracin C Feeding Expt.



ES+
(M+H) scan

ES−
(M-H) scan

Diode Array
HPLC
chromatogram

Figure 18

Dr Andrew Knaggs of GlaxoWellcome isolated chalcomoracin from our cell cultures, using ^{1}H NMR spectroscopy and mass spectromtery for confirmation. We used his results to identify natural chalcomoracin (the main peaks at 18.94-19.03 minutes) in our cell extracts. The peaks at 17.56-17.61 minutes and 21.11-21.34 minutes however, are for species with molecular ions of 633 (M+H) and 631 (M-H), i.e. deoxychalcomoracin. We found that the control experiment contained the peak at 17.56-17.61 minutes, indicating that this particluar species must be a natural compound similar to chalcomoracin. The peak at 21.11-21.34 minutes is not present in the control, however. This suggests that it arises as a result of the fed substrate. The experiments were stopped after 9 days, and the crude extract purified by preparative

HPLC. *Figure 19* shows the HPLC trace of the final crude extract. The peak at 5.08 minutes is natural chalcomoracin, while the band at 7.54 minutes corresponds to the compound we believe to be deoxychalcomoracin **374**. We are awaiting further results to confirm this.

Section of the HPLC of Deoxymoracin C Feeding Expt.

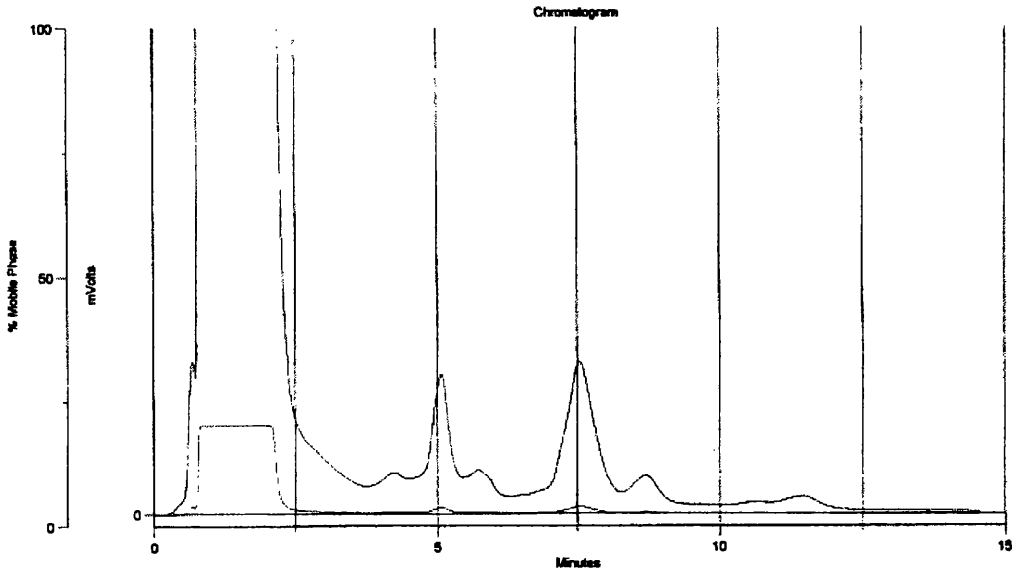


Figure 19

6.3 Conclusions and Outlook

6.3.1 Conclusions

The following has been achieved in this project:

- We have developed the most efficient synthesis of moracin C **97** to date, exploiting an acid-induced acyl migration, which we believe provides a general route to polyphenolic benzofurans.

- We have synthesised, both in protected and fully deprotected forms, the proposed diene **96** involved in the biosynthesis of chalcomoracin.

- Several protected forms of the dienophile, morachalcone A **95** have been made.

- Feeding studies have shown us that 6-deoxymoracin C **367** is a suitable modified substrate; it is easily incorporated into the biosynthesis of Diels-Alder adducts.

6.3.2 Future Aims of the Project

Further development of this work falls into two main areas:

- Continuation of the feeding studies - with the successful incorporation of deoxymoracin C, the next step is to feed the analogous diene to *M. alba*. As we have seen, the synthesis of deoxymoracin C is considerably shorter than that of moracin C, so the corresponding diene should be easy to prepare on a large scale.

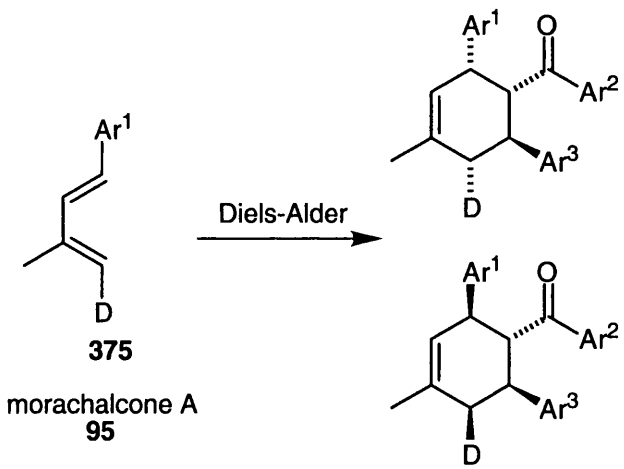
- Synthesis of chalcomoracin - in order to confirm that chalcomoracin is a genuine Diels-Alder adduct, a biomimetic synthesis involving Diels-Alder reaction between diene **96** and morachalcone A **95** must be performed. If too difficult, an alternative route would be to couple protected diene **232** with one of the protected morachalcone A compounds (**337**, **342**, or **353**) and then deprotect.

- At the moment, chalcomoracin extracted from *M. alba* has been purified by crystallisation. This may have increased the enantiopurity of the compound. The exact optical purity of natural chalcomoracin must be determined in order to prove that an enantiomerically pure/enriched adduct is being formed prior to purification.

- Assay - the assay for this Diels-Alderase enzyme will be based on morachalcone A **95** and diene **96**. Cell-free extracts will be used, and the Diels-Alder reaction between **95** and **96** followed, either by analytical HPLC or by UV spectroscopy (the Diels-Alder reaction would break the conjugation of the chalcone). A parallel experiment using denatured enzyme suspension will show the rate of spontaneous cycloaddition. Chiral HPLC will be used to distinguish between spontaneous (racemic) and enzymatic chalcomoracin. Comparison of these experiments should show rate acceleration, enantioselectivity, and confirm incorporation of diene **96** into chalcomoracin.

- Isolation of enzyme - this may be done by affinity chromatography using precursors attached on solid support. Morachalcone A **95** can be attached by the 2,4 or 2"- hydroxyls. Diene **96** can be attached by the 6-hydroxyl which we have shown is not necessary for enzyme binding. If necessary, purification could be attempted using ion-exchange or size-exclusion chromatography.

- Stereospecificity of enzyme - to confirm the stereospecificity of the enzyme with respect to diene **96**, we can feed deuterium-labelled dienes (such as **375**) to cell cultures (*Scheme 149*). We would expect the sole product to be the *endo*-adduct as the *exo*- has never been isolated, but by examining the 3,6 relative stereochemistry of the product, we can confirm on which face of the diene the Diels-Alder reaction occurs.



Scheme 149

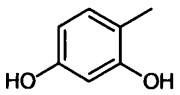
7

Experimental for Chapter 3

General details

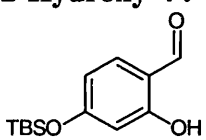
Reagents were purchased from Aldrich Chemical Company (Gillingham, UK) or Lancaster Synthesis (UK) and were used without further purification. Organic solvents were obtained from Rhône-Poulenc-Rorer and were dried, where necessary, using the procedures described by Leonard, Lygo and Procter. Melting points were recorded in open capillaries using a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ with tetramethylsilane as an internal standard on a Bruker AM-200 spectrometer operating at 200 and 50 MHz respectively or on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz respectively, unless otherwise stated. ^{13}C NMR spectra were assigned with the aid of Distortionless Enhancement by Polarisation Transfer (DEPT)-edited spectra. All coupling constants are measured in Hz. Thin layer chromatography was performed using Merck aluminium-backed silica plates of 0.25 mm thickness. Chromatograms were visualised using UV conditions at 254 nm, staining with iodine or using a variety of common stains prepared by the methods described in Leonard, Lygo and Procter. Column chromatography was carried out on silica gel (particle size 70-230 mesh) or deactivated neutral alumina gel (standard grade, ca. 150 mesh). Mass spectra (MS) were recorded on AEI MS12 or MS902 spectrometers using the electron-impact ionisation (EI) mode or, if stated, chemical ionisation (CI) or fast atom bombardment (FAB) modes. Infra-red (IR) spectra were recorded on Nicolet Impact 410 or Jasco FT-IR spectrometer. Combustion analysis was carried out on a Carlo-Erba 1106 elemental analyser.

4-Methyl resorcinol 189



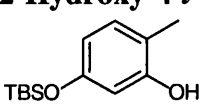
2,4-Dihydroxybenzaldehyde **188** (2.000 g, 14.49 mmol) was dissolved in methanol (20 cm^3) and 10% palladium on carbon added (0.20 g, 10% by mass of catalyst : aldehyde). This mixture was stirred under a hydrogen atmosphere at RT for 15 hours. After this time, the catalyst was removed by filtering twice through Celite®. The methanol was then removed under reduced pressure to leave a grey solid. This was recrystallised from 1:1 toluene:pet. ether to leave **189** as cubes (1.707 g, 13.77 mmol, 95%). m.p.: 100-103 °C (Lit.[121] 105 °C. δ_H(200MHz; CD_3OD): 3.43 (3H, s, -Me), 7.55 (1H, dd, *J* 2.4 and 8.1, 5-H), 7.63 (1H, d, *J* 2.4, 3-H), and 8.18 (1H, d, 8.0, 6-H). The ^{13}C , IR and mass spectra were identical to those reported.[121]

2-Hydroxy-4-*t*-butyldimethylsilyloxybenzaldehyde 190



2,4-Dihydroxybenzaldehyde **188** (3.0 g, 21.74 mmol), *t*-butyldimethylsilyl chloride (3.913 g, 26.09 mmol, 1.2 eq) and imidazole (1.768 g, 26.09 mmol, 1.2 eq) were dissolved in dry DMF (100 cm^3) and stirred under nitrogen at room temperature overnight. The reaction was poured into H_2O (50 cm^3) then extracted into Et_2O (3 × 50 cm^3). The combined extracts were washed with water (50 cm^3) and brine (2 × 50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography in silica (hexane-Et_2O, 1:1) gave the *aldehyde* **190** (4.934 g, 19.58 mmol, 72%) as a colourless oil; R_F[hexane-Et_2O (1:1)] 0.58; υ_{max}(soln)/cm^{-1}: 3256 (OH), 2932 (C-H), 1702 (C=O), 1595 (Ar), 1570 (Ar), 1256 and 841 (Si-C), and 1118 (Si-O); δ_H(200MHz; $CDCl_3$): 0.28 (6H, s, -$SiMe_2$), 0.99 (9H, s, ^{t}Bu), 6.32 (1H, d, *J* 2.2, 3-H), 6.48 (1H, dd, *J* 2.2 and 8.5, 5-H), 7.41 (1H, d, 8.5, 6-H), 9.73 (1H, s, -CHO), and 11.35 (1H, br s, -OH); δ_C(50MHz; $CDCl_3$): –3.95 (CH_3), 18.72 (C), 26.02 (CH_3), 108.02 (CH), 113.46 (CH), 116.22 (C), 135.82 (CH), 164.17 (C), 164.48 (C), and 194.87 (CH); *m/z* (CI) 253 [$(M+H)^+$, 45%]; (Found: *M*, 253.1260. $C_{13}H_{21}O_3Si$ requires 253.1266).

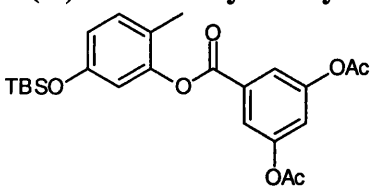
2-Hydroxy-4-*t*-butyldimethylsilyloxytoluene 191



2-Hydroxy-4-*t*-butyldimethylsilyloxybenzaldehyde **190** (0.500 g, 1.98 mmol) was dissolved in methanol (20 cm^3) and 10% palladium on carbon (50 mg, 10% by mass) added. This was stirred under a hydrogen atmosphere for 20 hours. The catalyst was

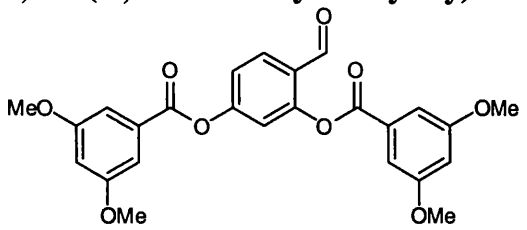
removed by filtering through Celite®, then the solvent was removed under reduced pressure to leave a brown oil. This was purified by column chromatography eluting with 1:1 diethyl ether:hexane to give the *phenol* **191** (0.449 g, 1.88 mmol, 95%) as a colourless oil; R_F[hexane-Et_2O (1:1)] 0.63; υ_{max} (soln)/cm^{-1}: 3602 (-OH), 1590 (Ar), 1571 (Ar), 1256 and 842 (Si-C), and 1106 (Si-O); δ_H(200MHz; $CDCl_3$): 0.26 (6H, s, -$SiMe_2$), 1.10 (9H, s, ^tBu), 2.28 (3H, s, -Me), 5.01 (1H, br s, -OH), 6.47 (2H, m, 3 and 5-H), 7.06 (1H, d, *J* 8.0Hz, 6-H); δ_C(50MHz; $CDCl_3$): -4.48 (CH_3), 15.05 (CH_3), 16.18 (C), 25.67 (CH_3), 107.27 (CH), 112.30 (CH), 116.60 (C), 131.04 (CH), 154.26 (C), and 154.61 (C); *m/z* (EI): 238 (M^+, 30%), 181 (100), and 75 (5); (Found: M^+, 238.1389. $C_{13}H_{22}O_2Si$ requires *M*, 238.1390).

2-(3',5'-Diacetoxybenzoyloxy)-4-*t*butyldimethylsilyloxy toluene 193



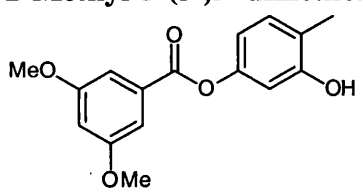
3,5-Diacetoxybenzoic acid **192** (0.5 g, 2.18 mmol) was dissolved in dry CH_2Cl_2 (35 cm^3) and to this was added, sequentially, dimethylaminopyridine (0.043 g, 0.35 mmol, 0.16 eq), 2-hydroxy-4-*t*-butyldimethylsilyloxytoluene **191** (0.702 g, 2.950 mmol, 1.35 eq), and dicyclohexylcarbodiimide (0.567 g, 2.75 mmol, 1.26 eq) in CH_2Cl_2 (5 cm^3). This was stirred at RT under nitrogen for 24 hours. After this time, the white precipitate was filtered off and the organic solution washed well with water and brine (2 × 50 cm^3 each), and then dried (Na_2SO_4). Filtration through a short silica plug to remove baseline material followed by removal of the solvent *in vacuo* left the *ester* **193** (0.520 g, 1.14 mmol, 57%) as a pale yellow oil; R_F[hexane-Et_2O (1:2)] 0.40; υ_{max} (film)/cm^{-1}: 1742 (C=O), 1617 (Ar), 1594 (Ar), 1560 (Ar), 1262 and 841 (Si-C), and 1107 (Si-O); δ_H(200MHz; $CDCl_3$): 0.21 (6H, s, -$SiMe_2$), 0.98 (9H, s, ^tBu), 2.14 (3H, s, -Me), 2.29 (6H, s, -OAc), 6.64 (1H, d, *J* 2.3, 3-H), 6.70 (1H, dd, *J* 2.4 and 8.5, 5-H), 7.10 (1H, d, *J* 8.3, 6-H), 7.23 (1H, t. *J* 2.1, 4'-H), and 7.85 (2H, d, *J* 2.1, 2' and 6'-H); δ_C(50MHz; $CDCl_3$): -4.53 (CH_3), 15.50 (CH_3), 18.13 (C), 20.98 (CH_3), 25.80 (CH_3), 113.62 (CH), 118.02 (CH), 120.77 (CH), 120.78 (CH), 122.60 (C), 131.21 (CH), 131.58 (C), 149.39 (C), 151.05 (C), 154.36 (C), 162.89 (C), and 168.76 (C); *m/z* (CI): 459 [$(M+H)^+$, 20%], 401 (35), 352 (20), 281 (20), 238 (42), 181 (97), and 124 (100); [Found: $(M+H)^+$, 459.1812. $C_{24}H_{31}O_7Si$ requires *M*, 459.1839).

2,4-Di(3',5'-dimethoxybenzoyloxy)benzaldehyde 194



To a solution of 3,5-dimethoxybenzoic acid **187** (3.00 g, 16.5 mmol) in dry CH_2Cl_2 (80 cm^3) under nitrogen was added sequentially: 4-dimethylaminopyridine (0.29 g, 2.4 mmol), 2,4-dihydroxybenzaldehyde **188** (1.03 g, 7.5 mmol) and a solution of dicyclohexylcarbodiimide (3.92 g, 19.0 mmol) in dry CH_2Cl_2 (10 cm^3). The mixture was stirred at RT for 24 h. After this time, dicyclohexylurea was filtered off, and the organic solution washed twice with water, then dried over $MgSO_4$. The solvent was then removed under reduced pressure. Recrystallisation from ethyl acetate gave *aldehyde* **194** (2.910 g, 13.90 mmol, 84%) as needles; m.p. 145-148°C; $R_F(Et_2O)$ 0.45; υ_{max} (KBr)/cm^{-1} 1743 (ester C=O), 1695 (aldehyde C=O), and 1608 (Ar); δ_H(200 MHz, $CDCl_3$) 3.86 (6H, s, 2 × OMe), 3.87 (6H, s, 2 × OMe), 6.74 (1H, t, *J* 2.4 , 4'-H), 6.75 (1H, t, *J* 2.4, 4"-H), 7.31-7.36 (6H, m, Ar-H), 8.03 (1H, d, *J* 7.4, 6-H), and 10.20 (1H, s, CHO); δ_C(50 MHz, $CDCl_3$) 55.61 (2 × CH_3), 106.75 (CH), 106.87 (CH), 107.73 (CH), 107.81 (CH), 117.23 (CH), 120.00 (CH), 125.98 (C), 130.04 (C), 130.32 (C), 131.15 (CH), 153.05 (C), 155.85 (C), 160.79 (C), 160.85 (C), 163.85 (C), 164.33 (C), and 187.20 (CH); *m/z* (EI) 466 (M^+, 23%), and 165 (100); (Found: C, 64.6; H 4.8%; M^+ 466.1253. $C_{25}H_{22}O_9$ requires C 64.37; H 4.75%; *M*, 466.1254).

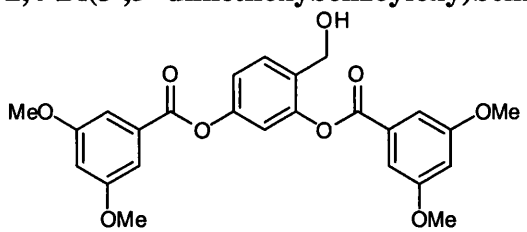
2-Methyl-5-(3',5'-dimethoxybenzoyloxy)phenol 196



Aldehyde **194** (0.100 g, 0.22 mmol) was dissolved in THF (10 cm^3) and cooled to 0°C. To this was added sodium borohydride (0.008 g, 0.22 mmol, 1 eq), and the reaction stirred at 0 °C for 0.5 h. After this time, the reaction mixture was poured into acetic acid (10 cm^3) and extracted into EtOAc (3 × 10 cm^3). The organic solution was washed with water and saturated sodium bicarbonate solution (2 × 10 cm^3 each), dried (Na_2SO_4) and the solvent removed *in vacuo* to leave a colourless oil which crystallised under high vacuum to give *phenol* **196** (0.050 g, 0.19 mmol, 81%) as fine needles: m.p. 88-92 °C; υ_{max} (KBr)/cm^{-1}: 3025 (-OH), 1733 (C=O), 1610 (Ar), and 1597 (Ar); δ_H(200MHz, $CDCl_3$): 2.18 (s, 3H, -Me), 3.81, (6H, s, 2 × -OMe), 6.47 (br s, 1H, -OH), 6.54 (d, 1H, *J* 2.2, 3-H), 6.61 (1H, dd, *J* 2.3 and 8.1, 5-H), 6.69 (1H, t, *J*

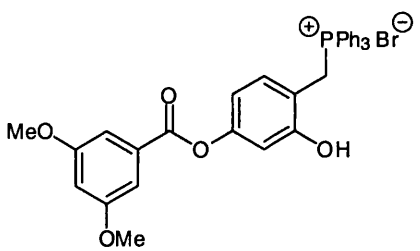
2.3, 4'-H), 7.08 (1H, d, *J* 8.3, 6-H), and 7.29 (2H, d, *J* 2.4, 2' and 6'-H); δ_C(50MHz, $CDCl_3$): 15.36 (CH_3), 55.61 (CH_3), 106.52 (CH), 107.67 (CH), 108.71 (CH), 113.03 (CH), 122.18 (C), 131.77 (CH), 149.50 (C), 150.00 (C), 154.70 (C), 160.68 (C), and 165.90 (C); *m/z* (EI) 288 (M^+, 45%), 165 (100), 137 (35), and 122 (25); (Found: C, 66.7; H 5.7%; M^+, 288.0995. $C_{16}H_{16}O_5$ requires C, 66.67; H, 5.56% ; *M*, 288.0998).

2,4-Di(3',5'-dimethoxybenzoyloxy)benzyl alcohol 197



Sodium cyanoborohydride (0.352 g, 5.60 mmol) was added to a suspension of aldehyde **194** (2.610 g, 5.60 mmol) in THF/H_2O (19:1, 100 cm^3). The solution was acidified to pH 3 with AcOH/THF/c.HCl (10:8:1) whereupon the slurry dissolved. The mixture was stirred at RT for 1 h, quenched with water, then extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous sodium bicarbonate and saturated brine, then dried over $MgSO_4$. The solvent was removed *in vacuo* to give *alcohol* **197** (5.360 g, 5.54 mmol, 99%) as an amorphous solid under vacuum mp 38-40°C. $R_F(Et_2O)$ 0.30; υ_{max} (KBr)/cm^{-1} 3058 (OH), 1739 (C=O), 1609 (Ar), 1596 (Ar), and 1500 (Ar); δ_H(200 MHz, $CDCl_3$) 2.27 (1H, br s, OH), 3.81 (6H, s, 2 × OMe), 3.82 (6H, s, 2 × OMe), 4.62 (2H, s, CH_2), 6.69 (2H, m, 2 × 4'-H), 7.14-7.18 (2H, m, 3- H, 5-H), 7.29 (2H, d, *J* 2.3, 2'-H), 7.30 (2H, d, *J* 2.3, 2'-H), and 7.56 (1H, d, *J* 9.0, 6-H); δ_C(50 MHz, $CDCl_3$) 55.57 (2 × CH_3), 59.71 (CH_2), 106.50 (CH), 106.57 (CH) 107.62 (CH), 107.74 (CH), 116.09 (CH), 119.71 (CH), 129.64 (C), 130.52 (CH), 130.89 (C), 130.96 (C), 148.67 (C), 150.59 (C), 160.72 (C), 160.77 (C), 164.63 (C), and 164.81 (C); *m/z* (EI) 468 (M^+, 5%), 182 (75), 165 (100), and 137 (20); (Found: M^+, 468.1423. $C_{25}H_{24}O_9$ requires *M*, 468.1420).

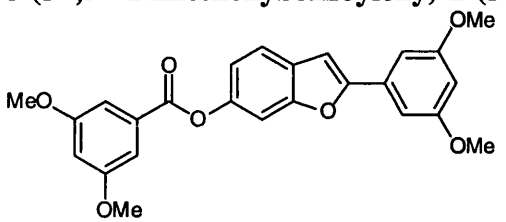
[4-(3',5'-Dimethoxybenzoyloxy)-2-hydroxybenzyl]triphenylphosphonium bromide 200



Alcohol **197** (4.670 g , 9.98 mmol) and triphenylphosphine hydrobromide (3.425 g, 9.98 mmol), were heated under reflux in dry acetonitrile (100 cm^3) under nitrogen for 3 h. The reaction was then allowed to cool to RT and stirred overnight. The

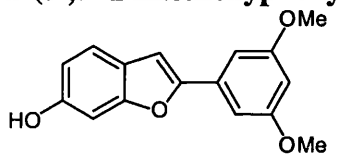
acetonitrile was removed *in vacuo*, and the residue taken up in CH_2Cl_2 (10 cm^3). Slow addition of diethyl ether gave a precipitate which was collected by filtration and recrystallised from ethanol to give *phosphonium salt* **200** (6.219 g, 9.48 mmol, 95%) as plates; m.p. 187-190°C. υ_{max} (KBr)/cm^{-1} 3443 (OH), 1736 (C=O), 1606 (Ar), 1592 (Ar), 1511 (Ar), and 714 (C-P); δ_H(400 MHz, CD_3OD) 3.74 (6H, s, 2 × OMe), 4.69 (2H, br d, *J* 14.0, CH_2-P), 6.45 (1H, s, 3-H), 6.48 (1H, dd, *J* 1.7 and 8.3, 5-H), 6.69 (1H, t, *J* 2.3, 4'-H), 6.88 (1H, dd, *J* 2.7 and 8.3, 6-H), 7.14 (2H, d, *J* 2.3, 2'-H), and 7.54-7.80 (15H, m, 3 × Ph); δ_C(100 MHz, CD_3OD) 25.77 (d, *J* 49.6, CH_2P), 56.56 (CH_3), 107.38 (CH), 109.06 (CH), 110.67 (d, *J* 2.7, CH), 113.52 (d, *J* 8.8, C), 114.67 (d, *J* 3.1, CH), 129.96 (d, *J* 85.7, C), 131.65 (d, *J* 12.5, CH), 132.66 (C), 133.60 (d, *J* 5.0, CH), 135.76 (d, *J* 9.7, CH), 136.71 (d, *J* 2.5, CH), 154.16 (d, *J* 4.0, C), 158.79 (d, *J* 5.0, C), 162.90 (C), and 166.46 (C); δ_P(81 MHz, $CDCl_3$) 21.3; (Found: C, 64.7; H, 4.75%. $C_{34}H_{30}BrO_5P$ requires C, 64.86; H, 4.80).

6-(3'',5''-Dimethoxybenzoyloxy)-2-(3',5'-dimethoxyphenyl)benzo[*b*]furan 201



Dicyclohexylcarbodiimide (0.28 g, 1.35 mmol) in dry CH_2Cl_2 (15 cm^3) was added to a solution of phosphonium salt **200** (0.91 g, 1.45 mmol), 4-dimethylaminopyridine (0.021 g, 0.17 mmol), and 3',5'-dimethoxybenzoic acid **187** (0.20 g, 1.07 mmol) in dry CH_2Cl_2 (50 cm^3) under nitrogen, and the mixture was stirred overnight. The solution was concentrated and the residue dissolved in dioxane (50 cm^3). Triethylamine (0.84 cm^3, 6.03 mmol) was added and the mixture heated under reflux under nitrogen for 12 h. After cooling, the solution was filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, CH_2Cl_2) of the residue gave *benzofuran* **201** (230 mg, 0.803 mmol, 75%) as needles; m.p. 110-113°C; R_F(CH_2Cl_2) 0.25; υ_{max} (soln)/cm^{-1} 1752 (C=O), 1602 (Ar), 1573 (Ar), and 1519 (Ar); δ_H(200 MHz, $CDCl_3$) 3.71 (6H, s, 2 × OMe), 3.74 (6H, s, 2 × OMe), 6.33 (1H, t, *J* 2.2, 4'-H), 6.59 (1H, t, *J* 2.3, 4''-H), 6.85 (1H, s, 3-H), 6.86 (2H, d, *J* 2.2, 2'-H), 6.96 (1H, dd, *J* 2.0 and 8.4, 5-H), 7.24 (2H, d, *J* 2.2, 2''-H), 7.29 (1H, d, *J* 1.8, 7-H), and 7.42 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) 55.39 (CH_3), 55.59 (CH_3), 101.00 (CH), 101.61 (CH), 102.87 (CH), 105.24 (CH), 106.30 (CH), 107.65 (CH), 117.25 (CH), 120.92 (CH), 127.05 (C), 131.28 (C), 131.88 (C), 148.21 (C), 154.60 (C), 156.72 (C), 160.74 (C), 161.06 (C), and 165.16 (C); *m/z* (EI) 434 (M^+, 30%), 165 (100), and 137 (22); (Found: C, 69.0; H 5.1%; M^+, 434.1364. $C_{25}H_{22}O_7$ requires C, 69.10; H, 5.07% ; *M*, 434.1366).

2-(3',5'-Dimethoxyphenyl)-6-hydroxybenzo[*b*]furan 202

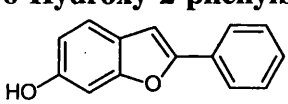


Benzofuran **201** (0.308 g, 0.71 mmol) and potassium hydroxide (0.100 g, 1.71 mmol) were dissolved in ethanol (5 cm^3) and heated under reflux for 2 h. After cooling, the solution was diluted with aqueous NaOH (1 mol dm^{-3}), acidified to pH 2 with aqueous HCl (1 mol dm^{-3}), and then extracted into CH_2Cl_2. The organic solution was washed twice with water, then dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue filtered through a short silica plug (eluting with CH_2Cl_2) to give benzofuran **202** (0.306 g, 0.65 mmol, 92%) as needles; m.p. 114-116°C (lit.[73] 112-115 °C); $R_F(CH_2Cl_2)$ 0.2; υ_{max}(soln)/cm^{-1} 3448 (OH), 1624 (Ar), 1600 (Ar), 1576 (Ar), and 1508 (Ar); δ_H(200 MHz, $CDCl_3$) 3.78 (6H, s, 2 × OMe), 5.42 (1H, br s, OH), 6.37 (1H, t, *J* 2.2, 4'-H), 6.70 (1H, dd, *J* 2.2 and 8.4, 5-H), 6.84 (1H, s, 3-H), 6.88 (2H, d, *J* 2.3, 2'-H), 6.94 (1H, *J* 1.9, d, 7-H), and 7.31 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) 55.48 (CH_3), 98.24 (CH), 100.57 (CH), 101.73 (CH), 102.56 (CH), 112.18 (CH), 121.19 (CH), 122.56 (C), 132.36 (C), 153.93 (C), 154.85 (C), 155.89 (C), and 160.95 (C); *m/z* (EI) 270 (M^+ ,100); (Found: C, 71.1; H 5.3% ; M^+, 270.0983; $C_{16}H_{14}O_4$ requires C, 71.10; H 5.22%; *M*, 270.0982).

2-(3',5'-Dimethoxyphenyl)-6-hydroxybenzo[*b*]furan 202

In a similar way, a solution of acetate **212** (1.230 g, 3.94 mmol) and potassium hydroxide (0.530 g, 9.46 mmol, 2.4 eq) in ethanol-H_2O (5:1, 20 ml) was heated under reflux for 1h and *benzofuran* **202** (0.958 g, 3.550 mmol, 90%) was then obtained following the same work-up procedure.

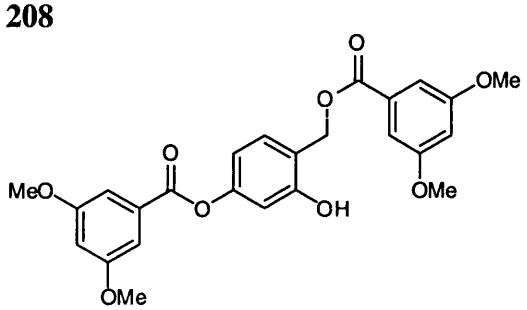
6-Hydroxy-2-phenylbenzo[*b*]furan 203



A solution of dicyclohexylcarbodiimide (0.34 g, 1.64 mmol) in dry CH_2Cl_2 (5 cm^3) was added to a solution of phosphonium salt **200** (1.10 g, 1.75 mmol), 4-dimethylaminopyridine (0.030 g, 0.21 mmol), and benzoic acid (0.16 g, 1.30 mmol) in dry CH_2Cl_2 (20 cm^3), under nitrogen, and the mixture stirred overnight. The solution was concentrated and the residue dissolved in dioxane (20 cm^3). Triethylamine (1.02 cm^3, 7.34 mmol) was added and the reaction heated under reflux under nitrogen for 12 h. After cooling, the solution was filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, CH_2Cl_2) gave crude 6-(3'',5''-dimethoxybenzoyloxy)-2-phenylbenzo[*b*]furan (0.82 g). This crude material was dissolved in EtOH (20 cm^3), KOH (0.12 g, 4.4 mmol) was added and the

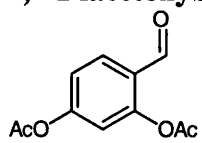
mixture was heated under reflux for 2 h. The reaction was quenched with aqueous NaOH (2.5 mol dm^{-3}), acidified with aqueous HCl (2 mol dm^{-3}) and extracted into CH_2Cl_2. The organic layer was extracted twice with aqueous NaOH (2.5 mol dm^{-3}). The basic aqueous extracts were acidified as before and re-extracted into CH_2Cl_2. The CH_2Cl_2 extract was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was filtered through a short silica column eluting with CH_2Cl_2, the solvent was removed, and the residue was recrystallised from diethyl ether-hexane to give benzofuran **203** (0.90 g, 0.260 mmol, 20%) as pale yellow needles; m.p. 165-170 °C (lit.,[122] 167 °C). δ_H[200 MHz, $(CD_3)_2CO$] 6.83 (1H, dd, *J* 2.1 and 8.4, 4-H), 7.02 (1H, d, *J* 1.9, 2'-H), 7.18 (1H, d, *J* 0.8, 3-H), 7.30-7.50 (4H, m, 5-H and 3 × Ph-H), 7.86 (2H, d, *J* 7.1, 2 × Ph-H), and 8.55 (1H, s, OH); [lit.,[117] 60 MHz, $(CD_3)_2CO$].

[4'-(3'',5''-Dimethoxybenzoyloxy)-2'-hydroxybenzyl]-3,5-dimethoxybenzoate 208



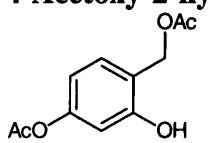
Sodium cyanoborohydride (0.205 g, 3.26 mmol) was added to a suspension of aldehyde **194** (1.520 g, 3.26 mmol) in THF/H_2O (19:1, 75 cm^3). The solution was acidified to pH 3 with AcOH/THF/c.HCl (10:8:1) whereupon the slurry dissolved. The mixture was stirred at RT overnight, quenched with water, then extracted with CH_2Cl_2 (3 × 50 cm^3). The organic layer was washed with saturated aqueous sodium bicarbonate and saturated brine (2 × 50 cm^3 each), and dried ($MgSO_4$). The solvent was removed *in vacuo* to give *phenol* **208** (1.374 g, 2.94 mmol, 90%) as an oil which crystallised under vacuum; m.p. 124-126 °C; $R_F(Et_2O)$ 0.26; υ_{max} (KBr)/cm^{-1} 3380 (OH), 1724 (C=O), 1609 (Ar), 1535 (Ar), and 1467 (Ar); δ_H(200 MHz, $CDCl_3$) 3.83 (6H, s, 2 × OMe), 3.85 (6H, s, 2 × OMe), 5.36 (2H, s, CH_2), 6.67 (1H, t, *J* 2.3, 4''-H or 4-H), 6.71 (1H, t, *J* 2.3, 4-H or 4''-H), 6.80 (1H, dd, *J* 2.3 and 8.2, 5'-H), 6.84 (1H, d, *J* 2.3, 3'-H), 7.20 (2H, d, *J* 2.3, 2''/6''-H or 2/6-H), 7.31 (2H, d, *J* 2.3, 2/6-H or 2''/6''-H), 7.41 (1H, d, *J* 8.2, 6'-H), and 8.39 (1H, br s, OH); δ_C(50 MHz, $CDCl_3$) 56.01 (CH_3), 56.04 (CH_3), 63.85 (CH_2), 106.84 (CH), 106.99 (CH) 107.90 (CH), 108.11 (CH), 111.88 (CH), 114.38 (CH), 119.86 (C), 131.25 (C), 131.57 (C), 133.58 (CH), 153.49 (C), 157.32 (C), 161.08 (C), 161.16 (C), 165.03 (C), and 169.28 (C); *m/z* (FAB) 468 (M^+, 15%), 451 (10), 307 (10), 287 (30), 219 (10), 165 (100), 154 (50), 137 (45), 107 (25), and 73 (12); (Found: C, 64.0; H 5.0%; M^+ 468.1416. $C_{25}H_{24}O_9$ requires C 64.10; H 5.16%; M^+, 468.1420).

2,4-Diacetoxybenzaldehyde 209



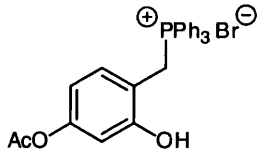
Following the procedure of Malkin and Nierenstein[84] 2,4-dihydroxybenzaldehyde **188** (5.012 g, 36.32 mmol) gave, after recrystallisation from hexane, aldehyde **z209** (7.365 g, 33.05 mmol, 91%) as needles; m.p. 66-68°C (lit., 69-70 °C [84]), our ^{1}H NMR data do not completely correspond to those previously reported;[84] υ_{max} (KBr)/cm^{-1} 1767 (ester C=O), 1753 (ester C=O), 1690 (aldehyde C=O), 1606 (Ar), 1585 (Ar) 1545 (Ar), and 1492 (Ar); δ_H(200 MHz, $CDCl_3$) 2.33 (3H, s, OAc), 2.39 (3H, s, OAc), 7.04 (1H, d, *J* 2.2, 3-H), 7.17 (1H, dd, *J* 2.2 and 8.5, 5-H), 7.95 (1H, d, *J* 8.5, 6-H), and 10.07 (1H, s, CHO); δ_C(50 MHz, $CDCl_3$) 20.66 (CH_3), 21.03 (CH_3), 116.97 (CH), 119.64 (CH), 125.54 (C), 132.06 (CH), 152.23 (C), 155.46 (C), 168.20 (C), 168.78 (C), and 187.50 (CH); *m/z* (CI) 240 [100%, $(M+NH_4)^+$]; *m/z* (EI) 222 (M^+, 5%), 180 (35), 179 (15), 138 (100); (Found: C, 59.5; H, 4.6%. $C_{11}H_{10}O_5$ requires C, 59.46; H 4.54%).

4-Acetoxy-2-hydroxybenzyl acetate 210



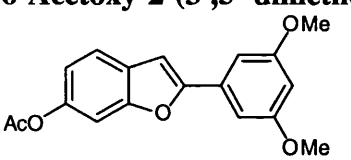
Sodium cyanoborohydride (1.277 g, 20.28 mmol) was added to a stirred solution of aldehyde **209** (3.001 g, 13.52 mmol) in 19:1 THF/H_2O (60 cm^3). The solution was acidified to pH 3 with AcOH-THF-c.HCl (10:8:1). After stirring at RT for 1 h, the mixture was diluted with water (100 cm^3) and extracted into CH_2Cl_2 (3 × 100 cm^3). The organic extract was washed with saturated bicarbonate solution (3 × 100 cm^3) and brine (100 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo* to give *phenol* **210** (2.670 g, 11.92 mmol, 88%) as an oil. R_F[diethyl ether-hexane (2:1)] 0.43; υ_{max} (film)/cm^{-1} 3392 (OH), 1764 (C=O), 1736 (C=O), 1610 (Ar), 1516 (Ar), and 1501 (Ar); δ_H(200 MHz, $CDCl_3$) 2.05 (3H, s, CH_2OAc), 2.23 (3H, s, ArOAc), 5.07 (2H, s, CH_2), 6.57-6.62 (2H, m, 3-H and 5-H), 7.23 (1H, d, *J* 8.9, 6-H), and 8.09 (1H, s, OH); δ_C(50 MHz, $CDCl_3$) 20.80 (CH_3), 20.91 (CH_3), 62.10 (CH_2), 109.97 (CH), 113.23 (CH), 119.78 (C), 131.90 (CH), 151.89 (C), 156.09 (C), 169.85 (C), and 172.95 (C); *m/z* (EI) 224 (M^+, 30%), 182 (30), 164 (20), 122 (100), and 94 (30); (Found: M^+, 224.0862. $C_{11}H_{12}O_5$ requires *M*, 224.0865).

(4-Acetoxy-2-hydroxybenzyl)triphenylphosphonium bromide 211



Triphenylphosphine hydrobromide (1.534 g, 4.47 mmol) was added to a solution of *phenol* **210** (1.002 g, 4.47 mmol) in dry acetonitrile (25 cm^3) under nitrogen and the mixture heated under for 2 h. The solvent was removed *in vacuo* and the residue taken up in CH_2Cl_2 (10 cm^3). Diethyl ether (100 cm^3) was added and the resulting precipitate was filtered off and dried under suction to give the *phosphonium salt* **211** as a white powder (2.231 g, 4.40 mmol, 98%); m.p. 204-206°C; υ_{max}(film)/cm^{-1} 3422 (OH), 1763 (C=O), 1603 (Ar), 1588 (Ar), 1511 (Ar), and 689 (C-P); δ_H(400 MHz, CD_3OD) 2.13 (3H, s, OAc), 4.66 (2H, d, *J* 13.9, -CH_2P), 6.33 (1H, s, 3-H), 6.35 (1H, dd, *J* 2.0 and 8.2, 5-H), 6.82 (1H, dd, *J* 2.8 and 8.2, 6-H), and 7.51-7.79 (15H, m, 3 × Ph); δ_C(100 MHz, CD_3OD) 21.34 (CH_3), 25.73 (d, *J* 49.6, CH_2P), 110.62 (d, *J* 2.9, CH) 113.24 (d, *J* 8.8, C), 114.64 (d, *J* 3.0, CH), 119.96 (d, *J* 85.7, C), 131.64 (d, *J* 12.6, CH), 133.48 (d, *J* 5.1, CH), 135.75 (d, *J* 9.8, CH), 136.69 (d, *J* 2.7, CH), 154.04 (d, *J* 4.0, C), 158.66 (d, *J* 5.0, C), and 171.21 (C); δ_P(81 MHz, $CDCl_3$) 21.67; *m/z* (EI) 262 (100%, $Ph_3P^{\circ+}$), 183 (55), 108 (15); (Found: C, 64.0; H, 4.9; Br, 16.0%. $C_{27}H_{24}BrO_3P$ requires C, 63.91; H, 4.73; Br, 15.80).

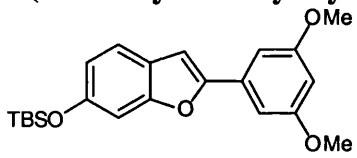
6-Acetoxy-2-(3',5'-dimethoxyphenyl)benzo[*b*]furan 212



Dicyclohexylcarbodiimide (5.398 g, 26.20 mmol) in dry CH_2Cl_2 (15 cm^3) was added to a solution of phosphonium salt **211** (10.544 g, 20.80 mmol), 4-dimethylaminopyridine (0.406 g, 3.33 mmol), and 3,5-dimethoxybenzoic acid **187** (3.823 g, 21.00 mmol) in dry CH_2Cl_2 (200 cm^3) under nitrogen, and the mixture was stirred overnight. The solution was concentrated *in vacuo* and the residue dissolved in dry dioxane (100 cm^3). Triethylamine (16.30 cm^3, 117.71 mmol) was added and the mixture heated under reflux under nitrogen overnight. After cooling, the solution was filtered and the solvent removed *in vacuo*. Flash column chromatography [SiO_2, hexane-diethyl ether (2:1)] of the residue gave *benzofuran* **212** as an amorphous solid (4.874 g, 15.96 mmol, 76%); m.p. 109-110°C; R_F[diethyl ether-hexane (1:2)] 0.21; υ_{max} (film)/cm^{-1} 1753 (C=O), 1652 (Ar), 1602 (Ar), 1573 (Ar), and 1518 (Ar); δ_H(200 MHz, $CDCl_3$) 2.35 (3H, s, OAc), 3.87 (6H, s, 2 × OMe), 6.48 (1H, t, *J* 2.2, 4'-H), 6.99-6.93 (4H, m, 2''-H, 3-H and 5-H), 7.30 (1H, s, 7-H), and 7.58 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) 21.17 (CH_3), 55.47 (CH_3), 100.99 (CH), 101.54

(CH), 102.86 (CH), 105.05 (CH), 117.12 (CH), 120.91 (CH), 126.97 (C), 131.88 (C), 147.90 (C), 154.54 (C), 156.67 (C), 161.04 (C), and 169.78 (C); *m/z* (EI) 312 (M^+, 25%), 270 (100); (Found: M^+, 312.0994. $C_{18}H_{16}O_5$ requires 312.0998).

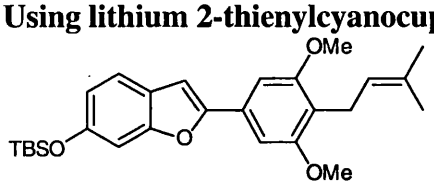
6-(*tert.*-Butyldimethylsilyloxy)-2-(3',5'-dimethoxyphenyl)benzo[*b*]furan 213



A solution of benzofuran **202** (0.105 g, 0.40 mmol), imidazole (0.060 g, 0.80 mmol), and *tert.*-butyldimethylsilylchloride (0.12 g, 0.80 mmol) in dry DMF (5 cm^3) was stirred under nitrogen at RT for 24 h. The mixture was poured into water and extracted into CH_2Cl_2. The organic extract was washed with brine, then with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was filtered through a short silica column (eluting with CH_2Cl_2) to leave the *benzofuran* **213** (0.142 g, 0.372 mmol, 93%) as an oil. $R_F(CH_2Cl_2)$ 0.80. υ_{max} (soln)/cm^{-1} 1600 (Ar), 1570 (Ar), 1508 (Ar), and 1155 (Si-C). δ_H(200 MHz, $CDCl_3$) 0.15 (6H, s, $SiMe_2$), 0.93 (9H, s, Me_3C), 3.77 (6H, s, 2 × OMe), 6.36 (1H, t, *J* 2.2, 4'-H), 6.69 (2H, dd, *J* 2.1 and 8.4, 5-H), 6.84 (1H, s, 3-H), 6.88 (2H, d, *J* 2.3, 2'-H), 6.92 (1H, d, *J* 1.6, 7-H), and 7.30 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) –4.56 (CH_3), 18.22 (C), 25.68 (CH_3), 55.44 (CH_3), 100.57 (CH), 101.65 (CH), 102.51 (CH), 102.81 (CH), 116.74 (C), 120.75 (C), 123.11 (CH), 132.40 (CH), 153.64 (C), 155.06 (C), 155.57 (C), and 161.01 (C); *m/z* (CI) 385 [$(M+H)^+$, 100%]; (Found: M^+ 384.1752. $C_{22}H_{28}O_4Si$ requires *M*, 384.1752).

6-(*tert.*-Butyldimethylsilyloxy)-2-[3',5'-dimethoxy-4'-(3''-methylbut-2''-enyl)phenyl]benzo[*b*]furan 214

Using lithium 2-thienylcyanocuprate



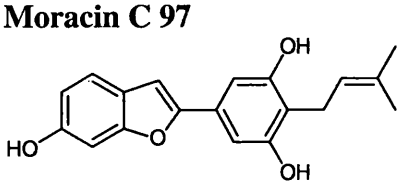
n-Butyllithium (0.85 cm^3, 1.42 mol dm^{-3} solution in hexane, 1.20 mmol) was added over 1 h to a stirred solution of benzofuran **213** (0.307 g, 0.80 mmol) in dry THF (20 cm^3) under nitrogen at –78 °C. The solution was warmed to –30°C, stirred for a further 1 h, and then added *via* canula to a solution of lithium 2-thienylcyanocuprate (4.8 cm^3, 0.25 mol dm^{-3} solution in THF, 1.20 mmol) under nitrogen at –30 °C. After 1 h prenyl bromide (0.14 cm^3, 1.20 mmol, 1.5 eq) was added. The solution was stirred at –30 °C for 2 h, warmed to RT and stirred overnight. The reaction was poured into water and extracted into diethyl ether. The organic solution was washed

twice with brine solution and twice with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. Flash column chromatography [SiO_2, hexane-diethyl ether (4:1)] gave the *benzofuran* **214** (0.250 g, 0.553 mmol, 69%), as an amorphous solid; m.p. 64-67°C. R_F[hexane-diethyl ether (4:1)] 0.50. υ_{max} (soln)/cm^{-1} 1618 (Ar), 1560 (Ar), 1508 (Ar), 1165 (Si-C), and 972 (=C-H). δ_H(200 MHz, $CDCl_3$) 0.30 (6H, s, $SiMe_2$), 1.08 (9H, s, Me_3C), 1.74 (3H, s, =CMe), 1.85 (3H, s, =CMe), 3.43 (2H, d, *J* 7.0, CH_2), 3.95 (6H, s, 2 × OMe), 5.27 (1H, br t, *J* 7.1, CH=), 6.83 (1H, dd, *J* 2.1 and 8.4, 5-H), 6.95 (1H, s, 3-H), 7.05 (2H, s, 2'-H), 7.10 (1H, d, *J* 1.8, 7-H), and 7.42 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) –4.48 (CH_3), 17.69 (CH_3), 18.16 (C), 22.29 (CH_2), 25.65 (CH_3), 29.05 (CH_3), 55.76 (CH_3), 100.30 (CH), 100.69 (CH), 102.74 (CH), 116.57 (CH), 118.70 (C), 120.49 (CH), 122.52 (CH), 123.25 (C), 129.21 (C), 131.28 (C), 153.46 (C), 155.45 (C), 155.52 (C), and 158.15 (C); *m/z* (EI) 452 (M^+, 100%), 437 (117), 395 (12); (Found: M^+, 452.2378. $C_{27}H_{36}O_4Si$ requires 452.2382).

Using copper(ii) bromide-dimethyl sulfide complex

Benzofuran **213** (0.100 g, 0.26 mmol) was dissolved in dry THF (10 cm^3) and cooled to –78 °C under nitrogen. *n*-Butyllithiun (1.06 mol dm^{-3} in hexane, 0.30 cm^3, 0.26 mmol, 1 eq) was added slowly, the solution warmed to –20 °C, then copper bromide-diemthyl sulfate complex (0.040 g, 0.26 mmol, 1 eq) added portionwise over 1 h. Prenyl bromide (0.05 cm^3, 0.38 mmol, 1.45 eq) was added in one portion and the dark green solution stirred at RT overnight. The reaction was poured into water then extracted into Et_2O (3 × 20 cm^3). The combined extracts were washed with water (20 cm^3) and brine (2 × 20 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (4:1 hexane-Et_2O) gave *benzofuran* **214** (0.060 g, 0.14 mmol, 51%) as an amorphous solid; All data matched those reported above.

Moracin C 97



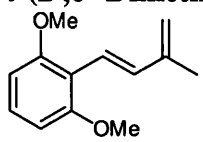
n-Butyllithium (2.83 cm^3, 1.42 mol dm^{-3} in hexane, 4.01 mmol) was added over 1 h to a stirred solution of diphenylphosphine (0.70 cm^3, 4.01 mmol) in dry THF (5 cm^3) at 0°C under nitrogen. Benzofuran **214** (0.302 g, 0.668 mmol) in dry THF (2.5 cm^3) was added and the solution was allowed to warm to RT. The mixture was heated under reflux for 16 h and was then poured into aqueous NaOH (2.5 mol dm^{-3}), acidified with aqueous HCl (2.5 mol dm^{-3}) and extracted into ethyl acetate. The organic extract was dried with Na_2SO_4 and the solvent removed *in vacuo*. Tetrabutylammonium fluoride (4.1 cm^3, 1 mol dm^{-3} in THF, 4.10 mmol) was added

and the resulting solution was stirred under nitrogen at RT overnight. Aqueous acetic acid (2 mol dm^{-3}) was added and the mixture extracted into ethyl acetate. The organic layer was extracted with aqueous NaOH (2.5 mol dm^{-3}). The basic aqueous solution was acidified with HCl (2.5 mol dm^{-3}) and extracted into ethyl acetate. The organic extract was washed with water, dried over Na_2SO_4 and the solvent was removed *in vacuo*. Flash column chromatography [SiO_2, CH_2Cl_2-methanol (9:1)] of the residue gave moracin C **97** (71 mg, 0.227 mmol, 34%) as plates. m.p. 196-198°C. (lit.,[52] 198-199°C); R_F[CH_2Cl_2-MeOH (9:1)] 0.30; υ_{max} (soln)/cm^{-1} 3398 (OH), 1624 (Ar), 1560 (Ar), 1508 (Ar), and 1117 (=C-H); δ_H[200 MHz, $(CD_3)_2CO$] 1.57 (3H, s, =CMe), 1.68 (3H, s, =CMe), 3.37 (2H, d, *J* 7.0, CH_2), 5.15 (1H, br t, *J* 7.0, CH=), 6.79 (1H, dd, *J* 2.0 and 8.3, 5-H), 6.91 (2H, s, 2'-H), 6.95 (1H, s, 3-H), 6.97 (1H, s, 7-H), and 7.22 (1H, d, *J* 8.3, 4-H); *m/z* (EI) 310 (M^+, 67%), 295 (26), 261 (28), 255 (57), 183 (20), 152 (30); (Found: *M*, 310.1202. $C_{19}H_{18}O_4$ requires 310.1205). ^1H NMR matched that reported.[58]

8

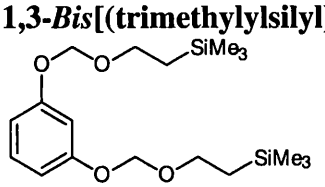
Experimental for Chapter 4

4-(2',6'-Dimethoxyphenyl)-2-methylbuta-1,3-diene 222



1,3-Dimethyoxybenzene **220** (1.90 cm^3, 14.50 mmol) was dissolved in dry THF (20 cm^3) and cooled to –35 °C under nitrogen. *n*-Butyllithium (1.60 mol dm^{-3} in hexane, 10.0 cm^3, 16.00 mmol, 1.1 eq) was added over 15 min, then the bright red solution stirred at –35 °C for 1 h. 3-Methylbut-2-enal **216** (0.92 cm^3, 16.0 mmol, 1.1 eq) was added in one portion and the reaction was warmed to RT then heated at reflux for 4 h. After cooling to RT, the reaction was quenched with water and extracted into Et_2O (3 × 20 cm^3). The combined extracts were washed with water (20 cm^3) and brine (2 × 20 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. This oil was taken up in pyridine (14.00 cm^3, 174.0 mmol, 12 eq) and cooled to 0 °C under nitrogen. Phosphorus oxychloride (1.60 cm^3, 17.40 mmol, 1.2 eq) was added slowly and the yellow slurry stirred at RT overnight. Et_2O (20 cm^3) was added and this solution washed with dilute aqueous HCl (1 mol dm^{-3}, 20 cm^3), water (20 cm^3) and brine (2 × 20 cm^3), then dried ($MgSO_4$). Concentration *in vacuo* followd by chromatography on silica (1:1 hexane/Et_2O) gave the diene **222**[94,87] (2.669 g, 13.08 mmol, 90%) as a bright yellow oil; R_F [hexane-Et_2O (1:1)] 0.72; υ_{max} (film)/cm^{-1} 3009 (=C-H), 1592 (Ar), and 1493 (Ar); δ_H(200 MHz, $CDCl_3$) 2.03 (3H, s, Me), 3.87 (6H, s, 2 × OMe), 5.06 (1H, br s, $=CH_AH_B$), 5.10 (1H, br s, $=CH_ACH_B$), 6.58 (2H, d, *J* 8.4, 3'- and 5'-H), 6.89 (1H, d, *J* 16.5, 3-H), 7.15 (1H, t, *J* 8.4, 4'-H), and 7.36 (1H, d, *J* 16.5, 4-H); δ_C(50 MHz, $CDCl_3$) 18.40 (CH_3), 55.71 (CH_3), 103.92 (CH), 106.13 (C), 116.30 (CH_2), 119.85 (CH), 127.95 (CH), 135.48 (CH), 143.67 (C), and 158.47 (C); *m/z* (EI) 204 (M^+, 70%), 189 (20), 173 (100), 158 (90), 91 (32), 77 (30), and 43 (23); (Found: M^+, 204.1151. $C_{13}H_{16}O_2$ requires *M*, 204.1150).

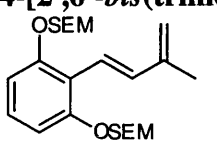
1,3-*Bis*[(trimethylylsilyl)ethoxymethoxy]benzene 223



Resorcinol **109** (0.300 g, 2.70 mmol) was suspended in dry CH_2Cl_2 (5.0 cm^3) under nitrogen. Ethyldiisopropylamine (3.80 cm^3, 21.60 mmol, 8 eq) and (trimethylsilyl)ethoxymethyl chloride (2.40 cm^3, 13.50 mmol, 5 eq) were added and

the solution stirred at RT overnight. The reaction was quenched with water and extracted into Et_2O (3 × 20 cm^3). The combined extracts were washed with dilute aqueous HCl (1 mol dm^{-3}, 20 cm^3) and brine (2 × 20 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (5:1 hexane/Et_2O) gave the *acetal* **223** (0.820 g, 2.21 mmol, 81%) as a colourless oil; R_F [hexane-Et_2O (5:1)] 0.75; υ_{max} (film)/cm^{-1} 1607 (Ar), 1593 (Ar), 1490 (Ar), 1249 and 836 (Si-C); δ_H(400 MHz, $CDCl_3$) 0.04 (18H, s, 2 × $SiMe_3$), 1.00 (4H, t, *J* 7.2, 2 × CH_2Si), 3.75 (4H, t, *J* 7.2, 2 × OCH_2), 5.20 (4H, s, 2 × OCH_2O), 6.69 (2H, dd, *J* 2.3 and 8.2, 4- and 6-H), 6.74 (1H, d, *J* 2.3, 2-H), and 7.17 (1H, t, *J* 8.2, 4-H); δ_C(100 MHz, $CDCl_3$) 0.00 (CH_3), 19.47 (CH_2), 67.59 (CH_2), 94.34 (CH_2), 106.38 (CH), 110.86 (CH), 131.21 (CH), and 159.97 (C); *m/z* (EI) 370 (M^+, 5%), 269 (20), 254 (100), 239 (70), 147 (10), 103 (13), and 73 (75); (Found: M^+, 370.1994. $C_{18}H_{34}O_4Si_2$ requires *M*, 370.1996).

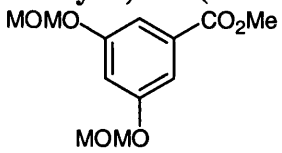
4-[2',6'-*bis*(trimethylylsilyl)ethoxymethoxy]-2-methylbuta-1,3-diene 224



Acetal **223** (0.568 g, 1.54 mmol) was dissolved in dry THF (10 cm^3) and cooled to –35 °C under nitrogen. *n*-Butyllithium (1.38 mol dm^{-3} in hexane, 1.70 cm^3, 2.30 mmol, 1.5 eq) was added over 15 min, then the solution stirred at –35 °C for 30 min. 3-Methylbut-2-enal **216** (0.25 cm^3, 2.30 mmol, 1.5 eq) was added and the reaction was warmed to RT then heated at reflux for 4 h. After cooling to RT, the reaction was quenched with water and extracted into Et_2O (3 × 20 cm^3). The combined extracts were washed with water (10 cm^3) and brine (2 × 10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale brown oil. This oil was taken up in pyridine (1.50 cm^3, 18.42 mmol, 12 eq) and cooled to 0 °C under nitrogen. Phosphorus oxychloride (0.17 cm^3, 1.84 mmol, 1.2 eq) was added slowly and the yellow slurry stirred at RT overnight. Et_2O (20 cm^3) was added and this solution washed with dilute aqueous HCl (1 mol dm^{-3}, 10 cm^3), water (10 cm^3) and brine (2 × 10 cm^3), then dried ($MgSO_4$). Concentration *in vacuo* followd by chromatography on silica (5:1 hexane/Et_2O) gave the diene **224** (0.403 g, 0.92 mmol, 60%) as a dark yellow oil; R_F [hexane-Et_2O (5:1)] 0.60; υ_{max} (soln)/cm^{-1} 1587 (Ar), 1477 (Ar), 1246 and 850 (Si-C); δ_H(400 MHz, $CDCl_3$) 0.02 (18H, s, 2 × $SiMe_3$), 0.90 (4H, t, *J* 7.2, 2 × CH_2Si), 1.97 (3H, s, Me), 3.60 (4H, t, *J* 7.2, 2 × OCH_2), 5.01 (1H, br s, $=CH_ACH_B$), 5.03 (1H, br s, $=CH_ACH_B$), 5.23 (4H, s, 2 × OCH_2O), 6.77 (2H, d, *J* 8.2, 4- and 6-H), 6.79 (1H, d, *J* 16.5, 3-H), 7.05 (1H, t, *J* 8.2, 4-H), and 7.26 (1H, d, *J* 16.5, 4-H); δ_C(100 MHz, $CDCl_3$) 0.00 (CH_3), 19.53 (CH_2), 19.78 (CH_3), 66.34 (CH_2), 94.76 (CH_2), 110.04 (CH), 117.83 (CH_2), 118.47 (C), 121.37 (CH), 129.24

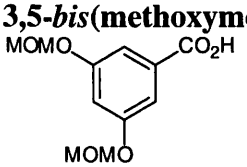
(CH), 137.36 (CH), 144.91 (C), and 157.63 (C); *m/z* (EI) 436 (M^+, 2%), 370 (10), 269 (15), 254 (97), 239 (60), 147 (15), 103 (17), and 73 (100); (Found: M^+, 436.2465. $C_{23}H_{40}O_4Si_2$ requires *M*, 436.2466).

Methyl 3,5-*bis*(methoxymethoxy)benzoate 226



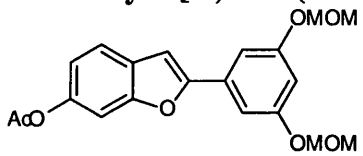
Methyl 3,5-dihydroxybenzoate **225** (8.414 g, 50.08 mmol) and ethyl diisopropylamine (21.5 cm^3, 0.123 mol, 2.46 eq) were dissolved in dry CH_2Cl_2 (60 cm^3) and cooled to 0 °C. Chloromethyl methyl ether (8.20 cm^3, 0.108 mol, 2.16 eq) was added dropwise, then the reaction stirred for 1 hour at RT under nitrogen. The reaction was then poured into saturated sodium bicarbonate, and extracted into CH_2Cl_2 (3 × 100 cm^3). The organic extract was washed with saturated brine (2 × 50 cm^3), dried (K_2CO_3), then poured through a short silica column eluting with dichloromethane. Concentration gave the *ester* **226** (7.950 g, 31.05 mmol, 62%) as a colourless oil; $R_F(CH_2Cl_2)$ 0.42; υ_{max} (film)/cm^{-1}: 1724 (ester C=O), 1597 (Ar), and 1545 (Ar); δ_H(200 MHz, $CDCl_3$): 3.47 (6H, s, 2 × OMe), 3.89 (3H, s, CO_2Me), 5.19 (4H, s, 2 × OCH_2O), 6.92 (1H, t, *J* 2.3, 4-H), and 7.36 (2H, d, *J* 2.3, 2-H and 6-H). δ_C(50 MHz, $CDCl_3$): 52.06 (CH_3), 55.94 (CH_3), 94.22 (CH_2), 109.41 (CH), 110.37 (CH), 131.99 (C), 157.99 (C), and 166.34 (C); *m/z* (EI) 256 (M^+, 100%), and 225 (30); (Found: M^+, 256.0946. $C_{12}H_{16}O_6$ requires *M*, 256.0946).

3,5-*bis*(methoxymethoxy)benzoic acid 227



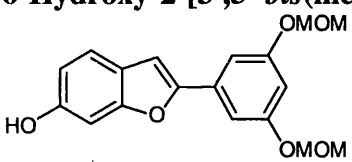
Ester **226** (7.950 g, 31.05 mmol) was dissolved in ethanol (70 cm^3) and to this was added aqueous KOH (4 mol dm^{-3}, 46.5 cm^3). The reaction was left to stir at RT overnight. The reaction was diluted with water (100 cm^3) and carefully acidified to pH 3 with dilute HCl (1 mol dm^{-3}). The white precipitate was filtered and dried under suction. Recrystallisation from ethanol/water gave the *acid* **227** (8.525 g, 35.23 mmol, 70%) as needles. m.p. 106-108°C; R_F[hexane–Et_2O (1:1)] 0.19; υ_{max} (KBr)/cm^{-1}: 3422 (OH), 1697 (C=O), 1655 (Ar), 1637 (Ar), and 1596 (Ar); δ_H(400 MHz, $CDCl_3$) 3.50 (6H, s, 2 × OMe), 5.21 (4H, s, 2 × OCH_2O), 6.98 (1H, t, *J* 2.3, 4-H), and 7.44 (2H, d, *J* 2.3, 2-H and 6-H). δ_C(100 MHz, $CDCl_3$) 56.98 (CH_3), 94.88 (CH_2), 110.89 (CH), 111.65 (CH), 131.67 (C), 158.57 (C), and 171.78 (C); *m/z* (EI) 242 (M^+, 100%), and 212 (10); (Found: C, 54.3; H 5.7%; M^+, 242.0793. $C_{11}H_{14}O_6$ requires C, 54.5; H, 5.8%; *M*, 242.0791).

6-Acetoxy-2-[3',5'-*bis*(methoxymethoxy)phenyl]benzo[*b*]furan 228



Dicyclohexylcarbodiimide (1.130 g, 5.49 mmol, 1.26 eq) in dry CH_2Cl_2 (10 cm^3) was added to a solution of phosphonium salt **211** (2.959 g, 5.84 mmol, 1.34 eq), 4-dimethylaminopyridine (0.085 g, 0.697 mmol, 0.16 eq), and acid **227** (1.054 g, 4.36 mmol, 1 eq) in dry CH_2Cl_2 (50 cm^3) under nitrogen, and the mixture was stirred overnight. The solution was concentrated *in vacuo* and the residue dissolved in dry toluene (50 cm^3). Triethylamine (3.40 cm^3, 24.61 mmol, 5.65 eq) was added and the mixture heated under reflux under nitrogen overnight. After cooling, the solution was filtered and the solvent removed *in vacuo*. Flash column chromatography of the residue followed by recrystallisation from hexane/chloroform gave *benzofuran* **228** (1.278 g, 3.44 mmol, 79%) as needles. m.p. 50-52°C; R_F[hexane–CH_2Cl_2 (1:1)] 0.15; υ_{max} (film)/cm^{-1} 1761 (C=O), 1613 (Ar), 1594 (Ar), and 1568 (Ar); δ_H(400 MHz, $CDCl_3$) 2.28 (3H, s, OAc), 3.48 (6H, s, 2 × OMe), 5.19 (4H, s, 2 × OCH_2O), 6.73 (1H, t, *J* 2.1, 4'-H), 6.93-6.98 (2H, m, 5-H and 7-H), 7.17 (2H, d, *J* 2.1, 2'-H and 6'-H), 7.28 (1H, s, 3-H), and 7.47 (1H, d, *J* 8.4, 4-H); δ_C(100 MHz, $CDCl_3$) 21.43 (CH_3), 56.48 (CH_3), 94.87 (CH_2), 102.19 (CH), 105.54 (CH), 105.63 (CH), 106.60 (CH), 117.59 (CH), 121.30 (CH), 127.33 (C), 132.48 (C), 148.46 (C), 155.01 (C), 156.81 (C), 158.72 (C), and 170.05 (C); *m/z* (EI) 372 (M^+, 100%), 330 (90), and 225 (15); (Found: C, 64.1; H 5.4%; M^+, 372.1210. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%; *M*, 372.1209).

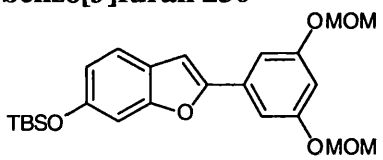
6-Hydroxy-2-[3',5'-*bis*(methoxymethoxy)phenyl]benzo[*b*]furan 229



Benzofuran **228** (0.703 g, 1.89 mmol) and potassium hydroxide (0.254 g, 4.54 mmol, 2.4 eq) were dissolved in ethanol:water (5:1, 10 cm^3) and heated under reflux for 1 h. After cooling, the solution was diluted with water, then carefully acidified to pH 3 with aqueous HCl (1 mol dm^{-3}), and then extracted into CH_2Cl_2 (2 × 50 cm^3). The organic solution was washed with brine (2 × 50 cm^3), then dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue filtered through a short silica plug (eluting with CH_2Cl_2). Recrystallisation from hexane–diethyl ether gave the *benzofuran* **229** (0.370 g, 1.12 mmol, 60%) as pale yellow needles; m.p. 94-96°C; $R_F(CH_2Cl_2)$ 0.16; υ_{max} (film)/cm^{-1} 3398 (OH), 1614 (Ar), 1600 (Ar), and 1577 (Ar); δ_H(400 MHz, $CDCl_3$) 3.48 (6H, s, 2 × OMe), 5.25 (4H, s, 2 × OCH_2O), 6.40 (1H, br

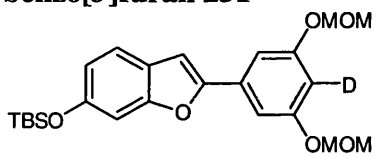
s, OH), 6.70 (1H, t, *J* 2.2, 4'-H), 6.79 (1H, dd, *J* 2.2 and 8.4, 5-H), 6.92 (1H, s, 3-H), 7.01 (1H, d, *J* 1.8, 7-H), 7.15 (2H, d, *J* 2.2, 2'-H), and 7.36 (1H, d, *J* 8.4, 4-H); δ_C(100 MHz, $CDCl_3$) 55.14 (CH_3), 93.45 (CH_2), 97.26 (CH), 100.92 (CH), 103.81 (CH), 104.92 (CH), 111.12 (CH), 120.20 (CH), 121.59 (C), 131.57 (C), 152.89 (C), 153.60 (C), 154.72 (C), and 157.50 (C); *m/z* (EI) 330 (M^+, 100%), and 226 (10); (Found: C, 65.3; H 5.4%; M^+, 330.1102. $C_{18}H_{18}O_6$ requires C, 65.4; H, 5.4% ; *M*, 330.1104).

6-(*tert*-Butyldimethylsilyloxy)-2-[3',5'-*bis*(methoxymethoxy)phenyl] benzo[*b*]furan 230



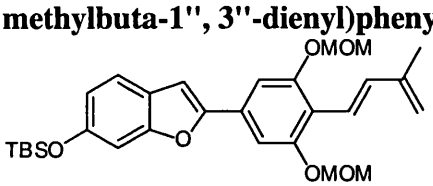
A solution of benzofuran **229** (0.730 g, 2.21 mmol), imidazole (0.376 g, 5.53 mmol, 2.5 eq), and *tert.*-butyldimethylsilylchloride (0.832 g, 5.53 mmol, 2.5 eq) in dry DMF (40 cm^3) was stirred under nitrogen at 60 °C for 24 h. The mixture was poured into water and extracted into Et_2O (3 × 50 cm^3), then the organic extract washed with brine (3 × 50 cm^3), dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was filtered through a short silica column (eluting with CH_2Cl_2) to leave the *benzofuran* **230** (0.974 g, 2.19 mmol, 98%) as a colourless oil; R_F(CH_2Cl_2) 0.56; υ_{max} (film)/cm^{-1} 1613 (Ar), 1569 (Ar), and 1153 (Si-C); δ_H(400 MHz, $CDCl_3$) 0.14 (6H, s, $SiMe_2$), 0.92 (9H, s, Me_3C), 3.40 (6H, s, 2 × OMe), 5.13 (4H, s, 2 × OCH_2O), 6.61 (1H, t, *J* 2.2, 4'-H), 6.68 (1H, dd, *J* 2.1 and 8.4, 5-H), 6.83 (1H, s, 3-H), 6.91 (1H, d, *J* 1.7, 7-H), 7.07 (2H, d, *J* 2.2, 2'-H and 6'-H), and 7.27 (1H, d, *J* 8.4, 4-H). δ_C(100 MHz, $CDCl_3$) –4.03 (CH_3), 18.66 (C), 26.12 (CH_3), 56.46 (CH_3), 94.88 (CH_2), 102.32 (CH), 103.26 (CH), 105.19 (CH), 106.30 (CH), 117.19 (CH), 121.22 (CH), 123.52 (C), 133.00 (C), 154.14 (C), 155.26 (C), 156.08 (C), and 159.02 (C); *m/z* (CI) 445 [100%, $(M+H)^+$], and 444 (25%, M^+); [Found: $(M+H)^+$ 445.2042. Found: M^+ 444.1955. $C_{24}H_{33}O_6Si$ requires *M+H*, 445.2046: $C_{24}H_{33}O_6Si$ requires *M*, 444.1968).

6-(*tert*-Butyldimethylsilyloxy)-2-[4'-deutero-3',5'-*bis*(methoxymethoxy)phenyl] benzo[*b*]furan 231



Benzofuran **230** (0.203 g, 0.458 mmol) was dissolved in dry THF (10 cm^3) and cooled to –78°C. n-Butyllithium (1.415 mol dm^{-3} in hexane, 0.50 cm^3, 6.86 mmol, 1.5 eq) was added over 1 h. The reaction was then stirred at –30 °C for 1 h under nitrogen, then allowed to warm to RT before being quenched with D_2O (20 cm^3) and extracted into Et_2O (2 × 50 cm^3). The organic extract was washed with brine (2 × 50 cm^3), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified on alumina (deactivated with 6% water) to give the *benzofuran* **231** (0.125 g, 0.282 mmol, 82%) as a yellow oil; R_F[CH_2Cl_2–hexane (1:2)] 0.76; υ_{max} (KBr)/cm^{-1} 1620 (Ar), 1606 (Ar), and 1564 (Ar); δ_H(400 MHz, $CDCl_3$) 0.14 (6H, s, $SiMe_2$), 0.92 (9H, s, Me_3C), 3.39 (6H, s, 2 × OMe), 5.11 (4H, s, 2 × OCH_2O), 6.67 (1H, dd, *J* 2.1 and 8.4, 5-H), 6.77 (1H, s, 3-H), 6.91 (2H, s, 2'-H and 6'-H), 7.07 (1H, d, *J* 2.2, 7-H), and 7.26 (1H, d, *J* 8.4, 4-H); δ_C(100 MHz, $CDCl_3$) –4.02 (CH_3), 18.65 (C), 26.12 (CH_3), 56.51 (CH_3), 94.91 (CH_2), 102.28 (CH), 103.26 (CH), 105.03 (C-D, t, *J* 13.6), 106.32 (CH), 117.17 (CH), 121.18 (CH), 123.99 (C), 132.99 (C), 154.12 (C), 155.23 (C), 156.06 (C), and 158.98 (C); *m/z* (EI) 445 (M^+, 100%), and 388 (40); (Found M^+, 445.2030. $C_{24}H_{31}DO_6Si$ requires *M*, 445.2031).

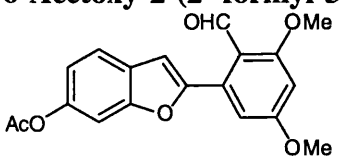
***E*-6-(*tert*-Butyldimethylsilyloxy)-2-[3',5'-*bis*(methoxymethoxy)-4'-(3''-methylbuta-1'', 3''-dienyl)phenyl]benzo[*b*]furan 232**



Benzofuran **230** (0.210 g, 0.473 mmol) was dissolved in dry THF (20 cm^3) and cooled to –78 °C. n-Butyllithiun (1.415 mol dm^{-3} in hexane, 0.50 cm^3, 0.71 mmol, 1.5 eq) was added over 1 h. The reaction was then stirred under nitrogen for 1 h at –30 °C. *N*, *N*'-Dimethylpropyleneurea (0.12 cm^3, 0.946 mmol, 2 eq) was added, followed by 3-methylbutenal (0.070 cm^3, 0.71 mmol, 1.5 eq), and the reaction heated to reflux for 4 h. The reaction was cooled, poured into water, and extracted into Et_2O (3 × 50 cm^3). The organic extract was washed with brine (2 × 50 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil. This oil was dissolved in dry CH_2Cl_2 (2 cm^3) and dry pyridine (0.50 cm^3, 5.68 mmol, 12 eq) and cooled to 0 °C. Phosphorus oxychloride (0.050 cm^3, 0.568 mmol, 1.2 eq) was added slowly, and the reaction stirred overnight under nitrogen. The solution was poured into saturated

sodium bicarbonate and extracted into Et_2O (3 × 50 cm^3). The organic extract was washed with brine (2 × 50 cm^3), dried (Na_2SO_4) and concentrated *in vacuo.* Chromatography of the residue on alumina (deactivated with 6% water) gave the pure product which was recrystallised from propan-2-ol to give the *diene* **232** (0.145 g, 0.284 mmol, 60%) as yellow plates; m.p. 86-89°C; R_F[hexane–CH_2Cl_2 (1:1)] 0.69; υ_{max} (KBr)/cm^{-1} 1618 (Ar), 1601 (Ar), and 1559 (Ar); δ_H(400 MHz, $CDCl_3$) 0.26 (6H, s, $SiMe_2$), 1.01 (9H, s, Me_3C), 2.02 (3H, s, Me), 3.50 (6H, s, 2 × OMe), 5.07 (1H, s, =CH), 5.10 (1H, s, =CH), 5.31 (4H, s, 2 × OCH_2O), 6.76 (1H, dd, *J* 2.1 and 8.4, 5-H), 6.87 (1H, d, *J* 16.5, 2"-H), 6.92 (1H, s, 3-H), 7.01 (1H, d, *J* 1.7, 7-H), 7.25 (2H, s, 2'-H), 7.37 (1H, d, *J* 8.4, 4-H), and 7.38 (1H, d, *J* 16.5, 1"-H); δ_C(100 MHz, $CDCl_3$) -4.00 (CH_3), 18.67 (C), 18.76 (CH_3), 26.13 (CH_3), 56.76 (CH_3), 95.40 (CH_2), 102.31 (CH), 103.28 (CH), 105.23 (CH), 117.22 (CH), 117.38 (CH_2), 120.07 (CH), 121.13 (CH), 123.65 (C), 130.55 (C), 136.69 (CH), 143.98 (C), 154.13 (C), 155.24 (C), 156.12 (C), 156.71 (C), and 159.03 (C); *m/z* (CI) 511 [$(M+H)^+$, 100%], 510 (M^+, 40%), and 445 (20) (Found M^+, 510.2348. $C_{29}H_{36}O_6Si$ requires *M*, 510.2348).

6-Acetoxy-2-(2'-formyl-3', 5'-dimethoxyphenyl)benzo[*b*]furan 297



Phosphorus oxychloride (0.11 cm^3, 1.16 mmol, 1.2 eq) was added dropwise to a flask containing dry DMF (0.20 cm^3, 2.51 mmol, 2.6 eq) at 0 °C. After stirring at RT for 15 min, the resulting complex was slowly added to a solution of 6-acetoxy-2-(3', 5'-dimethoxyphenyl)benzofuran **212** (0.301 g, 0.965 mmol) in dry DMF (0.70 cm^3) at 100 °C under nitrogen. Stirring was maintained at 100 °C and the reaction monitored by TLC. After 1 h, the reaction was cooled to RT, then quenched by pouring into water made slightly alkaline with aqueous $NaHCO_3$. This solution was extracted into EtOAc (3 × 50 cm^3), and the combined extracts washed successively with aqueous HCl (1 mol dm^{-3}, 50 cm^3), water (50 cm^3) and brine (3 × 50 cm^3). The extract was then dried (Na_2SO_4) and concentrated *in vacuo.* Chromatography on silica (5% EtOAc in DCM) followed by recrystallisation from hexane-chloroform gave *aldehyde* **297** (0.183 g, 0.54 mmol, 56%) as pale yellow plates: m.p. 104-106 °C; R_F (5% EtOAc in DCM) 0.36; υ_{max} (KBr)/cm^{-1} 1763 (ester C=O), 1686 (aldehyde C=O), 1597 (Ar), 1568 (Ar), and 1482 (Ar); δ_H(400 MHz, $CDCl_3$) 2.34 (3H, s, OAc), 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 6.54 (1H, d, *J* 2.2, 4'-H), 6.86 (1H, d, *J* 2.2, 6'-H), 6.95 (1H, s, 3-H), 6.99 (1H, dd, *J* 2.0 and 8.4, 5-H), 7.30 (1H, d, *J* 1.3, 7-H), 7.57 (1H, d, *J* 8.4, 4-H), and 10.24 (1H, s, CHO); δ_C(100 MHz, $CDCl_3$) 21.60 (CH_3), 56.17 (CH_3), 56.74 (CH_3), 99.54 (CH), 105.66 (CH), 106.85 (CH),

108.58 (CH), 117.82 (CH), 121.80 (CH), 126.88 (C), 135.87 (C), 148.81 (C), 154.23 (C), 155.28 (C), 161.18 (C), 162.90 (C), 164.47 (C), 170.11 (C), and 189.67 (CH); *m/z* (EI) 340 (M^+ 50%), 298 (100), 254 (45) and 228 (15); (Found M^+, 340.0950. $C_{19}H_{16}O_6$ requires *M*, 340.0947).

Attempted synthesis of 6-*tert*-Butyldimethylsilyloxy-2-(4'-formyl-3',5'-dimethoxyphenyl)-benzo[*b*]furan 298

1. Using DMF

A solution of 6-*tert*-butyldimethylsilyloxy-2-(3', 5'-dimethoxyphenyl)-benzofuran **213** (0.235 g, 0.61 mmol) in dry THF (5 cm^3) under nitrogen was cooled to –78 °C. Over 1 h, *n*-BuLi (1.6M in hexane, 0.60 cm^3, 0.92 mmol, 1.5 eq) was added, then the reaction warmed to –30 °C and stirred for a further 1 h. Dry DMF (0.10 cm^3, 1.22 mmol, 2 eq) was then added, and the reaction heated to reflux for 4 h. After cooling to RT, the reaction was quenched by addition of water, and this aqueous solution extracted with Et_2O (3 × 30 cm^3). The combined extracts were washed with brine (3 × 50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to leave a pale brown oil. ^1H NMR and TLC (1:1 hexane:Et_2O) of this oil showed the presence of only starting material and desilylated material.

2. Using a boronate ester aldehyde equivalent

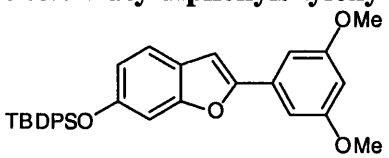
A solution of 6-*tert*-butyldimethylsilyloxy-2-(3', 5'-dimethoxyphenyl)-benzofuran **213** (0.153 g, 0.40 mmol) in dry THF (3 cm^3) under nitrogen was cooled to –35 °C. Over 15 min, *n*-butyllithium (1.44 mol dm^{-3} in hexane, 0.33 cm^3, 0.48 mmol, 1.2 eq) was added, then the reaction stirred for a further 1 h. In a separate flask, a solution of dibromomethaneboronic acid propan-1,3-diol ester **299**[109] (0.100 g, 0.40 mmol, 1 eq) in dry THF (2 cm^3) was cooled to –35 °C. The aryllithium solution was then added dropwise to the boronate solution *via* canula, and allowed to warm slowly to RT. The reaction was the stirred at RT overnight. The reaction was quenched by addition of pH 9.2 phosphate buffer (0.20 cm^3) followed by dropwise addition of 30% H_2O_2 solution (0.10 cm^3). This was stirred for 15 min before being diluted with water. Extraction (Et_2O), washing (brine) and concentration as before gave a pale brown oil, ^1H NMR which showed only starting material and desilylated material.

3. Using paraformaldehyde

A solution of 6-*tert*-butyldimethylsilyloxy-2-(3', 5'-dimethoxyphenyl)-benzofuran **213** (0.179 g, 0.46 mmol) in dry THF (4 cm^3) under nitrogen was cooled to –35 °C. Over 15 min, *n*-butyllithium (1.44 mol dm^{-3} in hexane, 0.36 cm^3, 0.51 mmol, 1.1 eq) was added, then the reaction stirred for a further 1 h at –30 °C. Paraformaldehyde (0.03 g, 0.93 mmol, 2 eq) in THF (1 cm^3) was then added, and the reaction heated to

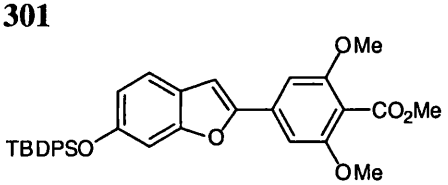
reflux for 4 h. After cooling to RT, the reaction was quenched by addition of water, and the reaction worked up as before to give colourless oil which proved to be starting material.

6-*tert*-Butyldiphenylsilyloxy-2-(3',5'-dimethoxyphenyl)-benzo[*b*]furan 300



A solution of 6-hydroxy-2-(3',5'-dimethoxyphenyl)-benzofuran **202** (0.367 g, 1.36 mmol), imidazole (0.231 g, 3.40 mmol, 2.5 eq) and *tert*-butyldiphenylsilylchloride (0.411 g, 1.49 mmol, 1.1 eq) in dry DMF (1 cm^3) was heated at 50 °C under nitrogen for 16 h. After cooling, the reaction was quenched by addition of saturated aqueous sodium bicarbonate (50 cm^3). This aqueous solution was extracted with $CHCl_3$ (3 × 30 cm^3), and the combined extracts washed well with brine (3 × 50 cm^3), then dried (K_2CO_3) and concentrated *in vacuo* to leave a pale brown oil which solidified on standing. Recrystallisation from methanol gave *benzofuran* **300** (0.329 g, 0.648 mmol, 48%) as plates: m.p. 116-118 °C; R_F [hexane-Et_2O (2:1)] 0.51; υ_{max} (KBr)/cm^{-1} 1619 (Ar), 1598 (Ar), 1571 (Ar), 1257 and 885 (Si-C), and 1150 (Si-O); δ_H(400 MHz, $CDCl_3$) 1.12 (9H, s, *tert*-Bu), 3.86 (6H, s, 2 × OMe), 6.41 (1H, t, *J* 2.2, 4'-H), 6.76 (1H, dd, *J* 2.2 and 8.4, 5-H), 6.87 (1H, s, 3-H), 6.90 (2H, d, *J* 2.2, 2' and 5'-H), 7.26-7.28 (2H, m, 4-H and 7-H), 7.36-7.46 (6H, m, 6 × Ph-H), and 7.75-7.77 (4H, m, 4 × Ph-H); δ_C(100 MHz, $CDCl_3$) 19.47 (C), 26.47 (CH_3), 55.43 (CH_3), 100.56 (CH), 101.62 (CH), 102.41 (CH), 116.35 (CH), 120.59 (CH), 122.83 (C), 127.80 (CH), 129.91 (CH), 132.34 (C), 132.74 (C), 134.77 (CH), 135.51 (CH), 153.59 (C), 154,94 (C), 155.32 (C), and 160.94 (C); *m/z* (CI) 509 [$(M+H)^+$ 100%], 508 (M^+, 30), and 431 (15); (Found: C, 75.5; H, 6.4%; M^+, 508.2063. $C_{32}H_{32}O_4Si$ requires C, 75.51; H, 6.34% ; *M*, 508.2070).

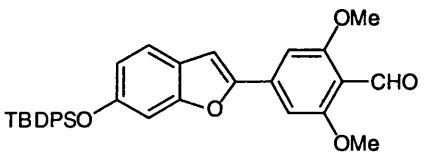
Methyl 4-[(6'-*tert*-butyldiphenylsilyloxybenzofuranyl)-2,6-dimethoxybenzoate 301



A solution of **300** (0.661 g, 1.30 mmol) in dry THF (30 cm^3) was cooled to –30 °C under nitrogen, and to this was added *n*-butyllithium (1.86 mol dm^{-3} in hexane, 0.84 cm^3, 1.56 mmol, 1.2 eq) over 15 min. After stirring at –30 °C for 15 min, methyl chloroformate (0.20 cm^3, 2.60 mmol, 2 eq) was added slowly and the resulting green solution stirred at RT for 2 h. The reaction was poured into saturated brine and

extracted with Et_2O (3 × 50 cm^3), and the combined organic extract washed with water and brine (2 × 50 cm^3 each), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica [hexane-Et_2O (1:2)] gave the *ester* **301** (0.550 g, 0.97 mmol, 75%) as a solid foam: m.p. 60-62 °C; R_F [hexane-Et_2O (1:2)] 0.44; υ_{max} (KBr)/cm^{-1} 1736 (ester C=O), 1609 (Ar), 1567 (Ar), 1488 (Ar), 1269 and 884 (Si-C), and 1155 (Si-O); δ_H(400 MHz, $CDCl_3$) 1.12 (9H, s, *t*-Bu), 3.84 (6H, s, 2 × OMe), 3.90 (3H, s, CO_2Me), 6.80 (1H, dd, *J* 2.0 and 8.4, 5'-H), 6.89-6.91 (4H, m, 3/5-H, 3'-H, and 7'-H), 7.28 (1H, d, *J* 8.4, 4'-H), 7.35-7.45 (6H, m, 6 × Ph-H), and 7.75-7.77 (4H, m, 4 × Ph-H); δ_C(100 MHz, $CDCl_3$) 19.91 (C), 26.91 (CH_3), 52.91 (CH_3), 56.52 (CH_3), 100.53 (CH), 102.90 (CH), 102.97 (CH), 112.80 (C), 117.10 (CH), 121.30 (CH), 123.15 (C), 128.28 (CH), 130.41 (CH), 133.14 (C), 133.79 (C), 135.95 (CH), 154.39 (C), 154.73 (C), 155.89 (C), 158.01 (C), and 167.19 (C); *m/z* (CI) 567 [$(M+H)^+$ 100%], 566 (M^+, 20), and 489 (10); [Found: C, 72.2; H, 6.18%; $(M+H)^+$, 567.2201. $C_{34}H_{34}O_6Si$ requires: C, 72.06; H, 6.05%; $(M+H)^+$, 567.2203].

6-*tert*-Butyldiphenylsilyloxy-2-(4'-formyl-3',5'-dimethoxyphenyl)-benzo[*b*]furan 302



1. By $LiAlH_4$ reduction / Dess-Martin oxidation

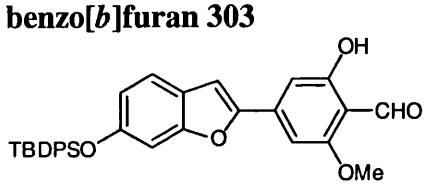
A solution of benzofuran **301** (0.096 g, 0.17 mmol) in dry Et_2O (0.50 cm^3) was added to a suspension of lithium aluminium hydride powder (0.009 g, 0.24 mmol, 1.4 eq) in dry Et_2O (0.50 cm^3) at 0 °C under nitrogen. The reaction was heated at reflux for 4 h then quenched by the addition of water (1.0 cm^3) and dilute aqueous HCl (~0.5 mol dm^{-3}, 1 cm^3). The aqueous slurry was extracted into Et_2O (2 × 20 cm^3), the combined organic extracts washed with brine (2 × 20 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude alcohol as a colourless oil (0.087 g, 0.16 mmol, 95%). This oil was dissolved in dry CH_2Cl_2 (0.60 cm^3) and added to a solution of Dess-Martin periodinane[111] (0.076 g, 0.18 mmol, 1.1 eq) in dry CH_2Cl_2 (0.73 cm^3) under nitrogen. The mixture was stirred at RT for 30 min then diluted with Et_2O (2.0 cm^3), poured into saturated aqueous $Na_2S_2O_4$ solution (5.0 cm^3), and stirred for 10 min. This solution was then extracted with Et_2O (2 × 30 cm^3). The combined organic extracts were washed with brine (3 × 30 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil. Chromatography on silica (2:1 hexane-EtOAc) gave *aldehyde* **302** (0.038 g, 0.07 mmol, 42%) as a pale brown foam: m.p. 55-57 °C; R_F [hexane-EtOAc (2:1)] 0.27; υ_{max} (KBr)/cm^{-1} 1684 (aldehyde C=O), 1604 (Ar), 1556 (Ar), 1487 (Ar), 1279 and 883 (Si-C), and 1156

(Si-O); δ_H(400 MHz, $CDCl_3$) 1.13 (9H, s, *t*-Bu), 3.89 (6H, s, 2 × OMe), 6.83 (1H, dd, *J* 2.0 and 8.4, 5-H), 6.86 (2H, s, 2'-and 6'-H), 6.91 (1H, d, *J* 2.0, 7-H), 7.00 (1H, s, 3-H), 7.31 (1H, d, *J* 8.4, 4-H), 7.36-7.46 (6H, m, 6 × Ph-H), 7.76-7.78 (4H, m, 4 × Ph-H), and 10.46 (1H, s, CHO); δ_C(100 MHz, $CDCl_3$) 19.44 (C), 26.41 (CH_3), 56.07 (CH_3), 99.51 (CH), 102.45 (CH), 104.35 (CH), 113.28 (C), 117.00 (CH), 121.26 (CH), 122.48 (C), 127.85 (CH), 130.00 (CH), 132.51 (C), 135.48 (CH), 137.24 (C), 153.58 (C), 154.48 (C), 155.72 (C), 162.41 (C), and 186.69 (CH); *m/z* (EI) 536 (M^+, 45%), 479 (100), 451 (20), 149 (43), and 69 (43); (Found M^+, 536.2019. $C_{33}H_{32}O_5Si$ requires: *M*, 536.2020).

2. By $LiAlH_4$ reduction / PDC oxidation

A solution of benzofuran **301** (0.230 g, 0.41 mmol) in dry Et_2O (2.50 cm^3) was added to a suspension of lithium aluminium hydride powder (0.022 g, 0.57 mmol, 1.4 eq) in dry Et_2O (2.50 cm^3) at 0 °C under nitrogen. The reaction was heated at reflux for 4 h then quenched by the addition of water (1.0 cm^3) and dilute aqueous HCl (~0.5 mol dm^{-3}, 1 cm^3). The aqueous slurry was extracted into Et_2O (2 × 20 cm^3), the combined organic extracts washed with brine (2 × 20 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude alcohol as a colourless oil (0.196 g, 0.36 mmol, 89%). A mixture of pyridine (0.35 cm^3, 4.37 mmol, 12 eq) and chromium trioxide (0.219 g, 2.19 mmol, 6 eq) were dissolved in dry CH_2Cl_2 (5.0 cm^3) under nitrogen, stirred at 0 °C for 5 min then allowed to warm to RT. A solution of the crude alcohol and Celite® in dry CH_2Cl_2 (1.0 cm^3) was added slowly and the resulting dark orange solution stirred at RT for 3 h. The reaction was quenched by the addition of dilute aqueous HCl (~0.5 mol dm^{-3}, 10 cm^3), and the mixture was then extracted with Et_2O (3 × 50 cm^3). The combined extracts were washed well with brine (3 × 50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. Chromatography on silica (2:1 hexane:EtOAc) gave *aldehyde* **302** (0.090 g, 0.17 mmol, 41%) as a pale brown foam. All data were identical to those reported above.

6-*tert*-Butyldiphenylsilyloxy-2-(3'-hydroxy-4'-formyl-5'-methoxyphenyl)-benzo[*b*]furan 303



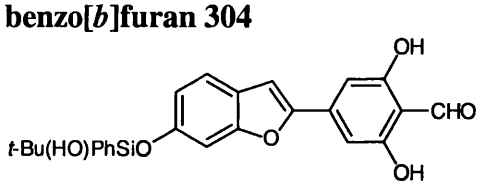
Aldehyde **302** (0.147 g, 0.27 mmol) was dissolved in dry CH_2Cl_2 (3.0 cm^3) and cooled to –78 °C under nitrogen. Boron tribromide (1.10 cm^3, 1 mol dm^{-3} in CH_2Cl_2, 1.10 mmol, 4 eq) was added slowly and the reaction warmed to RT. After 1

h, the reaction was quenched by addition of cold water, the extracted into EtOAc (2 × 20 cm^3). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (10 cm^3) and brine (2 × 20 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give *aldehyde* **303** (0.131 g, 0.25 mmol, 93%) as a pale brown oil; R_F [EtOAc-hexane (2:1)] 0.85; υ_{max} (film)/cm^{-1} 3384 (OH), 1638 (aldehyde C=O), 1619 (Ar), 1487 (Ar), 1281 and 884 (Si-C), and 1156 (Si-O); δ_H(400 MHz, $CDCl_3$) 1.13 (9H, s, *t*-Bu), 3.88 (3H, s, OMe), 6.71 (1H, d, *J* 1.2, 2'-H), 6.89 (1H, dd, *J* 2.0 and 8.5, 5-H), 6.84 (1H, d, *J* 1.2, 6'-H), 6.89 (1H, br s, 7-H), 6.97 (1H, s, 3-H), 7.28 (1H, d, *J* 8.5, 4-H), 7.36-7.44 (6H, m, 6 × Ph-H), 7.75-7.77 (4H, m, 4 × Ph-H), 10.22 (1H, s, CHO), and 12.05 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) 14.17 (C), 26.48 (CH_3), 55.88 (CH_3), 96.93 (CH), 102.48 (CH), 105.10 (CH), 105.13 (CH), 110.13 (C), 117.09 (CH), 121.38 (CH), 122.48 (C), 127.86 (CH), 130.02 (CH), 132.60 (C), 135.51 (CH), 139.44 (C), 153.41 (C), 154.69 (C), 155.90 (C), 162.64 (C), 163.72 (C), and 193.25 (CH); *m/z* (EI) 522 (M^+, 40%), 465 (100), and 387 (10); (Found M^+, 522.1861. $C_{32}H_{30}O_5Si$ requires: *M*, 522.1863).

Demethylation of 6-*tert*-butyldiphenylsilyloxy-2-(4'-formyl-3',5'-dimethoxyphenyl)-benzo[*b*]furan 302

Aldehyde **302** (0.236 g, 0.44 mmol) was dissolved in dry CS_2 (7.0 cm^3) under nitrogen. A solution of $AlBr_3$ (0.353 g, 1.32 mmol, 3 eq) in CH_2Br_2/CS_2 (1:1, 6.0 cm^3) was added slowly and the viscous red slurry stirred at RT overnight. The reaction was quenched with dilute aqueous HCl (3 mol dm^{-3}, 20 cm^3) and Et_2O (20 cm^3) and stirred at RT for 10 min. The two layers were separated and the aqueous solution further extracted into Et_2O (3 × 20 cm^3). The combined organics were washed with brine and water (2 × 20 cm^3 each), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (1:1 EtOAc/hexane) gave two products, **6-(phenyl-*tert*-butylhydroxy)silyloxy-2-(4'-formyl-3',5'-dihydroxyphenyl)benzo[*b*]furan 304** (0.075 g, 0.17 mmol, 38%), and **6-(*tert*-butyldihydroxy)silyloxy-2-(4'-formyl-3',5'-dihydroxyphenyl)benzo[*b*]furan 305** (0.097 g, 0.25 mmol, 57%);

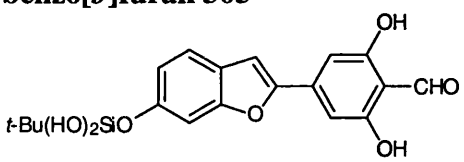
6-(phenyl-*tert*-butylhydroxy)silyloxy-2-(4'-formyl-3',5'-dihydroxyphenyl) benzo[*b*]furan 304



Yellow plates (EtOAc); m.p. 198-200 °C; R_F [hexane-EtOAc (1:1)] 0.70; υ_{max} (KBr)/cm^{-1} 3247 (OH), 1627 (C=O), 1617 (Ar), 1474 (Ar), 1275 and 825 (Si-C), and 1112 (Si-O); δ_H(400 MHz, d_6-acetone) 0.92 (9H, s, *t*-Bu), 6.35 (1H, br s, OH), 6.74

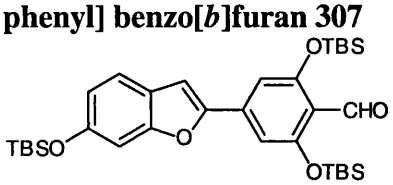
(2H, s, 2'/6'-H), 6.87 (1H, dd, *J* 2.0 and 8.4, 5-H), 7.03 (1H, s, 7-H), 7.16 (1H, s, 3-H), 7.19-7.30 (3H, m, 3 × Ph-H), 7.32 (1H, d, *J* 8.4, 4-H), 7.57-7.63 (2H, m, 2 × Ph-H), 10.17 (1H, s, CHO), and 10.72 (2H, br s, 2 × OH); δ_C(100 MHz, d_6-acetone) 19.61 (C), 26.57 (CH_3), 103.64 (CH), 103.73 (CH), 106.65 (CH), 111.06 (C), 118.45 (CH), 122.95 (CH), 124.10 (C), 128.95 (CH), 131.37 (CH), 134.07 (C), 136.34 (CH), 140.68 (C), 154.68 (C), 155.65 (C), 157.17 (C), 163.83 (C), and 194.55 (CH); *m/z* (EI) 448 (M^+, 80%), 391 (100), 270 (30), 195 (10), and 139 (10); (Found: M^+, 448.1348. $C_{25}H_{24}O_6Si$ requires *M*, 448.1341).

6-(*tert*-Butyldihydroxy)silyloxy-2-(4'-formyl-3',5'-dihydroxyphenyl) benzo[*b*]furan 305



Yellow plates (EtOAc); m.p. 210-212 °C; R_F [hexane-EtOAc (1:1)] 0.33; υ_{max} (KBr)/cm^{-1} 3323 (OH), 1642 (C=O), 1620 (Ar), 1489(Ar), 1279 and 823 (Si-C), and 1115 (Si-O); δ_H(400 MHz, d_6-acetone) 0.94 (9H, s, *t*-Bu), 5.84 (2H, br s, 2 × OH), 6.79 (2H, s, 2'/6'-H), 6.87 (1H, dd, *J* 2.0 and 8.4, 5-H), 7.11 (1H, s, 7-H), 7.22 (1H, s, 3-H), 7.36 (1H, d, *J* 8.4, 4-H), 10.19 (1H, s, CHO), and 10.73 (2H, br s, 2 × OH); δ_C(100 MHz, d_6-acetone) 18.47 (C), 27.00 (CH_3), 103.66 (CH), 106.70 (CH), 111.05 (C), 114.42 (CH), 118.52 (CH), 122.78 (CH), 140.79 (C), 154.59 (C), 155.49 (C), 157.28 (C), 163.87 (C), and 194.56 (CH); *m/z* (EI) 388 (M^+, 2%), and 270 (100); (Found: M^+, 388.1258. $C_{19}H_{20}O_7Si$ requires *M*, 388.1256).

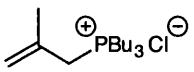
6-*tert*-Butyldimethylsilyloxy-2-[4'-formyl-3',5'-*bis*(*tert*-butyldimethylsilyloxy) phenyl] benzo[*b*]furan 307



Aldehydes **304** (0.033 g, 0.074 mmol) and **305** (0.092 g, 0.24 mmol) were dissolved in dry THF (2.0 cm^3) under nitrogen. TBAF (1 mol dm^{-3} in THF, 1.0 cm^3, 1.00 mmol, 14 eq) were added and the reaction stirred at RT overnight. The solution was then diluted with aqueous HCl (1 mol dm^{-3}, 5 cm^3), then extracted into EtOAc (3 × 10 cm^3). The combined extracts were washed with brine (3 × 10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (0.69 g, 0.26 mmol). This was taken up in dry DMF (1.50 cm^3), imidazole (0.087 g, 1.28 mmol, 5 eq) and *tert*-butyldimethylsilyl chloride (0.192 g, 1.28 mmol, 5 eq) added and the reaction stirred at 60 °C overnight under nitrogen. After cooling to RT, the reaction was

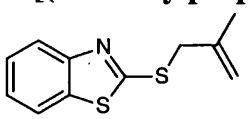
quenched with H_2O (5 cm^3) and extracted into Et_2O (3 × 10 cm^3). The combined extracts were washed with water and brine (2 × 10 cm^3 each), dried ($MgSO_4$) and concentrated *in vacuo* to give crude *aldehyde* **307** (0.114 g, 0.19 mmol, 72%) as a pale yellow oil; R_F [Et_2O-hexane (1:1)] 0.95; δ_H(400 MHz, $CDCl_3$) 0.26 (6H, s, $SiMe_2$), 0.32 (12H, s, 2 × $SiMe_2$), 1.03 (9H, s, ^tBu), 1.05 (18H, s, 2 × ^tBu), 6.80 (1H, dd, *J* 2.0 and 8.4, 5-H), 6.90 (2H, s, 2'/6'-H), 6.98 (1H, s, 3-H), 7.02 (1H, d, *J* 2.0, 7-H), 7.41 (1H, d, *J* 8.4, 4-H) and 10.44 (1H, s, CHO).

Tributylmethallylphosphonium chloride 309



Methallylchloride **308** (3.30 cm^3, 33.44 mmol, 1.01 eq) and tributylphosphine (8.20 cm^3, 33.11 mmol, 1 eq) were dissolved in dry toluene (30 cm^3) under nitrogen and heated under reflux for 1 week. The solution was then cooled to RT, Et_2O (5.0 cm^3) added and the mixture cooled to –10 °C. The precipitate was filtered off, washed with Et_2O and dried under suction to give phosphonium salt **309** (4.863 g, 16.62 mmol, 50%) as very hygroscopic plates;[123] υ_{max} (KBr)/cm^{-1} 3074 (=C-H), 1631 (C=C), 969 (=CH_2), and 798 (C-P); δ_H(400 MHz, $CDCl_3$) 0.90-0.99 (9H, m, 3 × CH_3), 1.50-1.64 (12H, m, 3 × CH_2CH_2), 1.93 (3H, s, CH_3), 2.43-2.60 (6H, m, 3 × CH_2), 3.52 (2H, d, *J* 16.2, CH_2P), 5.15 (1H, d, *J* 5.0, C=CH_AH_B), and 5.17 (1H, d, *J* 5.0, C=CH_AH_B); δ_C(100 MHz, $CDCl_3$) 13.55 (CH_3), 19.21 (d, *J* 46.3, CH_2), 21.33 (d *J* 49.6, CH_2), 23.77 (m, CH_2), 24.69 (CH_3), 28.25 (d, *J* 44.5, CH_2), 119.74 (CH2), and 133.45 (C); *m/z* (EI) 257 (M^+, 40%), 227 (100), 199 (30), 185 (20), 171 (30), 144 (35), 116 (65), 101 (35) and 77 (25); (Found M^+, 257.2390. $C_{16}H_{34}P$ requires: *M*, 257.2399).

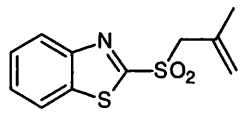
2'-[(2'-Methylprop-2'-enyl)thio]benzothiazole 311



Methallylchloride **308** (6.60 cm^3, 66.41 mmol, 1.1 eq) was added to a stirring suspension of 2-mercaptobenzothiazole **310** (10.083 g, 60.38 mmol, 1 eq) and potassium carbonate (9.165 g, 66.41 mmol, 1.1 eq) in dry acetone (150 cm^3) and the reaction heated to reflux for 5 h. After this time the suspension was cooled to RT, poured into cold water and extracted into Et_2O (3 × 70 cm^3). The combined organic extracts were washed with water and brine (2 × 50 cm^3 each), then dried ($MgSO_4$) and concentrated *in vacuo* to give the sulfide **311** (12.751 g, 57.69 mmol, 96%) as a pale yellow oil: R_F [hexane-Et_2O (1:1)] 0.73; $^1H/^{13}C$ NMR and MS already reported.[106]; δ_H(400 MHz, $CDCl_3$) 1.88 (3H, s, CH_3), 4.00 (2H, s, CH_2), 4.94 (1H, t, *J* 1.2, =CH_AH_B), 5.10 (1H, s, =CH_AH_B), 7.24-7.29 (1H, m, 6-H), 7.37-7.41 (1H, m,

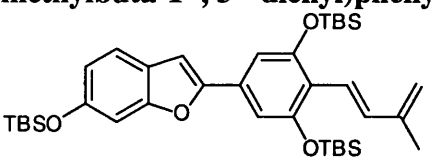
5-H), 7.73 (1H, d with fine splitting, *J* 8.0, 4-H), and 7.87 (1H, d with fine splitting, *J* 8.0, 4-H).
New data: υ_{max} (film)/cm^{-1} 3062 (=CH_2), 1784 (C=N), 1650 (Ar), 1590 (Ar), 1560 (Ar), and 902 (C=C).

2'-[(2'-Methylprop-2-enyl)sulfonyl]benzothiazole 290



2'-[(2'-Methylprop-2-enyl)thio]benzothiazole **311** (12.751 g, 57.69 mmol) was dissolved in aqueous EtOH (95%, 200 cm^3) and cooled to 0 °C. A solution of ammonium molybdate(VI) tetrahydrate (2.638 g, 2.13 mmol, 0.037 eq) in aqueous H_2O_2 (27.5% in water, 167.30 mmol, 2.9 eq) was added and the solution stirred at 0 °C for 18 h. Most of the solvent was removed *in vacuo* and the residue taken up in CH_2Cl_2 (100 cm^3). This was washed with dilute aqueous H_2SO_4 (0.5 mol dm^{-3}, 50 cm^3) and brine (2 × 50 cm^3) then dried ($MgSO_4$). Concentration *in vacuo* followed by recrystallisation from EtOH gave the sulfone **290** (12.862 g, 50.84 mmol, 88%) as pale yellow plates: m.p. 92-94 °C (Lit.[106] 94 °C); R_F [hexane-Et_2O (1:1)] 0.49; $^1H/^{13}C$ NMR, MS(CI), and microanalysis already reported.[106] δ_H(400 MHz, $CDCl_3$) 1.96 (3H, s, CH_3), 4.22 (2H, s, CH_2), 4.92 (1H, t, *J* 1.2, =C*H*$_A$H$_B$), 5.11 (1H, br t, *J* 1.6, =CH$_A$*H*$_B$), 7.58-7.67 (2H, m, 5-H and 6-H), 8.01 (1H, d with fine splitting, *J* 8.0, 4-H), and 8.23 (1H, d with fine splitting, *J* 8.0, 4-H).
New data: υ_{max} (KBr)/cm^{-1} 3063 (=CH_2), 1644 (Ar), 1552 (Ar), 1163 (SO_2), and 989 (C=C).

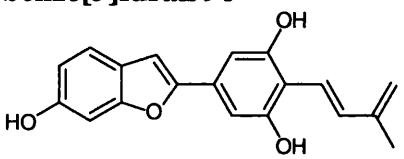
***E*-6-*tert*-Butyldimethylsilyloxy-2-[3',5'-*bis*(*tert*-butyldimethylsilyloxy)-4'-(3''-methylbuta-1'', 3''-dienyl)phenyl] benzo[*b*]furan 312**



A solution of LDA was prepared as follows: Diisopropylamine (0.14 cm^3, 1.00 mmol) was dissolved in dry THF (1.0 cm^3) and cooled to 0 °C under nitrogen. *n*-Butyllithium (1.38 mol dm^{-3} in hexane, 0.72 cm^3, 1.00 mmol) was added slowly and the pale yellow solution stirred at 0 °C for 15 min. In a separate flask, a solution of aldehyde **307** (0.023 g, 0.037 mmol) and sulfone **290** (0.011 g, 0.04 mmol, 1.1 eq) in dry THF (0.5 cm^3) were cooled to –78 °C under nitrogen. The LDA solution (0.10 cm^3, 0.04 mmol, 1.1 eq) was injected slowly then the bright orange solution stiired at –78 °C for 3 h, then warmed to RT and stirred for 1 h. The reaction was quenched with water then extracted into Et_2O (3 × 10 cm^3). The combined organics were

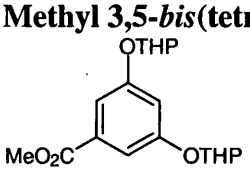
washed with water and brine (10 cm^3 each), then dried (Na_2SO_4) and concentrated *in vacuo* to give the crude *diene* **312** (0.017 g, 0.026 mmol, 71%); R_F [Et_2O-hexane (1:4)] 0.90; δ_H(400 MHz, $CDCl_3$) 0.17 (6H, s, $SiMe_2$), 0.21 (12H, s, 2 × $SiMe_2$), 0.93 (9H, s, ^{t}Bu), 0.96 (18H, s, 2 × ^{t}Bu), 1.90 (3H, s, Me), 4.96 (2H, br s, $=CH_2$), 6.66 (1H, d, *J* 16.8, 1"-H), 6.70 (1H, d,, *J* 2.0 and 8.4, 5-H), 6.76 (1H, s, 3-H), 6.84 (1H, s, 7-H), 7.18 (2H, s, 2'/6'-H), 7.22 (1H, d, *J* 16.8, 2"-H), and 7.29 (1H, d, *J* 8.4, 4-H).

_E_-6-Hydroxy-2-(3',5'-dihydroxy-4'-(3"-methylbuta-1", 3"-dienyl)phenyl benzo[*b*]furan 96



Diene **312** (0.014 g, 0.022 mmol) was dissolved in dry THF (1.0 cm^3), TBAF (1 mol dm^{-3} in THF, 0.14 cm^3, 0.14 mmol, 4 eq) was added slowly, and the dark orange slurry stirred at RT for 2 h. The reaction was quenched with phosphate buffer (pH 7) and extracted into EtOAc (3 × 5 cm^3) then washed with water and brine (10 cm^3 each) and dried (Na_2SO_4). Concentration *in vacuo* gave the crude *diene* **96** (0.003 g, 0.008 mmol, 38%) as a pale yellow oil; ^{1}H NMR indicated c.1% of **96** contaminated with excess TBAF; R_F [hexane-EtOAc (1:3)] 0.66; υ_{max} (soln)/cm^{-1} 3616 (OH), 3001 (=CH), 1682 (Ar), 1598 (Ar), and 1440 (Ar); δ_H(400 MHz, d_6-acetone) 1.81 (3H, s, Me), 4.76 (1H, br s, $=CH_AH_B$), 4.82 (1H, br s, $=CH_AH_B$), 6.72 (1H, s with fine splitting, 7-H), 6.80 (1H, dd, *J* 2.0 and 8.4, 5-H), 6.97 (1H, d, *J* 16.4, 1"-H), 7.17 (1H, d, *J* 8.4, 4-H), 7.39 (1H, s, 3-H), 7.47 (2H, s, 2'/6'-H), 7.52 (1H, d. *J* 16.4, 2"-H), 11.03 (1H, s, OH), and 11.18 (2H, s, 2 × OH).

Methyl 3,5-*bis*(tetrahydropyran-2'-yloxy)benzoate 313

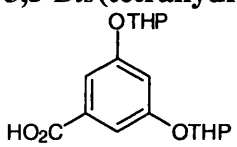


3,4-Dihydro-2*H*-pyran (9.50 cm^3, 103.02 mmol, 4 eq) was cooled to 0°C then 2-3 drops of conc. HCl added. Methyl 3,5-dihydroxybenzoate **225** (4.327 g, 25.76 mmol, 1 eq) was added portion wise over 10 min, then the ice bath removed and the solution stirred at RT. After 3 h, the reaction was diluted with Et_2O (50 cm^3) and washed with saturated aqueous sodium bicarbonate (3 × 20 cm^3), brine (3 × 20 cm^3), then dried (Na_2SO_4) and concentrated *in vacuo* to give a pale brown oil which crystallised on standing. The product was filtered off and washed with hexane and dried under suction. Recrystallisation from hexane gave the ester **313** (7.271 g, 21.63 mmol, 84%) as off-white plates: m.p. 85-86 °C (Lit.[125] 86-88 °C); R_F [hexane-Et_2O

(1:1)] 0.36; ^{1}H NMR already reported.[125] δ_H(400 MHz, $CDCl_3$) 1.56-2.05 (12H, m, 6 × -CH_2-), 3.60-3.64 (2H, m, -OCH_2-), 3.86-3.92 (2H, m, -OCH_2-), 3.88 (3H, m, CO_2Me), 5.44-5.47 (2H, m, 2 × -OCHO-), 6.97 (1H, t, *J* 2.4, 4-H), and 7.37 (2H, d, *J* 2.4, 2-H and 6-H).

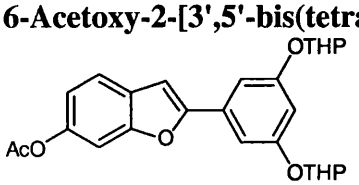
New data: υ_{max} (KBr)/cm^{-1} 1720 (C=O), 1594 (Ar), 1450 (Ar), and 1023 (COC); δ_C(100 MHz, $CDCl_3$) 19.03 (CH_2), 25.53 (CH_2), 30.62 (CH_2), 52.53 (CH_3), 62.37 (CH_2), 96.84 (CH), 110.49 (CH), 111.22 (CH), 132.23 (C), 158.32 (C), and 167.17 (C); *m/z* (EI) 336 (M^+, 2%), 252 (12), 168 (30), 137 (10), 85 (100), and 84 (50); (Found: C, 64.3; H, 7.2%; M^+, 336.1571. $C_{18}H_{24}O_6$ requires C, 64.27; H, 7.19% ; *M*, 336.1573).

3,5-*Bis*(tetrahydropyran-2'-yloxy)benzoic acid 314



Ester **313** (7.271 g, 21.63 mmol) was dissolved in EtOH (60 cm^3). Aqueous potassium hydroxide (4 mol dm^{-3}, 39.0 cm^3, 154.56 mmol, 6 eq) was added and the solution stirred at RT. After 2 h, the reaction was poured into water/$CHCl_3$ (50 cm^3 each), stirred vigorously and carefully acidified with dilute HCl (1 mol dm^{-3}). The $CHCl_3$ layer was removed and the aqueous layer further extracted with $CHCl_3$ (2 × 50 cm^3). the combined organic washings were washed with water (50 cm^3) and brine (2 × 50 cm^3) then dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from MeOH/water gave the *acid* **314** (5.642 g, 17.52 mmol, 81%) as plates: m.p. 114-116 °C; R_F [hexane-Et_2O (1:1)] 0.14; υ_{max} (KBr)/cm^{-1} 3441 (OH), 1694 (C=O), 1593 (Ar), 1451 (Ar), and 1024 (COC); δ_H(400 MHz, $CDCl_3$) 1.56-2.06 (12H, m, 6 × -CH_2-), 3.63-3.64 (2H, m, -OCH_2-), 3.87-3.93 (2H, m, -OCH_2-), 5.46-5.49 (2H, m, 2 × -OCHO-), 7.02 (1H, t, *J* 2.4, 4-H), and 7.43 (2H, d, *J* 2.4, 2-H and 6-H); δ_C(100 MHz, $CDCl_3$) 19.03 (CH_2), 25.51 (CH_2), 30.60 (CH_2), 62.46 (CH_2), 96.83 (CH), 111.26 (CH), 111.79 (CH), 131.45 (C), 158.37 (C), and 171.72 (C); *m/z* (EI) 322 (M^+, 2%), 238 (7), 85 (100), and 84 (35); (Found: C, 63.2; H, 6.9%; M^+, 322.1418. $C_{17}H_{22}O_6$ requires C, 63.34; H, 6.88% ; *M*, 322.1416).

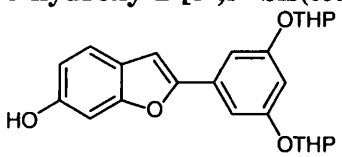
6-Acetoxy-2-[3',5'-bis(tetrahydropyran-2''-yloxy)phenyl]-benzo[*b*]furan 315



Acid **314** (2.643 g, 8.21 mmol, 1 eq) was dissolved in dry CH_2Cl_2 (100 cm^3) under nitrogen. To this was added sequentially, dimethylaminopyridine (0.160 g, 1.31 mmol, 0.16 eq), phosphonium salt **211** (5.576 g, 11.00 mmol, 1.34 eq), and

dicyclohexylcarbodiimide (2.130 g, 10.34 mmol, 1.26 eq) as a solution in dry CH_2Cl_2 (10 cm^3). The resulting slurry was stirred at RT. After 24 h, the solvent was removed *in vacuo* and the residue taken up in dry toluene (100 cm^3). Dry triethylamine (6.50 cm^3, 46.38 mmol, 5.65 eq) was added and the reaction heated to reflux for 6 h. After cooling to RT, the slurry was filtered, the precipitate washed with EtOAc (10 cm^3) and the filtrate concentrated *in vacuo*. Chromatography on silica (hexane-Et_2O, 1:1) gave the *benzofuran* **315** (2.499 g, 5.53 mmol, 67%) as a pale yellow oil: R_F [hexane-Et_2O (1:1)] 0.47; υ_{max} (film)/cm^{-1} 1763 (C=O), 1597 (Ar), 1572 (Ar), and 1020 (COC); δ_H(400 MHz, $CDCl_3$) 1.53-2.04 (12H, m, 6 × -CH_2-), 2.34 (3H, s, OAc), 3.63-3.67 (2H, m, -OCH_2-), 3.91-3.97 (2H, m, -OCH_2-), 5.49-5.51 (2H, m, 2 × -OCHO-), 6.80 (1H, t, *J* 2.0, 4'-H), 6.95-6.98 (2H, m, 3-H and 5-H), 7.19 (2H, d, *J* 2.0, 2-H and 6-H), 7.27 (1H, s, 7-H), and 7.51 (1H, d, *J* 8.4, 4-H); δ_C(100 MHz, $CDCl_3$) 19.05 (CH_2), 21.56 (CH_3), 25.60 (CH_2), 30.72 (CH_2), 62.39 (CH_2), 96.87 (CH), 101.88 (CH), 105.49 (CH), 106.17 (CH), 106.82 (CH), 117.44 (CH), 121.21 (CH), 127.45 (C), 132.20 (C), 148.26 (C), 154.99 (C), 157.21 (C), 158.79 (C), and 170.15 (C); *m/z* (EI) 452 (M^+, 3%), 368 (7), 284 (30), 242 (100), 213 (10), and 85 (32); (Found M^+, 452.1837. $C_{26}H_{28}O_7$ requires *M*, 452.1835).

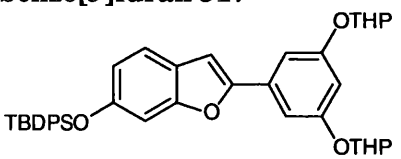
6-hydroxy-2-[3',5'-bis(tetrahydropyran-2''-yloxy)phenyl]-benzo[*b*]furan 316



Benzofuran **315** (2.499 g, 5.53 mmol) was dissolved in EtOH (30 cm^3), aqueous potassium hydroxide (4 mol dm^{-3}, 4.10 cm^3, 16.6 mmol, 3 eq) added, and the solution stirred at RT for 2 h. The dark solution was diluted with water/$CHCl_3$ carefully acidified with dilute HCl (1 mol dm^{-3}). The $CHCl_3$ layer was removed and the aqueous layer further extracted with $CHCl_3$ (2 × 50 cm^3). the combined organic washings were washed with water (50 cm^3) and brine (2 × 100 cm^3) then dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from hexane/EtOAc gave the *benzofuran* **316** (2.042 g, 4.98 mmol, 90%) as off-white plates: m.p. 154-156 °C; R_F [hexane-EtOAc (2:1)] 0.33; υ_{max} (KBr)/cm^{-1} 3244 (OH), 1608 (Ar), 1572 (Ar), and 1016 (COC); δ_H(400 MHz, $CDCl_3$) 1.60-2.08 (12H, m, 6 × -CH_2-), 3.63-3.68 (2H, m, -OCH_2-), 3.92-3.98 (2H, m, -OCH_2-), 5.07 (1H, br s, OH), 5.49-5.52 (2H, m, 2 × -OCHO-), 6.73-6.77 (2H, m, 4'-H and 5-H), 6.89 (1H, s, 3-H), 6.96 (1H, d, *J* 2.0, 7-H), 7.16 (2H, d, *J* 2.4, 2'-H and 6'-H), and 7.36 (1H, d, *J* 8.4, 4-H); δ_C(100 MHz, $CDCl_3$) 19.03 (CH_2), 25.61 (CH_2), 30.72 (CH_2), 62.38 (CH_2), 96.81 (CH), 98.66 (CH), 101.98 (CH), 105.69 (CH), 106.49 (CH), 112.38 (CH), 122.50 (CH), 123.18

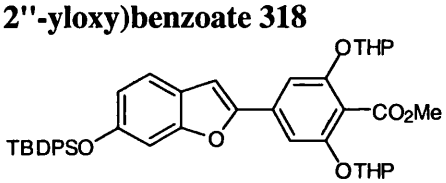
(C), 132.62 (C), 154.06 (C), 155.48 (C), 156.07 (C), and 158.78 (C); *m/z* (EI) 410 (M^+, 3%), 326 (7), 242 (100), 213 (10), and 85 (21); (Found: C, 69.9; H, 6.4%; M^+, 410.1732. $C_{24}H_{26}O_6$ requires C, 70.23; H, 6.38% ; *M*, 410.1730).

6-(*t*-Butyldiphenylsilyloxy)-2-[3',5'-bis(tetrahydropyran-2''-yloxy)phenyl]-benzo[*b*]furan 317



Benzofuran **316** (4.350 g, 10.61 mmol), imidazole (1.082 g, 15.91 mmol, 1.5 eq) and *t*-butyldiphenylchlorosilane (3.30 cm^3, 12.73 mmol, 1.2 eq) were dissolved in dry DMF (50 cm^3) and stirred at 50 °C under nitrogen. After 24 h, the reaction was cooled to RT then quenched by pouring into water. The aqueous solution was extracted with Et_2O (3 × 100 cm^3), washed with water (2 × 100 cm^3) and brine (3 × 100 cm^3), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on alumina (deactivated with 6% w/w H_2O, hexane-Et_2O, 1:1) gave the *benzofuran* **317** (5.310 g, 8.19 mmol, 77%) as a pale yellow oil; R_F [hexane-Et_2O (1:1)] 0.57; υ_{max} (KBr)/cm^{-1} 1612 (Ar), 1570 (Ar), 1487 (Ar), 1278 and 882 (Si-C), and 1156 (Si-O); δ_H(400 MHz, $CDCl_3$) 1.12 (9H, s, *t*Bu), 1.55-2.00 (12H, m, 6 × -CH_2-), 3.60-3.62 (2H, m, -OCH_2-), 3.88-3.93 (2H, m, -OCH_2-), 5.45-5.47 (2H, m, 2 × -OCHO-), 6.74-6.76 (2H, m, 4'-H and 5-H), 6.84 (1H, s, 3-H), 6.90 (1H, br s, 7-H), 7.11 (2H, d, *J* 2.0, 2'-H and 6'-H), 7.24 (1H, d, *J* 8.4, 4-H), 7.34-7.43 (6H, m, 6 × Ph-H), and 7.74-7.76 (4H, m, 4 × Ph-H); δ_C(100 MHz, $CDCl_3$) 19.08 (CH_2), 19.94 (C), 25.65 (CH_2), 26.99 (CH_3), 32.03 (CH_2), 62.35 (CH_2), 96.81 (CH), 102.00 (CH), 102.98 (CH), 105.66 (CH), 106.54 (CH), 116.75 (CH), 120.98 (CH), 123.42 (C), 128.26 (CH), 130.37 (CH), 132.67 (C), 133.28 (C), 135.98 (CH), 153.98 (C), 155.56 (C), 155.83 (C), and 158.83 (C); *m/z* (EI) 648 (M^+, 2%), 564 (30), 480 (40), 423 (100), 345 (10), and 199 (40); (Found: C, 73.6; H, 7.0%; M^+, 648.2908. $C_{40}H_{44}O_6Si$ requires C, 74.04; H, 6.84% ; *M*, 648.2907).

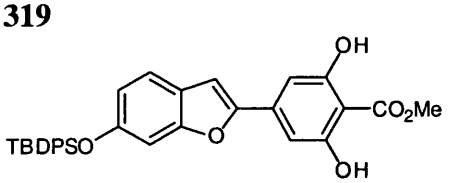
Methyl 4-[(6'-*tert*-butyldiphenylsilyloxybenzofuranyl)-2,6-bis(tetrahydropyran-2''-yloxy)benzoate 318



Benzofuran **317** (1.449 g, 2.24 mmol) was dissolved in dry THF (20 cm^3) and cooled to –30 °C under nitrogen. *n*-Butyllithium (2.15 mol dm^{-3}, 1.25 cm^3, 2.68 mmol, 1.2 eq) was added slowly, then the resulting yellow solution stirred at –30 °C

for 15 min. Methyl chloroformate (0.26 cm^3, 3.35 mmol, 1.5 eq) was added and the reaction warmed to RT then heated to reflux for 2 h. After cooling to RT, the reaction was quenched by pouring into water, and this aqueous solution then extracted with Et_2O (3 × 20 cm^3). The combined organic layers were washed with water (2 × 20 cm^3) and brine (3 × 20 cm^3) then dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on alumina (deactivated with 6% w/w H_2O, hexane-Et_2O, 2:1) gave the *ester* **318** (1.538 g, 2.18 mmol, 97%) as a pale yellow foam: m.p. 56-58 °C; R_F [hexane-Et_2O (2:1)] 0.27; υ_{max} (KBr)/cm^{-1} 1736 (C=O), 1609 (Ar), 1567 (Ar), 1487 (Ar), 1269 and 881 (Si-C), and 1156 (Si-O); δ_H(400 MHz, $CDCl_3$) 1.12 (9H, s, *t*Bu), 1.56-1.97 (12H, m, 6 × -CH_2-), 3.60-3.62 (2H, m, -OCH_2-), 3.87-3.94 (2H, m, -OCH_2-), 3.91 (3H, s, CO_2Me), 5.58-5.60 (2H, m, 2 × -OCHO-), 6.76 (1H, dd, *J* 2.0 and 8.4, 5-H), 6.84 (1H, s, 3-H), 6.89 (2 × 1H, 2 overlapping s, 3-H and 7-H), 7.20 (2H, s, 2'- and 6'-H), 7.25 (1H, d, *J* 8.4, 4-H), 7.32-7.44 (6H, m, 6 × Ph-H), and 7.74-7.76 (4H, m, 4 × Ph-H); δ_C(100 MHz, $CDCl_3$) 18.46 (CH_2), 19.91 (C), 25.62 (CH_2), 26.94 (CH_3), 30.40 (CH_2), 52.49 (CH_3), 61.92 (CH_2), 96.45 (CH), 96.58 (CH), 103.02 (CH), 105.04 (CH), 115.22 (C), 116.95 (CH), 121.13 (CH), 123.25 (C), 128.25 (CH), 130.37 (CH), 133.18 (C), 133.63 (C), 135.95 (CH), 154.23 (C), 154.83 (C), 155.11 (C), 155.93 (C), and 167.01 (C); *m/z* (EI) 706 (M^+, 2%), 538 (50), 481 (100), 449 (40), 300 (35), 242 (37), 85 (50), and 44 (40); (Found: M^+, 706.2964. $C_{42}H_{46}O_8Si$ requires *M*, 706.2962).

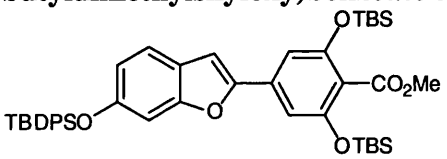
Methyl 4-[(6'-*tert*-butyldiphenylsilyloxybenzofuranyl)-2,6-dihydroxy benzoate 319



Benzofuran **318** (0.103 g, 0.14 mmol) was dissolved in 95% aqueous MeOH (2.0 cm^3), 5% aqueous oxalic acid (1.0 cm^3) added and the reaction stirred at RT overnight, during which time a white precipitate had formed. Most of the solvent was then removed under reduced pressure and the residue taken up in $CHCl_3$ (10 cm^3). The organic solution was washed with water (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from EtOH gave the ester **319** (0.059 g, 0.11 mmol, 75%) as off-white needles: m.p. 139-141 °C; R_F [hexane-Et_2O (1:1)] 0.28; υ_{max} (KBr)/cm^{-1} 3436 (OH), 1635 (C=O chelated to hydroxyl), 1642 (Ar), 1622 (Ar), 1592 (Ar), 1257 and 883 (Si-C), and 1157 (Si-O); δ_H(400 MHz, $CDCl_3$) 1.12 (9H, s, *t*Bu), 4.08 (3H, s, CO_2Me), 6.77 (1H, dd, *J* 2.1 and 8.5, 5-H), 6.89 (3H, 2 overlapping s, 2'/6'-H and 7-H), 6.99 (1H, s, 3-H), 7.29 (1H, d, *J* 8.5, 4-H), 7.36-7.46 (6H, m, 6 × Ph-H), 7.73-7.76 (4H, m, 4 × Ph-H), and

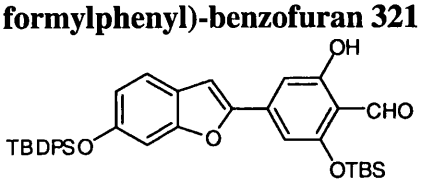
9.72 (2H, br s, 2 × OH); δ_C(100 MHz, $CDCl_3$) 19.50 (C), 26.51 (CH_3), 52.89 (CH_3), 99.09 (C), 102.54 (CH), 103.91 (CH), 104.69 (CH), 116.88 (CH), 121.18 (CH), 122.50 (C), 127.86 (CH), 130.01 (CH), 132.64 (C), 135.53 (CH), 137.93 (C), 138.12 (C), 153.27 (C), 154.48 (C), 155.81 (C), and 169.63 (C); *m/z* (EI) 538 (M^+, 50%), 481 (100), 449 (50), 371 (10), 224 (15), and 44 (18); (Found: C, 71.2; H, 5.5%; M^+, 538.1813. $C_{32}H_{30}O_6Si$ requires; C, 71.36; H, 5.61%; *M*, 538.1811).

Methyl 4-[(6'-*tert*-butyldiphenylsilyloxybenzofuranyl)-2,6-bis(*tert*-butyldimethylsilyloxy)benzoate 320



Benzofuran **319** (0.152 g, 0.28 mmol), imidazole (0.077 g, 1.13 mmol, 4 eq) and *t*-butyldimethylchlorosilane (0.128 g, 0.85 mmol, 3 eq) were dissolved in dry DMF (3 cm^3) and stirred at 50 °C under nitrogen. After 24 h, the reaction was cooled to RT then quenched by pouring into water. The aqueous solution was extracted with Et_2O (3 × 10 cm^3), washed with water (2 × 10 cm^3) and brine (3 × 10 cm^3), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica (hexane-Et_2O, 1:1) gave the *benzofuran* **320** (0.187 g, 0.24 mmol, 86%) as a colourless oil; R_F [hexane-Et_2O (1:1)] 0.67; υ_{max} (film)/cm^{-1} 1736 (C=O), 1607 (Ar), 1557 (Ar), 1265 and 840 (Si-C), and 1156 (Si-O); δ_H(400 MHz, $CDCl_3$) 0.30 (12H, s, 2 × $SiMe_2$), 1.02 (18H, s, 2 × ^{t}Bu), 1.16 (9H, s, *t*Bu), 3.87 (3H, s, CO_2Me), 6.77 (1H, dd, *J* 2.1 and 8.4, 5-H), 6.86 (1H, s, 3-H), 6.88 (2H, s, 2'- and 6'-H), 7.01 (1H, d, *J* 1.8, 7-H), 7.28 (1H, d, *J* 8.4, 4-H), 7.39-7.49 (6H, m, 6 × Ph-H), and 7.79-7.81 (4H, m, 4 × Ph-H); δ_C(100 MHz, $CDCl_3$) –4.37 (CH_3), 17.99 (C), 19.47 (C), 25.48 (CH_3), 26.47 (CH_3), 51.92 (CH_3), 102.17 (CH), 102.63 (CH), 107.31 (CH), 116.47 (CH), 118.98 (C), 120.56 (CH), 122.73 (C), 127.79 (CH), 129.92 (CH), 132.58 (C), 132.77 (C), 134.49 (CH), 138.44 (C), 153.81 (C), 154.17 (C), 155.60 (C), and 166.65 (C); *m/z* (CI) 767 [$(M+H)^+$, 100%], 735 (15), 709 (20), and 689 (10); [Found: $(M+H)^+$, 767.3619. $C_{44}H_{59}O_6Si_3$ requires $(M+H)^+$, 767.3620).

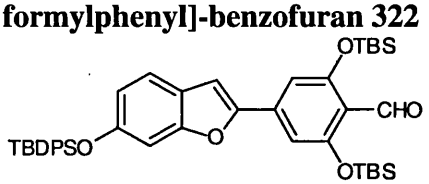
6-(*t*-Butyldiphenylsilyloxy)-2-(3'-*tert*-butyldimethylsilyloxy-3'-hydroxy-4'-formylphenyl)-benzofuran 321



Lithium aluminium hydride (0.056 g, 1.47 mmol, 1.5 eq) was suspended in dry Et_2O (8.0 cm^3) under nitrogen and cooled to 0 °C. Ester **320** (0.750 g, 0.98 mmol) in dry

Et_2O (8.0 cm^3) was added slowly, and the resulting slurry stirred at RT for 1.5 h. The solution was then cooled to 0 °C then H_2O (10 cm^3) added slowly. The two layers were separated and the aqueous solution further extracted into Et_2O (3 × 30 cm^3). The combined organics were washed with dilute aqueous HCl (1 mol dm^{-3}, 10 cm^3) and brine (2 × 10 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then taken up in dry $CH2Cl_2$ (8.0 cm^3), activated MnO_2 (0.256 g, 2.94 mmol, 3 eq) added, and the resulting black suspension stirred for 2 h at RT under nitrogen. After this time, further MnO_2 (0.170 g, 1.99 mmol, 2 eq) added and the reaction stirred at RT overnight. TLC showed the presence of remaining alcohol, so further MnO_2 (0.17 g, 1.98 mmol, 2 eq) was added and stirring continued for a further 12 h. The slurry was then filtered and the filtrate concentrated *in vacuo*. Chromatography on silica eluting with diethyl ether-hexane (1-1) gave the *aldehyde* **321** (0.302 g, 0.49 mmol, 50%) as a yellow oil; R_F [hexane-Et_2O (1:1)] 0.78; υ_{max} (film)/cm^{-1} 3072 (OH), 1643 (C=O), 1620 (Ar), 1590 (Ar), 1282 and 834 (Si-C), and 1157 (Si-O); δ_H(400 MHz, $CDCl_3$) 0.31 (6H, s, $SiMe_2$), 1.01 (9H, s, ^{t}Bu), 1.17 (9H, s, *t*Bu), 6.68 (1H, d, *J* 1.2, 6'-H), 6.74 (1H, dd, *J* 2.1 and 8.5, 5-H), 6.88 (1H, s, 3-H), 6.90 (1H, d, *J* 1.8, 7-H), 6.97 (1H, d, *J* 1.2, 2'-H), 7.30 (1H, d, *J* 8.5, 4-H), 7.34-7.44 (6H, m, 6 × Ph-H), 7.70-7.75 (4H, m, 4 × Ph-H), 10.25 (1H, s, CHO), and 11.88 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) –4.23 (CH_3), 18.37 (C), 21.50 (C), 25.69 (CH_3), 26.49 (CH_3), 102.63 (2 × CH), 105.05 (CH), 105.51 (CH), 112.79 (C), 117.02 (CH), 121.22 (CH), 122.48 (C), 127.85 (CH), 130.01 (CH), 132.64 (C), 135.69 (CH), 139.38 (C), 153.31 (C), 154.67 (C), 156.05 (C), 159.60 (C), 163.75 (C), and 193.62 (CH); *m/z* (CI) 623 [$(M+H)^+$, 100%], and 595 (10); [Found: $(M+H)^+$, 623.2641. $C_{37}H_{43}O_5Si_2$ requires $(M+H)^+$, 623.2649).

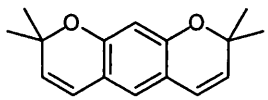
6-(*t*-Butyldiphenylsilyloxy)-2-[3',5'-bis(*tert*-butyldimethylsilyloxy)-4'-formylphenyl]-benzofuran 322



Aldehyde **321** (0.031 g, 0.05 mmol) was dissolved in dry CH_2Cl_2 (1.0 cm^3) under nitrogen. Dry Et_3N (0.05 cm^3, 0.36 mmol, 7 eq) was added followed by *tert*-butyldimethylsilyl triflate (0.08 cm^3, 0.36 mmol, 7 eq) then the yellow solution stirred at RT for 2 h. The reaction was quenched with water then extracted into Et_2O (3 × 50 cm^3). The combined organics were washed with water (10 cm^3) and brine (2 × 10 cm^3) then dried (Na_2SO_4) and concentrated *in vacuo*. Drying under high vacuum gave the *aldehyde* **322** (0.026 g, 0.035 mmol, 70%) as a pale yellow oil; R_F [hexane-Et_2O (3:1)] 0.72; υ_{max} (soln)/cm^{-1} 1703 (C=O), 1603 (Ar), 1419 (Ar), 1262 and 888 (Si-C), and 1162 (Si-O); δ_H(400 MHz, $CDCl_3$) 0.27 (12H, s, 2 × $SiMe_2$),

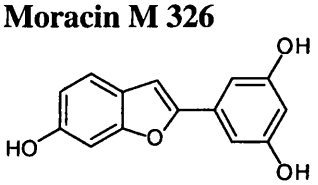
1.02 (18H, s, 2 × ^{t}Bu), 1.12 (9H, s, *t*Bu), 6.74 (1H, dd, *J* 2.0 and 8.4, 5-H), 6.79 (1H, d, *J* 8.4, 4-H), 6.84 (2H, s, 2'/6'-H), 6.91 (1H, s, 3-H), 6.96 (1H, d, *J* 2.0, 7-H), 7.35-7.46 (6H, m, 6 × Ph-H), 7.73-7.76 (4H, m, 4 × Ph-H), and 10.43 (1H, s, CHO); *m/z* (CI) 737 [$(M+H)^+$, 65%], 679 (65), 613 (100), 555 (75), 499 (15), 391 (20), 373 (20), and 133 (35); [Found: $(M+H)^+$, 737.3509. $C_{43}H_{57}O_5Si_3$ requires $(M+H)^+$, 737.3514).

2,2,8,8-Tetramethyl-2*H*, 8*H*-pyranochromene 325



Resorcinol **109** (0.300 g, 2.72 mmol), phenylboronic acid (0.333 g, 2.73 mmol) and 3-methylbutenal **216** (0.26 cm^3, 2.73 mmol) were dissolved in a mixture of dry toluene (100 cm^3) and glacial acetic acid (13.5 cm^3) and heated under reflux in Dean-Stark apparatus under nitrogen overnight. After cooling to RT, the solvent was removed *in vacuo* and the residue taken up in water. The aqueous solution was extracted into DCM (3 × 50 cm^3), washed with water (20 cm^3), saturated aqueous sodium bicarbonate (20 cm^3), and brine (20 cm^3) and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow oil which was purified by flash chromatography on silica (9:1 hexane-EtOAc). Recrystallisation from hexane gave chromene **325** (0.080 g, 0.331 mmol, 12%) as plates: m.p. 79-81 °C (Lit.[126] 77-79 °C); R_F [hexane-EtOAc (9:1)] 0.72; υ_{max} (KBr)/cm^{-1} 1627(Ar), 1561 (Ar), and 1489 (Ar); δ_H(400 MHz, $CDCl_3$) 1.40 (12H, s, 4 × Me), 5.45 (2H, d, *J* 9.8, 3-H and 7-H), 6.22 (2H, d, *J* 9.8, 4-H and 6-H), 6.24 (1H, s, 5-H), and 6.59 (1H, s, 10-H); δ_C(100 MHz, $CDCl_3$) 28.42 (CH_3), 76.72 (C), 105.05 (CH), 114.88 (C), 122.17 (CH), 124.09 (CH), 128.28 (CH), and 154.50 (C); *m/z* (EI) 242 (M^+, 25%), 227 (100), 211 (10), and 106 (10); (Found: C, 79.3; H, 7.45%; M^+, 242.1309. $C_{16}H_{18}O_2$ requires: C, 79.31; H, 7.49%; *M*, 242.1307).

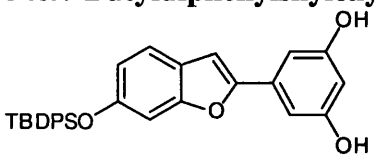
Moracin M 326



6-Acetoxy-2-(3',5'-dimethoxyphenyl)-benzofuran **212** (0.500 g, 1.60 mmol) was dissolved in dry CH_2Cl_2 (20 cm^3) and cooled to –78 °C under nitrogen. Boron tribromide (4.81 cm^3, 1 mol dm^{-3} in CH_2Cl_2, 4.81 mmol, 3 eq) was added slowly over 15 min, then the reaction allowed to warm slowly up to RT. After stirring overnight, the reaction was quenched by pouring into cold water, followed by stirring for 10 min. This aqueous solution was extracted with EtOAc (3 × 50 cm^3),

washed well with water (50 cm^3) and brine (3 × 50 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (2:1 EtOAc-hexane) followed by recrystallisation from MeOH-H_2O gave benzofuran **326** (0.380 g, 1.57 mmol, 98%) as pale yellow needles: m.p. 259-261 °C (Lit.[127] 259-262 °C); R_F [EtOAc-hexane (2:1)] 0.61; υ_{max} (KBr)/cm^{-1} 3290 (OH), 1616 (Ar), 1578 (Ar), and 1506 (Ar); δ_H[400 MHz, $(CD_3)_2CO$] 6.39 (1H, t, *J* 2.0, 4'-H), 6.83 (1H, dd, *J* 8.4 and 2.0, 5-H), 6.88 (2H, d, *J* 2.0, 2' and 6'-H), 7.00 (1H, br s, 7-H), 7.04 (1H, s, 3-H), 7.41 (1H, d, *J* 8.4, 4-H), 7.81 (2H, br s, 2 × OH), and 7.83 (1H, br s, OH); δ_C(100 MHz, $(CD_3)_2CO$) 98.44 (CH), 102.32 (CH), 103.56 (CH), 103.84 (CH), 113.25 (CH), 122.01 (CH), 122.58 (C), 133.40 (C), 155.56 (C), 156.70 (C), 156.74 (C), and 159.82 (C); *m/z* (EI) 242 (M^+, 100%), 213 (11), and 121 (10); (Found M^+, 242.0580. $C_{14}H_{10}O_4$ requires: *M*, 242.0579).

6-*tert*-Butyldiphenylsilyloxy-2-(3',5'-dihydroxyphenyl)-benzo[*b*]furan 327

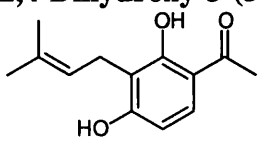


Benzofuran **300** (1.148 g, 2.26 mmol) was dissolved in dry CH_2Cl_2 (20 cm^3) and cooled to –78 °C under nitrogen. Boron tribromide (1 mol dm^{-3} in CH_2Cl_2, 6.80 cm^3, 6.78 mmol, 3 eq) was added slowly then the reaction stirred at RT. After 2 h, the reaction was quenched with water and extracted into EtOAc (3 × 30 cm^3). the combined extracts were washed with brine (2 × 50 cm^3), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography on silica (1:1 EtOAc/hexane) gave the benzofuran **327** (0.755 g, 1.57 mmol, 70%) as plates; m.p. 131-133 °C; R_F [hexane-EtOAc (1:1)] 0.50; υ_{max} (KBr)/cm^{-1} 3410 (OH), 1618 (Ar), 1575 (Ar), 1489 (Ar), 1277 and 823 (Si-C), and 1113 (Si-O); δ_H(400 MHz, MeOD) 1.08 (9H, s, *t*Bu), 5.08 (2H, br s, 2 × OH), 6.33 (1H, br s, 3-H), 6.71 (1H, br d, *J* 8.4, 5-H), 6.80-6.85 (4H, m, 7-, 2'/6'- and 4'-H), 7.20 (1H, d, *J* 8.4, 4-H), 7.30-7.41 (6H, m, 6 × Ph-H), and 7.63-7.74 (4H, m, 4 × Ph-H); δ_C(100 MHz, MeOD) 20.72 (C), 27.56 (CH_3), 102.67 (CH), 103.68 (CH), 104.24 (CH), 104.64 (CH), 117.85 (CH), 122.21 (CH), 124.93 (C), 129.43 (CH), 131.95 (CH), 133.99 (C), 134.04 (C), 137.09 (CH), 155.29 (C), 156.95 (C), 157.30 (C), and 160.36 (C); *m/z* (EI) 480 (M^+, 30%), 423 (100), 345 (15), and 211 (10); (Found: M^+, 480.1755. $C_{30}H_{28}O_4Si$ requires *M*, 480.1757).

9

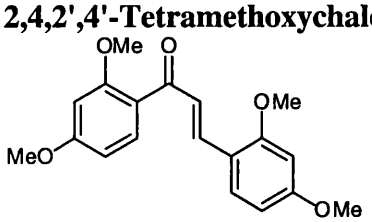
Experimental for Chapter 5

2,4-Dihydroxy-3-(3'-methylbut-2'-enyl)-acetophenone 331



Potassium hydroxide (12.910 g, 230.61 mmol, 3.5 eq) was dissolved in MeOH (80 cm^3), and cooled to 0 °C. A solution of 2,4-dihydroxyacetophenone **330** (10.015 g, 65.89 mmol) in MeOH (20 cm^3) was added followed by prenyl bromide (21.50 cm^3, 184.48 mmol, 2.8 eq), and the resulting brown solution warmed to 40 °C and stirred under nitrogen overnight. The solution was quenched with water, acidified with dilute aqueous HCL (1 mol dm^{-3}), then extracted into EtOAc (3 × 50 cm^3). The combined organic extracts were washed with water and brine (2 × 50 cm^3 each), dried ($MgSO_4$) and concentrated *in vacuo*. The dark red oil solidified on standing and was recrystallised from toluene to give the acetophenone **331** (1.919 g, 8.72 mmol, 13%) as pale orange plates; m.p. 150-153 °C (Lit.[128] 149-151 °C; 157-158 °C); R_F [hexane-Et_2O (1:1)] 0.32; υ_{max} (KBr)/cm^{-1} 3425 (OH), 1623 (C=O), 1584 (Ar), 1496 (Ar), and 792 (C=C); δ_H(400 MHz, $CDCl_3$) 1.76 (3H, s, Me), 1.83 (3H, s, Me), 2.56 (3H, s, COMe), 3.44 (2H, d, *J* 7.2, =CHCH_2), 5.26 (1H, t, *J* 7.2, =C*H*CH_2), 6.04 (1H, s, OH), 6.38 (1H, d, *J* 8.8, 5-H), 7.53 (1H, d, *J* 8.8, 6-H), and 13.20 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) 17.89 (CH_3), 21.58 (CH_2), 25.79 (CH_3), 26.20 (CH_3), 107.73 (CH), 107.91 (C), 113.70 (C), 114.02 (C), 121.04 (CH), 130.30 (CH), 135.52 (C), 161.54 (C), and 162.52 (C); *m/z* (EI) 220 (M^+, 65%), 205 (20), 177 (40), 165 (100), and 149 (45); (Found: C, 70.79; H, 7.24%; M^+, 220.1098. $C_{13}H_{16}O_3$ requires: C, 70.91; H, 7.27%; *M*, 220.1100). ^1H, IR, microanalysis and MS agree with data reported.[128]

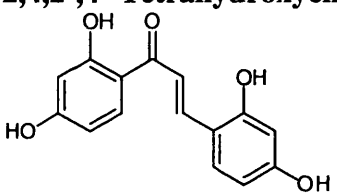
2,4,2',4'-Tetramethoxychalcone 334



2,4-Dimethoxybenzaldehyde **332** (1.521 g, 9.16 mmol) and 2,4-dimethoxyacetophenone **333** (1.649 g, 9.16 mmol) were dissolved in EtOH (25 cm^3) and sodium hydroxide (2-3 pellets) added and the reaction stirred at RT under nitrogen. After 16 h, the yellow solid product was filtered off, and washed under

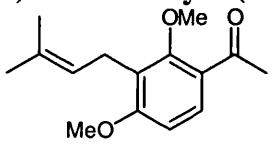
suction with water and cold EtOH. Recrystallisation from ethanol gave chalcone **334** (1.858 g, 5.66 mmol, 62%) as yellow needles: m.p. 120-123 °C (Lit.[94] 128-129 °C); R_F [EtOAc-hexane (3:1)] 0.66; υ_{max} (KBr)/cm^{-1} 1645 (C=O), 1501 (Ar), 1452 (Ar), and 937 (C=C); δ_H(400 MHz, $CDCl_3$) 3.84 (3H, s, OMe), 3.86 (6H, s, 2 × Me), 3.89 (3H, s, OMe), 6.45 (1H, d, *J* 2.3, 3'-H), 6.49 (1H, d, *J* 2.4, 3-H), 5.51 (1H, dd, *J* 2.3 and 8.6, 5'-H), 6.55 (1H, dd, *J* 2.4 and 8.6, 5-H), 7.46 (1H, d, *J* 15.9, COC*H*=CH), 7.54 (1H, d, *J* 8.6, 6'-H), 7.72 (1H, d, *J* 8.6, 6-H), and 7.94 (1H, d, *J* 15.9, COCH=C*H*); δ_C(100 MHz, $CDCl_3$) 55.45 (CH_3), 55.51 (2 × CH_3), 55.67 (CH_3), 98.30 (CH), 98.64 (CH), 104.91 (CH), 105.26 (CH), 117.49 (C), 122.75 (C), 125.37 (CH), 130.23 (CH), 132.62 (CH), 137.93 (CH), 160.08 (C), 160.09 (C), 162.60 (C), 163.67 (C), and 191.32 (C); *m/z* (EI) 328 (M^+, 15%), 297 (100), 165 (22), and 151 (16); (Found: C, 69.49; H, 6.17%; M^+, 328.1312. $C_{19}H_{20}O_5$ requires: C, 69.50; H, 6.14%; *M*, 328.1311).

2,4,2',4'-Tetrahydroxychalcone 335



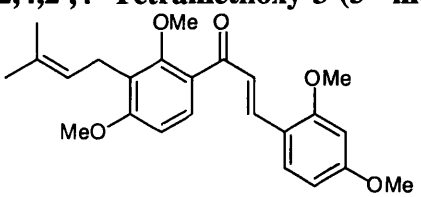
Chalcone **334** (0.512 g, 1.56 mmol) was dissolved in CH_2Cl_2 (20 cm^3) and cooled to –78 °C under nitrogen. Boron tribromide (9.40 cm^3, 1 mol dm^{-3} in CH_2Cl_2, 9.40 mmol, 6 eq) was added slowly, and the reaction allowed to warm to RT. After stirring for 3 h, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate and the resulting slurry was stirred for 30 min at RT. This aqueous solution was extracted into EtOAc (3 × 70 cm^3), washed well with brine (3 × 50 cm^3), dried ($MgSO_4$), and concentrated *in vacuo* to give a bright orange solid. Chromatography on silica (3:1 EtOAc-hexane) gave a bright orange solid which was recrystallised from EtOH/water to give chalcone **335** (0.251 g, 0.92 mmol, 59%) as orange plates: m.p. 310-311 °C(dec) (Lit.[117] >320 °C); R_F [EtOAc-hexane (3:1)] 0.35; υ_{max} (KBr)/cm^{-1} 3375 (OH), 1636 (C=O), 1550 (Ar), 1506 (Ar), 1466 (Ar), and 958 (C=C); δ_H(400 MHz, d_6-acetone) 6.31-6.43 (4H, m, 3',3,5'- and 5-H), 7.58 (1H, d, *J* 8.6, 6'-H), 7.68 (1H, d, *J* 15.4, COC*H*=CH), 7.95 (1H, d, *J* 8.6, 6-H), and 8.12 (1H, d, *J* 15.4, COCH=C*H*); δ_C(100 MHz, $CDCl_3$) 102.10 (CH), 104.00 (CH), 108.33 (CH), 109.58 (CH), 115.51 (C), 117.63 (CH), 132.24 (CH), 132.85 (CH), 141.48 (C), 141.85 (CH), 160.59 (C), 162.97 (C), 167.28 (C), 167.01 (C), and 193.81 (C).

2,4-Dimethoxy-3-(3'-methylbut-2'-enyl)-acetophenone 336



Ketone **331** (0.203 g, 0.923 mmol) and potassium carbonate (0.765 g, 5.54 mmol, 6 eq) were dissolved in dry acetone (10 cm^3) and dimethyl sulfate (0.26 cm^3, 2.77 mmol, 3 eq) added slowly. This was heated under reflux under nitrogen for 24 h. After cooling, the reaction mixture was concentrated *in vacuo* then the residue taken up in water. This aqueous solution was extracted with Et_2O (3 × 20 cm^3), then the combined extracts washed with brine (3 × 30 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was filtered through a short silica plug eluting with Et_2O-hexane (1:1) and concentrated to give ketone **336** (0.184 g, 0.742 mmol, 80%), as a pale orange oil: R_F [Et_2O-hexane (1:1)] 0.56; δ_H(400 MHz, $CDCl_3$) 1.68 (3H, s, Me), 1.74 (3H, s, Me), 2.61 (3H, s, COMe), 3.37 (2H, d, *J* 6.9, =CHCH_2), 3.74 (3H, s, OMe), 3.86 (3H, s, OMe), 5.17 (1H, t, *J* 6.9, =C*H*CH_2), 6.69 (1H, d, *J* 8.8, 5-H), and 7.60 (1H, d, *J* 8.8, 6-H); ^{1}H NMR data agreed with those reported.[114] ; δ_C(100 MHz, $CDCl_3$) 18.20 (CH_3), 23.18 (CH_2), 30.32 (CH_3), 32.21 (CH_3), 56.12 (CH_3), 63.13 (CH_3), 106.58 (CH), 122.95 (CH), 124.43 (C), 126.11 (C), 129.82 (CH), 133.95 (C), 159.51 (C), 162.26 (C), and 199.31 (C); *m/z* (EI) 248 (M^+, 37%), 233 (100), 179 (17), and 43 (15); (Found M^+, 248.1412. $C_{15}H_{20}O_3$ requires: *M*, 248.1413).

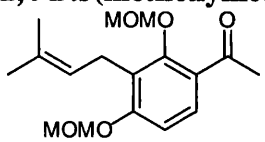
2,4,2',4'-Tetramethoxy-3-(3''-methylbut-2''-enyl) chalcone 337



2,4-Dimethoxybenzaldehyde **332** (1.067 g, 0.403 mmol) and ketone **336** (0.100 g, 0.403 mmol) were dissolved in EtOH (1 cm^3) and sodium hydroxide (1 pellets) added and the reaction stirred at RT under nitrogen. After 16 h, the reaction was quenched by addition of water (30 cm^3), and then extracted with Et_2O (3 × 30 cm^3). The combined extracts were washed with water (30 cm^3), and brine (3 × 30 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo* to give *chalcone* **337** (0.147 g, 0.370 mmol, 92%) as a yellow oil; R_F [Et_2O-hexane (1:1)] 0.28; υ_{max} (film)/cm^{-1} 1676 (C=O), 1653 (C=C), 1588 (Ar), 1504 (Ar), and 1481 (Ar); δ_H(400 MHz, $CDCl_3$) 1.63 (3H, s, Me), 1.71 (3H, s, Me), 3.32 (2H, d, *J* 6.9, =CHCH_2), 3.62 (3H, s, OMe), 3.75 (3H, s, OMe), 3.78 (3H, s, OMe), 3.79 (3H, s, OMe), 5.11 (1H, t, *J* 6.9, C*H*=CH_2), 6.37 (1H, d, *J* 2.3, 3'-H), 6.45 (1H, dd, *J* 2.3 and 8.6, 5'-H), 6.62 (1H, d, *J* 8.6, 5-H), 7.40 (1H, d, *J* 15.9, COC*H*=CH), 7.49 (2H, d, *J* 8.6, 6-H and 6'-H), and

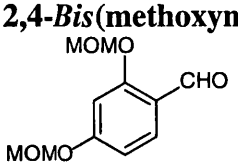
7.93 (1H, d, *J* 15.9, COCH=C*H*); δ_C(100 MHz, $CDCl_3$) 16.82 (CH_3), 21.77 (CH_2), 24.76 (CH_3), 54.43 (CH_3), 54.46 (CH_3), 54.77 (CH_3), 61.94 (CH_3), 97.30 (CH), 104.31 (CH), 105.13 (CH), 116.22 (C), 121.74 (CH), 122.69 (C), 123.30 (CH), 125.52 (C), 128.47 (CH), 129.09 (CH), 130.47 (C), 137.65 (CH), 157.72 (C), 159.12 (C), 160.10 (C), 161.80 (C), and 191.24 (C); *m/z* (EI) 396 (M^+, 40%), 362 (100), 217 (65), 163 (30), and 151 (70); (Found M^+, 396.1937. $C_{24}H_{28}O_5$ requires: *M*, 396.1936).

2,4-*Bis*(methoxymethoxy)-3-(3'-methylbut-2'-enyl)acetophenone 340



Sodium hydride (0.551 g, 60% dispersion in mineral oil, 13.8 mmol, 3 eq) was washed with dry hexane (3 × 10 cm^3), dried under vacuum, then suspended in dry DMF (10 cm^3) under nitrogen and cooled to 0 °C. Ketone **331** (1.010 g, 4.59 mmol) in dry DMF (25 cm^3) was added slowly and the solution stirred at RT for 30 min. The reaction was cooled to 0°C once more and chloromethylmethyl ether (1.05 cm^3, 13.77 mmol, 3 eq) added slowly, then the solution was stirred at 60 °C overnight. The reaction was cooled then quenched by pouring into water, and extracted into diethyl ether (3 × 100 cm^3). The organic extract was washed with brine (3 × 50 cm^3) dried (K_2CO_3) and concentrated *in vacuo*. The residue was poured through a short silica plug eluting with dichloromethane giving the *ketone* **340** (1.040 g, 3.38 mmol, 74%) as a pale brown oil; R_F[hexane:Et_2O (1:1)] 0.55; υ_{max} (soln)/cm^{-1} 1674 (C=O), 1632 (Ar), and 1586 (Ar); δ_H(400 MHz, $CDCl_3$) 1.67 (3H, s, Me), 1.78 (3H, s, Me), 2.58 (3H, s, COMe), 3.41 (2H, m, =CH-C$\underline{H}_2$), 3.46 (3H, s, OMe), 3.52 (3H, s, OMe), 5.10 (2H, s, OCH_2O), 5.18 (1H, m, C=CH), 5.24 (2H, s, OCH_2O), 6.90 (1H, d, *J* 8.7, 5-H), and 7.49 (1H, d, *J* 8.7, 6-H); δ_C(100 MHz, $CDCl_3$) 18.26 (CH_3), 23.78 (CH_2), 26.06 (CH_3), 30.39 (CH_3), 56.55 (CH_3), 58.21 (CH_3), 94.15 (CH_2), 101.72 (CH_2), 109.22 (CH), 122.72 (CH), 125.55 (C), 128.03 (C), 129.05 (CH), 132.07 (C), 155.92 (C), 159.34 (C), and 199.84 (C). *m/z* (CI) 309 [$(M+H)^+$, 100%), 277 (15), 265 (20), and 235 (15); [Found $(M+H)^+$, 309.1703. $C_{17}H_{25}O_5$ requires $(M+H)^+$, 309.1702].

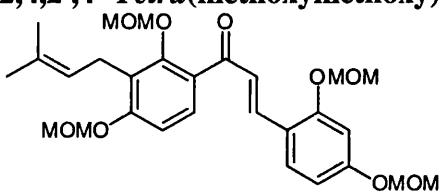
2,4-*Bis*(methoxymethoxy)benzaldehyde 341



Sodium hydride (2.623 g, 60% dispersion in mineral oil, 65.59 mmol, 3 eq) was washed with dry hexane (3 × 10 cm^3), dried under vacuum, suspended in dry DMF (50 cm^3) under nitrogen and cooled to 0 °C. 2,4-Dihydroxybenzaldehyde **188** (3.017

g, 21.86 mmol) in dry DMF (20 cm^3) was added slowly, then the solution stirred at RT for 30 min. The reacion was cooled to 0 °C once more, and chloromethylmethyl ether (5.00 cm^3, 65.59 mmol, 3 eq) added slowly, then the solution was stirred at RT overnight. The reaction was quenched by pouring into water which was then extracted into diethyl ether (3 × 100 cm^3). The organic extract was washed with NaOH (1 mol dm^{-3}, 50 cm^3), brine (2 × 50 cm^3), then dried (K_2CO_3) and concentrated *in vacuo*. Recrystallisation from hexane gave the aldehyde **341** (3.096 g, 13.70 mmol, 63%) as needles; m.p. 44-45°C (Lit.[129] 47-49°C); R_F[hexane:Et_2O (1:1)] 0.58; υ_{max} (KBr)/cm^{-1} 1682 (C=O), 1602 (Ar), 1578 (Ar), and 1492 (Ar); δ_H(400 MHz, $CDCl_3$) 3.49 (3H, s, OMe), 3.53 (3H, s, OMe), 5.22 (2H, s, OCH_2O), 5.32 (2H, s, OCH_2O), 6.74 (1H, dd, *J* 2.0 and 8.7, 5-H), 6.83 (1H, d, *J* 2.0, 3-H), 7.80 (1H, d, *J* 8.7, 6-H), and 10.35 (1H, s, CHO); δ_C(100 MHz, $CDCl_3$) 56.78 (CH_3), 56.92 (CH_3), 94.54 (CH_2). 95.05 (CH_2), 103.00 (CH), 109.83 (CH), 120.60 (C), 130.55 (CH), 161.67 (C), 163.90 (C), and 188.71 (CH); *m/z* (EI) 226 (M^+, 100%), 181 (40), 166 (30) and 165 (20); (Found: C, 58.3; H 6.24%; Requires C, 58.4; H, 6.20%).

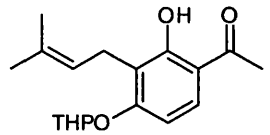
2,4,2',4'-*Tetra*(methoxymethoxy)-3-(3''-methylbut-2''-enyl)chalcone 342



Ketone **340** (0.428 g, 1.39 mmol) and aldehyde **341** (0.314 g, 1.39 mmol) were dissolved in dry ethanol (5 cm^3) with a catalytic amount of NaOH (0.056 g, 0.139 mmol, 0.10 eq), and stirred under nitrogen at RT overnight. The solution was diluted with water and extracted into Et_2O (3 × 50 cm^3). The organic extract was washed with brine (2 × 50 cm^3), dried (K_2CO_3), and concentrated *in vacuo*. Chromatography on silica eluting with ethyl acetate–hexane (1:1) gave the *chalcone* **342** (0.300 g, 0.581 mmol, 42%) as a bright yellow oil; R_F[hexane–Et_2O (1:1)] 0.58; υ_{max} (soln)/cm^{-1} 1729 (C=O), 1657 (C=C), 1571 (Ar), 1524 (Ar), and 1500 (Ar); δ_H(400 MHz, $CDCl_3$) 1.69 (3H, s, Me), 1.80 (3H, s, Me), 3.46-3.50 (14H, m, 4 × OMe and =CHCH_2), 4.96 (2H, s, OCH_2O), 5.17 (2H, s, OCH_2O), 5.18-5.28 (5H, m, 2 × OCH_2O and C=CH), 6.72 (1H, dd, *J* 2.4 and 8.8, 5'-H), 6.84 (1H, d, *J* 2.4, 3'-H), 6.94 (1H, d, *J* 8.4, 5-H), 7.34 (1H, d, *J* 16.0, COC*H*=CH), 7.49 (1H, d, *J* 8.8, 6'-H), 7.57 (1H, d, *J* 8.4, 6-H), and 7.99 (1H, d, *J* 16.0, COCH=C*H*); δ_C(100 MHz, $CDCl_3$) 17.94 (CH_3), 23.45 (CH_3), 56.14 (CH_3), 56.26 (CH_3), 56.39 (CH_3), 57.89 (CH_3), 65.86 (CH_2), 94.09 (CH_2), 94.30 (CH_2), 94.65 (CH_2), 101.32 (CH_2), 103.36 (CH), 109.41 (CH), 109.53 (CH), 118.69 (C), 122.66 (CH), 124.91 (C), 125.17 (CH), 128.31 (C), 128.88 (CH), 129.63 (CH), 131.61 (C), 138.42 (CH), 155.54 (C), 157.72

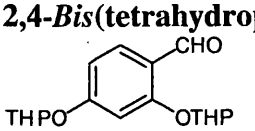
(C), 158.54 (C), 160.24 (C), and 192.51 (C); *m/z* (CI) 517 [$(M+H)^+$, 100%), and 473 (10); [Found $(M+H)^+$, 517.2442. $C_{28}H_{37}O_9$ requires $(M+H)^+$, 517.2438].

2-Hydroxy-3-(3'methylbut-2'-enyl)-4-(tetrahydropyran-2''-yloxy)acetophenone 343



3,4-Dihydro-2*H*-pyran (0.15 cm^3, 1.58 mmol, 4 eq) was cooled to 0°C then 2-3 drops of conc. HCl added. 2,4-Dihydroxy-3-(3'-methylbut-2'enyl)acetophenone **331** (0.087 g, 0.40 mmol, 1 eq) was added portion wise over 10 min, then the ice bath removed and the solution stirred at RT. After 3 h, the reaction was diluted with Et_2O (10 cm^3) and washed with saturated aqueous sodium bicarbonate (3 × 10 cm^3), brine (3 × 10 cm^3), then dried (Na_2SO_4) and concentrated *in vacuo* to give a pale brown oil. Chromatography on silica (1:1 hexane/Et_2O) gave the *ketone* **343** (0.133 g, 0.34 mmol, 86%) as a brown/orange oil; R_F [hexane-Et_2O (1:1)] 0.63; υ_{max} (film)/cm^{-1} 3371 (OH), 1624 (C=O), 1598 (Ar), 1493 (Ar), and 968 (C=C); δ_H(400 MHz, $CDCl_3$) 1.51-1.89 (6H, m, 3 × $-CH_2-$), 1.73 (3H, s, Me), 1.83 (3H, s, Me), 2.55 (3H, s, COMe), 3.42 (2H, d, *J* 6.0, $=CHCH_2$), 3.50-3.58 (2H, m, $-OCH_2-$), 4.92-4.97 (1H, m, -OCHO-), 5.24-5.28 (1H, m, $=CHCH_2$), 6.37 (1H, d, *J* 8.8, 5-H), 7.50 (1H, d, *J* 8.8, 6-H), and 13.03 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) 18.26 (CH_3), 20.10 (CH_2), 22.00 (CH_2), 25.80 (CH_2), 26.17 (CH_3), 26.54 (CH_3), 31.31 (CH_2), 63.34 (CH_2), 95.10 (CH), 108.00 (CH), 114.10 (C), 114.79 (C), 121.70 (CH), 130.56 (CH), 135.08 (C), 161.94 (C), 163.03 (C), and 203.16 (C); *m/z* (EI) 304 (M^+, 5%), 220 (85), 205 (30), 165 (100), 149 (40), 147 (25), 85 (35), and 43 (40); (Found: M^+, 304.1679. $C_{18}H_{24}O_4$ requires *M*, 304.1675).

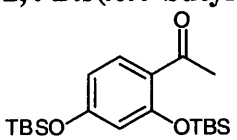
2,4-*Bis*(tetrahydropyran-2''-yloxy)benzaldehyde 344



3,4-Dihydro-2*H*-pyran (4.00 cm^3, 44.22 mmol, 6 eq) was cooled to 0°C then 2-3 drops of conc. HCl added. 2,4-Dihydroxybenzaldehyde **188** (1.017 g, 7.37 mmol, 1 eq) was added portion wise over 10 min, then the ice bath removed and the solution stirred at RT. After 3 h, the reaction was diluted with Et_2O (50 cm^3) and washed with saturated aqueous sodium bicarbonate (3 × 20 cm^3), brine (3 × 20 cm^3), then dried (Na_2SO_4) and concentrated *in vacuo* to give a pale brown oil. Chromatography on silica (2:1 hexane/Et_2O) gave the *aldehyde* **344** (1.691 g, 5.53 mmol, 75%) as a colourless oil; R_F [hexane-Et_2O (2:1)] 0.40; υ_{max} (film)/cm^{-1} 1725 (C=O), 1683 (Ar), 1601 (Ar), and 1500 (Ar); δ_H(400 MHz, $CDCl_3$) 1.54-2.04 (12H, m, 6 × $-CH_2-$

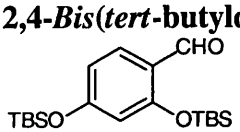
), 3.48-4.48 (4H, m, 2 × -OCH_2-), 5.10-5.57 (2H, m, 2 × -OCHO-), 6.59 (1H, d, *J* 2.0, 3-H), 6.88 (1H, dd, *J* 2.0 and 8.8, 5-H), 7.79 (1H, d, *J* 8.8, 6-H), and 10.40 (1H, s, CHO); δ_C(100 MHz, $CDCl_3$) 18.73 (CH_2), 20.01 (CH_2), 25.39 (CH_2), 25.70 (CH_2), 30.35 (CH_2), 31.31 (CH_2), 62.39 (CH_2), 63.71 (CH_2), 96.65 (CH), 98.85 (CH), 102.22 (CH), 109.68 (CH), 130.13 (CH), 138.51 (C), 161.59 (C), 163.99 (C), and 188.73 (CH); *m/z* (EI) 306 (M^+, 10%), 204 (65), 174 (20), 85 (100), 84 (20), and 41 (13); (Found: M^+, 306.1465. $C_{17}H_{22}O_5$ requires *M*, 306.1468).

2,4-*Bis*(*tert*-butyldimethylsilyloxy)acetophenone 349



2,4-Dihydroxyacetophenone **330** (0.527 g, 3.47 mmol), imidazole (0.943 g, 13.87 mmol, 4 eq) and *tert*-butyldimethylchlorosilane (1.304 g, 8.67 mmol, 2.5 eq) were dissolved in dry DMF (25 cm^3) and heated at 60 °C under nitrogen. After 16 h, the reaction was cooled to RT then quenched by the addition of water, then extracted into Et_2O (3 × 20 cm^3). The combined organic extracts were washed with water (2 × 50 cm^3) and brine (2 × 50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography on silica gave *ketone* **349** (1.235 g, 3.25 mmol, 94%) as a pale brown oil; R_F [Et_2O-hexane (2:1)] 0.80; υ_{max} (film)/cm^{-1} 1673 (ketone C=O), 1640 (Ar), 1561 (Ar), 1261 and 896 (Si-C) and 1179 (Si-O); δ_H(400 MHz, $CDCl_3$) 0.02 (6H, s, $SiMe_2$), 0.07 (6H, s, $SiMe_2$), 0.76 (9H, s, *tert*-Bu), 0.79 (9H, s, *tert*-Bu), 2.35 (3H, s, COMe), 6.11 (1H, d, *J* 2.2, 3-H), 6.26 (1H, dd, *J* 2.2 and 8.6, 5-H), and 7.41 (1H, d, *J* 8.6, 6-H); δ_C(100 MHz, $CDCl_3$) –4.25 (CH_3), –3.84 (CH_3), 18.25 (C), 18.55 (C), 25.71 (CH_3), 25.92 (CH_3), 31.33 (CH_3), 111.44 (CH), 113.58 (CH), 124.54 (C), 131.90 (CH), 156.83 (C), 160.27 (C), and 198.85 (C); *m/z* (CI) 381 [$(M+H)^+$ 100%], and 323 (30); [Found: $(M+H)^+$, 381.2279. $C_{30}H_{37}O_3Si_2$ requires *M*, 381.2281).

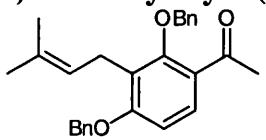
2,4-*Bis*(*tert*-butyldimethylsilyloxy)benzaldehyde 350



2,4-dihydroxybenzaldehyde **188** (0.510 g, 3.70 mmol), imidazole (1.005 g, 14.78 mmol, 4 eq) and *tert*-butyldimethylchlorosilane (1.390 g, 9.24 mmol, 2.5 eq) were dissolved in dry DMF (25 cm^3) and heated at 60 °C under nitrogen. After 16 h, the reaction was cooled to RT then quenched by the addition of water, then extracted into Et_2O (3 × 20 cm^3). The combined organic extracts were washed with water (2 × 50 cm^3) and brine (2 × 50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography on silica gave aldehyde **350** (1.101 g, 3.01

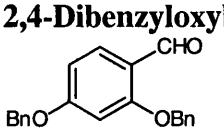
mmol, 81%) as a pale brown oil; R_F [Et_2O-hexane (2:1)] 0.89; υ_{max} (film)/cm^{-1} 1686 (aldehyde C=O), 1651 (Ar), 1625 (Ar), 1596 (Ar), 1256 and 898 (Si-C) and 1178 (Si-O); δ_H(400 MHz, $CDCl_3$) 0.23 (6H, s, $SiMe_2$), 0.27 (6H, s, $SiMe_2$), 0.95 (9H, s, *tert*-Bu), 0.98 (9H, s, *tert*-Bu), 6.29 (1H, d, *J* 2.2, 3-H), 6.50 (1H, dd, *J* 2.2 and 8.6, 5-H), 7.71 (1H, d, *J* 8.6, 6-H), and 10.28 (1H, s, CHO); ^1H NMR data agreed with those reported.[128] ; δ_C(100 MHz, $CDCl_3$) –4.30 (CH_3), –2.93 (CH_3), 18.28 (C), 18.36 (C), 25.66 (CH_3), 25.71 (CH_3), 110.99 (CH), 114.35 (CH), 121.83 (C), 129.92 (CH), 160.69 (C), 162.65 (C), and 188.91 (CH); *m/z* (CI) 367 [$(M+H)^+$ 100%], and 309 (40); [Found: $(M+H)^+$, 367.2122. $C_{19}H_{35}O_3Si_2$ requires *M*, 367.2124).

2,4-Dibenzyloxy-3-(3'-methylbut-2'-enyl)-acetophenone 351



Ketone **331** (0.873 g, 3.97 mmol), benzyl bromide (1.42 cm^3, 11.90 mmol, 3 eq) and potassium carbonate (2.190 g, 15.87 mmol, 4 eq) were stirred in dry DMF (15 cm^3) at 60 °C overnight under nitrogen. After cooling to RT, the reaction was quenched with water then extracted into Et_2O (3 × 50 cm^3). The combined extracts were washed with dilute aqueous HCl (1 mol dm^{-3}, 50 cm^3), and brine (2 × 50 cm^3) then dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (1:1 hexane/Et_2O) gave the *ketone* **351** (1.112 g, 2.78 mmol, 70%) as an orange oil; R_F [hexane-Et_2O (1:1)] 0.57; υ_{max} (film)/cm^{-1} 1672 (C=O), 1628 (Ar), and 1589 (Ar); δ_H(400 MHz, $CDCl_3$) 1.60 (3H, s, Me), 1.70 (3H, s, Me), 2.55 (3H, s, COMe), 3.45 (2H, m, =CH-C<u>H</u>$_2$), 4.87 (2H, s, $PhCH_2$), 5.12 (2H, s, $PhCH_2$), 5.23 (1H, m, C=CH), 6.75 (1H, d, *J* 8.7, 5-H), 7.29-7.45 (10H, m, 2 × Ph), and 7.56 (1H, d, *J* 8.7, 6-H); δ_C(100 MHz, $CDCl_3$) 15.70 (CH_3), 23.64 (CH_2), 26.22 (CH_3), 32.47 (CH_3), 70.68 (CH_2), 78.08 (CH_2), 103.74 (CH), 108.75 (CH), 122.41 (CH), 123.01 (CH), 127.66 (CH), 128.20 (CH), 128.95 (CH), 129.66 (CH), 130.54 (CH), 132.34 (C), 137.28 (C), 136.97 (C), 157.90 (C), 162.32 (C), 162.70 (C), 163.91 (C) and 203.29 (C); *m/z* (EI) 400 (M^+, 3%), 344 (7), 309 (20), 255 (15), and 91 (100); (Found: M^+, 400.2039. $C_{27}H_{28}O_3$ requires *M*, 400.2038).

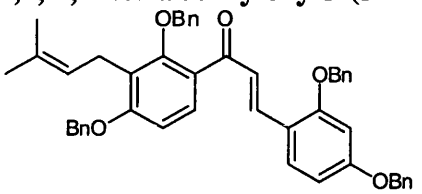
2,4-Dibenzyloxybenzaldehyde 352



2,4-Dihydroxybenzaldehyde **188** (2.000 g, 14.50 mmol), benzyl bromide (5.20 cm^3, 43.50 mmol, 3 eq) and potassium carbonate (8.000 g, 58.00 mmol, 4 eq) were stirred in dry DMF (30 cm^3) at 60 °C overnight under nitrogen. After cooling to RT, the

reaction was quenched with water then extracted into Et_2O (3 × 50 cm^3). The combined extracts were washed with dilute aqueous HCl (1 mol dm^{-3}, 50 cm^3), and brine (2 × 50 cm^3) then dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from hexane gave the aldehyde **352** (4.380 g, 13.78 mmol, 95%) as plates; m.p. 86-88 °C (Lit.[130] 87-88 °C); R_F [hexane-Et_2O (1:1)] 0.50; δ_H(400 MHz, $CDCl_3$) 5.09 (2H, s, $PhCH_2$), 5.13 (2H, s, $PhCH_2$), 6.59 (1H, d, *J* 2.1, 3-H), 6.63 (1H, dd, *J* 2.1 and 8.6, 5-H), 7.33-7.43 (10H, m, 2 × Ph), 7.83 (1H, d, *J* 8.6, 6-H), and 10.38 (1H, s, CHO); mp, ^1H NMR, IR and microanalysis match existing data.[130]
New Data: δ_C(100 MHz, $CDCl_3$) 70.78 (CH_2), 70.84 (CH_2), 100.50 (CH), 107.41 (CH), 119.90 (C), 127.67 (CH), 127.94 (CH), 128.69 (CH), 128.78 (CH), 129.14 (2 overlapping CH), 130.90 (CH), 136.29 (C), 136.32 (C), 163.14 (C), 165.56 (C), and 188.63 (CH); *m/z* (EI) 318 (M^+, 20%), 91 (100), 83 (13), and 65 (10); (Found: M^+, 318.1258. $C_{21}H_{18}O_3$ requires *M*, 318.1256).

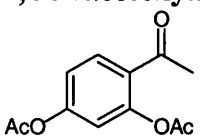
2,4,2',4'-*tetra*benzyloxy-3-(3''-methylbut-2''-enyl)chalcone 353



Ketone **351** (1.033 g, 2.58 mmol, 1.3 eq) and aldehyde **352** (0.636 g, 2.00 mmol) were dissolved in EtOH (20 cm^3) under nitrogen. Crushed NaOH (2 pellets) was added and the orange solution stirred overnight at RT. Most of the solvent was removed *in vacuo* and the residue taken up in $CHCl_3$ (50 cm^3). The organic solution was washed with water and brine (2 × 30 cm^3 each), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (1:1 hexane/Et_2O) gave the *chalcone* **353** (0.999 g, 1.43 mmol, 72 %) as a bright yellow oil; R_F [hexane-Et_2O (1:1)] 0.28; υ_{max} (soln)/cm^{-1} 1651 (C=O), 1593 (Ar), 1493 (Ar), and 1020 (=CH); δ_H(400 MHz, $CDCl_3$) 1.64 (3H, s, Me), 1.70 (3H, s, Me), 3.45 (2H, d, *J* 7.0, =CHC*H*$_2$), 4.78 (2H, s, $PhCH_2$), 5.03 (4H, 2s, 2 × $PhCH_2$), 5.17 (2H, s, $PhCH_2$), 5.20 (1H, t, *J* 7.0, =C*H*CH_2), 6.49 (1H, dd, *J* 2.4 and 8.4, 5'H), 6.54 (1H, d, *J* 2.4, 3'-H), 6.74 (1H, d, *J* 8.8, 5-H), 7.16-7.43 (XH, m, 4 × Ph and 6'-H), 7.52 (1H, d, *J* 16.0, COC*H*=CH), 7.54 (1H, d, *J* 8.8, 6-H), and 8.09 (1H, d, *J* 16.0, COCH=C*H*); δ_C(100 MHz, $CDCl_3$) 18.38 (CH_3), 23.63 (CH_2), 26.15 (CH_3), 65.64 (CH_2), 70.61 (CH_2), 70.78 (CH_2), 78.36 (CH_2), 100.99 (CH), 107.18 (CH), 108.11 (CH), 118.22 (C), 123.34 (CH), 124.94 (CH), 125.26 (C), 127.39 (CH), 127.63 (CH), 127.71 (CH), 127.96 (CH), 127.99 (CH), 128.36 (CH), 128.62 (C), 128.71 (CH), 128.83 (CH), 128.94 (CH), 128.98 (CH), 129.03 (CH), 129.11 (CH), 130.02 (CH), 130.81 (CH), 132.03 (C), 136.82 (C), 137.18 (C), 137.31 (C), 139.39 (CH), 141.38 (C), 157.67

(C), 159.58 (C), 160.85 (C), 162.22 (C), and 192.70 (C); *m/z* (EI) 700 (M^+, 3%), 609 (5), and 91 (100); (Found: M^+, 700.3185. $C_{48}H_{44}O_5$ requires *M*, 700.3189).

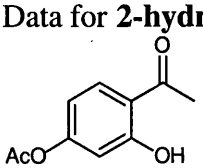
2,4-Diacetoxyacetophenone 360



2,4-Dihydroxyacetophenone **330** (2.310 g, 15.20 mmol) and potassium carbonate (8.389 g, 60.79 mmol, 4 eq) were suspended in dry Et_2O (60 cm^3) under nitrogen. Dry acetic anhydride (5.75 cm^3, 60.79 mmol, 4 eq) was added and the mixture stirred at RT for 48 h. The residue was filtered off and washed well with Et_2O, then the combined organics were washed with aqueous HCl (1 mol dm^{-3}, 20 cm^3), saturated aqueous sodium bicarbonate (20 cm^3) and brine (20 cm^3). The solution was then dried ($MgSO_4$) and concentrated *in vacuo* to give the ketone **360** (3.071 g, 13.01 mmol, 86%) as a pale yellow oil; R_F [Et_2O-hexane (2:1)] 0.35; υ_{max} (film)/cm^{-1} 1774 (ester C=O), 1666 (broad, ketone C=O), 1604 (Ar), 1579 (Ar), and 1492 (Ar); δ_H(400 MHz, $CDCl_3$) 2.26 (3H, s, OAc), 2.30 (3H, s, OAc), 2.50 (3H, s, COMe), 6.93 (1H, d, *J* 2.3, 3-H), 7.06 (1H, dd, *J* 2.3 and 8.6, 5-H), and 7.82 (1H, d, *J* 8.6, 6-H); IR and ^1H NMR data agreed with those reported.[131] ; δ_C(100 MHz, $CDCl_3$) 21.43 (2 × CH_3), 29.62 (CH_3), 117.75 (CH), 119.54 (CH), 128.34 (C), 131.79 (CH), 150.44 (C), 154.36 (C), 168.75 (C), 169.45 (C), and 196.71 (C); *m/z* (EI) 236 (M^+, 5%), 194 (40), 152 (90), and 137 (100); (Found: M^+, 236.0685. $C_{12}H_{12}O_5$ requires *M*, 236.0685).

NB: If the reaction time was shorter (stirring at RT for 1 h under nitrogen), a mixture of desired product and 2-hydroxy-4-acetoxyacetophenone was isolated in a combined yield of 93% (ratio approx. 1.6:1 mono:bis-acetylated).

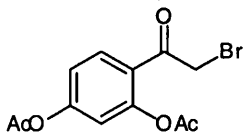
Data for **2-hydroxy-4-acetoxyacetophenone**:



Compound exists as needles; m.p. 71-72 °C (Lit.[130a] 70-72 °C); R_F [Et_2O-hexane (1:1)] 0.30; υ_{max} (KBr)/cm^{-1} 3479 (OH), 1745 (ester C=O), 1642 (ketone C=O), 1594 (Ar), 1565 (Ar), and 1503 (Ar); δ_H(400 MHz, $CDCl_3$) 2.31 (3H, s, OAc), 2.62 (3H, s, COMe), 6.68 (1H, dd, *J* 2.2 and 8.7, 5-H), 6.73 (1H, d, *J* 2.2, 3-H), 7.76 (1H, d, *J* 8.7, 6-H), and 12.45 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) 21.57 (CH_3), 27.09 (CH_3), 111.53 (CH), 113.31 (CH), 118.09 (C), 132.35 (CH), 156.97 (C), 164.29 (C), 168.92 (C), 203.97 (C); *m/z* (EI) 194 (M^+, 15%), 152 (45), and 137 (100); (Found:

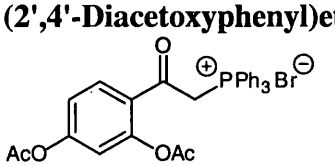
C, 61.72; H, 5.14%; M^+, 194.0580. $C_{10}H_{10}O_4$ requires: C, 61.90; H, 5.20%; *M*, 194.0580). All data agreed with those reported.[132a,b]

α-Bromo-2,4-diacetoxyacetophenone 361



2,4-Diacetoxyacetophenone **360** (0.410 g, 1.74 mmol) was dissolved in Et_2O:dioxane (2:1, 7.50 cm^3) under nitrogen. A solution of bromine (0.045 cm^3, 0.87 mmol, 0.5 eq) in dry Et_2O (2.0 cm^3) was added dropwise with the reaction vessel being regularly opened to the atmosphere. After addition of the bromine mixture, the reaction was quenched with saturated aqueous sodium bicarbonate and extracted with Et_2O (3 × 50 cm^3). The combined organic extracts were washed with saturated sodium bicarbonate solution (50 cm^3), water (50 cm^3) and brine (2 × 50 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo* to give *ketone* **361** (0.446 g, 1.42 mmol, 81%) as a pale yellow oil; R_F [Et_2O-hexane (2:1)] 0.35; υ_{max} (film)/cm^{-1} 1774 (ester C=O), 1687 (broad, ketone C=O), 1605 (Ar), 1580 (Ar), and 1421 (Ar); δ_H(400 MHz, $CDCl_3$) 2.29 (3H, s, OAc), 2.35 (3H, s, OAc), 4.41 (2H, s, CH_2Br), 7.02 (1H, d, *J* 2.2, 3-H), 7.09 (1H, dd, *J* 2.2 and 8.6, 5-H), and 7.85 (1H, d, *J* 8.6, 6-H); δ_C(100 MHz, $CDCl_3$) 21.07 (CH_3), 21.13 (CH_3), 33.93 (CH_2), 116.44 (CH), 119.17 (CH), 124.87 (C), 131.65 (CH), 150.48 (C), 154.55 (C), 168.21 (C), 168.70 (C), and 189.46 (C); *m/z* (CI) 317 [$(M+H)^+$, ^{81}Br, 5%], 315 [$(M+H)^+$, ^{79}Br, 5), 274 (25), 272 (25), 232 (40), 230 (40), 179 (5), 137 (100), and 123 (15); [Found $(M+H)^+$, ^{81}Br, 316.9810. $C_{12}H_{11}O_5{}^{81}Br$ requires: *M*, 316.9847: Found $(M+H)^+$, ^{79}Br, 314.9825. $C_{12}H_{12}O_5{}^{79}Br$ requires: *M*, 314.9868].

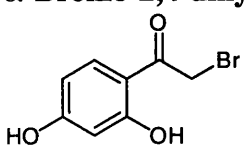
(2',4'-Diacetoxyphenyl)ethanoyl-2-triphenylphosphonium bromide 362



Triphenylphosphine (0.371 g, 1.42 mmol) in dry toluene (3.5 cm^3) was added dropwise to a solution of bromoketone **361** (0.446 g, 1.42 mmol) in dry toluene (3.5 cm^3) under nitrogen. The reaction was stirred at RT overnight during which time a precipitate formed. This was filtered off, washed with Et_2O and dried under suction. Recrystallisation from MeOH/H_2O gave *salt* **362** (0.490 g, 0.85 mmol, 60%) as plates; m.p. 170-172 °C; υ_{max} (film)/cm^{-1} 1775 (ester C=O), 1683 (broad, ketone C=O), 1604 (Ar), 1578 (Ar), and 690 (C-P); δ_H(400 MHz, $CDCl_3$) 1.94 (3H, s, OAc), 2.29 (3H, s, OAc), 6.36 (2H, d, *J* 12.2, CH_2P), 6.89 (1H, d, *J* 2.3, 3-H), 7.20 (1H, dd, *J* 2.3 and 8.4, 5-H), 7.54-7.77 (9H, m, 3 × Ph), 7.87-7.93 (6H, m, 3 × Ph),

and 9.06 (1H, d, *J* 8.4, 6-H); δ_C(100 MHz, $CDCl_3$) 20.81 (CH_3), 21.18 (CH_3), 40.78 (d, *J* 60.2, CH_2), 116.76 (CH), 118.15 (C), 119.44 (d, *J* 77.8, C), 129.14 (CH), 130.05 (d, *J* 13.3, CH), 133.81 (CH), 134.35 (d, *J* 10.7, CH), 134.68 (d, *J* 2.4, CH), 149.44 (C), 155.09 (C), 168.18 (C), 168.95 (C), and 191.07 (d, *J* 5.7, C); *m/z* (FAB) 497 [$(M-Br)^+$ 100%], 455 (10), 262 (10), and 183 (7); [Found: C, 62.4; H, 4.4%; $(M-Br)^+$, 497.1517. $C_{30}H_{26}O_5P$ requires: C, 62.40; H, 4.54%; *(M-Br)*$^+$, 497.1518].

α-Bromo-2,4-dihydroxyacetophenone 365

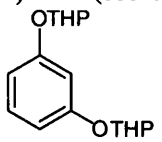


Bromoketone **361** (0.537 g, 1.70 mmol) was dissolved in methanol (20 cm^3) and potassium carbonate (0.706 g, 5.10 mmol, 3 eq) added. The reaction was stirred at RT for 1 h, then diluted with water, acidified with aqueous HCl (1 mol dm^{-3}) then extracted into EtOAc (3 × 30 cm^3). the combined organic extracts were washed with brine (2 × 50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give ketone **365** (0.122 g, 0.53 mmol, 31%) as an amorphous yellow solid; m.p. >200 °C (dec); υ_{max} (KBr)/cm^{-1} 1664 (C=O), 1617 (Ar), 1585 (Ar), and 1524 (Ar); δ_H(400 MHz, CD_3OD) 4.54 (2H, s, CH_2Br), 6.35 (1H, d, *J* 1.9, 3-H), 6.47 (1H, dd, *J* 1.9 and 8.6, 5-H), 7.38 (1H, d, *J* 8.6, 6-H); ^1H NMR data agreed with those reported.[133] ; δ_C(100 MHz, CD_3OD) 77.07 (CH_2), 99.75 (CH), 113.66 (CH), 114.54 (C), 126.64 (CH), 169.61 (C), 178.75 (C), and 200.47 (C).

10

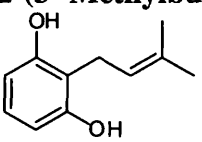
Experimental for Chapter 6

1,3-*Bis*(tetrahydropyran-2'-yloxy)benzene 62



Dihydropyran (16.60 cm^3, 0.18 mol, 4 eq) was cooled to 0 °C and then 2-3 drops of conc. HCl added. Resorcinol **109** (5.000 g 45.4 mmol, 1 eq) was then added slowly. The reaction was then left to stir for 3 hours at RT. After this time, Et_2O (100 cm^3) was added, the organic solution washed with 10% aqueous sodium hydroxide solution (50 cm^3) and brine (2 × 50 cm^3) and dried ($MgSO_4$). Concentration *in vacuo* gave a colourless oil which solidified under vaccum. Recrystallisation from hexane gave the acetal **368** (11.359 g, 40.86 mmol, 90%) as plates; m.p. 72-75 °C.(Lit.[136] 76-77 °C); δ_H(200MHz; $CDCl_3$) 1.57 (12H, m, 6 × CH_2), 3.64 (4H, m, 2 × CH_2O), 5.40 (2H, m, 2 × OCHO), 6.68 (2H, dd, *J* 2.1 and 8.1, 4- and 6-H), 6.76 (1H, d, *J* 2.1, 2-H), and 7.16 (1H, t, *J* 8.1, 5-H). All other data matched that reported.[134]

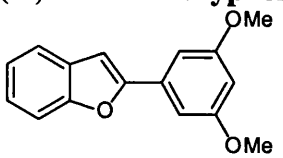
2-(3'-Methylbut-2'-enyl)resorcinol 366



THP-protected resorcinol **368** (2.506 g, 9.01 mmol) was dissolved in dry THF (20 cm^3) and cooled to –30°C under nitrogen. *n*-Butyllithium (1.40 mol dm^{-3} in hexane, 7.70 cm^3, 10.82 mmol, 1.2 eq) was added over 15 min then the reaction stirred at –30°C for a further 15 min. Bromo-3-methylbut-2-ene (1.60 cm^3, 13.52 mmol, 1.5 eq) was added and the reaction stirred at RT. After 2 h, the reaction was quenched by pouring into water. This was then extracted into Et_2O (3 × 30 cm^3), the combined extracts washed with aqueous NaOH (1 mol dm^{-3}, 50 cm^3), water (50 cm^3) and brine (2 × 50 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo*. This crude oil was taken up in MeOH-H_2O (9:1, 20 cm^3) and aqueous oxalic acid (5%, 2.0 cm^3) added slowly. The resulting slurry was stirred at RT overnight. The solution was diluted with water and extracted into Et_2O (3 × 50 cm^3), the combined organic extracts washed with water and brine (2 × 20 cm^3 each), dried and concentrated *in vacuo*. Chromatography on silica (Et_2O-hexane, 1:1) followed by recrystallisation from hexane/$CHCl_3$ gave the phenol **366** (0.964 g, 5.41 mmol, 60%) as plates: m.p. 69-70 °C (Lit.[10] 71.5-72.5 °C); R_F [hexane-EtOAc (1:1)] 0.71; ^1H NMR, IR and MS already reported.[10,57,135]; δ_H(400 MHz, $CDCl_3$) 1.72 (3H, s, Me), 1.88 (3H, s, Me),

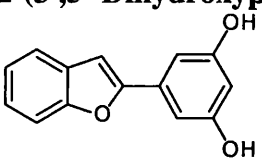
3.41 (2H, d, *J* 7.1, =CH-CH_2-), 5.26 (1H, t, *J* 7.1, =C*H*-CH_2), 6.38 (2H, d, *J* 8.1, 4-H and 6-H), and 6.90 (1H, t, *J* 8.1, 5-H).
New data: δ_C(100 MHz, $CDCl_3$) 18.27 (CH_3), 23.10 (CH_2), 26.17 (CH_3), 108.81 (CH), 114.30 (C), 122.03 (CH), 127.72 (CH), 135.83 (C), and 155.34 (C).

(3',5'-Dimethoxyphenyl)benzo[*b*]furan 370



Dicyclohexylcarbodiimide (1.900 g, 14.2 mmol, 1.26 eq) in dry CH_2Cl_2 (30 cm^3) was added to a solution of 2-hydroxybenzyltriphenylphosphonium bromide **369** (6.60 g, 15.0 mmol, 1.34 eq), 4-dimethylaminopyridine (0.220 g, 1.8 mmol, 0.16 eq), and 3,5-dimethoxybenzoic acid **187** (2.000 g, 11.0 mmol) in dry CH_2Cl_2 (100 cm^3) under nitrogen, and the mixture was stirred overnight. The solution was concentrated *in vacuo* and the residue dissolved in dry toluene (100 cm^3). Triethylamine (8.60 cm^3, 62.0 mmol, 5.65 eq) was added and the mixture heated under reflux under nitrogen overnight. After cooling, the solution was filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, CH_2Cl_2) followed by recrystallisation from propan-2-ol gave the *benzofuran* **370** (1.820 g, 7.17 mmol, 65%) as needles; m.p. 57-59 °C; R_F(CH_2Cl_2) 0.65; υ_{max} (KBr)/cm^{-1}: 1599 (Ar), 1570 (Ar ring), and 1156 (C-O-C); δ_H(200MHz; $CDCl_3$) 3.88 (6H, s, 2 × OMe), 6.51 (1H, t, *J* 2.3, 4'-H), 7.01 (1H, s, 3-H), 7.07 (2H, d, *J* 2.3, 2'-H), and 7.22-7.56 (4H, m, 4 × Ar-H); δ_C(50MHz; $CDCl_3$) 55.45 (CH_3), 100.99 (CH), 101.83 (CH), 102.93 (CH), 111.17 (CH), 120.97 (CH), 122.96 (CH), 124.38 (CH), 129.10 (C), 132.18 (C), 154.78 (C), 155.67 (C), and 161.06 (C); *m/z* (EI) 254 (M^+, 100%), 211 (9), and 169 (11); (Found: C, 75.8; H 5.6% ; M^+, 254.0943; $C_{16}H_{14}O_3$ requires C, 75.59; H 5.55%; *M*, 294.0944).

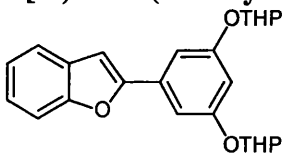
2-(3',5'-Dihydroxyphenyl)-benzo[*b*]furan 371



Benzofuran **370** (0.751 g, 2.96 mmol) was dissolved in dry CH_2Cl_2 (25 cm^3) and cooled to –78 °C under nitrogen. Boron tribromide (1 mol dm^{-3} in CH_2Cl_2, 8.80 cm^3, 8.87 mmol, 3 eq) was added slowly then the reaction stirred at RT. After 2 h, the reaction was quenched with water and extracted into EtOAc (3 × 30 cm^3). the combined extracts were washed with brine (2 × 50 cm^3), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography on silica (1:1 EtOAc/hexane) gave the benzofuran **371** (0.434 g, 1.92 mmol, 65%) as plates; m.p. 140-143 °C; R_F [hexane-

EtOAc (1:1)] 0.40; υ_{max} (KBr)/cm^{-1} 3332 (OH), 1621 (Ar), 1577 (Ar), and 1500 (Ar); δ_H(400 MHz, d_6-acetone) 6.29 (1H, t, *J* 2.0, 4'-H), 6.80 (2H, d, *J* 2.0, 2'/6'-H), 7.03 (1H, s, 3-H), 7.08-7.19 (2H, m, 5- and 6-H), 7.42 (1H, d, *J* 8.0, 4- or 7-H), 7.48 (1H, d with fine splitting, *J* 8.0, 7- or 4-H) and 8.34 (2H, br s, 2 × OH); δ_C(100 MHz, d_6-acetone) 102.77 (CH), 104.57 (CH), 104.76 (CH), 112.15 (CH), 122.28 (CH), 124.29 (CH), 125.63 (CH), 130.54 (C), 133.39 (C), 155.95 (C), 157.27 (C), and 160.29 (C); *m/z* (EI) 226 (M^+, 100%), 197 (15), 113 (10), and 83 (50); (Found: M^+, 226.0630. $C_{14}H_{10}O_3$ requires *M*, 226.0630).

2-[3',5'-*Bis*(tetrahydropyran-2''-yloxy)phenyl]-benzo[*b*]furan 372

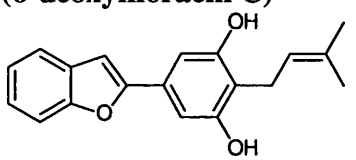


Acid **314** (2.348 g, 7.29 mmol, 1 eq) was dissolved in dry CH_2Cl_2 (80 cm^3) under nitrogen. To this was added sequentially, dimethylaminopyridine (0.142 g, 1.17 mmol, 0.16 eq), phosphonium salt **369** (4.387 g, 9.77 mmol, 1.34 eq), and dicyclohexylcarbodiimide (1.893 g, 9.19 mmol, 1.26 eq) as a solution in dry CH_2Cl_2 (10 cm^3). The resulting slurry was stirred at RT. After 24 h, the solvent was removed *in vacuo* and the residue taken up in dry toluene (50 cm^3). Dry triethylamine (5.50 cm^3, 41.20 mmol, 5.65 eq) was added and the reaction heated to reflux for 6 h. After cooling to RT, the slurry was filtered, the precipitate washed with EtOAc (10 cm^3) and the filtrate concentrated *in vacuo*. Chromatography on silica (hexane-CH_2Cl_2, 1:1) followed by recrystallisation from propan-2-ol gave the *benzofuran* **372** (1.900 g, 4.82 mmol, 66%) as colourless plates: m.p. 110-112 °C; R_F [hexane-CH_2Cl_2 (1:1)] 0.24; υ_{max} (film)/cm^{-1} 1612 (Ar), 1590 (Ar), and 1567 (Ar); δ_H(400 MHz, $CDCl_3$) 1.57-2.08 (12H, m, 6 × -CH_2-), 3.63-3.67 (2H, m, -OCH_2-), 3.92-3.98 (2H, m, -OCH_2-), 5.50-5.52 (2H, m, 2 × -OCHO-), 6.79 (1H, t, *J* 2.4, 4'-H), 6.99 (1H, s, 3-H), 7.19-7.29 (4H, m, 5-H, 6-H, 2'-H and 6'-H), 7.59 (1H, d with fine splitting, *J* 8.4, 4-H), and 7.56 (1H, d with fine splitting, *J* 8.4, 7-H); δ_C(100 MHz, $CDCl_3$) 19.02 (CH_2), 25.62 (CH_2), 30.72 (CH_2), 62.37 (CH_2), 96.85 (CH), 102.12 (CH), 105.87 (CH), 106.90 (CH), 111.58 (CH), 121.28 (CH), 123.25 (CH), 124.65 (CH), 129.56 (C), 132.47 (C), 155.19 (C), 156.17 (C), and 158.86 (C); *m/z* (EI) 394 (M^+, 3%), 226 (100), and 83 (70); (Found: C, 73.0; H, 6.5%; M^+, 394.1777. $C_{24}H_{26}O_5$ requires C, 73.08; H, 6.64% ; *M*, 394.1780).

Alternative preparation of 2-[3',5'-bis(tetrahydropyran-2''-yloxy)phenyl]-benzo[*b*]furan 372

3,4-Dihydro-2*H*-pyran (1.10 cm^3, 11.58 mmol, 4 eq) was cooled to 0°C then 2-3 drops of conc. HCl added. Benzofuran **371** (0.654 g, 2.89 mmol, 1 eq) was added portion wise over 10 min, then the ice bath removed and the solution stirred at RT. After 3 h, the reaction was diluted with Et_2O (20 cm^3) and washed with saturated aqueous sodium bicarbonate (3 × 10 cm^3), brine (3 × 10 cm^3), then dried (Na_2SO_4) and concentrated *in vacuo* to give an off-white oil which crystallised on standing. The product was filtered off and washed with hexane and dried under suction. Recrystallisation from hexane gave the *benzofuran* **372** (0.393 g, 1.00 mmol, 35%). All data matched those reported above.

2-[3',5'-Dihydroxy-4'-(3''-methylbut-2''-enyl)phenyl]-benzo[*b*]furan 367 (6-deoxymoracin C)



Benzofuran **372** (1.404 g, 3.56 mmol) was dissolved in dry THF (10 cm^3) and cooled to –30°C under nitrogen. *n*-Butyllithium (1.16 mol dm^{-3} in hexane, 3.70 cm^3, 4.28 mmol, 1.2 eq) was added over 15 min then the reaction stirred at –30°C for a further 15 min. Bromo-3-methylbut-2-ene (0.85 cm^3, 7.13 mmol, 2 eq) was added and the reaction stirred at RT. After 2 h, the reaction was quenched by pouring into water. This was then extracted into Et_2O (2 × 30 cm^3), the combined extracts washed with water (50 cm^3) and brine (2 × 50 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo*. This crude oil was taken up in MeOH-H_2O (9:1, 10 cm^3) and aqueous oxalic acid (5%, 1.0 cm^3) added slowly. The resulting slurry was stirred at RT for 2 h. Most of the solvent was removed *in vacuo*, then the residue taken up in EtOAc (50 cm^3). This was then washed with water and brine (2 × 20 cm^3 each), dried and concentrated *in vacuo*. Recrystallisation from $CHCl_3$ gave the *benzofuran* **372** (0.645 g, 2.19 mmol, 62%) as off-white plates: m.p. 158-160 °C; R_F [hexane-EtOAc (2:1)] 0.65; υ_{max} (KBr)/cm^{-1} 3462 (OH), 1624 (Ar), 1575 (Ar), 1505 (Ar), and 1043 (=C-H); δ_H(400 MHz, d_6-acetone) 1.52 (3H, s, Me), 1.65 (3H, s, Me), 3.27 (2H, d, *J* 7.1, =CH-CH_2-), 5.19 (1H, t, *J* 7.1, =C*H*-CH_2-), 6.85 (2H, s, 2'-H and 6'-H), 6.90 (1H, s, 3-H), 7.03-7.16 (2H, m, 5-H and 6-H), 7.37 (1H, d with fine splitting, *J* 8.1, 4-H), 7.46 (1H, d with fine splitting, *J* 8.1, 7-H), and 8.22 (2H, br s, 2 × OH); δ_C(100 MHz, d_6-acetone) 18.32 (CH_3), 23.52 (CH_2), 26.31 (CH_3), 101.90 (CH), 101.91 (CH), 104.80 (CH), 112.03 (CH), 117.49 (C), 122.12 (CH), 124.22 (CH), 125.38 (CH), 129.83 (C), 130.64 (C), 131.52 (C), 155.87 (C), 157.49 (C), and

157.68 (C); *m/z* (EI) 294 (M^+, 85%), 279 (35), 239 (100), and 57 (35); (Found: M^+, 294.1258. $C_{19}H_{18}O_3$ requires; *M*, 294.1256).

Cell Culture Feeding Experiments

General details

All feeding experiments were conducted in a sterile cabinet. For all experiments, cell cultures were stored in sterile 100 cm^3 conical flasks stoppered with sterile cotton wool. Samples were taken with Sterile Gilson apparatus into 5 cm^3 epindorphs. Centrifugations were done on Mistral 3000E or Sanyo 'Microcentaur' centrifuges spinning at 2500 and 13000 rpm, respectively. Mass spectrometry was carried out on a Micromass Platform LCMS with a C_{18} column (4.6 × 150 mm) using solvent A (10 mM ammonium acetate/0.1% fomic acid) and solvent B (10 mM ammonium acetate/90% acetonitrile/0.07% formic acid) in a 30 min gradient (100%A→100%B). Chromatography was carried out on a Gilson Unipoint Autopreparative HPLC system with a Spherisil ODS2 (C_{18}) column (10 × 150 mm, particle size, 5 μm), using solvent A (0.1 M ammonium dihydrogen phosphate/0.003% *ortho*-phosphoric acid) and solvent B (75% acetonitrile/25% solvent B). Solvent systems were isocratic (70% solvent B/30% solvent A) or on a 40 min gradient (100%A→100%B) with a flow rate of 5 cm^3/min.

CELL CULTURE FEEDING EXPTS

Six experiments were carried out in total, three experiments with each of the substrates:

	Suspension Solvent	Substrate Addition Solvent
1.	H_2O	DMSO
2.	H_2O/MS4 Growth Medium	DMSO
3.	H_2O	Aqueous Tween 80

Typical Procedure (under sterile conditions):
90-100 cm^3 of original cell suspension was centrifuged gently and the supernatant carefully decanted. The cell pellet was then gently resuspended in 30 cm^3 of sterile H_2O (or 30 cm^3 of 1:1 H_2O/MS4 growth medium) in a 100 cm^3 conical flask.

The substrate (for solvents, see below) was then added in one protion.

5 mg substrate in 0.3 cm^3 DMSO (expts. 1 and 2)
5 mg substrate in 1 cm^3 Tween solution (10 cm^3 of sterile H_2O + 2 drops Tween 80).

The cell suspensions were then shaken at 25 °C.

Sampling Technique (sterile)
(Samples taken after 2, 6 and 9 days.)
0.5 cm^3 of each cell suspension was pipetted into a 2 cm^3 epindorph. This was centrifuged at 13,000 rpm for 5 min, then the supernatant A decanted and analysed. The cell pellet was then resuspended in 0.5 cm^3 MeOH and vortexed for ~30 s. The MeOH solution was then centrifuged as before and the supernatant B analysed by LCMS.
[**NB.** In each experiment, supernatant A (the original cell liquid) was analysed after 2 days, but contained no starting material, desired product, or naturally-occurring chalcomoracin.]

Work-up

The cell suspension was transferred to Falcon 50 cm^3 centrifuge tubes, the experiment flask rinsed with a small amount of sterile H_2O, and the combined solution centrifuged at 2500 rpm for 30 min. The supernatant was decanted off and stored. 10 cm^3 of sterile water was added to the cell pellet and vortexed. This was centrifuged as before, the supernatant decanted off and this process repeated. After a second wash with sterile H_2O, 10 cm^3 of MeOH was added to the pellet, vortexed well (~1 min) and centrifuged at 13000 rpm for 10 min.. The supernatant was transferred to a preweighed glass vial and dried, either by speedivac, or by blowing with N_2.

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