STUDIES ON NEW APPROACHES FOR THE RADIOLABELLING OF (+)-CATECHIN

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

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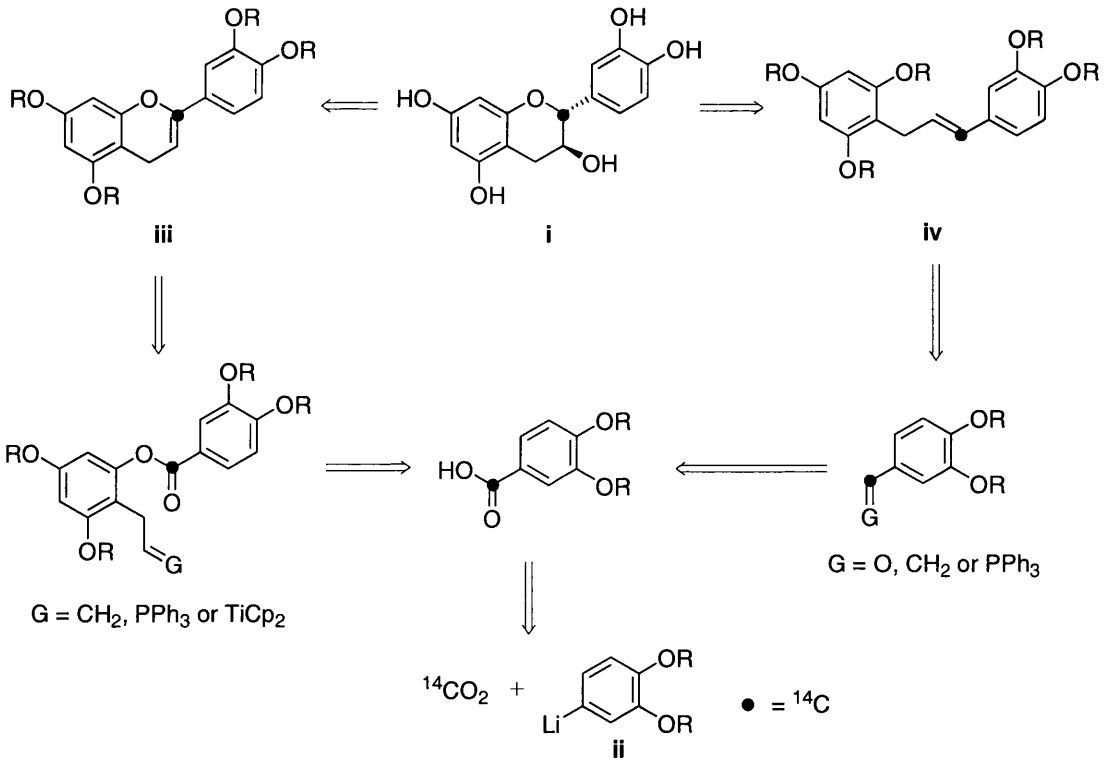
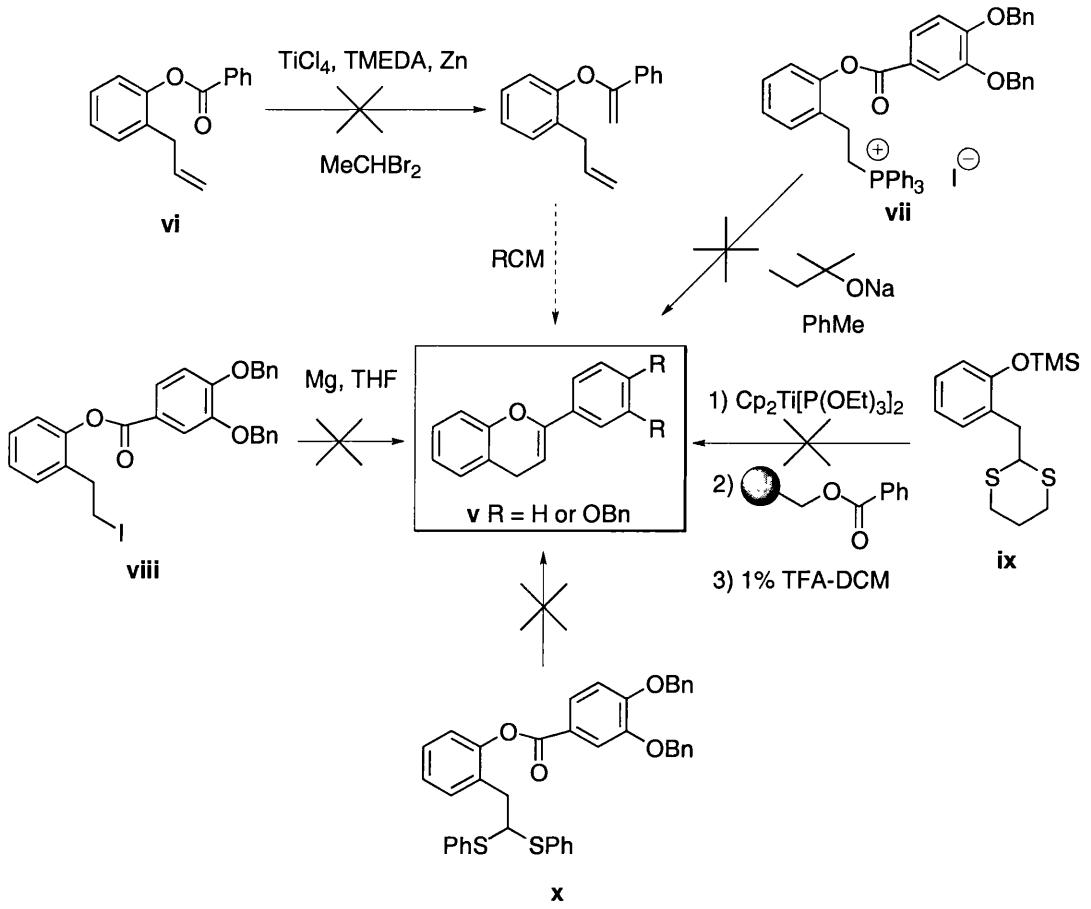
Abstract

Flavonols are polyphenolic plant secondary metabolites found in high concentrations in fruits, vegetables and beverages such as tea and red wine. Many possess antioxidant and free radical scavenging activity and epidemiological studies indicate that consumption of flavonols is associated with a reduced risk of coronary heart disease. (+)-Catechin is one such compound found in red wine and green tea. The absorption and metabolism of (+)-catechin is poorly understood and radiolabelled material is required to determine its bioavailability and role as an *in vivo* antioxidant.

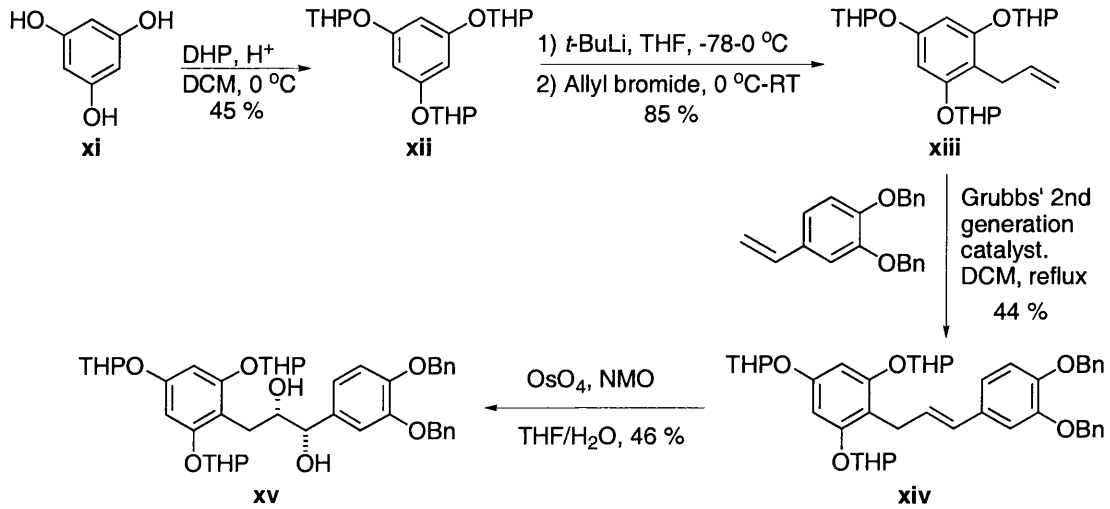
We envisaged two main approaches in our retrosynthesis of labelled (+)-catechin **i** from aryllithium **ii** and radiolabelled carbon dioxide. The first involved flavene **iii** as a key intermediate whilst the second relied on the preparation of 1,3-diarylpropene **iv**.



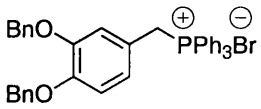
A number of routes to model flavenes **v** were attempted. A range of potential synthetic intermediates **vi-x** were prepared, but all failed to give the cyclised product **v**.



Various routes to synthetic intermediates corresponding to the 1,3-diarylpropene synthon **iv** were then investigated. The most successful approach proved to be cross-metathesis. Thus, phloroglucinol **xi** was protected as its tris-THP ether **xii**, lithiated and allylated to give a mixture of diastereomeric compounds **xiii**. Cross-metathesis then gave 1,3-diarylpropene **xiv** and dihydroxylation provided the racemic *syn* diol **xv**.



Other potential substrates for alkenation reactions were prepared including phosphonium salt **xvi** and sulfone **xvii** and a range of novel benzothiazole chemistry is discussed.



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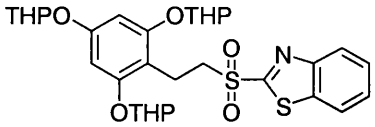

xvii

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Finally, I would like to thank my family for their encouragement and support throughout my time at Glasgow.

Abbreviations

Å	angstrom
Ac	acetyl
AD	Asymmetric dihydroxylation (AD-mix)
AIBN	2,2'-azobis(2-methylpropionitrile)
Allyl	2-propenyl
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad (NMR)
BT	benzothiazol-2-yl
Bz	benzoyl
Bu	butyl
n-BuLi	*n*-butyllithium
t-Bu	*tert*-butyl
CI	chemical ionization
d	doublet (NMR)
d	day(s)
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	Dichlorodicyanoquinone
DEAD	Diethyl azodicarboxylate
de	diastereomeric excess
DEPT	Distortionless Enhancement through Polarisation Transfer
DHP	2,3-Dihydropyran
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine (Hünigs base)
DIPT	Diisopropyltartrate

DMAP	4-dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N,N'*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dr	diastereomeric ratio
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EGC	(-)-epigallocatechin
EGCG	(-)-epigallocatechin gallate
EI	electron impact
eq	equivalents
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
Hz	Hertz
IBX	*O*-Iodoxybenzoic acid
Ipc	Isopinocampheyl
IR	infrared
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
m	multiplet (NMR)
M	molarity
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megaHertz
min.	minute(s)

mL	millilitre(s)
mmol	millimole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MS	Mass spectrum
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium *para*-toluenesulfonate
i-Pr	*iso*-propyl
PTSA	*para*-toluenesulfonic acid
q	quartet (NMR)
RCM	ring closing metathesis
RT	room temperature
SAR	Structure-activity relationship
s	singlet (NMR)
t	tertiary
t	triplet (NMR)
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl (TBDMS)
temp.	temperature
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography

TMEDA	*N*, *N*, *N*', *N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl (tosyl)

CHAPTER 1 – Introduction

1.1 What are flavonoids?

Flavonoids are a large family of phenolic plant secondary metabolites. In fact, they are the largest subset of naturally occurring phenols.[1] Despite over 3000 different examples being known,[2] flavonoids share a common core structure, a chroman system, which makes them very similar in structure. The diversity in structure comes from differing hydroxylation patterns in the A-ring of the chroman and substitution at either the 2- or 3-position with a hydroxylated aromatic B-ring. The core structure, numbering pattern and designation of the A, B and C rings is shown below (**Figure 1.1**).

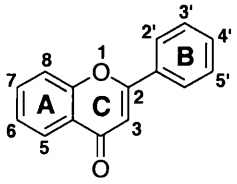


Figure 1.1

Flavonoids are divided into eight main subsets according to the oxidation of the C-2-C-3 bond, the oxidation of the C-4 position and the substitution at the 2- and 3-positions. Four other subsets also exist. These are the aurones, coumarins, chalcones and dihydrochalcones, which while strictly speaking not flavonoids, are usually included due to their physical properties being similar to flavonoids. A summary of the subsets is shown below (**Table 1.1**).

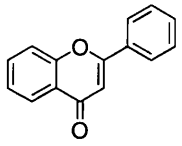
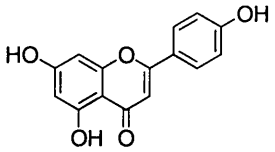
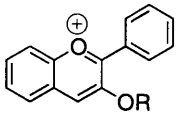
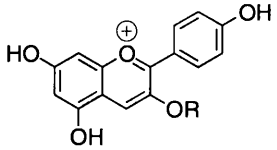
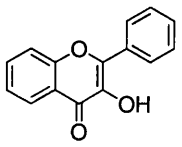
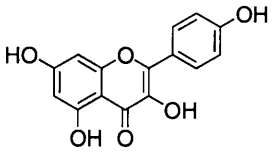
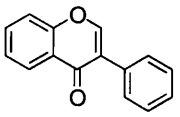
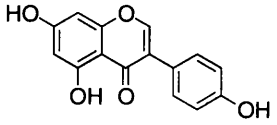
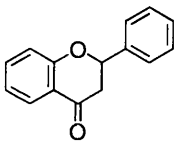
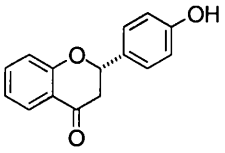
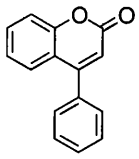
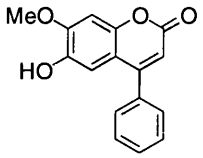
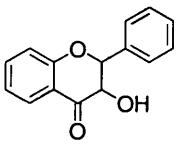
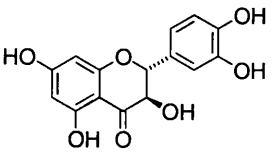
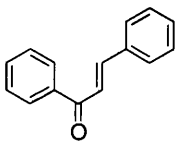
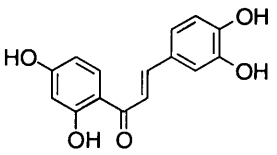
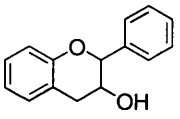
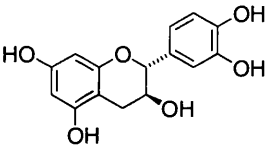
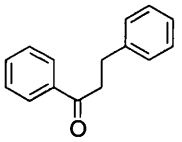
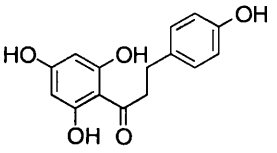
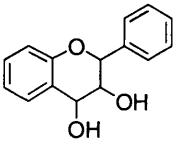
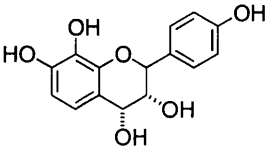
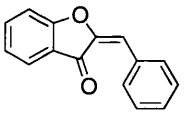
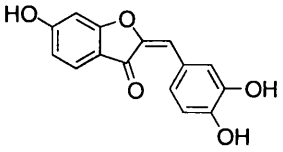
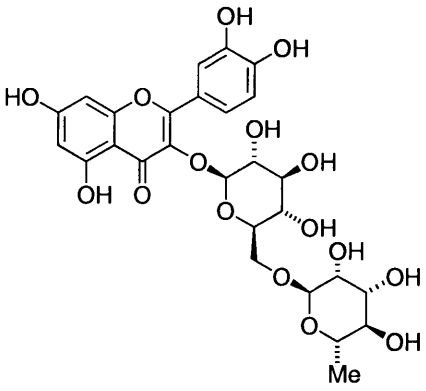
FLAVONOID	EXAMPLE	FLAVONOID	EXAMPLE
FLAVONES	APIGENIN	ANTHOCYANIDINS R = H ANTHOCYANINS R = SUGAR	PELARGONIDIN PELARGONIDIN GLUCOSIDE
			
FLAVONOLS	KAEMPFEROL	ISOFLAVONES	GENISTIEN
			
FLAVANONES	NARINGENIN	COUMARINS	DALBERGIN
			
DIHYDROFLAVONES	TAXIFOLIN	CHALCONES	BUTIEN
			
FLAVAN-3-OLS	(+)-CATECHIN	DIHYDROCHALCONES	PHLORETIN
			
FLAVAN-3,4-DIOLS	TERACACIDIN	AURONES	SULPHURETIN
			

Table 1.1

Flavonoids occur mainly as glycosides in plants and plant-derived products e.g. rutin **1** (**Figure 1.2**). The aglycones are well known too, with 500 different examples reported in the literature by 1997.[3]

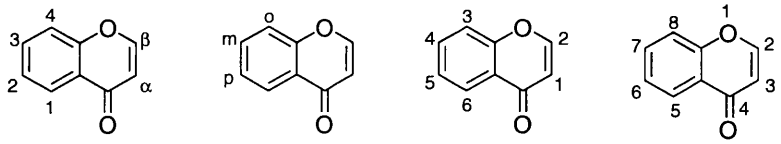


1

Figure 1.2

1.2 Nomenclature

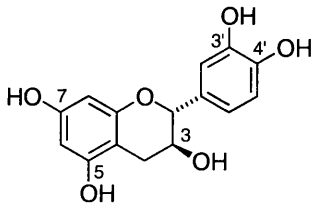
The nomenclature of flavonoids has changed several times since their discovery in the late 19th century.[4,5] The various numbering systems that have been used for chromone are shown in **Figure 1.3** (**2-5**). Chromone has had a variety of different names over the years which include 2,3-benzopyrone-(4), 4-oxochromen, 4*H*-1-benzopyran-4-one and chromen-4-one, of which 4*H*-1-benzopyran-4-one was adopted by Chemical Abstracts in 1972. This name can also be the basis for naming flavones and flavonols.



2 **3** **4** **5**

Figure 1.3

The names of flavonoids may also be based on the flavonoid core structure. For example, (+)-catechin **6** (**Figure 1.4**) could be named (2*R*, 3*S*)-3', 4', 3, 5, 7-pentahydroxyflavan. For simplicity, the flavonoids discussed in this thesis will be referred to by their "trivial" names e.g. (+)-catechin or by the parent flavonoid structure e.g. (2*R*, 3*S*)-3', 4', 3, 5, 7-pentahydroxyflavan.



6

(+)-catechin
(2*R*,3*S*)-3', 4', 3, 5, 7-pentahydroxyflavan

Figure 1.4

1.3 Biological activity

Flavonoids are widespread in nature and are continuously synthesised within plants. As well as being implicated in the defence of plants from harmful ultraviolet and visible light,[6] flavonoids are responsible for the colour of a wide variety of plants.

High flavonoid levels in plants have been associated with high boron levels. This is an interesting observation when considered with the fact that many hydroxyflavones form stable complexes with boric acid, as well as with a wide variety of metals.[7] Indeed, the ability of these compounds to chelate metals, combined with their free-radical scavenging ability, has led to the suggestion that flavonoids act as dietary antioxidants. It is this property as potential inhibitors of free-radical-mediated diseases such as coronary heart disease, stroke and cancers that has received the most attention in recent literature.

It has been found that the average dietary intake of quercetin in the Netherlands is 16 mg/day obtained mainly from tea, onions and apples.[8] It has also been estimated that the human consumption of flavonoids may exceed 800 mg/day.[8] Due to the potentially high consumption of these compounds, a vast amount of research has gone into studying the *in vivo* and *in vitro* properties of flavonoids.

Many flavonoids are known to possess a variety of biological properties in mammals including anti-inflammatory, anti-allergenic, anti-hepatotoxic, anti-anginal, anti-ulcer and anti-oxidant properties.[9] Some flavonoids have also been shown to possess *in*

vitro and *in vivo* anti-viral properties against several viruses such as the rhinovirus, herpes simplex virus, poliovirus and HIV.[9]

Moderate consumption of red wines, which are a rich source of flavonoids, is associated with a reduced risk of coronary heart disease. A high intake of saturated fats has been linked to higher levels of coronary heart disease, yet this is not true in certain regions of France where red wine is consumed instead of beer (the French paradox).[9,10] There is a rapid increase in the antioxidant activity of the serum of human volunteers after consuming red Bordeaux wine and it is the phenolic components of the wine, rather than the alcohol content, which exert the effect.[11]

Resveratrol **7**, a non-flavonoid phenolic also found in red wine, has received a lot of attention in the popular press due to its ability to prevent platelet aggregation in coronary arteries and reduce the incidence of cancer (**Figure 1.5**). However, the hydroxybenzoate gallic acid **8** and certain flavonoids, in particular the flavan-3-ols (+)-catechin **6** and (-)-epicatechin **9**, as well as the flavonols quercetin **10** and myricetin **11**, are present in much higher concentrations and show similar, if not greater, antioxidant and anti platelet aggregation activity.[11]

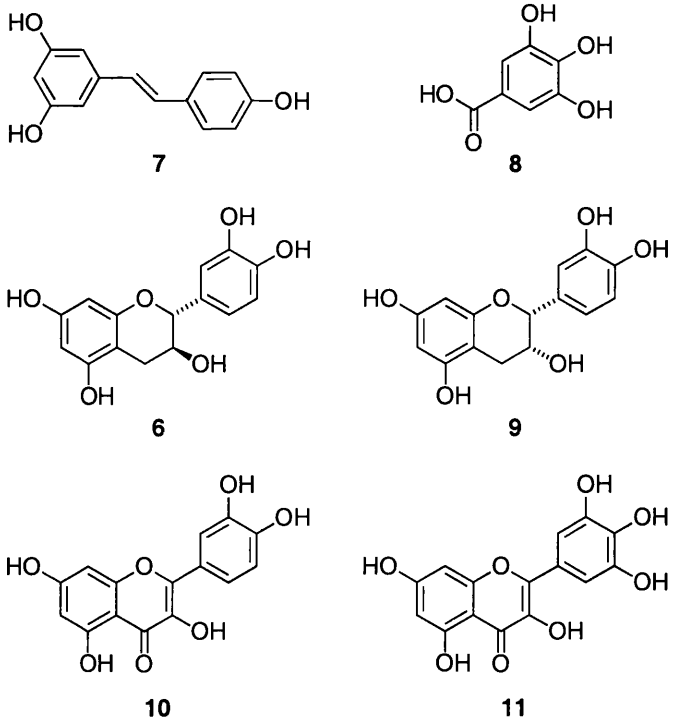


Figure 1.5

1.4 Antioxidant ability of phenols

Despite the increasing amount of evidence showing flavonoids acting as antioxidants *in vitro*, their efficacy *in vivo* is still poorly understood. This may be attributed to the lack of information regarding the bioavailability of these compounds. It has only recently been proved that flavonoids from dietary sources are absorbed at levels that could allow them to act as antioxidants. It is widely believed that flavonoid glycosides are initially hydrolysed to the aglycones, however it has recently been proved that glycosides can be absorbed. The absorption of catechins has also been studied and it was found that (-)-epigallocatechin gallate (EGCG) **12** and epicatechin gallate (EGC) **13** (**Figure 1.6**) could be detected after the consumption of green tea, decaffeinated green tea extracts and dark chocolate and that glucuronide and sulfate conjugates of (+)-catechin and 3'-*O*-methyl-(+)-catechin were detected after consumption of red wine.[12]

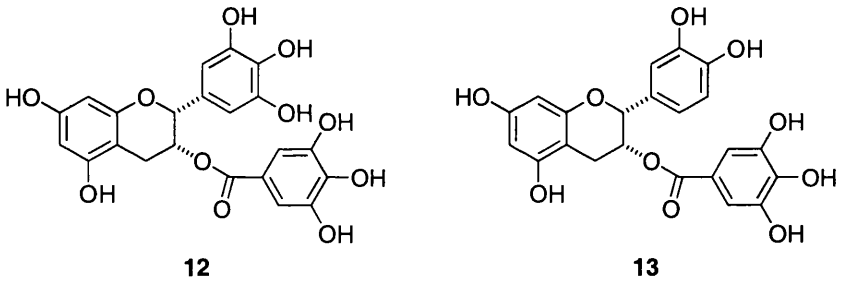


Figure 1.6

The level of absorption does not normally exceed a few percent of the ingested dose and food composition may be an important factor that affects the bioavailability. Binding to proteins would reduce the availability, whereas alcohol may increase the availability.[12] Evidence for the latter suggestion has been observed in the increased uptake of red wine phenolics compared to the levels observed after consumption of alcohol-free red wine.[12] Recent data also suggests that specific flavonoids may have improved absorption in the presence of fats. For example, catechins from green tea are absorbed to a greater extent when administered as phospholipid complexes compared to the free flavonoids.[12]

A variety of mechanisms have been proposed that account for phenols, including flavonoids acting as biological antioxidants. Flavonoids could act as antioxidants by inhibiting enzymes such as xanthine oxidase, which is involved in the generation of reactive superoxide radicals.[13] The chelation of low valent metal ions like Fe^{2+} and Cu^{+}, which can generate the highly reactive hydroxyl radical by the Haber-Weiss and Fenton reactions (**eq 1** and **eq 2**) may also contribute to their effect.[14]

$$H_2O_2 + M^{n+} + O_2^{\bullet -} \longrightarrow HO^{-} + O_2 + M^{n+} + HO^{\bullet} \quad \text{(eq 1)}$$

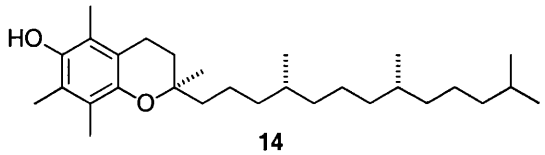
$$H_2O_2 + M^{n+} \longrightarrow HO^{-} + M^{(n+1)+} + HO^{\bullet} \quad \text{(eq 2)}$$

$$M = Fe^{2+} \text{ or } Cu^{+}$$

Phenols in general may act as antioxidants by directly quenching free radicals *via* hydrogen atom abstraction from a free phenolic hydroxyl (**Scheme 1.1**).[8] If the resulting phenolic radical is stable, then the generation of harmful radicals will be terminated.

Scheme 1.1

This property of phenols led to the suggestion that flavonoids may combat diseases where oxidative damage occurs e.g. cancers and coronary heart disease. This can be explained by flavonoids regenerating natural antioxidants such as α-tocopherol (vitamin E) **14** (**Figure 1.7**).[15]

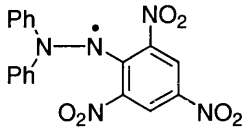


14

Figure 1.7

1.4.1 Antioxidant ability

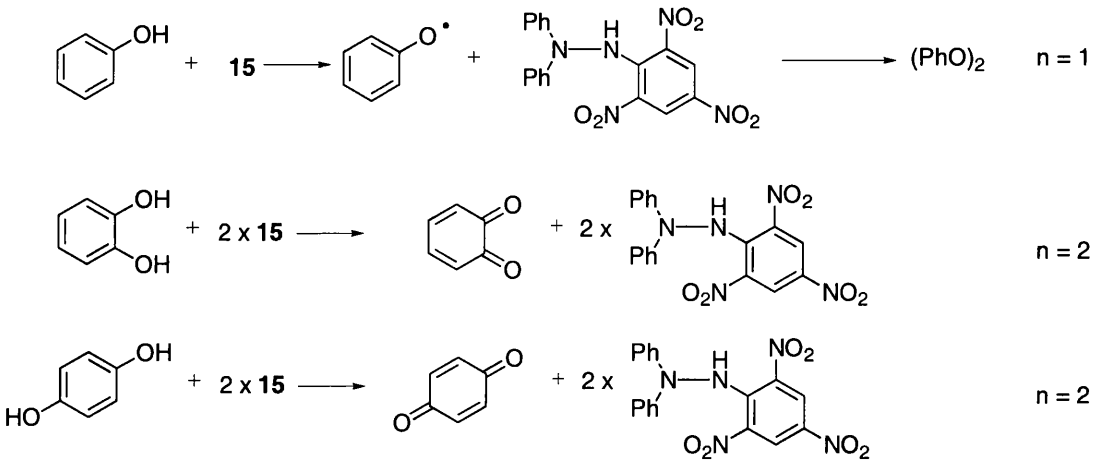
Many different methods have been used to determine the ability of phenols to quench free radicals so acting as chemical reductants and thus antioxidants. The most widely applied method is to react the phenol with a stable radical and simply monitor the disappearance of the radical species' ultraviolet absorbance. A commonly used stable radical is diphenylpicrylhydrazyl (DPPH) **15** (**Figure 1.8**). DPPH has been used to quantify the antioxidant ability of many flavonoids by titrating the flavonoid against the DPPH.[14-16]



15

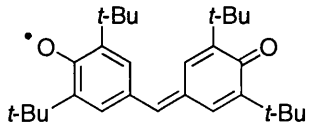
Figure 1.8

Antioxidants are characterised by their stoichiometry, n, which is defined as the number of DPPH molecules reduced by one molecule of the antioxidant. The greater the value for n, the better the antioxidant. This only applies *in vitro*. The stoichiometry is determined by the structure and the oxidation mechanism of the antioxidant. For example, a monophenol (ArOH) could react with DPPH to give aryloxy radical (ArO•), which can dimerise giving $(ArO)_2$. If the dimer is unreactive towards DPPH n will be one. If, however, the dimer can be further oxidised by DPPH, then n will be higher than one. In the case of *o*- and *p*-diphenols, which can be oxidised twice by DPPH, the corresponding *o*- and *p*-quinones are formed. If these quinones are unreactive to DPPH, then n will be two. If the quinones can react further with DPPH, then n will be higher than two. This is illustrated in **Scheme 1.2**.



Scheme 1.2

This method has been used to determine stoichiometries for quercetin **10** and rutin **1**, two of the most commonly studied and significant dietary-derived flavonoids. The values obtained ranged between 3.19 (± 0.02) and 4.53 (± 0.04) for quercetin and 2.1 (± 0.01) and 2.57 (± 0.01) for rutin. The variation in values arises from solvent effects. In this case, the lower values were obtained from studies carried out in DMF and the higher values were obtained using MeOH. Stoichiometries for a variety of flavonoids including quercetin and rutin have also been measured using another stable radical, galvinoxyl **16** (**Figure 1.9**).[17] In this case the values of 3.27 ± 0.04 for quercetin and 3.18 ± 0.01 for rutin were obtained using EtOH as solvent. This study also showed (+)-catechin to be a good antioxidant with a value of 2.96 ± 0.01. Interestingly, all of these values are greater than that obtained for vitamin E (2.14 ± 0.12) under the same conditions. Vitamin E is the main lipid-soluble small molecule involved in the human antioxidant defence.

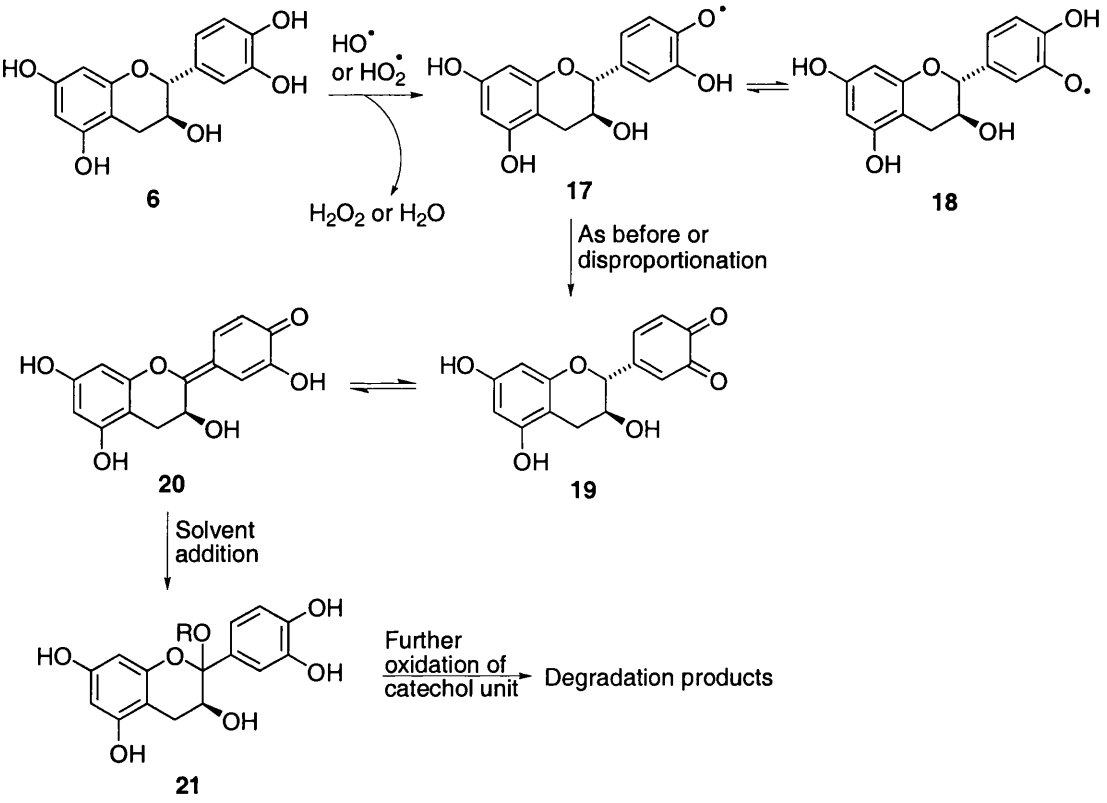


16

Figure 1.9

A proposed mechanism for the high reaction stoichiometry of catechin is shown below in **Scheme 1.3**. This mechanism is based on Dangles proposed mechanism for the oxidation of quercetin.[14] One-electron oxidation (H-atom abstraction) of catechin

6 gives aryloxy radicals **17** and **18**. These are stabilised by H-bonding and by conjugation. A further H-atom abstraction from radicals **17** and **18** leads to a tautomeric mixture of *ortho* and *para*-quinones **19** and **20**. Solvent addition to *para*-quinone **20** gives alcohol **21** and regenerates the catechol-moiety of the B-ring. The newly reformed catechol system can then be re-oxidised, which will lead to degradation products. The regeneration of the catechol-moiety allows further H-atom abstractions to occur thus explaining the higher than expected value for catechin's stoichiometry (i.e. >2).



Scheme 1.3

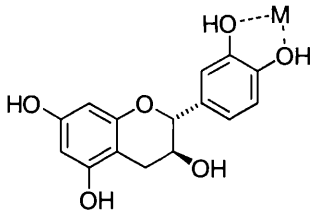
1.4.2 Effect of hydroxylation pattern

A potentially crucial discovery to understanding the antioxidant ability of flavonoids was made by Cos when investigating SAR studies of flavonoids as inhibitors of xanthine oxidase, one of the enzymes responsible for the generation of superoxide radicals.[13] Cos found that the A-ring hydroxylation pattern was important for good binding to the enzyme. The most important positions for good enzyme inhibition were found to be the 5- and 7-positions, while a free 3-hydroxyl reduced the observed

inhibition. It can be concluded from this that any hydroxylation pattern may prove to be important depending on the mode of action *in vivo*.

1.4.3 Prooxidant ability

While investigating the antioxidant and prooxidant potential of a variety of phenolic compounds, Fukumoto and Mazza found that almost all phenolics tested exhibited some prooxidant behaviour i.e. they have the ability to cause cellular damage.[16] The ability of flavonoids to chelate metals such as iron and copper may be vital to their ability to act as antioxidants, but may also allow them to act as prooxidants. The B-ring catechol moiety has been reported to bind metals strongly (**Figure 1.10**).[8] It is believed that the redox potential of the chelated metal is reduced, allowing the formation of low valent metal ions that can assist the formation of damaging radicals *via* the Fenton reaction.[8,18] As stated above, the ability of flavonoids to sequester metal ions may allow them to act as antioxidants, however, it may also promote their prooxidant potential. [19]



M = Metal

Figure 1.10

Flavonoids have also been shown to cause strand scission of DNA molecules in the presence of copper ions leading to the suggestion that they can act as mutagens and carcinogens.[20] The damage caused has been attributed to the various radical and quinonoid species formed during the oxidation process. However, it has been suggested that solvent addition onto the quinones is rapid, resulting in the formation of innocuous products and hence preventing potentially harmful side reactions.[14]

1.5 Metabolism

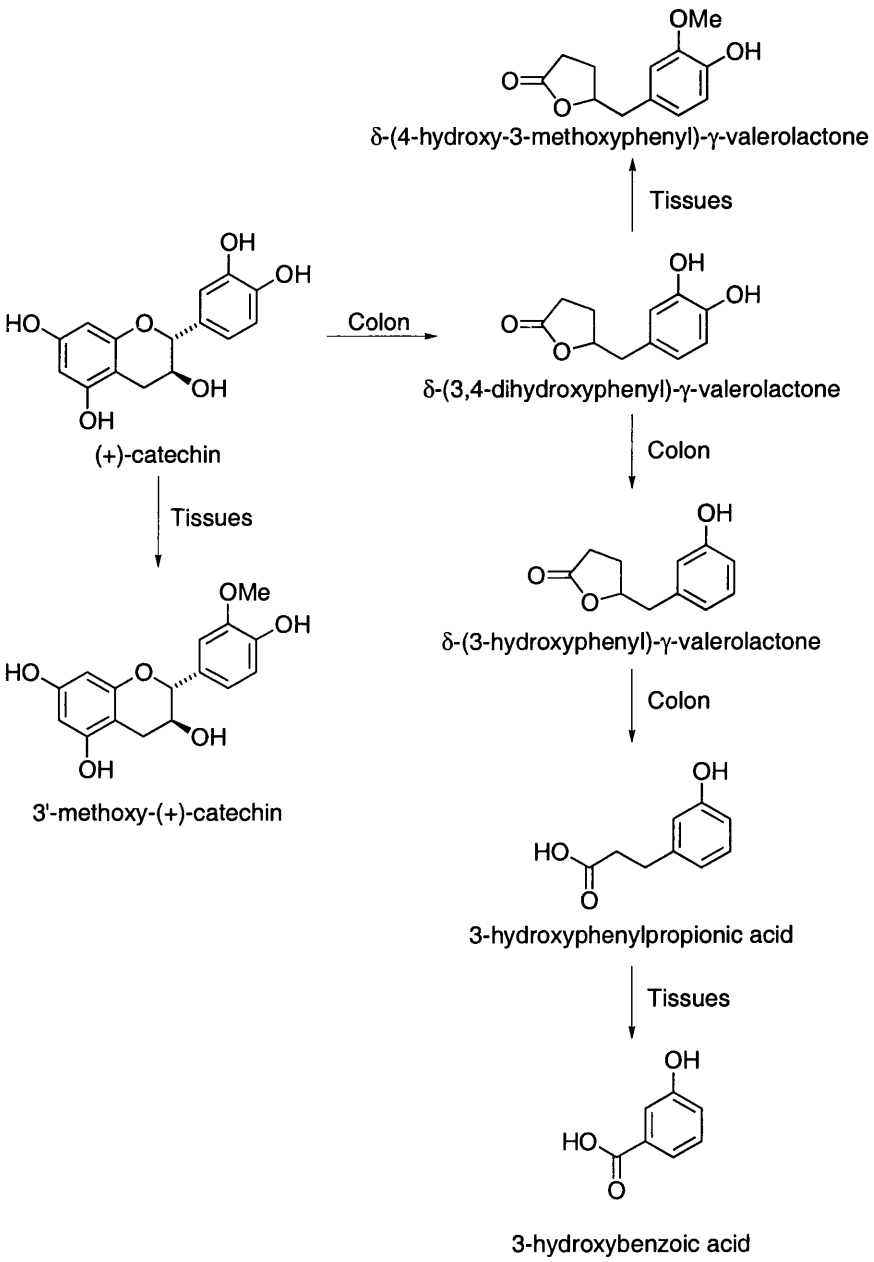
The metabolism of flavonoids in plants, fungi, microorganisms and mammals has been extensively studied and reviewed.[21-23] The metabolism of flavonoids in mammals is discussed below.

1.5.1 Metabolism of Catechins

The two most important areas involved in the metabolism of flavonoids are the liver and colon. The liver is responsible for forming soluble conjugates e.g. sugar conjugates and sulfates and also for *O*-methylation by catechol-*O*-methyltransferase. Bacteria in the colon are responsible for the removal of the sugar moieties, which potentially allows the flavonoids to be reabsorbed.[24] The colonic bacteria are also responsible for the opening of the C-ring to give a variety of phenolic acids, which may themselves contribute to the antioxidant activity of the parent flavonoid.[25,26]

Early studies showed that catechins are extensively metabolized in humans. Oral administration of [U-^{14}C]-(+)-catechin to humans results in around 50 % of the radioactivity being recovered in urine with only 0.5 – 3 % of this as the catechin aglycone.[27] Glucuronation and sulfation in body tissues has been shown to occur, with rats and humans excreting sulfates and glucuronides of 3-methoxy-(+)-catechin in urine, plasma and bile after intravenous injection.[28] Conjugates of (-)-epigallocatechin-3-gallate, (-)-EGCG, and (-)-epicatechin from green tea identified in plasma were sulfates, whereas (-)-epigallocatechin was detected as the glucuronide after oral administration to humans.[12] Of the (-)-EGCG administered, 20 % was also detected unchanged. In addition to these metabolites, glucuronides of the main colonic metabolites δ-(4-hydroxy-3-methoxyphenyl)-γ-valerolactone, δ-(3,4-dihydroxyphenyl)-γ-valerolactone and δ-(3-hydroxyphenyl)-γ-valerolactone and 3-hydroxyphenylpropionic acid were detected in the urine of humans.[29] Sulfates of δ-(3-hydroxyphenyl)-γ-valerolactone and 3-hydroxyphenylpropionic acid were also detected. *In vitro* incubation of (+)-catechin in liver homogenates resulted in the formation of 3'-methoxy-(+)-catechin, proving that *O*-methylation does occur.[30]

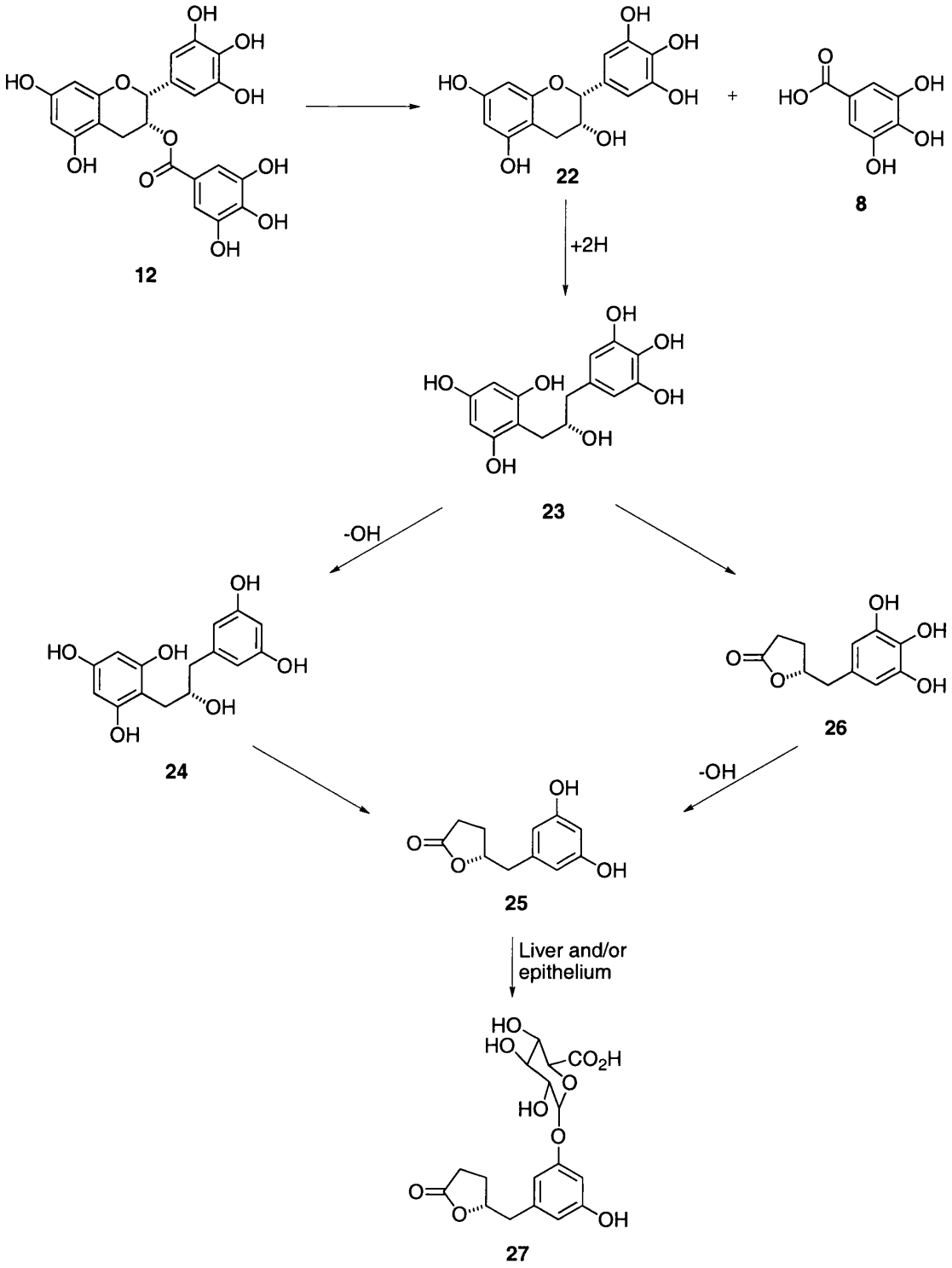
It has been concluded from this data that liver enzymes metabolise catechins giving sulfates and glucuronides and that *O*-methylation by catechol-*O*-methyl transferase also occurs. The basic metabolic processes proposed for catechins are summarised below (**Scheme 1.4**). However, these early studies give at best a patchy and qualitative picture since very many metabolites could not be identified and quantified.



Scheme 1.4

1.5.3.1 Recent work on (-)-EGCG

The metabolic fate of (-)-EGCG in rats has been investigated using (-)-[4-^{3}H]-epigallocatechin gallate administered intravenously and orally.[31] This oral feeding study is one of the key modern investigations into the metabolic fate of this compound. The study revealed that very little intact (-)-EGCG is absorbed from oral dosing. Although 32 % of the radioactivity had appeared in the urine after 72h, showing that absorption of material derived from (-)-EGCG does take place, 68 % of the 30 % excreted by 48h was 3'-glucuronidated 5-(3', 5'-dihydroxyphenyl)-γ-valerolactone. The compound was convincingly identified by NMR spectroscopy and mass spectrometry. 35 % of the total radioactivity appeared in the feces and 41 % of this was (-)-epigallocatechin and 17 % 5-(3', 5'-dihydroxyphenyl)-γ-valerolactone. Thus, a third of the total radioactivity was not recovered and only about 45 % of the radioactivity was found in compounds that could be identified by the researchers e.g. the identified (3', 5'-dihydroxyphenyl)-γ-valerolactone and its glucuronide only accounted for 28 % of the total radioactivity. Similar results were obtained when feeding beagles the same radiolabelled material.[32] The results obtained allowed the authors to propose a metabolic route for (-)-EGCG, which is shown below (**Scheme 1.5**).



Scheme 1.5

The first transformation is the hydrolysis of the galloyl group giving (-)-epigallocatechin (EGC) **22** and gallic acid **8**, which occurs in the intestine. Reductive cleavage of the C-ring of EGC leads to propan-2-ol derivative **23**. This compound then undergoes dehydroxylation at the 4'-position of the B-ring giving alcohol **24**, the

phloroglucinol unit (A-ring) is decomposed and subsequent lactonisation of the C^2-OH with the residual carbonyl group leads to formation of lactone **25** (detected in the feces). An alternative pathway is degradation of the A-ring of propan-2-ol derivative **23** to form lactone **26** after which dehydroxylation at the 4'-position of the B-ring gives lactone **25**. Glucuronidation of lactone **25** gives the major urinary metabolite, glucuronide **27**. Other examples of ring fission on (+)-catechin,[29] (-)-epicatechin[33] and (-)-EGC[33] by intestinal bacteria have been reported.

This paper is the leading metabolic study in the metabolism of flavan-3-ol derivatives despite the low recovery of radioactivity and the lack of conclusive evidence for the assignment of some metabolites. However, in the last few years a new method that overcomes the problems of quantification and identification of metabolites has been introduced, but not yet applied to flavan-3-ols.

1.5.3.2 The technique of HPLC-radiocounting and tandem mass spectrometry

In 2002, a feeding study carried out in rats was published that revolutionised the field.[34] The study used reversed-phase HPLC with on-line radioactivity detection and ion-trap mass spectrometry capable of performing data dependent MS-MS studies.[35] This technique allows structural information to be obtained using low-nanogram quantities of material. The use of tandem mass spectrometry provides structural information on HPLC peaks and allows the conclusive identification of each peak. The ion-trap mass spectrometer "traps" the parent ion of the compound and excludes all other ions. The "trapped" ion is then fragmented and a specific fragment ion produced. This method has been applied to [2-^{14}C]-quercetin-4'-glucoside where its radioactivity allowed the location and quantification of [2-^{14}C]-quercetin-4'-glucoside derived material in different tissues. The HPLC separates the metabolites, the radioactivity identifies and quantifies those derived from [2-^{14}C]-quercetin-4'-glucoside and the tandem MS allows structural determination of the metabolites so that the HPLC peak assignment is unambiguous. The ion trap method allows all contributors to HPLC peaks to be identified. The results of this study were that 93.6 % of ingested radioactivity was recovered and 18 metabolites were detected. The use of this technique allowed 17 of these metabolites to be identified.

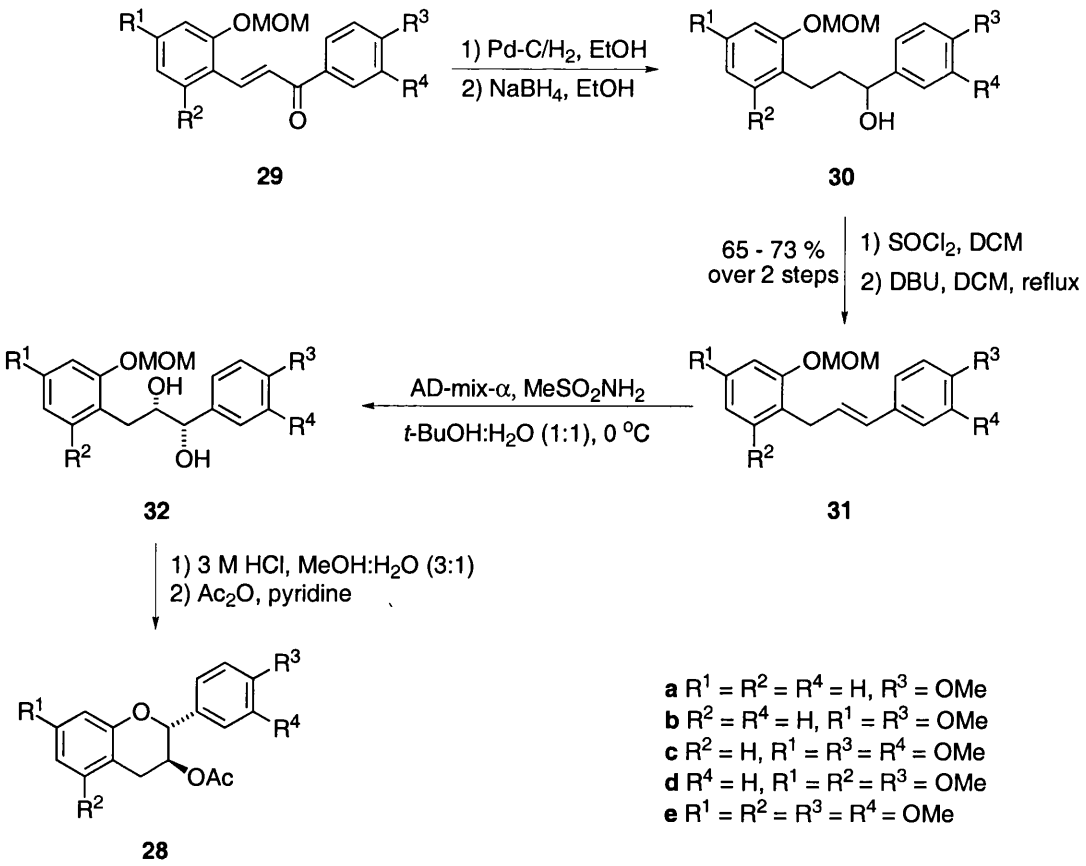
CHAPTER 2 – Synthesis and labelling of Flavan-3-ols

2.1 Introduction

The aim of my research was to investigate new potential routes for the carbon-14 radioisotopic labelling of (+)-catechin. In this chapter, I will survey the various methods that have been used to make catechin and epicatechin, including methods by which they have been isotopically labelled. I will then discuss routes to a related flavan-3-ol of dietary importance, (-)-epigallocatechin gallate and methods of accessing labelled dimers of catechin (found in many beverages) from labelled catechin-derived monomers. The use of biosynthesis for ^{14}C-labelling of flavan-3-ols and the synthesis of catechin and EGCG labelled with isotopes of hydrogen will then be discussed briefly. Most of the work reviewed here was published during the course of my PhD research, which began in October 2000.

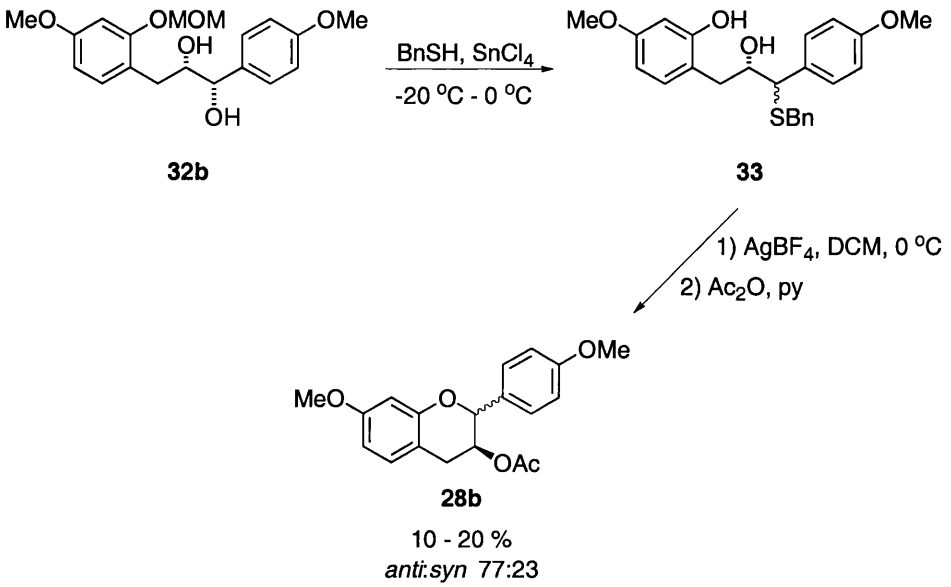
2.2 Ferreira's approach: Asymmetric dihydroxylation of 1,3-diarylpropenes and acid-induced cyclisation

Ferreira has reported the synthesis of a number of flavan-3-ol acetates **28a-e** from simple 1,3-diarylpropenes (one enantiomeric series shown in **Scheme 2.1**).[36,37] To accomplish this, chalcones **29a-e** were synthesised. Hydrogenation, followed by borohydride reduction to alcohols **30a-e** proceeded in almost quantitative yield. Treatment with thionyl chloride followed by elimination of the chloride gave the required 1,3-diarylpropenes **31a-e** in moderate to good yield. Sharpless asymmetric dihydroxylation with AD-mix-α gave (+)-(1*S*, 2*S*) diols **32a-e** in good yield and excellent enantiomeric excess. The authors noted that the (-)-(1*R*, 2*R*)-*syn*-diols were formed on treatment with AD-mix-β only after prolonged reaction times (12 - 48 h). The absolute configuration for the diols was tentatively assigned according to the Sharpless model for AD-mix.



Scheme 2.1

Ferreira's work on the synthesis of dihydroflavonols[38] by Lewis acid catalysed phenylmethanethiol ring-opening and cyclisation of chalcone epoxides led to the investigation of this method for the cyclisation of diols **32b** (**Scheme 2.2**). Selective substitution of the benzylic hydroxyl using tin tetrachloride and phenylmethanethiol at -20 °C and subsequent removal of the methoxymethyl group at 0 °C gave benzylthio derivative **33** in 70 % yield as a mixture of *syn* and *anti* isomers. Treatment of ether **33** with silver tetrafluoroborate in DCM at 0 °C resulted in slow and low conversion (24 h, 10 - 20 %) to the flavan-3-ols, which were then converted into the corresponding acetates *anti* and *syn* **28b**.

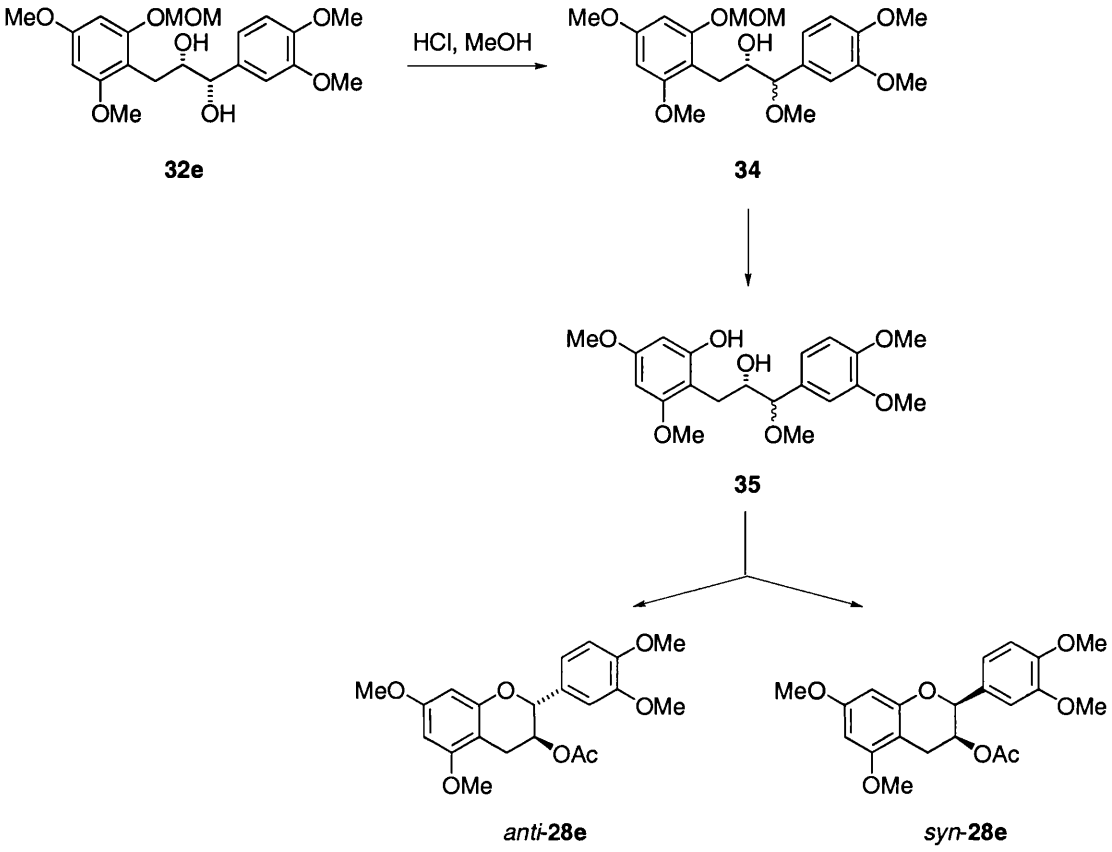


Scheme 2.2

Exploration of methods aimed at selective removal of the methoxymethyl group and subsequent ring-closure under mild acidic conditions was more successful. It was found that simultaneous deprotection and cyclisation of diols **32a-e** in the presence of 3 M hydrochloric acid in methanol, followed by acetylation, gave 2,3-*anti*-**28a-e** (48 - 68 %) and for the first time 2,3-*syn*-flavan-3-ol methyl ether acetate derivatives **28a-e** (17 - 22 %) in excellent enantiomeric excesses (>99 %). The optical purity was measured using a chiral shift reagent [Eu(hfc)$_3$], which consistently showed only one enantiomer to be present.

Attempted cyclisation of oxygen-rich diol **32e** led to the formation of two separable intermediate products **34** and **35** (**Scheme 2.3**). Formation of **34** can be rationalised by methanol initially acting as a nucleophile in an S_N1-type acid-catalysed solvolysis of the benzylic hydroxyl group, giving a mixture of *syn* and *anti* isomers. It was found that prolonged exposure (2 h) of the mixture led to the deprotection of the MOM group to give phenol derivative **35**. This is surprising as phenolic MOM ethers are acid-labile, yet in this case exposure to 3 M hydrochloric acid in refluxing methanol for two hours was required for complete removal. The authors report that this surprising stability was also observed in the synthesis of isoflavans.[39] Phenol derivative **35** is then susceptible to cyclisation to give both the 2,3-*anti*- and 2,3-*syn*-flavan-3-ols **28e**. Formation of a mixture of isomers can be explained by formation of

a benzylic carbocation by protonation of the benzylic methoxy group, followed by an S_N1 cyclisation leading to the predominant formation of the thermodynamically more stable *anti* arrangement.

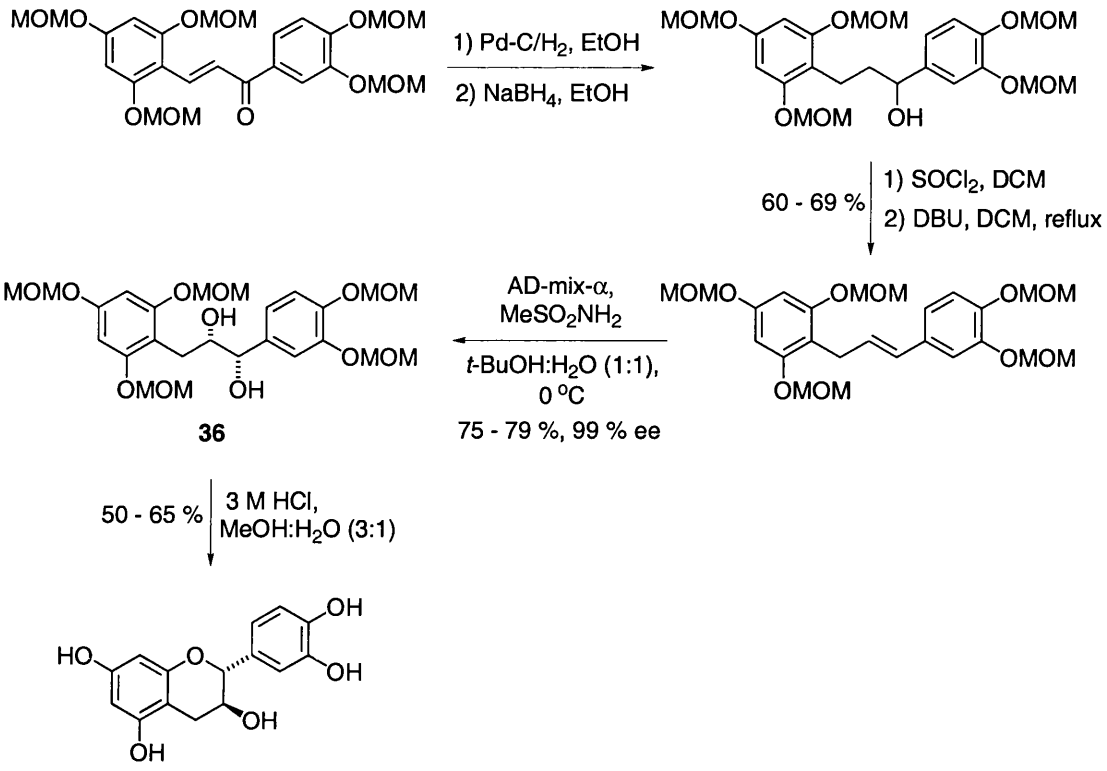


Scheme 2.3

Thus, the authors had reported the development of the first and highly efficient synthesis of essentially enantiopure flavan-3-ols of both the 2,3-*anti* and 2,3-*syn* configurations. They had successfully demonstrated the use of polyoxygenated diarylpropane-1,2-diols as intermediates in the synthesis of flavan-3-ols, however, all of the flavan-3-ols synthesised had the phenolic hydroxyls protected as methyl ethers. The synthesis of flavan-3-ols with free phenolic hydroxyls would have been more biologically relevant. The potential of this route in the chemistry of proanthocyanidins and condensed tannins in general was evident. However, there is evidence in the literature that removal of methyl ethers from such compounds would be problematic.[40] Indeed, a search of the literature reveals several syntheses of related compounds in which the synthesis ends one step from the natural product, with the methyl ethers

still attached.[36,37,40-42] There is no comment made as to why having made the flavan-3-ols, the authors then decided to acetylate them. This is presumably carried out to aid the purification of the final compounds, which was achieved by preparative thin-layer chromatography. This last point indicates that the route may be unsuitable for the synthesis of large quantities of these compounds.

In 1999, Ferreira and co-workers published the asymmetric synthesis of both enantiomers of catechin and epicatechin in their free phenolic forms.[43] The synthetic route is effectively the same as previously reported with only a change in protecting groups from methyl ethers to methoxymethyl ethers (one enantiomeric series shown in **Scheme 2.4**). The authors again reported the slow conversion to the enantiomer of diol **36** with AD-mix-β_The authors also reported that the dihydroxylation procedure worked when applied to 4-*O*-benzyl-2'-*O*-methoxymethylchalcone providing that acetone was used as co-solvent. However since the two-phase system could not be maintained above 20 % acetone, the limited solubility of benzyl ethers excludes their use in this synthesis. This synthesis was reported as the first asymmetric synthetic route providing access to both enantiomers of the two diastereoisomers of free phenolic flavan-3-ols in essentially enantiopure form (>99 % ee). It was suggested that the route would be extended to the synthesis of radiolabelled compounds required for biosynthetic studies. Its applicability to radiolabelling is not yet clear. The proposed position of the label was not disclosed and any label incorporated in the synthesis will be split between catechin and epicatechin, which is not ideal. No information was provided as to how the compounds were purified, so it is difficult to assess whether this would pose a difficulty in a radiochemical synthesis or affect scale-up.



Scheme 2.4

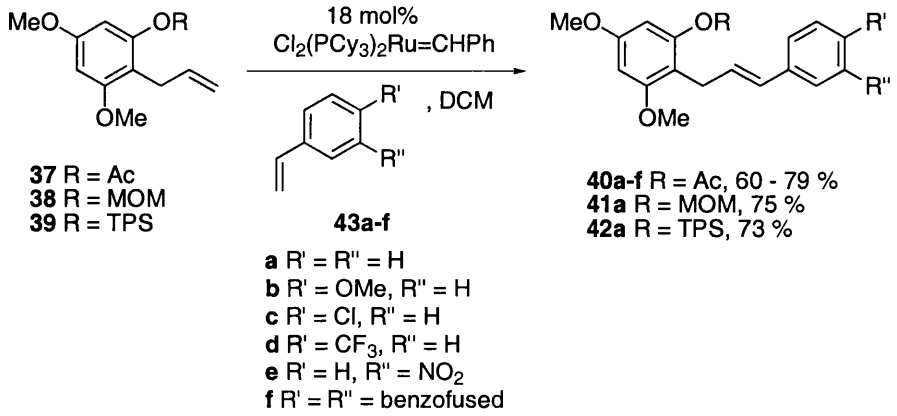
In summary, the key steps in Ferreira's approach are access to 1,3-diarylpropenes by reduction of chalcones, asymmetric dihydroxylation of these and acid-induced cyclisation. Using this approach, both enantiomers of catechin and epicatechin were prepared with >99 %ee.

2.3 Gesson's and Grubbs' cross-metathesis routes to make 1,3-diarylpropenes

The first example of the synthesis of flavan-3-ols using cross-metathesis was reported in 2001 by Gesson.[44] Starting from three readily prepared protected 2-allylphenols **37** - **39**, which were prepared by Claisen rearrangement of 1-allyloxy-3,5-dimethoxybenzene, a variety of 1,3-diarylpropenes **40a-f**, **41a**, **42a** were synthesised in moderate to good yield by reaction with styrenes derivatives **43a-f** in the presence of Grubbs' first generation catalyst (**Scheme 2.5**).

The authors report that the optimum yields were obtained on reaction with two equivalents of styrene and 18 mol% catalyst in DCM for 48 hours. In the case of **40a**, a 75 % yield was obtained using these conditions. This dropped to 55 % with one

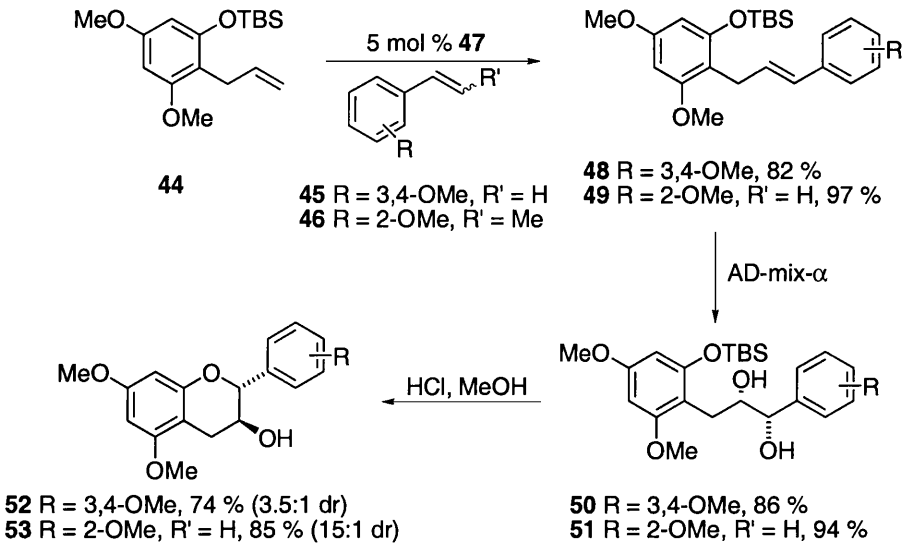
equivalent of styrene and dropped further still to 28 % with 10 mol% catalyst. Reducing the reaction time gave a yield of 51 % and conducting the reaction in refluxing DCM also lowered the yield. Changing the protecting group was found to make no significant difference to the results. Two other noteworthy points made by the author are that no significant amounts of symmetrical cross-metathesis products were observed and that only the *E*-isomers were observed. The authors concluded that the cross-metathesis of protected 2-allylphenols with styrenes would provide a general route to 1,3-diarylpropenes, useful for the synthesis of flavan-3-ols, but that further experiments with more efficient catalysts were needed to lower the amount of catalyst to more attractive levels. This is a very attractive procedure for the synthesis of 1,3-diarylpropenes.

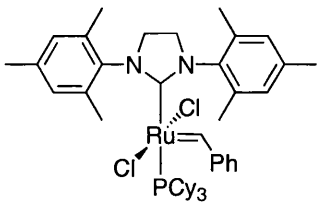


Scheme 2.5

Grubbs has also reported the synthesis of two flavan-3-ols as part of an investigation into the cross-metathesis of styrenes (**Scheme 2.6**).[42] Treatment of silyl ether **44** with either **45** or **46** in refluxing DCM in the presence of Grubbs' second generation catalyst **47** gave the *E*-diarylpropenes **48** and **49** in high yield. Asymmetric dihydroxylation of both alkenes proceeded again in high yield to give diols **50** and **51**. Deprotection and cyclisation of the diols gave the permethyl flavan-3-ols **52** and **53** in good yields and moderate to good selectivities. Grubbs' route appears to combine ideas from three other syntheses already discussed with his own modification, the use of his second-generation catalyst, to good effect. The commercial availability of a wide variety of variously substituted styrenes would allow the efficient and rapid synthesis of a large number of flavan-3-ols and derivatives although, in most cases,

the protecting group would need to be changed in order to obtain the natural free phenolic flavanols. The route also appears to be suitable for labelled syntheses. This last point will be discussed in more detail later.





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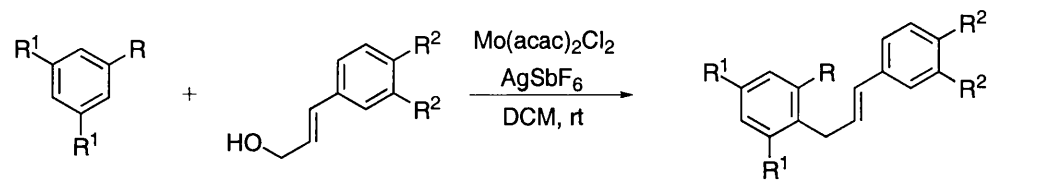
Scheme 2.6

In summary, cross-metathesis is a potentially useful approach to 1,3-diarylpropenes, but neither the group of Gesson nor that of Grubbs prepared an intermediate that was appropriately protected to allow access to catechin itself.

2.4 Vercauteren's use of dibenzyloxycinnamyl alcohol to prepare 1,3-diarylpropenes

Vercauteren has also achieved the synthesis of 1,3-diarylpropenes e.g. **54** and **55** by coupling phloroglucinol and cinnamyl alcohol moieties in the presence of a molybdenum (IV) catalyst.[45] Two examples are shown below (**Scheme 2.7**). Benzyl ether **56** and alcohol **57** coupled in moderate yield to give propene **54**. The best example was achieved with TBS protected phloroglucinol **58**. Unfortunately the

product could not be obtained in a pure form due to the difficulty in removing the starting TBS ether. Employing the chemistry developed by Ferreira could then lead to the synthesis of a variety of flavanols.



56 R = R^1 = OBn
58 R = R^1 = OTBS

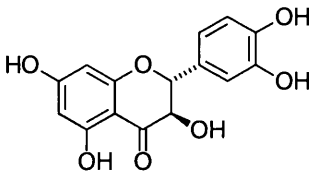
57 R^2 = OBn

54 R = R^1 = R^2 = OBn, 52 %
55 R = R^1 = OTBS, R^2 = OBn, 70-80 %

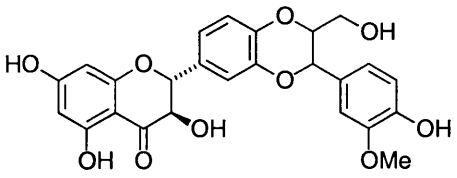
Scheme 2.7

2.5 Jew and Park's approach: Asymmetric dihydroxylation prior to assembly of carbon framework

3-Hydroxyflavanone natural products also have interesting biological properties.[46] Two examples of these compounds are taxifolin **59** and silybin **60** (**Figure 2.1**), which have strong hepatoprotective effects due to their strong antioxidant effect.[47]



59

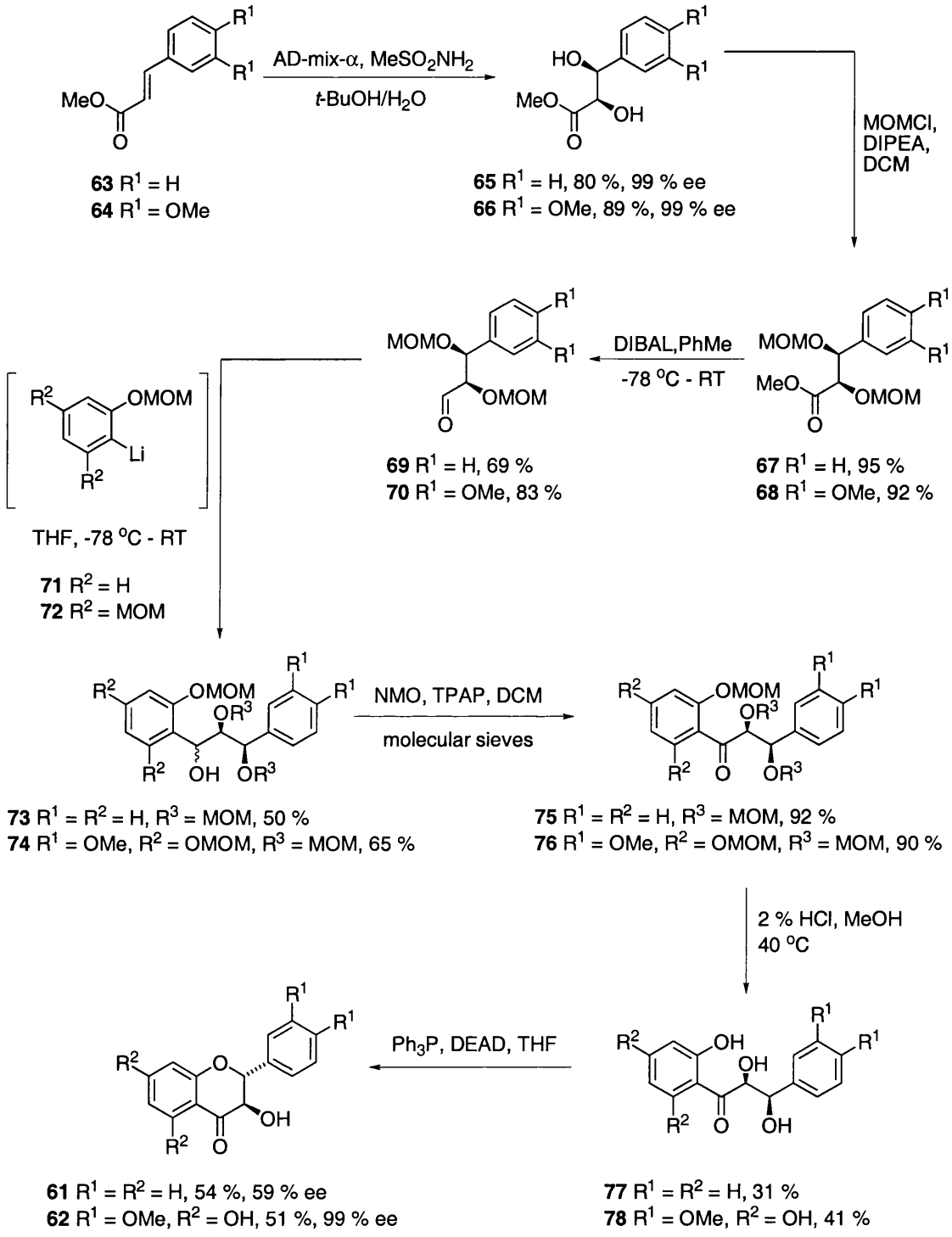


60

Figure 2.1

In 2000, Jew and Park reported a new method for the enantioselective synthesis of the parent structure (2*R*, 3*R*)-3-hydroxyflavanone **61** and its application to the synthesis of (2*R*, 3*R*)-3',4'-*O*-dimethyltaxifolin **62** from which they later developed an asymmetric synthesis of catechin (**Scheme 2.8**).[48] Sharpless asymmetric dihydroxylation of methyl cinnamates **63** and **64** gave optically active diols **65** and **66** in high yield and excellent enantiomeric excess. The enantiomeric excesses were determined by analysis of the ^{1}H NMR spectra of the Mosher's esters of **65** and **66**. Protection of the diols with MOMCl using Hünigs base gave **67** and **68** in excellent

yield. DIBAL reduction gave aldehyde **69** in good yield and **70** in high yield. Addition of aryllithium **71** to aldehyde **69** and **72** to aldehyde **70** proceeded to give alcohols **73** and **74** in moderate yield. Oxidation with *N*-methylmorpholine-*N*-oxide (NMO) using catalytic tetrapropylammonium perruthenate gave ketones **75** and **76**. Deprotection of the MOM groups was accomplished with dilute acid giving phenols **77** and **78** in excellent yield. The formation of the C-ring was achieved by an intramolecular Mitsunobu reaction giving **61** and **62** in moderate yields and moderate to excellent enantiomeric excesses. No comment about the removal of the methyl ethers was made. It is possible that as previously mentioned, the deprotection of the methyl ethers was not trivial and proved inconvenient. In this paper the authors have reported a general and relatively efficient enantioselective synthesis of 3-hydroxyflavanones.



63 R^1 = H
64 R^1 = OMe

65 R^1 = H, 80 %, 99 % ee
66 R^1 = OMe, 89 %, 99 % ee

67 R^1 = H, 95 %
68 R^1 = OMe, 92 %

69 R^1 = H, 69 %
70 R^1 = OMe, 83 %

71 R^2 = H
72 R^2 = MOM

73 R^1 = R^2 = H, R^3 = MOM, 50 %
74 R^1 = OMe, R^2 = OMOM, R^3 = MOM, 65 %

75 R^1 = R^2 = H, R^3 = MOM, 92 %
76 R^1 = OMe, R^2 = OMOM, R^3 = MOM, 90 %

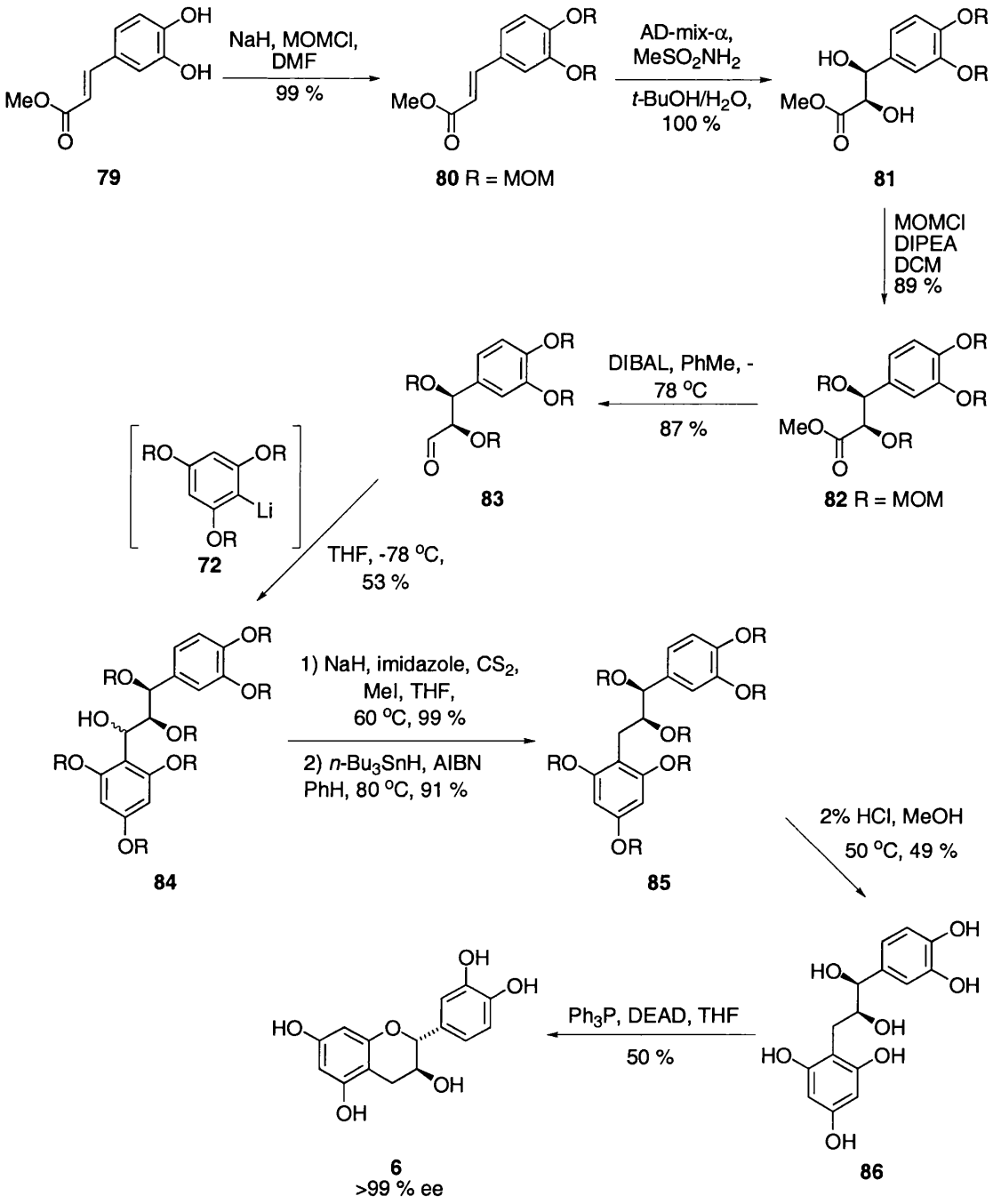
77 R^1 = R^2 = H, 31 %
78 R^1 = OMe, R^2 = OH, 41 %

61 R^1 = R^2 = H, 54 %, 59 % ee
62 R^1 = OMe, R^2 = OH, 51 %, 99 % ee

Scheme 2.8

In 2002, Jew and Park published a relatively short asymmetric synthesis of (+)-catechin **6** to allow SAR studies as part of an ongoing program to find new candidates for anticancer and psychoactive drugs.[49] The synthesis was achieved using a similar approach to their preparation of the flavanones and avoids the epimerisation problem encountered by Ferreira during the acid-catalysed cyclisation by using an

intramolecular Mitsunobu reaction for the cyclisation. The synthesis starts from commercially available methyl 3,4-dihydroxy-cinnamate **79** (**Scheme 2.9**). Methoxymethyl protection of the phenols gave ester **80** in essentially quantitative yield. Asymmetric dihydroxylation of ester **80** gave diol **81** in quantitative yield and >99 % ee. The enantiomeric excess was determined by analysis of the ^{1}H NMR spectrum of the corresponding Mosher's esters. Protection of the diol, again using methoxymethyl ethers, gave ester **82** in excellent yield. Reduction of ester **82** with DIBAL gave aldehyde **83** in excellent yield. Addition of organolithium **72** proceeded in moderate yield to give alcohol **84**. Subsequent Barton-McCombie deoxygenation gave 1,3-diarylpropane derivative **85** in 90 % yield over two steps. Global deprotection of the methoxymethyl ethers was achieved by treatment with dilute acid in methanol to give polyphenol **86** in moderate yield. An intramolecular Mitsunobu reaction then gave (+)-catechin **6** in moderate yield and good enantioselectivity (50 %, >99 % ee). The absolute configuration of the new chiral centre was assigned as *R* on the basis of the coupling constant between C(2)H and C(3)H (J = 7.3 Hz). This asymmetric synthesis was achieved in nine steps with an overall yield of 9 % and >99 % ee. The synthetic route devised by Jew and Park is good for several reasons. The starting materials are both cheap and commercially available, the synthesis is relatively short, all diastereoisomers can be synthesised and the route, although not ideal, could be applied to the radiolabelled synthesis of these compounds. The use of MOM protection is fully exploited to the authors' advantage. The ability of MOM groups to allow *ortho*-metallation is well known, as is their acid lability. These factors combined make MOM ethers the ideal choice for this synthesis. Indeed, this synthesis relies on these properties of the MOM group. For this reason, it is all the more frustrating that no experimental details are given for the synthesis of MOM protected phloroglucinol from which organolithium **72** is synthesised. This omission raises questions as to the ease of synthesis of MOM protected phloroglucinol and casts doubt on the use of the route for the large-scale synthesis of the catechin flavonoids.

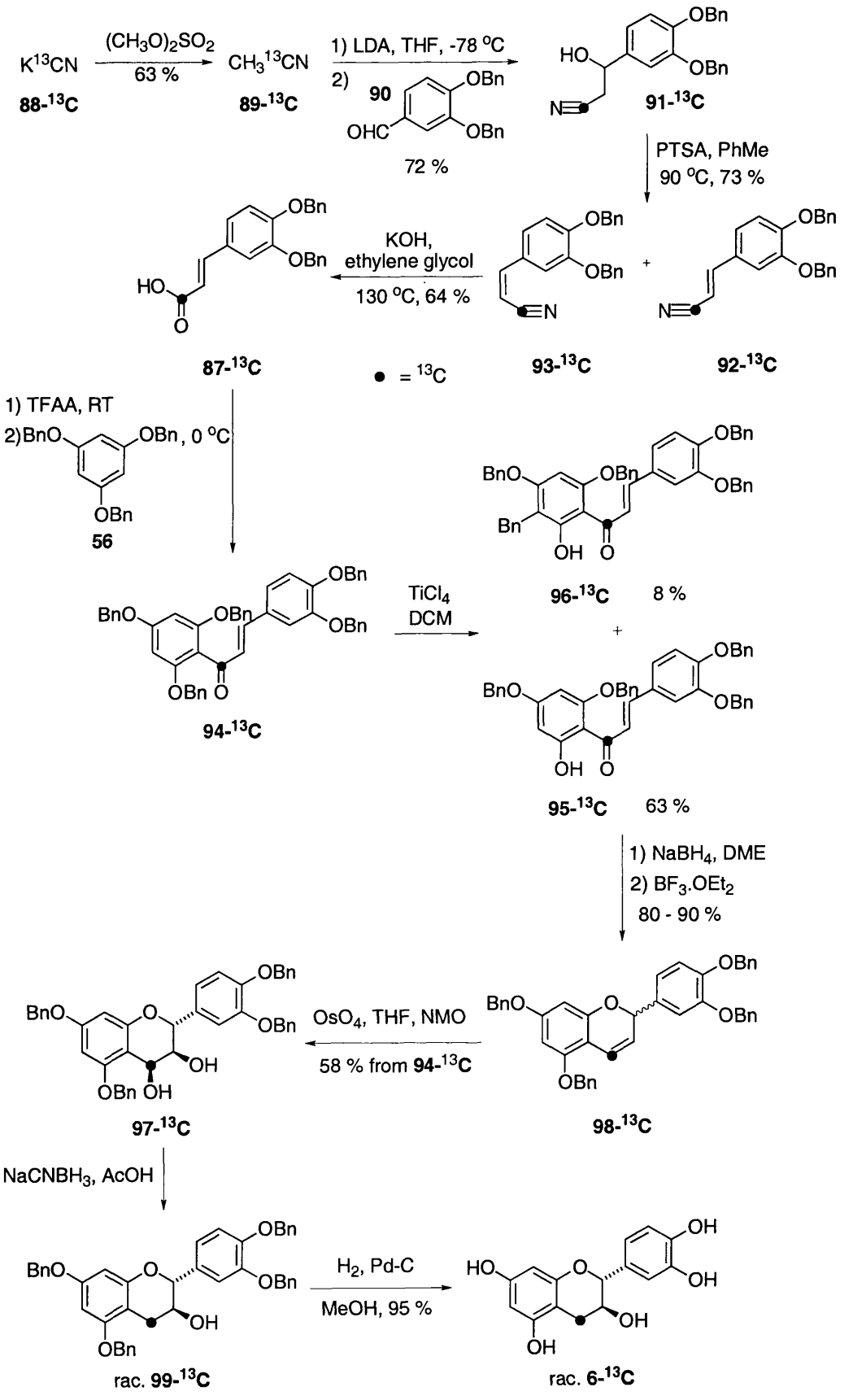


Scheme 2.9

In summary, Jew and Park's synthesis of (+)-catechin involved asymmetric dihydroxylation of a caffeic acid derivative, followed by construction of the carbon framework by alkylating an aldehyde intermediate with lithiated, fully MOM-protected phloroglucinol. Barton-McCombie deoxygenation was used to remove the 4-OH, only MOM protection was used to allow global deprotection and cyclisation was carried out under Mitsunobu conditions to ensure complete inversion of configuration at C-2.

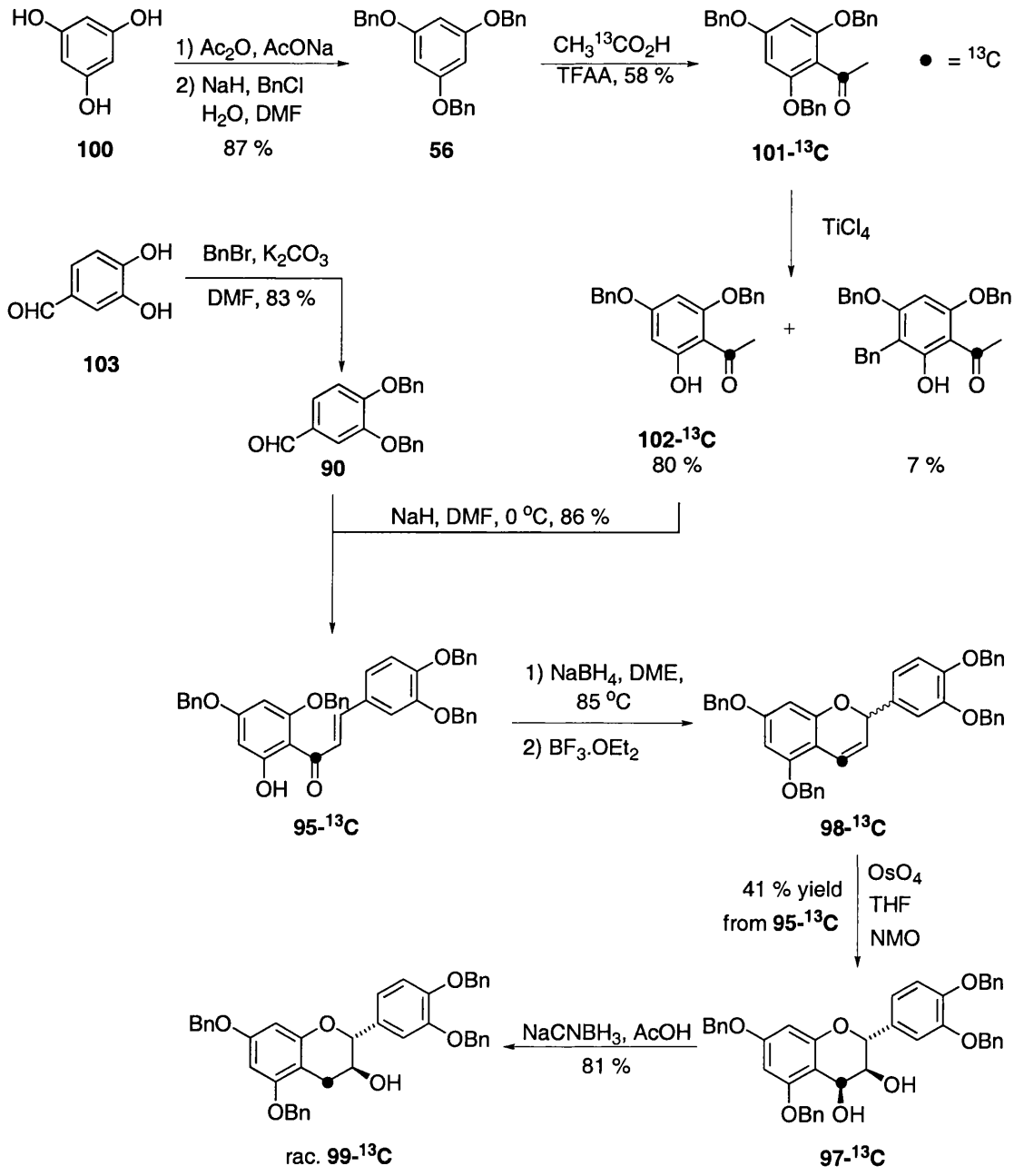
2.6 Vercauteren's carbon-13 labelling of (+)-catechin and (-)-epicatechin

In 2000, Vercauteren reported the first total synthesis of racemic catechin containing a carbon-13 label.[50] The key C-C forming step in the synthesis involved the coupling of dibenzyloxycaffeic acid **87-^{13}C** and benzyl protected phloroglucinol **56** (**Scheme 2.10**). Commercially available potassium [^{13}C]-cyanide **88-^{13}C** was methylated with dimethylsulfate in moderated yield to give 1-[^{13}C]-acetonitrile **89-^{13}C**. Deprotonation with LDA and quenching with benzaldehyde derivative **90** gave the β-hydroxynitrile **91-^{13}C** in good yield, which was dehydrated to give a 3:1 mixture of *E*- and *Z*-cinnamonitrile derivatives **92-^{13}C** and **93-^{13}C**. The mixture was hydrolysed to dibenzyloxycaffeic acid **87-^{13}C** in 64 % yield. At this stage the *Z*-isomer could not be recovered which was attributed to complete isomerisation to the *E*-isomer during the hydrolysis. Activation of carboxylic acid **87-^{13}C** with trifluoroacetic anhydride allowed acylation of 1,3,5-tribenzyloxybenzene to proceed in moderate yield to give pentabenzyloxychalcone derivative **94-^{13}C**. The 2'-hydroxychalcone derivative **95-^{13}C** was prepared by selective deprotection with titanium tetrachloride, however this procedure also led to a small amount of chalcone **96-^{13}C** being formed. Employing the Clark-Lewis method the synthesis of flavan-3,4-diol **97-^{13}C** was accomplished in three steps and in 58 % yield from chalcone derivative **95-^{13}C**. Borohydride reduction of **95-^{13}C** followed by Lewis acid catalysed cyclisation gave racemic flavene **98-^{13}C**, which is very labile and was subjected to osmium catalysed dihydroxylation without purification. Dihydroxylation of flavene **98-^{13}C** proceeded in moderate yield and high diastereoselectivity (the all *cis*-isomer was not observed). Diol **97-^{13}C** is an interesting compound in its own right, since it can be used as a precursor for the synthesis of several flavonoid classes. In this case, reduction of **97-^{13}C** with sodium cyanoborohydride in acetic acid gave the protected flavonol **99-^{13}C**. Subsequent hydrogenolysis gave the racemic catechin **6** in quantitative yield. The synthesis was completed in ten steps and 4 % overall yield from a readily available, easy to incorporate, relatively cheap source of carbon-13. Contrary to Vercauteren's belief, this synthesis would not be easily extended to carbon-14. The main problems associated with the synthesis are the use of labelled compounds from the start, the length, the overall yield and the fact that the product is racemic.


K13CN
(CH3O)2SO2
63 %
CH3 13CN
88-13C
89-13C
1) LDA, THF, -78 °C
2)
90
72 %
91-13C
PTSA, PhMe
90 °C, 73 %
KOH,
ethylene glycol
130 °C, 64 %
87-13C
93-13C
92-13C
● = 13C
1) TFAA, RT
2)
56
96-13C 8 %
94-13C
TiCl4
DCM
95-13C 63 %
1) NaBH4, DME
2) BF3.OEt2
80 - 90 %
OsO4, THF, NMO
58 % from 94-13C
97-13C
98-13C
NaCNBH3, AcOH
H2, Pd-C
MeOH, 95 %
rac. 99-13C
rac. 6-13C

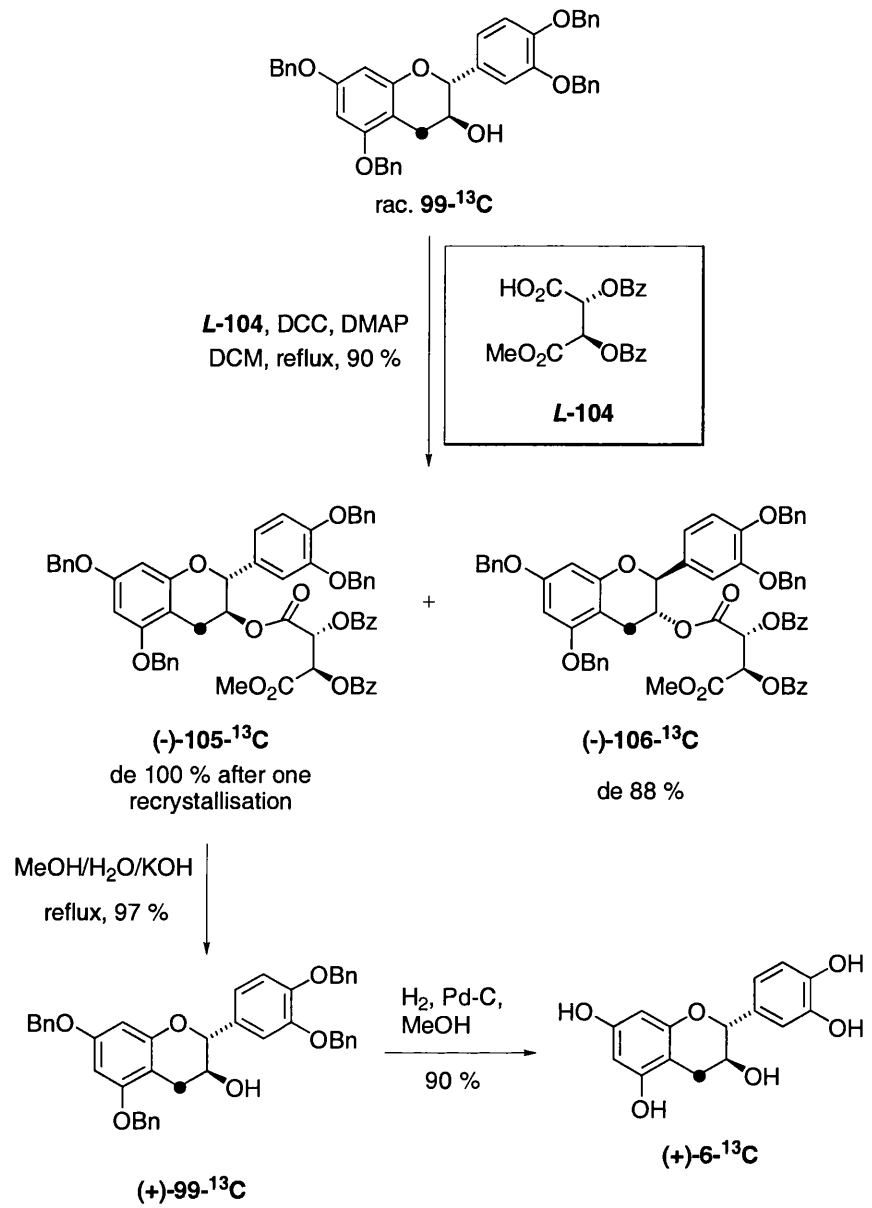
Scheme 2.10

Vercauteren later published the first synthesis of optically pure 4-[^{13}C]-(+)-catechin (**Scheme 2.11**).[51] The synthesis is very similar to his previous synthesis described above, however alterations were made to allow Vercauteren to synthesise multi-gram quantities of labelled (+)-catechin for biological testing. His previous route yielded 40 mg of racemic catechin. The synthesis of benzyl ether **56** using standard conditions is problematic due to the *C*-benzylation that occurs with highly electron-rich phenols e.g. phloroglucinol **100**.[51] This problem was avoided by using Kawamoto's[52] procedure allowing the synthesis of ether **56** on a large scale. The use of three equivalents of 1-[^{13}C]-acetic acid allowed the straightforward introduction of the label *via* cheaper and substantially less toxic materials (avoiding potassium cyanide). Treatment of ether **56** with the labelled acetic acid in the presence of trifluoroacetic anhydride gave labelled acetophenone derivative **101-^{13}C** in moderate yield. Conversion of fully protected acetophenone derivative **101-^{13}C** into phenol derivative **102-^{13}C** was achieved using titanium tetrachloride. Monodebenzylation of the hydroxyl group that forms an intramolecular hydrogen bond with the ketone is a key step in both of Vercauteren's syntheses. Monodebenzylation of acetophenone derivative **101-^{13}C** was more efficient than the corresponding reaction on chalcone derivative **94-^{13}C** in the previous synthesis. However, a similar amount of *C*-benzylation occurred in both. Standard benzylation of 3,4-dihydroxybenzaldehyde **103** gave benzyl protected aldehyde **90** in high yield. Condensation of aldehyde **90** with phenol derivative **102-^{13}C** gave chalcone derivative **95-^{13}C** also in high yield. Chalcone derivative **95-^{13}C** was converted into diol **97-^{13}C** in moderate yield as described earlier. Reduction of the 4-hydroxyl gave racemic catechin **99-^{13}C** in good yield as before.



Scheme 2.11

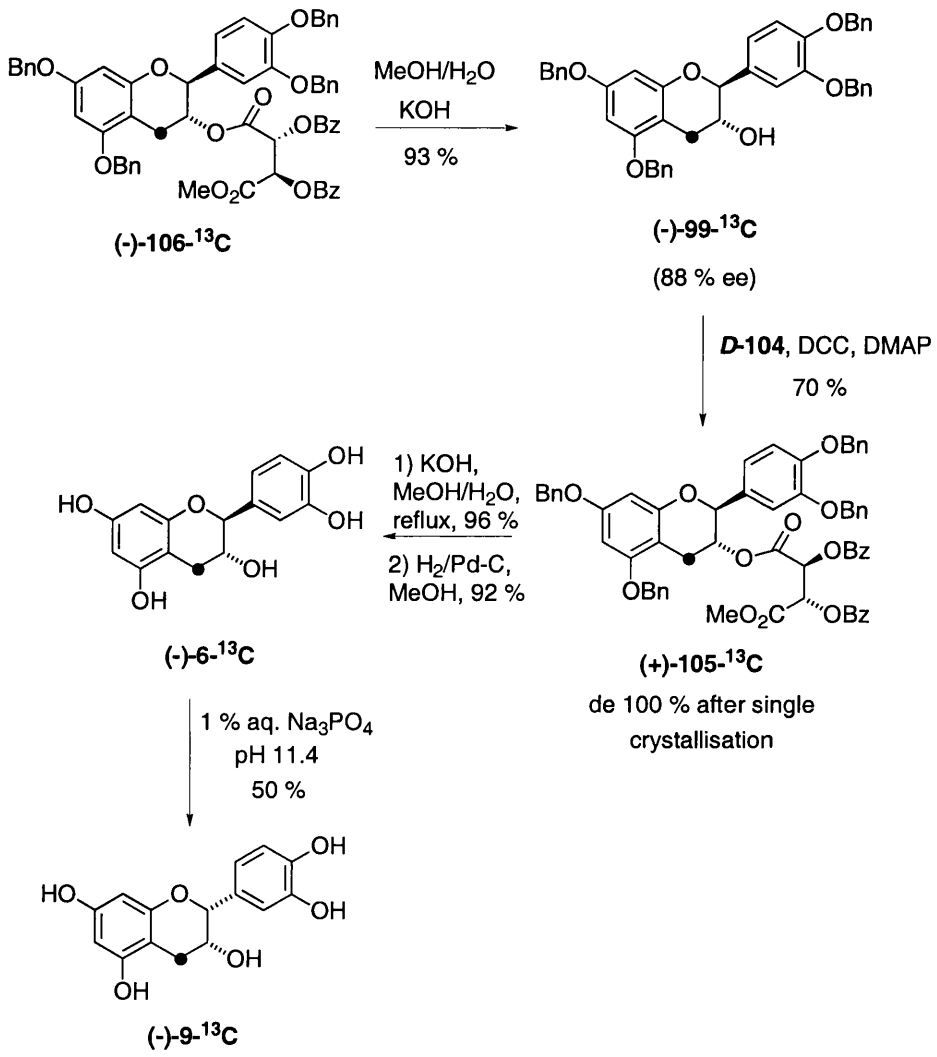
At this point, the enantiomers were resolved using a procedure developed by Vercauteren (**Scheme 2.12**).[53] Esterification of the racemic mixture with dibenzoyl-*L*-tartaric acid monomethyl ester ***L*-104** in refluxing DCM in the presence of DCC and DMAP gave a mixture of esterified diastereomers **(-)-105-^{13}C** and **(-)-106-^{13}C**. It was discovered that ester **(-)-105-^{13}C** crystallised selectively from a hexane/DCM mixture (3:1). When subjected to a single recrystallisation from the same solvent mixture, ester **(-)-105-^{13}C** was obtained (de > 99% based on HPLC).



Scheme 2.12

Hydrolysis of the ester followed by hydrogenolysis gave the optically pure (+)-catechin **6-^{13}C** in excellent yield (**Scheme 2.13**). The other diastereoisomer **(-)-106-^{13}C** (de 88 %) did not crystallise. It has been reported that (+)-catechin can epimerise at C-2 through reversible opening of the C-ring in basic media to form (-)-epicatechin.[54-56] To this end, ester **(-)-106-^{13}C** was hydrolysed to give protected (-)-catechin **99-^{13}C** and esterified with ***D*-104** to give optically pure (+)-**105** (de > 99 %) after chromatography and crystallisation. Hydrolysis of the ester followed by hydrogenolysis gave the unnatural (-)-catechin **6-^{13}C** in excellent yield. Treatment of **(-)-6-^{13}C** with 1 % (w/v) sodium phosphate at pH 11.4 gave a mixture of (-)-catechin **6-^{13}C** and (-)-4-[^{13}C]-epicatechin **9-^{13}C** in a 3:1 ratio after 20 h at room temperature.

The desired epicatechin **9-^{13}C** was purified and the recovered starting material was recycled four times to obtain a gram quantity of **9-^{13}C** (50 %, ee > 99 % based on HPLC). Some starting material was also recovered.



Scheme 2.13

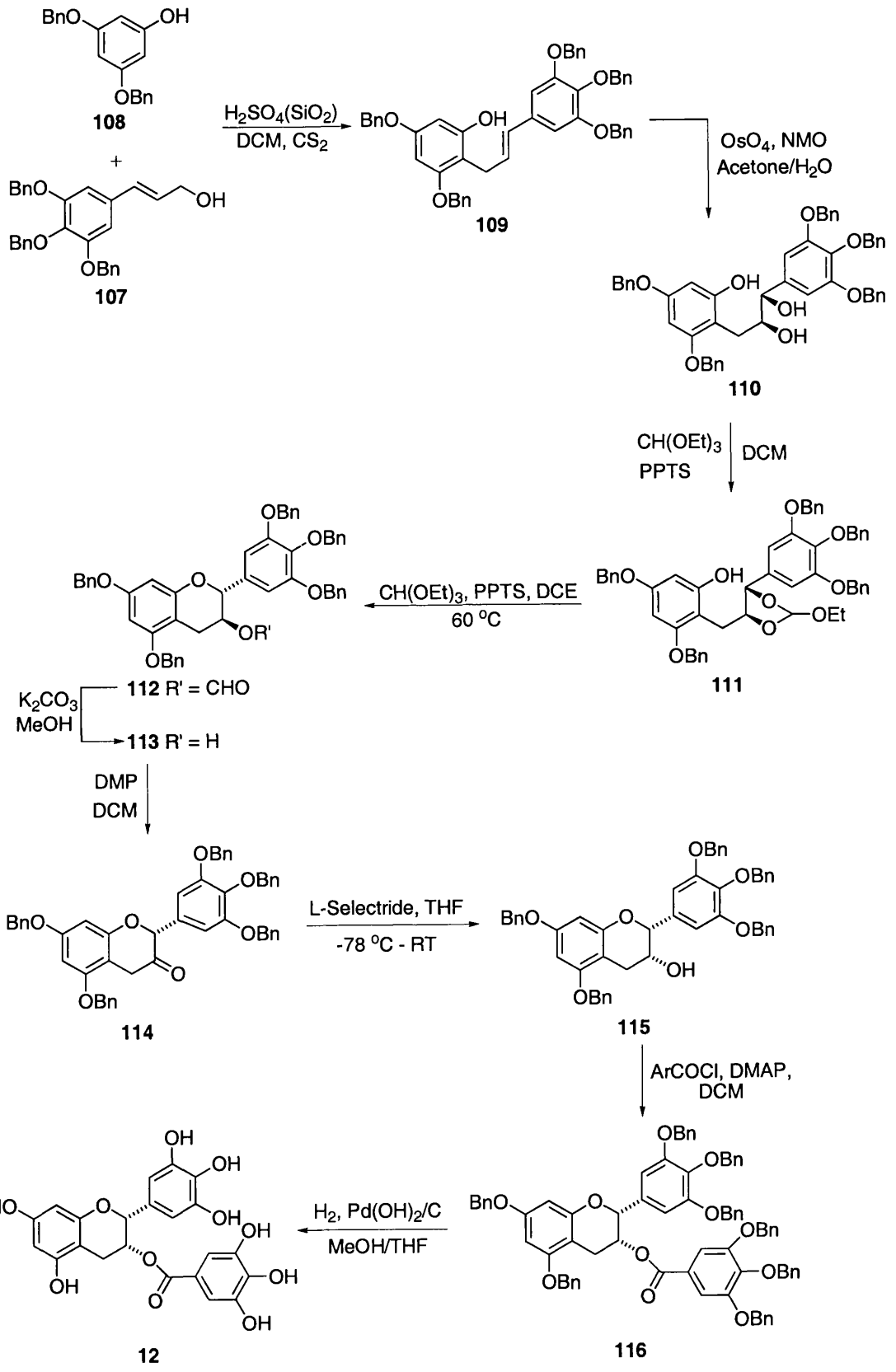
The authors[51] report the total synthesis of gram amounts of ^{13}C-labelled natural (+)-catechin **6-^{13}C** and (-)-epicatechin **9-^{13}C** in 6.2 % overall yield from phloroglucinol **100**. They believe that they have significantly improved the yields in comparison to their previous strategy and that their new route gives enantiomerically pure material. Although access to the catechins in an optically pure form has been achieved, the new synthesis has not significantly improved the yield over the previous synthesis (6.2 % vs 4 %). It is not a truly asymmetric route since obtaining enantiomerically pure material relies on the resolution of a racemic mixture of protected (±)-catechin. The

quoted overall yield is ambiguous as there are several different yields quoted for some reactions and it appears to be a combined yield for catechin and epicatechin. Furthermore, the yield reported for the epimerisation to give (-)-epicatechin is the combined yield for four cycles of the epimerisation reaction, which is not ideal.

In summary, Vercauteren's group prepared racemic [4-^{13}C]-catechin, (+)-[4-^{13}C]-catechin, (-)-[4-^{13}C]-catechin and (-)-[4-^{13}C]-epicatechin using potassium [^{13}C]-cyanide or [1-^{13}C]-acetic acid as the source of the label. Like the syntheses of Ferreira's group and Jew and Park, chalcones were key intermediates, but these were converted into 3-flavenes before dihydroxylation. A weakness in the approach is that enantiomeric enrichment was achieved late in the sequence by resolution and this deficiency was accentuated in the preparation of (-)-[4-^{13}C]-epicatechin by the necessity of repeated equilibration of (-)-[4-^{13}C]-catechin and separation of enantiomers. None-the-less, these are the only published routes for labelling simple flavan-3-ols with a carbon isotope and gram quantities of the enantiomerically enriched materials were obtained.

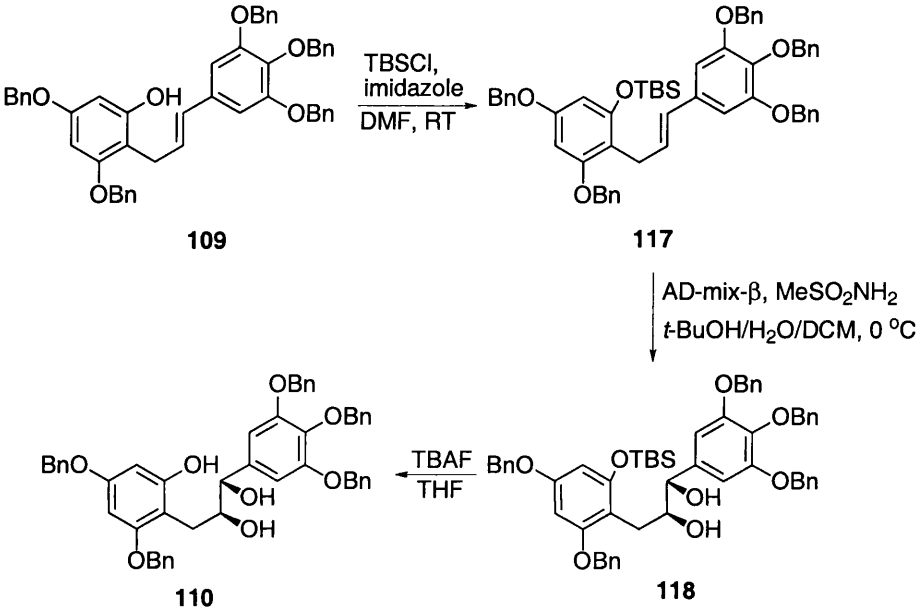
2.7 Chan and co-worker's preparation of (-)-epigallocatechin gallate

In 2001, Chan published a synthesis of the main constituent of green tea extract, (-)-epigallocatechin gallate **12**.[40] Since (-)-EGCG is closely related to catechin and epicatechin, synthetic approaches to EGCG should be applicable to these other flavan-3-ols. The main challenges of the synthesis lie in the selective formation of the thermodynamically less stable *cis*-disubstituted benzopyran and maintaining the stereochemical integrity at the benzylic C-2 position, which is activated by the electron-donating groups on the B-ring. Coupling of 3,4,5-tribenzyloxycinnamyl alcohol **107** with 3,5-dibenzyloxyphenol **108** gave coupled product **109**, which when dihydroxylated gave **110** (**Scheme 2.14**). Formation of the orthoester **111**, followed by cyclisation gave **112**, which was deprotected to give **113**. Dess-Martin oxidation of **113** gave **114** and reduction with L-selectride gave **115**. Treatment of **115** with 3,4,5-tri-*O*-benzylgalloyl chloride and DMAP in DCM gave protected EGCG **116**. Deprotection of **116** by catalytic hydrogenation gave racemic EGCG **12**. No yields were reported for any of the transformations.


BnO
OH
OBn
108
+
BnO
OH
BnO
OBn
107
$H_2SO_4(SiO_2)$
DCM, CS_2
OBn
OBn
BnO
OH
OBn
OBn
109
OsO_4, NMO
Acetone/H_2O
OBn
OBn
BnO
OH
OH
OH
OBn
OBn
110
$CH(OEt)_3$
PPTS
DCM
OBn
OBn
BnO
OH
OBn
O
O
OEt
OBn
111
$CH(OEt)_3$, PPTS, DCE
60 °C
OBn
OBn
BnO
O
OBn
OR'
OBn
112 R' = CHO
K_2CO_3
MeOH
113 R' = H
DMP
DCM
OBn
OBn
BnO
O
OBn
O
OBn
114
L-Selectride, THF
-78 °C - RT
OBn
OBn
BnO
O
OBn
OH
OBn
115
ArCOCl, DMAP,
DCM
OBn
OBn
BnO
O
OBn
OBn
O
OBn
OBn
OBn
116
H_2, $Pd(OH)_2/C$
MeOH/THF
OH
OH
HO
O
OH
OH
O
OH
OH
OH
12

Scheme 2.14

The previous attempts to asymmetrically dihydroxylate **109** had proved unsuccessful, but it was found that protection of the phenol as the TBS ether allowed AD-mix to be successfully used, thus allowing access to both enantiomers of EGCG **12** (**Scheme 2.15**). TBS protection of **109** gave silyl ether **117**. Asymmetric dihydroxylation with AD-mix-β gave diol **118**, which when deprotected with TBAF gave optically active **110**. This sequence of reactions was repeated using AD-mix-α to complete the synthesis of (+)-EGCG **12.**



Scheme 2.15

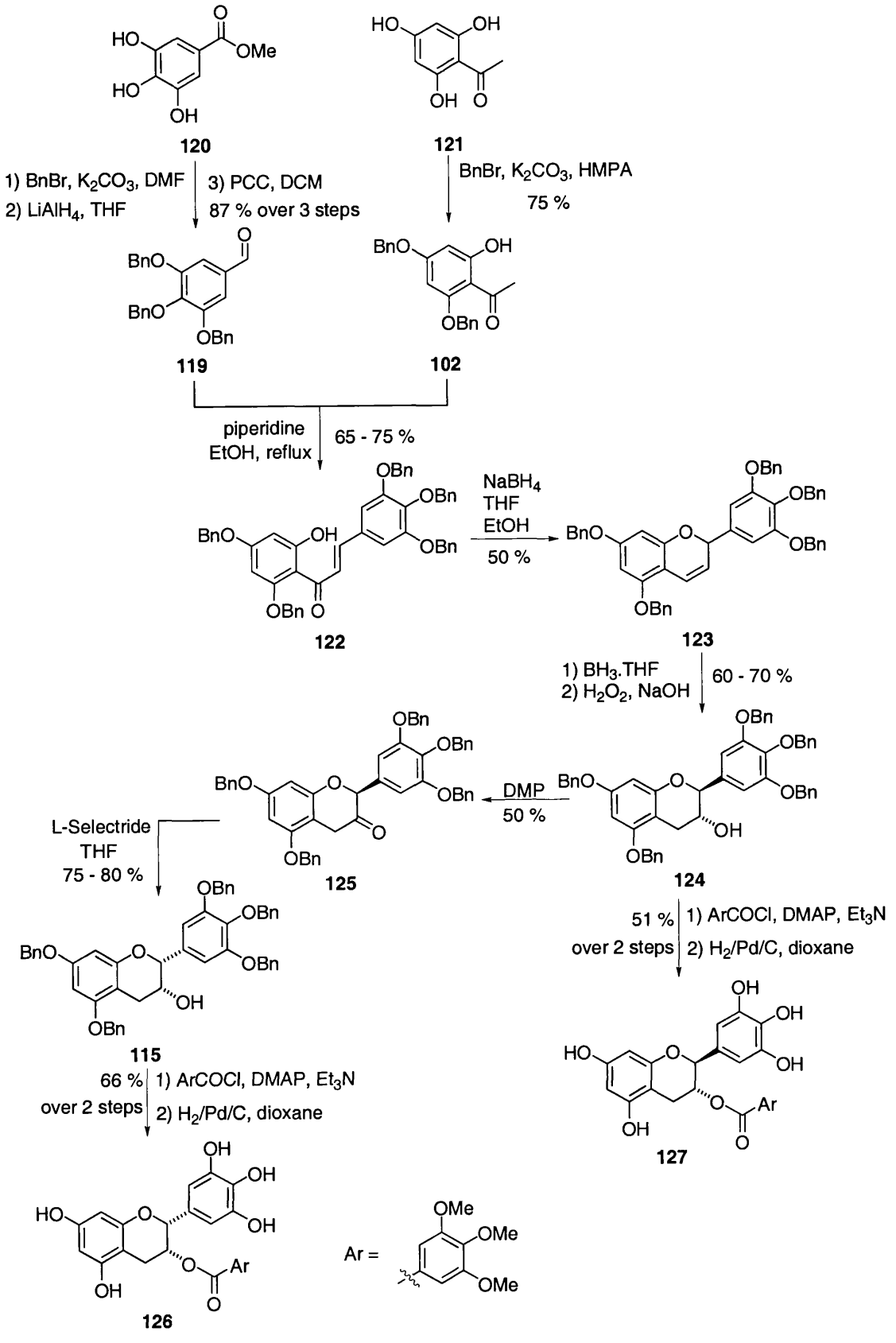
The synthesis achieved the diastereo- and enantioselective synthesis of (-)-EGCG. The overall yield of (-)-**12**, based on cinnamyl alcohol derivative **107**, was 19 %. This is a viable route for the synthesis of analogues with varying substituted aromatic rings.

In summary, Chan and co-worker's synthesis of (-)-EGCG involved constructing a 1,3-diarylpropene by a Friedel-Crafts reaction. Following the approach of Ferreira and co-workers, this was subjected to asymmetric dihydroxylation. Inversion at C-2 was maximised by converting the diol to an orthoformate before cyclisation to the gallocatechin derivative. Rather than relying on equilibration as Vercauteren and co-workers did in their synthesis of (-)-epicatechin, oxidation of the 3-OH and reduction

of the ketone with a bulky hydride source ensured clean conversion to the epigallocatechin derivative.

2.8 Zaveri's synthesis of partially methylated gallocatechin and epigallocatechin gallates

At the same time as Chan was developing his route to EGCG, Zaveri was also developing a route to EGCG which is a combination of chemistry similar to Vercauteren and Chan.[41] The route is shown below (**Scheme 2.16**). The protected benzaldehyde **119** was synthesised by a published procedure in 87 % over three steps from methyl gallate **120**. Condensation with the acetophenone **102**, formed by benzylation of trihydroxyacetophenone **121** gave the chalcone **122** in moderate to good yield. Cyclisation to the flavene **123** was achieved using sodium borohydride in a mixture of THF and ethanol. Hydroboration of the flavene **123** gave the *anti*-flavan-3-ol **124** with less than 5 % of the *syn*-compound. The stereochemistry was assigned based on coupling constants obtained from the ^{1}H NMR and from nOe experiments. The synthesis was completed using the same chemistry as Chan. The *anti*-flavonol was converted to the *syn*-isomer by Dess-Martin oxidation to give ketone **125**, which was selectively reduced to the racemic *syn*-flavanol **115** using L-selectride. Esterification with trimethoxygalloyl chloride, followed by global deprotection of the benzyl ethers by hydrogenation gave trimethoxy EGCG derivative **126**. The *anti*-isomer **127** was synthesised using the same esterification and deprotection procedure.

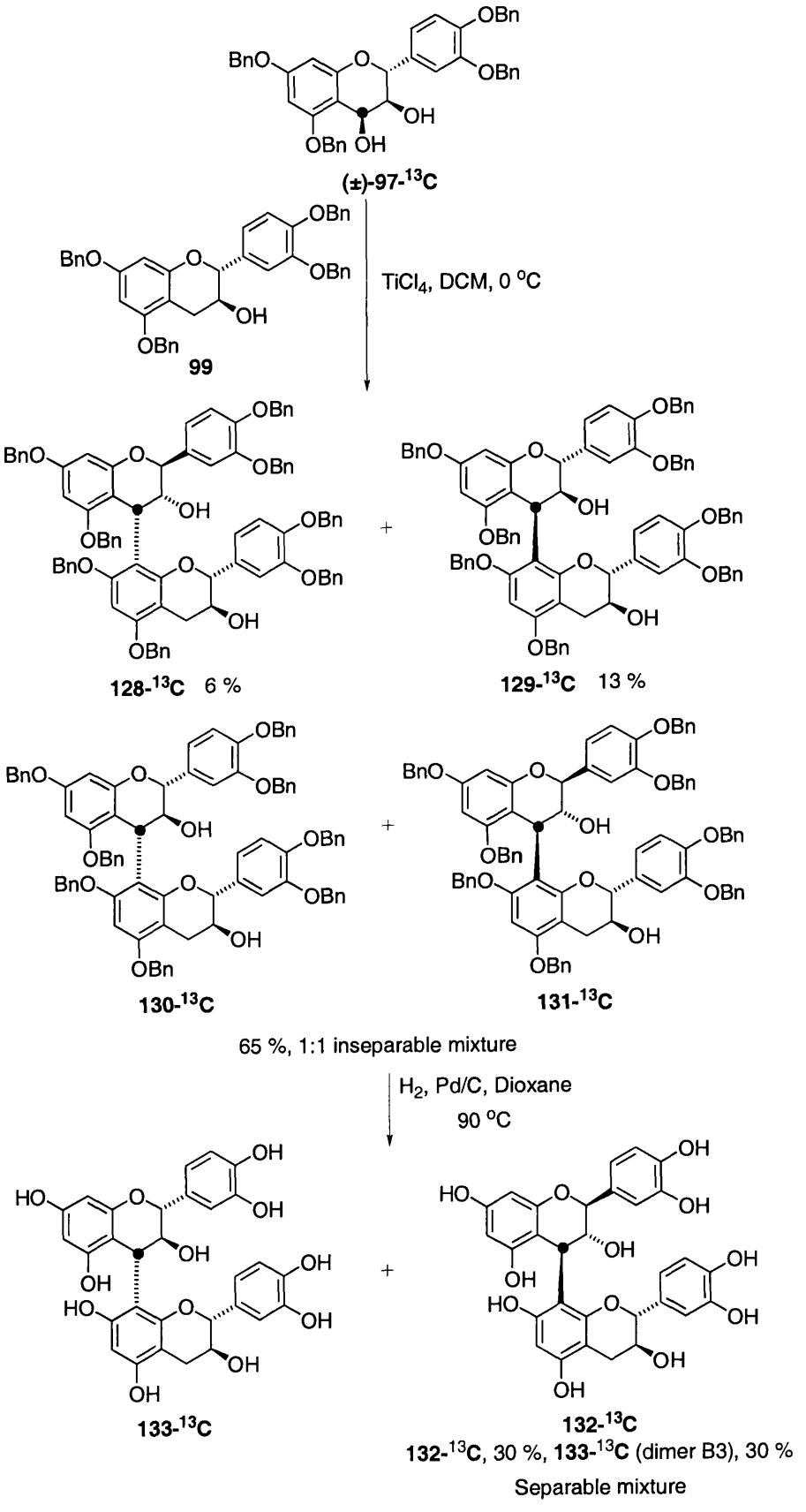

120
121
1) BnBr, K2CO3, DMF
2) LiAlH4, THF
3) PCC, DCM
87 % over 3 steps
BnBr, K2CO3, HMPA
75 %
119
102
piperidine
EtOH, reflux
65 - 75 %
122
NaBH4
THF
EtOH
50 %
123
1) BH3.THF
2) H2O2, NaOH
60 - 70 %
DMP
50 %
124
125
L-Selectride
THF
75 - 80 %
115
51 %
over 2 steps
1) ArCOCl, DMAP, Et3N
2) H2/Pd/C, dioxane
127
66 %
over 2 steps
1) ArCOCl, DMAP, Et3N
2) H2/Pd/C, dioxane
126
Ar =

Scheme 2.16

In summary, Zaveri's syntheses of racemic methylated gallocatechin and epigallocatechin gallates resemble Vercauteren's method for the construction of catechin and epicatechin, except that the 3-flavene derivative undergoes hydroboration-oxidation rather than dihydroxylation-reduction and the oxidation-reduction sequence employed by Chan and co-workers is employed to access the *syn* stereochemistry of epigallocatechin.

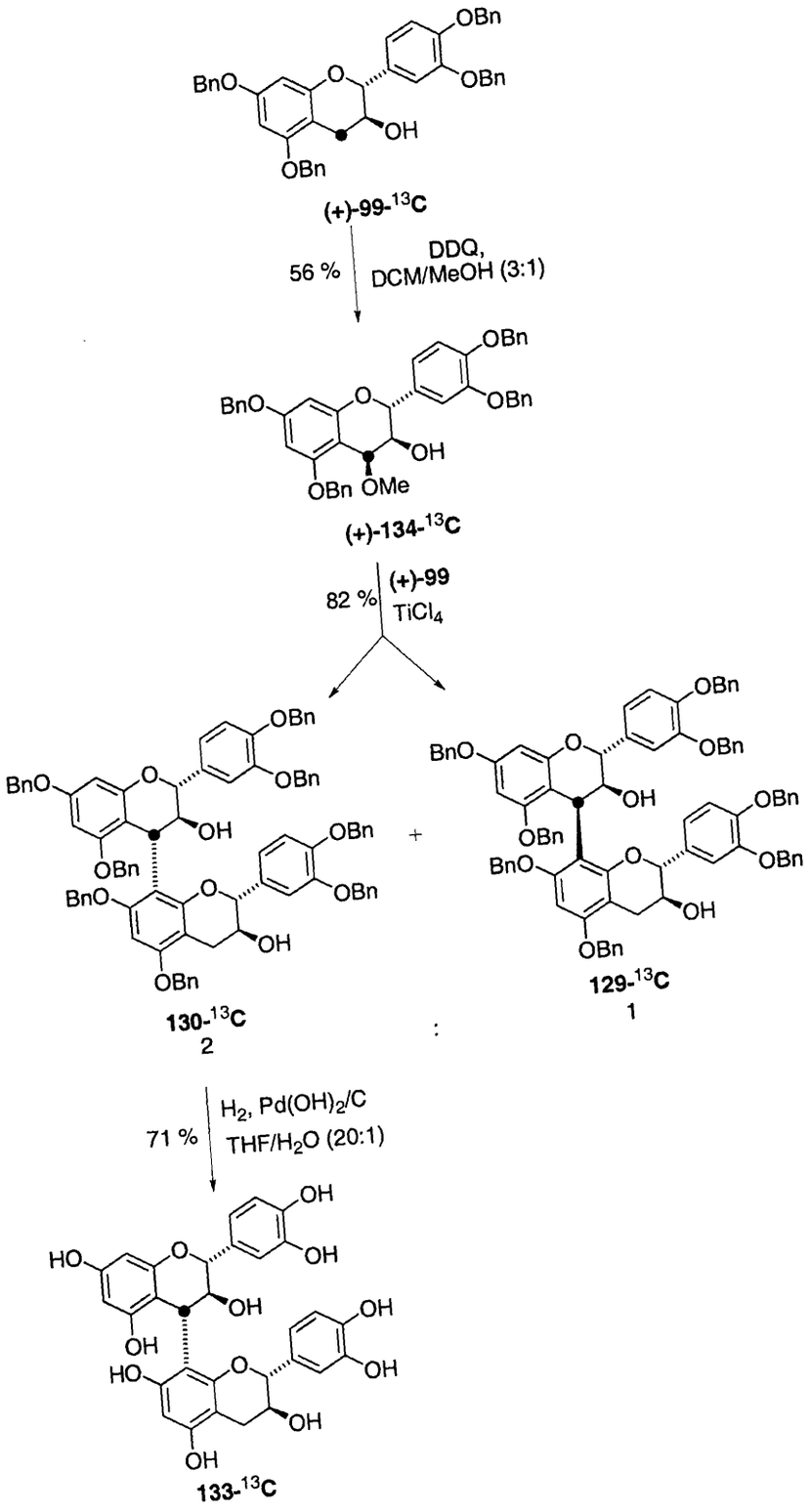
2.9 Labelling catechin dimers found in the diet

The condensation of racemic **97-^{13}C**, derived from **56** in six steps, with tetrabenzyloxycatechin **99** produced the dimer diastereoisomers **128-^{13}C**, **129-^{13}C**, **130-^{13}C** and **131-^{13}C** (**Scheme 2.17**).[57] The major dimers **130-^{13}C** and **131-^{13}C** were formed as an inseparable 1:1 mixture in moderate yield. The other two dimers contain unnatural stereochemistry at the C-ring centres and were formed in small amounts (6 % and 13 %). The mixture of **130-^{13}C** and **131-^{13}C** was deprotected by hydrogenation to give a separable mixture of dimers **132-^{13}C** and **133-^{13}C**. A small amount of catechin (8 %) was also isolated which was attributed to the reduction of the interflavanolic linkage. The authors report the synthesis of procyanidin B3 **133-^{13}C** in eight steps and 6 % overall yield from 1,3,5-tribenzyloxybenzene **56** and 1-[^{13}C]-acetic acid.[57] Considering the availability of both 2-[^{13}C]- and 1,2-[^{13}C]$_2$-acetic acid, the authors have devised a flexible route to the isotopic labelling of procyanidins. The drawbacks to the route are the use of three equivalents of the labelled acetic acid and the low yields associated with the dimerisation and the hydrogenation. The reduction of the interflavanolic linkage is also undesirable as this wastes 8 % of the label. These problems would be accentuated in a radiochemical synthesis as radiolabelled acetic acid is expensive and use in excess would not be good.


(±)-97-13C
99
TiCl4, DCM, 0 °C
128-13C 6 %
129-13C 13 %
130-13C
131-13C
65 %, 1:1 inseparable mixture
H2, Pd/C, Dioxane
90 °C
133-13C
132-13C
132-13C, 30 %, 133-13C (dimer B3), 30 %
Separable mixture

Scheme 2.17

Having previously synthesised procyanidin B3 *via* a route unsuitable for large-scale syntheses, Vercauteren developed a route applicable to the synthesis of large quantities of procyanidin B3 (**Scheme 2.18**).[58] The previous route was mildy altered, but the changes simplified the purification of the crude dimers and eliminated the undesired reduction of the interflavanolic linkage. Their synthesis of large quantities of (+)-catechin provided them with the desired starting material. They found that the best conditions for the re-oxidation of the C-4 position of protected labelled (+)-catechin **99-^{13}C** were those described by Ferreira.[59] These conditions led to a moderate yield of diastereomerically pure ether **134-^{13}C**. Coupling of ether **134-^{13}C** with (2*R*, 3*S*)-tetrabenzyloxcatechin **99** using the same conditions as before gave a mixture of only two diastereomeric dimers **129-^{13}C** and **130-^{13}C** in a 1:2 ratio and in 82 % yield. This compares favourably to the mixture of four dimers obtained previously. Separation of the mixture gave the desired dimer **130-^{13}C** in 55 % yield, which was then deprotected to give procyanidin B3 **133-^{13}C** in 71 % yield after purification. The authors found that the use of non-acidic $Pd(OH)_2/C$ in a mixture of THF and water at room temperature instead of Pd/C (which often contains traces of acid) in dioxane at 90 °C, eliminated the problem of reduction of the sensitive linkage. At first glance, this procedure looks essentially identical to the previous synthetic route. However, the relatively minor changes had a major beneficial effect on the useability of the route. Although there are still problems with the route, it is now much more feasible as a useful route to radiolabelled procyanidins.


(+)-99-13C
56 %
DDQ,
DCM/MeOH (3:1)
(+)-134-13C
82 %
(+)-99
TiCl4
130-13C
2
129-13C
1
71 %
H2, Pd(OH)2/C
THF/H2O (20:1)
133-13C

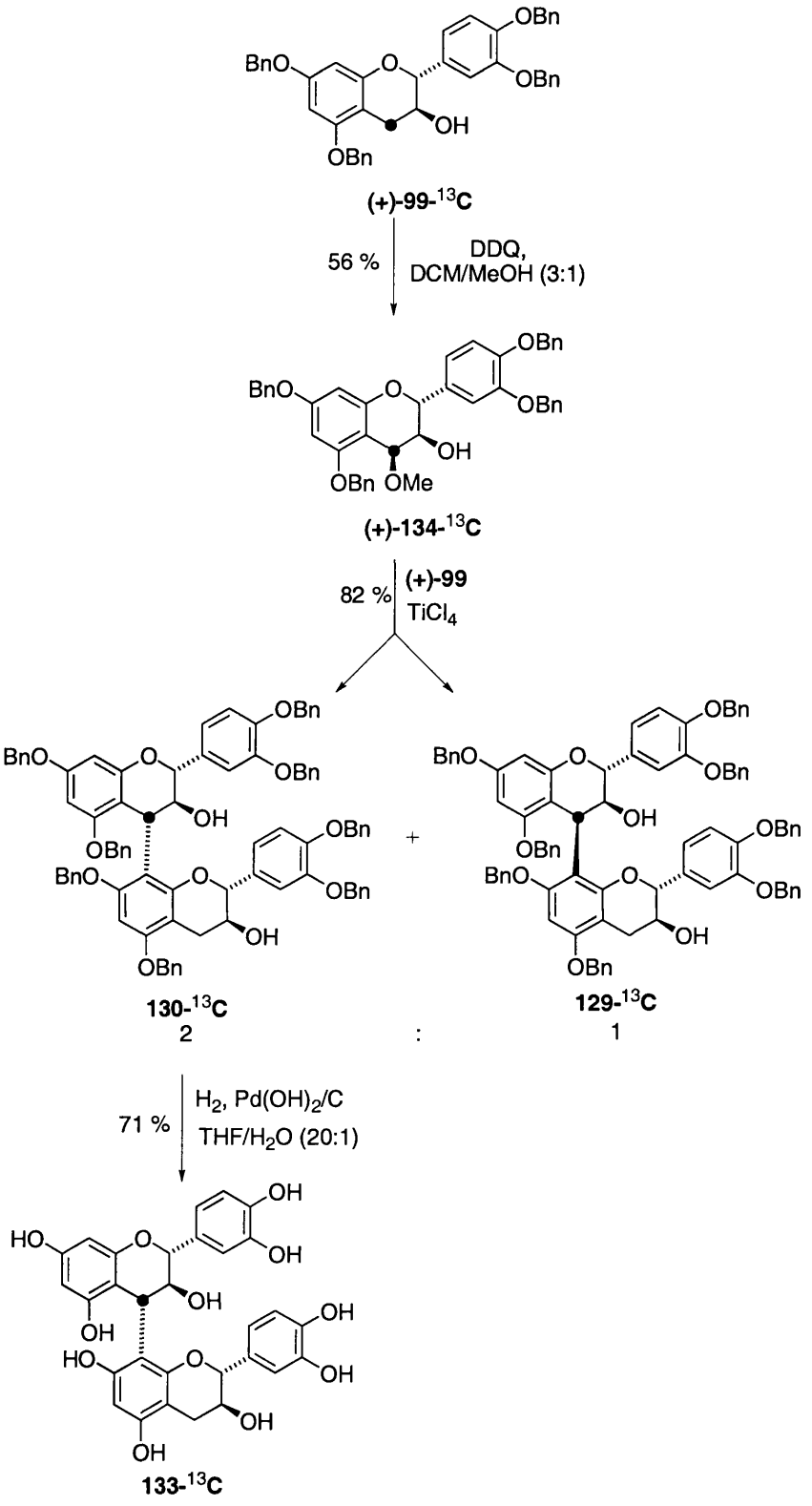
Scheme 2.18

2.10 Biosynthesis for labelling flavan-3-ols

The [U-^{14}C]-(+)-catechin and A-ring labelled (+)-catechin used in early studies of catechin metabolism were prepared by feeding radioactive materials to plants or plant cell cultures. Recently, cell-suspension cultures of ohelo and grape provided with uniformly labelled [^{14}C]-sucrose were used to prepare ^{14}C-enriched flavonoid fractions containing (+)-catechin.[60] Unfortunately, such methods lead to complex mixtures of compounds that have to be extracted from the plant cells and separated to obtain the radiolabelled catechin required for feeding studies.

2.11 Labelling of flavan-3-ols with isotopes of hydrogen

The synthesis of [4-^{2}H]-procyanidin B3 **133-^{2}H** has also been reported by Vercauteren and is shown in **Scheme 2.19**.[61] Benzylation of (+)-taxifoliol **135** gave a 3:7 mixture of compounds **136** and **137**. The positive optical rotation obtained from the mixture after hydrogenation suggests that (2*R*, 3*S*)-alcohol **137** is the major product. The mixture was reduced with $NaBD_4$ to give a 1:1 mixture of deuterium labelled alcohols **138-^{2}H**, **139-^{2}H** and **140-^{2}H**, **141-^{2}H**. Using the same procedure as described previously (**Section 2.9**), [4-^{2}H]-procyanidin B3 and its diastereomer were synthesised in a 7:3 ratio and separated by preparative HPLC. The structure was corroborated by ^{2}H NMR and by comparison of the ^{1}H NMR spectrum with the unlabelled compound.



Scheme 2.18

In summary, the synthesis of [4-^{2}H]-procyanidin B3 was achieved in 4 steps from (+)-taxifoliol. However, there are two main drawbacks associated with the synthesis. The use of isotopes of hydrogen may lead to inconclusive metabolic results due to the

possibility of the label being exchanged in the body. The position of the label is also potentially problematic as this position can be cleaved during metabolism, potentially leading to the loss of the label.

2.12 Summary

Since our aim was to synthesise ^{14}C-labelled (+)-catechin, some of the chemistry discussed in this chapter was a useful starting point for our studies. Vercauteren has synthesised racemic catechin *via* a 3-flavene intermediate. He has successfully applied his strategy to the synthesis of [4-^{13}C]-labelled catechin. The synthesis of [4-^{13}C]-labelled (+)-catechin was also achieved, however, this relied on the resolution of the racemic catechin. This is not ideal an ideal process for labelling (50 % of the label is lost) or synthesis in general as the maximum recovery of material is 50 %.

Ferreira, Jew and Park and Chan have successfully applied asymmetric dihydroxylation as the key step in the synthesis of flavan-3-ols. Grubbs used cross-metathesis followed by asymmetric dihydroxylation in his synthesis of tetramethylcatechin. This strategy has the advantage over Vercauteren's approach that asymmetric dihydroxylation allows high enantioselectivities to be more readily achieved in fewer steps than resolution.

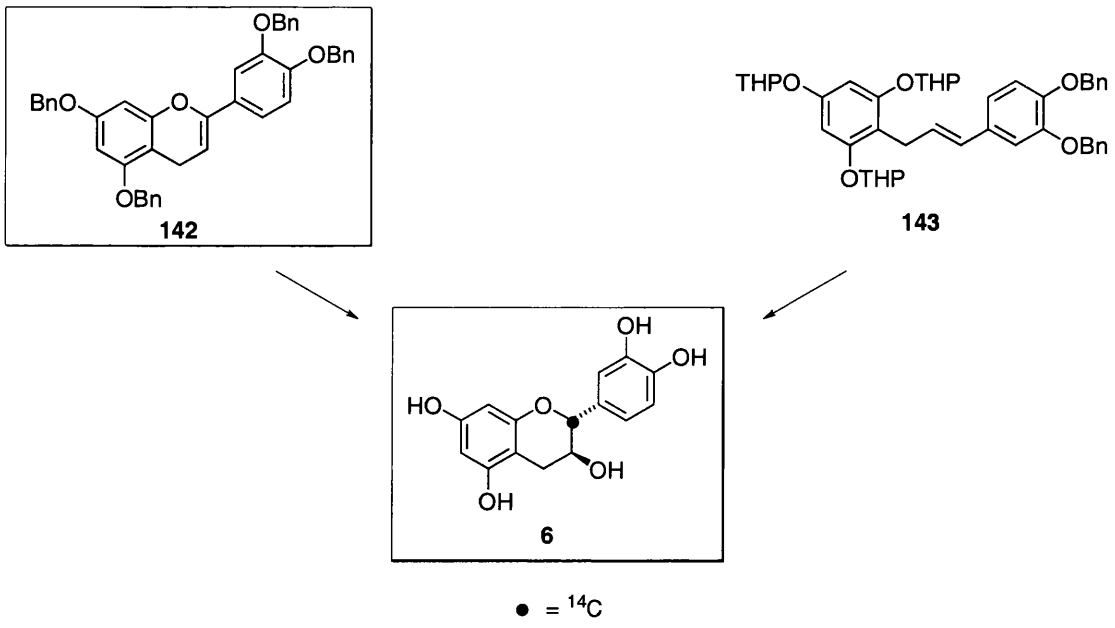
Our initial goal was to synthesise ^{14}C-labelled (+)-catechin using a novel asymmetric hydroboration route. However, as will become clear in chapter 3, this proved difficult. As a result of the difficulties encountered, we devised a route based on a combination of Grubbs' cross-metathesis and Ferreira's dihydroxylation strategies already discussed in this chapter. Our studies based on this revised route are discussed in chapter 4.

CHAPTER 3 – First approach: Asymmetric hydroboration of 2-flavenes

3.1 Introduction

The inconclusive evidence in the literature on the bioavailability of flavonoids makes the synthesis of these compounds in a labelled form appropriate for biological studies vitally important. The aim of this project was to investigate novel approaches to the radiochemical synthesis of the flavan-3-ol, (+)-catechin to allow its absorption, metabolism and excretion to be investigated. By labelling (+)-catechin in a position that is stable under normal physiological conditions, its potential as a dietary antioxidant could be assessed. The ^{14}C-labelled material would be used for feeding studies in rats to determine the metabolites of this compound and where they arise in the body. The synthesis of the ^{14}C-labelled material should be as short as possible from the introduction of the label. Each step should be as high yielding as possible and also allow easy purification of the compounds. It is also highly desirable to avoid column chromatography as this can generate large quantities of contaminated material that is very expensive to dispose of.

Two routes for the synthesis of (+)-catechin were investigated. Asymmetric hydroboration of flavene **142** (**Scheme 3.1**) should allow access to (+)-catechin. Thus, the first route involved the syntheses of model flavene intermediates, which could then be used to test the asymmetric hydroboration step. The chemistry involved in these studies will be discussed in this chapter. An alternative synthesis of catechin was also envisaged employing a dihydroxylation-cyclisation strategy of 1,3-diarylpropene **143**, which will be discussed in more detail in chapter 4.

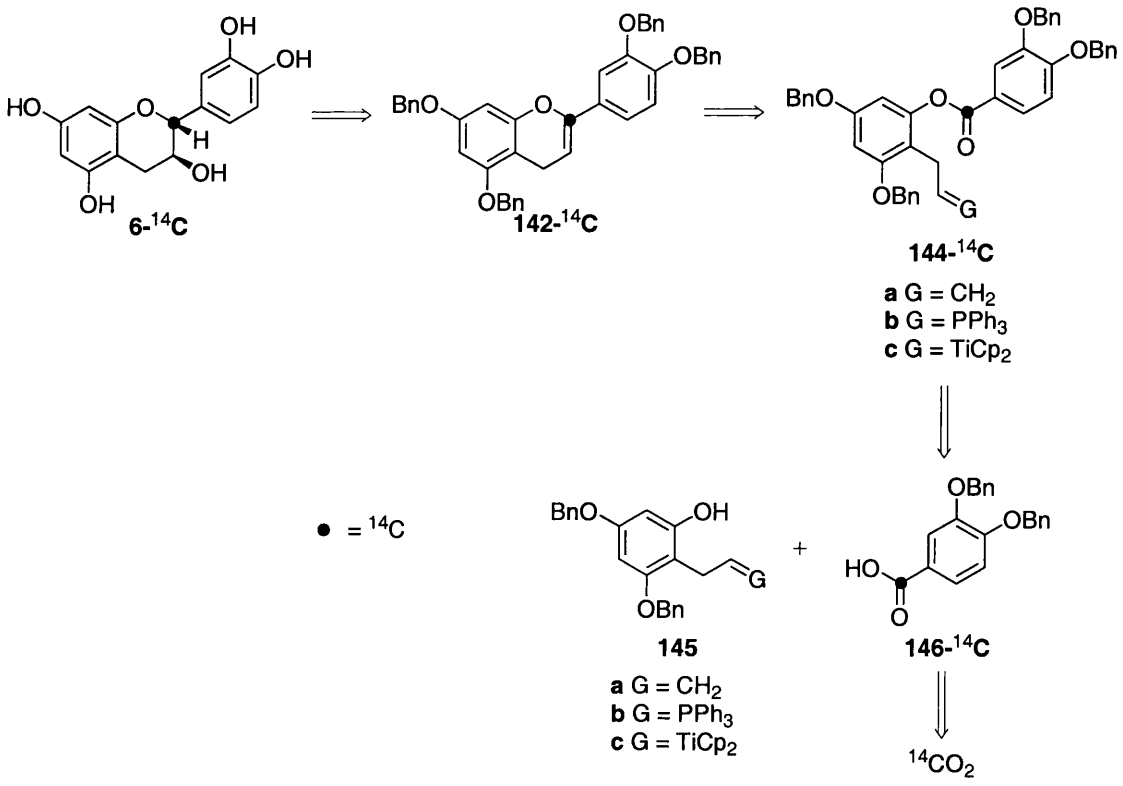


Scheme 3.1

The main approach to the model flavene system focused on titanium alkylidenation chemistry. Literature precedence for titanium alkylidenation of similar systems will be discussed later in this chapter. Some time was also devoted to the investigation of intramolecular Wittig and Grignard reactions to give model flavene systems. Our initial retrosynthesis and proposed synthetic route to (+)-catechin will now be discussed in more detail.

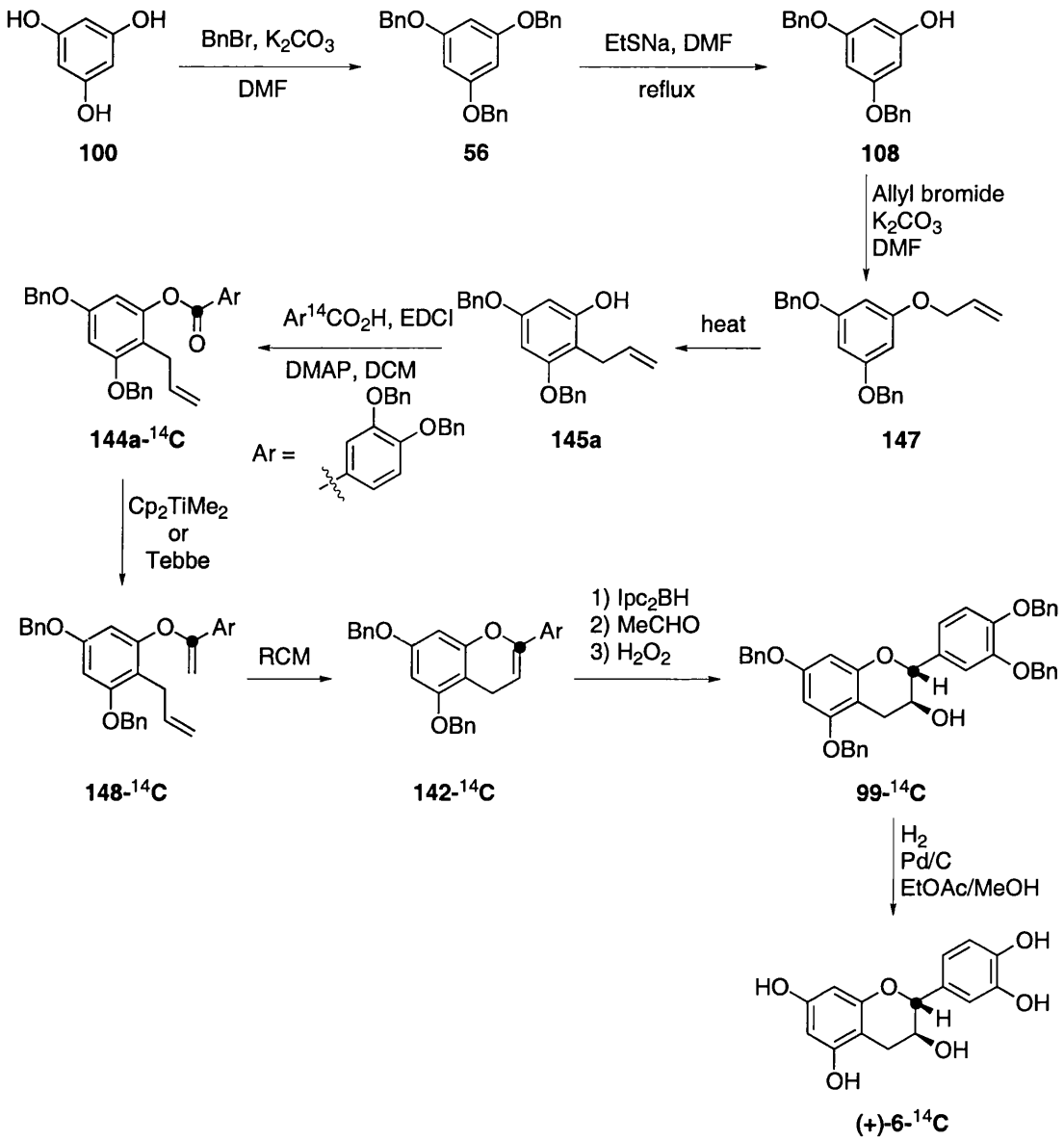
3.2 General synthetic strategy

Our retrosynthesis of (+)-catechin **6-^{14}C** is shown below (**Scheme 3.2**). (+)-Catechin could be synthesised from flavene **142-^{14}C** by asymmetric hydroboration. Flavene **142-^{14}C** could in turn be synthesised from ester **144-^{14}C**, which could be synthesised from phenol derivative **145a** and benzoic acid derivative **146-^{14}C**. Benzoic acid derivative **146-^{14}C** should be easy to prepare in a single step from radiolabelled carbon dioxide.



Scheme 3.2

This retrosynthesis led to our first proposed synthetic route (**Scheme 3.3**). Benzylation of phloroglucinol[62] **100** should give tribenzyl ether **56**, which could be deprotected with sodium ethanethiolate[62] to give phenol derivative **108**. Allylation of **108** to give **147** followed by a Claisen rearrangement should give phenol derivative **145a**. Esterification of **145a** with benzoic acid derivative **146-^{14}C** should give ester **144a-^{14}C**, which could be methylenated to give enol ether **148-^{14}C**. Subsequent ring-closing metathesis (RCM) should give flavene **142-^{14}C**. Asymmetric hydroboration-oxidation should lead to the tetrabenzylated (+)-catechin **99-^{14}C**. Finally, global deprotection of **99-^{14}C** should give (+)-catechin **6-^{14}C**. The key steps in this approach are a) Claisen rearrangement to *C*-allylate phloroglucinol b) alkylidenation-RCM to prepare the 2-flavene and c) asymmetric hydroboration. I shall consider the literature precedent for each of these key steps before discussing our model studies on the formation of 2-flavenes. Our original route employed the synthesis of phenol derivative **145a**. However, as will become clear later, we were forced into investigating both **145b** and **145c** derivatives as well.

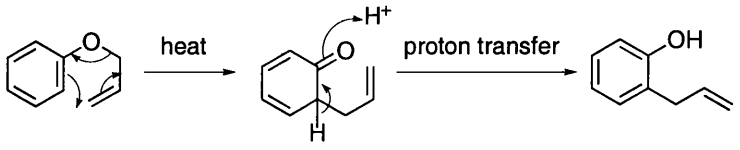


Scheme 3.3

3.2.1 Claisen rearrangement of aryl allyl ethers

The Claisen rearrangement was the first sigmatropic rearrangement to be discovered. An example of the rearrangement occurs when an aryl allyl ether is heated with no solvent present to give an *o*-allyl phenol. The mechanism is shown below (**Scheme 3.4**). When heated, allyl ether **149** undergoes a [3,3]sigmatropic rearrangement to give intermediate **150**, which re-aromatises *via* a proton transfer to give allyl phenol **151**. In the *ortho* migration the allylic group always undergoes an allylic shift i.e. a substituent α to the oxygen will become γ to the ring and vice versa. If both *ortho*-positions are filled, the allylic group migrates to the *para*-position (*para*-Claisen

rearrangement). A double allylic shift occurs in the *para* migration and no reaction takes place if the *para* and both *ortho* positions are filled.

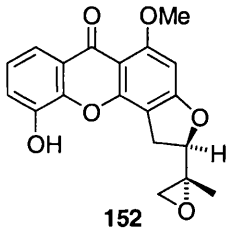


149 **150** **151**

Scheme 3.4

Claisen rearrangements have been used in the synthesis of a wide variety of compounds. Some examples on systems similar to our own (**147** → **145**, **Scheme 3.3**) are discussed below.

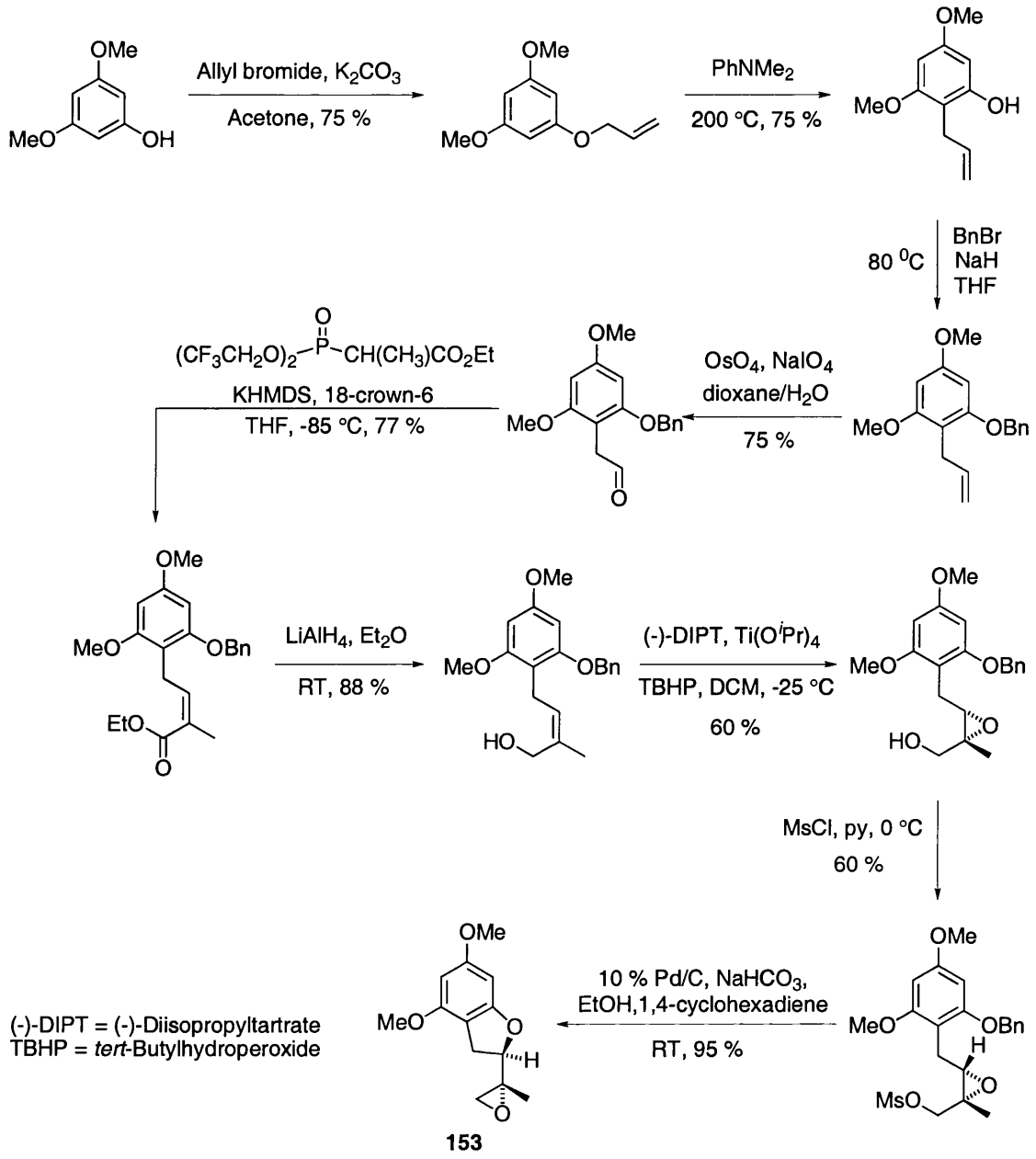
Psorospermin **152** (**Figure 3.1**) is a plant-derived natural product possessing significant activity in several animal tumour models.[63]



152

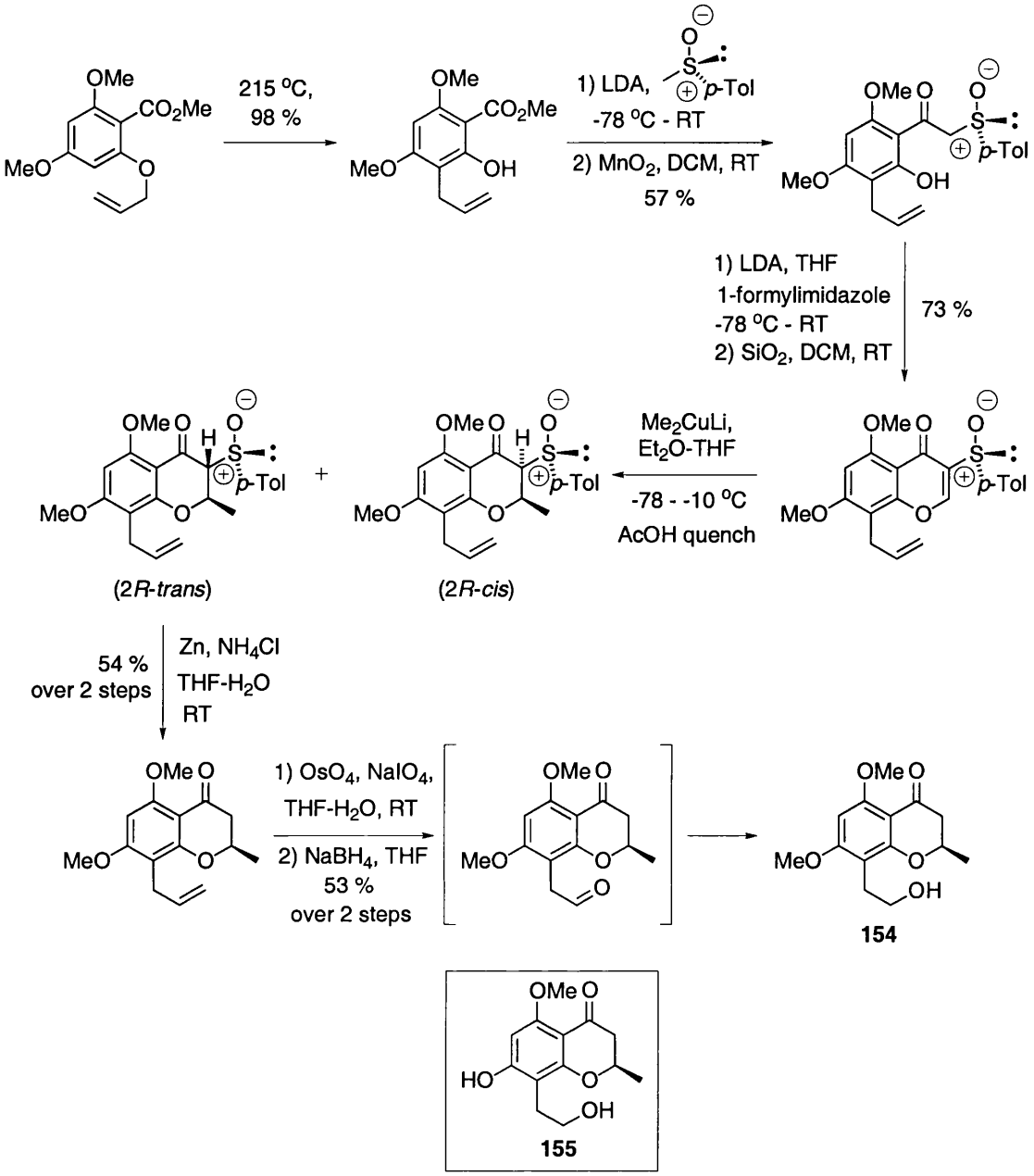
Figure 3.1

In developing an enantioselective route to **152**, Cassady and co-workers chose the dimethyl ether **153** as a model target to establish the synthesis of the epoxydihydrobenzofuran system.[63] A Claisen rearrangement was used early in the synthesis to construct the side chain (**Scheme 3.5**).



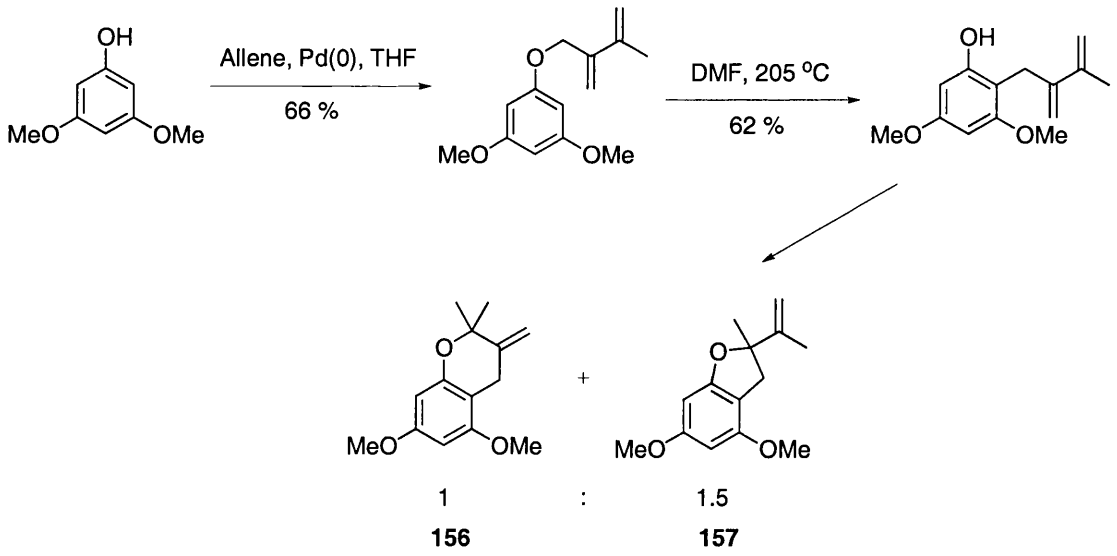
Scheme 3.5

A wide variety of biologically and medicinally interesting compounds contain the chroman ring system and new examples are continually emerging. Wallace *et al* used (*R*)-(+)-methyl *p*-tolyl sufoxide to allow access to chromans in high enantiomeric purity.[64] A Claisen rearrangement was used to install the necessary side-chain in their route to the methyl ether derivative **154** of the antibiotic LL-D253α **155** (**Scheme 3.6**).



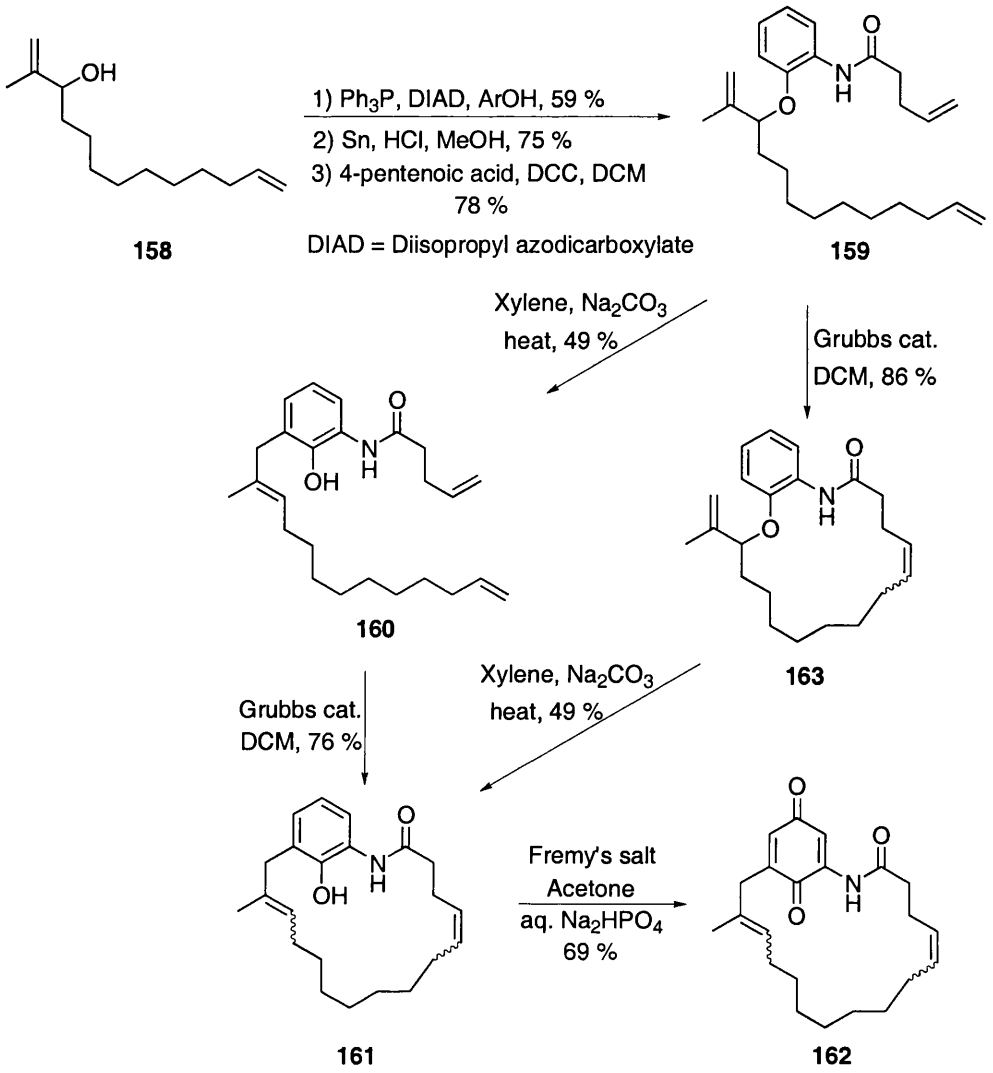
Scheme 3.6

Grigg *et al* employed a Claisen rearrangement to synthesise *C*-dienyl phenols to investigate their acid-catalysed cyclisation products.[65] A range of mixtures of *exo*-methylene chromans e.g. **156** and dihydrobenzofurans e.g. **157** were synthesised. These ring systems are found in many natural products and this procedure provides a short, convenient approach to these systems with no need for protecting groups to be used. An example is shown below (**Scheme 3.7**).



Scheme 3.7

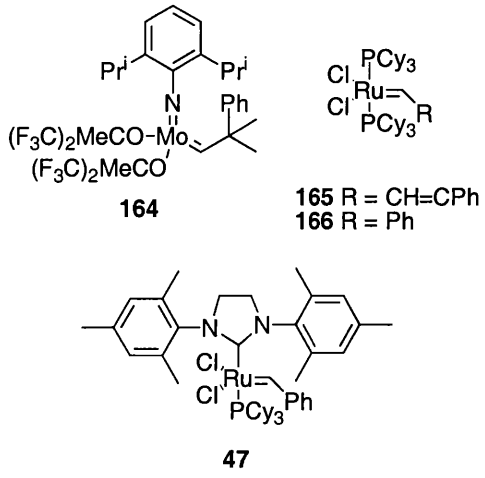
In the recent literature, Moody and Davis devised a novel use for the Claisen rearrangement in their synthesis of macrocyclic lactams related to the ansamycin antibiotics (**Scheme 3.8**).[66] Mitsunobu coupling of dienol **158** with 2-nitrophenol followed by reduction of the nitro group and amide formation with 4-pentenoic acid gave amide **159** in 78 % over three steps. Claisen rearrangement gave phenol derivative **160** in moderate yield, which underwent RCM with Grubbs catalyst $[(PCy_3)_2Cl_2Ru{=}CHPh]$ to give the 19-membered macrocycle **161** as a 1:1 mixture of *E*:*Z* isomers in good yield. Oxidation with Fremy's salt gave the final benzoquinone derivative **162** in good yield. Alternatively, RCM of amide **159** gave the 17-membered macrocycle **163** in good yield as a mixture of *E*- and *Z*-isomers. Claisen rearrangement of **163** gave the ring-expanded 19-membered macrocycle **161** in moderate yield. Oxidation as before gave the final macrocycle **162**. The expansion of an *n*-membered 1,2-bridged macrocycle to an *n*+2-membered ring represents a novel use of the Claisen rearrangement.



Scheme 3.8

3.2.2 Synthesis of cyclic olefins using alkylidenation and ring-closing metathesis

Throughout the 1990's, ring-closing metathesis (RCM) reactions have developed into one of the most powerful ways of synthesising cyclic olefins. A number of catalysts have been developed for RCM reactions including Schrock's molybdenum based catalyst[67] **164** and several ruthenium based catalysts **165**,[68] **166**[69] and **47**[70] developed by Grubbs (**Figure 3.2**).



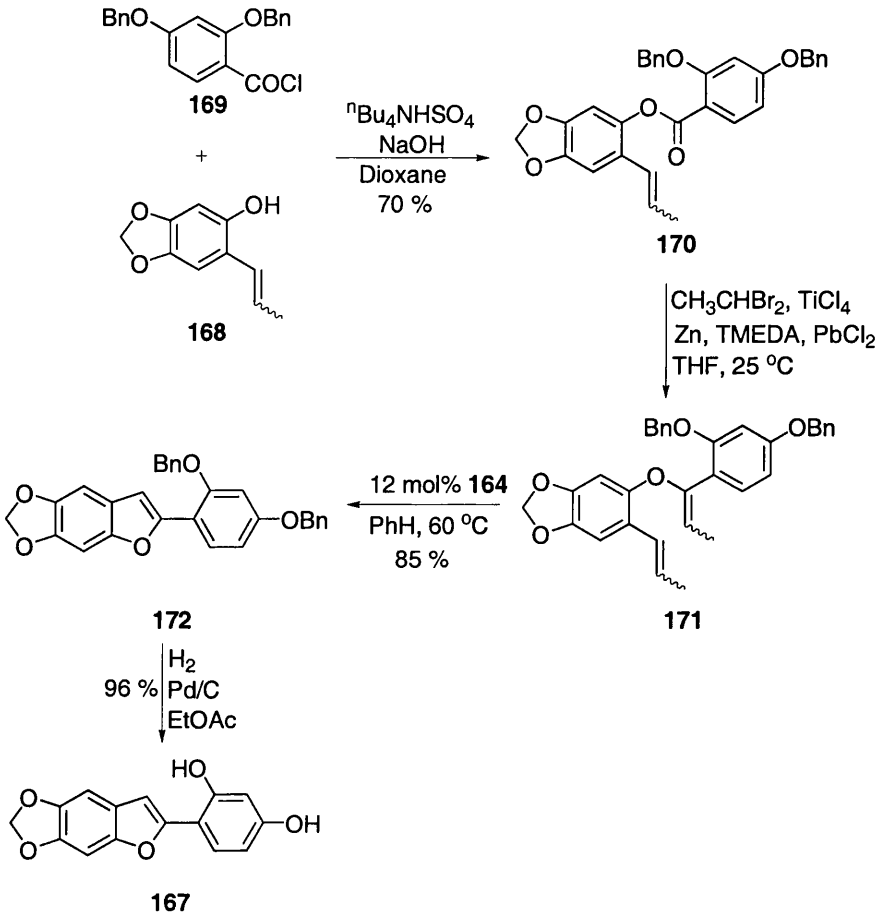
164

165 R = CH=CPh
166 R = Ph

47

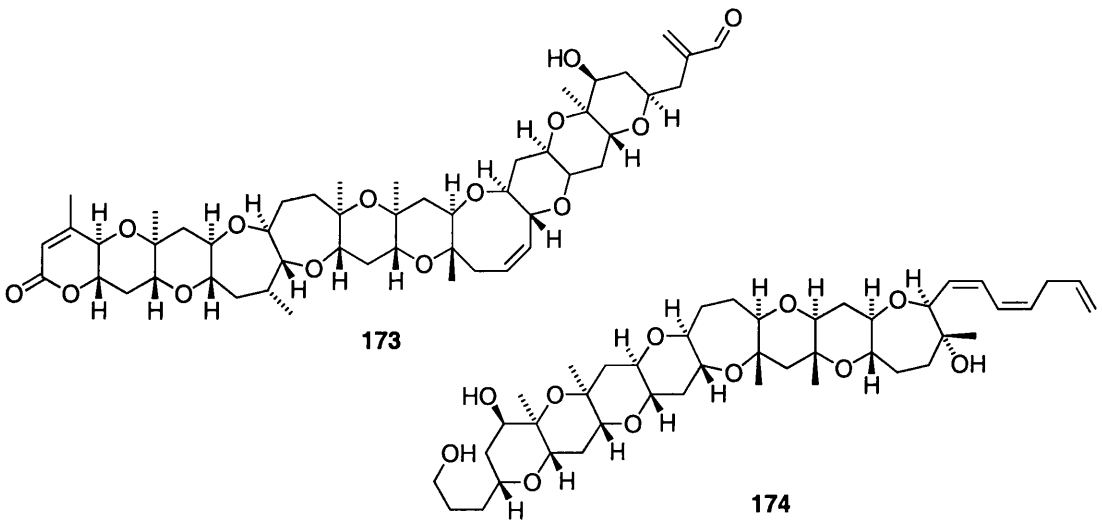
Figure 3.2

In 1994, a two step procedure for the synthesis of simple five and six membered cyclic enol ethers by intramolecular metathesis of alkenes with enol ethers was reported by Grubbs.[71] The procedure involved Tebbe methylenation or Takai alkylidenation of esters followed by RCM using Schrock's catalyst **164**. Grubbs found that his own catalyst **165** did not give the desired enol ethers. This procedure has been successfully employed in the synthesis of phytoalexine **167**, an antifungal agent (**Scheme 3.9**).[72] Esterification of phenol derivative **168** with acid chloride **169** under phase-transfer conditions gave ester **170** in good yield. Takai ethylidenation gave enol ether **171**, which when treated with catalyst **164** in refluxing benzene, gave benzofuran derivative **172** in high yield. Removal of the benzyl ethers by hydrogenation proceeded to give phytoalexine **167** in almost quantitative yield.



Scheme 3.9

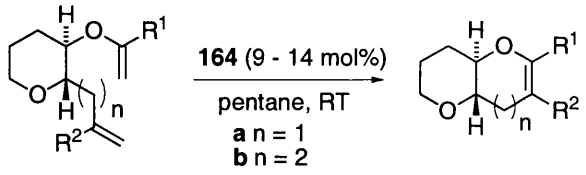
The procedure was expanded to the synthesis of fused bicyclic enol ethers containing six and seven membered rings during the synthesis of polycyclic ether structures found in marine neurotoxins such as brevetoxin B **173** and gambierol **174** (**Figure 3.3**).[73]



173 **174**

Figure 3.3

A variety of enol ether precursors **175-177** were constructed to investigate the alkylidenation-RCM reaction (**Scheme 3.10**). The results are summarised below (**Table 3.1**).



175 $R^1 = R^2 = H$
176 $R^1 = H$, $R^2 = Me$
177 $R^1 = Et$, $R^2 = H$

177 $R^1 = R^2 = H$
178 $R^1 = H$, $R^2 = Me$
179 $R^1 = Et$, $R^2 = H$

Scheme 3.10

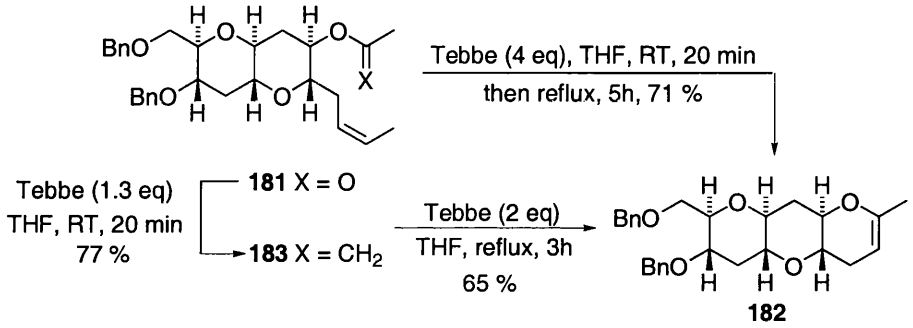
Substrate	Enol ether	Yield (%)
175a	**178a**	64
175b	**178b**	65
176a	**179a**	93
176b	**179b**	94
177a	**180a**	72
177b	**180b**	40

Table 3.1

From the table it can be seen that treatment of enol ethers **175-177** with a sub-stoichiometric amount of catalyst gave the desired cyclic enol ethers in good to excellent yield, the best results being obtained with the trisubstituted enol ethers **176a** and **176b**. The authors attributed this to the metal alkylidene reacting with **176** at the less hindered enol ether in the initial step of the metathesis sequence and that ring-closure then occurs by rapid reaction of the resulting alkylidene with the

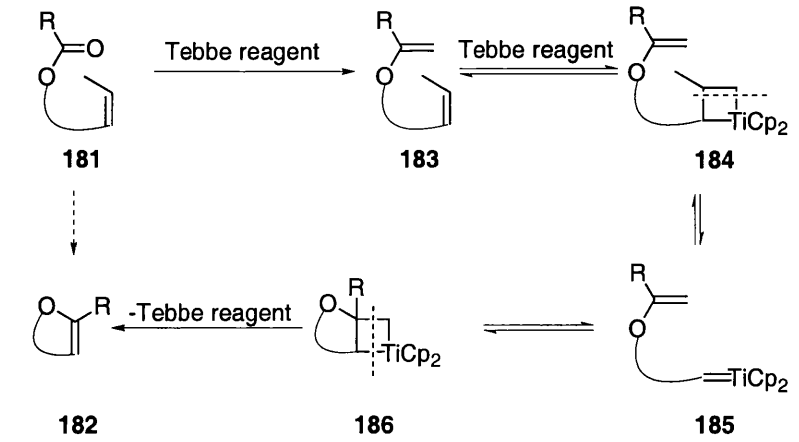
electronically more reactive 1,1-disubstituted alkene. For substrates **175** and **177** the opposite would apply thus extending the lifetime of the intermediate olefin alkylidene and allowing potential side-reactions to take place.

The concept of a tandem alkylidenation-RCM procedure using the Tebbe reagent was reported by Nicolaou in the synthesis of polycyclic ether marine neurotoxin skeletons[74] e.g. the conversion of bicyclic acetate **181** into tricyclic enol ether **182** *via* enol ether **183** (**Scheme 3.11**). Enol ether **183** was proven to be the intermediate by isolation and full spectral characterisation.



Scheme 3.11

The proposed mechanism is shown below (**Scheme 3.12**). Initial methylenation of ester **181** gives enol ether **183**, which could then react with another equivalent of Tebbe reagent to give titanacyclobutane derivative **184**. Fragmentation of **184** would lead to the generation of titanium alkylidene **185**. Intramolecular reaction of alkylidene **185** would lead to titanacyclobutane derivative **186**, which could undergo a regioselective fragmentation to form the desired enol ether **182**.

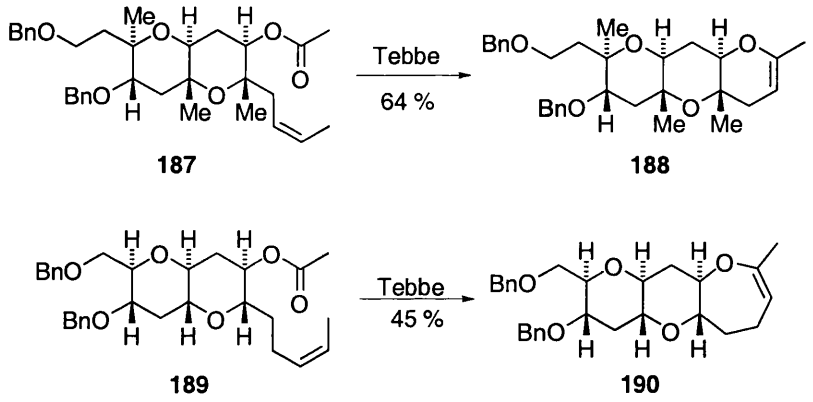


181 **183** **184**

182 **186** **185**

Scheme 3.12

Nicolaou *et al* investigated the generality and scope of the reaction and found that the reaction successfully formed six- and seven-membered cyclic enol ethers in good yields e.g. acetate **187** to enol ether **188** and acetate **189** to enol ether **190** (**Scheme 3.13**).[74]

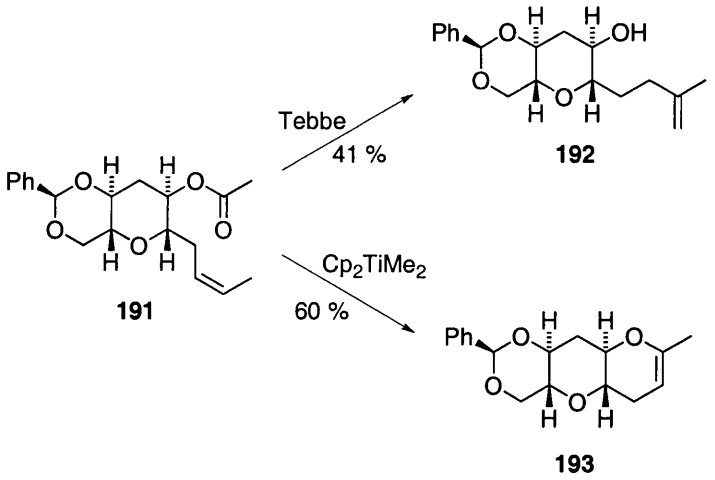


187 **188**

189 **190**

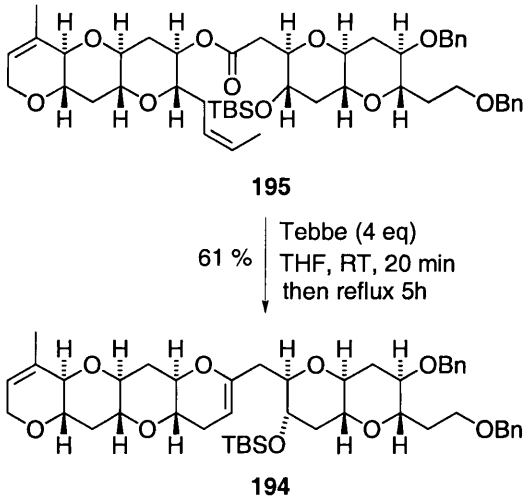
Scheme 3.13

It was found that dimethyltitanocene can be used instead of the Tebbe reagent and allows the isolation of labile cyclic enol ethers (**Scheme 3.14**).[74] For example, acetate **191** gives alkene **192** when treated with the Tebbe reagent, but the desired cyclic enol ether **193** on treatment with dimethyltitanocene.



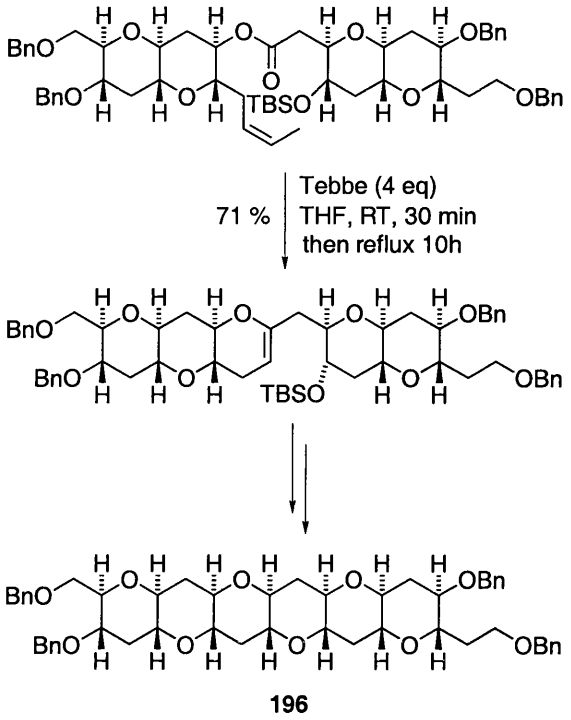
Scheme 3.14

The applicability of this procedure to the synthesis of complex polyether frameworks has already been shown (**Schemes 3.11** and **3.13**), however an important example of its use is illustrated in the synthesis of hexacycle **194** from ester **195** (**Scheme 3.15**).[74]



Scheme 3.15

This example shows that the reaction will tolerate trisubstituted alkenes elsewhere in the molecule. Another example of the power of this procedure is demonstrated in the synthesis of the complex hexacycle **196** (**Scheme 3.16**).[74] The strategy employed in this synthesis was made possible by this reaction.

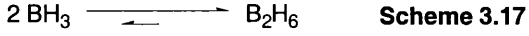


196

Scheme 3.16

3.2.3 Hydroboration and asymmetric hydroboration

Hydroboration reactions provide a convenient procedure for the conversion of alkenes into alcohols. The first examples were reported in 1956 and since then hydroboration has found many important applications in organic synthesis.[75] Unhindered alkenes react rapidly with borane to give in the first instance monoalkylboranes, followed by di- and trialkylboranes. The second and third hydroborations become increasingly difficult with increasing steric hindrance around the double bond. Borane, BH_3, is the simplest borane hydride, which exists in equilibrium with diborane, B_2H_6 (**Scheme 3.17**). The equilibrium lies greatly in favour of diborane under normal temperature and pressure.

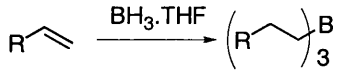


Scheme 3.17

Several stable sources of borane are available e.g. BH_3.THF, $BH_3.SMe_2$. The empty p-orbital on boron can accept a lone pair of electrons from a Lewis base to give a neutral species or can combine with a nucleophile to form a negatively charged anion.

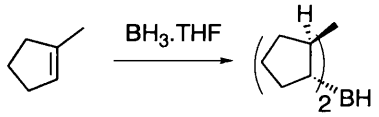
Hydroboration reactions exhibit three main characteristics:

a) The boron atom adds preferentially to the less hindered end of an unsymmetrical double bond i.e. anti-Markovnikov (**Scheme 3.18**).



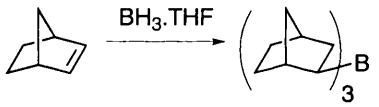
Scheme 3.18

b) Stereospecific *syn*-addition occurs (**Scheme 3.19**).



Scheme 3.19

c) Stereoselective addition takes place on the less hindered face of the molecule (**Scheme 3.20**).



Scheme 3.20

These characteristic features of hydroborations are consistent with a concerted four-centre transition state (**Figure 3.4**).

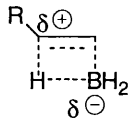


Figure 3.4

Borane can transform a wide range of alkenes into trialkylboranes under mild conditions, however the trifunctional nature of borane and its trialkylborane products causes some limitations in their use. Many synthetically useful reactions of trialkylboranes use all three alkyl substituents, however some reactions use only two or even one of the substituents. This imposes a limit on the maximum yield based on the alkene for these reactions. This is clearly undesirable particularly if the alkene

requires a multi-step synthesis. Another problem associated with borane is the formation of intractable polymers on addition to dienes and alkynes. To solve these problems mono- and dialkylborane reagents were developed.

The commonly employed borane reagents thexylborane ($ThBH_2$), disiamylborane (Sia_2BH), 9-borabicyclo[3.3.1]nonane (9-BBN) and dicyclohexylborane (Cy_2BH) are shown below (**Figure 3.5**).

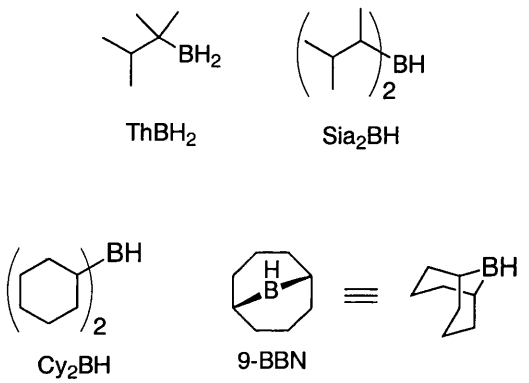
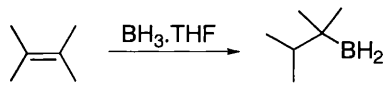


Figure 3.5

Thexylborane is prepared by hydroboration of 2,3-dimethylbut-2-ene with BH_3.THF (**Scheme 3.21**).

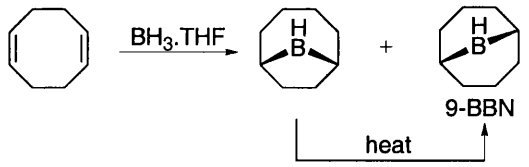


Scheme 3.21

It is ideal for the hydroboration of dienes due to the presence of two boron-hydrogen bonds. The hydroboration is more reliable than the corresponding borane reaction, which generally forms polymeric organoboranes. Thexylborane is normally prepared and used immediately as the *tert*-alkyl group slowly isomerises to a primary alkyl group on standing at room temperature.

The preparation of 9-BBN is also relatively straightforward. Addition of BH_3.THF to 1,5-cyclooctadiene gives a mixture of 9-borabicyclo[4.2.1]nonane and 9-

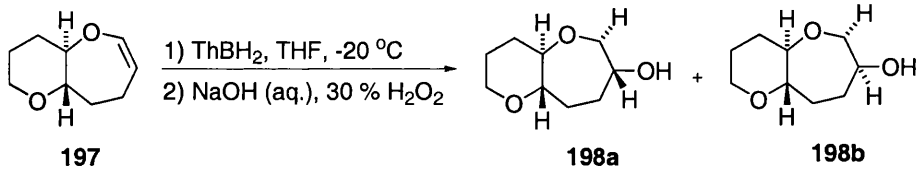
borabicyclo[3.3.1]nonane. The [4.2.1] system isomerises to the thermodynamically favoured [3.3.1] system on heating (**Scheme 3.22**).



Scheme 3.22

9-BBN is a very popular hydroborating reagent since it is a crystalline, relatively air and heat stable commercially available compound. The greater steric bulk of 9-BBN makes it far more regioselective in hydroboration reactions compared to borane. Clean hydroboration of internal alkynes can also be achieved with 9-BBN whereas the corresponding reaction with borane generally gives polymeric material. It is, however, less useful for the hydroboration of terminal alkynes as monohydroboration can only be achieved with an excess of alkyne.

Our synthesis of 2-flavenes requires the hydroboration of an enol ether. Clark and Kettle employed such a hydroboration step in their synthesis of polyether frameworks.[73] They found that hydroboration-oxidation of enol ether **197** with thexylborane gave a 90:10 mixture of diastereomeric alcohols **198** (**Scheme 3.23**).



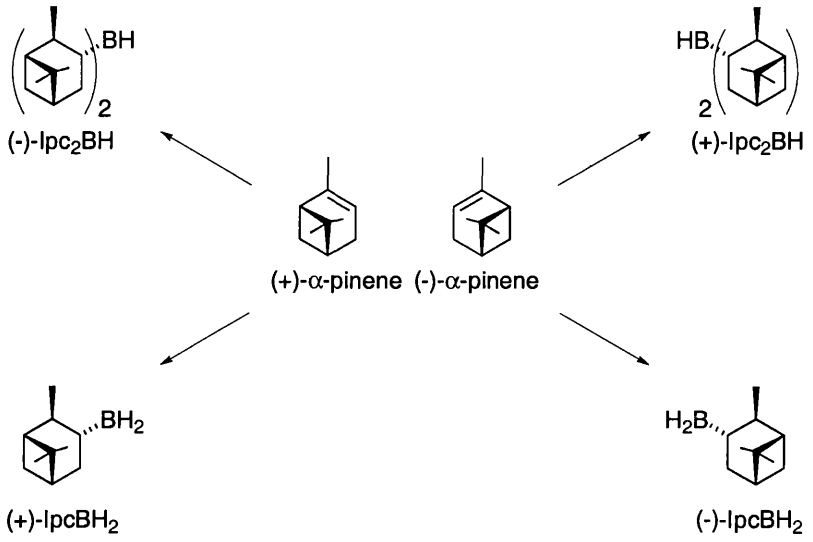
197 **198a** **198b**

Scheme 3.23

The hydroborating reagents discussed above are generated from achiral alkenes. Addition of borane to enantiopure alkenes from the chiral pool produces enantiopure alkylboranes that can be used for asymmetric hydroborations. Some examples are discussed below.

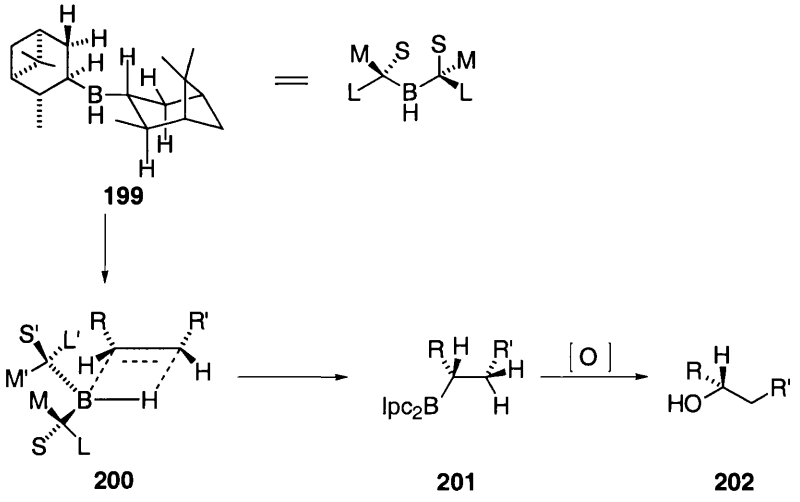
Two of the most commonly used borane reagents in asymmetric hydroboration are diisopinocampheylborane (Ipc_2BH) and monoisopinocampheylborane ($IpcBH_2$). The

reagents are prepared by hydroboration of α-pinene (**Scheme 3.24**). Both enantiomers of α-pinene are readily available thereby allowing easy access to both enantiomers of Ipc_2BH and $IpcBH_2$.



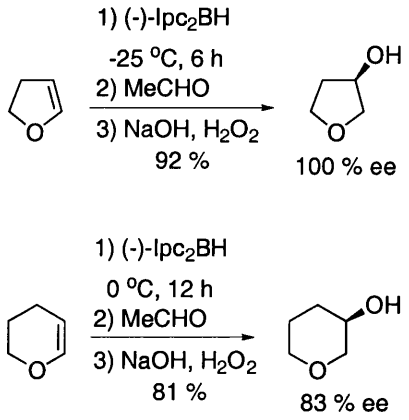
Scheme 3.24

In the mid 1960's, Brown *et al* proposed a model for the asymmetric hydroboration of *cis*-alkenes (**Scheme 3.25**).[76] Borane **199** is the most stable rotameric conformation for (-)-Ipc_2BH. This can be simplified further as shown in **200** where S = H, M = C-4 methyl, and L = C-2 methyl group. Hydroboration leads to borane **201**, which after oxidation gives the (*R*)-alcohol **202**.



Scheme 3.25

The lack of reports on asymmetric hydroboration of heterocyclic olefins prompted Brown *et al* to investigate several five- and six-membered heterocyclic enol ethers.[77] The furan and pyran results are shown in **Scheme 3.26**. This is the only literature precedent for our transformation.

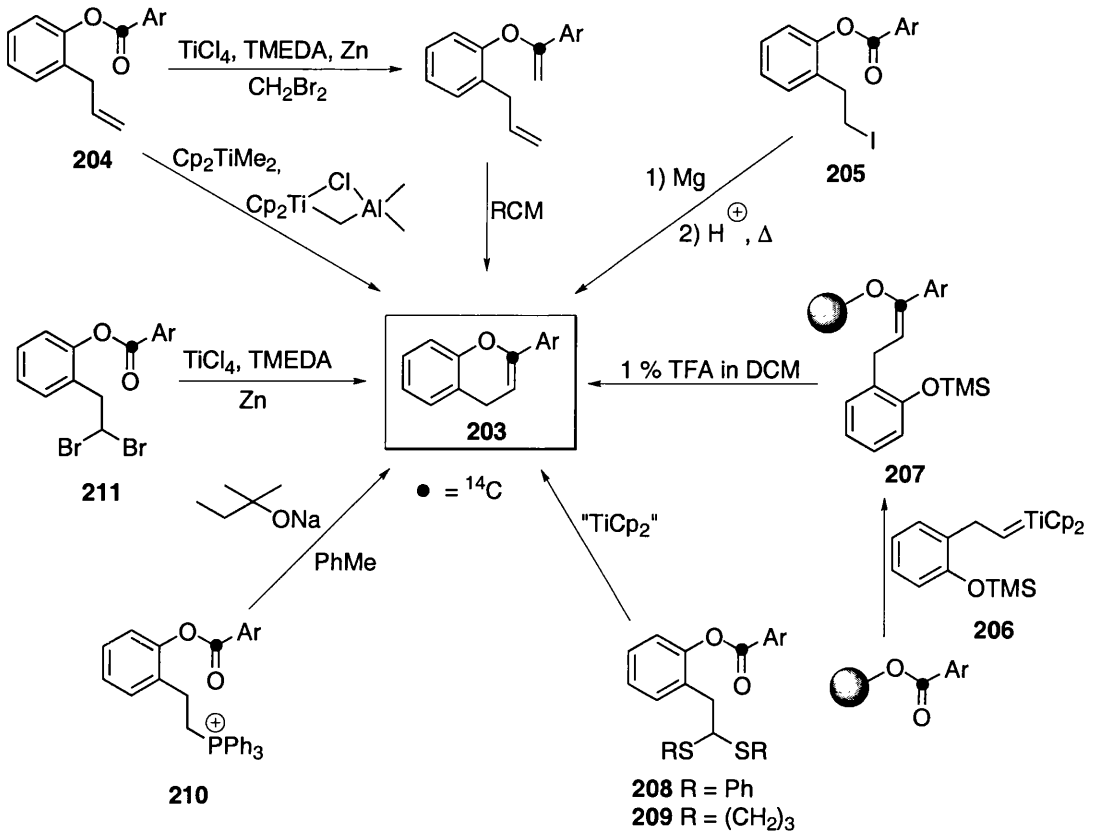


Scheme 3.26

In summary, the synthetic use of the Claisen rearrangement in similar systems to our own has been shown. Also discussed is the applicability of an alkylidenation-RCM type strategy in the synthesis of cyclic enol ethers. An overview of hydroborations and asymmetric hydroborations was given, describing the reagents used in both cases. The origin of the stereoselectivity observed in asymmetric hydroborations was also discussed.

3.3 Proposed routes to 2-flavenes

Model systems are often used in organic synthesis to allow the latter, potentially vital stages of a synthesis to be evaluated more readily. One potential route to flavene **142** from ester **144** using an alkylidenation-RCM strategy has been described (**Scheme 3.3**). A variety of other routes to a model 2-flavene system **203** from structurally similar systems to ester **144** are shown in **Scheme 3.27**.



Scheme 3.27

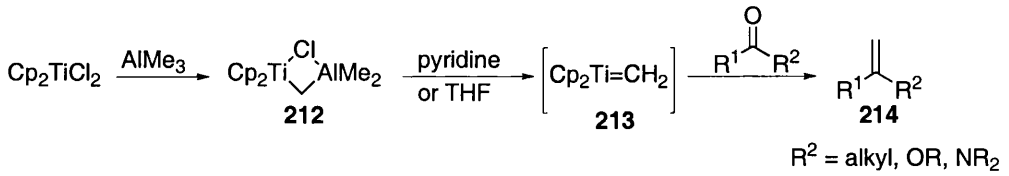
Flavene **203-^{14}C** could be synthesised using Nicolaou's one-pot methylenation and RCM of ester **204-^{14}C**.[74] Alternatively, Takai alkylidenation followed by RCM could also give flavene **203-^{14}C**. Intramolecular Barbier reaction of iodide **205-^{14}C** could also be envisaged. Methodology developed within the Hartley group suggests that alkylidenation of a suitable resin-bound ester with titanium alkylidene **206** followed by cyclisation of enol ether **207-^{14}C** could provide a viable route to the flavene.[78] Intramolecular cyclisation of thioacetals **208-^{14}C** and **209-^{14}C** using Takeda's methodology may allow flavene **203-^{14}C** to be synthesised, although there are only a few examples of successful intramolecular Takeda reactions in the literature.[79,80] Phosphonium salts similar to **210-^{14}C** have been cyclised under Wittig conditions to give chromenes[81] and benzofurans.[82,83] Alkylidenation and cyclisation of dibromide **211-^{14}C** could also be employed, however only one example on a similar system exists in the literature and this proceeded in poor yield.[84]

3.4 Titanium alkylidenes in 2-flavene synthesis

Some background to the titanium chemistry needed for some of the proposed routes in **Scheme 3.27** will now be given.

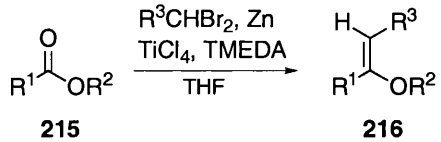
3.4.1 Titanium alkylidene reagents

The discovery of titanium alkylidenes by Tebbe has had a huge impact in the field of synthetic organic chemistry.[85] Tebbe found that the reaction of trimethylaluminium with titanocene dichloride gave the bridged titanium-aluminium metallacycle **212**, which can be used for the effective methylenation of ketones and amides. Esters, including lactones, can also be methylenated. When **212** is treated with a Lewis base such as pyridine or THF, the highly reactive methylidene **213** is formed, which can be used to methylenate carboxylic and carbonic acid derivatives to give alkenes **214** (**Scheme 3.28**).[72] Methylenation of aldehydes and ketones in the presence of amides or esters can be easily achieved. The Tebbe reagent has also been shown to catalyse RCM reactions (**Section 3.2.2**).



Scheme 3.28

In 1987, Takai reported a general procedure for the stereoselective alkylidenation of esters **215** to give *Z*-enol ethers **216** (**Scheme 3.29**).[86]

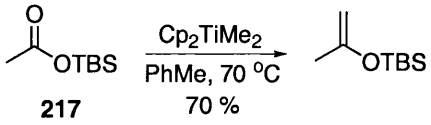


Scheme 3.29

The titanium alkylidene is generated from a 1,1-dibromoalkane, activated zinc, TMEDA and titanium (IV) chloride. Takai alkylidenations are *Z*-selective and usually

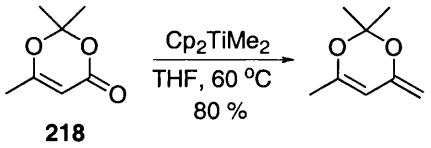
give high stereoselectivities. A noteworthy point is that the reaction is not very sensitive to the bulk of R^3 however, bulky R^2 substituents reduce the stereoselectivities and branching α to the carbonyl group in R^1 gives only *Z*-isomers.[72]

In 1990, Petasis reported the synthesis of dimethyl titanocene from titanocene dichloride and methyllithium.[87] Petasis has shown that this compound will methylenate carbonyl compounds, including esters and lactones (e.g. **217** and **218** respectively), when heated in THF or toluene (**Scheme 3.30** and **3.31**).[87,88]



217

Scheme 3.30



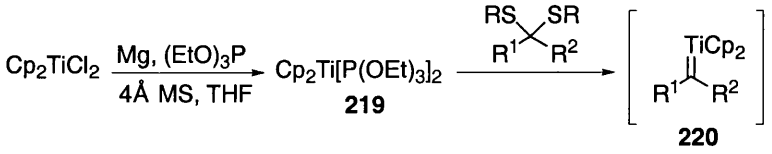
218

Scheme 3.31

The advantage of the Petasis reagent over the previously mentioned alkylidenes is that it is relatively air and water stable and it is not pyrophoric.[72] As with the Tebbe reagent, aldehydes and ketones can be methylenated in the presence of less reactive carbonyl groups e.g. amides, carbamates and esters.[72] Dimethyltitanocene has also been shown to catalyse RCM reactions (**Section 3.2.2**). It has also been shown that it is possible to selectively methylenate the less hindered of two esters by careful consideration of the conditions used.[89,90]

Takeda has shown that titanium alkylidenes can be formed by the reduction of thioacetals with the low valent titanium species $Cp_2Ti[P(OEt)_3]_2$ **219** (**Scheme 3.32**). The complex is formed by the reduction of titanocene dichloride with magnesium in the presence of triethylphosphite.[91] Molecular sieves are used to aid the rapid reduction of the titanocene dichloride. Complex **219** is then added to thioacetals to generate titanium alkylidenes **220**. Both 1,3-dithianes and diphenyldithioacetals can

be used,[91] but the diphenyldithioacetals are more reactive.[92] Takeda has published many examples and the procedure has also been applied to solid-phase synthesis.

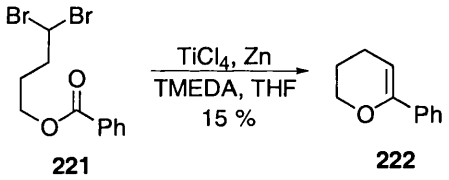


Scheme 3.32

Alkylidenations using titanium reagents has recently been reviewed.[72]

3.4.2 Intramolecular alkylidenation

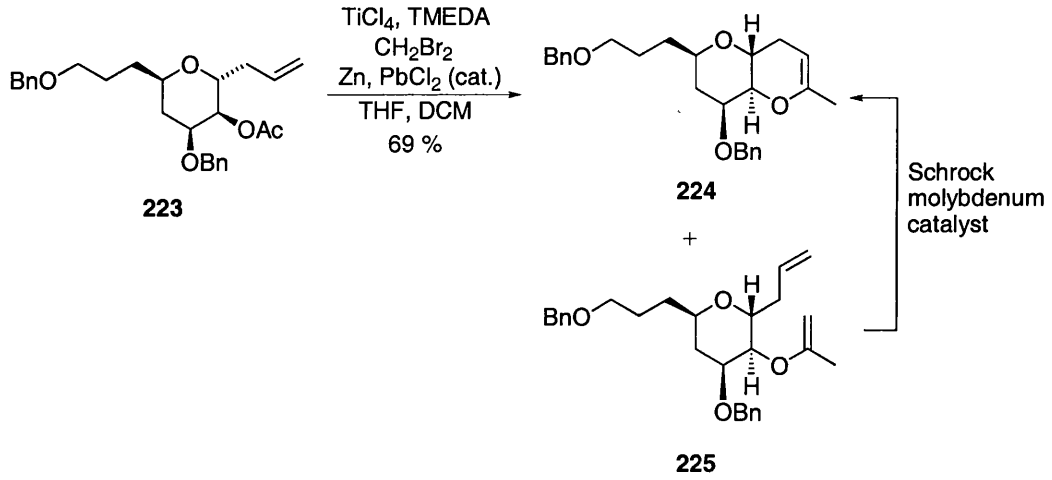
In 1988, Mortimore and Kocienski reported an early example of an intramolecular alkylidenation using a Takai-type procedure (**Scheme 3.33**).[84] Exposure of dibromide **221** to titanium(IV) chloride gave cyclic enol ether **222** in poor yield.



221 **222**

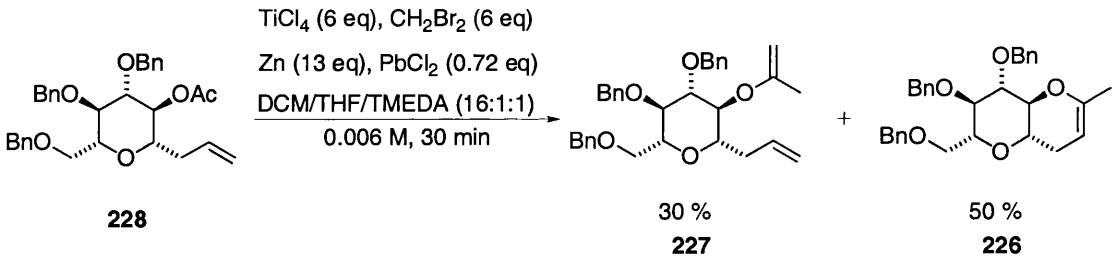
Scheme 3.33

In 2001, Rainier *et al.* reported the first example of metathesis-type products formed by the Takai procedure (**Scheme 3.34**).[93]



Scheme 3.34

When exposed to Takai conditions, acetate **223** gave a mixture of bicyclic and monocyclic enol ethers **224** and **225** respectively in good yield. Treating the mixture with Schrock catalyst **164** converts enol ether **225** to **224** allowing cyclic enol ether **224** to be isolated in 93 % yield. A similar monocyclic enol ether to **225** did not cyclise under Takai conditions which led to the proposal that a titanium alkylidene is generated from the allyl group on acetate **223**, which then intramolecularly alkylidenates the ester. Further investigation revealed that the cyclised product is favoured by increasing the amount of lead(II) chloride and using mainly DCM as solvent under high dilution conditions.[94] Using these modified conditions, bicyclic enol ether **226** was formed preferentially over monocyclic enol ether **227** from acetate **228** (**Scheme 3.35**).

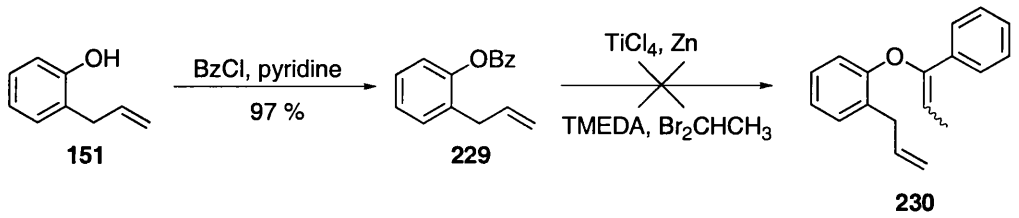


Scheme 3.35

It was noted that resubjecting monocyclic enol ether **227** to the reaction conditions did not give bicyclic enol ether **226** confirming that intramolecular alkylidenation rather than metathesis is involved. It was found that the intramolecular alkylidenation was

substrate dependent, as the homoallylic analogue of acetate **228** gave no cyclised products.

Our first attempt at the synthesis of flavene **203** using a Takai alkylidenation is shown below (**Scheme 3.36**). Benzoylation of 2-allylphenol **157** proceeded in high yield to give benzoate **229**. Unfortunately, when benzoate **229** was treated under modified Takai alkylidenation conditions, a violent reaction occurred giving a complex mixture of products that contained very little, if any desired enol ether **230**.

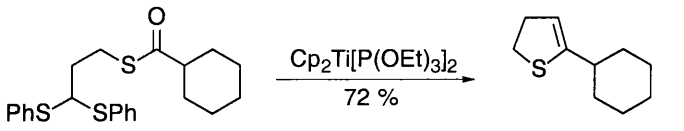


151 **229** **230**

Scheme 3.36

The route based on this strategy was unsuccessful and no further optimisation was carried out. Therefore, we decided to investigate intramolecular Takeda alkylidenations to allow acces to flavene **201**.

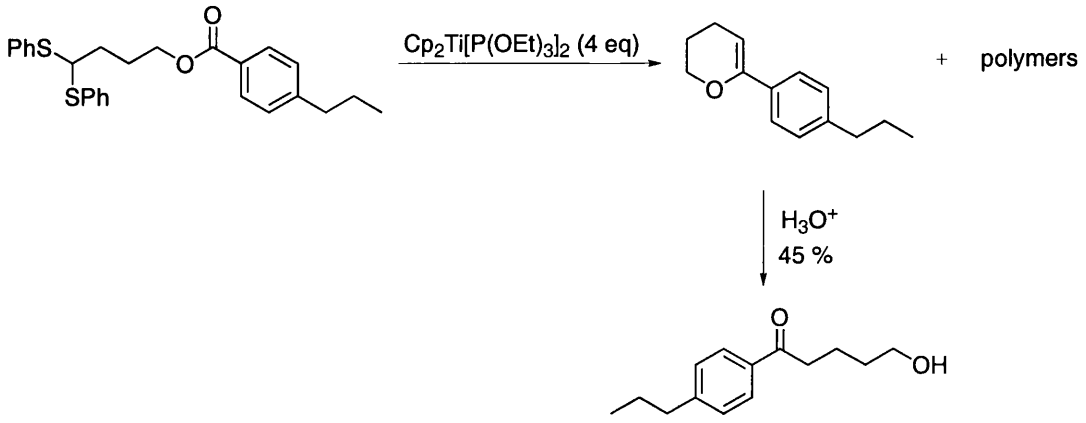
Intramolecular alkylidenations are also possible using the low valent titanium species developed by Takeda. Takeda has used the methodology to synthesise a number of interesting compounds. When *S*-[3,3-bis(phenylthio)propyl]thioalkanoates were treated with 4 equivalents of $Cp_2Ti[P(OEt_3)]_2$ in THF the products obtained were 5-substituted 2,3-dihydrothiophenes.[95] The best example obtained contained only 3 % of the isomerised material (**Scheme 3.37**). It was found that the products isomerised to the corresponding exocyclic compounds on exposure to light. Consequently, reactions and work-ups were performed in the dark.



97 % *endo* isomer

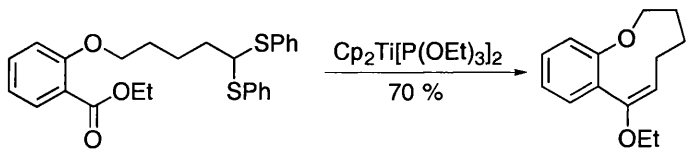
Scheme 3.37

Takeda has employed this methodology to synthesise a variety of ω-hydroxy ketones.[96] An example is shown below (**Scheme 3.38**). However, the route was not effective for the preparation of cyclic enol ethers due to competitive polymer formation. Although this route is not appropriate for the synthesis of cyclic enol ethers, it is effective for the synthesis of ω-hydroxy ketones as the polymeric material formed also forms the desired ketones on treatment with acid.



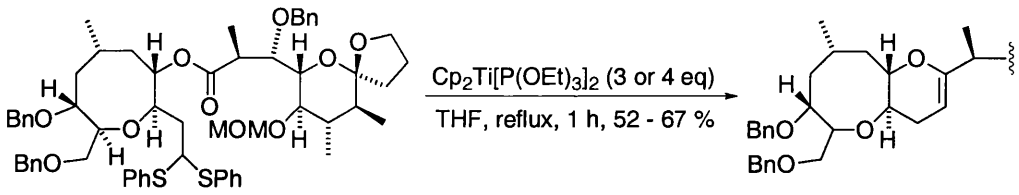
Scheme 3.38

When the oxygen atom of the enol ether is *exo* to the formed ring intramolecular alkylidenation is more successful. The synthesis of 5-, 6-, 7- and 9-membered rings has also been accomplished using this procedure.[79] An example of a 9-membered system is shown below (**Scheme 3.39**).



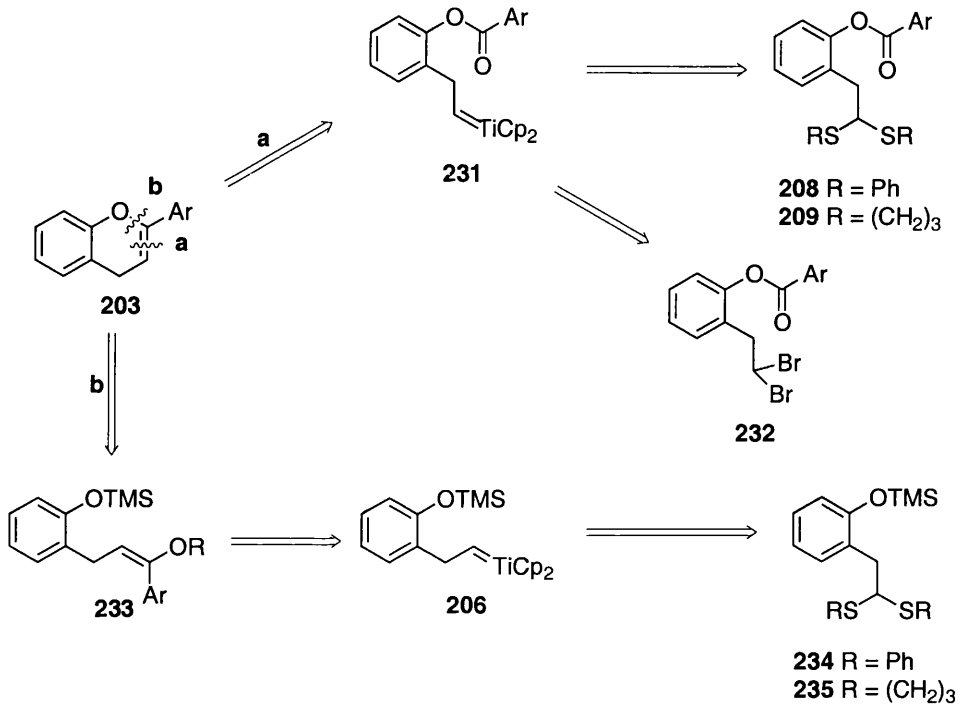
Scheme 3.39

However, there was some hope for our cyclisation, which would put the oxygen atom within the formed ring. Recently, Oishi *et al.* used an intramolecular Takeda cyclisation in the synthesis of the HIJKLM ring segment of ciguatoxin CTX3C to overcome the unreliability of a related RCM reaction when carried out using the Tebbe reagent.[80] The transformation is illustrated below (**Scheme 3.40**).



Scheme 3.40

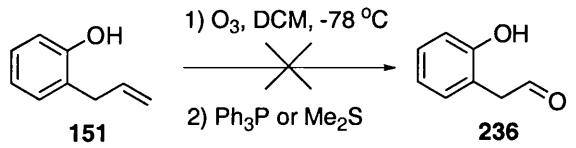
Our proposed retrosynthesis of flavene **203** based on Takeda's methodology is shown below (**Scheme 3.41**).



Scheme 3.41

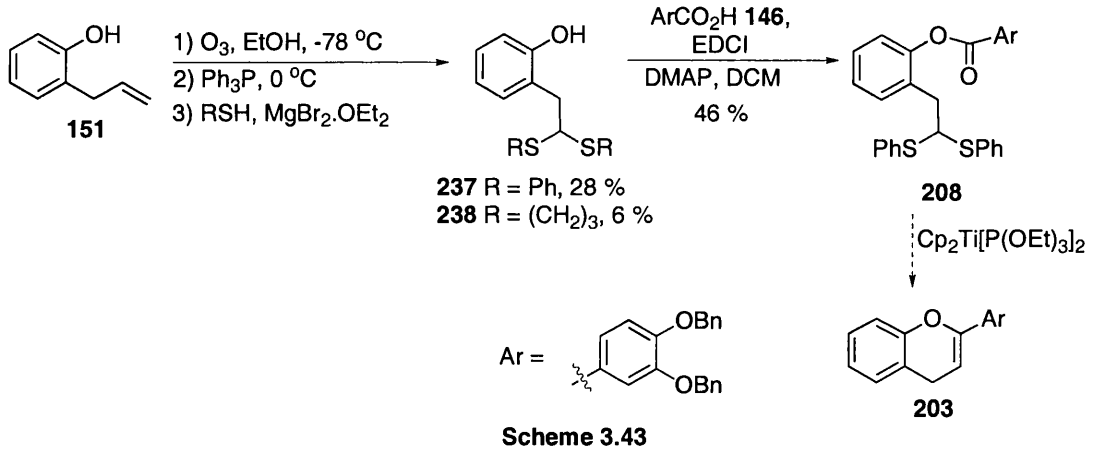
Disconnection by route **a** gives titanium alkylidene **231**, which can be made from thioacetals **208** and **209** or *gem*-dibromide **232**. We decided to use thioacetals **208** and **209** because thioacetals have been successfully used within our group and a search of the literature gave only one example of an intramolecular cyclisation of a *gem*-dibromide to a pyran system, which proceeded in poor yield.[84] Alternatively, disconnection by route **b**, gives enol ether **233**, which can be made from the alternative titanium alkylidene **206**. This alkylidene can in turn be made from thioacetals **234** and **235**. Route **b** is derived from work in the Hartley group on benzofurans and indoles, which will be explained in **section 3.4.4**.[78,97,98] Both routes were investigated at the same time and the routes used are described below.

Looking first at route **a**, the synthesis of the thioacetals proved to be quite difficult. Initially, we attempted to synthesise aldehyde **236** (**Scheme 3.42**) but despite several attempts, never managed to isolate it.



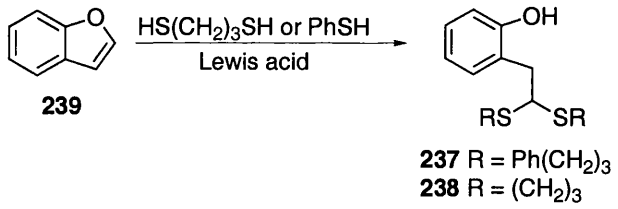
Scheme 3.42

This led us to attempt the thioacetalisation *in situ*. Following the procedure of Overman,[99] ozonolysis of 2-allylphenol **151**, reduction of the ozonide and thioacetalisation gave thioacetals **237** and **238** in poor yields (**Scheme 3.43**). Thioacetal **237** was then esterfied with benzoic acid derivative **146** to give ester **208** in moderate yield.



Scheme 3.43

An alternative synthesis of thioacetals **237** and **238** was attempted (**Scheme 3.44**). A search of the literature found an example of the synthesis of thioacetals from benzofuran **239**.[100] Treatment of benzofuran **239** with the appropriate thiol in the presence of a Lewis acid was carried out several times with varying conditions (**Table 3.2**) but with no success. In all cases a complex mixture was obtained with the best example for this route being 2 % (entry 3). Purification of the reactions containing product (as shown by the ^1H NMR spectrum) was attempted but no appropriate method was found.



239

237 R = $Ph(CH_2)_3$
238 R = $(CH_2)_3$

Scheme 3.44

Run Number	Reagents	Result
1	AcOH, $BF_3.OEt_2$, PhMe, propanedithiol, RT	Complex mixture of starting material, product and unidentified material
2	TFA, propanedithiol, RT	Complex mixture of starting material, product and unidentified material
3	TFA, $BF_3.OEt_2$, propanedithiol, RT	Unidentified material and trace of product (2 %)
4	*p*-TsOH, TMSCl, propanedithiol, RT	Unidentified material and trace of product
5	TFA, hexane, propanedithiol, RT	Starting material recovered
6	TFA, $BF_3.OEt_2$, thiophenol, RT	Unidentified material

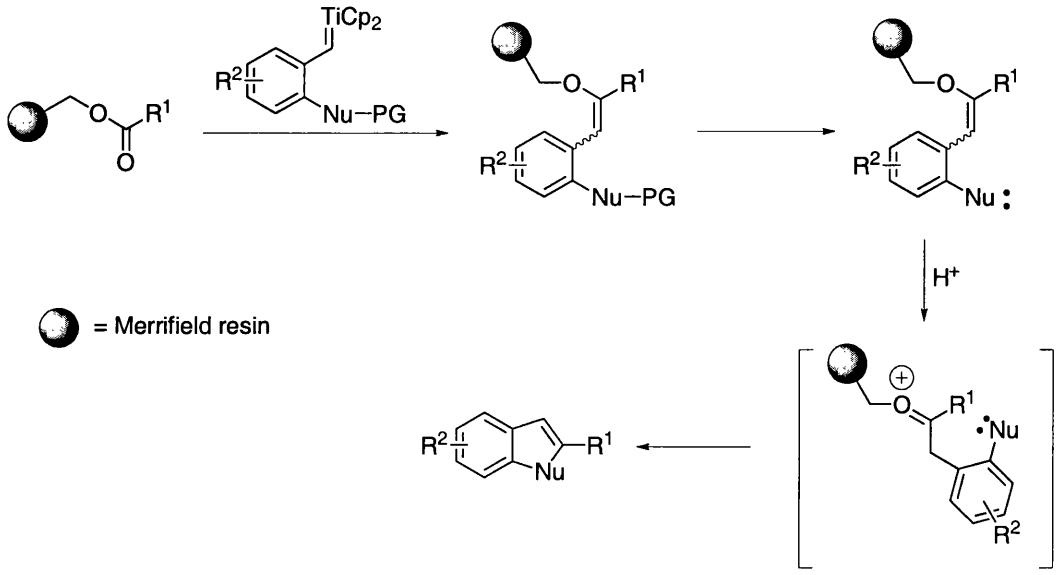
Table 3.2

At this point three factors prompted us to move away from this route. The first problem was the low yield. The esterification to give **208** in particular was unacceptably low. This step would ultimately be used to introduce the label and was not efficient enough. The second factor was the difficulty forming enol ethers. The third problem was precedent within the group that solution phase Takeda reactions are very difficult to purify. For these reasons this route was stopped after the synthesis of ester **208** (**Scheme 3.43**).

3.4.3 Intermolecular alkylidenation on solid-phase

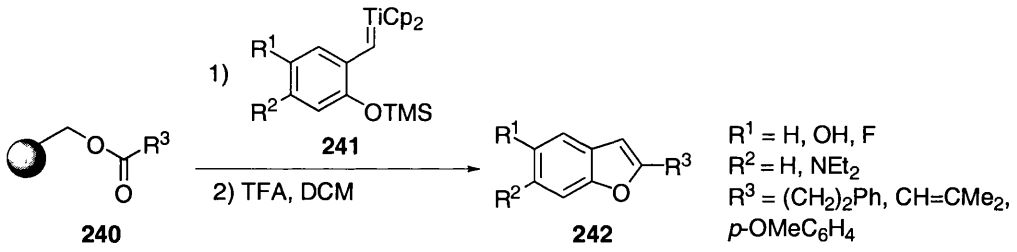
We then concentrated our efforts on route **b** (**Scheme 3.41**). Although this route still depends on a Takeda reaction, the purification problem is avoided by loading the acid onto resin and using the resin-bound ester for the cyclisation. Takeda's methodology

for the generation of titanium alkylidenes has successfully been applied to the synthesis of benzofurans and indoles within the Hartley group.[78,97,98] The general strategy is shown in **Scheme 3.45**.



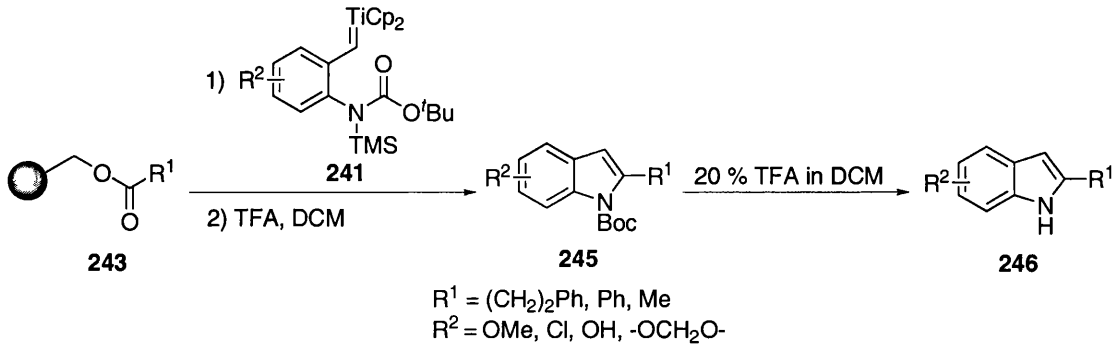
Scheme 3.45

This approach was used for the synthesis of a library of benzofurans and indoles (**Schemes 3.46** and **3.47** respectively).



Scheme 3.46

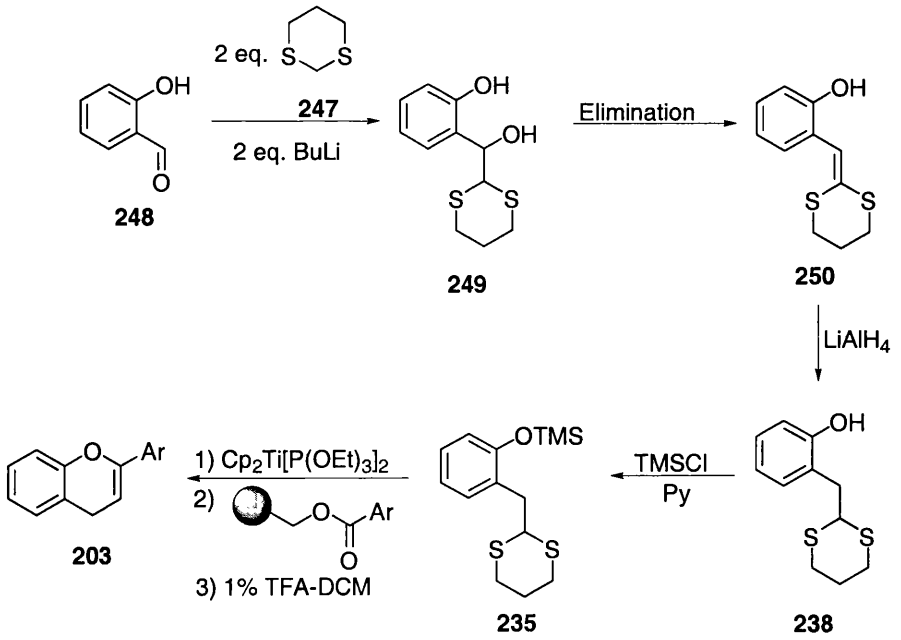
The benzofurans[78,97] were synthesised from resin-bound esters **240** made by reaction of Merrifield resin with the corresponding cesium carboxylate. Reaction with titanium alkylidene **241** followed by treatment with TFA gave benzofurans **242** in moderate to excellent yields (33 – 91 %).



Scheme 3.47

In a similar manner, resin-bound esters **243** were reacted with titanium alkylidene **244** followed by TFA to give Boc-protected indoles **245** in moderate to good yields (58 – 72 %).[78,98] In the case where R^2 = 7-OMe, significant spontaneous deprotection of the *N*-Boc indoles was observed, hence these compounds were fully deprotected by treatment with 20 % TFA in DCM to give 7-methoxyindoles **246**.

In order to adopt this procedure to the synthesis of flavene **203** a longer but more convenient and reliable synthesis of thioacetal **238** was devised (**Scheme 3.48**).



Scheme 3.48

Lithiation of two equivalents of commercially available 1,3-dithiane **247** and quenching with salicylaldehyde **248** would give thioacetal **249**. We then envisaged

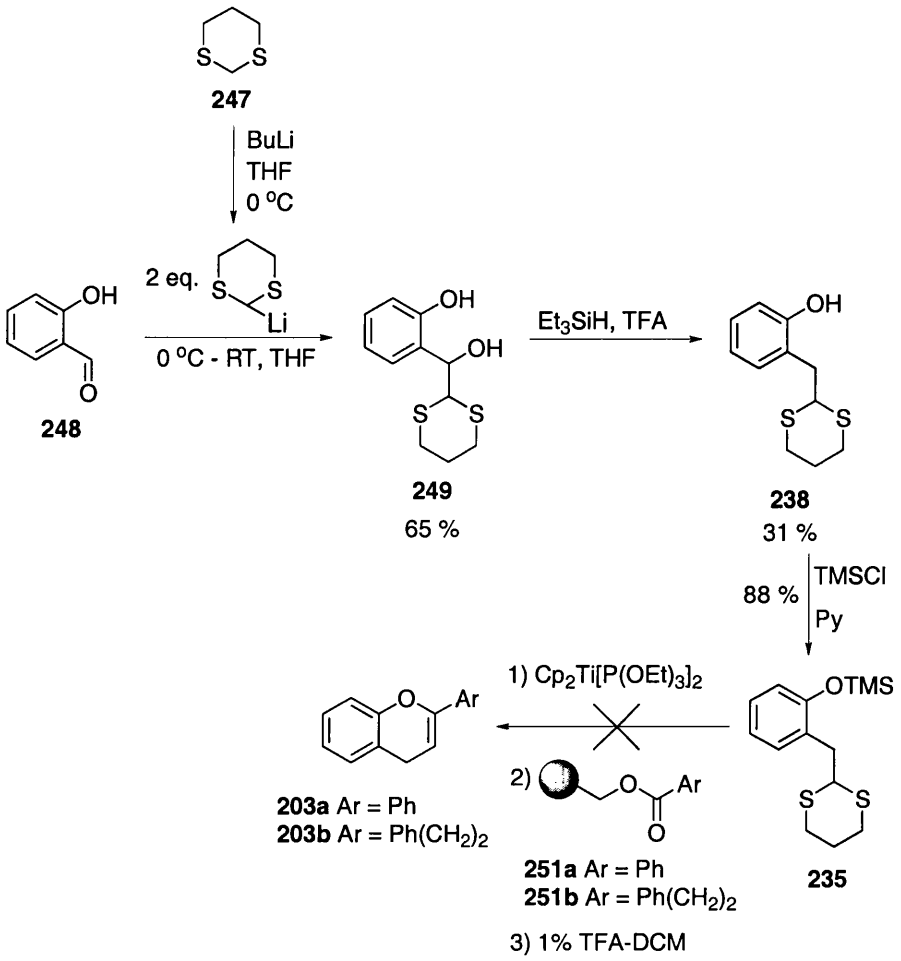
elimination of the benzylic hydroxyl would give thioacetal **250**, which could be reduced with lithium aluminium hydride to give thioacetal **238**. Protection of the phenol with TMSCl would give silyl ether **235**, the required precursor for the Takeda reaction. In practice, lithiated dithiane gave alcohol **249** in 65 % yield, but thioacetal **250** was never made. Several different conditions were tried for the elimination but all were unsuccessful (**Table 3.3**). The majority of attempts resulted in recovered starting material whilst others gave a complex mixture of unidentified materials, presumably from decomposition of the starting material. In one case (entry 4) tosylation of the phenol was observed.

249 **250**

Run Number	Reagents	Result
1	MsCl, Et_3N, DCM, RT	Complex mixture of unidentified material
2	$LiAlH_4$, THF, RT	Unidentified material
3	$NaBH(OAc)_3$, AcOH, THF, RT	Starting material recovered
4	TsCl, Et_3N, DCM, RT	Tosylation of phenol
5	$NaBH_4$, THF, RT	Starting material recovered
6	$NaBH_4$, EtOH, RT	Starting material recovered
7	*p*-TsOH, PhMe, reflux	Unidentified material
8	$NaBH_4$, THF, RT (10 x conc. of 5)	Starting material recovered
9	$NaBH_4$, EtOH, RT (10 x conc. of 6)	Starting material recovered

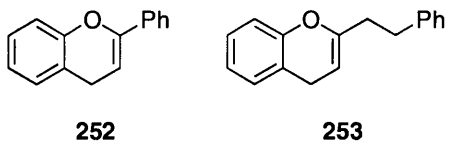
Table 3.3

We eventually found reductive conditions that allowed the synthesis of thioacetal **238** directly, albeit in low yield (**Scheme 3.49**).



Scheme 3.49

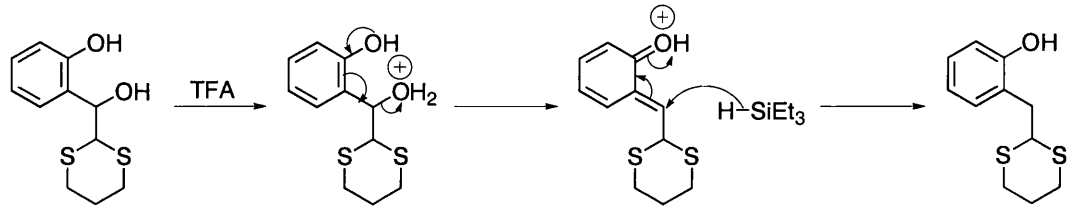
Protection of phenol **238** with TMSCl in pyridine gave silyl ether **235** in excellent yield. The Takeda reaction was tested using two resin-bound esters **151a** and **151b**. Unfortunately, an intractable mixture was obtained.



252 **253**

Figure 3.6

The mechanism for the reduction of alcohol **249** is shown below in **Scheme 3.50**.



249

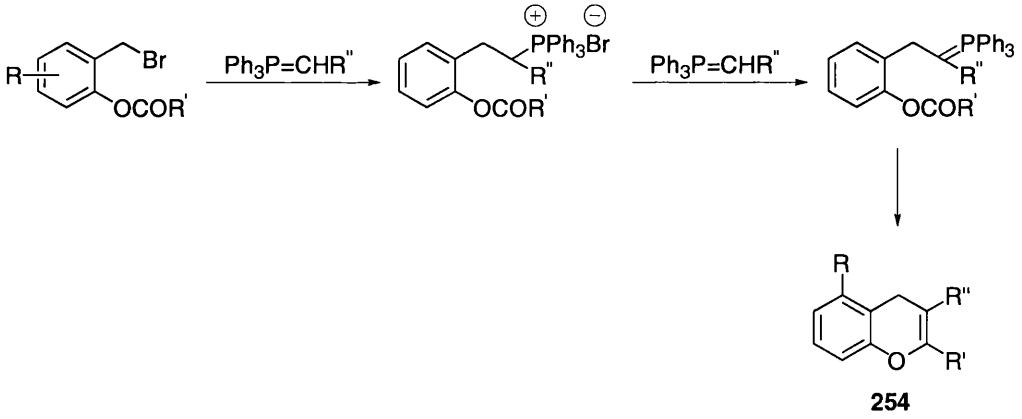
Scheme 3.50

3.5 Routes to 2-flavenes *via* an iodide intermediate

Due to the unsuccessful alkylidenation routes discussed in the previous sections, we turned our attention to a route based on ester **144b** (**Scheme 3.2**) and iodide **205** (**Scheme 3.27**) using an intramolecular Wittig procedure and an intramolecular Grignard procedure respectively.

3.5.1 Intramolecular Wittig reaction

Hercouet and Le Corre used an intramolecular Wittig reaction to synthesise a variety of chromenes **254** using stabilised ylids (**Scheme 3.51**).[81]



254

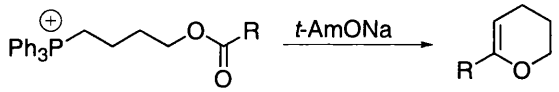
Scheme 3.51

Some of the chromenes synthesised are shown in **Table 3.4**.

R	R'	R''	% yield
H	Et	Ph	66
H	Me	Ac	87
H	Et	Ac	87
H	Me	CO_2Me	98
H	Ph	CO_2Me	98
OBz	Ph	CO_2Me	95

Table 3.4

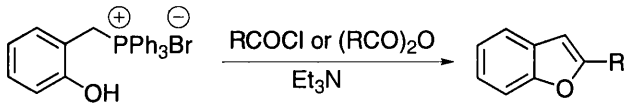
This procedure was also applied to the synthesis of several dihydropyrans **255** where R was *n*-heptyl, furyl, phenyl and styryl (**Scheme 3.52**).[101]



255
76 - 86 %

Scheme 3.52

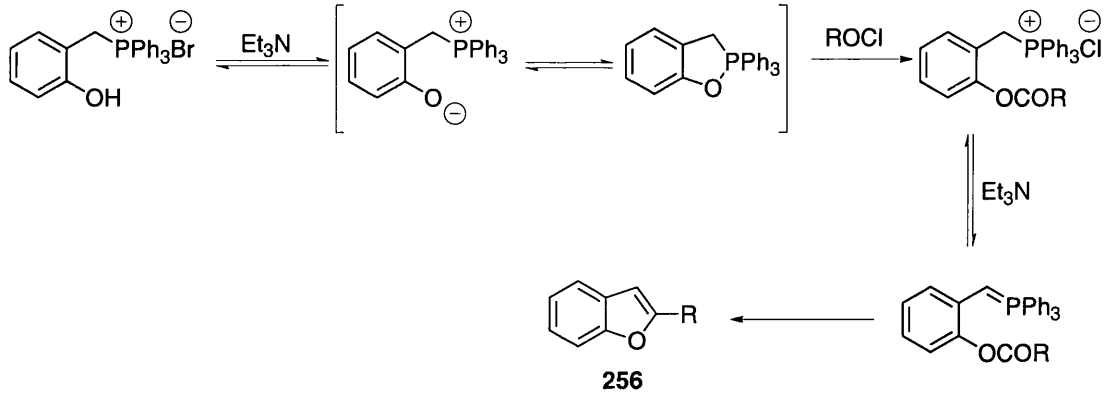
A related procedure has also been used in the synthesis of benzofurans **256** (**Scheme 3.53**).[82,83]



256

Scheme 3.53

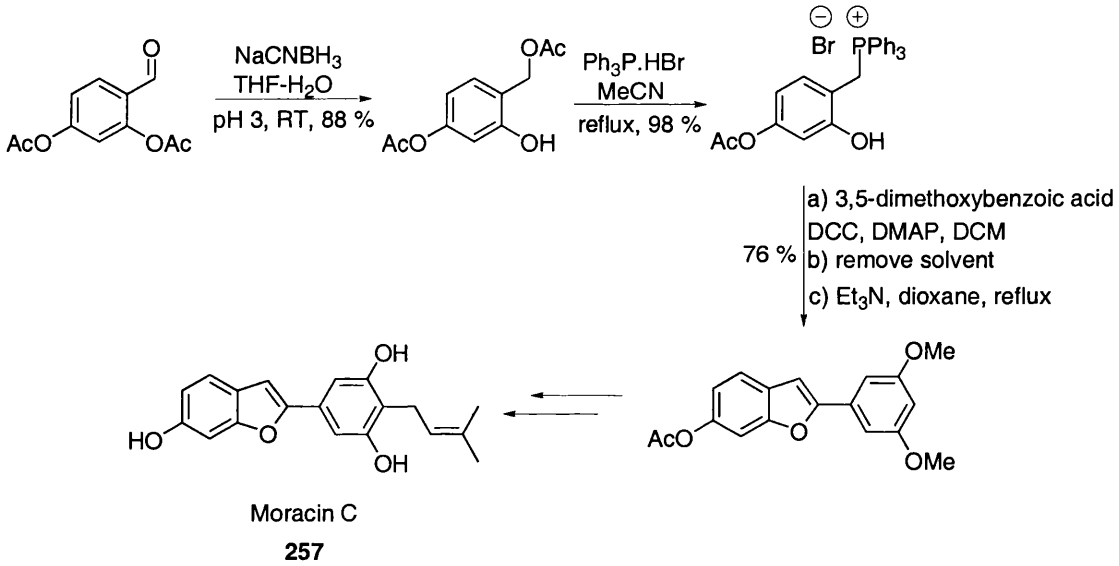
The proposed mechanism for the reaction is illustrated in **Scheme 3.54**.



256

Scheme 3.54

Using this method a variety of benzofurans where R ranged from alkyl, alkenyl, styryl, phenyl and furyl were synthesised in moderate to good yields (50 – 93 %). Indeed, the total synthesis of Moracin C **257** (**Scheme 3.54**), a powerful antifungal natural product, has been achieved within the Hartley group using this procedure.[102]

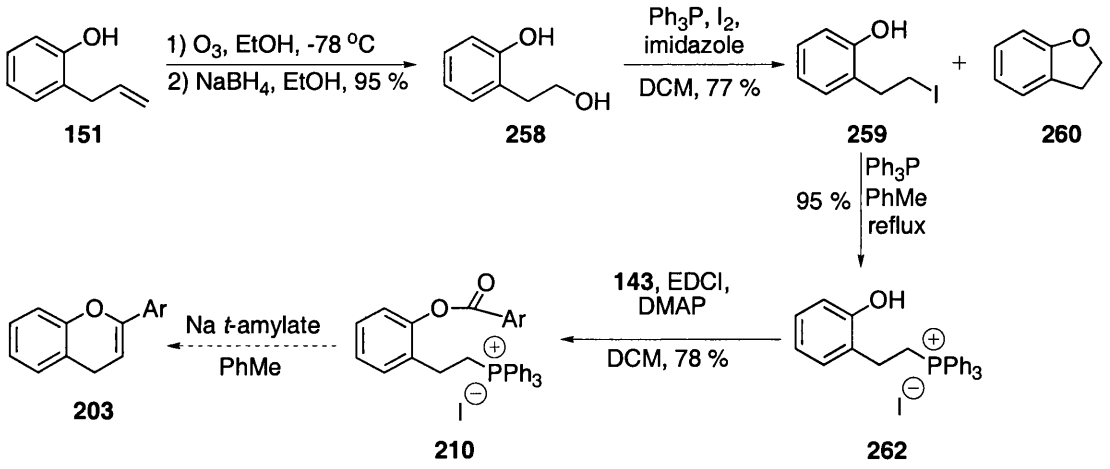


Moracin C

257

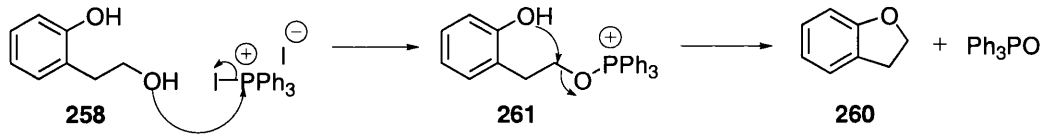
Scheme 3.55

We applied this methodology to the synthesis of flavene **203**. The synthetic route is shown in **Scheme 3.56**.



Scheme 3.56

Ozonolysis of 2-allylphenol **151** gave alcohol **258** in almost quantitative yield with no purification required. Iodination of alcohol **258** gave iodide **259** in good yield. A quantity of 2,3-dihydrobenzofuran **260** was also isolated from the reaction. This suggests that 2,3-dihydrobenzofuran **260** is formed from the competing intramolecular cyclisation of phenol intermediate **261** (**Scheme 3.57**) and not from cyclisation of the iodide itself.



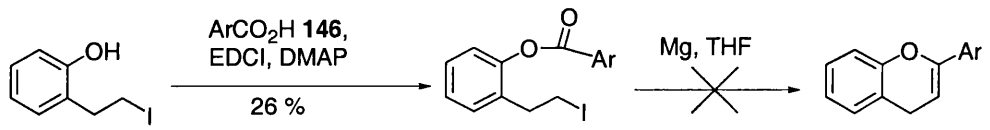
Scheme 3.57

More evidence supporting this suggestion comes from the lack of dihydrobenzofuran **260** observed on treatment of iodide **259** with triphenylphosphine in refluxing toluene, to give phosphonium salt **262** in excellent yield. Subsequent esterification with benzoic acid derivative **146** gave ester **210** in moderate yield although there were some impurities that proved difficult to remove. We decided to use the crude ester and purify after the cyclisation. This would be more convenient as the impurities would be of vastly differing polarities, which would aid in its purification. A more appropriate alternative for the labelled synthesis would be to use polymer supported triphenylphosphine, which would remove the problem of the impurities. Indeed, this procedure has been used for the traceless solid-phase synthesis of a variety of different compounds including indoles.[103] Unfortunately, when ester **210** was treated

with the literature conditions only starting material was recovered. Several variations were attempted (sodium *t*-amylate and LiHMDS in PhMe and THF at room temperature and reflux), but starting material was recovered in every case.

3.5.2 Cyclisation of a Grignard reagent

An alternative route to flavene **203** is shown below (**Scheme 3.58**). Esterification of iodide **259** with benzoic acid derivative **146** gave ester **205** in poor yield. Formation of the Grignard reagent should allow cyclisation to flavene **203**. The magnesium was activated by warming with a crystal of iodine and also by stirring under an atmosphere of nitrogen overnight. Unfortunately, treatment of iodide **205** with activated magnesium in THF consistently failed to give the flavene.

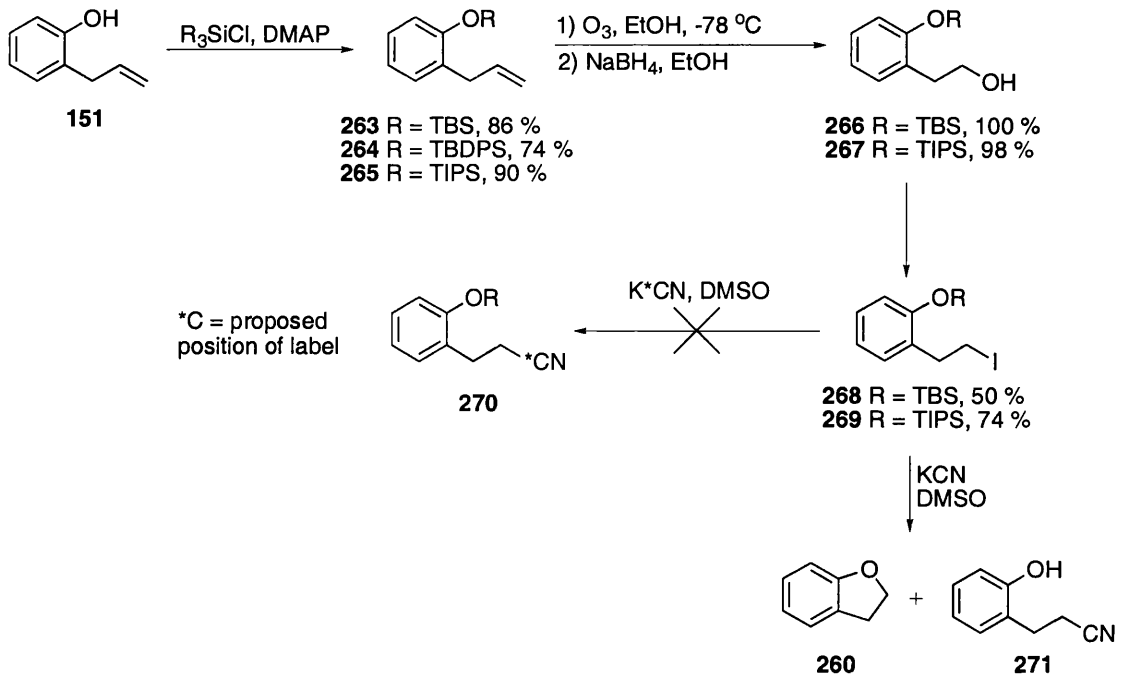


259 **205** **203**

Scheme 3.58

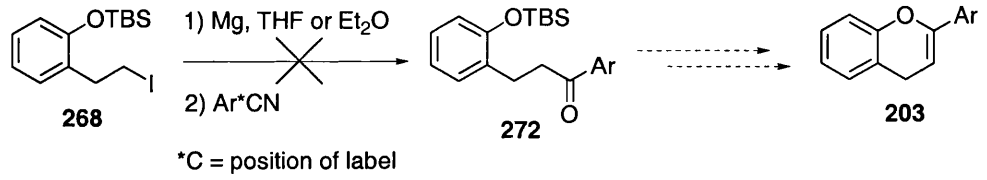
3.5.3 Cyclisation of ketones derived from nitriles

Swapping the source of the label from $^{14}CO_2$ (from $Ba^{14}CO_3$) to $^{14}CN^-$ (from $K^{14}CN$) would allow a different approach to be considered (**Scheme 3.59**). 2-Allylphenol **151** was protected as the TBS, TBDPS and TIPS[104] silyl ethers **263-265** in good to excellent yield. Ozonolysis of **263** and **264** proceeded uneventfully in quantitative yield to give alcohols **266** and **267**, which were iodinated in moderate to good yield to give **268** and **269** respectively. Unfortunately, when iodides **268** and **269** were treated with potassium cyanide, nitrile **270** was not formed. The products isolated from the reaction were dihydrobenzofuran **260** and nitrile **271** (3:1, 75 % from **268** and 1:0, 44 % from **269**).



Scheme 3.59

A second route using iodide **268** as a key intermediate was also investigated (**Scheme 3.60**). Reacting the Grignard reagent generated from iodide **268** with an appropriate nitrile should give ketone **272**, which could be cyclised to give flavene **203**. Several attempts at forming the Grignard reagent were attempted (Mg/I_2 and potassium napthalenide), however the reaction was unsuccessful.



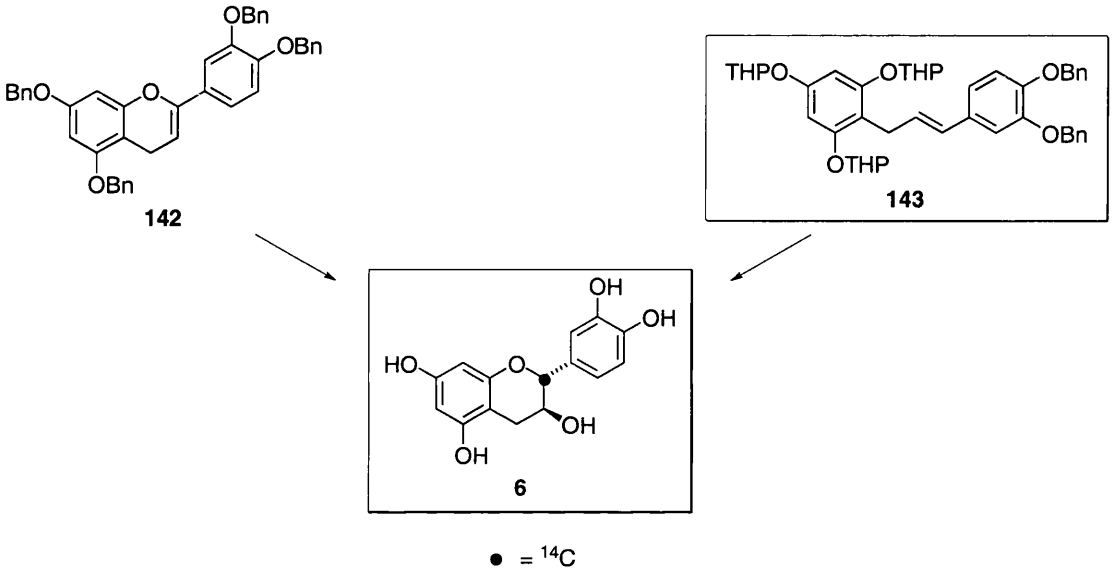
Scheme 3.60

At this stage we abandoned the routes based on 2-flavenes and turned our attention to an alternative based on Ferreira's 1,3-diarylpropene intermediates.

CHAPTER 4 - Second Approach: Alkene dihydroxylation-cyclisation

4.1 Introduction

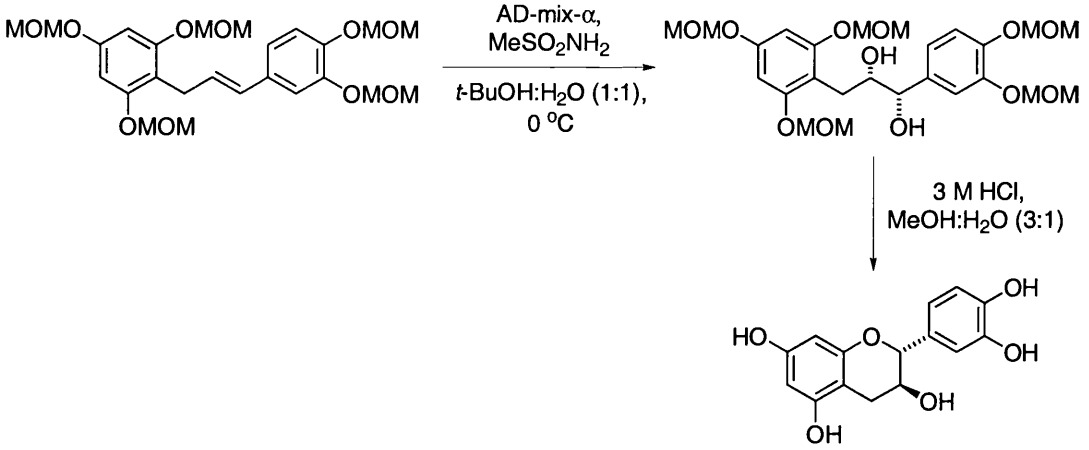
The unsuccessful routes to 2-flavenes (for asymmetric hydroboration reactions) discussed in Chapter 3, led us to consider an alternative approach to (+)-catechin. We chose to study the dihydroxylation-cyclisation of 1,3-diarylpropenes such as alkene **143** (**Scheme 4.1**). The two approaches to alkene **143** we chose to study were the Julia olefination and cross-metathesis.



Scheme 4.1

4.2 General synthetic strategy

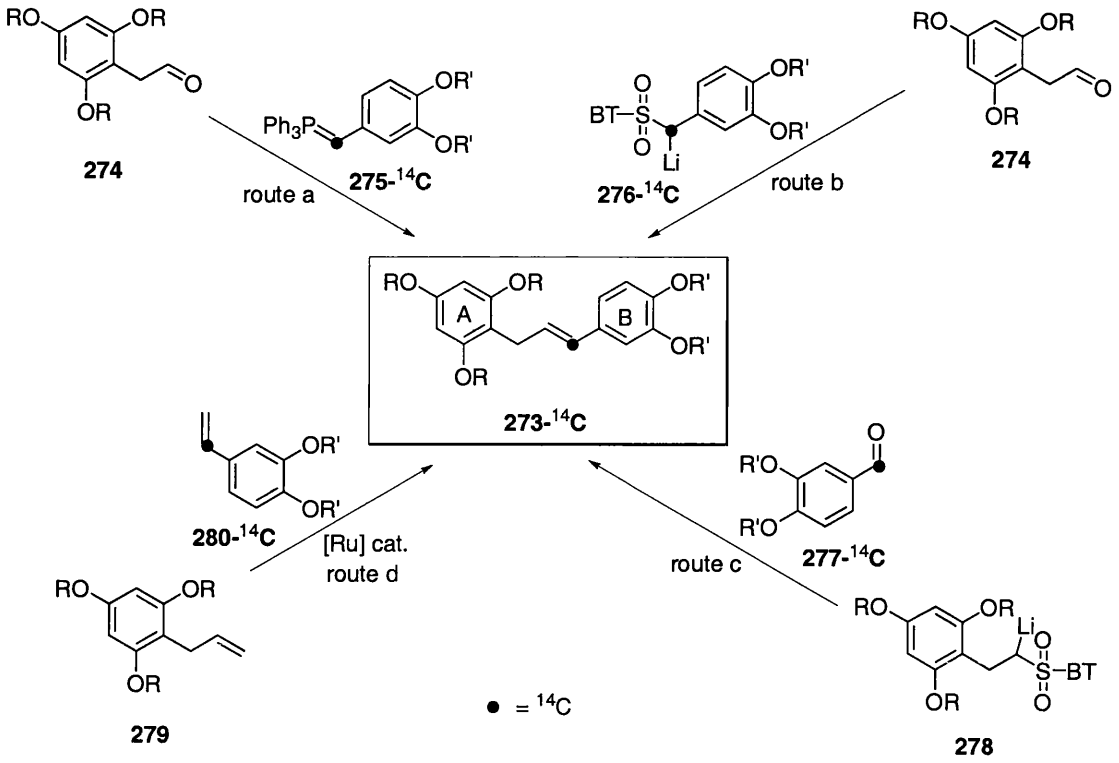
As discussed in Chapter 2, Ferreira has reported the asymmetric synthesis of both enantiomers of (+)-catechin and (-)-epicatechin from 1,3-diarylpropenes by asymmetric dihydroxylation and acid-induced cyclisation (**Scheme 4.2**). Jew and Park and Chan and co-workers have improved on the acid-induced cyclisation by using Mitsunobu conditions or preparing an *ortho*-ester intermediate to encourage inversion of configuration to set the C-2 stereochemistry of the flavan-3-ols.



Scheme 4.2

The key intermediate in the alkene dihydroxylation-cyclisation strategy is 1,3-diarylpropene **273-^{14}C**. We envisaged a variety of new routes to *E*-alkene **273-^{14}C** based on the stereocontrolled formation of the alkene C=C bond from a fragment derived from a radiolabelled protected 3,4-dihydroxybenzoic acid, which would be easy to prepare and a phloroglucinol-derived C_6-C_2 fragment (**Scheme 4.3**). These routes included coupling of aldehyde **274** with a Wittig reagent **275-^{14}C** (route a) or a lithiated sulfone **273-^{14}C** (route b), or reversing the nucleophilic and electrophilic fragments and using aldehyde **277-^{14}C** with lithiated sulfone **278** (route c). The recent reports from Grubbs and others, also encouraged us to investigate the cross-metathesis of allyl phloroglucinol-derivative **279** and styrene derivative **280-^{14}C** (route d), but with protecting groups R and R' that could easily be removed (i.e. not methyl). The protecting group issue proved very significant in all routes as will become apparent later.

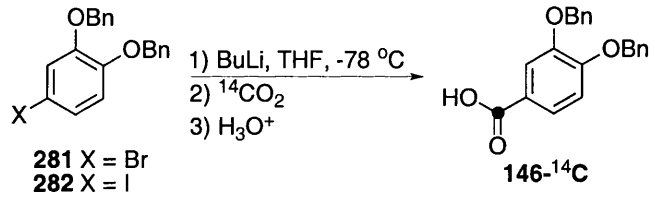
Essential to these strategies is preparation of the radiolabelled compounds **275-^{14}C**-**277-^{14}C** and **280-^{14}C**, which would be derived from 3,4-dihydroxybenzoic acid and the C_6-C_2 compounds **274**, **278** and **279** by *C*-alkylation or *C*-allylation of phloroglucinol.



Scheme 4.3

4.3 B-ring and label

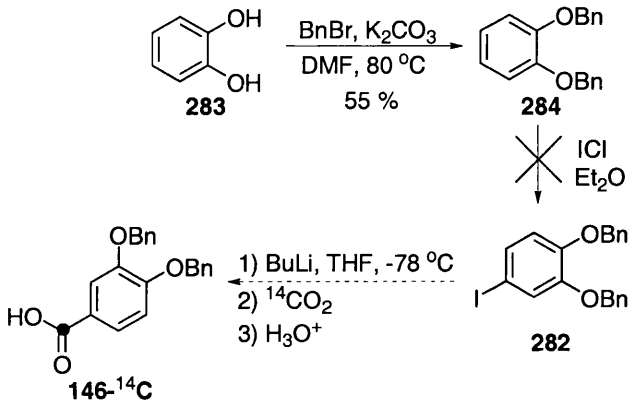
We aimed to introduce the label by trapping ^{14}C-enriched carbon dioxide using an aryllithium[105,106] generated from either bromide **281** or iodide **282** by lithium-halogen exchange (**Scheme 4.4**). It could also be introduced using a Grignard reagent.[107]



Scheme 4.4

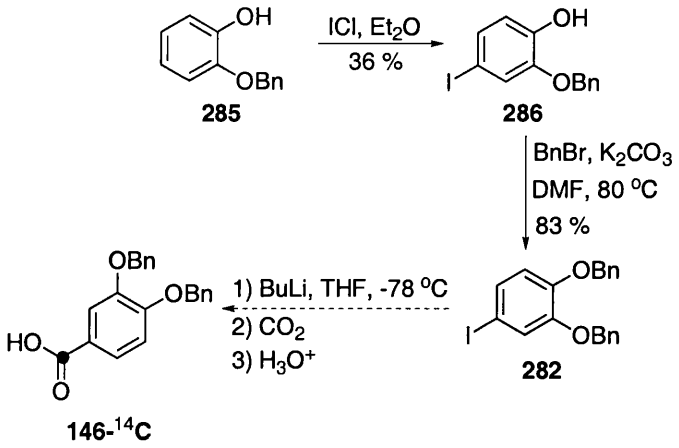
^{14}C-labelled barium carbonate is commercially available and is one of the cheapest sources of ^{14}C-enriched carbon compounds. Treating the labelled barium carbonate with acid easily generates the ^{14}C-enriched carbon dioxide. Other methods for the synthesis of labelled benzoic acid derivatives are available, for example, the oxidation of labelled toluene derivatives.[108] We chose to use the barium carbonate method due to the low cost and the simple chemistry involved.

Our proposed synthesis of benzoic acid derivative **146-^{14}C** is shown in **Scheme 4.5**. Benzylation of catechol **283** gave dibenzyl ether **284** in moderate yield. Iodination of **284** with iodine monochloride[109] was expected to give iodide **282** which would then be carboxylated to give benzoic acid derivative **146-^{14}C**. Unfortunately, when the iodination was attempted essentially no product was formed. The evidence for this was the unchanged multiplet of the aromatic protons from the starting material in the ^{1}H NMR spectrum between 6.83 – 6.94 ppm. Several different conditions for the iodination (ICl/THF, RT; ICl/Et_2O, RT; ICl/Et_2O, reflux) were attempted but gave recovered starting material.



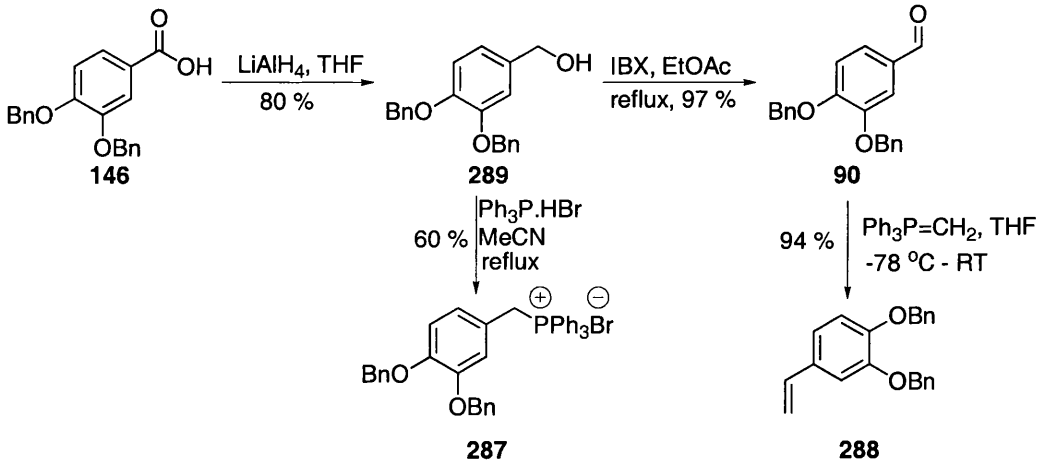
Scheme 4.5

This led to the minor modification in the synthesis shown below (**Scheme 4.6**). Iodination of 2-benzyloxyphenol **285** with iodine monochloride[110] gave iodide **286** in low yield. Benzylation of **286** gave iodide **282** in good yield. Subsequent carboxylation should then give benzoic acid derivative **146-^{14}C**. The carboxylation was only attempted once with $Ba^{13}CO_3$ due to time constraints but gave a complex mixture of products. Subsequent investigation within the group has found this reaction to be problematic.



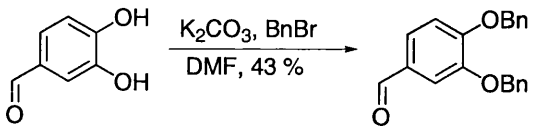
Scheme 4.6

The labelled benzoic acid derivative could then be manipulated to give phosphonium salt **287**, benzaldehyde derivative **90** or styrene derivative **288**. All three of these compounds were synthesised to test the feasibility of each route. Reduction of non-labelled benzoic acid derivative **146** gave alcohol **289**, which was then converted into phosphonium salt **287** in moderate yield or oxidised with *O*-iodoxybenzoic acid (IBX) to give benzaldehyde derivative **90** in good yield (**Scheme 4.7**).



Scheme 4.7

Aldehyde **90** was converted into styrene derivative **288** in high yield. Aldehyde **90** could also be prepared from commercially available 3,4-dihydroxybenzaldehyde **103** (**Scheme 4.8**).



103 **90**

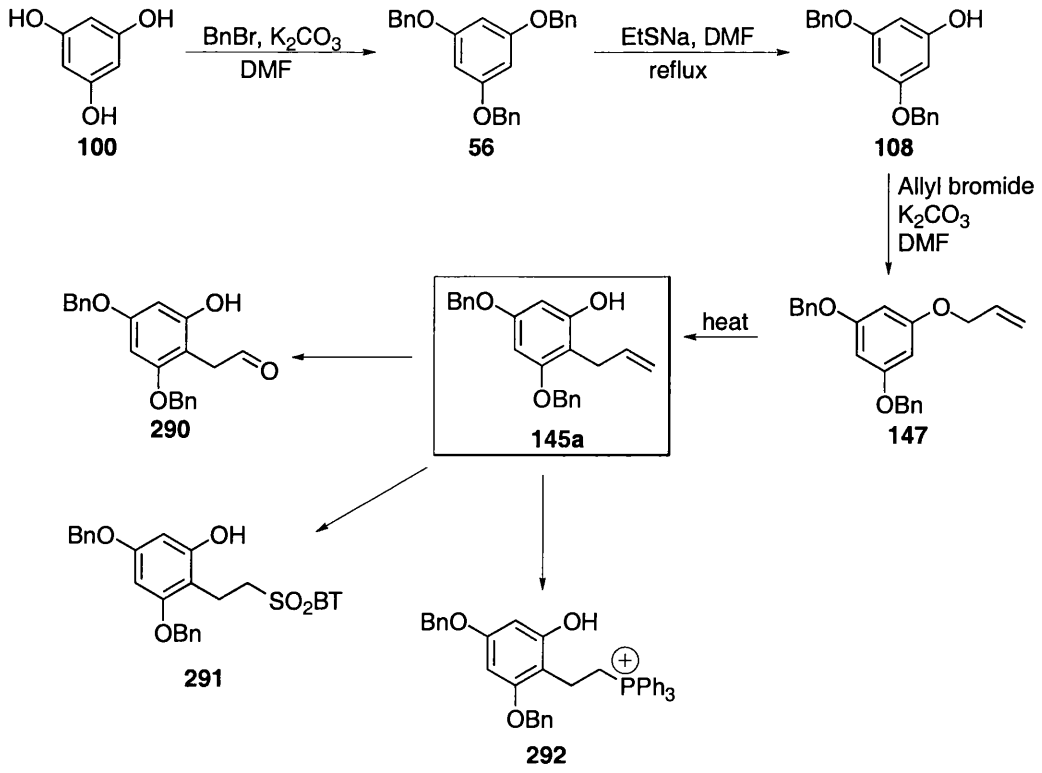
Scheme 4.8

Importantly, all three compounds **90**, **287** and **288** could be easily purified. Simple filtrations through silica were employed for aldehyde **90** and styrene derivative **288**, whereas phosphonium salt **287** precipitated from the reaction mixture.

4.4 Protected *C*-Alkylated and *C*-Allylated Phloroglucinol derivatives

4.4.1 Route to 3,5-dibenzyloxyphenol 108 for *C*-allylation *via* Claisen rearrangement

Phenol **145a** previously discussed in Chapter 3 (**Scheme 3.3**) is still an important intermediate, which we intended to synthesise *via* a Claisen rearrangement of allyl ether **147**. The successful synthesis of styrene derivative **288** necessitated the synthesis of phenol **145a**. An updated synthetic overview is shown in **Scheme 4.9**.

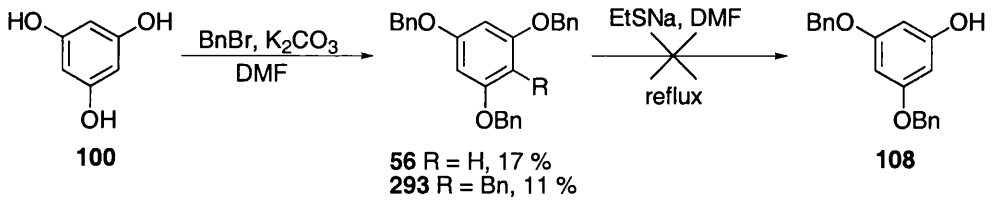


Scheme 4.9

Three new alternative routes can be added. Phenol derivative **145a** should allow access to aldehyde **290**, BT-sulfone (BT = Benzothiazol-2-yl) **291** and phosphonium salt **292**. Clearly, the synthesis of phenol derivative **145a** is vitally important and it is the key intermediate in all of the three routes shown. The syntheses of simpler structures related to aldehyde **290** and phosphonium salt **292** have already been discussed (**Section 3.4.3** and **3.5.1** respectively). Sulfones similar to **291** will be discussed later (**Section 4.5.2**).

The synthesis of the required phenol **145a** was expected to proceed smoothly. Both the benzylation of phloroglucinol[62] **100** and the monodeprotection of **56** with sodium ethanethiolate[62] to give phenol derivative **108** had been reported in the literature. Allylation of **108** should give ether **147**. Claisen rearrangement of **147** should then give the desired phenol derivative **145a**.

Following the method of Chow, benzylation of phloroglucinol **100** proceeded in low yield to give the desired tribenzyl ether **56** and *C*-benzylated derivative **293** also in low yield (**Scheme 4.10**).



100

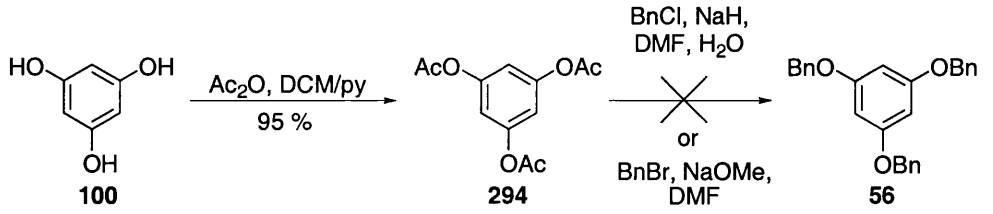
56 R = H, 17 %
293 R = Bn, 11 %

108

Scheme 4.10

The literature procedure reports a 59 % yield after recrystallisation. Despite several attempts we could not obtain tribenzyl ether **56** in reasonable yield. This can partly be attributed to using column chromatography to separate the close running products, as the literature recrystallisation did not work in our hands. Although not mentioned by Chow, *C*-benzylation of phloroglucinol has been reported as a major problem.[51] A slightly modified version of Chow's procedure was used for the monodeprotection of tribenzyl ether **56** to give phenol derivative **108**, i.e. in order to avoid stench we decided to use commercially available sodium ethanethiolate rather than generating the salt *in situ* from fresh reagents. Unfortunately, the reaction failed. At this point an alternative procedure for synthesising **56** was sought.

Kawamoto has reported the synthesis of tribenzyl ether **56** *via* acetate **294**.[52] Our attempted synthesis *via* the same intermediate is shown below (**Scheme 4.11**).



100

294

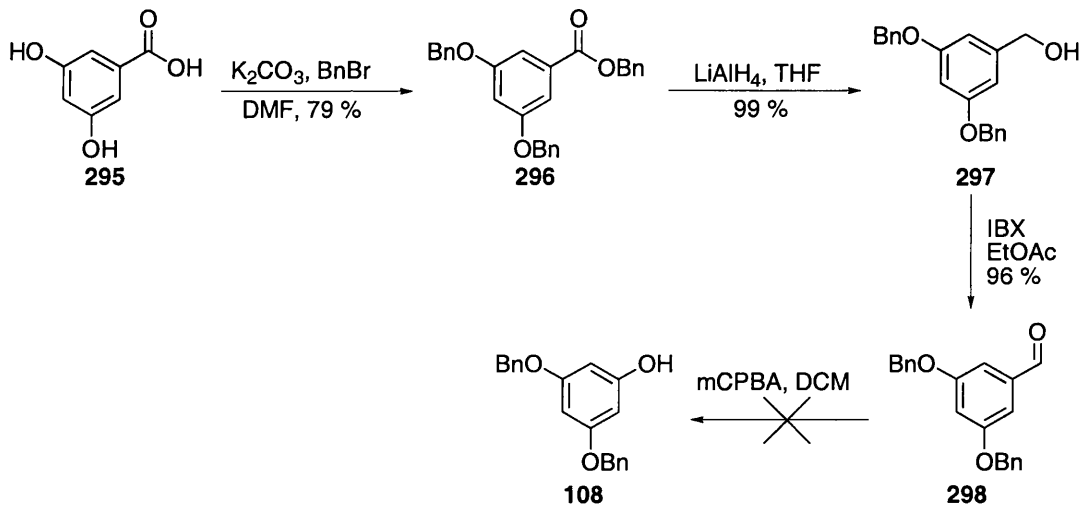
56

Scheme 4.11

Acetylation of phloroglucinol **100** proceeded smoothly to give acetate **294** essentially in quantitative yield. Following Kawamoto's procedure, water was added to a mixture of acetate **294**, benzyl chloride and sodium hydride in DMF at 0 °C. Unfortunately, the addition of water caused a dangerous exotherm that could not be controlled.

Consequently we adopted an alternative approach to **56**, also shown in **Scheme 4.11**, where the acetate **294** was treated with sodium methoxide and benzyl bromide. Unfortunately, tribenzyl ether **56** was not formed.

A second alternative route to ether **56** is shown in **Scheme 4.12**. Benzylation of benzoic acid derivative[111] **295** proceeded in good yield to give benzyl ester **296**, which was reduced with $LiAlH_4$[111] to give benzyl alcohol derivative **297** in quantitative yield. The oxidation of alcohol **297** was performed with both manganese dioxide and IBX. Both proceeded in high yield however, IBX was found to give superior yields of aldehyde **298** (96 % vs 81 % respectively). Unfortunately, when aldehyde **298** was treated with mCPBA no useful product was isolated..



Scheme 4.12

A table summarising the variety of different methods used for the benzylation of phloroglucinal **100** is shown below (**Table 4.1**).

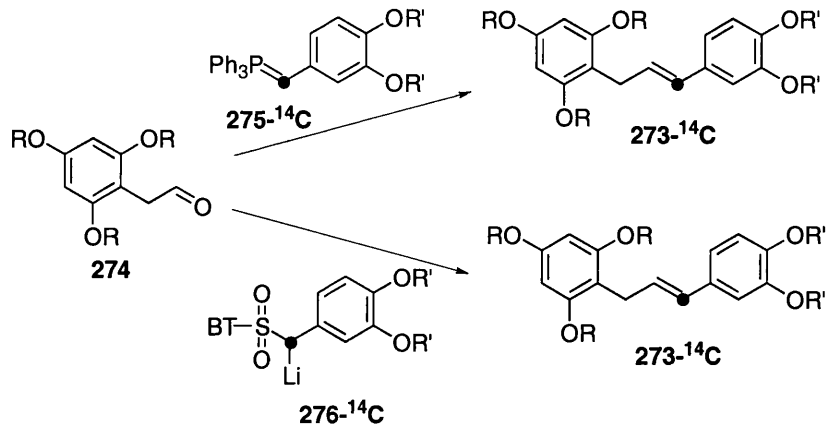
Run Number	Conditions	Result
1	**100** (1 eq.), BnBr (4 eq.), K_2CO_3 (3 eq.), DMF, 70 °C, 3 d	Mainly **293** formed
2	**100** (1 eq.), BnBr (4 eq.), K_2CO_3 (4.3 eq.), DMF, RT, 2 d	17 % **56** and 11 % **293**
3	**100** (1 eq.), BnCl (3 eq.), NaH (3 eq.), DMSO, RT, 1 h	Starting material recovered
4	**100** (1 eq.), trichlorobenzyl imidate (6 eq.), $BF_3.OEt_2$ (0.3 eq.), MeCN, -30 °C – RT, 1 d	Recovered imidate
5	**294** (1 eq.), BnCl (3.6 eq.), NaH (3.6 eq.), H_2O, DMF, 0 °C, 2 h	Dangerous exotherm
6	**294** (1 eq.), BnCl (3 eq.), 1.43 M NaOH (3 eq.), DMF, RT, 2 h	Starting material recovered
7	**294** (1 eq.), BnCl (3 eq.), 10 M KOH (3 eq.), DMF, RT, 6 h	Starting material recovered
8	**294** (1 eq.), NaOMe (0.5 M in MeOH, 2 eq.), BnBr (2 eq.), DCM, 2 d	Complex mixture obtained (7 compounds by tlc)

Table 4.1

4.4.2 Alternative approach to 2-[(3',5'-dibenzyloxy)-1'-hydroxyphenyllethanal 290

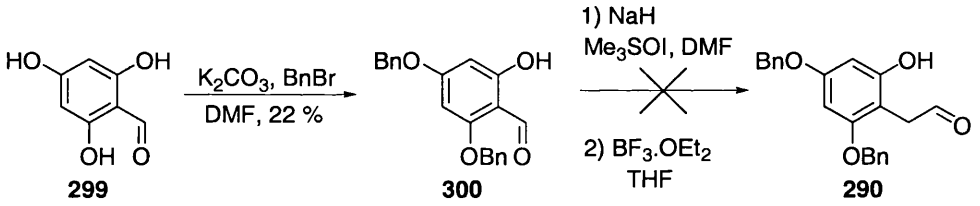
After the unsuccessful attempts to synthesise *C*-allylated phloroglucinol derivative **145a**, we needed an alternative synthesis of aldehyde **274**.

Aldehyde **274** is an important intermediate in routes a and b (**Scheme 4.3**). It could be reacted with either a labelled phosphonium salt **275-^{14}C** or a labelled sulfone **276-^{14}C** to give the diarylpropene **273-^{14}C** required for the dihydroxylation-cyclisation strategy **(Scheme 4.13)**.



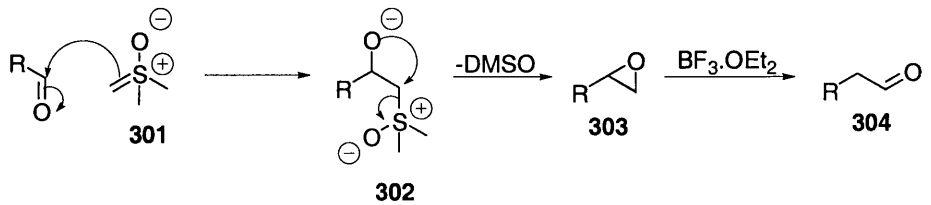
Scheme 4.13

An alternative synthesis of aldehyde **274** is shown below (**Scheme 4.14**). Benzylation of phloroglucinal **299** gave aldehyde **300** in poor yield. Unfortunately, treatment of aldehyde **300** with Corey's ylid followed by $BF_3.OEt_2$[112] did not give the desired phenylacetaldehyde **290**. Only starting material was recovered with no evidence of epoxide formation. No further investigation of this reaction was attempted.



Scheme 4.14

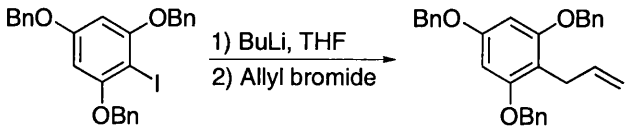
The mechanism for the proposed transformation of **300** into **290** is shown in **Scheme 4.15**. Addition of the sulfoxonium ylid **301** to an aldehyde gives intermediate **302**. Elimination of DMSO gives epoxide **303**, which when treated with $BF_3.OEt_2$ gives the chain-extended aldehyde **304**.



Scheme 4.15

4.4.3 Substrates for lithiation

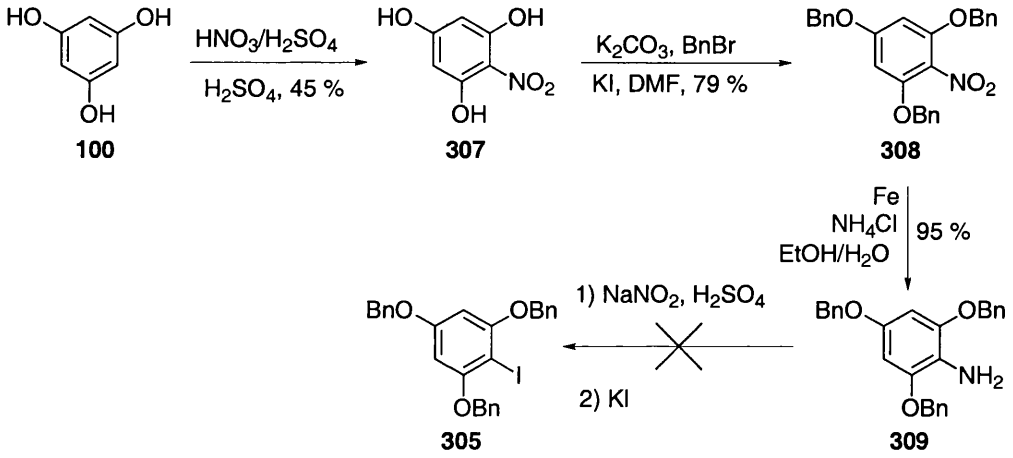
We also looked at alternative ways to the Claisen rearrangement of introducing the allyl group to obtain substrate **279**, which could be used for cross-metathesis reactions (**Scheme 4.3**, route d). Lithiation of iodide **305** followed by quenching with allyl bromide should give ether **306 (Scheme 4.16)**.



305 **306**

Scheme 4.16

The synthesis of iodide **305** again involved the benzylation of a phloroglucinol core **(Scheme 4.17)**.



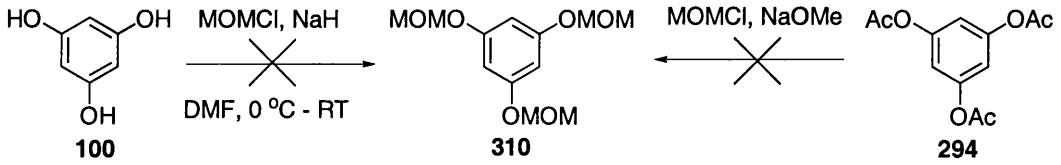
100 **307** **308**

305 **309**

Scheme 4.17

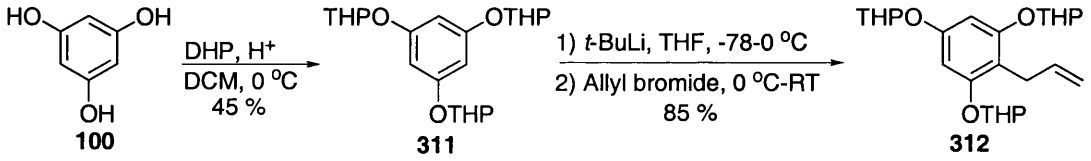
Nitrating the ring should make the aromatic ring sufficiently electron-poor to prevent the *C*-benzylation side-reaction from occurring. Nitration of phloroglucinol **100** gave 2-nitrophloroglucinol **307** in moderate yield. Benzylation of 2-nitrophloroglucinol **307** then proceeded to give benzyl ether **308** in good yield, with no *C*-benzylation observed. Reduction of nitro compound **308** gave aniline derivative **309** in excellent yield. However, the diazotisation-iodination returned only starting material. This was attributed to the insolubility of the aniline in the dilute sulfuric acid used as the reaction solvent.

We also considered an *ortho*-lithiation approach. Protection of phloroglucinol as the tris(methoxymethyl)ether **310** would have allowed us to *ortho*-lithiate and quench with allyl bromide. Our attempted syntheses of ether **310** are shown in **Scheme 4.18**. Unfortunately, we could not synthesise ether **310**.



Scheme 4.18

Switching to tetrahydropyranyl (THP) ethers instead of MOM ethers led to the successful protection of phloroglucinol in moderate yield (**Scheme 4.19**). Acetal **311** was isolated as a 2:1 mixture of diastereoisomers as indicated by the presence of two singlets in the ^{1}H NMR spectrum at δ 6.43 and 6.44 corresponding to the aromatic protons. Allylation of **311** proceeded uneventfully to give ether **312** as a 10:1 ratio of product:starting material indicated from the integrations of the aromatic signals in the starting material and the multiplet at δ 6.48-6.52 corresponding to the mixture of diastereomeric products.

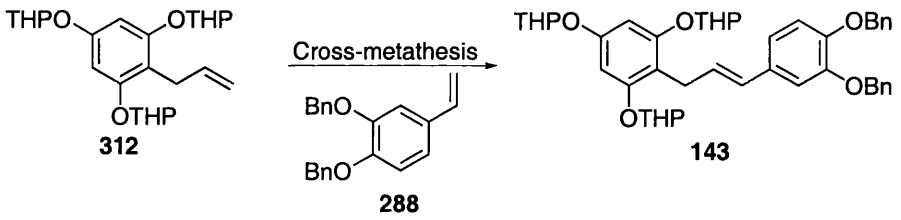


Scheme 4.19

4.5 Cross-metathesis-Dihydroxylation route

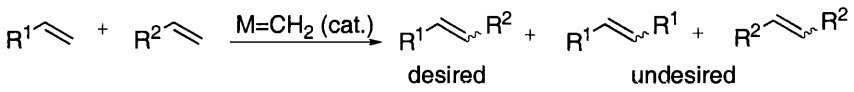
4.5.1 Cross-metathesis

With allyl compound **312** and styrene derivative **288** in hand, we considered the cross-metathesis reaction to give alkene **143** (**Scheme 4.20**).



Scheme 4.20

The intermolecular coupling of two different alkenes *via* cross metathesis potentially forms three new alkenes; the desired cross-coupled product and the undesired products of self-metathesis (**Scheme 4.21**).[113]



Scheme 4.21

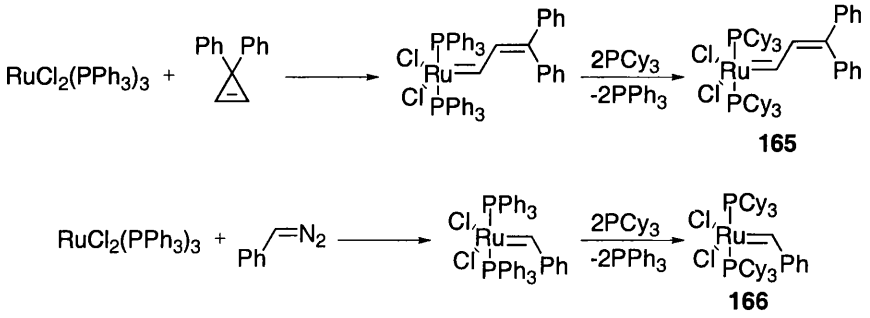
Minimising the formation of unproductive self-metathesis products (homodimers) and hence maximising the desired cross-metathesis process is of crucial importance. In addition to this, stereocontrol of the newly formed double bond is also an important factor. Although the production of homodimers is undesirable, they may be isolable and can be resubjected to the reaction conditions in place of the corresponding monomer to produce the desired cross-metathesis product.[114]

In recent years, well-defined single component metal carbene complexes have been synthesised and applied to olefin metathesis.[113] A number of titanium and tungsten catalysts have been developed. However, Schrock's molybdenum complex[67] **164**, and the ruthenium-based catalysts **165**,[68] **166**[69] and **47**[70] (**Figure 3.2**) developed by Grubbs are the most widely used catalysts.

A major advantage of Schrock's catalyst **164** is its high reactivity towards a wide range of substrates with a number of steric or electronic variations.[113] The alkoxy groups can be readily altered to adjust the catalyst's activity.[113] There are however, some important drawbacks to this system. It possesses only moderate to poor functional group tolerance, is highly sensitive to air, moisture and even to trace

impurities in solvents.[113] Thermal instability on storage and the high cost of preparation are also problematic.[113]

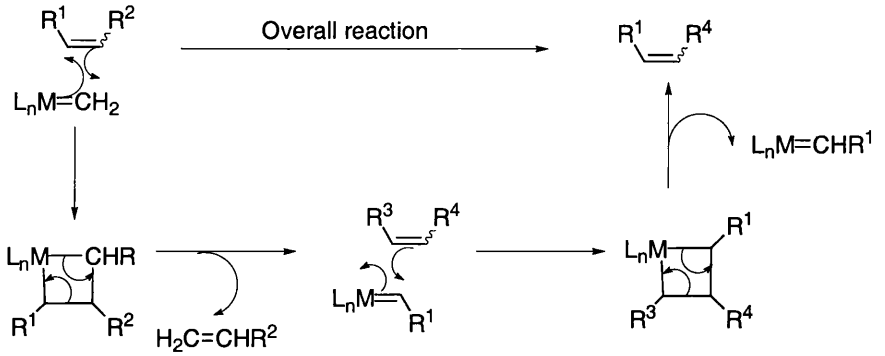
In contrast to this, ruthenium complexes **165** and **166** can be easily prepared by reaction of $RuCl_2(PPh_3)_3$ with 3,3-diphenylcyclopropene and phenyldiazomethane respectively followed by ligand exchange with tricyclohexylphosphine (**Scheme 4.22**).[113]



Scheme 4.22

The ruthenium-based catalyst have gained a lot of attention because they exhibit high reactivity in a variety of cross-metathesis, RCM and ring-opening metathesis polymerisation (ROMP) processes and possess a remarkable tolerance towards a wide range of organic functional groups.[113] Their catalytic activity is not significantly reduced in the presence of air, moisture or trace impurities in solvents.[113] They can be conveniently stored, even under air without appreciable decomposition for several weeks.[113] They often exhibit lower propagation rates, particularly with bulky substrates compared to Schrock's catalyst, but their availability and ease of use make these the catalysts of choice with the exception of the most difficult metathesis substrates.[113]

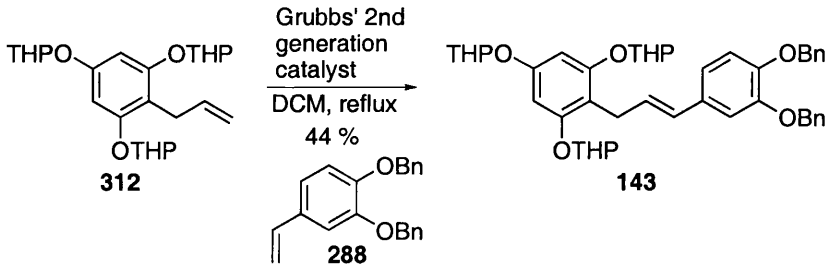
The generally accepted mechanism for both cyclic and acyclic olefin metatheses proceeds through a series of metallacyclobutanes and carbene complexes (**Scheme 4.23**).[115]



Scheme 4.23

Interestingly, although the stability of the carbenes and metallacyclobutanes can change with reaction conditions, catalyst composition and alkene substituents, the mechanism appears to be the same for all catalysts. As discussed earlier, Gesson has reported the synthesis of a variety of 1,3-diarylpropenes from substituted allylphenols and styrenes using cross-metathesis **(Section 2.3)**.[44] More recently Grubbs reported the synthesis of two flavan-3-ols using a cross-metathesis strategy **(Section 2.3)**.[42]

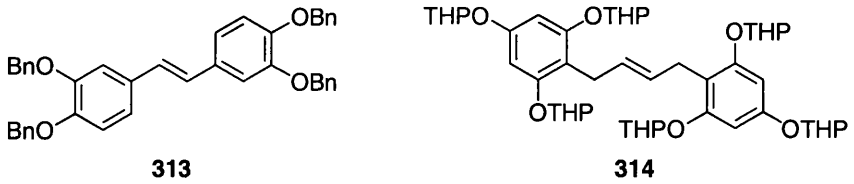
Following the procedure used by Grubbs for the synthesis of tetramethylcatechin we attempted the cross-metathesis of ether **312** with styrene derivative **288** and obtained *E*-alkene **143** as a mixture of diastereomers in moderate yield **(Scheme 4.24)**.



Scheme 4.24

Analysis of the crude ^{1}H NMR spectrum shows the presence of only the *E*-alkene determined by the large coupling constant (15.8 Hz) of the doublet at δ 6.23 corresponding to the benzylic methine proton of the alkene system. The multiplet at δ 6.48-6.53 indicates the presence of a mixture of diastereomers. The low yield can be partly attributed to the dimerisation of styrene derivative **288** to stilbene derivative **313 (Figure 4.1)**, which precipitates from the reaction mixture during the work-up

procedure. Another by-product was isolated during purification, which was expected to be dimerised alkene **314 (Figure 4.1)**. However, analysis of the ^{1}H NMR spectrum did not agree with this and the compound remains unidentified.

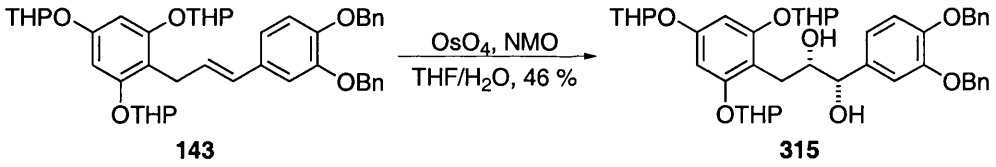


313 **314**

Figure 4.1

4.5.2 Dihydroxylation

With alkene **143** in hand we turned our attention to the dihydroxylation. Initial attempts at the asymmetric dihydroxylation of alkene **143** with AD-mix-α proved unsuccessful. This was attributed to the limited solubility of the alkene in the reaction solvent mixture. We repeated the dihydroxylation using osmium tetroxide and NMO. The reaction proceeded smoothly and diol **315** was obtained in moderate yield after purification (**Scheme 4.25**).



143 **315**

Scheme 4.25

The diol was obtained as a racemic mixture of six diastereomers, the evidence for which can be readily obtained from the ^{1}H NMR spectrum and is easily rationalised. The stereospecificity of dihydroxylations is well understood and addition to the double bond occurs in a *syn* manner. The two newly formed chiral centres can either be *R,R*- or *S,S*-configuration. If we consider the new chiral centres in the desired *S,S*-configuration and label the THP groups in a clockwise fashion as A, B and C (**Figure 4.2**) then the possible combinations of diastereomers are shown in **Table 4.2**. The same situation applies for the *R,R*-configuration giving the enantiomeric series.

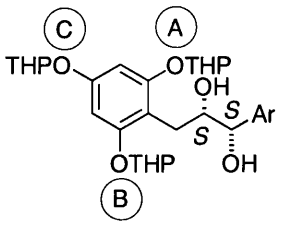
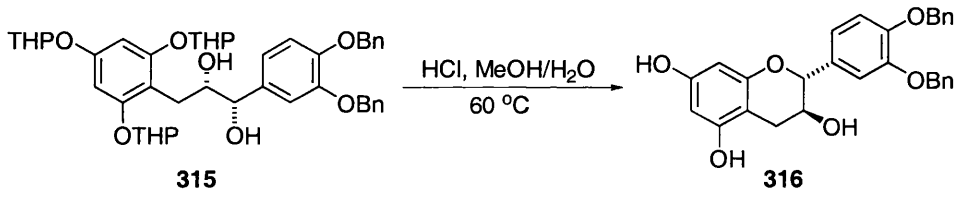


Figure 4.2

Diol configuration	(A)	(B)	(C)
S,S	*R*	*R*	*R*
S,S	*S*	*S*	*S*
S,S	*R*	*R*	*S*
S,S	*R*	*S*	*R*
S,S	*S*	*S*	*R*
S,S	*S*	*R*	*S*

Table 4.2

Cyclisation of **315** to give **316** was attempted, using 3 M HCl in methanol/water (3:1) at 60 °C (**Scheme 4.26**).



Scheme 4.26

These conditions were tried twice but no product was obtained. A third attempt using 10 % HCl in methanol/water (3:1) at 60 °C was also attempted but again no product was formed. In each case a complex mixture was isolated making interpretation of the ^{1}H NMR spectra very difficult. Due to time constraints no further attempt was made to cyclise the diol **315**.

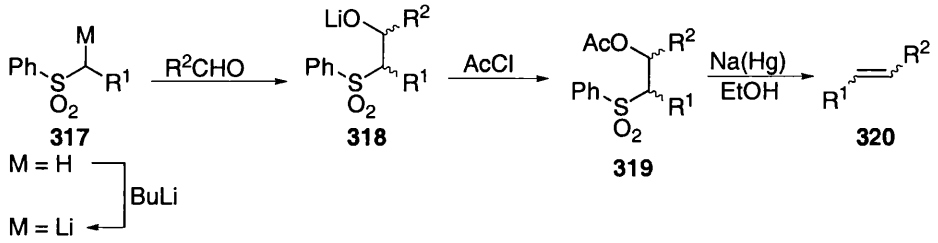
4.6 Modified Julia alkenation in *E*-alkene synthesis

A potentially successful approach to catechin was found employing the cross-metathesis strategy. While investigating the synthesis of alkene **143** *via* cross-metathesis (**Scheme 4.24**), studies on the synthesis of alkene **143** using the Julia

alkenation were also being carried out in parallel. The background of the Julia alkenation is briefly discussed below.

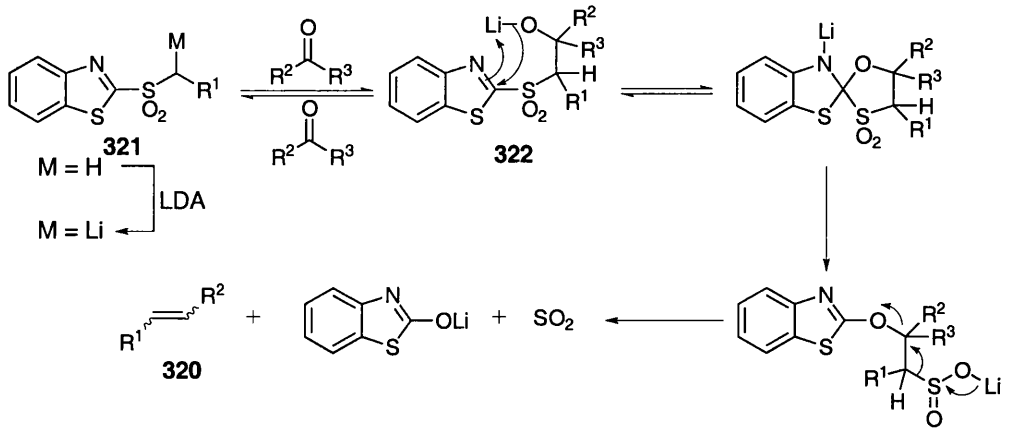
4.6.1 Choice of Julia alkenation explained

In 1973, the process now known as the classical Julia alkenation was reported.[116] The process was a novel method of synthesising alkenes from phenyl sulfones. The general method is outlined in **Scheme 4.27**. Lithiation of sulfone **317**, followed by addition of an aldehyde gives β-alkoxysulfone **318**. Acetylation of sulfone **318** gives β-acyloxysulfone **319**, which is reduced with sodium-mercury amalgam to give alkene **320**. Although useful, the classical Julia alkenation is quite a long process. All four steps can be carried out in one pot but yields are higher if the β-hydroxy sulfones are isolated and purified.



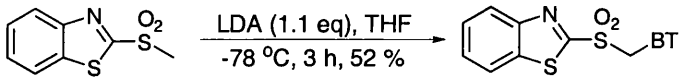
Scheme 4.27

In 1991, Julia and co-workers published a novel one-pot synthesis of alkenes employing the reaction of lithiated benzothiazol-2-yl sulfones (BT sulfones) with carbonyl compounds (**Scheme 4.28**).[117] The reaction proceeds by the addition of the lithiated sulfone **321** to the carbonyl compound to give alkoxide **322**, which undergoes a series of rearrangements resulting in the loss of sulfur dioxide, lithium benzothiazolone and the formation of the new olefin **320**.



Scheme 4. 28

Julia found that some lithiated benzothiazolyl sulfones are unstable, undergoing self-condensation even at low temperatures (**Scheme 4.29**).[118]



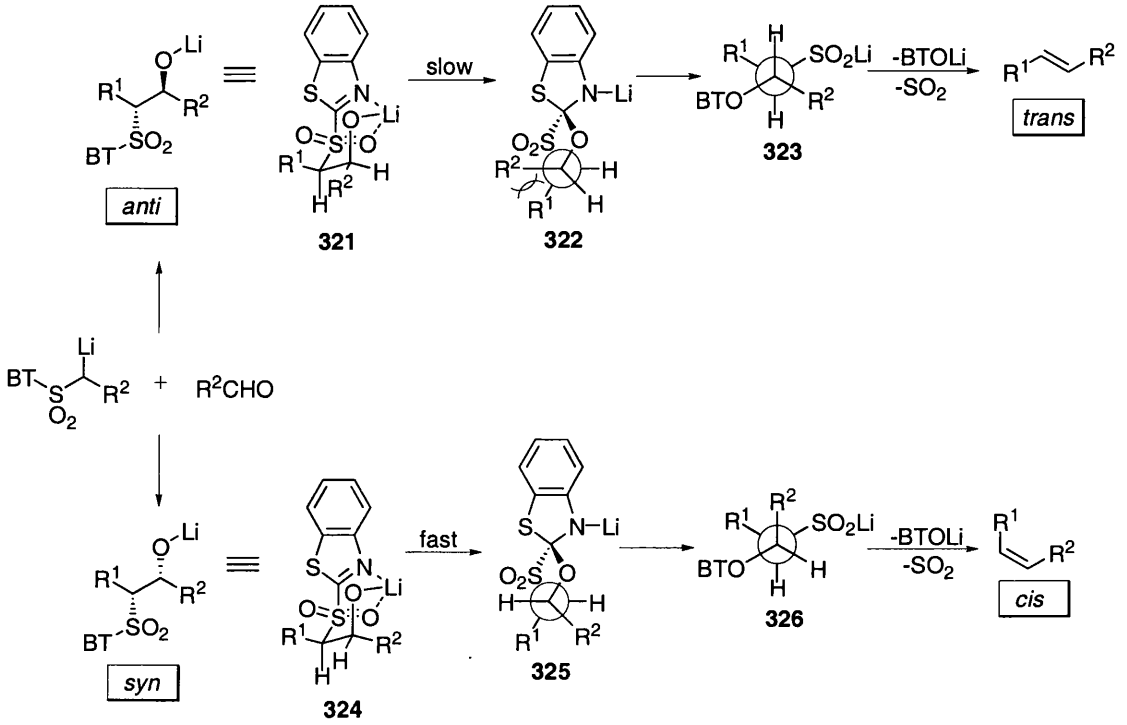
Scheme 4.29

This problem was avoided by adding the base to a mixture of the sulfone and aldehyde i.e. Barbier-type protocol. Using this procedure, the sulfone is lithiated *in situ* and addition of the lithiated sulfone to the aldehyde occurs faster than self-condensation. Using the Barbier method, Julia found that enolisable aldehydes or ketones and allylic or benzylic BT-sulfones could be used.[118]

Julia progressed from the early work to carry out a detailed study of the stereochemistry of the alkenes formed from lithiated heterocyclic sulfones.[118] Using the Barbier conditions and saturated carbonyl compounds, several simple alkenes were synthesised albeit in low to moderate yield and essentially as a 50:50 mixture of *E* - and Z - isomers.

The stereochemical outcome of the BT-modified Julia alkenation is substrate controlled but can be affected by the reaction conditions.[119] An investigation into the base-mediated elimination of stereodefined β-hydroxy-BT-sulfones showed that simple β-oxy-BT-sulfones (i.e. **321**, **324** with R^1 and R^2 = alkyl) breakdown

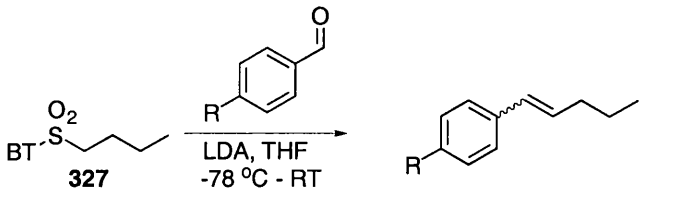
stereospecifically with the *anti*-diastereoisomer **323** giving *E*-olefins and the *syn*-diasteroisomer **326** giving *Z*-olefins (**Scheme 4.30**).[120]



Scheme 4.30

The disappointing selectivities observed by Julia can therefore be attributed to poor diasterocontrol in the nucleophilic addition to the carbonyl compound.

The most synthetically useful reaction of BT-sulfones is the synthesis of conjugated 1,2-disubstituted *E*-alkenes.[119] Most structural varieties of BT-sulfones will react with α,β-unsaturated aldehydes, including aromatic aldehydes, to give *E*-alkenes with high stereoselectivity.[119] The reactions of simple alkyl BT-sulfones with electron-rich conjugated aldehydes are particularly successful.[119] An example is shown in **Scheme 4.31**.



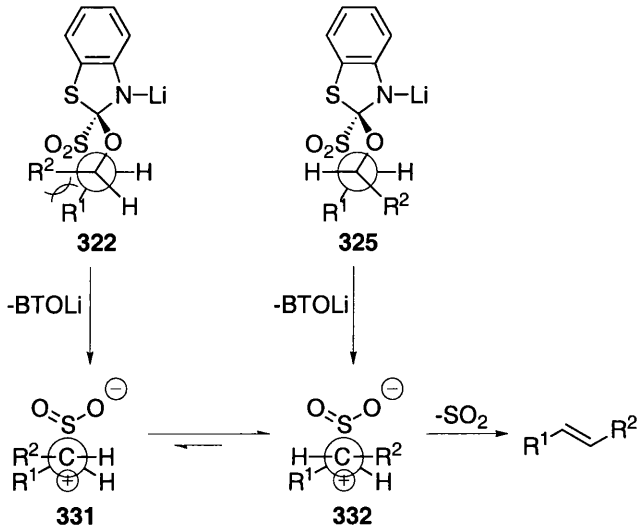
327

328 R = OMe, 95 %, 99:1 *E:Z*
329 R = H, 68 %, 94:6 *E:Z*
330 R = Cl, 51 %, 77:23 *E:Z*

Scheme 4.31

Reaction of lithiated 2-(butylsulfonyl)benzothiazole **327** with *para*-substituted benzaldehydes gave the expected products **328-330** with moderate to high stereoselectivity. This example also shows the beneficial effect an electron donating *para*-substituent on the ring to stereoselectivity of the reaction.[119]

Lithiated oxy-BT-sulfones, **322** and **325** with R^2 = vinyl or aryl do not breakdown stereospecifically to give alkene products.[119] It has also been shown that some lithiated *syn*-β-hydroxy-BT-sulfones with R^2 = vinyl or aryl collapse giving mainly *E*-alkene products.[120] A direct pathway for this transformation must therefore exist. Julia's proposed pathway is shown below (**Scheme 4.32**).[118]

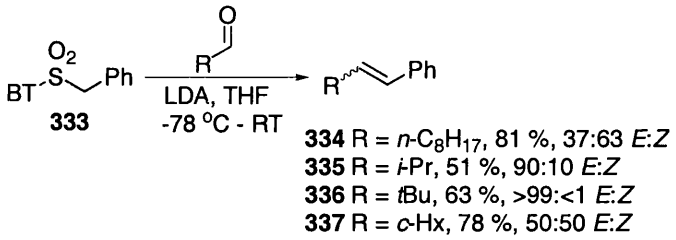


Scheme 4.32

Loss of benzothiazolone from intermediates **322** and **325** may lead to zwitterionic conformers **331** and **332** respectively. Equilibration of the betaine intermediates favours **332**, which gives an *E*-alkene on loss of sulfur dioxide. Unsaturated

substituents at R^2 will provide stabilisation for the carbocation ion in **331** and **332** and therefore, could promote this pathway.[119] This proposed route also accounts for the influence of *para*-substituents on the stereochemical outcome of aromatic aldehyde alkenations discussed previously.[119]

Julia *et al* investigated the alkenation of a vast array of BT-sulfones and aldehydes.[118] They found that alkenations with saturated aldehydes and allylic or benzylic heterocyclic sulfones are generally not very stereoselective although there were some exceptions (**Scheme 4.33**).



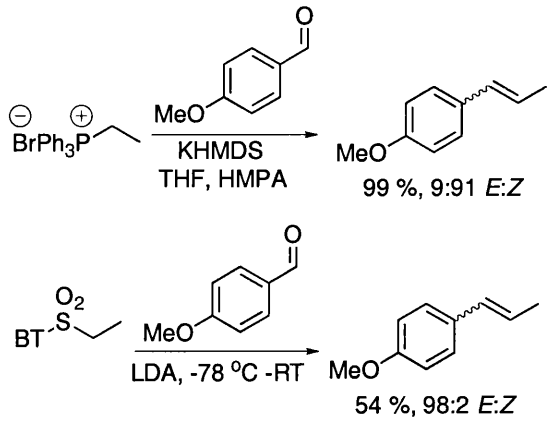
333

334 R = *n*-C_8H_{17}, 81 %, 37:63 *E*:*Z*
335 R = *i*-Pr, 51 %, 90:10 *E*:*Z*
336 R = *t*Bu, 63 %, >99:<1 *E*:*Z*
337 R = *c*-Hx, 78 %, 50:50 *E*:*Z*

Scheme 4.33

These results were obtained by adding the aldehyde to the lithiated sulfone. Interestingly, using Barbier conditions, alkenes **334** and **335** were formed in 80 % yield and as a 23:77 mixture of *E*:*Z*-isomers and in 69 % yield as a 45:55 mixture of *E*:*Z*-isomers respectively. The high selectivities obtained in alkenes **335** and **336** were attributed to the branched alkyl groups forcing the reaction through the alternative pathway previously discussed (**Scheme 4.32**).

Also of interest is the switch in selectivity observed between olefinations with saturated alkyl BT-sulfones compared to saturated alkyl phosphonium salts (**Scheme 4.34**).

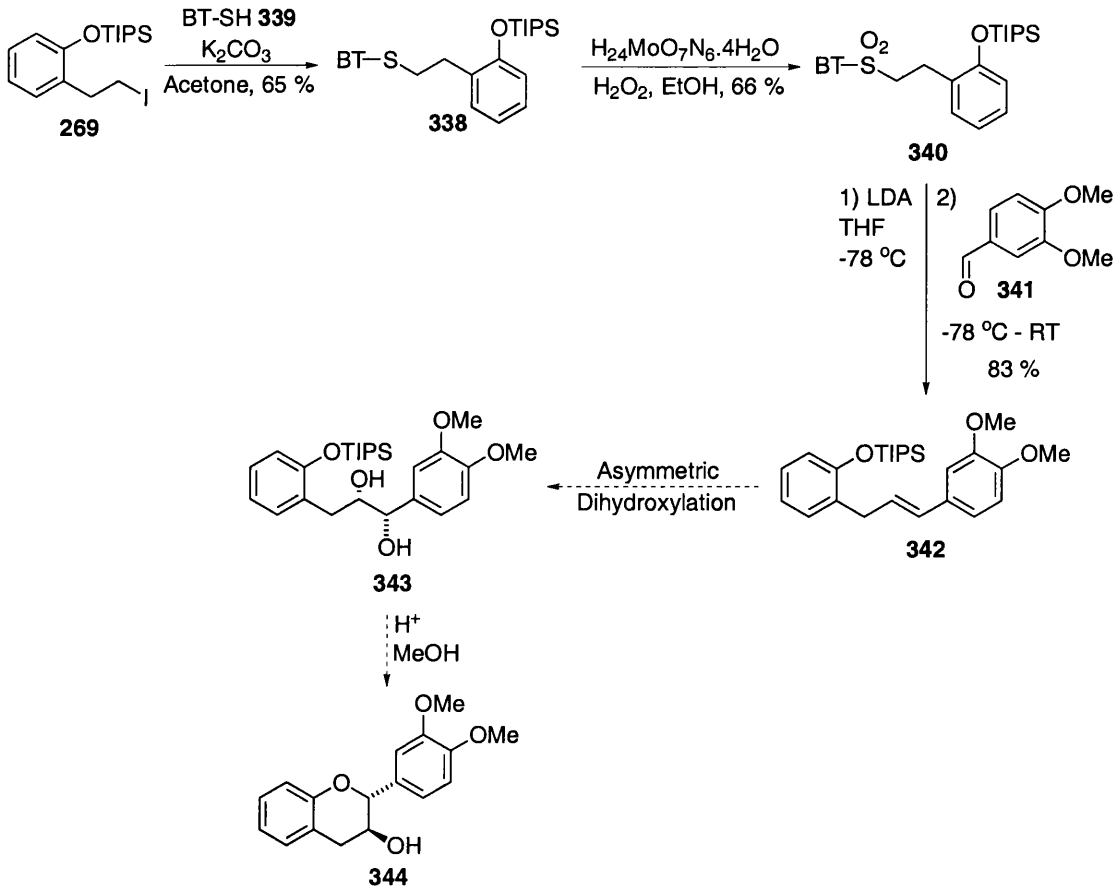


Scheme 4.34

In summary, the modified Julia alkenation is a powerful synthetic tool for the synthesis of *E*-alkenes. High selectivities are obtained with saturated BT-sulfones and aromatic aldehydes and also from benzylic BT-sulfones and branched saturated, α,β-ethylenic or aromatic aldehydes.

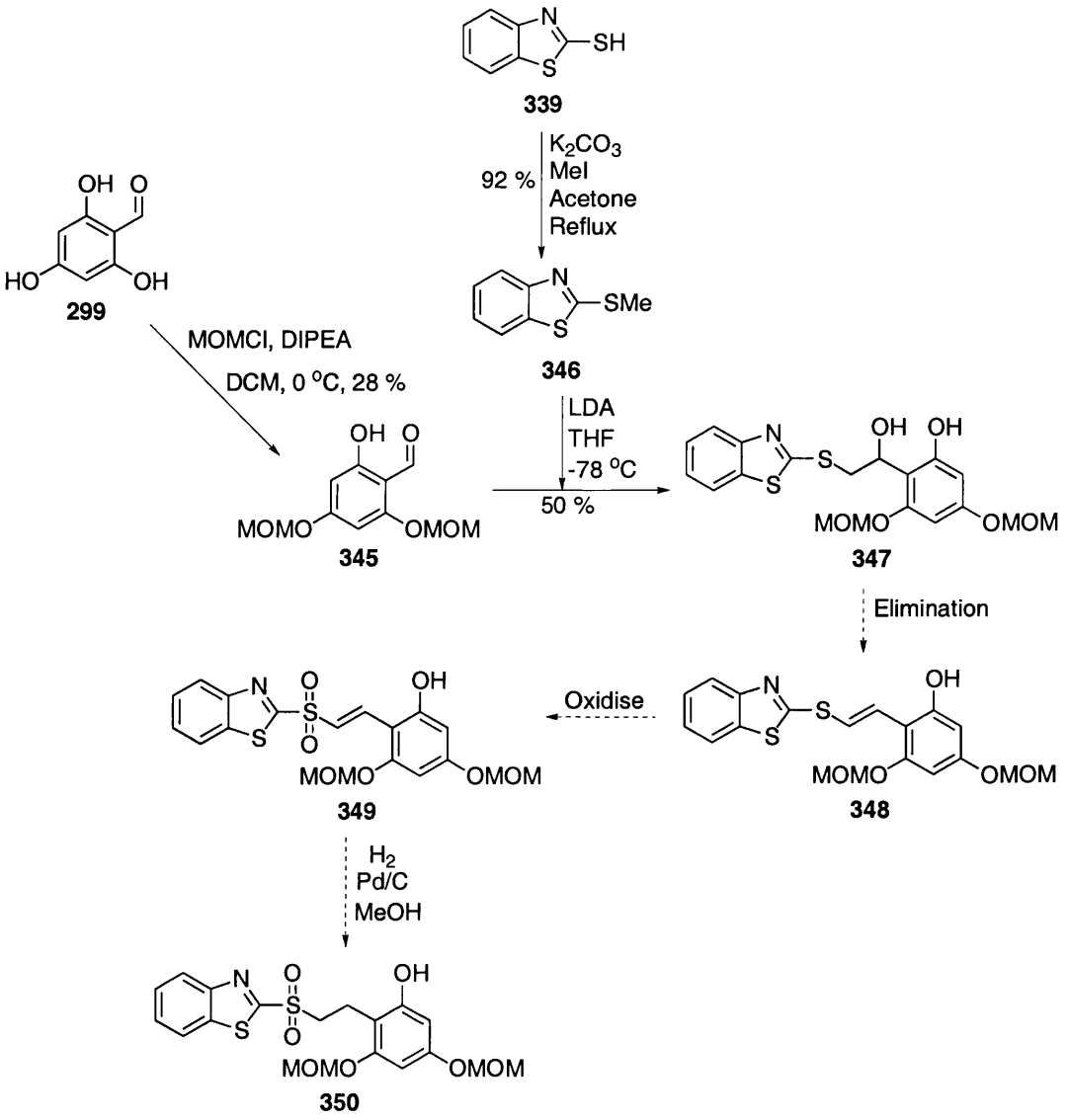
4.6.2 Synthesis and use of sulfones

After the unsuccessful solid-phase route (**Scheme 3.49**), we devised another route employing the ozonolysis chemistry previously discussed (**Scheme 3.59**) and investigated Julia alkenations using iodide **269**. The route is shown in **Scheme 4.35**. Sulfide **338** was readily prepared using Julia's methodology[118] in moderate yield from iodide **269** and the commercially available 2-mercaptobenzothiazole **339**. Oxidation[118] of sulfide **338** proceeded smoothly to give sulfone **340** in moderate yield. To test the alkenation procedure we used veratraldehyde **341** to compare our results to those obtained by Julia.[118] Our results were very encouraging (83 %, *E*:*Z* 100:0). However, despite several attempts, the reaction did not go to completion. Purification of alkene **342** was attempted but a pure sample was not obtained. Dihydroxylation of olefin **342** should give diol **343** which should cyclise under acidic conditions[36,37,43] to give alcohol **344**.



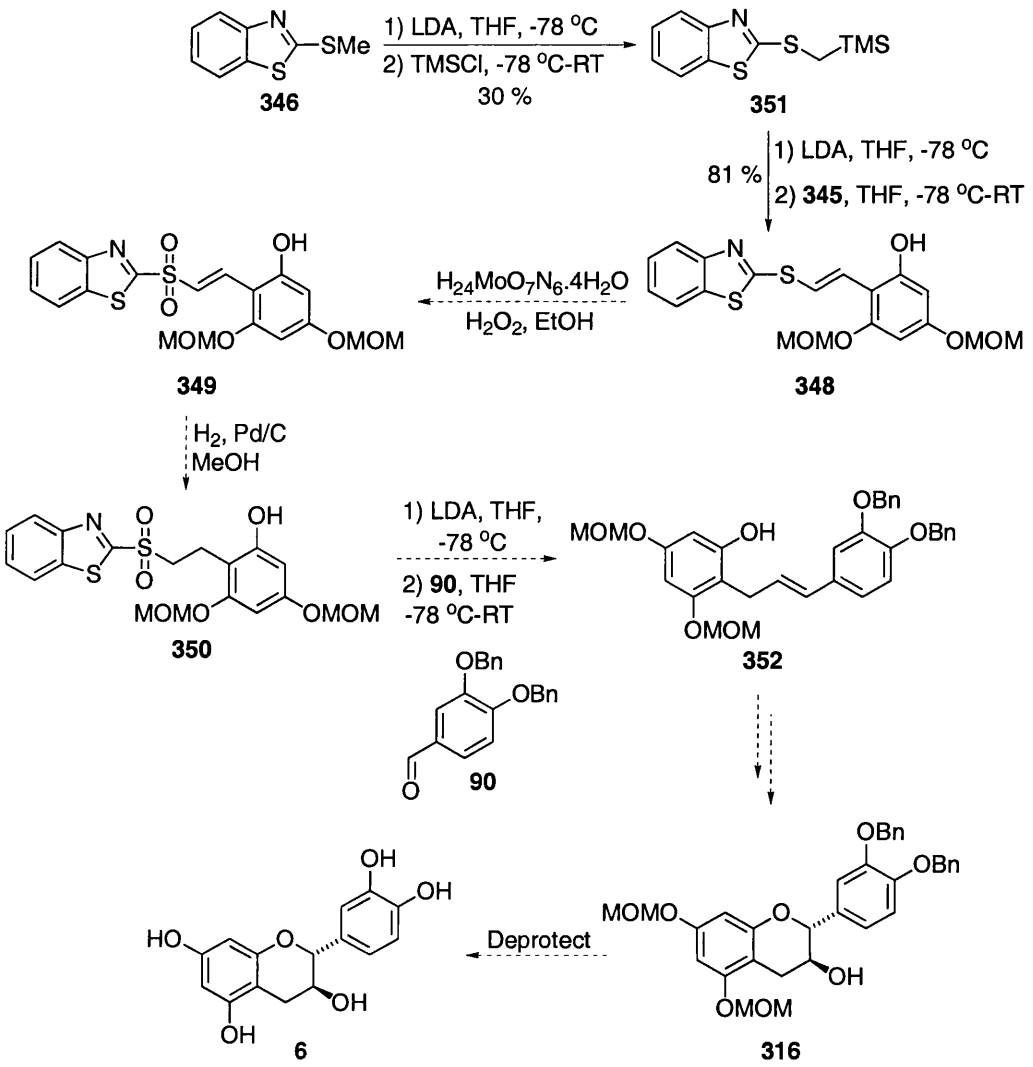
Scheme 4.35

We decided at this stage that the Julia alkenation was a good method to use on model compounds and two new routes were developed for the real system. Our routes are shown in **Schemes 4.36** and **4.37**. Our attention was first devoted to protecting 2,4,6-trihydroxy benzaldehyde **299** which proceeded in poor yield to give the 2,4-bis(methoxymethyl)ether[121] **345**. Methylation[122] of 2-mercaptobenzothiazole **339** gave methyl sulfide derivative **346** in excellent yield, which when lithiated reacted with aldehyde **345** to give sulfide **347** in moderate yield. Elimination of water would give vinyl sulfide **348**, which could then be oxidised to sulfone **349** and hydrogenated to give the desired precursor **350**. However, all attempts to synthesise **348** were unsuccessful.



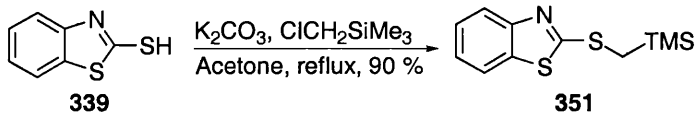
Scheme 4.36

Alternatively, lithiating sulfide **346** and quenching with chlorotrimethylsilane gave sulfide[123] **351** in poor yield but the reaction was easily scaled up. Lithiation of sulfide **351** followed by quenching with aldehyde **345** gave vinyl sulfide **348** in good yield as a 10:1 ratio of *E/Z* isomers. Subsequent oxidation would potentially give sulfone **349** which might undergo hydrogenation to give sulfone **350**. The alkenation with aldehyde **90** should then give olefin **352**, which could be dihydroxylated and cyclised to the secondary alcohol **316**. Finally, deprotection would give (+)-catechin **6**.



Scheme 4.37

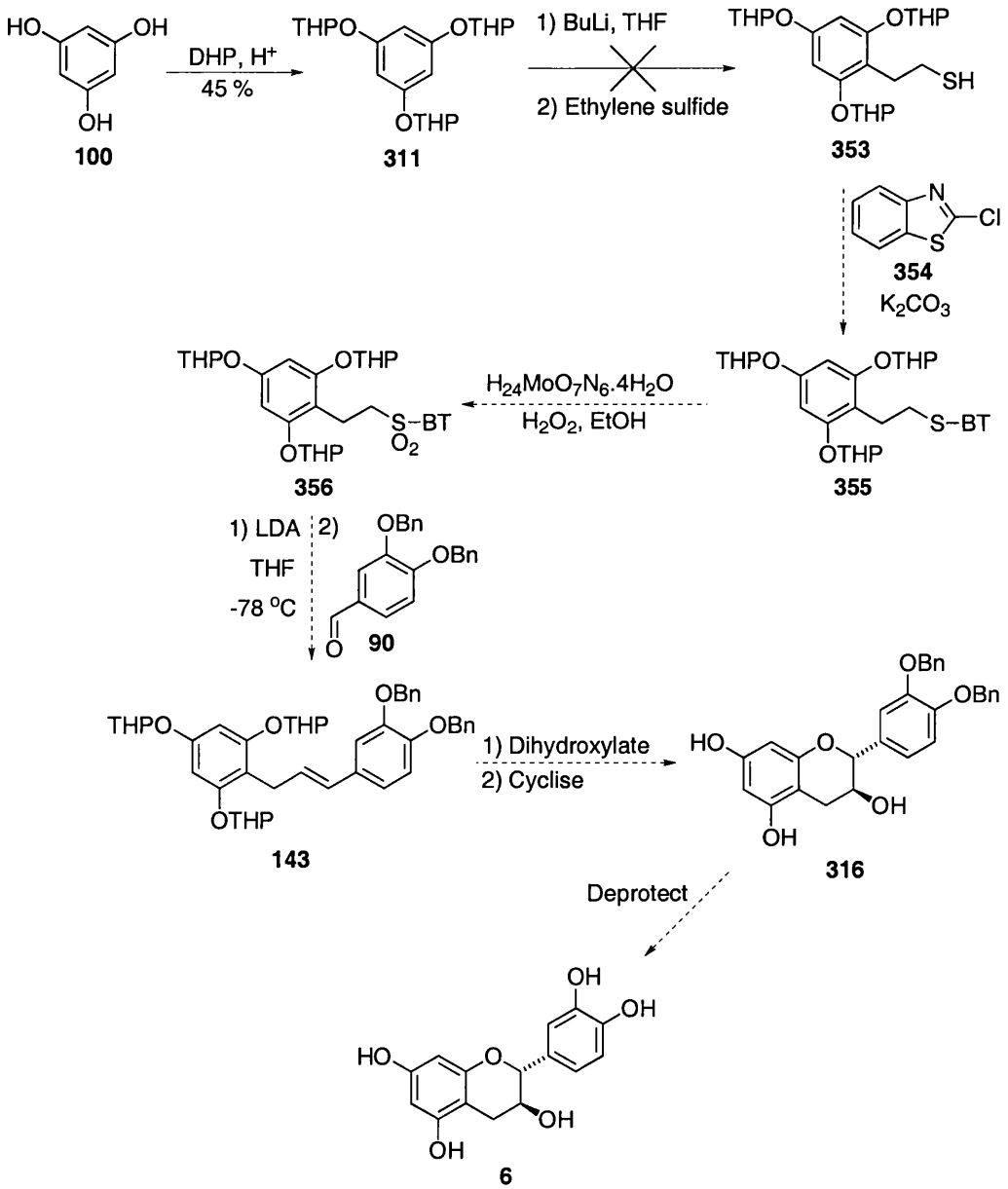
The first step in the above synthesis was improved by alkylating 2-mercaptobenzothioazole **339** with (chloromethyl)trimethylsilane to give sulfide **351** in excellent yield. This is shown below in **Scheme 4.38**.



Scheme 4.38

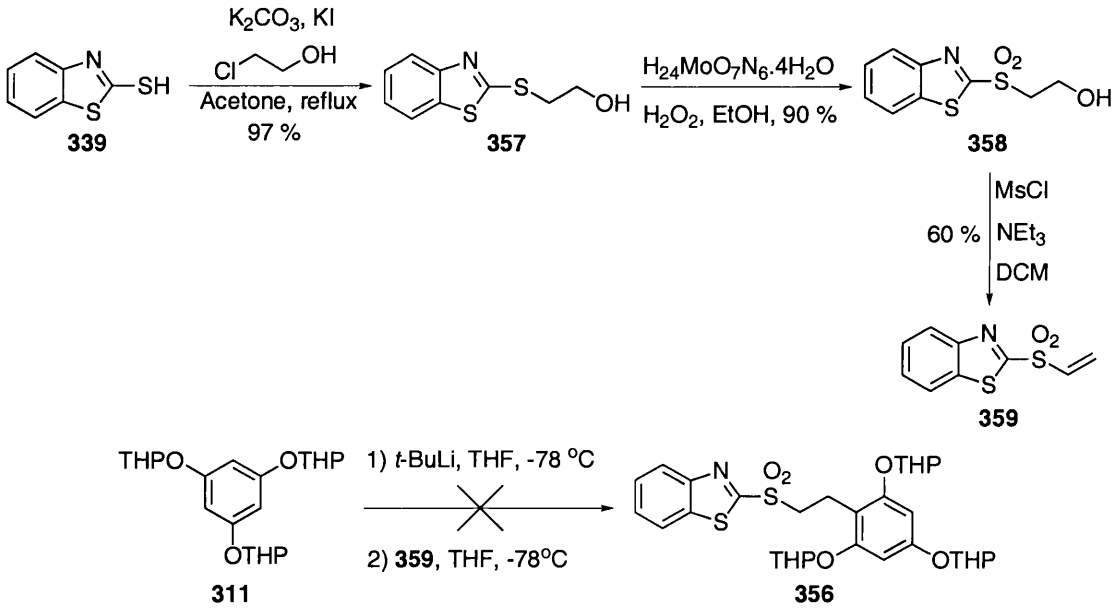
Since the yield of diprotected phenol **345** was poor and manipulation of vinyl sulfide **348** was expected to be convoluted, we considered that an alternative route to sulfone **278** should be attempted.

Using the idea of using a protecting group to direct lithiation on the ring and modifying our benzothiazole chemistry, we proposed the route shown below in **Scheme 4.39**. Tetrahydropyranyl ether **311** was lithiated and quenched with ethylene sulfide in the hope of producing thiol **353** but this failed. Reacting **353** with commercially available 2-chlorobenzothiazole **354**, should then have given sulfide **355**. Oxidation to sulfone **356**, followed by olefination with aldehyde **90** should give olefin **143**. Dihydroxylation of **143**, followed by cyclisation should give protected (+)-catechin **316**. Cleavage of the protecting groups should give (+)-catechin **6**.



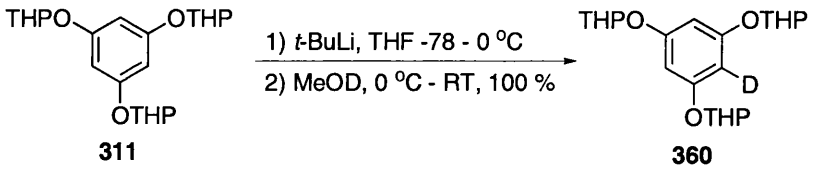
Scheme 4.39

We then decided to investigate whether reaction between a lithiated derivative of THP ether **311** and a vinyl sulfone would give the desired sulfone **356** (**Scheme 4.40**). Alkylation of 2-mercaptobenzothiazole **339** proceeded smoothly to give hydroxy sulfide **357** in excellent yield.[124] Oxidation with ammonium molybdate gave hydroxy sulfone **358** also in excellent yield. Elimination with mesyl chloride and triethylamine gave vinyl sulfone **359** in moderate yield. Coupling of vinyl sulfone **359** with acetal **311** to give sulfone **355** was initially problematic. After the reaction we isolated acetal **311** in almost quantitative yield but the vinyl sulfone was consumed.



Scheme 4.40

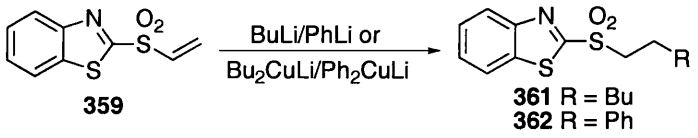
To confirm that acetal **311** was being deprotonated, we treated it with *n*-butyllithium and *tert*-butyllithium and quenched with deuterated methanol to form **360** (**Scheme 4.41**). The experiments showed we got complete incorporation of deuterium onto the ring when we used either *n*-butyllithium or *tert*-butyllithium. Evidence for this comes from the change in integration size of the signals at 6.43 and 6.44 ppm from three protons to two protons. This led us to believe that conjugate addition of the aryllithium was leading to the formation of a sulfone anion that could add to another molecule of vinyl sulfone **359** leading to polymerisation.



311 360

Scheme 4.41

At this stage, we decided to try adding *n*-butyllithium, phenyllithium and the corresponding cuprates to sulfone **359** to check whether it would add to the vinyl group to give sulfone **361** and **362 (Scheme 4.42)**.

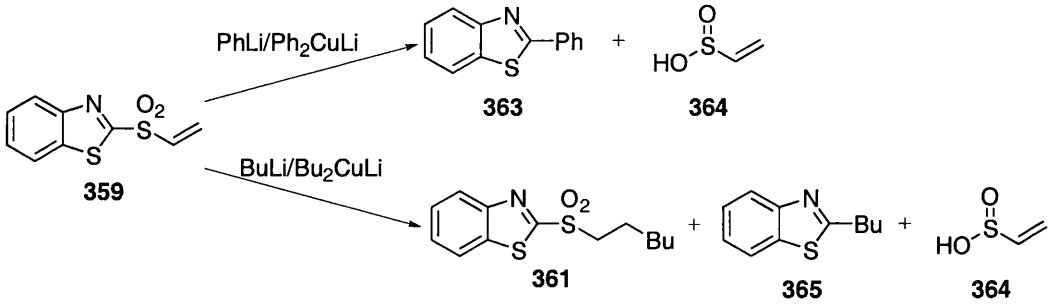


359

361 R = Bu
362 R = Ph

Scheme 4.42

It is not clear what happened on addition of phenyllithium. It did not give sulfone **362** or polymerise sulfone **359**. It is possible that it added directly to the benzothiazole ring to give 2-phenylbenzothiazole **363** and vinyl sulfinic acid **364** (**Scheme 4.43**). The lack of the two expected triplets of the product and the disappearance of the vinyl protons from the starting material support this suggestion. The phenyllithium-derived cuprate gave similar results.



359 **363** **364**

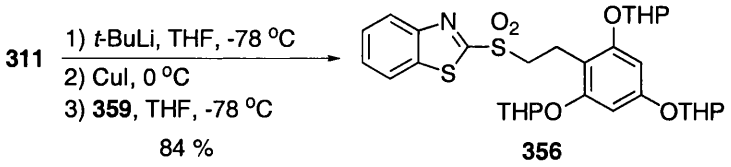
361 **365** **364**

Scheme 4.43

Addition of *n*-butyllithium gave a mixture of products that were difficult to separate. It is clear from the ^{1}H NMR spectrum that a small amount of the desired sulfone **361** was present. The triplet at 3.12 ppm, coupling constant 7.7 Hz is evidence of this compound. A synthesis of sulfinic acids has been reported where benzothiazole

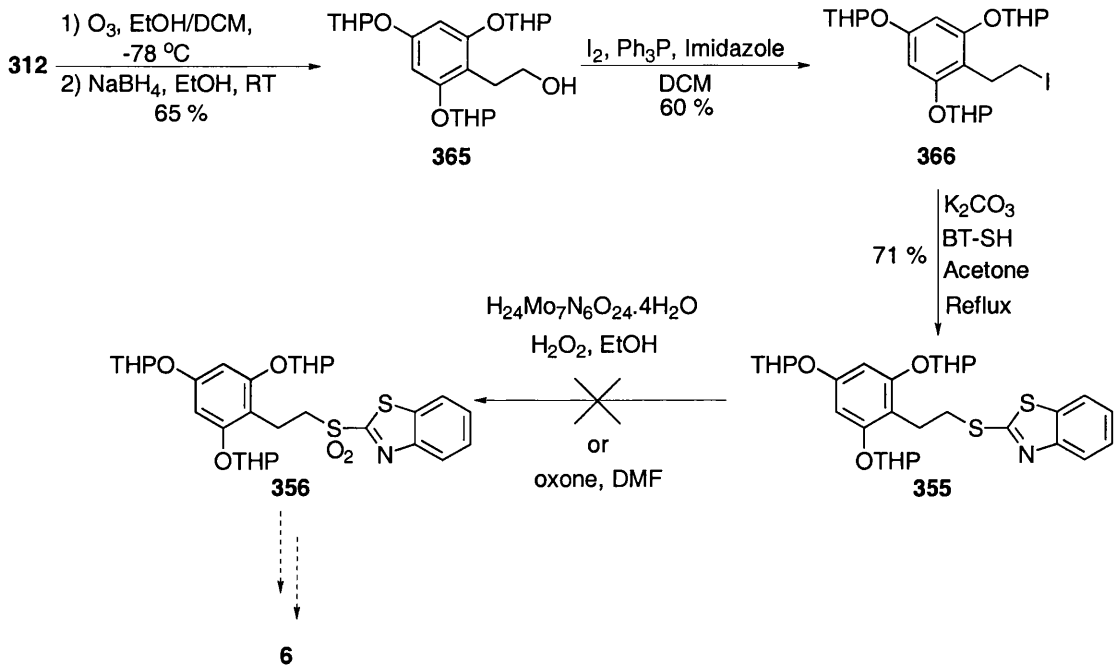
sulfones with varying lengths of chain have been synthesised by treating the sulfone with alkyllithiums[123] and sodium borohydride.[125] Katritzky's group also isolated a small percentage of 2-alkylbenzothiazoles as side products. It is therefore probable that some 2-butylbenzothiazole **365** was also formed. The evidence for this comes from the aromatic protons from 7.26 - 7.39 ppm and 7.42 - 7.48 ppm integrating to exactly eight protons instead of the expected four for the product. Addition of the butyl cuprate gave similar results (**Scheme 4.43**).

We decided at this stage to try forming the organocopper species derived from acetal **311**. This initially gave us the same problem as lithiated **311**. However, if the copper iodide was freshly ground and dried by azeotrope prior to use, the reaction proceeded to give the required sulfone **356** in good yield as a 4.5:1 mixture of product to starting material (**Scheme 4.44**). Unfortunately, impurities that proved difficult to remove were formed on scaling–up the reaction hence alternative routes were sought. Julia alkenation should give alkene **143** which could be dihydroxylated and cyclised in acidic methanol to give phenol derivative **316**. Subsequent hydrogenation should give (+)-catechin **6**.



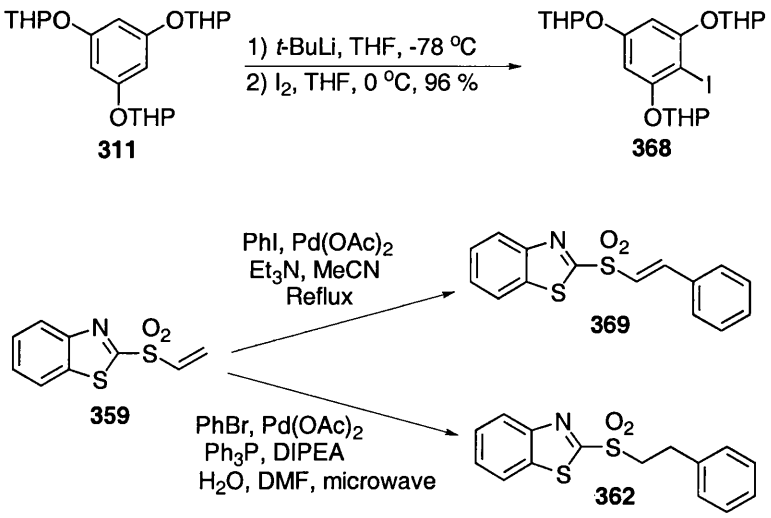
Scheme 4.44

Along with the route described above a new graduate working with me, Lisa Sloan, investigated the route shown in **Scheme 4.45**. Ozonolysis of acetal **312** followed by reduction of the ozonide gave alcohol **366** in moderate yield. Iodination of alcohol **366** gave iodide **367** in moderate yield. We found iodide **367** to be moderately unstable and therefore, we used it without purification to give sulfide **355** in good yield. Sulfide **355** was also found to be unstable. Attempts to oxidise sulfide **355** to the sulfone **356** were unsuccessful and this route was discontinued. Much of this work was originally done jointly between Lisa and me, however I later repeated the route.



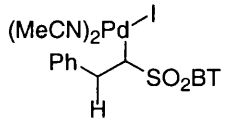
Scheme 4.45

A brief amount of time was spent investigating Heck couplings onto sulfone **359**. To this end iodide **368** was synthesised but never used **(Scheme 4.46)**. Three model Heck couplings were attempted. The first attempt gave a messy mixture of products, but some desired product, alkene **369** was formed. Evidence of this came from the presence of two doublets at 7.15 and 7.89 with coupling constants of 15.4 Hz in the ^{1}H NMR spectrum. After purification it became clear that the reaction had not worked to any useful extent. Two attempts were made using microwave irradiation. Unfortunately, neither worked to any useful extent either. Interestingly, the product obtained from the microwave reactions is not alkene **369**, but the reduced form **361**. The presence of triplet-like peaks at 3.64 and 4.03 in the ^{1}H NMR spectrum suggests this compound is present. These results are summarised in **Scheme 4.46**.



Scheme 4.46

This last result suggests that protonation of the 16-electron adduct **370 (Figure 4.3)** is faster than the β-hydride elimination step and would account for the low yields observed with this system.

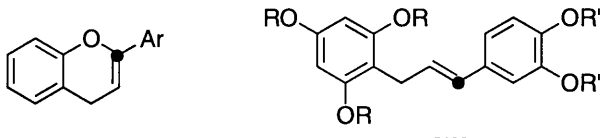


370

Figure 4.3

4.7 Conclusions

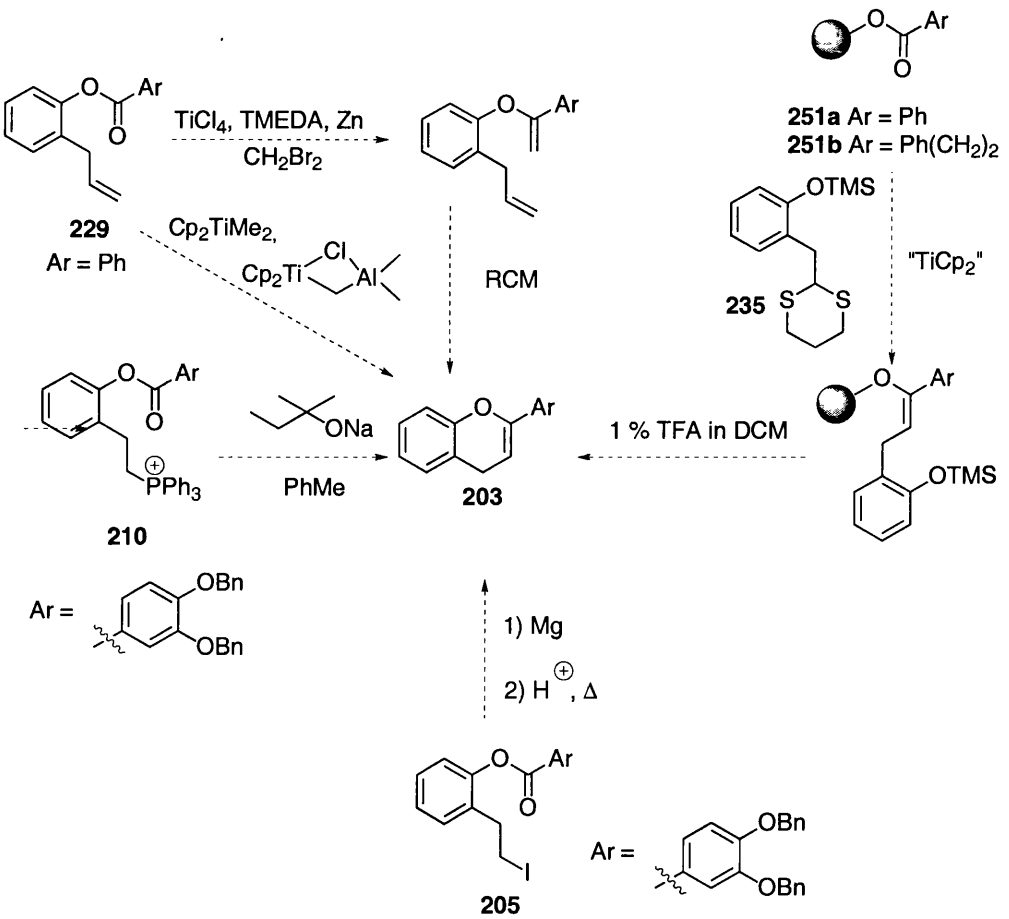
Two main routes, covering a wide range of chemistry have been attempted towards the synthesis of isotopically labelled (+)-catechin. The two routes involved either flavene **203** or 1,3-diarylpropene **273** as the key intermediates (**Figure 4.4**).



203 **273**

Figure 4.4

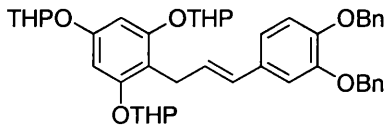
Our studies have focused on a number of routes with flavene **203** as the common intermediate (**Scheme 4.47**). A variety of intermediates were synthesised but unfortunately failed to give the desired flavene. For example, methylenation of ester **229** to give an enol ether which could then undergo RCM to **203** was unsuccessful. Likewise, the intramolecular Wittig reaction of phosphonium salt **210** did not yield **203**. Barbier reaction of iodide **205** also failed to synthesise **203**. It was hoped that the solid phase methodology developed within the Hartley group for the synthesis of benzofurans and indoles could also be extended to the synthesis of benzopyrans. However, despite several attempts, the Takeda reaction of thioacetal **235** did not produce **203**.



Scheme 4.47

Several different routes to 1,3-diarylpropene **273** (**Figure 4.4**) were investigated. Of the routes investigated, the cross metathesis route was particularly successful. This

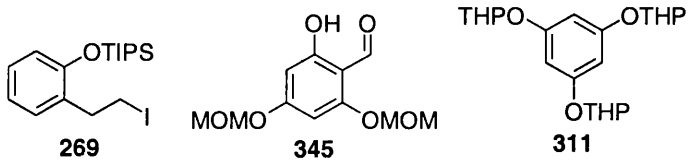
route involved a novel procedure for the protection of phloroglucinol that avoids the problem of *C*-alkylation (**Scheme 4.19**). The procedure allows the synthesis of material that can be rapidly converted into 1,3-diarylpropene **143** (**Figure 4.5**). Dihydroxylation of **143** was successful, however, the subsequent cyclisation failed to give (+)-catechin **6**.



143

Figure 4.5

A model study of the Julia alkenation using iodide **269** (**Figure 4.6**) was very encouraging and led to the investigation of several other described routes. Unfortunately, the same encouraging results were not obtained with the initial routes employing aldehyde **345** or acetal **311**, which could have led to the synthesis of (+)-catechin **6**.



269 **345** **311**

Figure 4.6

Further development of the Julia chemistry led to the successful coupling of acetal **311**with vinyl sulfone **359** to give the required sulfone precursor for the synthesis of (+)-catechin, however further optimisation of this step is required to allow large-scale reactions to be carried out efficiently (**Scheme 4.44**).

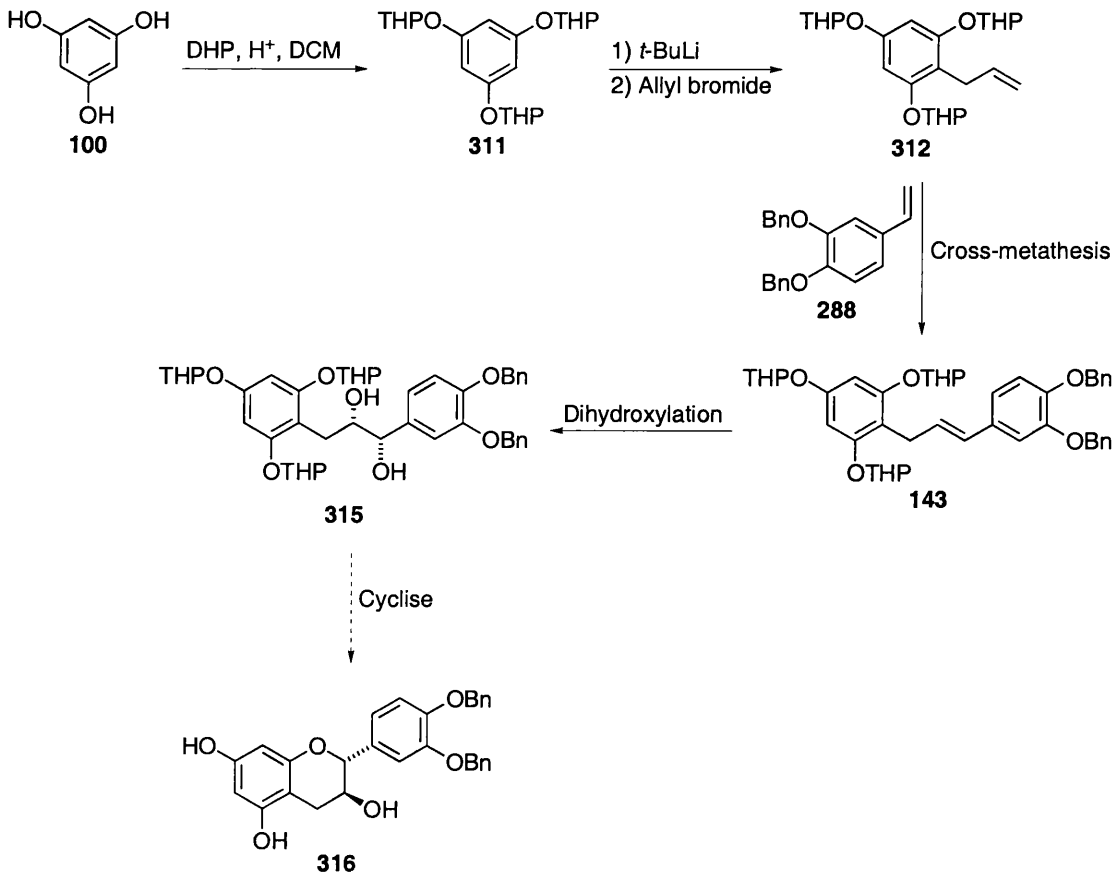
We have described a novel procedure for the protection of phloroglucinol that avoids the problem of *C*-alkylation and allows the rapid synthesis of key 1,3-diarylpropene structures used in the synthesis of flavan-3-ols. An exhaustive investigation into the synthesis of flavene structures is also described.

A novel and promising route to alkene **143** has been investigated which would allow the use of the Julia alkenation. The synthesis of alkene **143** using this methodology could then lead to (+)-catechin using known literature procedures i.e. dihydroxylation-cyclisation. We have also applied Grubbs' cross-metathesis methodology to the synthesis of alkene **143**. Although neither of the routes we have investigated to (+)-catechin are entirely novel, they would provide a new method for the synthesis of radiolabelled (+)-catechin and other flavan-3-ols.

4.8 Future work

There are two routes in particular that are deserving of further investigation.

The successful protection of phloroglucinol and subsequent allylation allowed us to synthesise the desired 1,3-diarylpropene for the dihydroxylation-cyclisation procedure. At this stage the cross metathesis is not efficient and requires optimisation to minimise the formation of homodimer side-products. The dihydroxylation also requires optimisation and a way to allow the use of AD-mix needs to be found. The cyclisation step requires thorough investigation as preliminary studies were unsuccessful and very little time was available to investigate this procedure.



Scheme 4.48

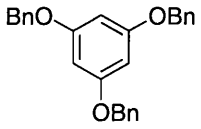
The conjugate addition to sulfone **359** is potentially the most interesting route (**Scheme 4.44**). If the problems encountered during scale-up could be overcome then this would be a novel approach to the 1,3-diarylpropene compounds. There is also the potential for the conjugate addition and subsequent olefination to be developed into a one-pot procedure. In addition to its application in the synthesis of (+)-catechin this chemistry could be applied to the synthesis of a variety of other interesting molecules.

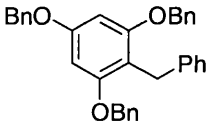
CHAPTER 5 - Experimental

General Considerations

THF and diethyl ether were freshly distilled from sodium/benzophenone. DCM, hexane, toluene, acetonitrile and triethylphosphite were distilled from calcium hydride prior to use. Pyridine was distilled from potassium hydroxide. DMF and triethylamine were distilled from calcium hydride and stored over 4 Å molecular sieves. The solid-phase reactions were carried out in normal glassware, but with the resin (particle size = 150-300 μm diameter) contained within porous polypropylene reactors that had an internal volume of 2.4 mL and a pore size of 74 μm. Reagents obtained from commercial suppliers were used without further purification. Purification by column chromatography was carried out on silica gel (particle size 70-230 mesh) or deactivated neutral alumina (particle size ~150 mesh) as stationary phase. TLC was carried out using Merck silica gel foil-backed plates (0.25 mm layer thickness) the plates were visualised by illumination with UV light, permanganate or DNP stains. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DPX/400 spectrometer operating at 400 and 100 MHz. Chemical shifts are relative to tetramethylsilane. The multiplicities of the ^{13}C nuclei were determined using the DEPT pulse sequence. The data reported for compounds **143**, **311**, **312**, **315**, **355**, **356**, **360**, **366** and **367** corresponds to all isomers present. Mass spectra were recorded on a Jeol JMS700 spectrometer. Microanalysis was carried out using a Carlo-Erba 1106 elemental analyser. IR spectra were recorded using a Nicolet Impact 410 FT-IR spectrometer.

1,3,5-tris(Benzyloxy)benzene 56 and 2-Benzyl-1,3,5-tris(benzyloxy)benzene 293





By the published procedure,[62] benzyl bromide (18.9 mL, 158.6 mmol, 4 eq) was added to a solution of phloroglucinol **100** (5.00 g, 39.7 mmol, 1 eq) and potassium carbonate (23.6 g, 170.5 mmol, 4.3 eq) in DMF (65 mL) and the mixture was stirred at room temp. for 48 h. The reaction mixture was poured into ice-water (100 mL), the

aqueous layer was decanted and the oily residue extracted into EtOAc (100 mL). The organics were washed with brine (20 mL) and concentrated under reduced pressure to give the title mixture (15.09 g) as a yellow oil that crystallised on standing. Purification by column chromatography [silica, eluting petroleum ether (60 – 80 °C)/toluene (2:3)] gave the pure title compound[62] **56** (2.69 g, 17.1 %) as a white powder. ^{1}H and ^{13}C NMR and melting point for **56** in agreement with published data.

δ_H (400 MHz; $CDCl_3$)

4.98 (s, 6H, 3 x -OC*H*$_2$), 6.26 (s, 3H, *H*-2, 4, 6), 7.29-7.41 (m, 15 H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

70.06 (CH_2), 94.87 (CH), 127.54 (CH), 127.97 (CH), 128.55 (CH), 136.78 (C), 161.09 (C).

MS *m/z* (EI^+) 396.1 ($M^{+\cdot}$, 25 %), 91.1 (100), 18.0 (12); $C_{27}H_{24}O_3$ calculated 396.1725, observed 396.1729.

Microanalysis $C_{27}H_{24}O_3$ requires C 81.79 %, H 6.10 % found C 81.67 %, H 6.15 %.

IR ν_{max} (golden gate) 2931 (CH_2), 2868 (CH_2), 1610 (aromatics), 1593 (aromatics), 1496 (aromatics), 739 (aromatics).

mp = 95.8 – 96 °C [lit.[62] 93 – 94 °C (EtOAc/EtOH)].

R_f = 0.28 [silica, petroleum ether (40 – 60 °C):toluene (2:3)].

293[126] (2.20 g, 11.4 %) was also isolated as a white powder.

δ_H (400 MHz; $CDCl_3$)

4.04 (s, 2H, ArC*H*$_2$), 4.96 (s, 2H, -OC*H*$_2$), 4.99 (s, 4H, 2 x –OC*H*$_2$), 6.28 (s, 2H, *H*-4 + *H*-6), 7.10-7.40 (m, 20H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

28.74 (CH_2), 70.19 (CH_2), 93.09 (CH), 111.49 (C), 125.22 (CH), 127.22 (CH), 127.54 (CH), 127.70 (CH), 127.88 (CH), 127.99 (CH), 128.40 (CH), 128.58 (CH), 128.69 (CH), 136.91 (C), 137.09 (C), 142.23 (C), 157.88 (C), 158.65 (C).

MS *m/z* (EI^+) 486.2 ($M^{+\cdot}$, 25 %), 91.1 (100); $C_{34}H_{30}O_3$ calculated 486.2195, observed 486.2192.

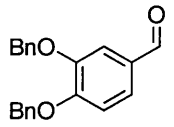
Microanalysis $C_{34}H_{30}O_3$ requires C 83.92 %, H 6.21 % found C 83.91 %, H 6.31 %.

IR ν_{max} (golden gate) 2922 (CH_2), 2866 (CH_2), 1601 (aromatics), 1496 (aromatics), 754 (aromatics), 729 (aromatics).

mp = 100.3 – 100.5 °C [lit.[126] 101 – 103 °C (EtOH)].

R_f = 0.34 [silica, petroleum ether (40 – 60 °C):toluene (2:3)].

3,4-bis(Benzyloxy)benzaldehyde 90



Benzyl bromide (69.6 mL, 586.4 mmol, 3 eq) was added to a stirring solution of 3,4-dihydroxybenzaldehyde **103** (27.0 g, 195.5 mmol, 1 eq), potassium carbonate (81.1 g, 586.4 mmol, 3 eq) and potassium iodide (3.25 g, 19.6 mmol, 0.1 eq) in DMF (350 mL). The resulting mixture was heated to reflux for 5 d, allowed to cool then filtered. The filtrate was diluted with Et_2O (1250 mL) and washed with water (3 x 700 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde[127] (57.7 g, 92.7 %) as a pale yellow oil that crystallised on standing. Recrystallisation from EtOAc/hexane gave the pure aldehyde (37.9 g, 60.8 %) as a light yellow/brown solid.

Alternative procedure:

IBX (1.85 g, 6.63 mmol, 3 eq), was added to a solution of alcohol **289** (707.7 mg, 2.21 mmol, 1 eq) in EtOAc (15 mL) at room temp. The mixture was heated to reflux for 6 h then cooled to room temp. and filtered. The filtered solid was washed with EtOAc (30 mL) and the filtrate was concentrated under reduced pressure to give the crude aldehyde (475.8 mg, 95.8 %) as an amorphous solid.

δ_H (400 MHz; $CDCl_3$)

5.18 (s, 2H, -OC*H*$_2$Ph), 5.21 (s, 2H, -OC*H*$_2$Ph), 6.99 (d, 1H, J = 8.2 Hz, *H*-5), 7.27-7.47 (m, 12H, Ar-*H*), 9.77 (s, 1H, -C*H*O).

δ_C (100 MHz; $CDCl_3$)

70.70 (CH_2), 70.85 (CH_2), 112.26 (CH), 112.98 (CH), 126.57 (CH), 126.97 (CH), 127.21 (CH), 127.91 (CH), 128.00 (CH), 128.47 (CH), 128.55 (CH), 130.20 (C), 136.14 (C), 136.46 (C), 149.08 (C), 154.15 (C), 190.69 (CH).

MS *m/z* (EI^+) 318.2 ($M^{+\cdot}$, 55 %), 227.1 (59), 181.2 (27), 91.1 (100), 65.1 (27); $C_{21}H_{18}O_3$ calculated 318.1256, observed 318. 1255.

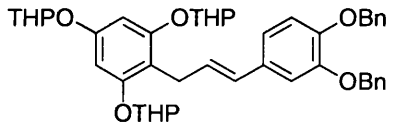
Microanalysis $C_{21}H_{18}O_3$ requires C 79.23 %, H 5.70 %, found C 79.03 %, H 5.59 %.

mp = 85 – 86 °C (lit.[127] 91 °C, EtOH).

IR ν_{max} (golden gate) 2819 (CH_2), 1674 (CHO), 1597 (aromatics), 1581 (aromatics), 1510 (aromatics).

R_f = 0.40 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

1-[3',4'-bis(Benzyloxy)phenyl]-3-[2'',4'',6''-tris(tetrahydropyranyloxy)phenyl]propene 143



Grubbs' 2nd generation catalyst **47** (108.6 mg, 0.13 mmol, 0.057 eq) was added to a solution of acetal **312** (1.87 g, 4.47 mmol, 2 eq) and styrene **288** (707.5 mg, 2.24 mmol, 1 eq) in DCM (22.5 mL) at room temp. under argon. The resulting solution was heated to reflux for 5 d then Grubbs' 2nd generation catalyst (108.6 mg, 0.057 eq) was added and heating continued for a further 2 d. Grubbs' 2nd generation catalyst **47** (54.3 mg, 0.029 eq) was added and heating continued for a further 17 h. The reaction mixture was allowed to cool and filtered through a pad of deactivated alumina eluting Et_2O/hexane (1:1). The precipitated styrene dimer **313** was filtered and the filtrate was concentrated under reduced pressure to give the crude *E-alkene* (1.71 g) as a dark green/brown gum. Purification by column chromatography [alumina deactivated with 6 % water, eluting with hexane/Et_2O (3:1)] gave the *title compound* (706.0 mg, 44.7 %) as a pale yellow foam.

δ_H (400 MHz; $CDCl_3$)

1.50-1.60 (m, 9H, -C*H*$_2$), 1.75-1.78 (m, 6H, -C*H*$_2$), 1.88-1.99 (m, 3H, -C*H*$_2$), 3.45 (d, 2H, J = 6.6 Hz, ArC*H*$_2$), 3.49-3.53 (m, 2H, -OC*H*$_2$), 3.77-3.88 (m, 2H, -OC*H*$_2$), 5.05 (s, 4H, 2 x –OC*H*$_2$Ph), 5.30-5.35 (m, 3H, -OC*H*O), 6.05 (td, 1H, J = 6.6 Hz, 15.7 Hz, ArCH=C*H*), 6.23 (d, 1H, J = 15.7 Hz, ArC*H*=CH), 6.48 (s, 2H, Ar-*H*, minor B), 6.50 (s, 2H, Ar-*H*, major A), 6.53 (s, 2H, Ar-*H*, minor C), 6.71-6.77 (m, 2H, Ar-*H*), 6.86 (s, 1H, Ar-*H*), 7.19 –7.29 (m, 6H, Ar-*H*), 7.34-7.37 (m, 4H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

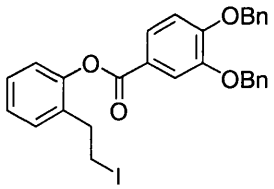
18.74 (CH_2), 18.75 (CH_2), 18.81 (CH_2), 25.23 (CH_2), 25.28 (CH_2), 26.92 (CH_2), 30.33 (CH_2), 30.42 (CH_2), 30.47 (CH_2), 61.74 (CH_2), 62.02 (CH_2), 71.34 (CH_2), 71.41 (CH_2), 96.01 (CH), 96.21 (CH), 96.30 (CH), 96.57 (CH), 96.78 (CH), 97.63 (CH), 111.49 (C), 112.53 (CH), 115.20 (CH), 119.40 (CH), 127.29 (CH), 127.71 (CH), 128.29 (CH), 128.41 (CH), 128.87 (CH), 132.22 (C), 137.39 (C), 147.96 (C), 149.02 (C), 155.78 (C), 155.96 (C), 156.75 (C).

MS *m/z* (FAB$^+$) 729.6 [(M+Na)$^+$, 5 %], 329.2 (45), 176.1 (100), 85.6 (37), 56.0 (20); $C_{44}H_{50}O_8Na$ calculated 729.3403, observed 729.3405.

IR ν_{max} (neat) 2943 (CH_2), 2873 (CH_2), 2853 (CH_2), 1606 (aromatics), 1510 (aromatics), 1493 (aromatics), 953 (alkene).

R_f = 0.19 [alumina, hexane:Et_2O (2:1)].

2-(2'-Iodoethyl)phenyl 3'',4''-dibenzyloxybenzoate 205



Acid **146** (2.39 g, 7.15 mmol, 1.1 eq), was added to a solution of iodide **259** (1.61 g, 6.50 mmol, 1 eq), EDCI (1.75 g, 9.11 mmol, 1.4 eq) and DMAP (79.4 mg, 0.65 mmol, 0.1 eq) in DCM (10 mL) at room temp. under nitrogen. The solution was stirred at room temp. for 24 h then diluted with DCM (50 mL), washed with saturated sodium bicarbonate (3 x 150 mL), water (2 x 150 mL) brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *ester* (2.15 g, 58.6 %) as a yellow/orange oil that crystallised on standing. Recyrstallisation from *i*-PrOH gave an

off-white amorphous solid that was filtered and washed with hexane to give the *ester* (937.9 mg, 25.6 %).

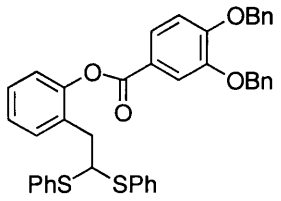
δ_H (400 MHz; $CDCl_3$)

3.30 (t, 2H, J = 7.7 Hz, ArCH_2), 3.21 (t, 2H, J = 7.7 Hz, -CH_2CH_2I), 5.15 (s, 2H, -OCH_2Ph), 5.17 (s, 2H, -OCH_2Ph), 6.92 (d, 1H, J = 8.5 Hz, *H*-3''), 7.06-7.40 (m, 14H, Ar-*H*), 7.68 (d, 1H, J = 1.9 Hz, *H*-6''), 7.72 (dd, 1H, J = 2.0 Hz, 8.4 Hz, *H*-2'').

δ_C (100 MHz; $CDCl_3$)

3.74 (CH_2), 34.93 (CH_2), 70.78 (CH_2), 71.19 (CH_2), 113.26 (CH)115.70 (CH), 121.72 (C), 122.77 (CH), 124.75 (CH), 126.11 (CH), 127.06 (CH), 127.31 (CH), 127.95 (CH), 128.02 (CH), 128.15 (CH), 128.52 (CH), 128.59 (CH), 130.24 (CH), 132.51 (C), 136.31 (C), 136.63 (C), 148.46 (C), 149.06 (C), 153.60 (C), 164.51 (C).

2-[2',2'-bis(Phenylsulfanyl)ethyl]phenyl 3'',4''-dibenzyloxybenzoate 208



3,4-Dibenzyloxybenzoic acid **146** (488 mg, 1.46 mmol, 1.1 eq) was added to a stirring solution of thioacetal **237** (450 mg, 1.33 mmol, 1 eq), EDCI (356 mg, 1.86 mmol, 1.4 eq) and DMAP (16 mg, 0.13 mmol, 0.1 eq) in dry DCM (2.26 mL) under nitrogen. The solution was stirred at room temp. for 24 h after which DCM (50 mL) was added and the organics washed with saturated bicarbonate (75 mL), water (2 x 75 mL) and brine (75 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* (596.6 mg, 68.6 %) as an off white amorphous solid. Chromatography on silica eluting petroleum ether (40 - 60 °C):EtOAc (4:1), followed by recrystallisation from *i*-PrOH gave the pure *ester* (400 mg, 46.0 %) as an off white amorphous powder.

δ_H (400 MHz; $CDCl_3$).

3.14 (d, 2H, J = 7.6 Hz, ArC*H*$_2$CH), 4.62 (t, 1H, J = 7.6 Hz, ArCH$_2$C*H*), 5.19 (s, 2H, PhC*H*$_2$), 5.29 (s, 2H, PhC*H*$_2$), 6.97 (d, 1H, J = 8.4 Hz, *H*-5''), 7.70-7.49 (m, 24H, Ar-*H*), 7.69 (dd, 1H, J = 1.9 Hz, 8.4 Hz, *H*-6''), 7.72 (d, 1H, J = 1.9 Hz, *H*-2'').

δ_C (100 MHz; $CDCl_3$)

37.54 (CH_2), 58.75 (CH), 70.80 (CH_2), 71.14 (CH_2), 113.29 (CH), 115.73 (CH), 121.90 (C), 122.54 (CH), 124.80 (CH), 125.81 (CH), 127.06 (CH), 127.42 (CH), 127.68 (CH), 128.01 (CH), 128.09 (CH), 128.19 (CH), 128.56 (CH), 128.66 (CH), 128.73 (CH), 130.25 (C), 131.73 (CH), 132.88 (CH), 133.94 (C), 136.43 (C), 136.65 (C), 148.47 (C), 149.54 (C), 153.43 (C), 164.52 (C).

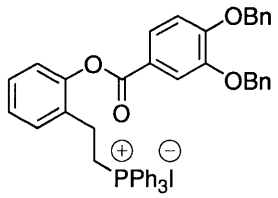
MS *m/z* (FAB$^+$) 677.5 [(M+Na)$^+$, 14 %], 427.4 (22), 317.3 (100), 225.1 (12), 176.1 (23), 154.1 (25), 91.5 (73); $C_{41}H_{34}S_2O_4Na$ calculated 654.1899, observed 654.1902

m.p = 81 - 82 °C.

IR ν_{max} KBr/cm^{-1} 1732 (C=O), 1597 (aromatics), 1508 (aromatics), 1491 (aromatics), 758 (aromatics).

R_f = 0.76 [silica, petroleum ether (40 - 60 °C):EtOAc (4:1)].

2-[2'-(Triphenylphosphonium iodide)ethyl]phenyl 3'',4''-dibenzyloxybenzoate 210



Acid **146** (756.0 mg, 2.26 mmol, 1.1 eq) was added to a stirring solution of salt **262** (1.00 g, 2.06 mmol, 1 eq), EDCI (552.0 mg, 2.88 mmol, 1.4 eq) and DMAP (25.0 mg, 0.21 mmol, 0.1 eq) in dry DCM (3.5 mL) at room temp. under argon. The solution was stirred for 24 h, diluted with DCM (100 mL), washed with saturated sodium bicarbonate (2 x 100 mL), water (2 x 100 mL), brine (2 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *ester* (1.24 g, 75.0 %) as an off white powder. A sample was recrystallised from EtOH for analysis.

δ_H (400 MHz; $CDCl_3$)

2.86-2.92 (m, 2H, ArCH_2), 3.81-3.88 (m, 2H, -CH_2P), 5.21 (s, 2H, -OCH_2), 5.36 (s, 2H, -OCH_2), 6.97-6.99 (m, 1H, Ar-*H*), 7.03 (d, 1H, J = 8.3 Hz, *H*-5''), 7.25-7.73 (m, 23H, Ar-*H*), 7.67-7.73 (m, 6H, Ar-*H*), 7.87-7.88 (m, 1H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

22.36 (CH_2), 23.91 (d, J = 48.2 Hz, CH_2), 70.73 (CH_2), 71.19 (CH_2), 113.36 (CH), 115.78 (CH), 117.32 (d, J = 86.2 Hz, C), 121.14 (C), 122.22 (CH), 124.93 (CH), 127.13 (CH), 127.36 (CH), 128.04 (CH), 128.20 (CH), 128.56 (CH), 128.70 (CH), 130.06 (CH), 130.22 (CH), 130.38 (d, J = 12.7 Hz, CH), 131.71 (CH), 133.57 (d, J = 10.0 Hz, CH), 135.01 (d, J = 3.1 Hz, CH), 136.27 (C), 136.53 (C), 148.38 (C), 148.52 (C), 153.61 (C), 164.83 (C).

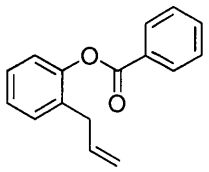
MS *m/z* (FAB$^+$) 699.6 [(M-I)$^+$, 100 %), 608.5 (16), 607.5 (15), 489.4 (12), 289.3 (13), 262.2 (41), 183.1 (16), 91.5 (37); $C_{47}H_{40}O_4P$ calculated 699.2664, observed 699.2664

Microanalysis $C_{47}H_{40}O_4PI$ requires C 68.29 %, H 4.88 %, I 15.35 %, found C 68.26 %, H 4.78 %, I 15.44 %.

IR ν_{max} (golden gate) 2920 (CH_2), 2864 (CH_2), 1728 (ester), 1597 (aromatics), 1583 (aromatics), 1506 (aromatics), 1437 (P-Ph), 739 (aromatics).

mp = 170 °C (dec.).

2'-[(Allyl)phenyl]benzoate 229

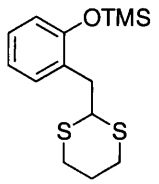


Benzoyl chloride (19.1 mL, 164.0 mmol, 1.1 eq) was added slowly to a stirring solution of 2-allylphenol **151** (20.0 g, 149.1 mmol, 1 eq) in a 50:50 mixture of DCM:pyridine (140 mL) at room temp. under nitrogen. The mixture was stirred at room temp. for 5 h then extracted into EtOAc (400 mL), washed with 1 M HCl (200 mL), saturated sodium bicarbonate (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude ester (34.2 g, 96.3 %) as an orange oil.

δ_H (400 MHz; $CDCl_3$)

3.36 (d, 2H, J = 6.6 Hz, ArCH_2), 4.99 (dd, 1H, J = 1.6 Hz, 10.2 Hz, -CH=CH_{cis}H), 5.03-5.05 (m, 1H, -CH=CH_{trans}H), 5.92 (tdd, 1H, J = 6.6 Hz, 10.3 Hz, 16.8 Hz, -C*H*=CH_2), 7.17 (dd, 1H, J = 1.7 Hz, 7.8 Hz, *H*-6), 7.24 (dd, 1H, J = 1.7 Hz, 7.0 Hz, *H*-3), 7.29 (dt, 2H, J = 2.0 Hz, 7.6 Hz, *H*-4 + *H*-5), 7.51 (dt, 2H, J = 1.6 Hz, 7.7 Hz, Ar-*H*), 7.64 (t, 1H, J = 7.4 Hz, *H*-), 8.20-8.22 (m, 2H, Ar-*H*).

2-(2'-Trimethylsilyloxybenzyl)-1,3-dithiane 235



Chlorotrimethylsilane (3.22 mL, 25.4 mmol, 2 eq) was added dropwise to a stirring solution of **238** (2.88 g, 12.7 mmol, 1 eq) in dry pyridine (50 mL) at room temp. under argon. Stirring was continued for 17 h before extracting into ether (500 mL). The organics were washed with water (2 x 400 mL), 0.5 M copper sulfate solution (2 x 500 mL), water (2 x 400 mL), brine (400 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* (3.35 g, 88.4 %). No further purification was required.

δ_H (400 MHz; $CDCl_3$)

0.31 (s, 9H, -SiCH_3), 1.83-1.90 (m, 1H, -SCH_2C*H*H), 2.07-2.13 (m, 1H, -SCH_2CH*H*), 2.81-2.83 (m, 4H,-SCH_2CH_2), 3.00 (d, 2H, J = 7.4 Hz, Ar-CH_2), 4.33 (t, 1H, J = 7.4 Hz, ArCH_2C*H*), 6.80 (dd, 1H, J = 1.0 Hz, 8.0 Hz, *H*-3'), 6.90 (dt, 1H, J = 1.1 Hz, 7.4 Hz, *H*-5'), 7.14 (dt, 1H, J = 1.8 Hz, 7.7 Hz, *H*-4'), 7.19 (dd, 1H, 1.7 Hz, 7.5 Hz, *H*-6').

δ_C (100 MHz; $CDCl_3$)

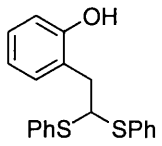
0.52 (CH_3), 25.87 (CH_2), 30.36 (CH_2), 36.79 (CH_2), 47.08 (CH), 118.56 (CH), 120.93 (CH), 128.06 (CH), 128.13 (C), 131.24 (CH), 154.60 (C).

MS *m/z* (EI^+) 298.1 ($M^{+\cdot}$, 13 %), 119.0 (100), 73.0 (13); $C_{14}H_{22}OS_2Si$ calculated 298.0881, observed 298.0880.

Microanalysis $C_{14}H_{22}OS_2Si$ requires C 56.18 %, H 7.41 %, S 21.69 %, found C 56.31 %, H 7.41 %, S 21.43 %.

IR ν_{max} (neat) 2954 (CH_2), 2898 (CH_2), 1601 (aromatics), 1583 (aromatics), 1491 (aromatics), 1431 (CH_2), 1188 [$Si(CH_3)_3$], 1101 (Si-O), 756 (aromatics).

2-[2', 2'-bis(Phenylsulfanyl)ethyl]phenol 237



Boron trifluoride diethyletherate (0.22 mL, 1.69 mmol, 1 eq) was added to a stirring solution of benzofuran **239** (200 mg, 1.69 mmol, 1 eq), thiophenol (0.36 mL, 3.38 mmol, 2 eq) and trifluoroacetic acid (0.13 mL, 1.69 mmol, 1 eq) in DCM (1.7 mL) at room temp. under nitrogen. The solution was stirred for 26 h then quenched with saturated aqueous bicarbonate (4 mL). The mixture was extracted with EtOAc (10 mL), which was then washed with saturated aqueous bicarbonate (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude mixture (251.2 mg) as an orange oil. ^1H NMR of the mixture showed essentially no desired product.

Alternative procedure:

Ozone (oxygen flow = 70, voltage = 120) was bubbled through a solution of 2-allylphenol **151** (1.00 g, 7.45 mmol, 1 eq) in DCM (37.2 mL) at –78 °C until all of the phenol was consumed (tlc – approximately 2.5 h). Oxygen was bubbled through the solution for 30 min while being allowed to warm to 0 °C. Triphenylphosphine (2.93 g, 11.2 mmol, 1.5 eq) was added and the solution was stirred at 0 °C for 30 min after which a vacuum was applied at 0 °C for 5 min to remove formaldehyde. Thiophenol (1.68 mL, 16.4 mmol, 2.2 eq) and freshly prepared $MgBr_2.OEt_2$ (2 M in Et_2O, 4.81 g, 18.6 mmol, 2.5 eq) were added, the ice-bath was removed and the solution was stirred at room temp. for 19 h. The reaction mixture was quenched with saturated bicarbonate (75 mL) and extracted into EtOAc (150 mL). The aqueous layer was re-extracted with EtOAc (75 mL) and the combined organics were washed with bicarbonate (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *thioacetal* as a brown oil. Purification by column chromatography [silica, eluting petroleum

ether (40 – 60 °C):EtOAc (4:1)] gave the pure *thioacetal* (720 mg, 28.5 %) as a clear colourless glass.

δ_H (400 MHz; $CDCl_3$)

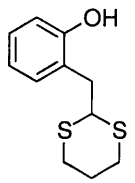
3.22 (d, 2H, J = 7.0 Hz, ArC*H*$_2$), 4.74 (t, 1H, J = 7.0 Hz, PhSC*H*SPh), 5.25 (s, 1H, -O*H*), 6.76 (d, 1H, J = 8.0 Hz, *H*-6), 6.87 (dt, 1H, J = 1.0 Hz, 7.5 Hz, *H*-4), 7.09-7.15 (m, 2H, *H*-3, *H*-5), 7.20-7.29 (m, 6H, Ar-*H*), 7.36-7.39 (m, 4H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

38.04 (CH_2), 58.52 (CH), 116.13 (CH), 120.96 (CH), 124.61 (C), 127.70 (CH), 128.50 (CH), 128.95 (CH), 132.00 (CH), 132.61 (CH), 134.33 (C), 154.03 (C).

MS *m/z* (EI^+) 229.1 ($M^{+\cdot}$, 44 %), 228.1 (20), 135.1 (100), 118.1 (52), 110.1 (46), 91.1 (44), 65.1 (12), 32.0 (11); $C_{20}H_{22}S_2O$ calculated 338.0799, observed 338.0796.

2-(2'-Hydroxybenzyl)-1,3-dithiane 238



Boron trifluoride diethyletherate (0.22 mL, 1.69 mmol, 1 eq) was added to a stirring solution of benzofuran **239** (200 mg, 1.69 mmol, 1 eq), 1,3-propanedithiol (0.17 mL, 1.69 mmol, 1 eq) and trifluoroacetic acid (0.13 mL, 1.69 mmol, 1 eq) at room temp. under nitrogen. The solution was stirred for 24 h then diluted with DCM (10 mL). The solution was washed with saturated aqueous bicarbonate (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude mixture (101.4 mg) as a yellow oil. ^{1}H NMR of the mixture showed essentially no desired product.

Alternative procedure:

Trifluoroacetic acid (18.8 mL, 247.0 mmol, 6 eq) was added dropwise to a suspension of alcohol **249** (10.00 g, 41.2 mmol, 1 eq) in triethylsilane (26.2 mL, 164.6 mmol, 4 eq) at –10 °C. The reaction was stirred at this temp. for 1 h, diluted with DCM (500 mL), washed with water (400 mL), brine (2 x 300 mL), dried ($MgSO_4$) and

concentrated under reduced pressure to give the crude *title compound* (10.04 g). Purification by column chromatography on silica eluting DCM gave the *thioacetal* (2.88 g, 30.8 %) as a white amorphous solid.

δ_H (400 MHz; $CDCl_3$)

1.79-1.94 (m, 1H,), 2.03-2.12 (m, 1H,), 2.81-2.84 (m, 4H,), 3.09 (d, 2H, J = 7.4 Hz, Ar-C*H*$_2$), 4.38 (t, 1H, J = 7.4 Hz, $ArCH_2CH$), 6.76 (d, 1H, J = 8.0 Hz, *H*-3'), 6.87 (t, 1H, J = 7.4 Hz, *H*-5'), 7.10-7.22 (m, 2H, *H*-4' + *H*-6').

δ_C (100 MHz; $CDCl_3$)

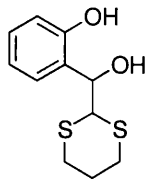
25.61 (CH_2), 30.03 (CH_2), 36.43 (CH_2), 46.69 (CH), 115.65 (CH), 120.55 (CH), 123.92 (C), 128.30 (CH), 131.47 (CH), 153.69 (C).

MS *m/z* (EI^+) 226.0 ($M^{+\cdot}$, 60 %), 119.0 (100), 91.1 (41), 77.0 (27), 75.0 (17), 45.0 (22); $C_{11}H_{14}OS_2$ calculated 226.0486, observed 226.0485.

Microanalysis $C_{11}H_{14}OS_2$ requires C 58.37%, H 6.23 %, S 28.33 %, found C 58.49%, H 6.24 %, S 28.43 %.

mp = 117 – 118 °C.

(α, 2'-dihydroxybenzyl)-1,3-dithiane 249



n-Butyllithium (2.5 M in hexanes, 100.0 mL, 250.0 mmol, 2.1 eq), was added dropwise to a solution of 1,3-dithiane **247** (30.06 g, 250.0 mmol, 2.1 eq) in THF (300 mL) at 0 °C under argon. The solution was allowed to warm to room temp. and stirred for 1 h then cooled to –78 °C and salicylaldehyde **248** (12.70 mL, 119.05 mmol, 1 eq) was added slowly. The resulting yellow solution was allowed to warm to room temp. over 2 h, diluted with DCM (500 mL), washed with 10 % sodium bisulfite (2 x 500 mL) and 2 M KOH (2 x 400 mL). The aqueous layer was extracted with DCM (2 x 500 mL), acidified with 2 M HCl, extracted into DCM (2 x 500 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the *thioacetal* (26.18 g, 90.8 %) as a

yellow solid. Recrystallisation from *i*-PrOH gave the pure *thioacetal* (24.1 g, 83.5 %) as off-white fine needles.

δ_H (400 MHz; $CDCl_3$)

1.98-2.13 (m, 2H, -C*H*$_2$), 2.67-2.73 (m, 2H, -C*H*$_2$), 2.96-3.02 (m, 2H, -C*H*$_2$), 3.80 (br s, 1H, ArCH-O*H*), 4.14 (d, 1H, J = 8.7 Hz, -SC*H*S), 5.04 (d, 1H, J = 8.7 Hz, ArC*H*-OH), 6.85-6.89 (m, 2H, *H*-3' + *H*-5'), 7.12 (dd, 1H, J = 1.6 Hz, 8.0 Hz, *H*-6'), 7.22 (dt, 1H, J = 1.6 Hz, 7.7 Hz, *H*-4'), 7.64 (br s, 1H, Ar-O*H*).

δ_C (100 MHz; $CDCl_3$)

25.00 (CH_2), 26.42 (CH_2), 27.11 (CH_2), 49.87 (CH), 74.97 (CH), 117.40 (CH), 119.59 (CH), 123.02 (C), 129.52 (CH), 129.73 (CH), 155.35 (C).

MS *m/z* (EI^+) 242.1 ($M^{+\cdot}$, 0.8 %), 119.0 (100), 77.1 (11); $C_{11}H_{14}O_2S_2$ calculated 242.0435, observed 242.0434.

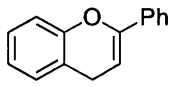
Microanalysis $C_{11}H_{14}O_2S_2$ requires C 54.51 %, H 5.82 %, S 26.46 %, found C 54.53 %, H 5.83 %, S 26.63 %.

IR ν_{max} (golden gate) 3491 (OH), 3182 (OH), 2958 (CH_2), 2931 (CH_2), 2889 (CH_2), 1597 (aromatics), 1504 (aromatics).

mp = 139.8 – 140.1 °C.

R_f = 0.14 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

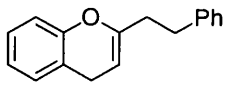
2-Phenyl-4H-chromene 203a



Titanocene dichloride (956.1 mg, 3.84 mmol, 4 eq), magnesium turnings (102.6 mg, 4.22 mmol, 1.1 eq), and 4Å molecular sieves (200 mg) were warmed with stirring under vacuum. The mixture was allowed to cool under vacuum and flushed with argon. Triethylphosphite (1.38 mL, 8.06 mmol, 2.1 eq) and dry THF (5 mL) were added and stirring was continued for 3 h. A solution of thioacetal **235** (287.4 mg, 0.96 mmol, 1 eq) in dry THF (4 mL) was added and the mixture was stirred for a further 15 min before being syringed into a flask containing the Merrifield resin bound benzoate ester **251a** (0.311 mequiv/reactor prepared from 170 mg of commercial Merrifield resin with a loading of 1.83 mequiv (of benzylic chloride)/g) in 2 porous

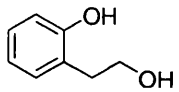
polypropylene reactors in dry THF (6 mL) under argon. The mixture was stirred overnight at room temp. and the reactors were washed with THF (x 4), alternate MeOH/DCM (x 4), ether and dried under vacuum. A 1 % solution of TFA in DCM (5 mL) was added to each reactor, followed by shaking for 30 min. Concentration under reduced pressure, gave the crude mixture (6.5 mg) as a solid. Spectral data showed no product.[128]

2-Phenylethyl-4H-chromene 203b



Procedure as above gave the crude mixture (13.8 mg) as a brown solid. Spectral data indicated at least 4 compounds. Purification was unsuccessful.

2'-(Hydroxy)-2-phenylethyl alcohol 258

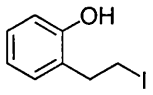


Ozone (oxygen flow = 70, voltage = 120) was bubbled through a solution of **151** (3.50 g, 37.3 mmol, 1 eq) in EtOH (140 mL) at –78 °C until all starting material had been consumed (tlc, approx. 7 h). Oxygen was bubbled through the solution for 10 min and $NaBH_4$ (2.82 g, 74.5 mmol, 2 eq) was added. The solution was stirred at room temp. overnight then acidified to pH 3 with 2 M HCl and extracted into DCM (2 x 250 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the alcohol (3.43 g, 95.3 %) as a colourless oil. ^{1}H NMR in agreement with published data.

δ_H (400 MHz; $CDCl_3$)

2.90 (t, 2H, J = 5.3 Hz, ArCH_2), 3.99 (t, 2H, J = 5.3 Hz, -CH_2CH_2OH), 6.86 (dt, 1H, J = 1.1 Hz, 7.4 Hz, *H*-4), 6.91 (dd, 1H, J = 0.9 Hz, 8.0 Hz, *H*-6), 7.06 (dd, 1H, J = 1.6 Hz, 7.5Hz, *H*-3), 7.15 (dt, 1H, J = 1.6 Hz, 7.7 Hz, *H*-5).

2-(2'-Hydroxyphenyl)ethyl iodide 259



Triphenylphosphine (23.46 g, 89.5 mmol, 1.2 eq), imidazole (6.09 g, 89.5 mmol, 1.2 eq) and iodine (22.71 g, 89.5 mmol, 1.2 eq) were added in that order to a stirring solution of alcohol **258** (10.30 g, 74.6 mmol, 1 eq) in dry DCM (340 mL) at room temp., under argon. After 18 h, the mixture was washed with water (200 mL), 10 % aqueous sodium thiosulfate solution (2 x 150 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *iodide* as a yellow solid. Purification by column chromatography [silica, eluting petroleum ether (40 – 60 °C):EtOAc (2:1)] gave the pure iodide (14.30 g, 77.3 %) as a white amorphous solid pure enough for the next step. A sample was recrystallised from hexane for analysis.

δ_H (400 MHz; $CDCl_3$)

3.21 (t, 2H, J = 7.7 Hz, ArC*H*$_2$), 3.40 (t, 2H, J = 7.8 Hz, -C*H*$_2$I), 4.75 (s, 1H, -O*H*), 6.73 (dd, 1H, J = 0.7 Hz, 7.9 Hz, *H*-3'), 6.89 (dt, 1H, J = 1. 0 Hz, 7.5 Hz, *H*-5'), 7.11-7.17 (m, 2H, *H*-4' + *H*-6').

δ_C (100 MHz; $CDCl_3$)

4.77 (CH_2), 35.14 (CH_2), 115.47 (CH), 121.03 (CH), 127.09 (C), 128.21 (CH), 130.66 (CH), 153.29 (C).

MS *m/z* (EI^+) 248.0 ($M^{+\cdot}$, 22 %), 121.1 (100), 103.1 (22), 91.1 (17), 77.1 (17); C_8H_9OI calculated 247.9698, observed 247.9698.

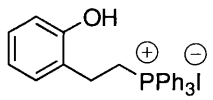
Microanalysis C_8H_9OI requires C 38.74 %, H 3.66 %, I 51.16 %, found C 38.73 %, H 3.65 %, I 51.24 %.

IR ν_{max} (neat) 3512 (OH), 2960 (CH_2), 2931 (CH_2), 2852 (CH_2), 1608 (aromatics), 1591 (aromatics), 1500 (aromatics), 752 (aromatics).

mp = 39 – 40 °C.

R_f = 0.55 [silica, petroleum ether (40 – 60 °C:EtOAc (2:1)].

2-(2'-Hydroxyphenyl)ethyl triphenylphosphonium iodide 262



Triphenylphosphine (2.36 g, 8.99 mmol, 1 eq) was added to a solution of iodide **259** (2.23 g, 8.99 mmol, 1 eq) in dry toluene (15.8 mL) at room temp. under nitrogen. The resulting mixture was heated to reflux for 16 h. The mixture was cooled to room temp. and the toluene was decanted. The remaining oil was washed with toluene and dried under vacuum to give the *phosphonium salt* (3.53 g, 80.8 %) as a white foam. No further purification was required.

δ_H (400 MHz; $CDCl_3$)

2.82-2.88 (m, 2H, ArCH_2), 3.41-3.48 (m, 2H, -CH_2P), 6.57 (dt, 1H, J = 0.8 Hz, 7.4 Hz, *H*-5'), 6.91-6.94 (m, 2H, *H*-3' + *H*-4'), 7.42 (d, 1H, J = 7.8 Hz, *H*-6'), 7.69-7.83 (m, 15H, Ar-*H*), 8.28 (br s, 1H, O*H*).

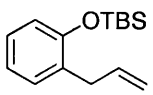
δ_C (100 MHz; $CDCl_3$)

22.72 (d, J = 47.9 Hz, CH_2), 24.78 (CH_2), 117.13 (CH), 117.73 (d, J = 85.6 Hz, C), 119.78 (CH), 124.32 (C), 128.70 (CH), 129.50 (CH), 130.60 (CH), 130.73 (CH), 133.45 (CH), 133.55 (CH), 135.25 (CH), 135.27 (CH), 154.95 (c).

MS *m/z* (EI^+) 382.1 [$(M-HI)^+$, 11 %), 305.1 (19), 262.1 (100), 261.1 (15), 183.0 (51), 108.0 (19), 91.1 (10); $C_{26}H_{23}OP$ calculated 382.1487, observed 382.1485.

IR ν_{max} (neat) 3209 (OH), 2877 (CH_2), 1589 (aromatics), 1500 (aromatics), 1437 (P-Ph), 733 (aromatics).

1-Allyl -2-(*tert*-butyldimethylsilyloxy)benzene 263



tert-Butyldimethylchlorosilane (6.18 g, 41.0 mmol, 1.1 eq) was added to a stirring solution of 2-allylphenol **151** (5.00 g, 37.3 mmol, 1 eq), DMAP (0.455 g, 3.73 mmol, 0.1 eq) and triethylamine (7.79 mL, 55.9 mmol, 1.5 eq) in dry DCM (110 mL). The

solution was stirred at room temp., under argon for 18 h and *tert*-butyldimethylchlorosilane (3.04 g, 0.54 eq) was added. The solution was left to stir at room temp. for a further 3.5 h at which point the solution was washed with brine (100 mL), water (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (10.62 g) as a green runny oil. Purification by column chromatography (silica, eluting pentane) gave the pure title compound[129] (8.00 g, 86.4 %) as a colourless runny oil. Spectral data similar to published data.[129]

δ_H (400 MHz; $CDCl_3$)

0.21 (s, 6H, -SiC*H*$_3$), 0.99 (s, 9H, -C(C*H*$_3$)$_3$), 3.35 (d, 2H, J = 6.5 Hz, Ar-C*H*$_2$), 4.99-5.03 (m, 2H, -CH=C*H*$_2$), 5.95 (tdd, 1H, J = 6.5 Hz, 9.4 Hz, 16.0 Hz, -C*H*=CH$_2$), 6.77 (d, 1H, J = 8.0 Hz, *H*-3), 6.86 (dt, 1H, J = 0.6 Hz, 7.4 Hz, *H*-5), 7.05 (dt, 1H, J = 1.7 Hz, 7.7 Hz, *H*-4), 7.11 (dd, 1H, J = 1.5 Hz, 7.5 Hz, *H*-6).

δ_C (100 MHz; $CDCl_3$)

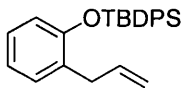
-4.15 (CH_3), 18.26 (C), 25.81 (CH_3), 34.44 (CH_2), 115.42 (CH_2), 118.41 (CH), 121.08 (CH), 127.03 (CH), 130.14 (CH), 130.68 (C), 137.05 (CH), 153.35 (C).

MS *m/z* (EI^+) 191.1 ($M^{+\cdot}$, 100 %), 163.1 (40), 149.0 (22), 147.1 (10), 86.0 (18), 84.0 (26), 73.1 (11); $C_{15}H_{24}OSi$ calculated 248.1596, observed 248.1957.

IR ν_{max} (neat) 3076 (C=CH_2), 2958 (CH_2), 2931 (CH_2), 1599 (aromatics), 1583 (aromatics), 1491 (aromatics), 1390 [$C(CH_3)_3$], 1362 [$C(CH_3)_3$], 1255 [$Si(CH_3)_2$], 1007 (Si-O), 839 [$Si(CH_3)_2$], 756 (aromatics).

R_f = 0.61 [silica, pentane].

1-Allyl -2-(*tert*-butyldiphenylsilyloxy)benzene 264



tert-Butyldiphenylchlorosilane (2.09 mL, 8.1 mmol, 1.08 eq) was added to a stirring solution of 2-allylphenol **151** (1.00 g, 7.5 mmol, 1 eq), DMAP (0.019 g, 0.8 mmol, 0.1 eq) and imidazole (0.548 g, 8.1 mmol, 1.08 eq) in dry DCM (14.9 mL) at room temp. under argon. The solution was stirred at room temp. for 3 d, diluted with DCM (50 mL), washed with brine (100 mL), water (100 mL), brine (100 mL), dried

($MgSO_4$) and concentrated under reduced pressure to give the crude mixture (3.81 g) as a colourless oil. Purification by filtration through a plug of silica eluting petroleum ether (40 – 60 °C), gave the pure silyl ether (2.04 g, 73.5 %) as a colourless oil.

δ_H (400 MHz; $CDCl_3$)

1.09 (s, 9H, -C(C*H*$_3$)$_3$), 3.58 (d, 2H, J = 6.4 Hz, ArC*H*$_2$), 5.08-5.13 (m, 2H, -CH=C*H*$_2$), 6.11 (tdd, 1H, J = 6.5 Hz, 9.9 Hz, 16.7 Hz, -C*H*=CH$_2$), 6.41 (dd, 1H, J = 1.3 Hz, 7.8 Hz, *H*-3), 6.77 (dt, 1H, J = 2.0 Hz, 7.6 Hz, *H*-4), 6.81 (dt, 1H, J = 1.3 Hz, 7.3 Hz, *H*-5), 7.15 (dd, 1H, J = 1.9 Hz, 7.3 Hz, *H*-6), 7.34-7.44 (m, 6H, Ar-*H*), 7.71 (dd, 4H, J = 1.4 Hz, 7.9 Hz, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

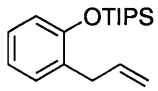
19.49 (C), 26.54 (CH_3), 34.69 (CH_2), 115.48 (CH_2), 118.77 (CH), 120.93 (CH), 126.79 (CH), 127.78 (CH), 129.86 (CH), 130.03 (CH), 132.73 (C), 135.41 (CH), 137.12 (CH), 153.13 (C).

MS *m/z* (EI$^+$) 315.1 (M$^{+\cdot}$, 100 %), 287.1 (22), 237.1 (100), 211.1 (69), 197.0 (31), 165.1 (25), 135.1 (10), 105.0 (26), 91.1 (37), 82.9 (17); $C_{25}H_{28}OSi$ calculated 372.1909, observed 372.1910.

IR ν_{max} (neat) 3072 (C=CH$_2$), 2958 (CH_2), 2931 (CH_2), 1599 (aromatics), 1583 (aromatics), 1491 (aromatics), 1390 [C(CH$_3$)$_3$], 1362 [C(CH$_3$)$_3$], 1043 (Si-O), 756 (aromatics), 702 (aromatics).

R_f = 0.16 [silica, petroleum ether (40 – 60 °C)].

1-Allyl -2-(triisopropylsilyloxy)benzene 265



By the published procedure,[104] triisopropylchlorosilane (2.39 mL, 11.2 mmol, 1.5 eq) was added to a stirring solution of 2-allylphenol **151** (1.00 g, 7.5 mmol, 1 eq), DMAP (0.091 g, 0.8 mmol, 0.1 eq) and triethylamine (1.46 mL, 11.2 mmol, 1.5 eq) in dry DCM (10 mL) at room temp. under argon. The solution was stirred at room temp. for 5 d, washed with brine (50 mL), water (50 mL), brine (50mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (2.57 g). Purification

by filtration through a plug of silica eluting petroleum ether (40 – 60 °C) gave the silyl ether[104] (1.94 g, 89.7 %) as a colourless oil. ^{1}H NMR data in agreement with published data.[104]

δ_H (400 MHz; $CDCl_3$)

1.11 (d, 18H, J = 7.3 Hz, -C*H*$_3$CH), 1.32 (sep, 3H, J = 7.5 Hz, CH$_3$C*H*), 3.41 (d, 2H, J = 6.4 Hz, ArC*H*$_2$), 5.04 (dd, 1H, J = 1.1 Hz, 10.2 Hz, -CH=C*H*$_{cis}$), 5.05 (dd, 1H, J = 1.5 Hz, 17.0 Hz, -CH=C*H*$_{trans}$), 5.99 (tdd, 1H, J = 6.6 Hz, 10.3 Hz, 16.8 Hz, -C*H*=CH$_2$), 6.79 (d, 1H, J = 8.1 Hz, *H*-3), 6.87 (t, 1H, J = 7.4 Hz, *H*-5), 7.06 (t, 1H, J = 7.7 Hz, *H*-4), 7.13 (d, 1H, J = 7.4 Hz, *H*-6).

δ_C (100 MHz; $CDCl_3$)

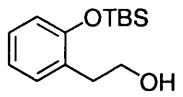
13.08 (CH), 18.08 (CH$_3$), 34.58 (CH$_2$), 115.35 (CH$_2$), 117.89 (CH), 120.71 (CH), 126.97 (CH), 130.03 (CH), 130.25 (C), 137.09 (CH), 153.70 (C).

MS *m/z* (EI$^+$) 290.2 (M$^{+\cdot}$, 34 %), 247.1 (62), 205.1 (100), 177.1 (98), 163.1 (40), 149.0 (49), 135.0 (16), 115.1 (13); $C_{18}H_{30}OSi$ calculated 290. 2066, observed 290.2065.

IR ν_{max} (neat) 3076 (C=CH$_2$), 2945 (CH$_2$), 2893 (CH), 2868 (CH$_2$), 1599 (aromatics), 1581 (aromatics), 1491 (aromatics), 1387 [C(CH$_3$)$_2$],1107 (Si-O), 754 (aromatics).

R_f = 0.39 [silica, petroleum ether (40 – 60 °C)].

2-[2'-(*tert*-Butyldimethylsilyloxy)phenyl]ethyl alcohol 266



Ozone (oxygen flow = 70, voltage = 120) was bubbled through a solution of **263** (11.0 g, 46.3 mmol, 1 eq) in EtOH (230 mL) at –78 °C until all starting material had been consumed (tlc). Oxygen was bubbled through the solution for 15 min and $NaBH_4$ (3.45 g, 92.6 mmol, 2 eq) was added. The solution was stirred at room temp. overnight then acidified to pH 3 with 2 M HCl and extracted into DCM (2 x 300 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the alcohol[130] (11.68 g, 100 %) as a colourless oil.

δ_H (400 MHz; $CDCl_3$)

0.25 (s, 6H, SiCH_3), 1.02 [s, 9H, -C(CH_3)$_3$], 2.88 (t, 2H, J = 6.5 Hz, -ArCH_2), 3.83 (t, 2H, J = 6.5 Hz, -CH_2OH), 6.81 (d, 1H, J = 8.0 Hz, *H*-3'), 6.90 (dt, 1H, J = 0.8 Hz, 7.4 Hz, *H*-5'), 7.11 (dt, 1H, J = 1.7 Hz, 7.7 Hz, *H*-4'), 7.17 (dd, 1H, J = 1.6 Hz, 7.4 Hz, *H*-6').

δ_C (100 MHz; $CDCl_3$)

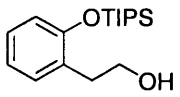
-4.15 (CH_3), 18.21 (C), 25.76 (CH_3), 34.30 (CH_2), 62.75 (CH_2), 118.52 (CH), 121.20 (CH), 127.55 (CH), 129.04 (C), 131.06 (CH), 153.86 (C).

MS *m/z* (CI^+) 253.2 [$(M+H)^+$, 100 %], 235.2 (33), 195.1 (18); $C_{14}H_{25}O_2Si$ calculated 253.1624, observed 253.1623.

IR ν_{max} (neat) 3350 (OH), 2956 (CH_2), 2931 (CH_2), 1601 (aromatics), 1581 (aromatics), 1493 (aromatics), 1390 [$C(CH_3)$], 1361 [$C(CH_3)$], 1255 [$Si(CH_3)_2$], 1009 (Si-O), 837 [$Si(CH_3)_2$], 737 (aromatics).

R_f = 0.38 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

2-[2'-(Triisopropylsilyloxy)phenyl]ethyl alcohol 267



Ozone (oxygen flow = 70, voltage = 120) was bubbled through a solution of **265** (5.00 g, 17.2 mmol, 1 eq) in EtOH (80 mL) at –78 °C until all starting material had been consumed (tlc). Oxygen was bubbled through the solution for 15 min and $NaBH_4$ (1.30 g, 34.4 mmol, 2 eq) was added. The solution was stirred at room temp. overnight then acidified to pH 3 with 2 M HCl and extracted into DCM (2 x 150 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the alcohol (4.96 g, 97.8 %) as a colourless oil.

δ_H (400 MHz; $CDCl_3$)

1.12 (d, 18H, J = 7.4 Hz, -CHCH_3), 1.27-1.36 (m, 3H, -C*H*CH_3), 2.92 (t, 2H, J = 6.6 Hz, ArCH_2), 3.85 (t, 2H, J = 6.6 Hz, -CH_2OH), 6.82 (d, 1H, J = 8.1 Hz, *H*-3'), 6.88 (dt, 1H, J = 1.1 Hz, 7.4 Hz, *H*-5'), 7.01 (dt, 1H, J = 1.8 Hz, 7.7 Hz, *H*-4'), 7.16 (dd, 1H, J = 1.7 Hz, 7.4 Hz, *H*-6').

δ_C (100 MHz; $CDCl_3$)

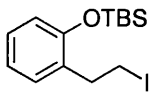
13.03 (CH), 18.04 (CH_3), 34.32 (CH_2), 62.70 (CH_2), 118.08 (CH), 120.84 (CH), 127.50 (CH), 128.51 (C), 131.04 (CH), 154.19 (C).

MS *m/z* (EI^+) 294.2 ($M^{+\cdot}$, 4 %), 251.1 (100), 233.1 (27), 209.1 (100), 181.1 (94), 163.1 (100), 149.1 (78), 131.1 (42), 103.1 (78), 75.0 (100), 61.0 (68), 59.0 (27); $C_{17}H_{30}O_2Si$ calculated 294.2015, observed 294.2016.

IR ν_{max} (neat) 3348 (OH), 2945 (CH_2), 2891 (CH_2), 2868 (CH_2), 1601 (aromatics), 1581 (aromatics), 1491 (aromatics), 1113 (Si-O), 922 (Si-O), 737 (aromatics).

R_f = 0.40 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

2-[2'-(*tert*-Butyldimethylsilyloxy)phenyl]ethyl iodide 268



Triphenylphosphine (6.10 g, 23.3 mmol, 1.2 eq), imidazole (1.58 g, 23.3 mmol, 1.2 eq) and iodine (5.90 g, 23.3 mmol, 1.2 eq) were added in order to a stirring solution of alcohol **266** (4.89 g, 19.4 mmol, 1 eq) in dry DCM (80 mL) at room temp., under argon. After 16.5 h, the mixture was washed with water (200 mL), 10 % aqueous sodium thiosulfate solution (2 x 150 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *iodide* (10.80 g) as a colourless oil. Purification by column chromatography [silica, eluting petroleum ether (40 - 60 °C)] gave the pure iodide (3.35 g, 47.7 %) as a colourless oil.

δ_H (400 MHz; $CDCl_3$)

0.25 (s, 6H, -SiC*H*$_3$), 1.03 (s, 9H, -C(C*H*$_3$)$_3$), 3.14-3.18 (m, 2H, $ArCH_2$), 3.29-3.33 (m, 2H, CH_2CH_2I) 6.79 (d, 1H, J = 8.0 Hz, *H*-3'), 6.89 (dt, 1H, J = 1.1 Hz, 7.4 Hz, *H*-5'), 7.12-7.16 (m, 2H, *H*-4' + *H*-6').

δ_C (100 MHz; $CDCl_3$)

-4.15 (CH_3), 4.45 (CH_2), 18.15 (C), 25.77 (CH_3), 36.04 (CH_2), 118.50 (CH), 121.13 (CH), 128.02 (CH), 130.36 (CH), 131.29 (C), 153.57 (C).

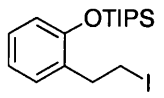
MS *m/z* (EI^+) 306.0 ($M^{+\cdot}$, 20 %), 305.0 (100), 177.1 (100), 151.1 (18), 135.0 (15), 73.1 (27); $C_{14}H_{23}OISi$ calculated 362.0563, observed 362.0566.

Microanalysis $C_{14}H_{23}OISi$ requires C 46.41 %, H 6.40 %, I 35.02 %, found C 46.63 %, H 6.49 %, I 35.19 %.

IR ν_{max} (neat) 2956 (CH_2), 2929 (CH_2), 1599 (aromatics), 1581 (aromatics), 1491 (aromatics), 1254 [$Si(CH_3)_2$], 1007 (Si-O), 839 [$Si(CH_3)_2$], 756 (aromatics).

R_f = 0.29 [silica, petroleum ether (40 – 60 °C)].

2-[2'-(Triisopropylsilyloxy)phenyl]ethyl iodide 269



Triphenylphosphine (7.06 g, 26.9 mmol, 1.2 eq), imidazole (1.83 g, 26.9 mmol, 1.2 eq) and iodine (6.84 g, 26.9 mmol, 1.2 eq) were added in order to a stirring solution of alcohol **267** (6.61 g, 22.4 mmol, 1 eq) in dry DCM (50 mL) at room temp., under argon. After 16.5 h, the mixture was washed with water (350 mL), 10 % aqueous sodium thiosulfate solution (2 x 250 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *iodide* as a colourless oil. Purification by column chromatography [silica, eluting petroleum ether (40 - 60 °C)] gave the pure iodide (6.71 g, 73.9 %) as a colourless oil.

δ_H (400 MHz; $CDCl_3$)

1.13 (d, 18H, J = 7.4 Hz, -CHC*H*$_3$), 1.27-1.36 (m, 3H, -C*H*CH_3), 3.18-3.22 (m, 2H, Ar-C*H*$_2$), 3.31-3.35 (m, 2H, -CH_2C*H*$_2$I), 6.79 (dd, 1H, J = 0.9 Hz, 8.2 Hz, *H*-3'), 6.87 (dt, 1H, J = 0.7 Hz, 7.4 Hz, *H*-5'), 7.10-7.14 (m, 2H, *H*-4' + *H*-6').

δ_C (100 MHz; $CDCl_3$)

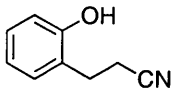
4.63 (CH_2), 13.04 (CH), 18.09 (CH_3), 36.22 (CH_2), 118.14 (CH), 120.81 (CH), 127.99 (CH), 130.38 (CH), 130.83 (C), 153.90 (C).

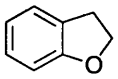
MS *m/z* (EI^+) 404.1 ($M^{+\cdot}$, 14 %), 362.1 (34), 361.0 (100), 319.0 (28), 291.0 (18), 233.1 (100), 191.1 (88), 163.1 (94), 149.1 (42), 135.0 (25), 84.0 (28), 59.0 (14); $C_{17}H_{29}OSiI$ calculated 404.1032, observed 404.1034.

IR ν_{max} (neat) 2943 (CH_2), 2866 (CH_2), 1599 (aromatics), 1581 (aromatics), 1489 (aromatics), 1387 [$C(CH_3)_2$], 1130 (Si-O), 754 (aromatics), 451 (C-I).

R_f = 0.33 [silica, petroleum ether (40 –60 °C):EtOAc (4:1)].

3-(2'-Hydroxyphenyl)propionitrile 271 and **dihydrobenzofuran 260**





Potassium cyanide (0.099 g, 1.52 mmol, 1.1 eq) was added to a stirring solution of iodide **268** (0.500 g, 1.38 mmol, 1 eq) in dry DMSO (4 mL) at room temp. under argon. The solution was stirred at room temp. for 19.5 h then poured into 0.02 M ferric chloride solution (25 mL) and extracted into DCM (25 mL). The aqueous layer was re-extracted with DCM (25 mL) and the combined organics were washed with water (2 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude mixture (272.2 mg) as a yellow oil. Purification by column chromatography on silica eluting petroleum ether (40 – 60 °C):EtOAc (6:1) gave compounds **260**[131] and **271**.

Data for **260**:

δ_H (400 MHz; $CDCl_3$)

3.18 (t, 2H, J = 8.8 Hz, ArC*H*$_2$), 4.55 (t, 2H, J = 8.8 Hz, -CH_2CH_2O), 6.80-7.20 (m, 4H, Ar-*H*).

Data for **271**:

δ_H (400 MHz; $CDCl_3$)

2.68 (t, 2H, J = 7.4 Hz, -C*H*$_2$CN), 2.97 (t, 2H, J = 7.4 Hz, ArC*H*$_2$), 5.48 (s, 1H, -O*H*), 6.74 (d, 1H, J = 8.0 Hz, *H*-3), 6.89 (dt, 1H, J = 1.0 Hz, 7.5 Hz, *H*-4), 7.12-7.17 (m, 2H, *H*-5 + *H*-6).

δ_C (100 MHz; $CDCl_3$)

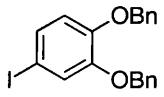
17.37 (CH_2), 26.76 (CH_2), 115.30 (CH), 119.69 (C), 120.93 (CH), 124.54 (C), 128.56 (CH), 130.58 (CH), 153.64 (C).

MS *m/z* (EI^+) 147 ($M^{+\cdot}$, 93 %), 146 (47), 107 (100), 91 (17), 77 (54), 63 (10), 51 (17); C_9H_9NO calculated 147.0684, observed 147.0684.

IR ν_{max} (neat) 3373 (OH), 2931 (CH_2), 2854 (CH_2), 2254 (CN), 1610 (aromatics), 1595 (aromatics), 1504 (aromatics), 1458 (CH_2), 756 (aromatics).

R_f = 0.19 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

3,4-bis(Benzyloxy)-1-iodobenzene 282



Benzyl bromide (6.30 mL, 53.5 mmol, 1.5 eq) was added to a solution of phenol **286** (11.63 g, 35.7 mmol, 1 eq) and potassium carbonate (7.39 g, 53.5 mmol, 1.5 eq) in DMF (50 mL) at room temp. The mixture was heated to 80 °C for 2 d then allowed to cool. The solution was diluted with Et_2O (500 mL), washed with water (3 x 300 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude iodide (15.0 g) as a brown solid. Recrystallisation from EtOH gave the pure iodide[132] (12.36 g, 83.3 %) as a white powder. Melting point in agreement with the published data.

δ_H (400 MHz; $CDCl_3$)

5.10 (s, 2H, -OC*H*$_2$Ph), 5.11 (s, 2H, -OC*H*$_2$Ph), 6.66 (d, 1H, J = 8.4 Hz, *H*-5), 7.18 (dd, 1H, J = 2.0 Hz, 8.4 Hz, *H*-6), 7.22 (d, 1H, J = 2.0 Hz, *H*-2), 7.28-7.44 (m, 10H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

71.28 (CH_2), 71.44 (CH_2), 83.19 (C), 116.97 (CH), 123.89 (CH), 127.22 (CH), 127.36 (CH), 127.89 (CH), 127.98 (CH), 128.50 (CH), 128.53 (CH), 130.50 (CH), 136.62 (C), 136.83 (C), 149.03 (C), 149.91 (C).

MS *m/z* (EI^+) 416.1 ($M^{+\cdot}$, 18 %), 91.1 (100); $C_{20}H_{17}O_2I$ calculated 416.0273, observed 416.0273.

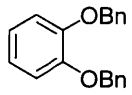
Microanalysis $C_{20}H_{17}O_2I$ requires C 57.71 %, H 4.12 %, found C 57.86 %, H 3.87 %.

IR ν_{max} (golden gate) 2935 (CH_2), 2866 (CH_2), 1574 (aromatics), 1495 (aromatics), 1454 (aromatics).

mp = 62 - 63 °C [lit.[132] 65 – 67 °C (MeOH)].

R_f = 0.66 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

1,2-bis(Benzyloxy)benzene 284



Potassium carbonate (50.34 g, 363.3 mmol, 4 eq) was added to a solution of catechol **283** (10.00 g, 90.8 mmol, 1 eq) and benzyl bromide (43.3 ml, 363.3 mmol, 4 eq) in DMF (100 ml) at room temp. The resulting mixture was heated to 80 °C for 18 h, after which the solution was cooled, acidified, extracted into ether (600 ml) and washed with 2 M KOH (300 ml). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude ether as an orange/brown oil that crystallised on standing. Recrystallisation from MeOH gave the pure ether (14.66 g, 55.5 %) as a fluffy white solid.

δ_H (400 MHz; $CDCl_3$)

5.12 (s, 4H, 2 x PhC*H*$_2$), 6.83-6.94 (m, 4H, *H*-3, *H*-4, *H*-5, *H*-6), 7.25-7.43 (m, 10H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

71.18 (CH_2), 115.16 (CH), 121.56 (CH), 127.22 (CH), 127.66 (CH), 128.37 (CH), 137.29 (C), 148.94 (C).

MS *m/z* (EI^+) 290.2 ($M^{+\cdot}$, 15 %), 91.1 (100), 83.0 (14); $C_{20}H_{18}O_2$ calculated 290.1307, observed 290.1308.

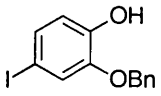
Microanalysis $C_{20}H_{18}O_2$ requires C 82.73 %, H 6.25 % found C 82.70 %, H 6.25 %.

mp = 58 - 60 °C [lit.[133]60 – 61 °C].

IR ν_{max} KBr/cm^{-1} 2941 (CH_2), 2882 (CH_2), 1589 (aromatics), 1522 (aromatics), 1504 (aromatics), 741 (aromatics).

R_f = 0.60 [silica, petroleum ether (40 - 60 °C):EtOAc (4:1)].

2-Benzyloxy-4-iodophenol 286



By the published procedure[110] a solution of iodine monochloride (23.2 g, 143 mmol, 1.43 eq) in dry ether (230 mL) was added dropwise to a solution of 2-benzyloxyphenol **285** (20.0 g, 99.8 mmol, 1 eq) in dry ether (100 mL) at room temp. under argon. The solution was shielded from the light and stirred at room temp overnight. The reaction mixture was diluted with ether (300 mL), washed with 10 % aqueous thiosulfate (3 x 300 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude iodide as a brown/red oil. The crude product was passed through a plug of silica eluting hexane:DCM (3:2), concentrated and recrystallised from ether:hexane to give the pure phenol[110] (11.63 g, 36 %) as colourless crystals. ^1H and ^{13}C NMR agree with the published data.

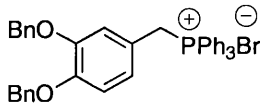
δ_H (400 MHz; $CDCl_3$)

5.09 (s, 2H, -OC*H*$_2$Ph), 5.64 (s, 1H, -O*H*), 6.73 (d, 1H, J = 8.1 Hz, *H*-6), 7.21-7.24 (m, 2H, *H*-3 + *H*-5), 7.39-7.47 (m, 5H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

71.42 (CH_2), 80.81 (C), 116.68 (CH), 121.08 (CH), 127.99 (CH), 128.66 (CH), 128.81 (CH), 130.81 (CH), 135.61 (C), 145.94 (C), 146.67 (C).

[3,4-bis(Benzyloxy)benzyl]triphenylphosphonium bromide 287



Triphenylphosphine hydrobromide (404.9 mg, 1.18 mmol, 1 eq) was added to a solution of alcohol **289** (378 mg, 1.18 mmol, 1 eq) in acetonitrile (11.8 mL) at room temp. under argon. The solution was heated to reflux for 5 h then allowed to cool to room temp. and stirred overnight. The precipitate that formed was filtered to give the crude phosphonium salt (469 mg, 60.1 %) as a white powder. A sample was recrystallised from ethanol for analysis.

δ_H (400 MHz; $CDCl_3$)

4.77 (s, 2H, -OC*H*$_2$Ph), 5.04 (s, 2H, -OC*H*$_2$Ph), 5.21 (d, 2H, J = 13.8 Hz, -C*H*$_2$P), 6.56-6.60 (m, 1H, Ar-*H*), 6.65 (d, 1H, J = 8.3 Hz, Ar-*H*), 6.86-6.87 (m, 1H, Ar-*H*), 7.23-7.37 (m, 10H, Ar-*H*), 7.55-7.74 (m, 15H, Ar-*H*).

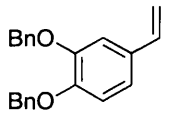
δ_C (100 MHz; $CDCl_3$)

30.10 (d, J = 46.9 Hz, CH_2), 70.57 (CH_2), 70.82 (CH_2), 114.79 (CH), 117.32 (d, J = 4.9 Hz, CH), 117.63 (d, J = 85.5 Hz, C), 124.32 (CH), 124.38 (CH), 127.09 (CH), 127.19 (CH), 127.53 (CH), 127.64 (CH), 128.17 (CH), 128.25 (CH), 129.92 (d, J = 12.5 Hz, CH), 134.22 (d, J = 9.7 Hz, CH), 134.74 (d, J = 2.7 Hz, CH), 136.67 (d, J = 6.2 Hz, C), 148.48 (C), 148.52 (C), 148.63 (C), 148.67 (C).

IR ν_{max} (golden gate) 2895 (CH_2), 2871 (CH_2), 2781 (CH_2), 1597 (aromatics), 1585 (aromatics), 1523 (aromatics), 1435 (P-Ph).

mp = 230 °C (dec.).

3,4-bis(Benzyloxy)styrene 288



n-Butyllithium (2.5 M in hexanes, 43.2 mL, 108.05 mmol, 2 eq) was added dropwise to a suspension of methyltriphenylphosphonium bromide (38.60 g, 108.05 mmol, 2 eq) in THF (240 mL) at -78 °C under argon. The bright yellow suspension was allowed to warm to room temp. and stirred for 2.5 h. The suspension was re-cooled to -78 °C and a solution of aldehyde **90** (17.20 g, 54.03 mmol, 1 eq) in THF (85 mL) was added slowly. The suspension was allowed to warm to room temp. and stirred for 19 h. The reaction mixture was diluted with Et_2O (1500 mL), washed with water (2 x 750 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude styrene[134] as an off-white solid. Purification by passing through a plug of silica eluting hexane/Et_2O (3:1) gave the pure styrene (16.00 g, 93.6 %) as a fluffy white solid.

δ_H (400 MHz; $CDCl_3$)

5.12 (dd, 1H, J = 0.7 Hz, 10.9 Hz, H_{cis}), 5.16 (s, 2H, -OC*H*$_2$Ph), 5.17 (s, 2H, -OC*H*$_2$Ph), 5.55 (dd, 1H, J = 0.8 Hz, 17.5 Hz, H_{trans}), 6.60 (dd, 1H, J = 10.9 Hz, 17.5

Hz, C*H*=CH_2), 6.88 (d, 1H, J = 8.2 Hz, *H*-5), 6.92 (dd, 1H, J = 1.9 Hz, 8.3 Hz, *H*-6), 7.04 (d, 1H, J = 1.9 Hz, *H*-2), 7.26-7.38 (m, 10H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

71.27 (CH_2), 71.41 (CH_2), 112.10 (CH_2), 112.64 (CH), 114.89 (CH), 120.07 (CH), 127.25 (CH), 127.35 (CH), 127.77 (CH), 127.80 (CH), 128.47 (CH), 131.44 (C), 136.32 (CH), 137.23 (C), 137.27 (C), 148.92 (C), 149.02 (C).

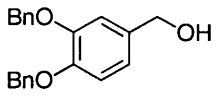
MS *m/z* (EI^+) 316.3 ($M^{+\cdot}$, 65 %), 225.2 (21), 181.2 (21), 91.1 (100), 83.0 (16), 65.1 (16); $C_{22}H_{20}O_2$ calculated 316.1463, observed 316.1464.

Microanalysis $C_{22}H_{32}O_2$ requires C 83.52 %, H 6.37 %, found C 83.34 %, H 6.32 %.

IR ν_{max} (golden gate) 3086 (alkene), 2937 (CH_2), 2871 (CH_2), 1599 (aromatics), 1549 (aromatics), 1514 (aromatics), 1003 (alkene), 912 (alkene), 746 (aromatics).

mp = 67 - 69 °C [lit.[134] 68 – 69 °C, EtOAc].

3,4-bis(Benzyloxy)benzyl alcohol 289

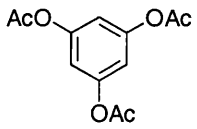


Lithium aluminium hydride (340.8 mg, 8.97 mmol, 1.5 eq) was added slowly to a solution of acid **146** (2.0 g, 5.98 mmol, 1 eq) in THF (20 mL) at 0 °C. The solution was allowed to warm to room temp. overnight then quenched with water (40 mL), extracted into EtOAc (40 mL) and washed with 1 M HCl (20 ml). The aqueous layer was re-extracted with EtOAc (60 ml) and the combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude alcohol (1.54 g, 80.2 %) as an amorphous solid. ^{1}H NMR data in agreement with published data.[135]

δ_H (400 MHz; $CDCl_3$)

4.49 (s, 2H, ArCH_2), 5.11 (s, 4H, 2 x -OCH_2Ph), 6.80 (dd, 1H, J = 1.9 Hz, 8.1 Hz, *H*-6), 6.87 (d, 1H, J = 8.2 Hz, *H*-5), 6.96 (d, 1H, J = 1.8 Hz, *H*-3), 7.25-7.35 (m, 10H, Ar-*H*).

1,3,5-tris(Acetoxy)benzene 294



Acetic anhydride (30.0 mL, 317.2 mmol, 4 eq) was added dropwise to a solution of phloroglucinol **100** (10.0 g, 79.3 mmol, 1 eq) in a 50:50 mixture of pyridine:DCM (100 mL). The resulting solution was stirred at room temp. for 45 mins, diluted with EtOAc (600 mL), washed with 1 M HCl (300 mL), saturated sodium bicarbonate (300 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the acetate[52] (19.06 g, 95.3 %) as a white solid sufficiently pure for the next step. A sample was recrystallised from *i*-PrOH to give the acetate as fine colourless needles.

δ_H (400 MHz; $CDCl_3$)

2.28 (s, 9H, 3 x CH_3CO), 6.86 (s, 3H, 3 x Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

20.97 (CH_3), 112.67 (CH), 151.04 (C), 168.45 (C).

MS *m/z* (EI^+) 252.1 ($M^{+\cdot}$, 8 %), 210.1 (20), 168.1 (35), 126.1 (100), 43.0 (42); $C_{12}H_{12}O_6$ calculated 252.0634, observed 252.0635.

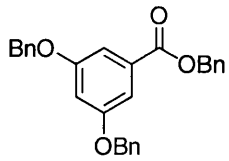
Microanalysis $C_{12}H_{12}O_6$ requires C 57.14 %, H 4.79 % found C 57.12 %, H 4.87 %.

IR ν_{max} (KBr) 1775 (ester), 1602 (aromatics).

mp = 107 – 108 °C [lit.[136] 100 – 102 °C].

R_f = 0.76 (silica, EtOAc).

Benzyl 3,5-bis(benzyloxy)benzoate 296



Benzyl bromide (30.8 mL, 259.5 mmol, 4 eq), was added to a solution of 3,5-dihydroxybenzoic acid **295** (10.00 g, 64.9 mmol, 1 eq), potassium carbonate (53.81 g, 389.3 mmol, 6 eq) and potassium iodide (1.08 g, 6.49 mmol, 0.1 eq) in DMF (150

mL). The resulting mixture was stirred for 27 h before being quenched with EtOAc (2 x 600 mL), washed with dilute aqueous ammonia (2 x 300 mL), water (3 x 300 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the ester[111] (21.65 g, 78.6 %) as an oil that crystallised on standing.

δ_H (400 MHz; $CDCl_3$)

5.06 (s, 4H, -OC*H*$_2$Ph), 5.34 (s, 2H, -CO_2C*H*$_2$Ph), 6.80 (t, 1H, J = 2.4 Hz, *H*-4), 7.27-7.44 (m, 17H, *H*-2, *H*-6 + Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

66.85 (CH_2), 70.32 (CH_2), 107.21 (CH), 108.57 (CH), 127.58 (CH), 128.12 (CH), 128.24 (CH), 128.58 (CH), 128.61 (CH), 132.02 (C), 135.93 (C), 136.43 (C), 159.78 (C), 166.09 (C).

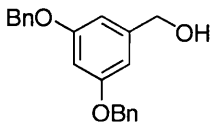
MS *m/z* (EI^+) 424.1 ($M^{+\cdot}$, 18 %), 227.1 (10), 181.1 (12), 91.1 (100); $C_{28}H_{24}O_4$ calculated 424.1675, observed 424.1671.

IR ν_{max} (KBr) 1740 (C=O), 1632 (aromatics), 1599 (aromatics), 1524 (aromatics).

mp = 57.0 – 57.5 °C (lit.[111] 63 – 66 °C benzene/hexane).

R_f = 0.91 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

3,5-bis(Benzyloxy)benzyl alcohol 297



Lithium aluminium hydride (671.0 mg, 17.7 mmol, 1.5 eq) was added slowly to a solution of ester **296** (5.00 g, 11.8 mmol, 1 eq) in dry THF (30 mL) at 0 °C under argon. The mixture was stirred for 2 h before being quenched with water (60 mL) and extracted into EtOAc (2 x 100 mL). The combined organics were washed with 2 M HCl (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude alcohol[111] (4.39 g) as a white solid. Recrystallisation from hexane/Et_2O gave the pure alcohol (3.72 g, 98.7 %) as an amorphous solid.

δ_H (400 MHz; $CDCl_3$)

4.60 (s, 2H, -C*H*$_2$OH), 5.02 (s, 4H, PhC*H*$_2$), 6.54 (t, 1H, J = 2.2 Hz, *H*-4), 6.61 (d, 2H, J = 2.1 Hz, *H*-2 + *H*-5), 7.29-7.41 (m, 10H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

65.22 (CH_2), 70.03 (CH_2), 101.27 (CH), 105.71 (CH), 127.48 (CH), 127.96 (CH), 128.55 (CH), 136.79 (C), 143.40 (C), 160.12 (C).

MS *m/z* (CI^+) 321.2 [$(M + H)^+$, 38 %], 303.2 (24), 57.1 (100); $C_{21}H_{21}O_3$ calculated 321.1491, observed 321.1493.

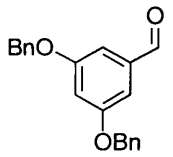
Microanalysis $C_{21}H_{20}O_3$ requires C 78.73 %, H 6.29 %, found C 78.42 %, 6.36 %.

IR ν_{max} (golden gate) 3315 (OH), 2902 (CH_2), 2866 (CH_2), 1591 (aromatics), 1496 (aromatics).

mp = 77 – 77.5 °C (lit.[111] 81.5 – 82 °C, benzene/hexane).

R_f = 0.20 [silica, petroleum ether (40 – 60 °C):EtOAc (2:1)]

3,5-bis(Benzyloxy)benzaldehyde 298



Manganese dioxide (5.24 g, 62.4 mmol, 40 eq) was added to a solution of alcohol **297** (500.0 mg, 1.56 mmol, 1 eq) in DCM (10 mL). The mixture was stirred at room temp. for 30 h. The mixture was filtered through a short plug of celite, which was then washed with DCM (100 mL). The organics were concentrated to give the aldehyde[111] (404.0 mg, 81.3 %) as a white solid. No further purification was required.

Alternative procedure:

IBX (1.31 g, 4.68 mmol, 3 eq) was added to a solution of alcohol **297** (500.0 mg, 1.56 mmol, 1 eq) in EtOAc (10 mL). The mixture was then heated to reflux for 4.5 h before being allowed to cool to room temperature. The mixture was filtered and the solid was washed with EtOAc (30 mL). The organics were concentrated under

reduced pressure to give the aldehyde[111] (475.8 mg, 95.8 %) as a white solid. No further purification was required.

δ_H (400 MHz; $CDCl_3$)

5.08 (s, 4H, -OC*H*$_2$Ph), 6.86 (t, 1H, J = 2.3 Hz, *H*-4), 7.10 (d, 2H, J = 2.3 Hz, *H*-2 + *H*-6), 7.31-7.43 (m, 10H, Ar-*H*), 9.88 (s, 1H, -C*H*O).

δ_C (100 MHz; $CDCl_3$)

70.34 (CH_2), 108.28 (CH), 108.65 (CH), 127.52 (CH), 128.19 (CH), 128.64 (CH), 136.19 (C), 138.39 (C), 160.35 (C), 191.77 (CH).

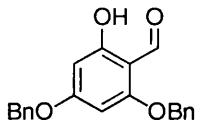
MS *m/z* (EI^+) 318.1 ($M^{+\cdot}$, 87 %), 181.1 (21) 91.1 (100), 65.0 (30); $C_{21}H_{18}O_3$ calculated 318.1256, observed 318.1257.

mp = 79.7 – 80.2 °C (lit.[111] 76.5 – 77 °C benzene/hexane).

R_f = 0.87 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

IR ν_{max} (KBr) 1682 (CHO), 1623 (aromatics), 1581 (aromatics), 1498 (aromatics).

4,6-bis(Benzyloxy)-2-hydroxybenzaldehyde 300



Benzyl bromide (3.50 mL, 29.25 mmol, 3 eq) was added to a stirring solution of Phloroglucinaldehyde **299** (1.50 g, 9.75 mmol) and potassium carbonate (2.70 g, 19.5 mmol, 2 eq) in DMF (25 mL) at room temp. under nitrogen. The resulting mixture was stirred at room temp. for 18 h then diluted with water (100 mL) and extracted with ether (100 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give a dark red oil. Recrystallisation from MeOH (x 2) yielded the pure *aldehyde* (720 mg, 22 %) as fine red/orange crystals.

δ_H (400 MHz; $CDCl_3$)

5.07 (s, 2H, -OC*H*$_2$Ph), 5.08 (s, 2H, -OC*H*$_2$Ph), 6.08 (d, 1H, J = 2.1 Hz, *H*-5), 6.11 (d, 1H, J = 2.1 Hz, *H*-3), 7.33-7.40 (m, 10H, Ar-*H*), 10.18 (s, 1H, C*H*O), 12.50 (s, 1H, O*H*).

δ_C (100 MHz; $CDCl_3$)

70.46 (CH_2), 70.52 (CH), 92.35 (CH), 94.13 (CH), 106.32 (C), 127.38 (CH), 127.63 (CH), 128.38 (CH), 128.44 (CH), 128.74 (CH), 135.60 (C), 135.67 (C), 162.61 (C), 166.31 (C), 167.09 (C), 191.93 (CH).

MS *m/z* (EI^+) 334.1 ($M^{+\cdot}$, 12 %), 91.0 (100); $C_{21}H_{18}O_4$ calculated 334.1205, observed 334.1203.

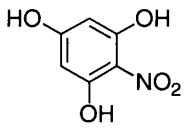
Microanalysis $C_{21}H_{18}O_4$ requires C 75.43 %, H 5.43 %, found C 75.45 %, H 5.50 %.

IR ν_{max} (KBr) 3433 (OH), 1644 (CHO), 1621 (aromatics), 1579 (aromatics), 1497 (aromatics).

mp = 91 – 92 °C.

R_f = 0.69 (silica, Et_2O).

2-Nitrophloroglucinol 307

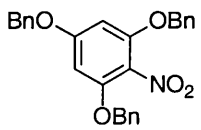


A mixture of concentrated nitric acid (0.8 mL) in 50 % sulphuric acid (5 mL) was added dropwise over 15 min to a suspension of phloroglucinol **100** (1.00 g) in 50 % sulphuric acid (15 mL) at 0 °C. The suspension was stirred for 6 h then diluted with water (50 mL). The solution was extracted with ether (2 x 100 mL) and the combined organics were washed with water (2 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude title compound (616.5 mg, 45.3 %) as a red powder. ^1H NMR spectrum identical to commercially available material apart from a small amount of starting material as impurity.

δ_H (400 MHz; d_6-Acetone)

6.10 (s, 3H, Ar-*H*), 10.25 (br s, 1H, -O*H*), 11.14 (br s, 2H, -O*H*).

2,4,6-tris(Benzyloxy)-nitrobenzene 308



Benzyl bromide (20.43 mL, 172.2 mmol, 6 eq) was added to a solution of 2-nitrophloroglucinol **307** (4.91 g, 28.7 mmol, 1 eq), potassium carbonate (23.8 g, 172.2 mmol, 6 eq) and potassium iodide (476.3 mg, 2.87 mmol, 0.1 eq) in DMF (100 mL). The mixture was then heated to 80 °C for 11 d before being allowed to cool to room temp. and diluted with water (200 mL). The solution was extracted into Et_2O (2 x 500 mL) and the combined organics were washed with water (2 x 500 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the crude *ether* (14.23 g) as a brown/yellow oil that crystallised on standing. Recrystallisation from EtOH gave the pure title compound (10.02 g, 79.1 %) as fine yellow needles.

δ_H (400 MHz; $CDCl_3$)

4.98 (s, 2H, -OC*H*$_2$Ph), 5.10 (s, 4H, -OC*H*$_2$Ph), 6.23 (s, 2H, H-3 + *H*-5), 7.31-.7.41 (m, 15H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

70.47 (CH_2), 70.95 (CH_2), 93.50 (CH), 126.96 (CH), 127.43 (CH), 128.15 (CH), 128.35 (CH), 128.62 (CH), 128.71 (CH), 135.47 (C), 135.72 (C), 152.19 (C), 160.87 (C).

MS *m/z* (EI^+) 441.3 ($M^{+\cdot}$, 15 %), 91.1 (100), 65.1 (10); $C_{27}H_{23}NO_5$ calculated 441.1576, observed 441. 1577.

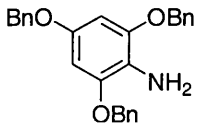
Microanalysis $C_{27}H_{23}NO_5$ requires C 73.46 %, H 5.25 %, N 3.17 % found C 73.43 %, H 5.15 %, N 3.15 %.

IR ν_{max} (golden gate) 1595 (aromatics), 1516 (aromatics), 1498 (aromatics), 1338 (NO_2).

mp = 119.5 – 120 °C.

R_f = 0.51 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

2,4,6-tris(Benzyloxy)aniline 309



A suspension of iron powder (3.00 g, 53.71 mmol, 3 eq), ammonium chloride (4.79 g, 89.51 mmol, 5 eq) and benzyl ether **308** (7.90 g, 17.90 mmol, 1 eq) in EtOH/H_2O

(4:1, 500 mL) was heated to reflux for 44 h. The mixture was allowed to cool to room temp. and filtered through a plug of celite eluting EtOAc (300 mL). The filtrate was concentrated under reduced pressure and the residue was extracted into EtOAc (700 mL), washed with water (400 mL), brine (2 x 400 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *aniline* (7.00 g, 95.1 %) as a black powder. No further purification was required.

δ_H (400 MHz; $CDCl_3$)

3.61 (br s, 2H, N*H*$_2$), 4.93 (s, 2H, -OC*H*$_2$Ph), 5.04 (s, 4H, -OC*H*$_2$Ph), 6.38 (s, 2H, *H*-3 + *H*-5), 7.29-7.43 (m, 15H, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

70.65 (CH_2), 70.85 (CH_2), 94.47 (CH), 120.17 (C), 127.44 (CH), 127.50 (CH), 127.78 (CH), 127.87 (CH), 128.44 (CH), 128.45 (CH), 137.00 (C), 137.23 (C), 146.97 (C), 151.18 (C).

MS *m/z* (EI^+) 411.2 ($M^{+\cdot}$, 45 %), 320.2 (45), 181.1 (10), 91.1 (100); $C_{27}H_{25}NO_3$ calculated 411.1834, observed 411.1834.

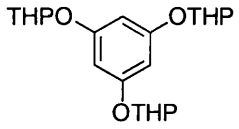
Microanalysis $C_{27}H_{25}NO_3$ requires C 78.81 %, H 6.12 %, N 3.40 % found C 78.65 %, H 6.04 %, N 3.53 %.

IR ν_{max} (golden gate) 3408 (NH_2), 3332 (NH_2), 1600 (aromatics), 1504 (aromatics).

mp = 80 – 81 °C.

R_f = 0.53 [silica, petroleum ether (40 – 60 °C):EtOAc (2:1)].

1,3,5-tris(Tetrahydropyranyloxy)benzene 311



Concentrated hydrochloric acid (2 drops) was added to a suspension of anhydrous phloroglucinol **100** (10.0 g, 79.3 mmol, 1 eq) in 2,3-dihydropyran (25.3 mL, 277.5 mmol, 3 eq). The solution was stirred at room temp. for 67 h then diluted with Et_2O (800 mL). The combined organics were washed with 10 % KOH (500 mL) and brine (2 x 500 mL) then dried ($MgSO_4$) and concentrated under reduced pressure to gave

the crude *ether* (30.68 g) as a yellow/orange viscous oil that crystallised slowly on standing. Recrystallisation from EtOH gave the pure *ether* (2:1 mixture of diastereomers, 13.53 g, 45.1 %) as a white amorphous solid.

δ_H (400 MHz; $CDCl_3$)

1.54-1.71 (m, 9H, -C*H*$_2$), 1.80-1.86 (m, 6H, -C*H*$_2$), 1.93-2.04 (m, 3H, -C*H*$_2$), 3.58-3.62 (m, 3H, -OC*H*$_2$), 3.89-3.94 (m, 3H, -OC*H*$_2$), 5.35-5.40 (m, 3H, -OC*H*O), 6.43 (s, 3H, Ar-*H*, minor), 6.44 (s, 3H, Ar-*H*, major).

δ_C (100 MHz; $CDCl_3$)

18.68 (CH_2), 18.73 (CH_2), 18.78 (CH_2), 25.19 (CH_2), 30.30 (CH_2), 61.92 (CH_2), 61.98 (CH_2), 62.03 (CH_2), 96.18 (CH), 96.35 (CH), 96.51 (CH), 98.47 (CH), 98.61 (CH), 98.73 (CH), 158.53 (C), 158.63 (C), 158.66 (C).

MS *m/z* (EI^+) 378.3 ($M^{+\cdot}$, 5 %), 294.3 (15), 210.2 (71), 126.1 (100), 85.1 (100), 84.1 (54), 57.1 (26); $C_{21}H_{30}O_6$ calculated 378.2042, observed 378.2042.

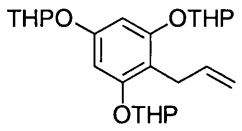
Microanalysis $C_{21}H_{30}O_6$ requires C 66.65 %, H 7.99 %, found C 66.76 %, H 8.01 %.

IR ν_{max} (golden gate) 2937 (CH_2), 2871 (CH_2), 1599 (aromatics), 1549 (aromatics), 1514 (aromatics).

mp = 100 – 101 °C.

R_f = 0.74 [silica, Et_2O].

1-Allyl-2,4,6-tris(tetrahydropyranyloxy)benzene 312



tert-Butyllithium (1.5 M in pentane, 1.76 mL, 2.64 mmol, 2 eq) was added dropwise to a solution of freshly dried acetal **311** (500 mg, 1.32 mmol, 1 eq) in THF (5 mL) at -78 °C under argon. The resulting yellow solution was allowed to slowly warm over 70 min. then cooled in an ice-bath and distilled allyl bromide (0.69 mL, 7.93 mmol, 6 eq) was added. The solution was allowed to warm to room temp. over 1 h then diluted with EtOAc (100 mL), washed with dilute ammonia (2 x 80 mL), water (2 x 80 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *acetal*

(471.5 mg, 85.3 %) as a cloudy colourless gum as a 10:1 ratio of products:starting material. The material was used without further purification. Recrystallisation of a sample from Et_2O/ hexane gave pure *acetal* as a 10:1:1 ratio of diastereomers A:B:C as colourless cubes.

δ_H (400 MHz; $CDCl_3$)

1.56-1.67 (m, 9H, -C*H*$_2$), 1.79-1.85 (m, 6H, C*H*$_2$), 1.93-2.07 (m, 3H, C*H*$_2$), 3.41 (d, 2H, J = 6.3 Hz, ArC*H*$_2$), 3.57-3.61 (m, 2H, -OC*H*$_2$), 3.85-3.95 (m, 2H, -OC*H*$_2$), 4.91 (d, 1H, J = 9.9 Hz,), 5.02 (dd, 1H, J = 1.7 Hz, 17.1 Hz,), 5.36-5.41 (m, 3H, -OC*H*O), 5.94 (tdd, 1H, J = 6.4 Hz, 10.1 Hz, 16.6 Hz, CH_2=C*H*), 6.55 (s, 2H, Ar-*H*, minor B), 6.57 (s, 2H, Ar-*H*, major A), 6.59 (s, 2H, Ar-*H*, minor C).

δ_C (100 MHz; $CDCl_3$)

18.70 (CH_2), 18.77 (CH_2), 25.19 (CH_2), 25.28 (CH_2), 27.80 (CH_2), 30.23 (CH_2), 30.29 (CH_2), 30.38 (CH_2), 30.43 (CH_2), 61.68 (CH_2), 61.71 (CH_2), 61.76 (CH_2), 61.84 (CH_2), 61.93 (CH_2), 95.98 (CH), 96.03 (CH), 96.26 (CH), 96.38 (CH), 96.52 (CH), 96.76 (CH), 96.96 (CH), 97.02 (CH), 97.59 (CH), 97.62 (CH), 98.71 (CH), 111.44 (CH), 113.69 (CH), 137.67 (CH), 155.68 (C), 155.86 (C), 156.66 (C).

MS *m/z* (EI^+) 418.3 ($M^{+\cdot}$, 1 %), 250.1 (12), 166.1 (100), 85.1 (55), 84.0 (40); $C_{24}H_{34}O_6$ calculated 418.2355, observed 418.2354.

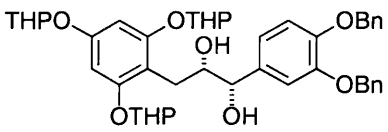
Microanalysis $C_{24}H_{34}O_6$ requires C 66.88 %, H 8.19 %, found C 66.89 %, H 8.19 %.

IR ν_{max} (golden gate) 2945 (CH_2), 2877 (CH_2), 1593 (aromatics), 1493 (aromatics), 1016 (alkene), 904 (alkene).

mp = 100 - 101 °C.

R_f = 0.74 [silica, Et_2O].

(1*R*,*S*,2*R*,*S*)-1-[3',4'-bis(Benzyloxy)phenyl]-3-[2'',4'',6''-tris(tetrahydropyranyloxy)phenyl]-propan-1,2-diol 315



Osmium tetroxide (0.02 M in water, 0.80 mL, 0.014 mmol, 0.1 eq) was added over 5 min to a solution of alkene **143** (100 mg, 0.14 mmol, 1 eq) and NMO (60 wt % in water, 0.08 mL, 3 eq) in THF:water (3:1, 2 mL) at room temp. The dark yellow/brown solution was stirred for 16 h then quenched with 10 % aqueous sodium thiosulfate (2 mL) and stirred for a further 30 min. The solution was filtered through a plug of celite eluting with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *diol* (98.3 mg, 93.8 %) as a brown gum. Purification by column chromatography [alumina deactivated with 10 % water, eluting with Et_2O:hexane (2:1)] gave the pure *diol* (47.6 mg, 45.4 %) as a yellow gum as a mixture of six diastereomers.

δ_H (400 MHz; $CDCl_3$)

1.55-1.64 (m, 9H, -C*H*$_2$), 1.67-1.70 (m, 6H, -C*H*$_2$), 1.78-1.80 (m, 3H, -C*H*$_2$), 2.66-3.14 (6 x d, 1H, J = 5.6 Hz, C(1)-O*H*), 2.76-2.85 (m, 2H, C(3)*H*$_2$), 3.45-3.47 (m, 1H, C(2)-O*H*), 3.57-3.60 (m, 3H, -OC*H*$_2$), 3.75-3.94 (m, 4H, -OC*H*$_2$ + *H*-1), 4.40-4.45 (m, 1H, *H*-2), 5.13 (s, 2H, -OC*H*$_2$Ph), 5.14 (s, 2H, -OC*H*$_2$Ph), 5.29-5.40 (m, 3H, -OC*H*O), 6.54-6.60 (m, 2H, *H*-5' + *H*-6'), 6.89 (s, 2H, *H*-3'' + *H*-5'' minor B + B'), 6.91 (s, 2H, *H*-3'' + *H*-5'' major A + A'), 6.94 (s, 2H, *H*-3'' + *H*-5'' minor C + C'), 7.09 (s, 1H, *H*-2'), 7.27-7.46 (m, 10H, Ar-*H*).

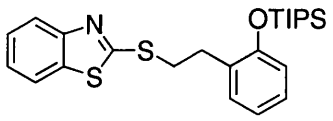
δ_C (100 MHz; $CDCl_3$)

18.63 (CH_2), 18.71 (CH_2), 18.89 (CH_2), 18.95 (CH_2), 25.02 (CH_2), 25.07 (CH_2), 25.17 (CH_2), 27.24 ((CH_2), 27.42 (CH_2), 27.58 (CH_2), 30.22 (CH_2), 30.32 (CH_2), 30.43 (CH_2), 61.99 (CH_2), 62.21 (CH_2), 62.30 (CH_2), 62.42 (CH_2), 71. 29 (CH_2), 71.38 (CH_2), 75.95 (CH), 76.45 (CH), 77.58 (CH), 77.66 (CH), 96.13 (CH), 96.51 (CH), 96.66 (CH), 96.88 (CH), 96.95 (CH), 97.20 (CH), 97.29 (CH), 97.37 (CH), 97.43 (CH), 97.78 (CH), 97.95 (CH), 98.29 (CH), 113.77 (CH), 114.95 (CH), 119.86 (CH), 119.98 (CH), 120.08 (CH), 127.22 (CH), 127.43 (CH), 127.71 (CH), 127.75 (CH), 128.42 (CH), 134.65 (C), 137.29 (C), 137.43 (C), 148.39 (C), 148.98 (C), 156.07 (C), 156.13 (C), 156.27 (C).

MS *m/z* (FAB$^+$) 763.7 [(M+Na)$^+$, 96 %], 471.4 (10), 319.3 (19), 229.2 (10), 139.1 (32), 85.6 (100), 58.0 (12); $C_{44}H_{52}O_{10}Na$ calculated 763.3458, observed 763.3442.

IR ν_{max} (neat) 3467 (OH), 2943 (CH_2), 2871 (CH_2), 1608 (aromatics), 1591 (aromatics), 1510 (aromatics), 1261 (OH), 1151 (C-OH).

2-[2'-(2''-Triisopropylsilyloxyphenyl)ethylsulfanyl]benzothiazole 338



A solution of iodide **269** (8.03 g, 18.1 mmol, 1.1 eq) in acetone (25 mL) was added to a solution of 2-mercaptobenzothiazole **339** (2.75 g, 16.5 mmol, 1 eq) and potassium carbonate (2.50 g, 18.1 mmol, 1.1 eq) in acetone (25 mL). The mixture was heated to reflux and stirred for 5 h. The mixture was diluted with water (30 mL) and extracted into ether (3 x 30 mL). The combined organics were washed with water (2 x 30 mL) and brine (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *sulfide* (1.15 g, 86.4 %) as a brown oil. Purification by filtration through a plug of silica eluting petroleum ether (40 – 60 °C) followed by ether gave the pure *sulfide* (4.76 g, 65.2 %) as a colourless oil.

δ_H (400 MHz; $CDCl_3$)

1.11 (d, 18H, J = 7.4 Hz, -CHC*H*$_3$), 1.26-1.36 (m, 3H, -C*H*CH$_3$), 3.15 (t, 2H, 7.6 Hz, ArC*H*$_2$), 3.59 (t, 2H, J = 7.6 Hz, -SC*H*$_2$), 6.81 (d, 1H, J = 8.1 Hz, *H*-3''), 6.89 (t, 1H, J = 7.4 Hz, *H*-5''), 7.10 (dt, 1H, J = 1.7 Hz, 7.7 Hz, *H*-4''), 7.21 (dd, 1H, J = 1.6 Hz, 7.4 Hz, *H*-6''), 7.28 (t, 1H, J = 7.6 Hz, *H*-6), 7.41 (t, 1H, J = 7.6 Hz, *H*-5), 7.75 (d, 1H, J = 7.9 Hz, *H*-7), 7.87 (d, 1H, J = 8.1 Hz, *H*-4).

δ_C (100 MHz; $CDCl_3$)

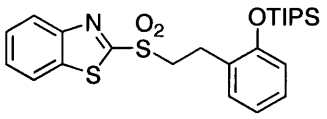
13.05 (CH), 18.08 (CH_3), 30.78 (CH_2), 33.48 (CH_2), 118.04 (CH), 120.77 (CH), 120.87 (CH), 121.49 (CH), 124.06 (CH), 125.93 (CH), 127.76 (CH), 129.59 (C), 130.66 (CH), 135.25 (C), 153.40 (C), 154.07 (C), 167.09 (C).

MS *m/z* (EI^+) 443.2 ($M^{+\cdot}$, 4 %), 400.1 (53), 276.2 (100), 233.1 (100), 191.1 (80), 163.1 (72), 149.0 (30), 135.0 (23), 59.0 (24); $C_{24}H_{33}NOS_2Si$ calculated 443.1773, observed 443.1774.

IR ν_{max} (neat) 2944 (CH_2), 2866 (CH_2), 1599 (aromatics), 1581 (aromatics), 1491 (aromatics), 1387 [$C(CH_3)_2$], 1099 (Si-O), 754 (aromatics).

R_f = 0.71 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

2-[2'-(2''-Triisopropylsilyloxyphenyl)ethylsulfonyl]benzothiazole 340



A solution of ammonium molybdate (490.3 mg, 0.40 mmol, 0.039 eq) in 30 % hydrogen peroxide (3.52 mL, 31.1 mmol, 2.9 eq) was added to a stirring solution of sulfide **338** (4.76 g, 10.7 mmol, 1 eq) in EtOH (38 mL) at 0 °C and the resulting solution was stirred for 18 h. Most of the solvent was removed under reduced pressure and the residue was dissolved in DCM (200 mL), washed with 0.5 M H_2SO_4 (100 mL), brine (2 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* (4.20 g, 82.3 %) as a brown solid. Recrystallisation from EtOH gave the pure *sulfone* (3.37 g, 66.0 %) as off-white needles.

δ_H (400 MHz; $CDCl_3$)

1.03 (d, 18H, J = 7.4 Hz, -CHC*H*$_3$), 1.18-1.27 (m, 3H, -C*H*CH$_3$), 3.22 (m, 2H, ArCH$_2$), 3.78 (m, 2H, -SO$_2$C*H*$_2$), 6.74 (d, 1H, J = 8.1 Hz, *H*-3''), 6.81 (dt, 1H, J = 0.8 Hz, 7.4 Hz, *H*-5''), 7.04 (dt, 1H, J = 1.7 Hz, 7.8 Hz, *H*-4''), 7.11 (dd, 1H, J = 1.6 Hz, 7.5 Hz, *H*-6''), 7.59 (dt, 1H, J = 1.4 Hz, 7.6 Hz, *H*-6), 7.63 (dt, 1H, J = 1.4 Hz, 7.6 Hz, *H*-5), 8.01 (dd, 1H, J = 1.2 Hz, 7.6 Hz, *H*-7), 8.20 (dd, 1H, J = 1.1 Hz, 8.6 Hz, *H*-4).

δ_C (100 MHz; $CDCl_3$)

13.04 (CH), 17.94 (CH$_3$), 24.52 (CH$_2$), 54.60 (CH$_2$), 118.01 (CH), 121.02 (CH), 122.23 (CH), 125.49 (CH), 126.86 (C), 127.51 (CH), 127.92 (CH), 128.23 (CH), 130.34 (CH), 136.86 (C), 152.78 (C), 154.02 (C), 165.75 (C).

MS *m/z* (FAB$^+$) 476.1 [(M+H)$^+$, 80 %], 432.1 (100), 312.1 (15), 277.2 (26), 163.1 (24), 115.3 (21), 73.8 (26), 60.0 (43); $C_{24}H_{34}NO_3S_2Si$ calculated 476.1749, observed 476.1749.

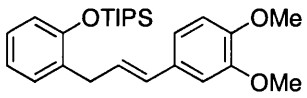
Microanalysis $C_{24}H_{33}NO_3S_2Si$ requires C 60.59 %, H 6.99, N 2.94 %, S 13.48 % found C 60.51 %, H 6.91 %, N 3.08 %, S 13.54 %.

IR ν_{max} (golden gate) 2918 (CH$_2$), 1591 (aromatics), 1491 (aromatics), 1327 (SO$_2$), 1130 (SO$_2$), 1061 (Si-O), 775 (aromatics).

mp = 135.5 – 136.0 °C.

R_f = 0.57 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

2-(3',4'-Dimethoxyphenyl)-3-(2''-triisopropylsilyl-phenyl)-propene 338

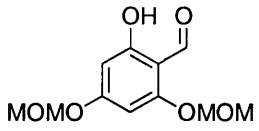


LDA (2 M in THF/heptane/ethylbenzene, 0.23 mL, 0.46 mmol, 1.1 eq) was added dropwise to a solution of sulfone **340** (200.0 mg, 0.42 mmol, 1eq) and veratraldehyde **341** (76.9 mg, 0.46 mmol, 1.1 eq) in dry THF (2 mL) at –78 °C under argon. The solution was allowed to slowly warm to room temperature over 24 h, then diluted with DCM (10 mL) and washed with 1 M HCl (10 mL). The aqueous layer was then extracted with DCM (2 x 10 mL) and the combined organics were washed with 1 M NaOH (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *E-alkene* (199.3 mg) as a brown oil. ^{1}H NMR showed a 5:1 mixture of product to starting material. Purification of the mixture was unsuccessful.

δ_H (400 MHz; $CDCl_3$)

1.13 (d, 18H, J = 7.4 Hz, -CHC*H*$_3$), 1.30-1.37 (m, 3H, -C*H*CH$_3$), 3.55 (d, 2H, J = 6.4 Hz, ArC*H*$_2$), 3.87 (s, 6H, -OC*H*$_3$), 6.25 (dt, 1H, J = 15.8 Hz, 6.5 Hz, ArCH=C*H*), 6.36 (d, 1H, J = 15.8 Hz, ArC*H*=CH), 6.78-6.88 (m, 5H, Ar-*H*), 7.08 (dt, 1H, J = 1.7 Hz, 7.7 Hz, Ar-*H*), 7.18 (dd, 1H, J = 1.7 Hz, 7.4 Hz, Ar-*H*).

2,4-bis(Methoxymethoxy)-6-hydroxybenzaldehyde 345



Diisopropylethylamine (11.8 mL, 58.2 mmol, 5.25 eq) was added dropwise over 10 min to a suspension of chloromethyl methyl ether (4.93 mL, 64.9 mmol, 5 eq) and aldehyde **299** (2.00 g, 13.0 mmol, 1 eq) in dry DCM (20 mL) at 0 °C under argon. The mixture was stirred for 4 h and the reaction mixture was concentrated under

reduced pressure. The residue was taken up in EtOAc (100 mL) and washed with water (100 mL). The aqueous layer was extracted with EtOAc (4 x 30 mL) and the combined organics were washed with cold 0.5 M HCl (30 mL), 2 M KOH (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde[3] (1.40 g, 44.6 %) as a brown oil. The base layer was carefully acidified and extracted into DCM (100 mL) which was then dried ($MgSO_4$) and concentrated under reduced pressure to give crude aldehyde[121] (1.27 g, 40.5 %) as a brown oil to give a combined yield of 85.1 %. The combined aldehyde was purified by column chromatography on silica, eluting DCM to give the pure aldehyde (1.03 g, 32.8 %) as a white solid.

δ_H (400 MHz; $CDCl_3$)

3.40 (s, 3H, -OC*H*$_3$), 3.44 (s, 3H, -OC*H*$_3$), 5.11 (s, 2H, -OC*H*$_2$O), 5.14 (s, 2H, -OC*H*$_2$O), 6.15 (d, 1H, J = 2.0 Hz, *H*-5), 6.18 (d, 1H, J = 2.1 Hz, *H*-3), 10.09 (s, 1H, -C*H*O), 12.21 (s, 1H, -O*H*).

δ_C (100 MHz; $CDCl_3$)

56.46 (CH_3), 56.60 (CH_3), 94.03 (CH_2), 94.08 (CH), 94.58 (CH_2), 96.54 (CH), 106.86 (C), 161.22 (C), 165.44 (C), 165.60 (C), 192.10 (CH).

MS *m/z* (EI^+) 242.1 ($M^{+\cdot}$, 100 %), 214.1 (20), 197.1 (78), 182.1 (18), 181.1 (15), 167.1 (14), 83.0 (17), 69.0 (18); $C_{11}H_{14}O_6$ calculated 242.0790, observed 242.0793.

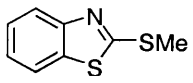
Microanalysis $C_{11}H_{14}O_6$ requires C 54.55 %, H 5.83 % found C 54.54 %, H 5.86 %.

IR ν_{max} (golden gate) 2908 (CH_2), 1614 (CHO) .

mp = 68 – 69 °C.

R_f = 0.18 (silica, DCM).

2-(Methylthio)benzothiazole 346



Methyl iodide (8.20 mL, 131.5 mmol, 1.1 eq) was added to a solution of 2-mercaptobenzothiazole **339** (20.00 g, 119.6 mmol, 1 eq) and potassium carbonate (18.20 g, 131.5 mmol, 1.1 eq) in acetone (200 mL). The mixture was then heated to reflux for 7.5 h before being quenched with EtOAc (2 x 400 mL), washed with approx. 2 M ammonia (400 mL), water (400 mL), dried ($MgSO_4$) and concentrated

under reduced pressure to give the sulfide[122] (20.01 g, 92.3 %) as a brown/yellow solid.

δ_H (400 MHz; $CDCl_3$)

2.78 (s, 3H, -SC*H*$_3$), 7.27 (dt, 1H, J = 1.1 Hz, 7.7 Hz, *H*-6), 7.40 (dt, 1H, J = 1.2 Hz, 7.7 Hz, *H*-5), 7.74 (dd, 1H, J = 1.1 Hz, 8.5 Hz, *H*-7), 7.87 (dd, 1H, J = 0.9 Hz, 8.7 Hz, *H*-4).

δ_C (100 MHz; $CDCl_3$)

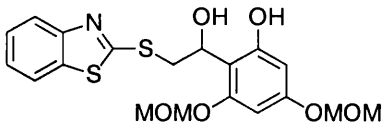
15.86 (CH_3), 120.89 (CH), 121.32 (CH), 124.02 (CH), 125.99 (CH), 135.09 (C), 153.31 (C), 167.99 (C).

MS *m/z* (EI^+) 181.0 ($M^{+\cdot}$, 100 %), 180.0 (22), 148.1 (70), 136.1 (17), 108.0 (33), 69.0 (17), 45.0 (13); $C_8H_7NS_2$ calculated 181.0020, observed 181.0021.

Microanalysis $C_8H_7NS_2$ requires C 53.01 %, H 3.89 %, N 7.73 %, S 35.38 %, found C 53.03 %, H 3.80 %, N 7.62 %, S 35.52 %.

mp = 46 – 47 °C.

2-[2'-(Benzothiazol-2''-ylsulfanyl)-1'-hydroxyethyl]-3,5-bis(methoxymethoxy)phenol 347



LDA (2 M in THF/heptane/ethylbenzene, 2.27 mL, 4.54 mmol, 2.2 eq), was added over 15 min to a solution of sulfide **346** (748.4 mg, 4.13 mmol, 2.0 eq) in dry THF (7 mL) at –78 °C under an atmosphere of argon. The mixture was stirred at –78 °C for 1 h then a solution of aldehyde **345** (500.0 mg, 2.06 mmol, 1 eq) in dry THF (5 mL) was added over 5 min and the solution was allowed to slowly warm to room temp. over 20 h. The reaction mixture was quenched with water (50 mL) and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organics were washed with water (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *sulfide* (853.3 mg, 97.6 %) as a viscous brown oil. Filtration through a plug of silica eluting petroleum ether (40 – 60 °C):EtOAc (6:1) then MeOH, gave cleaner *sulfide* (434.7 mg, 50.1 %) as a viscous yellow oil.

δ_H (400 MHz; $CDCl_3$)

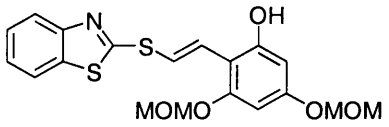
3.47 (s, 3H, -OC*H*$_3$), 3.48 (s, 3H, -OC*H*$_3$), 3.56 (dd, 1H, J = 2.1 Hz, 14.9 Hz, -C*H*$_a$H$_b$), 3.73 (dd, 1H, J = 7.2 Hz, 14.9 Hz, -CH$_a$*H*$_b$), 5.13 (s, 2H, -OC*H*$_2$O), 5.16 (d, 1H, J = 6.5 Hz, -OC*H*HO), 5.19 (d, 1H, J = 6.5 Hz, -OCH*H*O), *5*.70 (dd, 1H, J = 2.1 Hz, 7.2 Hz, -C*H*OH), 6.30 (d, 1H, J = 2.3 Hz, *H*-6), 6.32 (d, 1H, J = 2.3 Hz, *H*-4), 7.36 (dt, 1H, J = 1.0 Hz, 7.7 Hz, *H*-6''), 7.47 (dt, 1H, J = 1.1 Hz, 8.3 Hz, *H*-5''), 7.77 (d, 1H, J = 7.9 Hz, *H*-7''), 7.88 (d, 1H, J = 8.1 Hz, *H*-4''), 9.97 (br s, 1H, -O*H*).

δ_C (100 MHz; $CDCl_3$)

41.36 (CH_2), 56.08 (CH_3), 56.39 (CH_3), 72.52 (CH), 94.37 (CH_2), 94.53 (CH_2), 94.67 (CH), 98.64 (CH), 107.45 (C), 121.07 (CH), 121.19 (CH), 124.97 (CH), 126.53 (CH), 135.39 (C), 151.70 (C), 154.84 (C), 158.40 (C), 158.50 (C), 169.10 (C).

MS *m/z* (FAB$^+$) 446.0 [(M+Na)$^+$, 10 %], 406.0 (54), 281.0 (15), 207.0 (21), 180.9 (24), 147.0 (19), 73.7 (59), 46.1 (100); $C_{19}H_{21}NO_6S_2Na$ calculated 446.0708, observed 446.0709.

2-[2'-(Benzothiazol-2''-ylsulfanyl)-vinyl]-3,5-bis(methoxymethoxy)phenol 348



LDA (2 M in THF/heptane/ethylbenzene, 2.20 mL, 4.33 mmol, 2.1 eq), was added dropwise over 10 min to a solution of sulfide **351** (1.10 g, 4.33 mmol, 2.1 eq) in dry THF (20 mL) under argon at –78 °C. The solution was stirred for 1 h before a solution of aldehyde **345** (500.0 mg, 2.06 mmol, 1 eq) in dry THF (10 mL) was added over 10 min. The mixture was removed from the dry ice bath and allowed to warm slowly to room temp. over 17 h. The reaction was quenched with water (50 mL) and extracted into Et_2O (3 x 50 mL). The combined organics were washed with water (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the *vinyl sulfide* (786.0 mg, 81 %) as a yellow solid. The solid was washed with hexane and dried under high vacuum to give the pure vinyl sulfide (274.4 mg, 32.8 %) as an off-white solid [*E*:*Z* 10:1 from ^{1}H NMR]. Recrystallisation from *i*-PrOH gave the pure *E-vinyl sulfide* as an amorphous solid.

δ_H (400 MHz; $CDCl_3$)

3.43 (s, 3H, -OC*H*$_3$), 3.49 (s, 3H, -OC*H*$_3$), 5.08 (s, 2H, -OC*H*$_2$O), 5.16 (s, 2H, -OC*H*$_2$O), 6.27 (d, 1H, J = 2.2 Hz, *H*-6), 6.32 (d, 1H, J = 2.2 Hz, *H*-4), 7.29 (dt, 1H, J = 1.1 Hz, 8.1 Hz, *H*-6''), 7.32 (d, 1H, J = 15.5 Hz, -C*H*$_{2'}$=CH), 7.40 (dt, 1H, J = 1.1 Hz, 7.7 Hz, *H*-5''), 7.48 (d, 1H, J = 15.5 Hz, -CH=C*H*$_{1'}$), 7.75 (d, 1H, J = 7.7 Hz, *H*-7''), 7.90 (d, 1H, J = 8.1 Hz, *H*-4''), 7.99 (br s, 1H, -O*H*).

δ_C (100 MHz; $CDCl_3$)

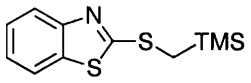
56.08 (CH_3), 56.33 (CH_3), 94.35 (CH_2), 94.77 (CH_2), 95.32 (CH), 97.75 (CH), 107.16 (C), 116.73 (CH), 120.97 (CH), 121.35 (CH), 124.31 (CH), 126.24 (CH), 132.29 (CH), 135.03 (C), 153.04 (C), 156.84 (C), 157.06 (C), 158.46 (C), 169.63 (C).

MS *m/z* (EI^+) 405.2 ($M^{+\cdot}$, 36 %), 238.2 (31), 194.1 (10), 167.1 (18), 162.1 (15); $C_{19}H_{19}NO_5S_2$ calculated 405.0705, observed 405.0704.

Microanalysis $C_{19}H_{19}NO_5S_2$ requires C 56.28 %, H 4.72 %, N 3.45 %, S 15.82 %, found C 56.32 %, H 4.73 %, N 3.68 %, S 15.98 %.

R_f = 0.62 [silica, ether].

2-(Trimethylsilylmethylthio)benzothiazole 351



Chloromethyltrimethylsilane (0.62 mL, 4.48 mmol, 1.5 eq) was added to a solution of 2-mercaptobenzothiazole **339** (500.0 mg, 2.99 mmol, 1.5 eq) and potassium carbonate (619.8 mg, 4.48 mmol, 1.5 eq) in acetone (10 mL) and the resulting mixture was heated to reflux for 75 min. After cooling, the mixture was diluted with Et_2O (150 mL), washed with dilute aqueous ammonia (2 x 50 mL), water (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude TMS sulfide[123] (680.7 mg, 89.8 %) as a yellow oil.

δ_H (400 MHz; $CDCl_3$)

0.21 (s, 9H, -SiC*H*$_3$), 2.62 (s, 2H, -SC*H*$_2$Si), 7.20 (dt, 1H, J = 1.2 Hz, 7.7 Hz, *H*-6), 7.28 (dt, 1H, J = 1.2 Hz, 7.6 Hz, *H*-5), 7.55 (dd, 1H, J = 0.5 Hz, 8.0 Hz, *H*-7), 7.66 (d, 1H, J = 8.1 Hz, *H*-4).

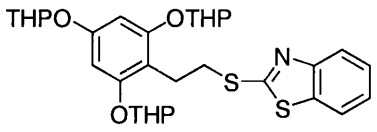
δ_C (100 MHz; $CDCl_3$)

-1.78 (CH_3), 18.94 (CH_2), 120.82 (CH), 121.19 (CH), 123.80 (CH), 126.88 (CH), 135.18 (C), 153.47 (C), 170.52 (C).

MS *m/z* (EI^+) 253.1 ($M^{+\cdot}$, 27 %), 238.0 (100) 206.1 (13), 192.0 (12), 149.0 (10), 83.0 (42), 73.1 (47); $C_{11}H_{15}NS_2Si$ calculated 253.0415, observed 253.0417.

R_f = 0.60 [silica, petroleum ether (40 – 60 °C):EtOAc (4:1)].

2-[2'-(2'',4'',6''-tris(Tetrahydropyranyloxy)phenyl)ethylsulfanyl]benzothiazole 355

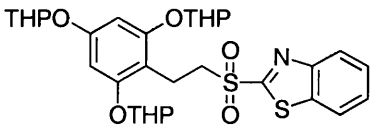


Potassium carbonate (117.0 mg, 0.85 mmol, 1.1 eq) was added to a solution of iodide **366** (410.0 mg, 0.77 mmol, 1 eq) and 2-mercaptobenzothiazole **339** (142.0 mg, 0.85 mmol, 1.1 eq) in acetone (8.2 mL) at room temp. The mixture was heated to reflux and left for 23 h. After cooling, the mixture was diluted with Et_2O (60 mL) and washed with 1 M KOH (30 mL). The aqueous layer was re-extracted with Et_2O (20 mL) and the combined organics were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *sulfide* (400.0 mg, 90.9 %) as a yellow gum. Purification by column chromatography [alumina 6 % water, hexane:Et_2O (20:1-5:1)] gave the pure *sulfide* (140.0 mg, 31.8 %) as a viscous oil as a 1:2:1 mixture of diastereomers A:B:C.

δ_H (400 MHz; $CDCl_3$)

1.44-1.92 (m, 18H, -C*H*$_2$), 3.05-3.22 (m, 2H, ArC*H*$_2$), 3.46-3.55 (m, 5H, -C*H*$_2$ and -C*H*$_2$S), 3.76-3.89 (m, 3H, -C*H*$_2$), 5.29-5.36 (m, 3H, -OC*H*O), 6.48 (s, 2H, Ar-*H*, minor B), 6.50 (s, 2H, Ar-*H*, major A), 6.53 (s, 2H, Ar-*H*, minor C), 7.19 (dt, 1H, J = 1.1 Hz, 8.1 Hz, *H*-6), 7.32 (dt, 1H, J = 1.1 Hz, 7.7 Hz, *H*-5), 7.66 (d, 1H, J = 7.7 Hz, *H*-7), 7.76 (d, 1H, J = 8.1 Hz, *H*-4).

2-{2'-[2'',4'',6''-tris(Tetrahydropyranyloxy)phenyl]ethanesulfonyl}benzothiazole 356



A solution of ammonium molybdate (11 mg, 0.009 mmol, 0.037 eq) in 30 % hydrogen peroxide (0.08 mL) was added to a solution of sulfide **355** (140 mg, 0.25 mmol, 1 eq) in EtOH (1 mL) at 0 °C. The solution was allowed to warm to room temp. and left overnight. Most of the EtOH was removed and the residue was dissolved in DCM (30 mL) and washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *sulfone* (7 mg) as a brown gum. ^1H NMR showed a complex mixture of many compounds.

Alternative procedure:

Oxone (3.67 g, 5.97 mmol, 3 eq) was added to a solution of sulfide **355** (853 mg, 1.49 mmol, 1 eq) in DMF (10 mL) at room temp. The resulting solution was stirred at room temp for 2.5 h, diluted with EtOAc (70 mL) washed with water (4 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *sulfone* (800.0 mg, 90.1 %) as a dark red glass. ^1H NMR showed no desired product.

Alternative procedure:

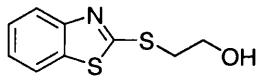
tert-Butyllithium (1.5 M in pentane, 0.59 mL, 0.89 mmol, 2 eq) was added dropwise to a solution of acetal **311** (337.5 mg, 0.89 mmol, 2 eq) in THF (1 mL) at –78 °C under argon. The yellow solution was allowed to warm slowly over 70 min. then placed in an ice-bath and freshly dried and ground copper iodide (178.3 mg, 0.94 mmol, 2.1 eq) was added. The resulting dark brown/yellow solution was stirred in the ice-bath for 15 min. then re-cooled to –78 °C and a solution of freshly dried vinyl sulfone **359** (100.0 mg, 0.45 mmol, 1 eq) in THF (0.5 mL) was added dropwise. The resulting solution was allowed to warm slowly over 70 min. then diluted with EtOAc

(15 mL). The organics were washed with NH_4Cl (3 x 30 mL), water (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *sulfone* (313.9 mg) as an off-white foam. Recrystallisation from EtOH gave the pure *sulfone* (46.6 mg, 17.3 %) as a 1:1:1 mixture of three diastereomers A:B:C as a clear cube.

δ_H (400 MHz; $CDCl_3$)

1.46-1.97 (m, 18H, -C*H*$_2$), 3.17-3.23 (m, 2H, -C*H*$_2$), 3.54-3.58 (m, 3H, -C*H*$_2$), 3.58-3.91 (m, 5H, -C*H*$_2$ + -SO_2C*H*$_2$), 5.30-5.39 (m, 3H, -OC*H*O), 6.48 (s, 2H, Ar-*H*, minor B), 6.49 (s, 2H, Ar-*H*, major A), 6.52 (s, 2H, Ar-*H*, minor C), 7.59 (dt, 1H, J = 1.5 Hz, 7.6 Hz, Ar-*H*), 7.63 (dt, 1H, J = 1.3 Hz, 7.4 Hz, Ar-*H*) 8.02 (dd, 1H, J = 0.9 Hz, 7.9 Hz, Ar-*H*), 8.20 (dd, 1H, J = 1.0 Hz, 7.3 Hz, Ar-*H*).

2-[(Benzothiazol-2'-yl)sulfanyl]ethanol 357



A mixture of 2-mercaptobenzothiazole **339** (40.00 g, 239.16 mmol, 1 eq), potassium carbonate (39.66 g, 286.99 mmol, 1.2 eq) potassium iodide (3.97 g, 23.92 mmol, 0.1 eq) and 2-chloroethanol (19.22 mL, 286.99 mmol, 1.2 eq) in acetone (400 mL) was heated to reflux for 3 d. The mixture was allowed to cool to room temp., filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in EtOAc (500 mL), washed with 1 M KOH (300 mL), dilute aqueous ammonia (300 mL), water (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude sulfide[124] (48.86 g, 96.7 %) as a yellow solid. A small quantity was recrystallised from Et_2O/hexane to give yellow needles.

δ_H (400 MHz; $CDCl_3$)

3.51 (t, 2H, J = 5.2 Hz, -SO_2C*H*$_2$), 4.08 (m, 3H, -CH_2C*H*$_2$ and -O*H*), 7.30 (dt, 1H, J = 1.0 Hz, 8.1 Hz, Ar-*H*), 7.41 (dt, 1H, J = 1.1 Hz, 8.2 Hz, Ar-*H*), 7.74 (dd, 1H, J = 0.4 Hz, 8.0 Hz, Ar-*H*), 7.84 (d, 1H, J = 8.2 Hz, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

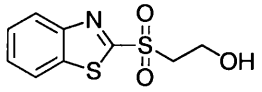
36.55 (CH_2), 62.56 (CH_2), 120.99 (CH), 121.29 (CH), 124.52 (CH), 126.18 (CH), 135.39 (C), 152.51 (C), 167.30 (C).

MS *m/z* (EI^+) 211.1 ($M^{+\cdot}$, 22 %), 181.1 (17), 167.0 (100), 148.1 (10), 136.1 (11), 108.1 (14); $C_9H_9NOS_2$ calculated 211.0126, observed 211.0126.

Microanalysis $C_9H_9NOS_2$ requires C 51.16 %, H 4.29 %, N 6.63 %, found C 51.17 %, H 4.24 %, N 6.60 %.

mp = 51 - 52 °C [lit.[124] 53 – 55 °C].

2-[(Benzothiazol-2'-yl)sulfonyl]ethanol 358



A solution of ammonium molybdate (5.49 g, 4.44 mmol, 0.037 eq) in 30 % hydrogen peroxide (39.2 mL, 348.32 mmol, 2.9 eq) was added slowly to a solution of sulfide **357** (25.38 g, 120.11 mmol, 1 eq) in EtOH (210 mL) at 0 °C. The solution was allowed to warm to room temp. and stirred for a further 40 h. The mixture was diluted with DCM (600 mL), washed with 0.5 M H_2SO_4 (250 mL), brine (250 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude sulfone[137] (26.35 g, 90.2 %) as a fluffy white solid.

δ_H (400 MHz; $CDCl_3$)

2.97 (t, 1H, J = 6.7 Hz, -O*H*), 3.77 (t, 2H, J = 5.2 Hz, -SO_2CH_2), 4.21 (m, 2H, -CH_2CH_2), 7.62 (dt, 1H, J = 1.4 Hz, 7.6 Hz, Ar-*H*), 7.67 (dt, 1H, J = 1.5 Hz, 7.6 Hz, Ar-*H*), 8.04 (dd, 1H, J = 1.4 Hz, 7.4 Hz, Ar-*H*), 8.22 (dd, 1H, J = 1.3 Hz, 7.4 Hz, Ar-*H*).

δ_C (100 MHz; $CDCl_3$)

56.38 (CH_2), 57.66 (CH_2), 122.38 (CH), 125.36 (CH), 127.84 (CH), 128.26 (CH), 136.52 (C), 152.32 (C), 166.16 (C).

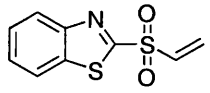
MS *m/z* (EI^+) 243.1 ($M^{+\cdot}$, 8 %), 151.1 (17), 135.1 (100), 108.0 (20); $C_9H_9NO_3S_2$ calculated 243.0024, observed 243.0022.

Microanalysis $C_9H_9NO_3S_2$ requires C 44.43 %, H 3.73 %, N 5.76 %, S 26.36 %, found C 44.24 %, H 3.62 %, N 5.71 %, S 26.26 %.

IR ν_{max} (golden gate) 3386 (OH), 2964 (CH_2), 2927 (CH_2), 2881 (CH_2), 1612 (aromatics), 1512 (aromatics), 1471 (aromatics), 1321 (SO_2), 1126 (SO_2), 754 (aromatics).

mp = 114 – 114.5 °C [lit.[137] 101 – 102 °C].

2-(Vinylsulfonyl)-benzothiazole 359



Methanesulfonyl chloride (0.64 mL, 8.22 mmol, 2 eq) was added slowly to a solution of sulfone **358** (1.00 g, 4.11 mmol, 1 eq) in a 50:50 mixture of DCM/Et_3N at 0 °C under argon. The solution allowed to warm to room temp. and stirred for 8 h. The solution was diluted with DCM (50 mL), washed with 2 M HCl (30 mL), $NaHCO_3$ (2 x 30 mL), water (3 x 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude vinyl sulfone[137] (604.7 mg, 65.6 %) as a brown solid. Purification by column chromatography (silica eluting DCM) gave the pure vinyl sulfone (420.3 mg, 45.6 %) as an amorphous off-white solid. A small quantity was recrystallised from EtOH, to give pure vinyl sulfone as an amorphous white solid.

δ_H (400 MHz; $CDCl_3$)

6.44 (dd, 1H, J = 0.7 Hz, 9.8 Hz, CH=C$H_{cis}H_{trans}$), 6.74 (dd, 1H, J = 0.7 Hz, 16.6 Hz, CH=C$H_{cis}H_{trans}$), 6.99 dd, 1H, 9.8 Hz, 16.6 Hz, H_c), 7.58 (dt, 1H, J = 1.4 Hz, 7.6 Hz, *H*-6), 7.64 (dt, 1H, J = 1.5 Hz, 7.6 Hz, *H*-5), 8.01 (dd, 1H, J = 1.1 Hz, 7.1 Hz, *H*-7), 8.22 (dd, 1H, J = 1.1 Hz, 7.2 Hz, *H*-4).

δ_C (100 MHz; $CDCl_3$)

122.28 (CH), 125.48 (CH), 127.66 (CH), 128.06 (CH), 132.23 (CH_2), 135.89 (C), 136.89 (CH), 152.80 (C), 165.98 (C).

MS *m/z* (EI^+) 225.1 ($M^{+\cdot}$, 100 %), 160.1 (91), 135.1 (81), 134.1 (43), 108.0 (42), 90.1 (32), 69.0 (24), 63.0 (22); $C_9H_7NO_2S_2$ calculated 224.9918, observed 224.9919.

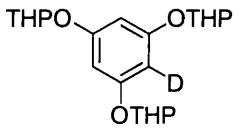
Microanalysis $C_9H_7NO_2S_2$ requires C 48.20 %, H 3.15 %, N 6.25 %, S 28.59 %, found C 47.98 %, H 2.95 %, N 6.18 %, S 28.61 %.

IR ν_{max} (golden gate) 1604 (aromatics), 1550 (aromatics), 1469 (aromatics), 1319 (SO_2), 1142 (SO_2), 984 ($CH{=}CH_2$), 945 ($CH{=}CH_2$), 764 (aromatics).

mp = 87 – 89 °C [lit.[137] 86 – 88 °C (n-PrOH)].

R_f = 0.26 (silica, DCM).

1-Deuterio-2,4,6-tris(tetrahydropyranyl)benzene 360

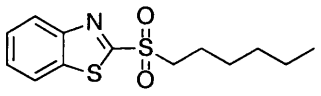


tert-Butyllithium (1.5 M in pentane, 0.35 mL, 0.53 mmol, 1 eq), was added to a solution of freshly dried acetal **311** (200 mg, 0.53 mmol, 1 eq) in THF (2 mL) at –78 °C under argon. The solution was allowed to warm 0 °C over 1 h then MeOD (0.5 mL) was added and the solution was allowed to warm to room temp. over 2 h. The mixture was concentrated under reduced pressure, the residue was dissolved in DCM (10 mL) and washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *acetal* (200 mg, 99.8 %) as a white amorphous solid as a 2:1 mixture of diastereomers A:B.

δ_H (400 MHz; $CDCl_3$)

1.54-1.71 (m, 9H, -C*H*$_2$), 1.80-1.86 (m, 6H, -C*H*$_2$), 1.93-2.04 (m, 3H, -C*H*$_2$), 3.58-3.62 (m, 3H, -OC*H*$_2$), 3.89-3.94 (m, 3H, -OC*H*$_2$), 5.35-5.40 (m, 3H, -OC*H*O), 6.43 (s, 2H, Ar-*H*, minor), 6.44 (s, 2H, Ar-*H*, major).

2-(Hexane-1'-sulfonyl)benzothiazole 361



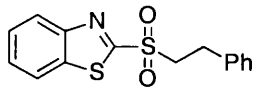
n-Butyllithium (1.6 M in hexanes, 0.56 mL, 0.89 mmol, 1 eq) was added to a solution of freshly dried sulfone **359** (200 mg, 0.89 mmol, 1 eq) in THF (2 mL) at 0 °C under argon. The bright yellow/orange solution was allowed to warm to room temp. over 15 h. The dark red solution was quenched with 0.5 M HCl (10 mL) and extracted into

DCM (30 mL). The organics were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude sulfone[118] (170.5 mg, 81.9 %) as a bright orange oil. Purification by column chromatography on silica eluting DCM gave purer sulfone (26 mg, 12.5 %) as a bright yellow oil. The ^1H NMR spectrum showed an inseparable mixture of **360** and **364**.

Alternative procedure:

n-Butyllithium (1.6 M in hexanes, 1.12 mL, 1.78 mmol, 2 eq) was added to a suspension of freshly dried copper iodide (169.8 mg, 0.89 mmol, 1 eq) in THF (2 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h then cooled to -78 °C and a solution of freshly dried sulfone **359** (200 mg, 0.89 mmol, 1 eq) in THF (1 mL) was added slowly. The resulting mixture was allowed to warm slowly to room temp. over 5.5 h, then worked-up as above to give the crude sulfone[118] (35.4 mg, 17 %) as a yellow oil. Analysis of the ^1H NMR spectrum showed the presence of the alkyl chain, but the integrations did not match the product.

2-(2'-Phenylethanesulfonyl)benzothiazole 362



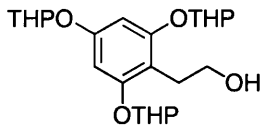
Phenyllithium (0.58 M in cyclohexane/ether, 1.51 mL, 0.89 mmol, 1 eq) was added to a solution of freshly dried sulfone **359** (200 mg, 0.89 mmol, 1 eq) in THF (1 mL) at -78 °C under argon. The resulting orange solution was allowed to warm to room temp. over 17 h then worked-up as above to give the crude sulfone[123] (190.5 mg, 70.6 %) as a yellow oil. The ^1H NMR spectrum showed no product, but what looked like benzothiazole **362**.

Alternative procedure:

Phenyllithium (0.58 M in cyclohexane/ether, 1.51 mL, 0.89 mmol, 1 eq) was added to a suspension of copper bromide dimethyl sulfide complex (183.3 mg, 0.89 mmol, 1 eq) in Et_2O (1 mL) at 0 °C under argon. The resulting mixture was stirred at 0 °C for 1

h then cooled to -78 °C and a solution of freshly dried sulfone **359** (200 mg, 0.89 mmol, 1 eq) in Et_2O (1 mL) was added slowly. The resulting mixture was allowed to warm to room temp. over 17 h the worked-up as above to give the crude sulfone[123] (156.4 mg, 58.0 %) as a yellow oil. The ^1H NMR spectrum was similar to that above.

2-[2',4',6'-tris(Tetrahydropyranyloxy)phenyl]ethyl alcohol 366



Ozone (oxygen flow = 70, voltage = 120) was bubbled through a solution of **312** [(5.19 g, 5.97 mmol, 1 eq), as a 1:1 mixture of **311:312**] in a 50:50 mix of EtOH:DCM (60 mL) at –78 °C for 3 h. Oxygen was bubbled through the solution for 15 min then EtOH (50 mL) and $NaBH_4$ (500 mg, 11.94 mmol, 2 eq) were added. The solution was stirred at room temp overnight then diluted with DCM (200 mL), washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *alcohol* (4.75 g) as a pale yellow viscous gum. Purification by column chromatography [alumina deactivated with 6 % water, eluting with Et_2O:hexane (3:2)] gave the pure *alcohol* (1.66 g, 66 %) as a 1:2:1 mixture of diastereomers A:B:C and recovered **311** (2.2 g, 85 %).

δ_H (400 MHz; $CDCl_3$)

1.54-1.69 (m, 9H, -C*H*$_2$), 1.80-2.02 (m, 9H, -C*H*$_2$), 2.98 (t, 2H, J = 6.3 Hz, ArC*H*$_2$), 3.59-3.63 (m, 3H, -C*H*$_2$), 3.78-3.94 (m, 5H, -C*H*$_2$ + -C*H*$_2$OH), 5.37-5.41 (m, 3H, -OC*H*O), 6.57 (s, 2H, Ar-*H*, minor B), 6.59 (s, 2H, Ar-*H*, major A), 6.61 (s, 2H, Ar-*H*, minor C).

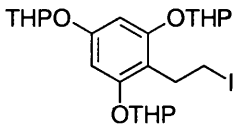
δ_C (100 MHz; $CDCl_3$)

18.60 (CH_2), 18.68 (CH_2), 18.74 (CH_2), 18.95 (CH_2), 19.01 (CH_2), 25.13 (CH_2), 25.16 (CH_2), 26.85 (CH_2), 30.19 (CH_2), 30.24 (CH_2), 30.32 (CH_2), 30.44 (CH_2), 30.49 (CH_2), 61.83 (CH_2), 61.91 (CH_2), 61.95 (CH_2), 62.17 (CH_2), 62.23 (CH_2), 63.02 (CH_2), 96.07 (CH), 96.45 (CH), 96.58 (CH), 96.64 (CH), 96.79 (CH), 96.90 (CH), 96.93 (CH), 97.04 (CH), 97.26 (CH), 97.83 (CH), 110.14 (C), 110.26 (C), 110.44 (C), 156.19 (C), 156.34 (C), 156.77 (C), 156.93 (C), 157.11 (C).

MS *m/z* (CI^+) 423.3 ($M^{+\cdot}$, 13 %), 339.3 (39), 311.3 (13), 255.2 (63), 227.2 (11), 171.1 (27), 170.1 (11), 85.1 (100), 84.1 (18); $C_{23}H_{34}O_7$ calculated 423.2383, observed 423.2382.

IR ν_{max} (neat) 3430 (OH), 2941 (CH_2), 2871 (CH_2), 1606 (aromatics), 1593 (aromatics), 1508 (aromatics), 1259 (OH), 1151 (C-OH).

2-[2', 4', 6'-tris(Tetrahydropyranyloxy)phenyl]ethyl iodide 367

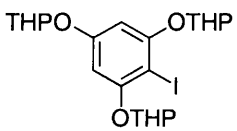


Triphenylphosphine (1.24 g, 4.71 mmol, 1.2 eq), imidazole (320.0 mg, 4.71 mmol, 1.2 eq) and iodine (1.20 g, 4.71 mmol, 1.2 eq) were added in order to a solution of alcohol **366** (1.66 g, 3.93 mmol, 1 eq) in DCM (16.6 mL) at room temp. under argon and shielded from the light. The resulting solution was stirred at room temp. for 6.5 h, diluted with DCM (150 mL) washed with 10 % aqueous sodium thiosulfate (2 x 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *iodide* (1.60 g) as a pale yellow viscous gum. The crude iodide was passed through a plug of alumina (6 % water) eluting hexane:Et_2O (5:1) and then columned [alumina eluting hexane:EtOAc (10:1)] to give cleaner iodide (410.0 mg, 20.5 %) as a viscous oil as a 2:1:1 mixture of diastereomers A:B:C. The iodide was found to be unstable and used immediately. Selected signals from the ^1H NMR spectrum are shown below.

δ_H (400 MHz; $CDCl_3$)

5.28-5.35 (m, 3H, -OC*H*O), 6.46 (s, 2H, Ar-*H*, minor B), 6.47 (s, 2H, Ar-*H*, major A), 6.50 (s, 2H, Ar-*H*, minor C).

1-Iodo-2,4,6-tris(tetrahydropyranyloxy)benzene 368

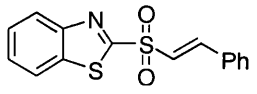


tert-Butyllithium (1.76 mL, 2.64 mmol, 2 eq) was added to a solution of acetal **311** (500 mg, 1.32 mmol, 1 eq) in THF (5 mL) at –78 °C under argon. The resulting yellow solution was allowed to warm over 70 min. then placed in an ice-bath. A solution of iodine (2.01 g, 2.64 mmol, 6 eq) in THF (10 mL) was added dropwise and the resulting solution was stirred for 75 min. then diluted with EtOAc (100 mL), washed with 10 % sodium thiosulfate (2 x 150 mL), water (2 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude *iodide* (641.2 mg, 96.2 %) as an off white sticky gum as a 5.5:1 mixture of products: starting material and as 2:1:1 mixture of diastereomers A:B:C. Purification by recrystallisation was unsuccessful and decomposed the product. Selected signals from the ^1H NMR spectrum are shown below.

δ_H (400 MHz; $CDCl_3$)

6.48 (s, 2H, Ar-*H*, minor B), 6.50 (s, 2H, Ar-*H*, major A), 6.57 (s, 2H, Ar-*H*, minor C).

2-(2'-Phenylethenesulfonyl)benzothiazole 369



Palladium acetate (4.9 mg, 0.02 mmol, 0.05 eq) was added to a solution of iodobenzene (0.05 mL, 0.43 mmol, 1 eq), triethylamine (0.08 mL, 0.54 mmol, 1.25 eq) and sulfone **359** (121.2 mg, 0.54 mmol, 1.25 eq) in acetonitrile (2 mL) at room temp. under argon. The resulting mixture was heated to reflux for 69 h, allowed to cool to room temp. then diluted with DCM (10 mL). The organics were washed with water (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude mixture (161.6 mg, 99.6 %) as a pale green oil. Purification by column chromatography on silica eluting DCM gave purer **369** (28.5 mg, 17.6 %) as a pale yellow oil. The ^1H NMR spectrum showed the presence of product as only the *trans* double bond, but only a small amount was present. Selected signals from the ^1H NMR spectrum are shown below.

δ_H (400 MHz; $CDCl_3$)

7.15 (d, 1H, J = 15.4 Hz, -CH=C*H*), 7.89 (d, 1H, J = 15.4 Hz, -C*H*=CH).

Alternative procedure A:

A mixture of sulfone **359** (44.9 mg, 0.2 mmol, 1 eq), palladium acetate (2.2 mg, 0.01 mmol, 0.05 eq) diisopropylethylamine (0.14 mL, 0.8 mmol, 4 eq) and bromobenzene (0.08 mL, 0.8 mmol, 4 eq) in 15 % aqueous DMF (1.38 mL) was placed in a microwave tube and degassed under an argon flow for 5 min. The tube was sealed and microwaved (50 W) for 10 min at 150 °C. The mixture was diluted with EtOAc (5 mL), washed with water (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude mixture (19.8 mg, 32.7 %) as a brown oil. The ^{1}H NMR spectrum showed what looked like saturated sulfone **361** and bromobenzene.

Alternative procedure B:

A mixture of sulfone **359** (44.9 mg, 0.2 mmol, 1 eq), palladium acetate (2.2 mg, 0.01 mmol, 0.05 eq) diisopropylethylamine (0.14 mL, 0.8 mmol, 4 eq), triphenylphosphine (6.3 mg, 0.024 mmol, 0.12 eq) and bromobenzene (0.08 mL, 0.8 mmol, 4 eq) in 15 % aqueous DMF (1.38 mL) was placed in a microwave tube and degassed under an argon flow for 5 min. The tube was sealed and microwaved (50 W) for 10 min at 150 °C. The mixture was diluted with EtOAc (5 mL), washed with water (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude mixture (19.8 mg, 32.7 %) as a brown oil. The ^{1}H NMR spectrum showed what looked like saturated sulfone **361** and bromobenzene. Selected signals from the ^{1}H NMR spectrum are shown below.

δ_H (400 MHz; $CDCl_3$)

3.64 (app. t, 2H, PhCH_2), 4.03 (app. t, 2H, -SO_2CH_2).

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