thesis titled:

"Investigations into the Synthesis of Dendralene Precursors and Epicatechins."

submitted for the Degree of Doctor of Philosophy (Ph.D.)

by

Penelope Jane Kerr

B.Sc. (Hons.)

from the

Department of Chemistry

The University of Adelaide

ADELAIDE
UNIVERSITY
AUSTRALIA

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Abstract

Two heterocyclic chemistry projects were investigated to establish whether new methods for the synthesis of substituted dendralene precursors and green tea catechins were viable.

The synthesis of a number of unique, substituted dendralene precursors was achieved in excellent yield using Stille coupling reactions with palladium catalysis between two different substituted vinyl triflates. Some of these precursors were oxidised using either OXONE or OXONE derivatives, to give sulfolene molecules or 'masked dendralenes' in high yields. The extrusion of sulfur dioxide from these unique substituted molecules using many different techniques proved to be extremely difficult compared to simple non-substituted sulfolenes. It was concluded that the combination of the two particular substituents acted to increase the stability of the sulfolene.

The second project investigated potentially new syntheses of the four main green tea catechins. Readily available, natural (+)-catechin (**1**) was transformed into epicatechin (**32**) and epicatechin gallate (**33**) derivatives by oxidation of the alcohol group at position-3 to the corresponding ketone. Of the many oxidising reagents investigated the Dess-Martin periodinane reagent provided the best yield of 38%. Reduction of the ketone using sodium borohydride and incorporating the use of stereoselective additives such as $CeCl_3$ afforded the epicatechin derivative (**32**). Esterification of the alcohol at position-3 of the epicatechin derivative (**32**) with 3,4,5-trimethoxybenzoic acid and DCC gave the epicatechin gallate derivative (**33**). Direct synthesis using allylation and acylation reactions were employed in an attempt to synthesise the other required catechin derivatives, epigallocatechin (**3**) and epigallocatechin gallate (**5**). Instead of providing the epicatechin molecules, the allylation reactions afforded a diallylated phloroglucinol species (**70**). The acylation

reaction of 1,3,5-trimethoxybenzene and a mixed anhydride formed from trifluoroacetic anhydride and a propiolic acid derivative furnished the novel chalcones such as **(95)** in one step, *via* acylation then Michael addition of 1,3,5-trimethoxybenzene to the β-position of the triple bond. The acylation reaction between 1,3,5-tribenzyloxybenzene and a substituted propioloyl chloride catalysed by a Lewis acid gave the aurone **(104)** in good yield when the Lewis acid was ferric chloride. A number of substituted acetylenic ketones and/or the corresponding hydrogen chloride adducts, were obtained in good yield when the Lewis acid was zinc chloride. The acetylenic ketones and the adducts had one of the benzyl group adjacent to the acyl substitutent removed *in situ* for which a mechanism is proposed, leaving these products perfectly set up for cyclisation. The cyclisation reactions of both the alkyne and hydrogen chloride-adducts using a broad range of reagents and conditions, gave aurones in excellent yields. In no case was the desired flavone observed indicating that the cyclisation of these species was not as simple as has been suggested in the literature.

Statement of Originality

This work contains no material which has been accepted for the award of any other degree of diploma in any university or other tertiary institution and, to the best of knowledge and belief, contains no material previously published or written by another person except where due reference has been made in the text.

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Penelope Jane Kerr

3/04/01
Date

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Part 1:

Investigations into the Synthesis of Substituted Dendralene Precursors.

(I)   Introduction

Dendralenes are unique acyclic, cyclic or bicyclic cross conjugated molecules.[1] These trienes are of particular interest since they contain the simplest possible cross-conjugated system,[2] represented by 3-dendralene (3-methylene-1,4-pentadiene) (**1**).
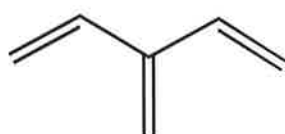
(1)

These novel systems are able to under go two successive Diels-Alder reactions; a reaction process termed the 'diene transmissive Diels-Alder' or 'Cascade Diels-Alder' reaction, as shown in Scheme 1.[3]

(2)   (3)   (4)
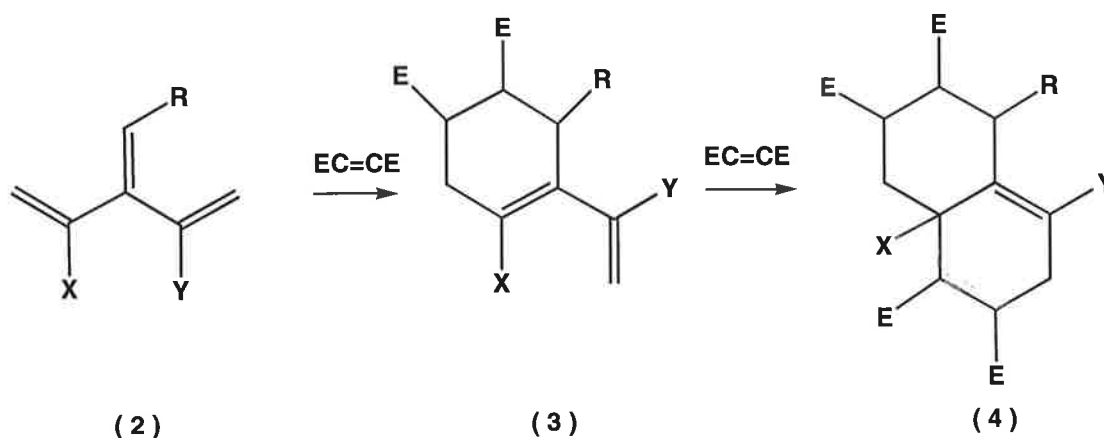
Scheme 1

An initial cycloaddition reaction with a dienophile across one of the diene parts of the triene (2) forms a ring and an endocyclic double bond (3) which then takes part in a second cycloaddition reaction with a dienophile which may be the same or different. A fused cyclic compound (4) is ultimately formed. The different moieties (**X, Y** and **R**), may play prominent roles in both activation of dienes and the regioselectivity of reactions,[1] whilst adding functionality onto the bicyclic product.[3] An attractive extension of the diene transmissive Diels-Alder, is a cross type of reaction in which two different dienophiles are used separately in each step.[4] This may be achieved by carefully controlling the reaction conditions.[5]

The regioselectivity of Diels-Alder cycloaddition can be controlled in a number of ways. Constraining one diene unit inside a cyclic structure such as in (5), forms a diene unit that is fixed in the *transoid* configuration and cannot participate in a Diels-Alder reaction.[6] Therefore a selective reaction at (**a**) is achieved. Secondly, regioselectivity may occur by the use of heteroatoms in place of carbon atoms, such as in (6). The heteroatom will usually confer electron deficiency to the diene and react preferentially with electron-rich dienophiles.[6] Another option combines inter- and intramolecular cycloadditions. In molecule (7), the intramolecular cycloaddition would be expected to proceed first regioselectively, because of geometric constraints. This would generate a diene which could then react intermolecularly.[6]

x = O, NR

(5)   (6)   (7)
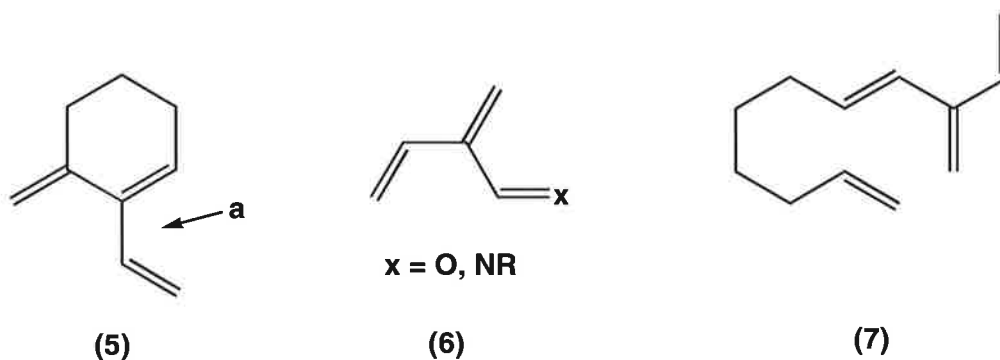
Regioselectivity of Diels-Alder cycloadditions can also be achieved by use of substituted dendralenes, such as (8).

a-diene　　　**b-diene**

(8)
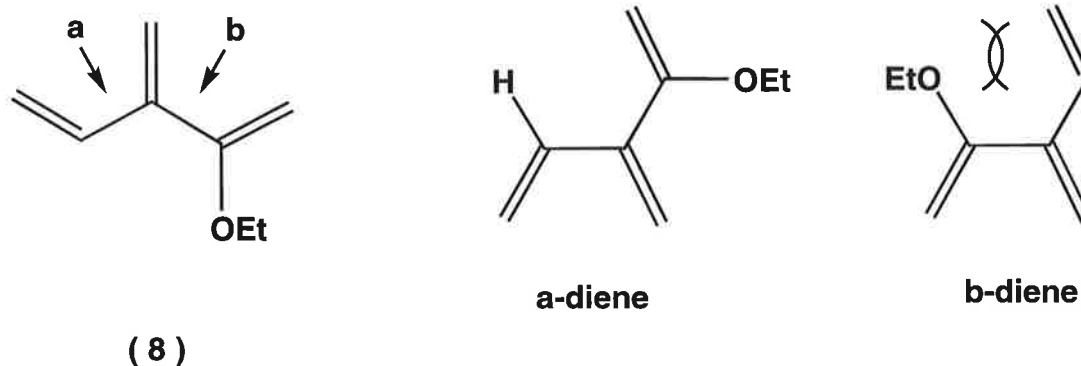
The initial Diels-Alder cycloaddition should occur at diene-**b**, due to electronic activation caused by the adjacent ethoxy group.　However, investigation of steric interactions revealed that diene-**b** cannot occupy a planar *s-cis* conformation because of hindrance between the ethoxy and vinyl substituents.　No serious hindrance was found to occur between the ethoxy-vinyl group and the hydrogen in the monosubstituted diene-**a**, which is why the reaction occurred across diene-**a**.[4]

The Diels-Alder reaction is one of the most reliable preparative methods in organic chemistry.[3]　With the aid of dendralenes, large sections of the carbon framework of complex polycycles may, in principle, be built up.[7]　The diene-transmissive Diels-Alder reaction, for example, has been used to generate complex quassinoid intermediates.[6]　The triene (**1**), for the same reason should be of interest as a cross-linking agent for vinyl polymers.[2]


(1)　　　　　　　　　　　　　　　　　　　**(9)**

Molecules like 3-dendralene (**1**), and 4-dendralene (**9**) are also interesting from a structural viewpoint, as it is not clear whether they prefer a planar structure,[7] or a

structure with a two-fold axis.[5,10] In order to study the spectroscopic and chemical properties of planar dendralenes, rotation about the single bonds must be prevented. Cyclic and bicyclic dendralenes have been used for such studies.[7] Another application of dendralenes is encountered in natural product and dyestuff chemistry, where π-systems in the majority of cases are polarised by heteroatoms and/or electron donating or accepting groups.[7] Such examples are provided by di- and tri-arylcarbenium dyes and their aza-analogues as well as many carbonyl dyes.[7]

Previous Syntheses of dendralenes.

Previously 3-dendralene has been prepared from (**10**) and (**11**) via ester pyrolysis, and Hofmann elimination of the ammonium salt (**12**) respectively (Scheme 2).[7]

OAc

OAc

(**10**)

(**1**)

(**11**) R=OAc
(**12**) R=$^+$NMe$_3$
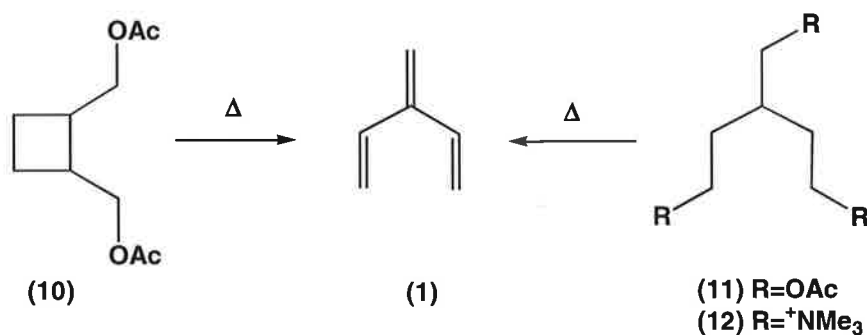
Scheme 2

In all cases 3-dendralene (**1**) was obtained in very small yields,[7,8] due to extensive losses caused by the formation of dimers during pyrolysis.[5]

It has been found that 3-dendralene can be prepared in good yields and in a pure state, as a stable and easily handled compound by masking the diene as a sulfone.[5] In a specific example, thermal extrusion of sulfur dioxide from the sulfolene derivative (**13**, R= CH=CH$_2$), afforded 3-dendralene cleanly and smoothly under flash vacuum pyrolytic conditions (Scheme 3).[5]
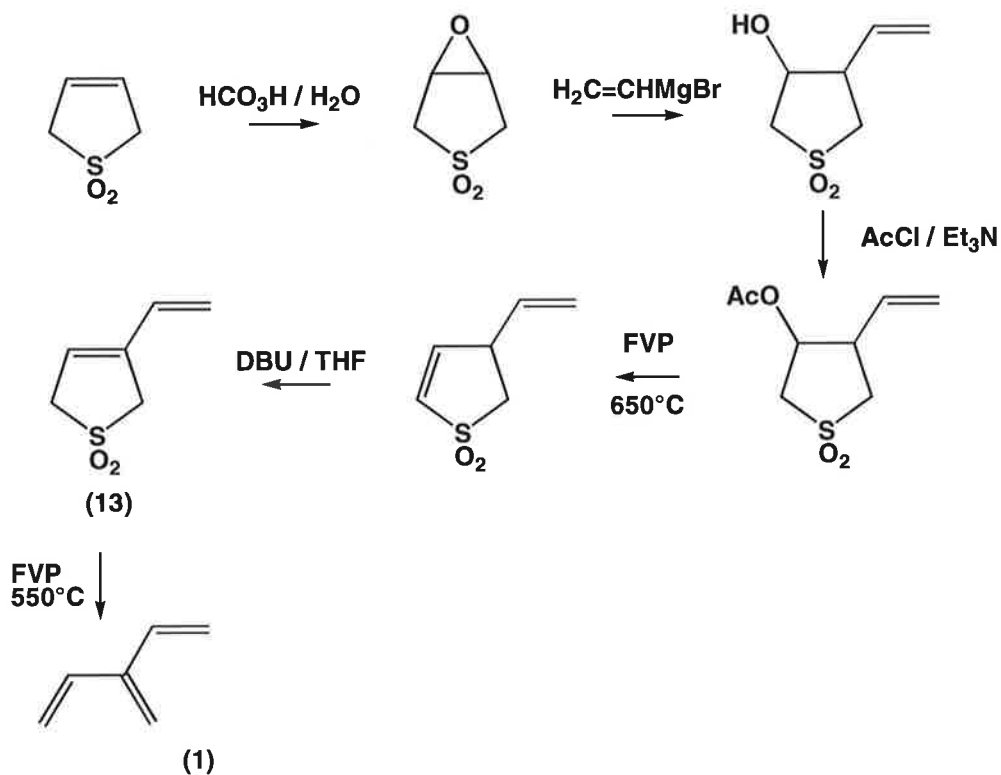
Scheme 3

However, this synthesis has drawbacks in that it is time consuming (the first steps take 45 days), provides poor overall yields of (**1**) (18% overall),[5] and does not allow for convergent introduction of functionality.

In the light of the documented instability of 3-dendralene (**1**),[5,9] a synthetic approach evolved involving the masking of each terminal butadiene residue as a 3-sulfolene (Scheme 4).[10]
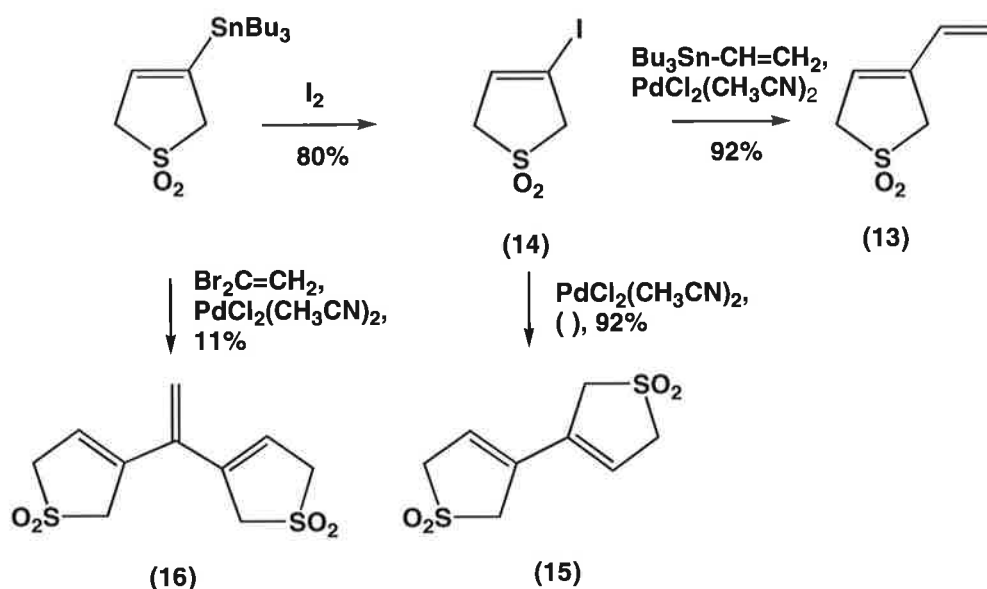
Scheme 4

Stille coupling provided a 3-dendralene precursor (**13**) from the iodo-sulfolene (**14**) in good yield. Similarly, a 4-dendralene precursor (**15**) and a 5-dendralene precursor (**16**) were synthesised using palladium catalysed coupling reactions in good and poor yields respectively.[10] Again this synthesis is designed to generate dendralene precursors containing no substitution.

A limited number of substituted dendralenes such as (**8**), have been synthesised in the past. Substituted dendralenes have been employed in the past as 3-dendralene has been found (in a number of cases)[11] to be too prone to polymerisation to be used in the diene-transmissive Diels-Alder reaction.[9] One method for the formation of substituted dendralenes used the two step procedure which is depicted in Scheme 5.[4]

(17)　　　　　　　**(18)**　　　　　　　**(19)**

(8)
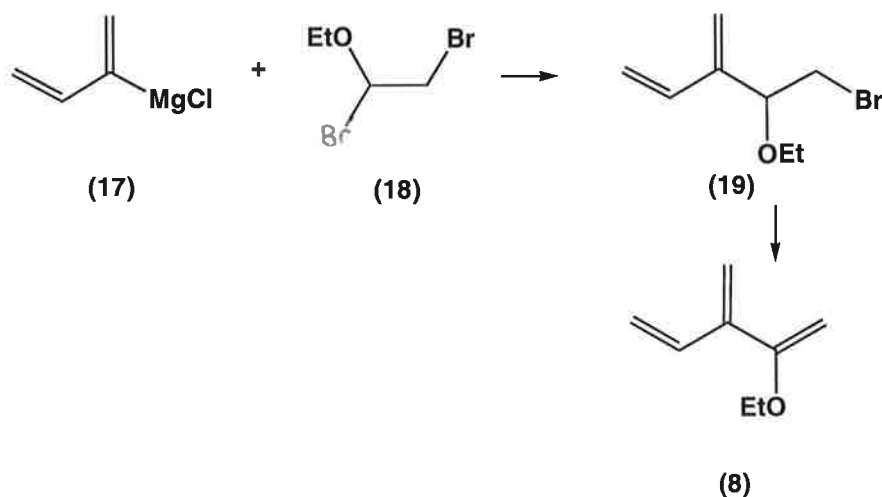
Scheme 5

The cross coupling reaction of 1-methylene-2-propenyl)magnesium chloride (**17**) with 1-ethoxy-1,2-dibromoethane (**18**), gave 2-(2-bromo-1-ethoxyethyl)-1,3-butadiene (**19**), which yielded the cross conjugated triene (**8**) upon dehydrobromination. Synthetically this procedure was low yielding, problems were encountered in the dehydrobromination step and contamination was observed in the final product.[4]

Alternate methods for synthesising conjugated dienes such as dendralenes include utilising organometallic reagents, modified Wittig reagents, thermal ring opening of cyclobutenes and most preferably, sulfolenes.[12]

Sulfolene chemistry as a precursor to dendralenes.

The use of functionalised 1,3-butadienes such as (**20**) in Diels-Alder reactions is a major route towards the formation of complex cyclic molecules.[13]

(21)　　　　　　　　　**(20)**

Scheme 6

7
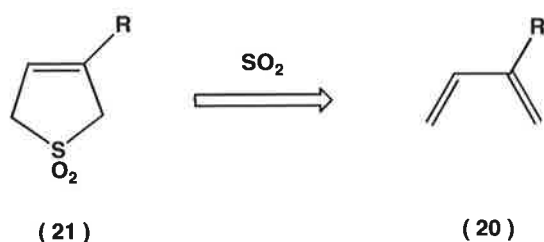
Recently there has been increased interest in studying deprotonation/substitution reactions of 3-sulfolenes such as (**21**), for the preparation of stable precursors for alkylated, acylated and silylated 1,3-butadienes.[13] When **R = CH=CH₂**, 3-dendralene (**1**) can be prepared upon elimination of sulfur dioxide from the sulfolene precursor (**21**) (Scheme 6).

Sulfolenes may be viewed as masked dienes in Diels-Alder reactions with a variety of dienophiles, and have the advantage of being stable to moderately basic, acidic and thermal conditions.[14] The masking of reactive dienes is important for the construction of polycylic molecules, such as (**22**) as shown in Scheme 7.[15] This is the basis of the approach by Cadogan and co-workers as discussed earlier,[5] and has allowed the controlled use of dendralenes as tandem-annealating reagents in Diels-Alder reactions.[5,16] In this example, the sulfolene molecule was utilised in two different ways resulting in different products. Firstly the reactivity of the furan moiety was increased by the fused sulfolene, with the result that it reacted intramolecularly with the attached vinyl group in preference to the masked diene, *via* route a. This intramolecular Diels-Alder reaction (IMDA) yielded product (**22**) after SO₂ extrusion.
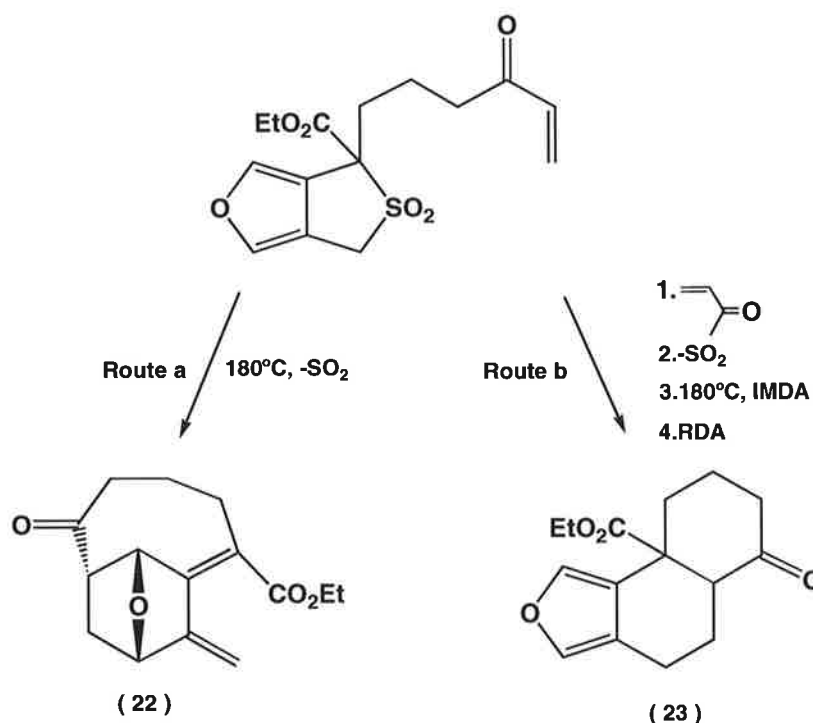
Scheme 7

Alternatively, the furan moiety can be protected using methyl vinyl ketone in an intermolecular Diels-Alder reaction. This means that the sulfolene itself may extrude SO_2, allowing the formation of an internal diene. The vinyl group will now react preferentially with the generated diene, in an intramolecular Diels-Alder reaction, *via* route b. A retro Diels-Alder reaction then generated the tricyclic molecule (**23**). The two routes shown in Scheme 7 highlight the utility of sulfolenes, and how they can be manipulated *via* Diels-Alder reactions to produce different products.

Sulfolenes are most commonly prepared by the cycloaddition of the appropriate diene with sulfur dioxide.[16] Alternatively, five-membered sulfur containing heterocycles may be oxidised to yield sulfolenes with reagents such as *meta*-chloroperbenzoic acid,[14] OXONE[®][17] or peracetic acid.[18] Some sulfolenes may contain functional groups that are sensitive to some oxidation techniques. To alleviate this problem a variety of different oxidation methods have been developed that are mild and oxidise sulfur selectively. An example of such an oxidant is the solid reagent system of OXONE[®]-wet alumina, which leaves alkenes and hydroxyl groups unaffected.[19] Similarly tetra-*n*-butylammonium OXONE oxidises sulfur chemoselectively in the presence of amines, ketones, esters, carbamates, olefins and hydroxyl groups.[20] Acid labile groups such as dimethyl acetals can be protected by buffering this system with anhydrous sodium carbonate.[20] Existing sulfolenes may be manipulated via alkylation, acylation or substitution reactions to produce more useful molecules, for example the alkylation of (**24**) allows the sulfolene to undergo an intramolecular Diels-Alder reaction upon sulfur dioxide extrusion (Scheme 8).[21]
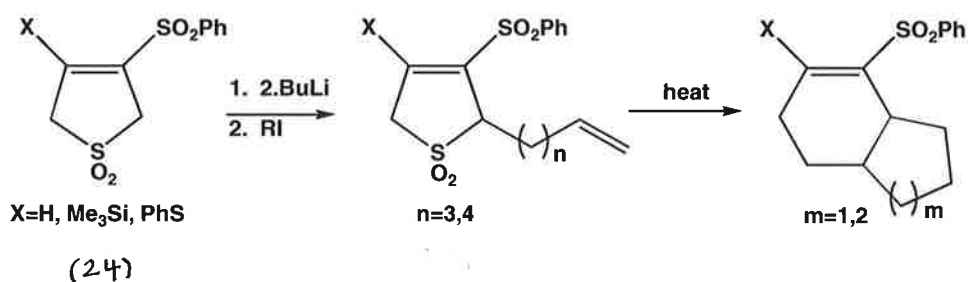
Scheme 8

In another example, the condensation reaction of (25) and the sulfone (26), in the presence of DDQ produced the sulfolene (27) (Scheme 9).[22] This quinoxalino-3-sulfolene is unique due to its remarkable thermal stability. This stability is due to the common bond between the quinoxaline ring and the 3-sulfolene ring having high single bond character.[22]
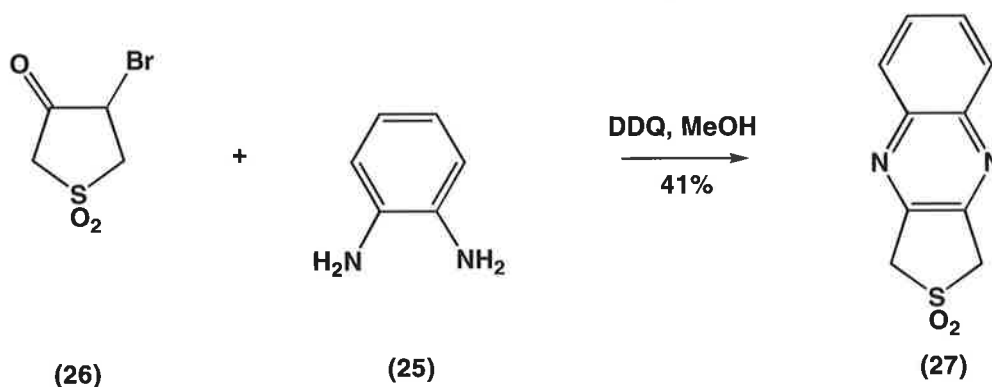
Scheme 9

The sulfolene precursor (13) to 3-dendralene (1), can also be prepared from 4-bromo-2-sulfolene (28), in a direct substitution reaction mode which is outlined in Scheme 10.[13]
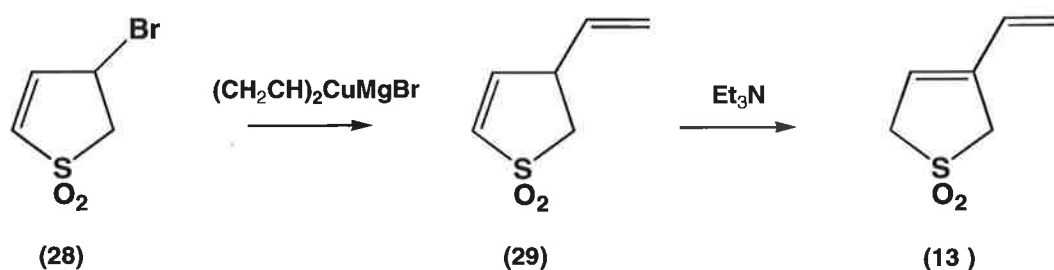
Scheme 10

Compound (29) was easily isomerised to give the double bond isomer (13).[13]

The elimination of sulfur dioxide from sulfolenes has been shown to occur in a cheleotropic [4+1] retrocycloaddition, a disrotatory process where the sulfur dioxide

departs in a concerted suprafacial manner as shown by the transition state (**30**), in Scheme 11.[16]
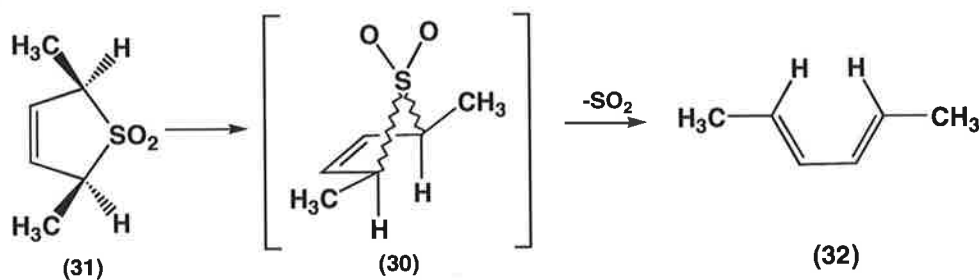
Scheme 11

Thus the *cis* sulfolene (**31**) gives the *E, E*-diene (**32**) upon sulfur dioxide elimination. Evidence suggests against a two-step mechanism where sulfur dioxide is extruded using dipolar or diradical intermediates, due to bond rotational and energetic arguments.[16]

Thermolysis is one of the most common ways of extruding sulfur dioxide from 3-sulfolenes (**21**) and usually occurs at temperatures of between 100-120°C (Figure 1).[22] Benzo-3-fused sulfolenes (**33**) and many heteroaromatic fused 3-sulfolenes (**34**) lose sulfur dioxide at temperatures of 160-200°C. The higher temperatures required for these extrusions are a result of aromaticity being destroyed during the reaction and because of the decreased double bond character between C3-C4.[22] In the case of sulfolane (**35**) where there is pure single bond character between C3-C4, the temperatures required for sulfur dioxide extrusion are greater than 500°C.[22] This effect was highlighted earlier, in the case of quinoxaline-3-sulfolene (**27**), which required high temperatures for sulfur dioxide extrusion. The steric and electronic effect of a particular substituent may also play a role in the temperature and / or conditions required for sulfur dioxide extrusion.
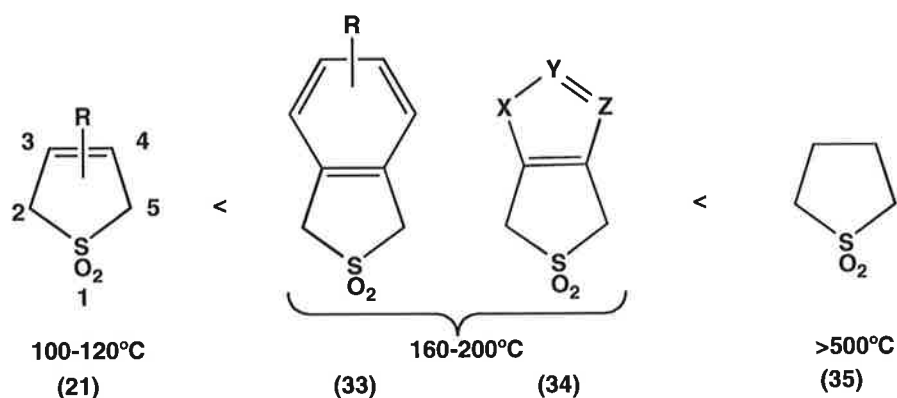
Figure 1: Temperatures required for sulfur dioxide extrusion from various sulfolenes.

Thermolysis may be conducted on the neat sulfolenes or on solutions of the sulfolene in solvents such as pyridine,[12] xylene,[21] or higher boiling solvents such as 1,2,4-trichlorobenzene.[23] The reactions may also contain a dienophile, to trap the generated diene *in situ*,[22] and may be conducted in a sealed tube to enhance reaction rate at lower temperatures.[22] In some cases the addition of a base such as K_2CO_3 or KOH, was found to increase the rate of desulfonylation when the reaction was conducted in a protic solvent.[24]

Flash vacuum pyrolysis (FVP) has been applied to some sulfolenes that may require higher temperatures >500°C, to extrude sulfur dioxide.[22] The advantage of FVP is that, due to the low pressure flow conditions, individual molecules spend only a short time in the reaction zone, so that thermally unstable molecules can be generated, and if need be, quenched without decomposition.[25] In this manner, 3-dendralene (**1**) has been obtained from the precursor sulfolene (**13**), under pyrolysis conditions; 550°C/0.001 Torr (Scheme 6).[25]
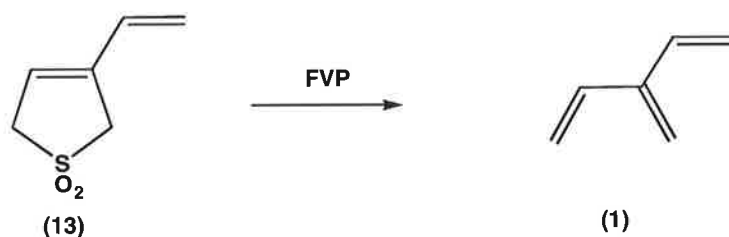
Scheme 6

Similarly, 3-dendralene (**1**) has been prepared using thermolytic conditions to extrude sulfur dioxide from the sulfolene (**13**), at 450°C (atmospheric pressure). This gave

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the dendralene (**1**) in good yield.[10] Although the thermolytic method of sulfur dioxide extrusion has been used most extensively, there are some cases where the use of LiAlH$_4$,[26] or ultrasonically dispersed potassium (UDP) is preferred.[27] Photolysis of 3-sulfolenes (**21**) is not a practical synthetic method because of low conversion rate and poor stereoselectivity.[27]

In an attempt to extrude sulfur dioxide from sulfolenes possessing thermally labile functional groups, LiAlH$_4$ was employed. However this method is restricted due to the sensitive nature of some substituents to LiAlH$_4$. In other cases, the use of LiAlH$_4$ and other extrusion techniques did not promote the loss of SO$_2$ from some sulfolenes (Scheme 12).[27]

250°C, 6h

or LiAlH$_4$, 4h, 60°C

or UDP, 2h, 40°C

No reaction

R=alkyl
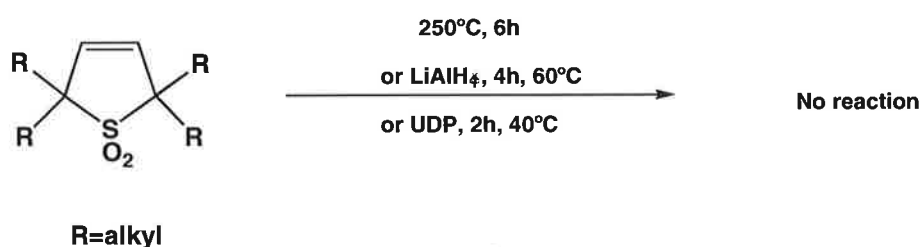
Scheme 12

However, at room temperature, a toluene suspension of ultrasonically dispersed potassium (UDP) was found to extrude sulfur dioxide only if a proton source such as tertiary butanol was present, as depicted in Scheme 13. Again this method has advantages for 3-sulfolenes containing thermally labile functional groups.

13
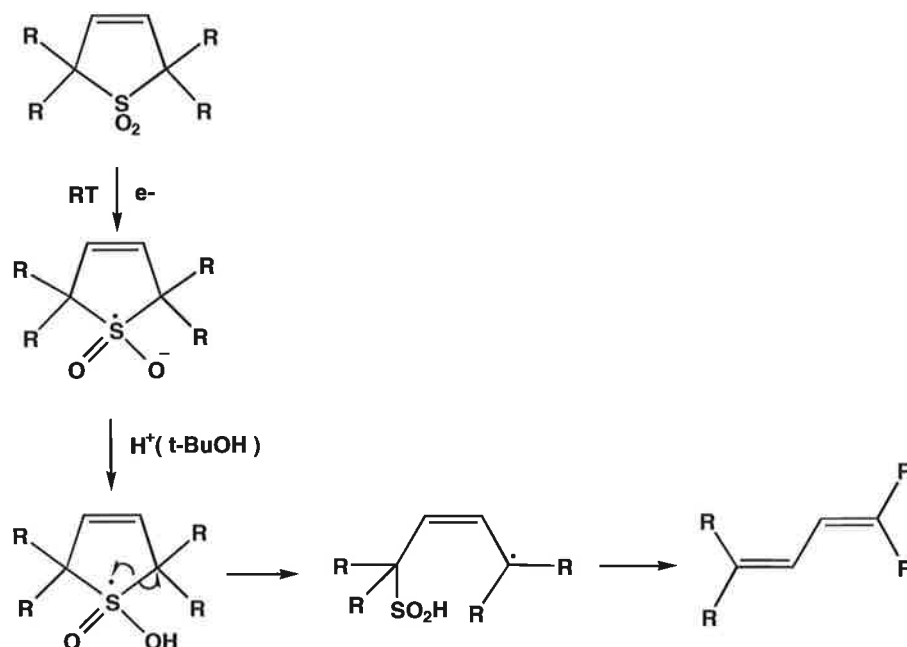
Scheme 13

Given the relative ease with which sulfur dioxide can usually be extruded from sulfolenes, substituted sulfolenes (**36**) would appear to be useful precursors for the preparation of substituted dendralenes (**37**) (Scheme 14).

(37)   (36)
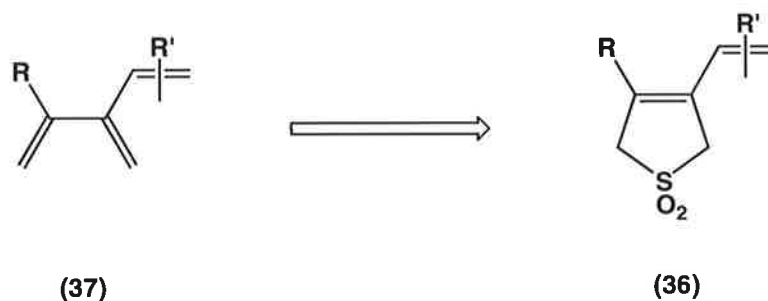
Scheme 14

Depending on the steric and electronic nature of the substituents on the sulfolene molecule, SO_2 may be extruded using mild conditions such as thermolysis in an appropriate solvent, or harsher conditions such as heating a solution of the sulfolene at high temperatures in a sealed tube.

Aims:

As discussed above, substituted dendralenes may in principle be obtained from appropriately substituted sulfolenes (**36**, Scheme 15). The aim of this project is to

synthesise substituted dendralene precursors as outlined in Scheme 15. This is a new and direct approach to the formation of these molecules, which also allows for the introduction of functionality at two places within the sulfolene molecule (**36**).
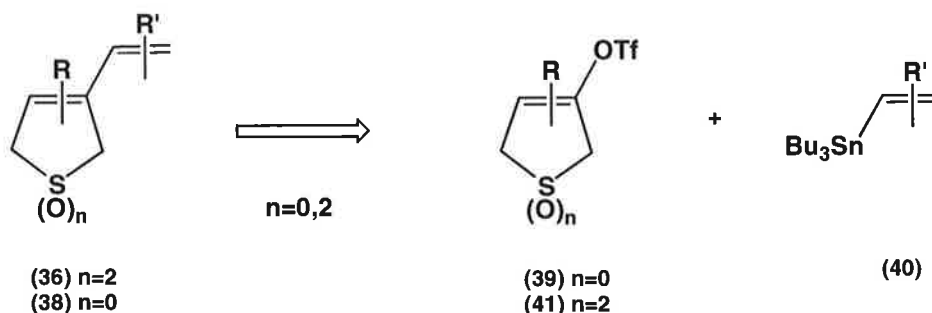
Scheme 15

These substituted sulfolenes may be formed by oxidising the corresponding vinylic heterocyclic sulfide compound (**38**). This compound may be prepared by palladium catalysed coupling reactions between a vinyl triflate (**39**) and tin (**40**) compound (Stille coupling). Alternatively the triflate (**39**) may be oxidised to a sulfone (**41**) and then coupled to give the sulfolene (**36**). The starting point for these reactions will be the preparation of the vinyl triflate (**39**), which may be obtained from reaction with the keto-sulfide (**42**).
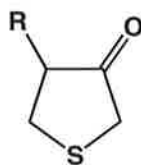
(**42**)

The advantage of this approach is that it is convergent and allows the introduction of functionality in a variety of positions such as in the initial keto-sulfide (**42**) and the stannane (**40**) (Scheme 15). To date this synthesis is the only proposed synthesis that is readily adaptable to the formation of substituted benralenes.

(II)   Results and Discussion.

In order to proceed with this new approach to substituted sulfolene molecules (**36**), the synthesis of the cyclic triflate species (**39**) was investigated. The triflate (**39**) would eventually couple with a vinyl stannane (**40**) to give the sulfolene (**36**) as described previously (Scheme 15). The two keto-sulfides (**43**) and (**44**) were the starting point of investigation for this research.

(**43**)   (**44**)

Synthesis of 4-methoxycarbonylthiolan-3-one (43).
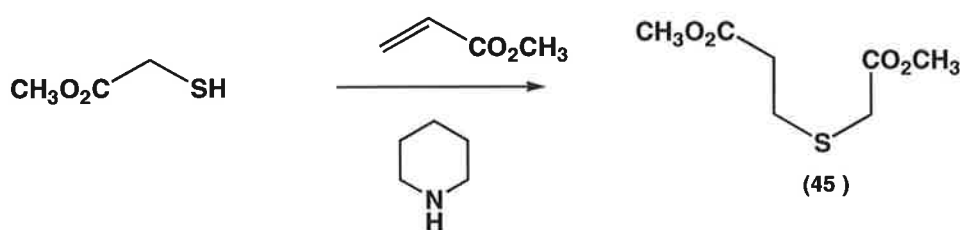
Scheme 16

The ester (**45**) was prepared by the piperidine catalysed addition of methyl thioglycolate to methyl acrylate (Scheme 16).[28]   The diester (**45**) showed two methoxy singlets at δ3.71 and 3.75 in the ^{1}H n.m.r spectrum. The advantage of this procedure is that the reaction is clean, gives good yields (85%) and does not require additional solvents, compared to other methods investigated.[29,30]

The diester functionality served a dual purpose. Firstly, one methoxy group was used as a leaving group in subsequent cyclisation reactions, whilst the other ester remained throughout the synthesis, to provide functionality on the 3-dendralene precursor.

Cyclisation Reactions.

It was thought that the action of base upon the methyl di-ester (**45**) would proceed to give the cyclic product (**43**) *via* a Dieckman cyclisation reaction according to Scheme 17.

(45)   (43)
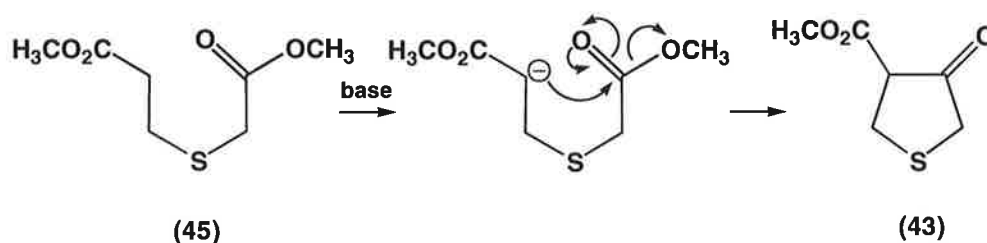
Scheme 17

Previous experiments[29] had given a mixture of isomers (**43**) and (**46**), when the reaction was conducted using sodium methoxide in refluxing methanol (Scheme 18).

(43)   (46)
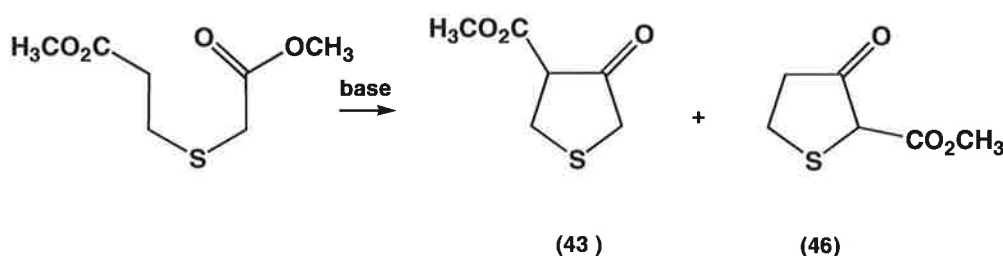
Scheme 18

However, the generation of the 3-keto-4-methoxyester isomer (**43**) in preference to the 2-methoxyester-3-keto isomer (**46**) was found to occur only if the reaction was performed in hot toluene (80-120° C), and was driven to completion by the distillation of the methanol-toluene azeotrope as the reaction progressed.[28,31] The 3-keto-4-methoxyester isomer (**43**) was obtained by this route as the major product in 51%, after exhaustive chromatography. The presence of a singlet at δ11.0 in the ^{1}H n.m.r spectrum, was attributed to a hydrogen bonded enol hydrogen, which indicated that cyclisation had occurred. It has been found[29] through previous

experiments that the isomer (**43**) is the thermodynamic product, whilst the isomer (**46**) is the kinetic product of the reaction.

Synthesis of cyclic vinyl triflates.

The ease of preparation of vinyl trifluoromethanesulfonates (triflates) in high regioselective purity from ketones and enones, and the availability of the starting materials, have expanded their use as vinyl cation synthons.[32] Vinyl triflates can be prepared from the corresponding carbonyl compound by trapping the enol with a triflating reagent [($CF_3SO_2)_2O$, $CF_3SO_2C_3H_3N_2$ or $PhN(SO_2CF_3)_2$][33], or by treating the carbonyl compound directly with triflic anhydride in the presence of a non-nucleophilic base.[34] The most commonly used base is pyridine, but lutidine, triethylamine and others have been used.[35] The use of diisopropylethylamine (Hunig's base) in inert solvents, most commonly dichloromethane but also carbon tetrachloride, pentane, chloroform or benzene, is widely reported to give vinyl triflates in moderate to good yields.[36,37] The purpose of the base is to neutralise the liberated acid as well as to serve as a catalyst for enolisation.[35]

The methyl keto-ester (**43**) was converted to the relatively stable enol triflate (**47**) using Hunig's base and freshly distilled triflic anhydride in dry dichloromethane at -78°C (Scheme 19).

$$(CF_3SO_2)_2O$$

Hunig's Base
-78 deg. C

(43)   (47)
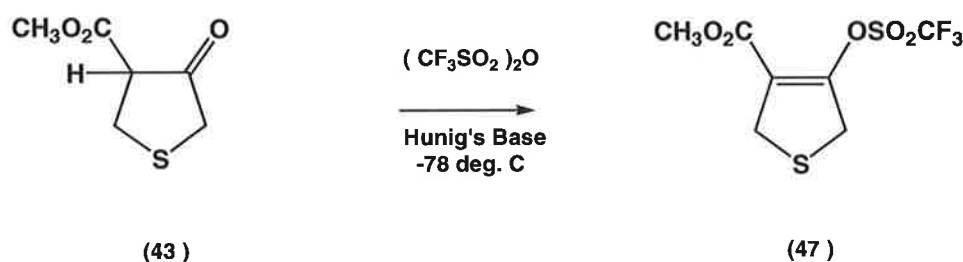
Scheme 19

The vinyl triflate (**47**) was obtained as colourless oil in 55% upon purification by chromatography. The disappearance of the enol hydrogen from the [1]H n.m.r spectrum, indicated that triflation of the keto-ester had occurred. This result was also

supported by the methylene protons appearing as one distinct singlet at $\delta 3.97$, unlike the starting material where they were split by the proton at position-3 and appeared at $\delta 3.21$-3.80. Further spectral evidence showed the disappearance of the extra peaks associated with the keto-enol forms in both the ^{1}H and ^{13}C n.m.r spectra. The ^{13}C n.m.r spectra also revealed a quartet at $\delta 119.00$ (J_{CF}=300 Hz) due to the CF$_3$ group of the triflate, and the infrared spectrum showed the required carbonyl (1730), and SO$_2$ (1440, 1145) peaks.

It was envisaged that the mechanism for the triflation reaction proceeded via the enol in preference to sulfonation of the carbonyl oxygen atom with formation of a cabenium ion and subsequent loss of a proton.[35] Carbonyl compounds that are difficult to enolise are known to react *via* the involvement of carbenium ions that get trapped by the initially liberated trifluoromethanesulfonate anion.[35] Since the keto-ester has an electron withdrawing group at the C-4 position, the C-4 hydrogens have increased acidity, enhancing and controlling the direction of enolisation away from the sulfur atoms. Thus the reaction should proceed via the enol, producing solely one isomer (**47**), as was indeed observed.

Palladium Catalysed Coupling Reactions and Sulfolene Chemistry.

Vinyl triflates can be coupled with organostannanes *via* palladium catalysed coupling reactions. These reactions afford the advantage of being mild, general and proceed in good yields.[38,39]

Sufolene derivatives may be generated by either oxidising the vinyl triflate, which could then couple to the organostannane (**Route A**), or by oxidising the coupled product (**Route B**), according to Scheme 20.
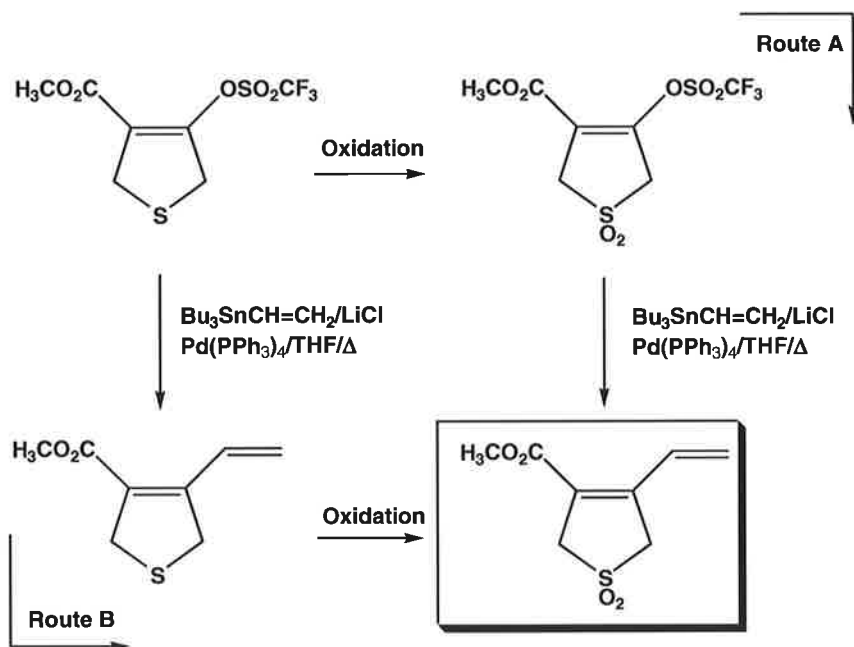
Scheme 20

Previous work had suggested that Route B would be the preferable pathway to follow; as epoxidation of the double bond during oxidation did not seem to be a major problem, however the palladium catalysed coupling of the sulfone triflate gave disappointing results.[29]

Route A.

The oxidation of the vinyl triflate (**47**) was conducted using a buffered oxidant system (Scheme 21), as vinyl triflates are cleaved under the mildly acidic conditions caused by OXONE®.[17]
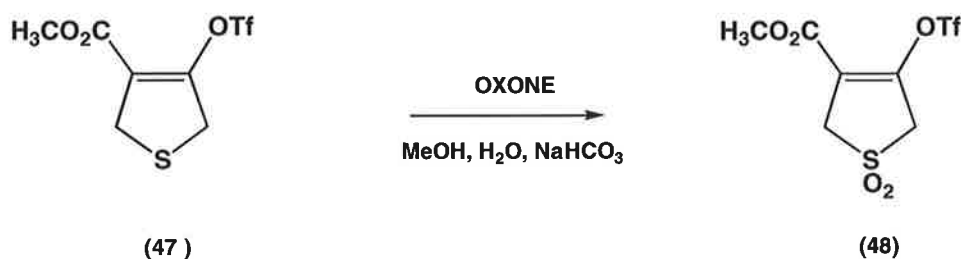
Scheme 21

The sulfone product (**48**) was obtained in 89% and identified by a molecular ion at m/z 325 in the mass spectrum. The protons at postions-2 and -5 showed a down

field shift and were resolved into two peaks in the ^{1}H n.m.r spectrum, compared to the starting sulfide.

Attempted palladium catalysed coupling reactions between the sulfone triflate (**47**) and vinyltributyltin using tetrakis(triphenylphosphine) palladium(0) in the presence of 2,6-tert-butyl-*p*-cresol (a radical trap that has been shown to prevent polymerisation)[29] at either 40° C or reflux were unsuccessful.

Route B.

The methyl ester triflate (**47**) however, was converted to the 1,3-diene (**49**), quickly and efficiently using 2 mol % of a palladium catalyst in the presence of 3 equivalents of lithium chloride in dry 1,4-dioxane (Scheme 22).
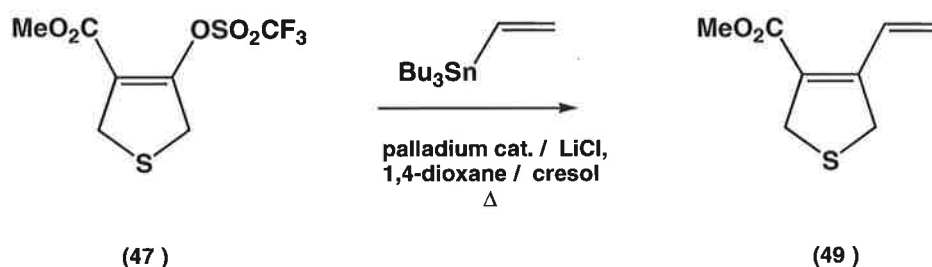
Scheme 22

Tetrakis(triphenylphosphine)palladium(0)   (Pd[PPh$_3$]$_4$)   or bis(dibenzylideneacetonyl)palladium(0) [Pd$_2$(dba)$_3$] were both suitable catalysts, in the presence of triphenylphosphine. These reagents furnished the sulfide (**49**) in 79% and 67% respectively.

The mass spectrum of the product (**49**) showed a strong molecular ion at *m/z* 170. The presence of vinylic hydrogen signals in the ^{1}H n.m.r spectrum (δ 5.46, 5.51, and 7.62), different to those present in the vinyltributyltin spectrum (δ 5.65, 6.13, and 6.45) and the absence of butyl peaks in the upfield region of the ^{1}H n.m.r spectra, suggested that the triflate had indeed coupled. The loss of the quartet at δ119

(J=319 Hz) in the ^{13}C n.m.r spectrum and the upfield shift of C3 from δ144.30 to 128.71 provided further supporting evidence.

Further coupling reactions were conducted upon the methyl ester triflate (**47**) using a variety of substituted stannanes and Pd(PPh$_3$)$_4$, to evaluate the scope of the reaction, with the aim of ultimately forming a doubly substituted dendralene precursor molecule (Scheme 23).

(**47**)
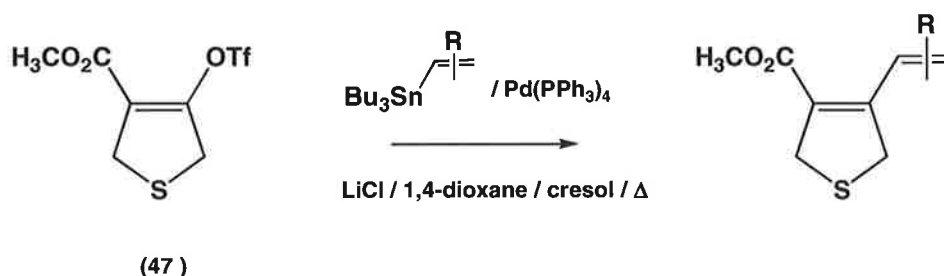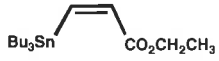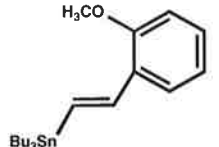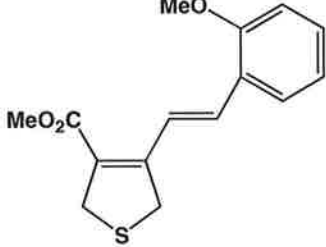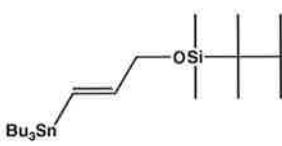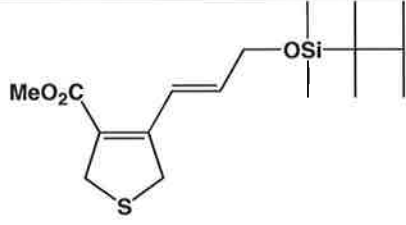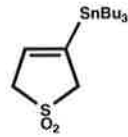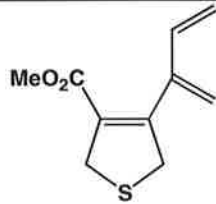
Scheme 23

Table 1 shows the results of coupling a number of stannanes possessing electron withdrawing and electron donating groups, to the triflate ester (**47**).

Table 1: Palladium catalysed coupling reactions of substituted stannanes to the triflate (47).

Entry	Stannane	Reaction time	Result	Yield
1		1 h, until dark brown	(50)	95%
2		4.5 h, until dark brown	(53)	51%

3	Bu₃Sn⌁CO₂CH₂CH₃	72 h	Complex mixture	-
4	H₃CO / Bu₃Sn structure	2.5 h, until dark brown	MeO₂C / MeO structure **(51)**	64%
5	Bu₃Sn / OSi structure	3 h, until dark brown	MeO₂C / OSi structure **(52)**	80%
6	SnBu₃ / S O₂ structure **(54)**	23 h	MeO₂C / S structure **(55)**	~10%

In most cases reaction completion was indicated by a colour change of the solution to dark brown, which was confirmed by t.l.c analysis.

When an electron donating substituent such as an ethoxy group, methoxyphenyl or dimethylthexylsilyoxy was present on the stannane (Table 1, entries 1, 4 and 5), the coupled products **(50)**, **(51)** and **(52)** were obtained in good yield (>64%) within a short period of time (<3 h).

The use of an electron withdrawing (*E*)-carboethoxy substituted stannane (Table 1, entry 2), reduced the product yield [of **(53)**] to 51% over a slightly greater time span. The reactions of the (*Z*)-isomer (Table 1, entry 3) consistently gave a complex

product mixture together with a very small amount of the coupled product. This was possibly due to the *cis* stereochemistry of the substituents on the double bond of the stannane, inhibiting the coupling reaction. The coupling reaction of the sulfolene stannane (**54**) (Table 1, entry 6) afforded the product (**55**), a result of sulfur dioxide extrusion from the coupled product (**56**) (Scheme 24). The high reaction temperature over an extended period of time (reflux in 1,4-dioxane / 23 h) was the likely cause of the extrusion reaction. The low yield (~10%) was a result of the possible dimerisation reactions of the diene (**55**) (evident by a smear at low Rf on the t.l.c plate), the fact that the reaction was conducted on a small scale and not optimised and that the reaction still contained some starting triflate. A similar coupling reaction[10] between the sulfolene stannane (**54**) and 3-iodo-3-sulfolene (**14**) afforded a di-sulfolene (**15**) in 95% yield at room temperature (as discussed previously, Scheme 4). No sulfur dioxide extrusion was evident during this coupling reaction[10] suggesting that high temperatures may have caused the extrusion from the sulfolene (**56**) (Scheme 24).

(**56**)   (**55**)
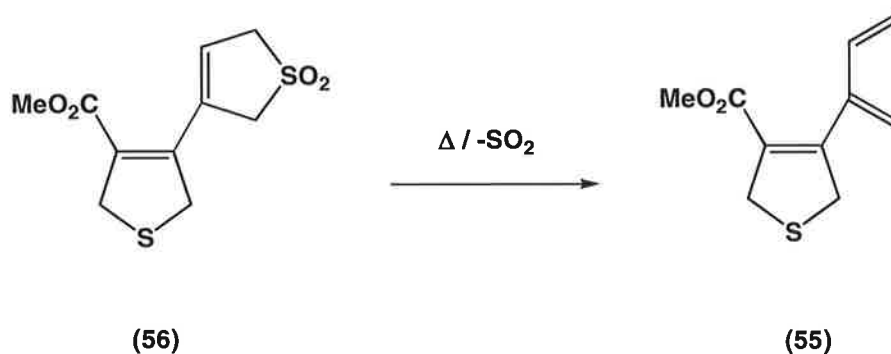
Scheme 24

The diene (**55**) was identified by a signal at $\delta 6.34$ (dd, $J=10.5$, 17.1 Hz) in the crude ^{1}H n.m.r spectrum corresponding to the single vinylic proton. The terminal protons of this alkene unit appeared at $\delta 5.04$ ($J=17.1$ Hz) and $\delta 5.06$ ($J=10.5$ Hz). The terminal protons of the other alkene unit appeared as singlets at $\delta 4.97$ and $\delta 5.18$. The methoxy group was evident at $\delta 3.77$. No other spectra could be recorded for (**55**) due to the small amount of crude product obtained, however the signals from the diene unit of (**55**), were consistent with the reported ^{1}H n.m.r spectrum of the diene portion of 3-dendralene (**1**).[10]

From these results it can be proposed that as the substituents on the stannane became more electron donating, the reaction time decreased and the product yield increased. This is consistent with results from other Stille coupling reactions.[39]

The stannane (**54**) can be prepared from 3-sulfolene (**57**), in a three step procedure (Scheme 25).[40] 3-Sulfolene (**57**) was firstly converted into a vinyl sulfide, which was then oxidised to the sulfone (**58**), using a methanolic solution of OXONE®.[40] The reaction generally gave a mixture of isomers; the required sulfone (**58**) being the major product. The phenyl sulfone (**58**) was then used to afford the stannane (**54**), which may be synthesised by a radical desulfurative stannylation reaction (Ueno Reaction)[41] (Scheme 25).
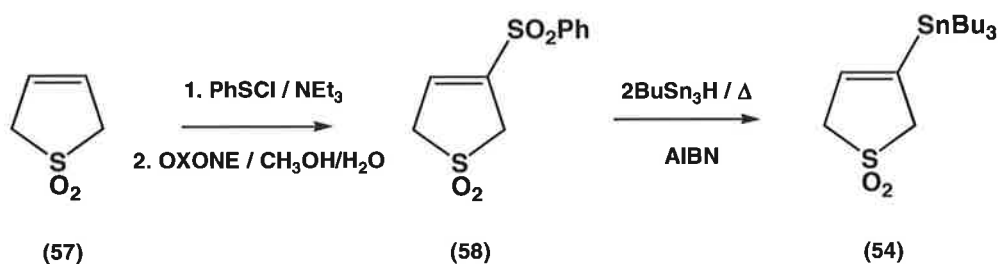
Scheme 25

The Ueno Reaction was attempted numerous times, under a variety of conditions. In all cases the reaction contained two equivalents of freshly distilled tributyltinhydride,[42] and 10 mol% of 2,2'-azobisisobutyronitrile (AIBN) under refluxing conditions. The reaction was initially attempted in refluxing benzene over 20-48 h, giving the stannane (**54**) at most in 5% yields. Changing to a refluxing solution of xylenes,[43] gave only tin hydride over short and long reaction times (2 and 21 h). The Ueno Reaction finally proceeded in degassed benzene but only if the reagents were purified and dried, giving the required 3-sulfone stannane (**54**) in 26%, as a clear oil. This product was clearly different from the starting sulfone (**58**) as it gave a strong molecular ion at *m/z* 407 in the mass spectrum. The product (**54**) also contained butyl signals at δ0.87-1.85 in the ^{1}H n.m.r spectrum and lacked the phenyl protons of the starting material at δ7.6-8.0, further suggesting that the stannane (**54**) had formed.

The known isomeric instability of sulfolenes[44] may have produced a mixture of 2-, 3-, 4-sulfolenes as outlined below respectively. This may be why the yields of the required stannane (**54**) were low.
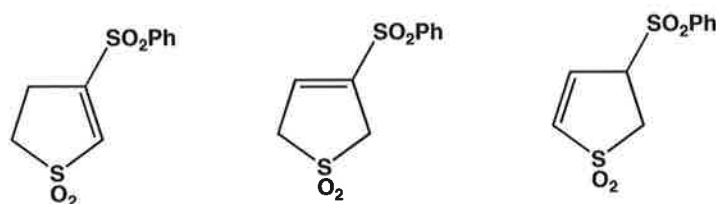
Since both allylic and vinyl sulfones undergo the Ueno Reaction, the corresponding stannanes may have been generated *via* either mechanism **A** or **B** respectively (Scheme 26).[43]
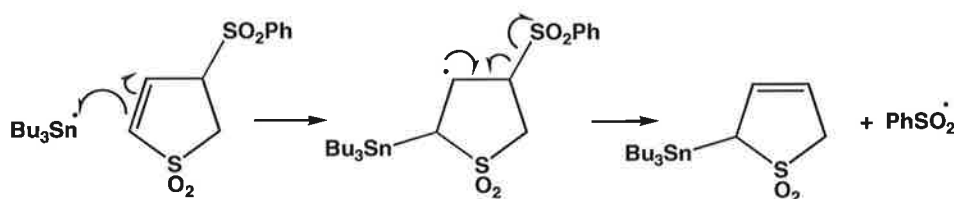
Mechanism A
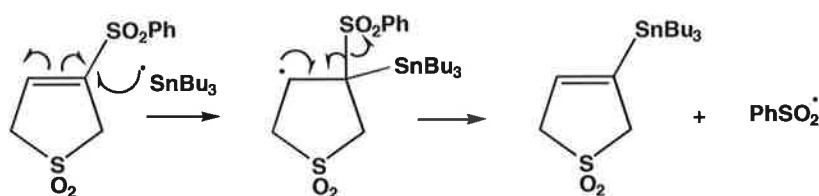
Mechanism B

Scheme 26

The reason for using two equivalents of tin hydride is shown below in Scheme 27. One equivalent underwent addition to the double bond, whilst the other trapped the phenylsulfonyl radical.

$$PhSO_2^{\bullet} \xrightarrow[\text{or } Bu_3Sn^{\bullet}]{Bu_3SnH} Bu_3SnSO_2Ph$$

Scheme 27

26
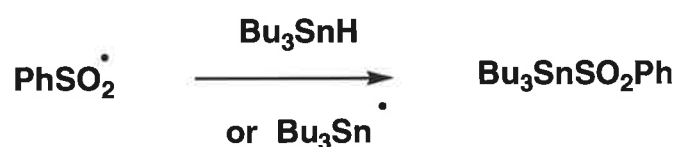
Oxidation of coupled sulfides.

Oxidation of the coupled product (**49**) was achieved using conditions that are known to chemoselectively oxidise the sulfur atom in preference to the vinyl group (Scheme 28).[17,19,20]

(**49**)   (**59**)
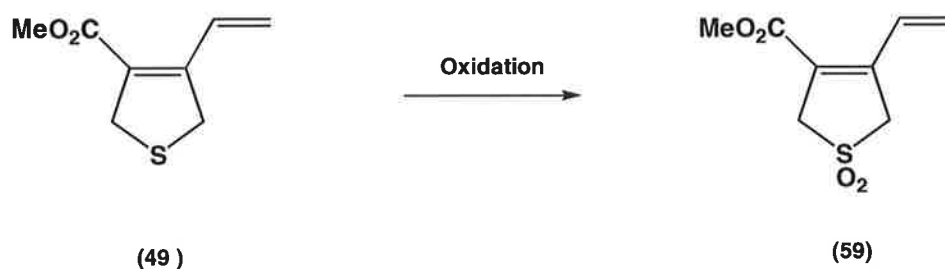
Scheme 28

The oxidised product (**59**) was obtained using many different oxidation methods as outlined in Table 2. The sulfone (**59**) was identified from the sulfide (**49**) by the splitting of the four methylene protons into two (2H) singlets, from one (4H) singlet. Additionally the sulfone (**59**) showed peaks at $\delta 57.64$ and 58.49 in the ^{13}C n.m.r spectrum for the carbons at positions-2 and –5, unlike those of the sulfide (**49**) which appeared at $\delta 39.85$ and 40.34.

Table 2: Conditions for the oxidation of the sulfide (49) to the sulfone (59).

Entry	Oxidant	Conditions	Yield of sulfone (59)
1	OXONE®	MeOH, H_2O, RT, 3h., $NaHCO_3$	50%
2a	TBA-OX	CH_2Cl_2, RT, 4h., Na_2CO_3	12%
2b	TBA-OX	CH_2Cl_2, RT, 5h.	15%
3	OXONE®-wet Al_2O_3	$CHCl_3$, Δ, 15.5h.	60%
4	n-Pr_4NRuO_4, NMO	CH_3CN, MS, 40°C, 21h.	-
5	KO_2, o-nitrobenzene-sulfonyl chloride	CH_3CN, -30-20°C, 6.5h.	5%

Oxidation was performed using a buffered OXONE® system as its mild acidity (pH 2-3)[17] had the potential to cause reaction with the diene system of the sulfide (**49**) (Table 2, entry 1). Some product loss was encountered as a result of polymerisation, evident by the formation of an insoluble gum. This occurred when the sulfone was purified on silica gel; the partial polymerisation being thought to be catalysed by the acidity of the gel. However, when purification was attempted on neutral alumina, separation of the required sulfone (**59**) could not be achieved.

The use of tetra-*n*-butylammonium oxone (TBA-OX) as an oxidant afforded the advantage of chemoselectivity under anhydrous conditions.[20] The oxidation was conducted under either buffered (Na_2CO_3) or non-buffered conditions (Table 2, entries 2a and 2b); both experiments resulting in similar yields (12%, 15%). These results indicated that the acidity of TBA-OX had no apparent effect on the diene system of (**49**) during oxidation. Again decreased yields of the sulfone (**59**) were a consequence of purification (using chromatography on silica gel); a result of problems incurred due to the isolation of the product rather than its initial conversion.

The supported reagent system of OXONE® and wet alumina[19] was found to oxidise the sulfide (**49**) chemoselectively to give the sulfone (**59**) in the highest yield of 60% (Table 2, entry 3). The heat generated during the reaction did not cause any harm to the substrate being oxidised. Increased yield may have been due to a simplified purification step, consisting of filtering the reaction mixture and washing the residue with chloroform.

The use of tetrapropylammonium perruthenate has been found to be an efficient catalyst for the conversion of sulfides to sulfones.[45] The reagent was found to tolerate a number of functional groups when in the presence of the co-oxidant *N*-methylmorpholine-*N*-oxide. However, this reagent gave a complex mixture in the present case (Table 2, entry 4). It has been noted previously that a mild, osmium tetroxide-catalysed oxidation method resulted in olefin hydroxylation as a major problem.[45] This may have contributed to the result encountered.

A peroxysulfur intermediate generated *in situ* from 2-nitrobenzenesulfonyl chloride and potassium superoxide has been reported to chemoselectively oxidise sulfoxides to sulfones in the presence of double bonds.[46] It was believed that this oxidation technique might also oxidise sulfides to sulfones. The sulfone (**59**) was obtained in low yield (Table 2, entry 5, 5%) which may have been due to the oxidation technique being more suitable for sulfoxides instead of sulfides.

Extrusion of Sulfur dioxide from the vinyl sulfolene (59).

Extrusion of sulfur dioxide was trialed from the substituted sulfone (**59**), in an attempt to generate the substituted dendralene (**60**) as outlined below in Scheme 29. The reaction was attempted using two main techniques; namely thermolysis and a method utilising ultrasonically dispersed potassium (UDP)[13] (Table 3).
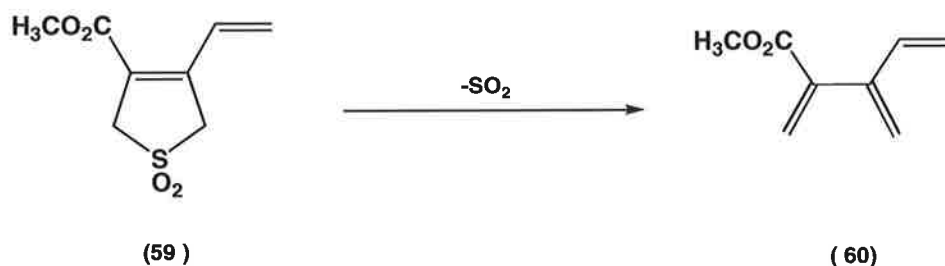
Scheme 29

Table 3: Methods of extruding sulfur dioxide from the sulfolene (59).

Entry	Method	Dienophile	Conditions	Product
1	thermolysis	maleic anhydride	200°C, 1,2,4-trichlorobenzene, 24 h	Complex mixture
2	sealed tube	maleic anhydride	200°C, benzene, 25 h	Sulfone & decomposition
3	sealed tube	ethylvinylether	140°C, benzene, 17 h	Sulfone & decomposition
4	thermolysis	-	200-250°C / 0.025 torr, Kugelrohr distillation	sulfone
5	F.V.P	-	560°C / 0.01 torr, Kugelrohr oven - 100°C	-
6	U.D.P	-	room temp., toluene, Bu^{t}OH in THF, 1 h	sulfone & complex mixture
7	U.D.P	-	room temp., toluene, Bu^{t}OH in THF, 2.5 h	complex mixture

The sulfone was thermolysed in a high boiling solvent (214°C) together with maleic anhydride (an electron deficient dienophile) at atmospheric pressure. The addition of maleic anhydride was to capture the dendralene molecule once formed, preventing it from polymerising with itself. This reaction (Table 3, entry 1) produced multiple products as indicated by numerous signals in the ^{1}H n.m.r spectrum. The reaction was repeated using a different solvent at higher pressure (Table 3, entry 2). After work up the starting material and decomposition material were obtained (baseline material by t.l.c). The reaction was repeated using ethylvinylether (an electron-donating dienophile) at a lower temperature (Table 3, entry 3) in hope of stimulating extrusion of sulfur dioxide without forming a decomposition product. The sulfone (**59**) was again recovered with a decomposition product (broad, complex peaks by ^{1}H n.m.r spectroscopy). These results suggest that the sulfone (**59**) was on

the whole, a rather stable molecule, requiring harsher than expected conditions to be induced to expel sulfur dioxide.

The sulfone alone was distilled using a Kugelrohr apparatus (Table 3, entry 4), hopefully to induce it to expel sulfur dioxide. The distillate obtained was a white solid, which was identified as being solely the sulfone (59). These results suggested that thermolysis *via* distillation was not going to lead to sulfur dioxide extrusion from the sulfone (59) and further indicates the stability of the sulfone (59).

Flash vacuum pyrolysis (FVP) affords the advantage of gas-phase pyrolysis reactions carried out under low pressure flow conditions.[25] Thus individual molecules spend only a short time in the reaction zone,[25] and may be trapped chemically in the condensed phase by the addition of dienophile. Preliminary attempts to extrude sulfur dioxide under FVP conditions (Table 3, entry 5) resulted in the vaporisation of half the sulfone into the pyrolysis oven, whilst the other half polymerised in the initial tube. The sulfone that entered the oven did not condense in the cold trap, even over extended time. A lower pressure vacuum may be needed to firstly vaporise all the sulfone before polymerisation occurred and to secondly force it through the oven.

Ultrasonically dispersed potassium (UDP) has been used to promote the stereoselective sulfur dioxide extrusion from substituted sulfones. This will only occur if a proton source is present.[13] Sonication over 1 h in the presence of a proton source (Table 3, entry 6), resulted in the formation of a complex mixture which contained the sulfone (59). Increased sonication time did not promote extrusion (Table 3, entry 7) but consumed the rest of the starting sulfone into a complex mixture of products when viewed by ^{1}H n.m.r spectroscopy.

The data summarised in Table 3 indicates that the sulfone (59) is a surprisingly stable molecule, requiring much harsher conditions to promote the extrusion of sulfur dioxide than for other sulfolene systems.[12,23]

Formation of 3-ethoxycarbonyl sulfolene (61).

Further work was undertaken in an attempt to investigate and explain the unusual stability of the sulfolene (**59**). Previous work has shown that the sulfolene molecule possessing just a vinyl group can extrude SO_2 smoothly using flash vacuum pyrolysis.[5] Thus it may be the presence of the ester group or a combination of the ester and vinyl group, that explains the stability of (**59**).

The sulfolene (**61**) was generated as outlined in Scheme 30, in the hope that it would extrude sulfur dioxide. This system was investigated to see whether the ester group was the major factor preventing the loss of sulfur dioxide from (**59**).
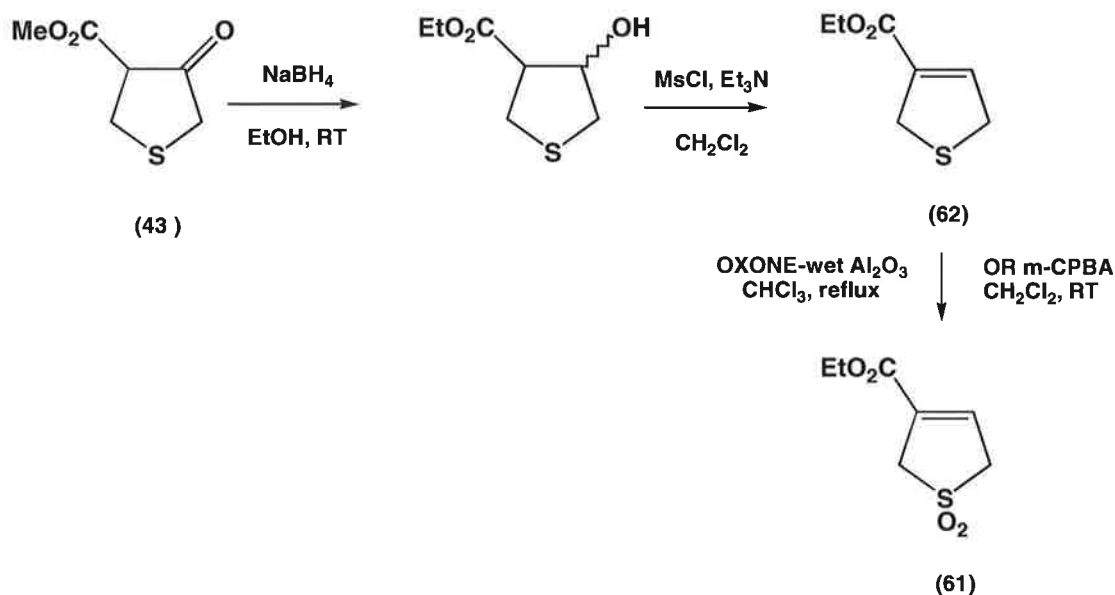
Scheme 30

Sodium borohydride reduction of (**43**) in ethanol was followed by treatment of the crude reaction mixture (73%) with methanesulfonyl chloride in the presence of excess triethylamine, afforded 3-ethoxycarbonyl-2,5-dihydrothiophene (**62**) as an orange oil in 57%. The structure of (**62**) was supported by a broad one-hydrogen singlet at $\delta 6.88$ in the [1]H n.m.r spectrum corresponding to the vinylic hydrogen, which is consistent with literature data for similar sulfides (methoxycarbonyl).[47] As the reduction was performed in ethanol, the carbomethoxy substituent was converted to

an ethyl ester as a result of *trans*-esterification. The sulfide (**62**) was oxidised using either OXONE-wet alumina in refluxing chloroform, or *m*-CPBA in dichloromethane at room temperature, giving the crystalline sulfolene (**61**) in 62% yield. The sulfolene showed n.m.r data consistent with that of the literature,[47] in particular, analysis by ^{1}H n.m.r spectroscopy revealed a downfield shift from δ6.88 to δ7.02 for the vinylic hydrogen singlet, which was split into a multiplet.

A small amount of the substituted sulfolene (**61**) was heated in refluxing toluene for 5 h, and in the absence of a dienophile, dimerisation occurred to give diethyl 4-vinyl-1-cyclohexene-1,4-dicarboxylate (**63**) in quantitative yield (Scheme 31).
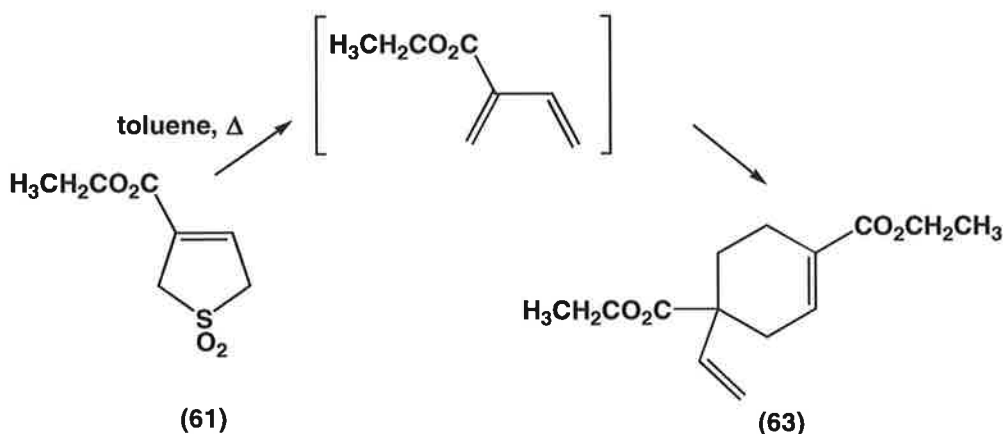
Scheme 31

^{1}H n.m.r analysis of the dimer (**63**) was consistent with the literature.[48] The spectrum of (**63**) showed the required vinylic hydrogens as an ABX pattern at δ5.09 (d, *J*=17.7 Hz), 5.15 (d, *J*=10.5 Hz), 5.87 (dd, *J*=10.5, 17.7 Hz) and a signal at δ7.03 (multiplet) for the vinylic ring proton.

These results suggest that the ester substituent may have little effect upon the ability of the sulfolene to extrude sulfur dioxide. It is possible that the combined effect of the bulky ester group and the vinyl substituent may interact in some way to prevent sulfur dioxide extrusion. It is also known that the nitrile sulfolene (**64**) extrudes sulfur dioxide under mild conditions as outlined in Scheme 32.[49]

(64)
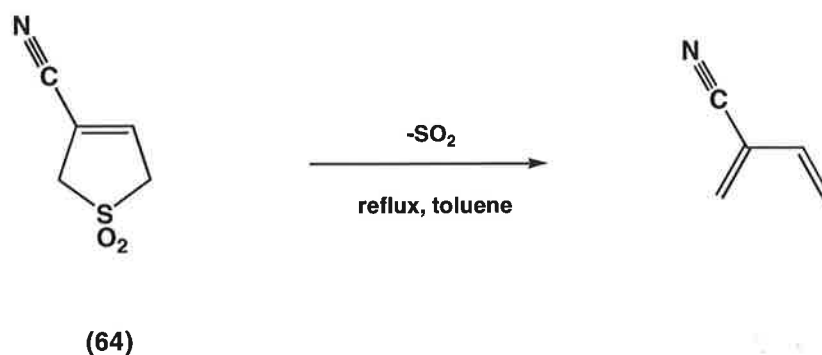
Scheme 32

Compared to the ester group, the nitrile substituent is linear and offers the advantage of further and varied chemical manipulation, such as conversion to a carboxylic acid or reduction to an amine, at a later stage. It was hoped that the combination of the nitrile and vinyl groups might reduce any serious steric hindrance, allowing extrusion of sulfur dioxide to form a nitrile substituted dendralene (**65**).

Reactions leading to a substituted nitrile dendralene (65).

The preparation of 3-cyano-4-ethenyl-2,5-dihydrothiophene-1,1-dioxide (**66**) was undertaken according to the reaction outlined in Scheme 33. This pathway is similar to the one used for the substituted ester compound; previous work indicating that the coupled product should be oxidised to give the sulfolene molecule (**66**) rather than the oxidised product being coupled.
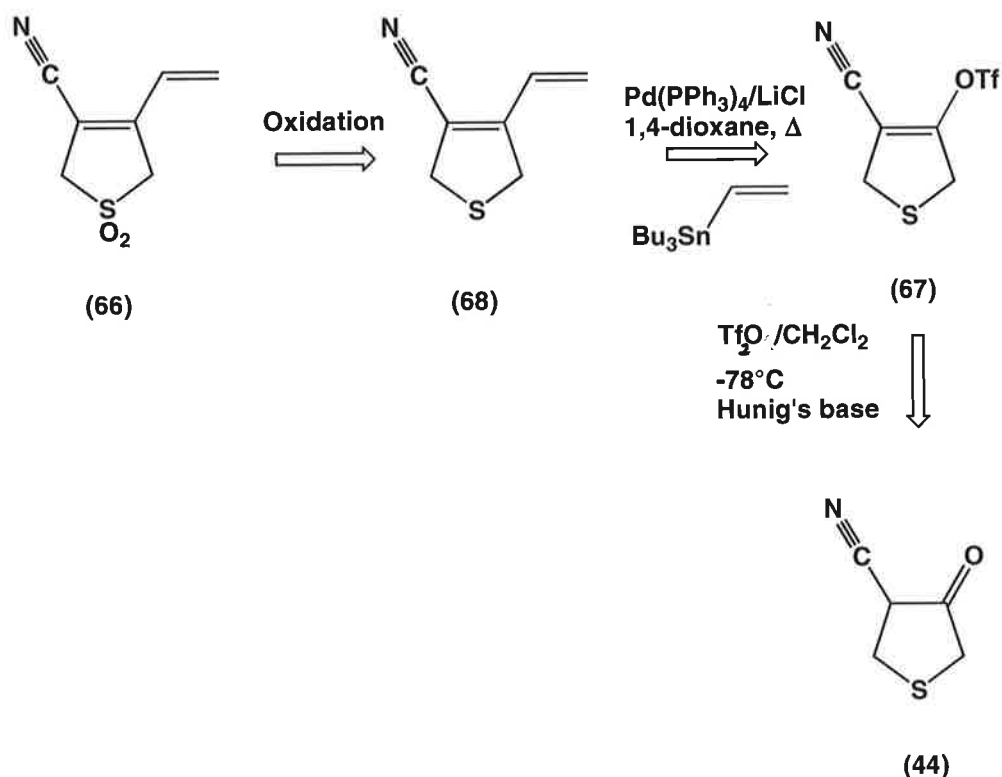
Scheme 33

The required 4-cyano-3-oxotetrahydrothiophene (**44**) was prepared from the Dieckmann cyclisation using sodium methoxide, of the Michael adduct between acrylonitrile and methyl thioglycolate (Scheme 34).[49-51]
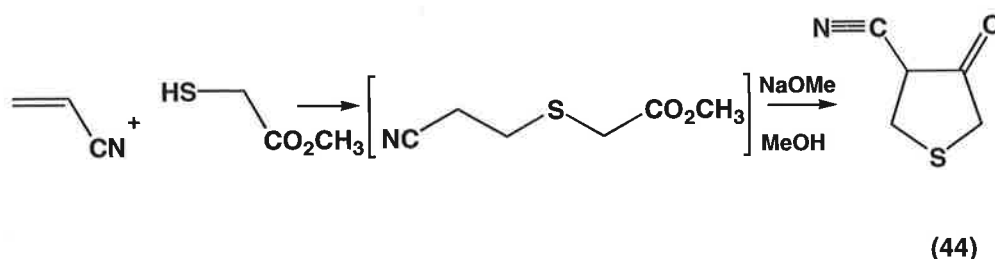
Scheme 34

The keto-nitrile (**44**) was obtained as a pale yellow solid (Mp: 62-63° C) in 42% after extensive chromatography and recrystallisation. The structure of the product was confirmed by a molecular ion at m/z 127 in the mass spectrum, and by the [1]H n.m.r spectrum, which showed one set of methylene protons at $\delta 3.42$ (singlet, 2H) and the other set as a doublet of doublets at $\delta 3.27$ (J=10.8, 11.8 Hz) and $\delta 3.36$ (J=7.8, 11.8 Hz). This was a result of the splitting effect created by the proton α to the nitrile group. The keto-nitrile (**44**) also showed the required infrared absorbances at 2248
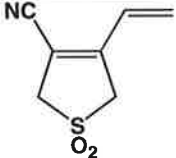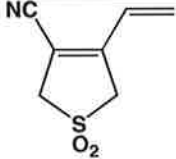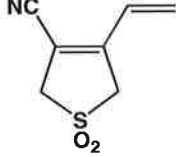
and 1747 cm^{-1} corresponding to the nitrile and ketone groups respectively. All of the spectral data was in agreement with the literature values.[50,51]

Conversion to the triflate (**67**) proceeded by addition of diisopropylethylamine to (**44**), which was dissolved in dry dichloromethane and maintained at -78°C. Freshly distilled triflic anhydride was added dropwise to this solution. 4-Cyano-2,5-dihydrothiophen-3-yl triflate (**67**) was obtained after chromatography on alumina, as a pale brown oil in 73%. The two sets of methylene protons appeared as two distinct singlets at δ3.86 and 4.05 in the ^{1}H n.m.r spectrum. The ^{13}C n.m.r spectrum showed a quartet at δ117 (*J*=317 Hz), which was indicative of the -CF$_3$ group of the triflate.

The triflate (**67**) was coupled to vinyltributyltin in the presence of 2,6-di-*t*-butyl-*p*-cresol using tetrakis(triphenylphosphine)palladium(0) as catalyst, yielding a yellow oil that was purified to give 3-cyano-4-ethenyl-2,5-dihydrothiole (**68**) as indicated by a strong molecular ion at *m/z* 137. The ^{1}H n.m.r spectrum of the product showed the appropriate vinylic hydrogen signals at δ5.49 (*J*=17.6 Hz), 5.60 (*J*=10.8 Hz) and 6.88 (*J*=10.8, 17.6 Hz).

Oxidation of the coupled nitrile product (**68**) was achieved using the three procedures outlined below in Table 4.

Table 4: Methods used to oxidise the vinyl nitrile (68).

Entry	Oxidant	Conditions	Product	Yield
1	OXONE® 4.1 eq.	MeOH-H$_2$O, NaHCO$_3$, pH 7, 3h, RT		79%
2	OXONE® 3 eq.	MeOH-H$_2$O, NaHCO$_3$, pH 7, 4h, RT		68%
3	OXONE®- wet alumina	CHCl$_3$, Δ, 8h		62%

It has been suggested that OXONE® in aqueous methanol could oxidise not only sulfide to sulfone, but also olefin to epoxide.[46] It has also been noted that an excess of OXONE® is required for rapid completion of the reaction.[17] Using excess OXONE® (4.1 eq) as oxidant, the sulfone (**66**) was obtained as indicated by its ^{1}H n.m.r spectrum (Table 4, entry 1). The sulfone (**66**) was identified by two singlets at δ4.00 and 4.03 which were resolved from two methylene multiplets (δ3.97, 3.99) present in the spectrum of the sulfide (**68**). The infrared spectrum confirmed the structure of (**66**) as it revealed peaks at 1320 and 1120 cm^{-1} attributed to the sulfone group.

The use of 3 equivalents (50% excess of OXONE®), generated the required sulfone (**66**) in a lower yield of 68% (Table 4, entry 2).

The sulfone (**66**) was also obtained (Table 4, entry 3) using an alternate oxidation system that is safe, involves non-aqueous conditions and which was run under simple operating conditions.[19]

4.1 Sulfur Dioxide Extrusion and Diels-Alder Reactions.

The extrusion of sulfur dioxide has been found to occur from the sulfolene (**64**), under mild conditions.[49] The extrusion of sulfur dixoide from the vinyl sulfolene (**66**) to give the dendralene (**65**), was investigated under analogous conditions (Scheme 35). The results are summarised in Table 5.

(**66**)   (**65**)
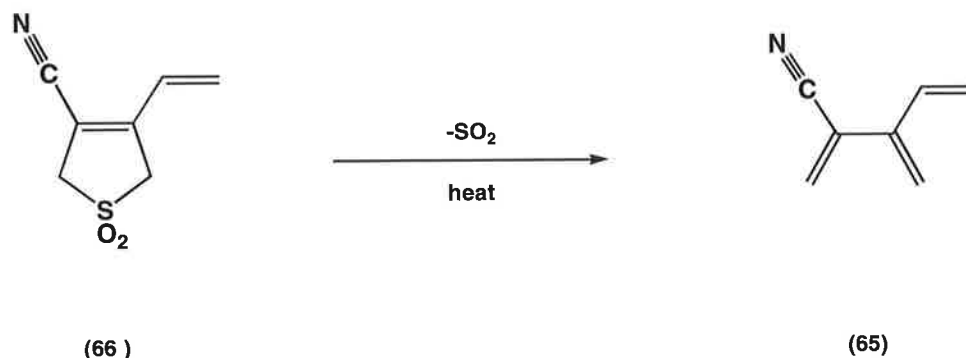
Scheme 35

Table 5: Method of extruding sulfur dioxide from the sulfolene (66).

Entry	Dienophile	Conditions	Product
1	excess maleic anhydride	Δ, toluene, 24 h	Sulfone
2	excess maleic anhydride	200°C, 1,2,4-trichlorobenzene, 4.5 h	Complex mixture
3	2 eq. maleic anhydride	250°C, 1,2,4-trichlorobenzene, 1 h	Polymer
4	2.5 eq. N-phenylmaleimide	250°C, 1,2,4-trichlorobenzene, 48 h, RT, 48 h	Complex mixture
5	excess N-phenylmaleimide	220°C, 1,2,4-trichlorobenzene, 2,6-di-t-butyl-p-cresol, 22.5 h	Complex mixture
6	-	150°C / 0.018 torr, Kugelrohr distillation	Sulfone, 70%
7	-	250°C / 0.018 torr, Kugelrohr distillation from preheated oven	Sulfone, 77%

To prevent the reaction of the initial dendralene (**65**) with itself, the majority of extrusion reactions were conducted in the presence of additional dienophiles. The dienophiles used were maleic anhydride and *N*-phenylmaleimide as both had simple ^{1}H n.m.r spectra (peaks appear at δ7-8) and were symmetrical, eliminating the added problem of regiochemistry in the cycloaddition.

Treatment of (**66**) in refluxing toluene (Table 5, entry 1) did not lead to any sulfur dioxide extrusion from the sulfone. This suggested that the vinyl substituent acted in some way to stabilise the sulfolene (**66**) against the loss of sulfur dioxide. This result was similar to the one encountered previously using the sulfolene ester (**59**). Since extrusion did not occur in toluene (bp. 110.6°C), a higher boiling solvent was employed.

n
The use of 1,2,4-trichlorobézene (bp. 214°C) has been widely documented for the thermolysis of sulfur dioxide from sulfolenes and fused sulfolenes.[23,52] The use of this solvent (at 200°C) and excess maleic anhydride (Table 5, entry 2) resulted in the generation of a number of products, none of which had the vinylic ^{1}H n.m.r resonances of the sulfone. The reaction mixture appeared as a smear when viewed by t.l.c. The ^{1}H n.m.r spectrum gave a large number of broad signals from δ0.86-4.00 and many signals from δ5.00-6.00 and from δ7.00-8.00 indicating a complex mixture.

The extrusion reaction was conducted for a shorter time (Table 5, entry 3), than for the previous reaction outlined in entry 2. However, the high temperatures employed (250°C) resulted in polymerisation of the sulfone (**66**), giving gummy, insoluble material.

N-phenylmaleimide was utilised in the next reactions (Table 5, entries 4 and 5) as the dienophile in place of maleic anhydride, in the hope of obtaining some cleaner results. Polymerisation did not occur at higher temperature (250°C) as in entry 3, which may have been a consequence of the new dienophile. One main spot was

seen by thin layer chromatography. However the ^{1}H n.m.r spectrum showed multiple vinylic signals (δ 5.13-6.17), indicating a complex mixture.

The extrusion reaction was carried out over a shorter reaction time (22.5 h), at lower temperature (220°C) and in the presence of a radical trap (cresol) (Table 5, entry 5). Two fractions were obtained by chromatography that both contained complex n.m.r spectra.

The extrusion of sulfur dioxide from (66) was attempted in the absence of dienophiles (Table 5, entries 6 and 7). These reactions were performed using a Kugelrohr apparatus at 150°C/0.018 torr (entry 6) and 250°C/0.018 torr (entry 7) in a preheated oven. In both cases the distillate obtained was identified as the starting sulfone. Even at these temperatures/pressure, sulfur dioxide extrusion did not occur. An explanation for this may be the fast reaction time over which the compound was heated. In comparison to these distillation reactions, sulfur dioxide seemed to have been lost from (66) over a longer reaction time (1 h), at   lower temperature (250°C) and under atmospheric pressure (Table 5, entry 3).

(III) Conclusions

This research has shown that the formation of substituted dendralene precursors (**38**) can be achieved easily and in good yields($\leqslant$95%) by using Stille coupling reactions between a substituted stannane (**40**) and a vinyl triflate (**39**) followed by oxidation. A number of unique, substituted dendralene precursors were formed, some of which were oxidised to give sulfolenes (**36**) (Scheme 36).
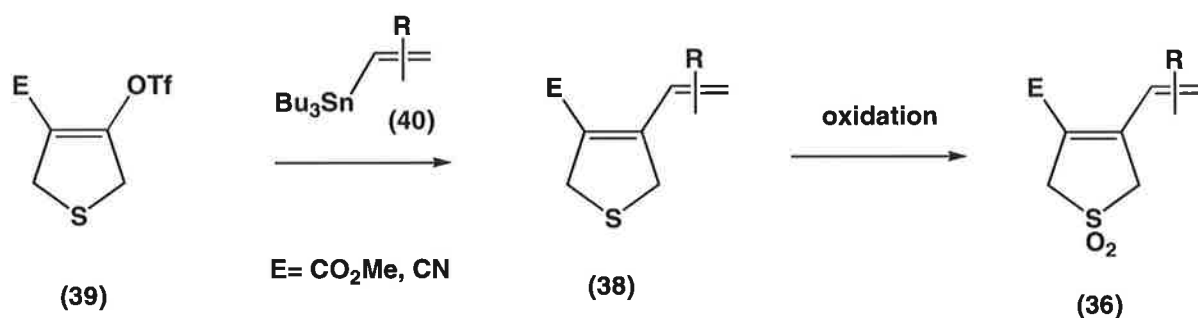
Scheme 36

The extrusion of sulfur dioxide from these substituted sulfolenes to give dendralenes was surprisingly difficult to achieve.   This was possibly due to the specific combination of substituents contained on the sulfolene molecules (**36**) where E= CO_2Me or CN and R= H, causing unusual stability.

(IV) Future Work

Future work will be to investigate more specialised means of extruding sulfur dioxide from the substituted sulfolene molecules. One such method may be the use of FVP, in apparatus designed and set up specifically for this kind of extrusion.

Secondly, the formation of substituted 4-dendralenes (**70**) based on exisiting methodology for non-substituted dendralenes,[10] may give insight into the conditions required for sulfur dioxide extrusion (Scheme 37).

<div align="center">

(41)   (54)   (69)   (70)

E= CO_2Me, CN

Scheme 37

</div>

Coupling of the two existing sulfolenes (**41**) and (**54**) using palladium catalysis should afford the product (**69**), which may extrude sulfur dioxide furnishing the substituted 4-dendralene (**70**). This reaction has been partially investigated with promising results using a sulfide triflate (**39**) instead of (**41**). Extension and optimisation of these results may allow the formation of substituted 4-dendralenes (**70**).

(V)   Experimental

General.

Melting points were determined on a Kofler hot-stage micro-melting point apparatus equipped with a Reichart microscope and are uncorrected.

Elemental analysis was performed at the University of Otago, New Zealand. High-resolution accurate mass spectra were performed by the University of Tasmania mass spectrometric service.

Ultraviolet-visible (UV-Vis) spectra were recorded on a Varian Cary 300 Bio UV-Visible Spectrophotometer as solutions in methanol in quartz cells.

Infrared spectra were recorded on a Hitachi 270-30 spectrometer, or a Perkin Elmer Spectrum BX, or a ATI Mattson Genesis FTIR as nujol mulls or liquid films between sodium chloride plates.

^{1}H n.m.r and ^{13}C n.m.r spectra were recorded on a Varian Gemini-200 (200.13 and 50.32 MHz, respectively) spectrometer or a Varian Gemini-2000 (300.13 and 74.47 MHz, respectively) spectrometer or a Varian Inova (599.95 and 150.87 MHz, respectively) spectrometer. Spectra were obtained for solutions in CDCl$_3$ [tetramethylsilane (δ_H 0.00 for SiMe$_4$) and CDCl$_3$ (δ_C 77.77) as internal standards] at 25°C, or in CDCl$_3$ containing either d$_6$-DMSO or d$_6$-Acetone [tetramethylsilane (δ_H 0.00 for SiMe$_4$) and CDCl$_3$ (δ_C 77.77) as internal standards] at 25°C. *J* values are expressed in Hz. Chemical shifts are quoted on the δ-scale in parts per million (ppm), followed by multiplicity, coupling constant(s) and assignment. The following

abbreviations have been used in reporting spectra data: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; broad b. A range is give when describing multiplets of well defined boundaries.

Electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded at 70 ev on a Vacuum Generators ZAB 2HF mass spectrometer. LCQ and GCQ mass spectra were recorded on Finnigan mass spectrometers.

Flash chromatography was performed on Silica Gel 60, 230-400 mesh (Merck). Thin layer chromatography was performed on either aluminium backed Silica Gel 60 plates (Merck) or Aluminium oxide 150 plates (Merck) and were visualised by UV light (254 nm) or by staining with either potassium permanganate dip [potassium permanganate (3 g) and potassium carbonate (20 g) dissolved in aqueous sodium hydroxide solution (5%, 5 ml) and water (100 ml)] or vanillin dip [vanillin (3 g) dissolved in ethanol (100 ml) containing sulfuric acid (0.5 ml)].

Solvents and general reagents were purified and dried using standard laboratory procedures, [53] and stored under an atmosphere of nitrogen. All organic extracts were dried over either anhydrous sodium sulfate or anhydrous magnesium sulfate. All reactions were conducted under an atmosphere of nitrogen, unless they involved hydrous conditions.

The following reagents were prepared according to published procedures: triflic anhydride,[54] $Pd(PPh_3)_4$,[55] tributyltin hydride,[42] tertrabutylammonium OXONE®,[20] wet alumina.[19]

Part 1, Chapter 1.

Methyl(2-methoxycarbonylethanethio)acetate (45).[28]

Methyl acrylate (8.11 g, 94 mmol) was added dropwise over 45 min to a stirred solution of methyl thioglycolate (10.0 g, 94 mmol) and piperidine (0.24 g, 2.9 mmol) maintained at 0-5°C. The reaction mixture was heated to 60°C for 5 min, cooled, washed with water (25 ml) and then dried over Na_2SO_4 yielding (45) as colourless oil (15.2 g, 84%). Found m/z 192.04633. Calcd for $C_7H_{12}O_4S$: 192.04731. υ_{max}(film) 1731 (C=O), 1650 (C=C) cm^{-1}. ^{1}H n.m.r (200 MHz, $CDCl_3$) δ: 2.66 [t, 2H, 7.1 Hz, C(2)H], 2.92 [t, 2H, 7.1 Hz, C(3)H], 3.27 [s, 2H, C(2')H], 3.71 [s, 3H, CH_3, ester], 3.75 [s, 3H, CH_3, ester]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 28.04 [C2], 33.93 [C2'], 34.57 [C3], 52.33 [CH_3-ester], 52.93 [CH_3-ester], 171.21 [C=O, ester], 172.55 [C=O, ester]. m/z 192 (M^+, 12%), 160 (67), 133 (48), 119 (36), 101 (14), 87 (32), 74 (35), 55 (29), 45 (100).

4-Methoxycarbonylthiolan-3-one (43).[31]

Methyl (2-methoxycarbonylethanethio)acetate (45) (5.0 g, 26.0 mmol) was added dropwise to a stirred solution of sodium (0.75 g, 32.5 mmol) and methanol (50 ml) in dry toluene (80 ml) at 80°C. The excess methanol was distilled from the reaction (b.p:63°C) as it proceeded. Once the production of methanol ceased (rise in the boiling point to above 80°C), the mixture was cooled, poured onto ice and acidified to pH 2-3 using concentrated hydrochloric acid. The orange organic phase was separated and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure to yield orange oil that contained a white solid. The oil and solid were dissolved in hexane (3 ml) and passed through a flash column (silica, with hexane initially as the elutant, and then increased amounts of dichloromethane) until the desired product (43), (Rf=0.14; hexane), was obtained as a white solid (2.12 g, 51%). Mp: 30-32°C. ν_{max}(nujol) 3150 (OH♠), 1675 (C=O, ester), 1625 (C=O) cm^{-1}. ^{1}H n.m.r

(200 MHz, CDCl$_3$) δ: 3.21 [dd, 1 H, 7.8, 11.7 Hz, C(4)H], 3.36, 3.38 [ABq, 2 H, 15 Hz, C(2)H], 3.43 [dd, 1 H, 9.0, 11.7 Hz, C(5)H], 3.56 [dd, 1 H, 7.8, 9.0 Hz, C(5)H], 3.80 [m, 10 H, C(2)H♠, C(4)H♠, CH$_3$-esters], 10.96 [s, 1 H, OH♠]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 29.60 [C5], 31.96 [C5♠], 36.59 [C2♠], 38.10 [C2], 52.20 [CH$_3$-ester♠], 53.42 [CH$_3$, ester♠], 55.95 [C4], 99.75 [C4♠], 149.11 [C3♠], 156.98 [C=O, ester♠], 158.66 [C=O, ester], 196.7 [C=O, C3]. ♠ -refers to the enol tautomer. *m/z* 160 (M$^+$, 70%), 128 (53), 101 (23), 87 (29), 69 (13), 45 (100).

Methyl 4-[(trifluro methyl)sulfonyl]oxy-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (47).[37]

A solution of 4-methoxycarbonylthiolan-3-one (**43**) (0.20 g, 1.25 mmol) in dichloromethane (10 ml) was cooled to -78°C under an atmosphere of nitrogen. Diisopropylethylamine (0.19 g, 1.45 mmol) was added to this solution and after 10 min stirring, triflic anhydride (0.41 g, 1.45 mmol) was added dropwise. The consequent mixture was allowed to warm to room temperature in which time it turned a dark orange colour. The solvent was removed under reduced pressure to give a brown oil that was purified by flash chromatography (neutral alumina, 20% ethyl acetate in hexane as elutant) to yield (**47**) as a pale green clear oil (0.37 g, 55%). ν$_{max}$ (film) 1730 (C=O), 1673 (C=C), 1440 (SO$_2$), 1145 (SO$_2$), 1021 (C-F) cm^{-1}. λ$_{max}$ (EtOH) 236 (logε 5.37) nm. ^{1}H n.m.r (200 MHz, CDCl$_3$) δ: 3.83 [s, 3H, CH$_3$, ester], 3.97 [s, 4H, C(2, 5) H]. ^{13}C n.m.r (200 MHz, CDCl$_3$) δ: 33.30 [C5], 36.20 [C2], 53.05 [CH$_3$-ester], 119.00 [q, J_{CF}=300 Hz, CF$_3$], 123.97 [C4], 151.43 [C3], 162.15 [C=O, ester].

Methyl 1,1-dioxy-4-[(trifluoromethyl)sulfonyl]oxy-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (48).

Methyl 4-[(trifluoromethyl)sulfonyl]oxy-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (**47**) (0.20 g, 0.68 mmol) was diluted in methanol (10 ml) to which was added NaHCO$_3$ (0.50 g). OXONE® (1.73 g, 2.80 mmol) was dissolved in water (20 ml) and added dropwise to the buffered methanol solution, which subsequently became

turbid. The pH of the reaction was maintained at pH 7 by the addition of $NaHCO_3$. The reaction was stirred at room temperature for 3 h, after which time the solvent was removed under reduced pressure. The white solid was re-dissolved in water (20 ml) and extracted with ethyl acetate (20 ml x 4) to yield a white solid upon solvent evaporation. Purification was achieved using flash chromatography (silica, 50% ethyl acetate in hexane as elutant) to give *methyl 1,1-dioxy-4-[(trifluoromethyl)sulfonyl]oxy-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate* (**48**) as a white solid (2.00 g, 89%). M.p: 54-55°C. Anal. Calcd. for $C_7H_7S_2F_3O_7$, C, 25.93; H, 2.18; S, 19.81%. Found: C, 25.93; H, 2.20; S, 16.96%. v_{max}(nujol) 1738 (C=O), 1662 (C=C), 1455 (SO_2), 1394 (SO_2), 1165 (SO_2) cm^{-1}. ^{1}H n.m.r (200MHz, $CDCl_3$) δ: 3.98 [s, 3H, CH_3, ester], 4.21 [s, 2H, C(5)H], 4.30 [s, 2H, C(2)H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 53.96 [CH_3, ester], 57.24 [C5], 57.97 [C2], 119 [q, 319 Hz, CF_3], 120.18 [C4], 144.30 [C3], 160.58 [C=O, ester]. *m/z*: 325 (MH$^+$, 6%), 293 (9), 261 (11), 229 (11), 127 (100), 69 (72), 45 (42).

Coupling of the sulfone triflate (48).

Vinyltributyltin.[56]

Vinyl bromide was obtained via distillation from a cylinder (Aldrich) using a dry ice/acetone condenser and stored in a flask cooled by a dry ice/acetone bath. Magnesium turnings (0.21 g, 8.60 mmol) were placed in a flask with enough THF to cover them. A dry ice/acetone condenser was fitted and vinyl bromide (1.00 g, 9.35 mmol) was added via a chilled syringe. Reaction occurred after the addition of methyliodide (0.2 ml), more vinyl bromide (0.50 g, 4.68 mmol) and THF (5 ml). After the initial reaction subsided the solution was heated at reflux for 30 min. The reaction was cooled to room temperature and the dry ice/acetone condenser replaced with a water condenser. Tributyltinchloride (1.10 g, 3.20 mmol) was added and the reaction mixture was heated to reflux for 20 h. The cooled solution was hydrolysed by the slow addition of saturated NH_4Cl (10 ml). The solution was then extracted with ether (3 x 10 ml) and concentrated under reduced pressure to yield a yellow oil that was passed through a silica column (hexane as elutant), yielding a clear, colourless oil (0.88 g, 87 %). ^{1}H n.m.r (200 MHz, $CDCl_3$) δ: 0.92 [m, 9H, CH_3 x 3], 1.35 [m, 12H, $CH_2\gamma$, CH_3], 1.37 [m, 6H, $CH_2\beta$], 1.58 [m, 6H, $CH_2\alpha$], 5.67 [dd, 1H,

3.6, 20.7 Hz, vinyl Hb-*trans*], 6.17 [dd, 1H, 3.6, 13.8 Hz, vinyl Hb-*cis*], 6.48 [dd, 1H, 13.8, 20.7 Hz, vinyl Ha]. ^{13}C n.mr (75.47 MHz, CDCl$_3$) δ: 10.05 [CH$_3$], 12.92 [Cγ], 27.57 [Cβ], 29.74 [Cα], 134.44 [Cb], 139.97 [Ca].

General procedure for coupling reactions.

Tetrakis(triphenylphosphine)palladium(0) (2 mol %) or (if specified) Pd$_3$(dba)$_2$ (2 mol %) and triphenylphosphine (1.5 eq), together with LiCl (3 eq.) and 2,6-di-*t*-butyl-*p*-cresol (2 grains) were suspended in 1,4-dioxane and stirred at room temperature. A vinyl triflate (1 eq.) and the required tributyltin (1 eq.) compound were added to the stirred yellow solution and brought to reflux. The reaction mixture was then cooled and diluted with pentane (20 ml). The mixture was then washed successively with water (20 ml), 10% ammonia solution (20 ml), water (20 ml) and brine solution (20 ml). The dried solution (MgSO$_4$) was concentrated and purified by flash chromatography or recrystallisation (hexane).

Coupling of the sulfone triflate (48), attempt 1.

Methyl   1,1-dioxy-4-[(trifluro methyl)sulfonyl]oxy-2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (48) (0.10 g, 0.29 mmol) and vinyltributyltin (0.10 g, 0.29 mmol) were left at reflux for 21 h. A brown oil was obtained that was purified by flash chromatography (silica, 50% ethyl acetate in hexane as elutant) to give a product that showed complex singals by n.m.r spectroscopy. The ^{1}H n.m.r spectrum showed multiple signals in the region δ5.5-8.0, but appeared to show no sign of the methylene protons nor the methyl group from the ester.

Attempt 2.

Methyl   1,1-dioxy-4-[(trifluro methyl)sulfonyl]oxy-2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (48) (0.10 g, 0.29 mmol) and vinyltributyltin (0.10 g, 0.29 mmol) were heated at 40°C for 36 h, then cooled to room temperature. A brown oil was obtained and purified by flash chromatography (silica, 50% ethyl acetate in hexane as elutant) that gave a product that could not be identified by n.m.r spectroscopy, but contained signals similar to what was found in entry 1.

Palladium coupling reactions of methyl 4-[(triflu'́ro methyl)sulfonyl]oxy-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (47).

Reaction 1.

$Pd_3(dba)_2$ (0.01 g, 0.02 mmol), triphenylphosphine (0.01 g, 0.03 mmol), methyl-4-[(trifluro methyl)sulfonyl]oxy-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (**47**) (0.23 g, 0.79 mmol) and vinyltributyltin (0.25 g, 0.79 mmol) were added simultaneously to the dark yellow solution and maintained at reflux for 18 h. Work up and purification by flash chromatography (silica; hexane followed by 50% ethyl acetate in hexane as elutant) gave *methyl-4-vinyl-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate* *(49)* as a yellow oil (0.09 g, 67%). Anal Calcd. for $C_3H_{10}SO_2$; C, 56.47; H, 5.88%. Found: C, 56.77; H, 5.72%. ν_{max}(nujol) 1710 (C=O), 1618 (C=C), 1120 (C-O) cm^{-1}. ^{1}H n.m.r (200 MHz, $CDCl_3$) δ: 3.80 [s, 3H, CH_3, ester], 4.09 [s, 4H, C(2, 5)H], 5.46 [dd, 1H, 0.82, 17.6 Hz, Hb *trans*], 5.51 [dd, 1H, 0.82, 10.9 Hz, Hb *cis*], 7.62 [dd, 1H, 10.9, 17.6 Hz, Ha]. ^{13}C n.m.r (200 MHz, $CDCl_3$) δ: 39.85, 40.34 [C2,5] , 52.59 [CH_3-ester], 122.35 [vinyl, C1'], 128.71 [C3], 131.75 [vinyl, C2'], 150.25 [C4], 165.00 [C=O, ester]. *m/z:* 170 (M$^+$, 60%), 155 (25), 139 (15), 111 (100), 85 (10), 45 (19).

Reaction 2.

The triflate (**47**) (0.80 g, 2.71 mmol) was heated with vinyl tributlytin (0.86 g, 2.71 mmol) at 140°C for ~4 h or until the reaction mixture turned dark brown. Purification was achieved by flash chromatography (silica, hexane [50 ml] initially followed by 20% ethyl acetate in hexane [100 ml] as elutant) giving *methyl 4-vinyl-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate* *(49)* as a pale yellow oil (0.39 g, 79%). The spectral data was consistent with what was reported previously.

Table 1, entry 1.

Methyl 4-(1-ethoxyvinyl)-4-vinyl-2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (50).

The triflate (**47**) (0.04 g, 0.15 mmol) was reacted with 1-ethoxyvinyltributyltin at 110°C for 1 h after which the reaction mixture turned dark brown. Purification by flash chromatography (silica, 20% ethyl acetate in hexane as elutant) resulted in *Methyl 4-(1-ethoxyvinyl)-4-vinyl-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (50)*, as a yellow oil (0.03 g, 95%). ν_{max}(nujol) 1740 (C=O), 1660 (C=C), 1590 (C=C) cm^{-1}. ^{1}H n.m.r (200 MHz, CDCl$_3$) δ: 1.30 [t, 3H, 7.0 Hz, CH$_3$, ethoxy], 3.76 [s, 3H, CH$_3$, ester], 3.78 [q, 2H, 7.0 Hz, CH$_2$, ethoxy], 4.00 [m, 4H, C(2)H, C(5)H], 4.22 [ABq, 1H, 2.6 Hz, vinyl], 4.27 [ABq, 1H, 2.6 Hz, vinyl]. ^{13}C n.m.r (75.47MHz, CDCl$_3$) δ: 30.30 [CH$_3$, ethoxy], 39.70, 40.20 [C2,5], 41.25 [CH$_2$, ethoxy], 53.28 [CH$_3$, ester], 132.72 [C2', vinyl], 133.50 [C3], 148.75 [C4], 152.76 [C1', vinyl], 164.64 [C=O].

Table 1, entry 2.

Separation of ethyl (*E/Z*)-3-[1,1,1-tri(*tert*-butyl)stannyl]-2-propenoate.[57]

The isomer mixture was passed through a flash column (silica, 2% ethyl acetate in hexane as elutant) giving tributyltinhydride (Rf=0.96) followed by the *Z* isomer (Rf=0.62, *J*=13 Hz) ^{1}H n.m.r (300 MHz). The column was eluted with 5% ethyl acetate in hexane resulting in the *E* isomer (Rf=0.14, *J*=19.4 Hz).

Methyl 4-[(*E*)-2-ethoxycarbonyl-1-ethenyl]-2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (53).

The triflate (**47**) (0.15 g, 0.51 mmol) was reacted with ethyl (*E*)-3-[1,1,1-tri(*tert*-butyl)stannyl]-2-propenoate at 120°C for 4.5 h, by which time the solution had turned dark brown. Purification was conducted by flash chromatography (silica, 20% ethyl acetate in hexane as elutant) yielding *methyl 4-[(E)-2-ethoxycarbonyl-1-ethenyl]-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (53)* (0.06 g, 51%) as a pale yellow oil. Found *m/z* 242.06062. Calcd for C$_{11}$H$_{14}$O$_4$S: 242.06296. ν_{max}(methanol): 1729 (conjugated ester), 1632, 1602 (diene)

cm^{-1}. ^{1}H n.m r (300 MHz, CDCl$_3$) δ: 1.33 [t, 3H, 7.2 Hz, CH$_3$], 3.83 [s, 3H, CH$_3$-methyl ester], 4.07 [m, 4H, C(2,5)H], 4.25 [q, 2H, 7.2 Hz, CH$_2$], 6.01 [d, 1H, 16.2 Hz, Ha-vinyl], 8.40 [d, 1H, 16.2 Hz, Hb-vinyl]. ^{13}C n.mr (75.47 MHz, CDCl$_3$) δ: 14.18 [CH$_3$-ethyl ester], 39.56, 40.45 [C2,5], 52.82 [CH$_3$-methyl ester], 60.93 [CH$_2$-ethyl ester], 126.08 [Ca-vinyl], 135.26 [C3], 137.72 [Cb-viny], 146.71 [C4], 167.00 [C=O , methyl ester], 172.23 [C=O, ethyl ester]. *m/z:* 242 (M$^+$, 29%), 210 (28), 169 (100), 137 (68), 109 (33).

Table 1, entry 3.

Methyl 4-[(Z)-2-ethoxycarbonyl-1-ethenyl]-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate.

The triflate (**47**) (0.21 g, 0.72 mmol) was reacted with ethyl (Z)-3-[1,1,1-tri(*tert*-butyl)stannyl]-2-propenoate at 120°C for 36 h after which time the solution appeared pale brown. T.l.c analysis revealed that a number of products had formed. Purification by flash chromatography gave fractions that contained complex mixtures of products (n.m.r).

Table 1, entry 4.

Methyl 4-[(E)-2-(2-methoxyphenyl)-1-ethenyl]-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (51).

The triflate (**47**) (0.20 g, 0.68 mmol) was heated at reflux with tributyl[(E)-2-(2-methoxyphenyl)-1-ethenyl]stannane for 2.5 h, after which time the solution appeared dark yellow. A yellow solid was obtained upon solvent evaporation that was recrystallised (hexane) to yield *methyl 4-[(E)-2-(2-methoxyphenyl)-1-ethenyl]-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate* *(51)* (0.12 g, 64%), as a pale yellow solid. M.p: 112-114°C. Found *m/z* 276.08300. Calcd for C$_{15}$H$_{16}$O$_3$S: 276.08369. ν$_{max}$(nujol) 1705 (C=O), 1615, 1600 (C=C, diene), 1500 (Ar-H), 1021 (C-O, ether), 750 (*ortho*-disubstituted Ar-H) cm^{-1}. ^{1}H n.m.r (200 MHz, CDCl$_3$) δ: 3.80 [s, 3H, CH$_3$-ester], 3.86 [s, 3H, -OCH$_3$], 4.10 [d, 2H, C(2)H], 4.22 [d, 2H, C(5)H], 6.86-6.99 [m, 2H, Ar-C(3,5)H], 7.15 [d, 1H, 16.8 Hz, vinyl-H2], 7.32 [m, 1H, Ar-C(4)H], 7.63 [m, 1H, Ar-C(6)H], 8.14 [d, 1H, 16.8 Hz, vinyl-H1].

^{13}C n.mr (75.47 MHz, CDCl$_3$) δ: 39.97 [C2,5], 52.25 [CH$_3$-ester], 56.17 [CH$_3$-ether], 110.38 [C3-phenyl], 121.57 [C1-vinyl], 123.78 [C3], 123.87 [C5-phenyl], 127.66 [C1-phenyl], 127.76 [C6-phenyl], 130.77 [C4-phenyl], 131.98 [C2-vinyl], 138.97 [C4], 151.22 [C2-phenyl], 179.05 [C=O]. *m/z* 276 (M$^+$, 100%), 244 (45), 217 (40), 184 (32), 141 (10), 121 (23), 91 (15), 59 (9).

Table 1, entry 5.

Methyl 4-((*E*)-3-{[1,1-dimethyl-1-(1,1,2-trimethylpropyl)silyl]oxy}-1-propenyl)-2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (52).

The triflate (47) (0.20 g, 0.66 mmol) was heated to reflux with tributyl((*E*)-3-{[1,1-dimethyl-1-(1,1,2-trimethylpropyl)silyl]oxy}-1-propenyl)stannane for 3 h, in which time the yellow solution turned pale brown. Purification was achieved by flash chromatography (neutral alumina, 20% ethyl acetate in hexane as elutant), follow by Kugelrohr distillation (120° C, 0.05 torr) giving *methyl 4-((E)-3-{[1,1-dimethyl-1-(1,1,2-trimethylpropyl)silyl]oxy}-1-propenyl)-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (52),*as a colourless oil (0.18 g, 80%). ν$_{max}$(film) 1712 (C=O), 1641, 1602 (C=C, diene), 1033, 843 (O-Si) cm^{-1}. ^{1}H n.m r (200 MHz, CDCl$_3$) δ: -0.06 [s, 6H, 2 x CH$_3$-Si], 0.78 [m, 12H, 4 x CH$_3$], 0.98 [m, 1H, thexyl], 3.65 [s, 3H, -OCH$_3$], 3.93 [s, 4H, C(2,5)H], 4.20 [d, 2H, 4.4 Hz, C(3')H], 5.87 [dt, 1H,4.4, 16.2 Hz, C(2')H], 7.38 [d, 1H, 16.2 Hz, C(1')H]. ^{13}C n.mr (75.47 MHz, CDCl$_3$) δ: -2.73 [Me$_2$-Si], 19.14 [Me$_2$-C-], 20.93 [Me$_2$-CH], 28.46 [Me$_2$-C], 34.78 [C1], 39.12 [C3, Me$_2$-CH], 52.25 [C6], 61.31 [C9], 123.44 [C2], 124.37 [C8], 137.63 [C4], 138.88 [C7], 149.27 [C=O].

Table 1, entry 6.

3-Tributylstannyl-sulfolene (54).[44]

3-Phenylsulfonyl-3-sulfolene (58) [40] (0.07 g, 0.27 mmol), 2,2'-azobisisobutyronitrile (5.00 mg, 0.03 mmol, 10 mol %, recrystallised from CHCl$_3$) and tributyltin hydride (0.16 g, 0.54 mmol, freshly distilled) were dissolved in benzene (2 ml, distilled and degassed prior to use) and the mixture heated to reflux for 22 h. The reaction was allowed to cool and concentrated under reduced pressure to give a clear, colourless oil. The oil was purified by flash chromatography (alumina, hexane [10 ml], followed

by 20% ethyl acetate in hexane as elutant). The second fraction off the column contained a clear oil that was identified as 3-tributylstannyl-sulfolene (**54**) (0.03 g, 26%). v_{max}(film) 2955, 293, 2850, 1304 (SO_2), 1123 (SO_2) cm^{-1}. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 0.83-1.52 [m, 27H, butyl], 3.67 [br-s, 2H, CH_2], 3.71 [br s, 2H, CH_2], 6.00 [m, 1H, vinyl-H]. ^{13}C. n.m.r (75.47 MHz, $CDCl_3$) δ: 10.23 [CH_3-butyl], 14.13 [CH_2-butyl], 27.81 [CH_2-butyl], 29.67 [CH_2-butyl], 56.97 [C5], 62.10 [C2], 132.93 [C4], 141.10 [C3]. *m/z* 407 (M^+, 12%), 177 (100), 117 (13), 135 (11).

The triflate (**47**) (0.10 g, 0.34 mmol) and 3-tributylstannylsulfolene (**54**) (0.34 mmol, 0.14 g) were added to a yellow solution containing the palladium catalyst, which subsequently went colourless. The reaction mixture was heated to reflux for 23 h, then purified by flash chromatography [hexane (20 ml), followed by 20% ethyl acetate in hexane as elutant]. A small amount of a colourless gum was obtained that was identified as *methyl 4-(1-methyleneallyl)-2,5-dihydro-3-thiophenecarboxylate* (**55**). ^{1}H n.m r (300 MHz, $CDCl_3$) δ: 3.77 [s, 3H, $-CH_3$, ester], 4.00 [m, 4H, C(2,4)H], 4.97 [s, 1H, terminal alkene-H], 5.04 [d, 1H, 17.1 Hz, terminal alkene-H], 5.06 [d, 1H, 10.5 Hz, terminal alkene-H], 5.18 [s, 1H, terminal alkene-H], 6.34 [dd, 1H, 10.5, 17.1 Hz, alkene-H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 33.32 [C2], 36.13 [C5], 53.01 [CH_3-ester], 110.66 [CH_2-alkene], 121.75 [C3], 123.79 [CH_2-alkene], 138.11 [CH-alkene], 147.45 [C4], 152.54 [C-alkene], 165.73 [C=O].

Oxidation of Methyl 4-vinyl-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (49).

Table 2, entry 1.

OXONE$^\circledR$ (2.49 g, 4.05 mmol) was dissolved in water (100 ml) and added dropwise to a buffered ($NaHCO_3$) solution of methyl 4-vinyl-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (**49**) (0.17 g, 1.00 mmol) in methanol (5 ml). The reaction was maintained at pH 7 by the monitored addition of $NaHCO_3$, and stirred at room temperature for 4 h. The methanol was removed under reduced pressure and the aqueous solution was extracted with ethyl acetate (3 x 50 ml). A white solid was obtained upon solvent evaporation which was purified by flash chromatography (silica, 50% ethyl acetate in hexane) yielding a white solid (0.10g, 50%) which was

identified as *methyl 1,1-dioxo-4-vinyl-2,5-dihydro-1H-1λ^6-thiophene-3-carboxylate (59)*. M.p: 176-180°C. ν_{max}(nujol): 1790 (C=O), 1630 (C=C), 1580 (C=C), 1320 (SO$_2$), 1120 (SO$_2$), 1020 (C-O) cm^{-1}. ^{1}H n.m.r (200 MHz, CDCl$_3$) δ: 3.38 [s, 3H, CH$_3$, ester], 4.15 [s, 2 H, C(5)] 4.20 [s, 2H, C(2)H], 5.47 [dd, 1H, 0.82, 17.6 Hz, H$_a$ *trans*], 5.66 [dd, 1H, 0.82, 10.9 Hz, H$_a$ *cis*], 7.70 [dd, 1H, 10.9, 17.6 Hz, H$_b$]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 53.07 [CH$_3$, ester], 57.64, 58.49 [C2,5], 125.32 [C1', vinyl], 128.03 [C3], 130.82 [C2', vinyl], 144.21 [C4], 162.05 [C=O, ester]. Attempts at gaining a mass spectrum were unsuccessful. This was thought to be due to the short lifetime of the sulfone, which could not be stored.

Table 2, entry 2a.[20]

3-Methoxycarbonyl-4-ethenyl-2,5-dihydrothiophene (49) (0.05 g, 0.29 mmol) was diluted and stirred in dichloromethane (3 ml) to which was added Na$_2$CO$_3$ (0.09 g). Tetrabutylammonium OXONE® (Bu$_4$NHSO$_5$) (0.83 g, 0.88 mmol) was slowly added to the reaction solution, which in time became orange. The mixture was stirred at room temperature for 4 h, after which it was diluted with ether (10 ml), washed with a 10% sodium hydroxide solution (10 ml), water (5 ml) and brine (10 ml). The orange solution was dried (MgSO$_4$) and purified by flash chromatography. A white solid (7.00 mg, 12%) was obtained that was identified as the sulfone (59), which showed spectral data consistent with that obtained for entry 1.

Table 2, entry 2b.

Tetrabutylammonium OXONE® (1.70 g, 1.76 mmol) was added to a solution of the sulfide (49) (0.10 g, 0.59 mmol) diluted in dichloromethane (5 ml) and stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (silica, 40% ethyl acetate in hexane) giving a pale yellow solid (0.02 g, 15%) upon solvent evaporation. The solid was identified as the sulfone (59) by comparison with data already obtained (entry 1).

Table 2, entry 3.[19]

The sulfide (**49**) (0.04 g, 0.24 mmol) was added to a vigorously stirred suspension of wet alumina (0.23 g) and OXONE® (0.43 g, 0.71 mmol) in chloroform (4 ml). The solution was maintained at reflux for 4.5 h, then cooled to room temperature. The mixture was filtered and the residue washed with chloroform (30 ml). Purification by flash chromatography (silica, 50% ethyl acetate in hexane) gave a pale yellow viscous oil (0.29 g, 60%), which was identified as the sulfone (**59**) by comparison with data obtained in entry 1.

Table 2, entry 4.[45]

Powdered 4Å molecular sieves (0.01 g) were added to a stirred solution of the sulfide (**49**) (0.05 g, 0.29 mmol) in acetonitrile (3 ml). N-Methylmorpholine N-oxide (0.10 g, 0.89 mmol) was added to the reaction and stirred for 5 min. N-Pr$_4$NRuO$_4$ (5 mg, 2 μmol) was then added and the solution was heated to 40°C for 21 h. The solvent was removed under reduced pressure to give material that could not be identified by spectroscopic means, even after flash chromatography. N.m.r spectroscopy (^{1}H, ^{13}C) showed multiple signals, none of which belonged to the sulfone.

Table 2, entry 5.[46]

The sulfide (**49**) (0.10 g, 0.59 mmol) was added to a solution of potassium superoxide (KO$_2$) (0.14 g, 1.96 mmol) and o-nitrobenzenesulfonylchloride (0.15 g, 0.65 mmol) in acetonitrile (5 ml), which was maintained between -30 - -20°C. The reaction was filtered after 6.5 h and the filtrate condensed to yield a brown/orange oil. Purification by chromatography (silica, ethanol as elutant) gave a pale yellow viscous oil (5 mg, 5%) that was identified as the sulfone (**59**) by comparison with data from entry 1.

Extrusion of Sulfur dioxide from 3-methoxycarbonyl-4-ethenyl-2,5-dihydrothiophene-1,1-dioxide (59).

Table 3, entry 1; Thermolysis.

3-Methoxycarbonyl-4-ethenyl-2,5-dihydrothiophene-1,1-dioxide (59) (20 mg, 80 μmol) was stirred in 1,2,4-trichlorobenzene (1 ml) to which maleic anhydride (7.0 mg, 8 μmol) was added. The reaction was heated to 200°C for 24 h, cooled and the solvent removed under reduced pressure (oil pump). ^{1}H n.m.r showed complex signals, none of which corresponded to the starting sulfone.

Table 3, entry 2, Sealed tube reaction.

The sulfone (59) (0.01 g, 0.03 mmol) was diluted in benzene (2 ml) to which was added maleic anhydride (0.01 g, 0.12 mmol). The mixture was heated in a sealed tube at 200°C for 25 h. The benzene was removed under reduced pressure and the yellow oil was passed through a silica column (40% ethyl acetate in hexane as elutant) yielding a small amount of starting sulfone (59) as well as decomposition material (baseline material-t.l.c, complex signals-^{1}H n.m.r).

Table 3, entry 3, Sealed tube reaction.

The sulfone (59) was diluted in benzene (1 ml) to which was added ethylvinylether (4 drops). The solution was heated in a sealed tube to 140°C for 17 h, the initial pale yellow solution turning an orange colour. The reaction mixture was concentrated under reduced pressure and passed down a silica column (40% ethyl acetate in hexane as elutant) revealing starting material and baseline material (t.l.c). ^{1}H n.m.r spectroscopy showed broad, complex signals as well as those of the sulfone (59).

Table 3, entry 4, Thermolysis.

The sulfone (59) was heated in a Kugelrohr Apparatus at 200-250°C / 0.025 torr. A clear, colourless oil was trapped in the receiver bulb, which slowly solidified on cooling. The solid was identified as the starting sulfone (59) (t.l.c, ^{1}H n.m.r).

Table 3, entry 5, Flash Vacuum Pyrolysis.

All glassware prior to use was washed in a 5% 2,6-di-*t*-butyl-*p*-cresol / acetone solution and dried over night in an oven.

The pyrolysis oven was preheated to 550° C, and the sulfone (**59**) (0.10 g, 0.50 mmol) was placed into the adjacent preheated (100° C) Kugelrohr Apparatus at a pressure of 0.01 torr. 1/5 of the sulfone vaporised and entered the pyrolysis oven, while the other 4/5 polymerised in the initial tube. The oven was heated to 560° C and left for 3 h. No product was detected in the receiver trap.

Table 3, entry 6, Ultrasonically dispersed potassium extrusion of sulfur dioxide.[27]

Potassium pieces (0.05 g, 1.19 mmol) were suspended in toluene (3 ml) and sonicated for 40 min resulting in the formation of a blue / grey colloid. The sulfone (**59**) (0.08 g, 0.40 mmol) was added in toluene (3 ml) causing the reaction to turn a yellow / brown colour. The reaction was sonicated for a further 1 h causing a darker brown colour change. Tertiary butanol (0.09 g, 1.16 mmol) in THF (3 ml) was added dropwise over 10 min. The solution was passed through a wad of alumina, and the solvent removed under reduced pressure. Analysis by ^{1}H n.m.r spectroscopy revealed the presence of starting sulfone (**59**) and a small amount of material that showed multiple, complex signals by ^{1}H n.m.r spectroscopy.

Table 3, entry 7, Ultrasonically dispersed potassium extrusion of sulfur dioxide.

The reaction was conducted as in Entry 6. However a blue potassium colloid was formed after 10 min sonication and the addition of extra toluene (4 ml). Upon the addition of the sulfone (**59**), the reaction mixture became orange, green then appeared brown after a further 2.5 h sonication. The solvent was removed under reduced pressure to give a complex mixture of products (t.l.c, ^{1}H n.m.r).

Ethyl 2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (62).[49]

Sodium borohydride (0.02 g, 0.63 mmol) was added to a stirred solution of 4-methoxycarbonylthiolan-3-one (43) (0.10 g, 0.63 mmol) in ethanol (5 ml) maintained at 0°C. The reaction mixture was warmed to room temperature, stirred for 5 h, then taken back to 0°C and acidified to pH 6 using acetic acid. The solvent was removed under reduced pressure and the residue was extracted into ethyl acetate (5 ml). The extracts were washed successively with water (15 ml) and brine solution (15 ml), then dried over Na_2SO_4. Crude methyl 4-hydroxytetrahydro-3-thiophenecarboxylate (0.08 g, 73%) was dissolved in dichloromethane (3 ml) and cooled to 0°C. Triethylamine (0.25 g, 2.50 mmol) and mesyl chloride (0.14 g, 1.25 mmol) were added dropwise to the reaction mixture, which was then stirred at room temperature for 12 h. The brown solution was diluted with dichloromethane (10 ml) and washed with a 0.5M aqueous solution of hydrochloric acid (2 x 10 ml). The dried extracts (Na_2SO_4) were concentrated and purified by column chromatography (silica, 60% ethyl acetate in hexane) giving ethyl 2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (62) (Rf=0.75, 0.04 g, 57%) as an orange oil. v_{max}(film): 1785 (C=O), 1640 (C=C), 1020 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 1.28 [t, 3H, 7.2 Hz, CH_3-ester], 3.92 [m, 4H, C(2,5)H], 4.22 [q, 2H, 7.2 Hz, CH_2-ester], 6.88 [s, 1H, C(4)H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 30.38 [CH_3-ester], 37.80 [C5], 39.65 [C2], 60.47 [CH_2-ester], 134.66 [C3], 143.78 [C4], 165.59 [C=O]. This data was consistent with that of the literature for the corresponding carbmethoxy derivative.[47]

Ethyl 1,1-dioxo-2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (61).[49]

Ethyl 2,5-dihydro-1*H*-1λ^6-thiophene-3-carboxylate (62) (5.0 mg, 0.03 mmol) was stirred in dichloromethane (2 ml) at 0°C to which was added *m*-CPBA (10 mg, 0.06 mmol). The mixture was stirred for 3 h, then at room temperature for 12 h. The filtered solution was washed with an aqueous saturated solution of Na_2CO_3, dried ($MgSO_4$) and concentrated to give a solid. The solid was purified through a small wad of silica (eluting with ethyl acetate). Solvent evaporation gave a white solid, (3.80 mg, 62%). M.p: 150-152°C. v_{max}(nujol): 1790 (C=O), 1630 (C=C), 1330, 1125 (SO_2) cm^{-1}. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 1.33 [t, 3H, 7.2 Hz, CH_3-ester], 4.01

[m, 4H, C(2,5)H], 4.28 [q, 2H, 7.2 Hz, CH$_2$-ester], 7.02 [m, 1H, C(4)H]. The spectral data was consistent with literature reported for similar molecules.[47,49] The solid was used directly without further analysis.

Diethyl 4-vinyl-1-cyclohexene-1,4-dicarboxylate (63).[48]

Ethyl 1,1-dioxosulfolene-3-carboxylate (**61**) (3.8 mg, 0.02 mmol) was diluted in toluene (1 ml) and refluxed for 5 h. Solvent evaporation gave a yellow gum in quantitative yield that had dimerised after sulfur dioxide extrusion. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 1.31 [t, 6H, -CH$_3$ x 2], 2.07 [t, 2H, C(2)H], 2.27 [t, 2H, C(4)H], 3.08 [m, 2H, C(3)H], 4.32 [m, 4H, -CH$_2$- x 2], 5.07 [d, 1H, 17.7 Hz, Hb'-*trans*], 5.12 [d, 1H, 10.5 Hz, Hb'-*cis*], 5.87 [dd, 1H, 10.5, 17.7 Hz, Ha'], 7.03 [m, 1H, H-ring vinyl]. This data was consistent with literature values.[48] The small amount of sample made further analysis difficult; no clear ^{13}C n.m.r spectrum could be obtained. A consistent mass spectrum could not be obtained suggesting that the product had decomposed.

4-Cyano-3-oxo-thiolane (44).[50]

Sodium metal (0.30 g, 13 mmol) was dissolved in methanol (3.5 ml) and maintained at 0°C, to which was added methylthioglycolate (1.0 g, 9.4 mmol) followed by freshly distilled acrylonitrile (0.50 g, 9.4 mmol). The resulting yellow solution was refluxed for 1 h, then left to cool (room temperature). The methanol was removed from the brown reaction mixture, which was then diluted with water (25 ml) and extracted with ether (2 x 20 ml). The aqueous layer was acidified to pH 1 using aqueous hydrochloric acid (1M), and extracted with ether (3 x 25 ml), yielding a yellow oil upon solvent evaporation. Purification by chromatography (60% ethyl acetate in hexane as elutant initially, followed by 100% hexane) gave a pale yellow solid, that was subsequently recrystallised (hexane) to give a white solid. The solid was identified as *4-cyano-3-oxo-thiolane (44)* (0.50 g, 42%). M.p: 62-63°C, (lit: 71-72°C).[51] Anal. Calcd for C$_5$H$_5$NSO: C, 47.2; H, 3.96; N, 11.09; S, 25.24. Found: C, 47.02; H, 4.15; N, 10.85; S, 25.32 %. ν$_{max}$ (nujol): 2248 (nitrile), 1747 (C=O) cm^{-1}. ^{1}H n.m.r (200 MHz, CDCl$_3$) δ: 3.27 [dd, 1H, 10.8, 11.8 Hz, C(5)H], 3.36 [dd, 1H, 7.8, 11.8 Hz, C(5)H], 3.42 [s, 1H, C(2)H], 3.66 [dd, 1H, 7.8, 10.8 Hz, C(4)H]. ^{13}C n.m.r

(75.47 MHz, CDCl$_3$) δ: 29.92 [C(5)], 36.90 [C(2)], 41.74 [C(4)], 103.12 [nitrile], 202.10 [C=O]. *m/z:* 127 (M$^+$, 91%), 99 (21), 74 (28), 55 (43), 47 (100).

O

4-[(trifluromethyl)sulfonyl]oxy-2,5-dihydro-1*H*-1λ^6-thiophene-3-carbonitrile (67).

A solution of 4-Cyano-3-oxo-thiolane (**44**) (2.10 g, 16.3 mmol) in dichloromethane (120 ml) was cooled under an atmosphere of nitrogen to -78°C. Diisopropylethylamine (2.40 g, 19.0 mmol) was added to this solution and after stirring for 10 min, triflic anhydride (5.30 g, 19.0 mmol) was added dropwise. The resulting solution was warmed to room temperature in which time it turned dark brown. The solvent was removed under reduced pressure yielding a brown oil that was purified by flash chromatography (neutral alumina, 20% ethyl acetate in hexane as elutant) to yield *4-[(trifluoromethyl)sulfonyl]oxy-2,5-dihydro-1H-1λ^6-thiophene-3-carbonitrile (67)* as a pale brown oil (3.10 g, 73%). Anal. Calcd for C$_6$H$_4$NS$_2$O$_3$F$_3$: C, 27.8; H, 1.5; N, 5.4; S, 24.8. Found: C, 28.02; H, 1.57; N, 5.41; S, 23.96 (interference from fluorine is the reason for this low value)%. ν$_{max}$(film): 2234 (nitrile), 1667, 1431, 1222 (SO$_2$), 1134 (SO$_2$), 1022 (C-F), 839 cm^{-1}. ^{1}H n.m r (200 MHz, CDCl$_3$) δ: 3.86 [m, 2H, C(5)H], 4.05 [m, 2H, C(2)H]. ^{13}C n.mr (75.4 MHz, CDCl$_3$) δ: 32.56 [C(5)], 35.00 [C(2)], 111.17 [nitrile], 117.34 [q, 317Hz, CF$_3$], 117.67 [C(4)], 157.96 [C(3)]. *m/z:* 259 (M$^+$, 44%), 194 (11), 174 (5), 148 (6), 126 (74), 69 (100). 45 (67).

4-Vinyl-2,5-dihydro-1*H*-1λ^6-thiophene-3-carbonitrile (68).

To a mixture of lithium chloride (460 mg, 10 mmol), tetrakis(triphenylphosphine)palladium(0) (80 mg, 0.07 mmol) and 2,6-di-*t*-butyl-*p*-cresol (few grains) in 1,4-dioxane was added 4-cyano-2,5-dihydrothieno-3-yl triflate (**67**) (930 mg, 3.6 mmol) and vinyltributyltin (1.14 g, 3.6 mmol). The reaction was heated at reflux for 3 h after which it turned dark brown. The solution was cooled, diluted with pentane (15 ml), and washed successively with water (20 ml), 10% ammonia solution (20 ml), water (20 ml) and a concentrated brine solution (20 ml). The organic solution was dried (MgSO$_4$) and concentrated to yield a yellow oil. Purification by flash chromatography (hexane [200 ml] followed by 20% ethyl acetate

in hexane [200 ml] as elutant) gave a pale yellow crystalline solid. Recrystallisation (hexane) yielded *4-vinyl-2,5-dihydro-1H-1λ^6-thiophene-3-carbonitrile* **(68)** (0.32 g, 65%) as a white solid. M.p: 72-73°C. Anal. Calcd for C_7H_7NS: C, 61.26; H, 5.14; N, 10.2; S, 23.39. Found: C, 61.17; H, 5.2; N, 10.04; S, 23.09%. v_{max}(nujol): 2214 (nitrile), 1586 (C=C) cm^{-1}. ^{1}H n.m r (300 MHz, CDCl$_3$) δ: 3.97, 3.99 [2 x m, 4H, C(2,5)H], 5.49 [d, 1H, 17.6 Hz, Hb-*trans*], 5.61 [d, 1H, 10.8 Hz, Hb-*cis*], 6.89 [dd, 1H, 10.8 Hz, 17.4 Hz, Ha]. ^{13}C n.mr (75.47 MHz, CDCl$_3$) δ: 37.88, 39.23 [C(2,5)], 123.87 [vinyl, C(1)'], 129.26 [C(3)], 130.25 [vinyl, C(2)'], 134.65 [nitrile]. *m/z* 137 (M$^+$, 31%), 122 (21), 119 (30), 85 (19), 63 (28), 51 (47), 45 (100).

1,1-Dioxo-4-vinyl-2,5-dihydro-1*H*-1λ^6-thiophene-3-carbonitrile (66).

Table 4, entry 1, Oxone method:[58]
4.1 equivalents of OXONE

OXONE® (0.93 g, 1.5 mmol) dissolved in water (4 ml), was added dropwise to a stirred solution of 4-vinyl-2,5-dihydro-1*H*-1λ^6-thiophene-3-carbonitrile **(68)** (0.05 g, 0.37 mmol) diluted in methanol (2 ml), which became turbid upon addition. The reaction mixture was maintained at pH 7 by the monitored addition of aqueous sodium hydrogen carbonate. The reaction was stirred at room temperature for 3 h, after which the methanol and water were removed under reduced pressure to yield a white solid that was diluted partially with water (10 ml). The aqueous mixture was extracted with ethyl acetate (20 ml x 4), to yield *1,1-dioxo-4-vinyl-2,5-dihydro-1H-1λ^6-thiophene-3-carbonitrile* **(66)**, (0.05 g, 79%) after solvent evaporation. M.p: 130-132°C. Anal. Calc for $C_7H_7NSO_2$: C, 49.65; H, 4.17; N, 8.27; S, 18.96. Found: C, 49.38; H, 3.91; N, 8.27; S, 18.63%. v_{max}(nujol) 2220 (nitrile), 1580 (C=C), 1320 (SO$_2$), 1120 (SO$_2$) cm^{-1}: ^{1}H n.m r (300 MHz, CDCl$_3$) δ: 4.00. 4.03 [s, 2H, C(2,5)H], 5.51 [d, 1H, 17.4 Hz, Hb-*trans*], 5.73 [d, 1H, 10.8 Hz, Hb-*cis*], 6.81 [dd, 1H, 10.8, 17.4 Hz, Ha).]. ^{13}C n.mr (75.47 MHz, CDCl$_3$) δ: 55.69, 57.45 [C2,5], 110 [nitrile], 126.91 [C1'], 129.12 [C3], 130.10 [C2'], 132.80 [C4]. *m/z* M$^+$ 169 (16%), 121 (2), 105 (100), 78 (85), 65 (36), 52 (34).

Table 4, entry 2, 3 equivalents of OXONE

OXONE® (1.3 g, 2.1 mmol) dissolved in water (5 ml), was added drop wise to a stirred solution of 3-cyano-4-ethenyl-2,5-dihydrothiophene (0.10 g, 0.70 mmol) diluted in methanol (2 ml), which became turbid upon addition. The reaction mixture was maintained at pH 7 by the monitored addition of $NaHCO_3$. The reaction was stirred at room temperature for 4 h, after which the methanol and water were removed under reduced pressure to yield a white solid that was diluted partially with water (10 ml). The aqueous mixture was extracted with ethyl acetate (20 ml x 4), to yield *1,1-dioxo-4-vinyl-2,5-dihydro-1H-1λ⁶-thiophene-3-carbonitrile (66)* (0.08 g, 68%) as a pale cream solid upon solvent evaporation. Spectral data was consistent with what was obtained for entry 1.

Table 4, entry 3, Wet Alumina Oxidation:[19]

3-cyano-4-ethenyl-2,5-dihydrothiophene (**68**) (0.03 g, 0.22 mmol) was added to a vigorously stirred suspension of wet Alumina (0.40 g, 0.66 mmol) in chloroform (2 ml). *(0·30g) and Oxone®* The reaction was maintained at reflux for 8 h, after which it was passed through a sintered glass funnel. The residue was washed with chloroform (20 ml), and a white solid was obtained (0.02 g, 62%) after solvent evaporation under reduced pressure. The solid was identified as sulfone (**66**), which showed spectral data consistent with entry 1.

Extrusion of sulfur dioxide from 1,1-dioxo-4-vinyl-2,5-dihydro-1*H*-1λ⁶-thiophene-3-carbonitrile (66).

General procedure for extrusion reactions.

The sulfone 1,1-dioxo-4-vinyl-2,5-dihydro-1*H*-1λ⁶-thiophene-3-carbonitrile (**66**), was diluted in solvent to which excess dienophile was added. The reaction mixture was heated, cooled to room temperature and the solvent removed under reduced pressure.

Table 5, entry 1.

The sulfone (**66**) (0.05 g, 0.30 mmol) was diluted in toluene (2 ml) and reacted with excess maleic anhydride at reflux for 24 h. The major product obtained was the starting sulfone (t.l.c, n.m.r).

Table 5, entry 2.

The sulfone (**66**) (0.05 g, 0.30 mmol) was diluted with 1,2,4-trichlorobenzene (2 ml) to which excess maleic anhydride was added. The reaction mixture was heated at 200°C for 4.5 h. Purification by chromatography (silica, 40% ethyl acetate in hexane as elutant) yielded a fraction that did not contain the sulfone (t.l.c) but appeared as a complex mixture (^{1}H n.m.r spectroscopy).

Table 5, entry 3.

The sulfone (**66**) (0.05 g, 0.30 mmol) was reacted with maleic anhydride (0.06 g, 0.60 mmol) in 1,2,4-trichlorobenzene (3.5 ml) at 250°C over 1 h. Purification by chromatography (silica, ethyl acetate) gave material that later proved to be insoluble.

Table 5, entry 4.

The sulfone (**66**) (0.05 g, 0.29 mmol) was diluted in 1,2,4-trichlorobenzene (5 ml) and reacted with *N*-phenylmalamide (0.13 g, 0.73 mmol) at 250°C for 48 h followed by stirring at room temperature for 48 h. The initial yellow solution turned brown in this time. Purification using a silica column with a combination of solvents gave one main fraction that appeared as a complex mixture (^{1}H n.m.r spectroscopy).

Table 5, entry 5.

The sulfone (**66**) (0.05 g, 0.29 mmol) was diluted in 1,2,4-trichlorobenzene and reacted with excess *N*-phenylmalamide in the presence of 2,6-di-*t*-butyl-*p*-cresol (1 grain) at 220°C. After 22.5 h the initial yellow solution appeared dark orange. Purification by column chromatography (silica, 40% ethyl acetate in hexane as

elutant), gave two fractions, both consisting of complex mixtures (^{1}H n.m.r spectroscopy).

Table 5, entry 6.

The sulfone (**66**) (0.08 g, 0.47 mmol) was distilled using a Kugelrohr Apparatus (150° C / 0.018 torr) to give a white solid (0.06 g, 70%). The product was identified as starting material by ^{1}H n.m.r spectroscopy.

Table 5 entry 7.

The sulfone (**66**) (0.06 g, 0.36 mmol) was distilled using a preheated Kugelrohr Apparatus (250° C / 0.018 torr) yielding a white solid (0.05 g, 77%) that was identified as starting sulfone by ^{1}H n.m.r spectroscopy.

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Part 2: Investigations into the Synthesis of Epicatechins. Chapter 1: Green tea Catechins; their importance, benefits and detection.

(I)   Green Tea Catechins

Tea is grown in about 30 countries but is consumed worldwide, although at greatly varying levels.[1] Tea is one of the most popular beverages in the world and is the most widely consumed aside from water.[1] The popularity of tea has encompassed the formation of over 300 different types of teas falling into one of three general forms: unfermented green tea, partially fermented oolong tea and fermented black tea.[2] China and Japan consume more green tea than most other nations whilst India and European countries consume the most black tea.

As to composition, polyphenols are the most abundant group of compounds found in the tea leaf. Of these, flavanols (catechins) constitute the major component, comprising up to 30% of the dry matter of the fresh leaf.[3] Other chemicals are also present in the leaf, such as gallic acid and other flavan-3-ols, however these are much less predominant. Flavanols are ubiquitous in the plant kingdom and are therefore present in many items of the human diet, such as wine and chocolate, making them of essential importance.

The major green tea catechins are (+)-catechin (**C**) (**1**), (-)-epicatechin (**EC**) (**2**), (-)-epigallocatechin (**EGC**) (**3**), (-)-epicatechin gallate (**ECG**) (**4**) and (-)-epigallocatechin gallate (**EGCG**) (**5**), as illustrated in figure 1. The three common rings of catechin molecules are denoted A, B or C (for the heterocyclic ring) according to the assignment shown for (+)-catechin (**1**) (figure 1). The atoms are

numbered according to the system shown, with position one being the heterocyclic oxygen.
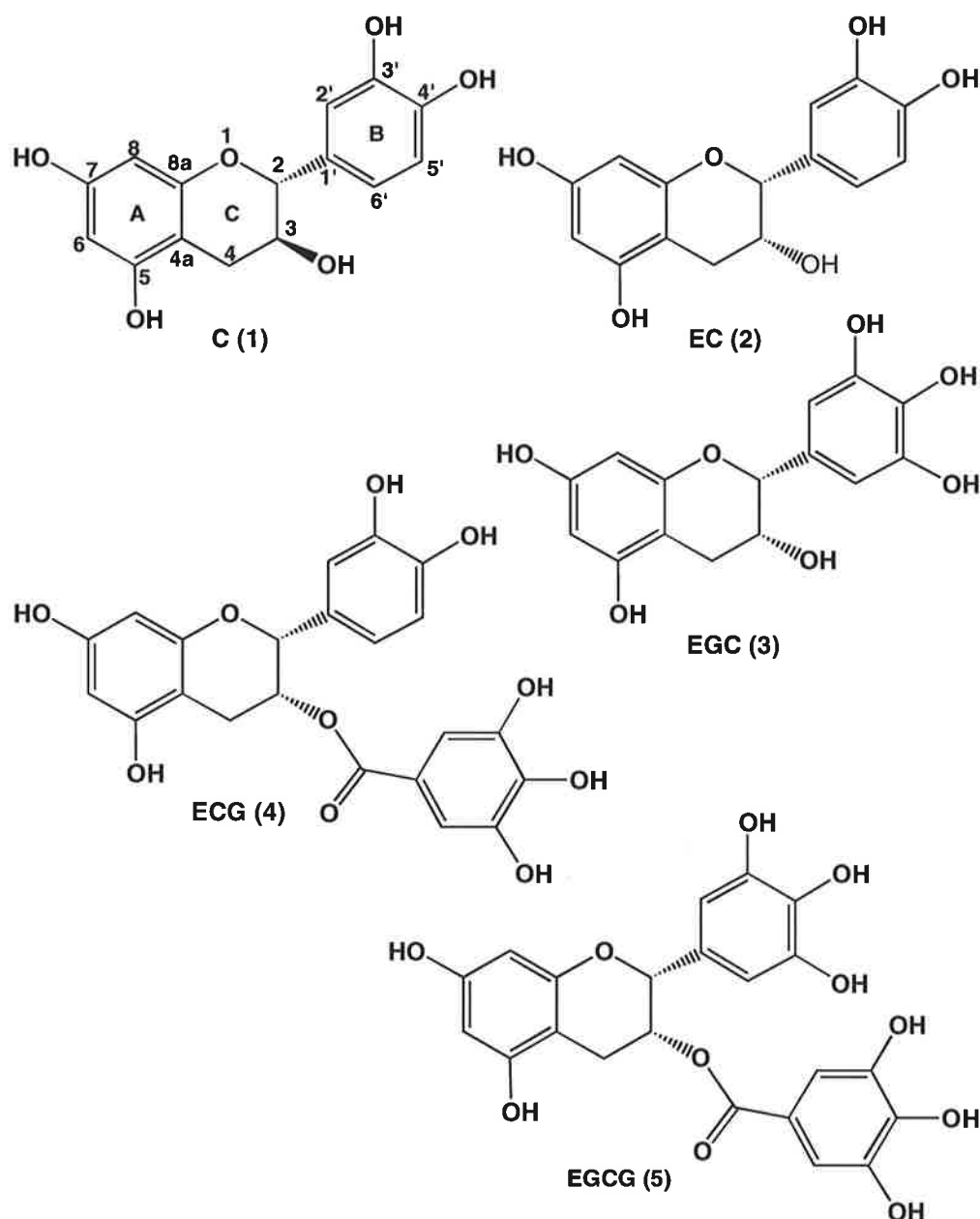
Figure 1: The labeling and structures of the major tea catechins.

Individual catechin concentrations are highly dependent on leaf age and it has been found that the leaf bud and the first leaf are richest in **EGCG** (5).[1] The concentrations may also vary between the different tea varieties.[1] A higher concentration of **EGC** (3) is found as the leaf matures. This is a result of hydroxylation reactions of the catechins generating **EGC** (3), gradually predominating

over esterification reactions, a process that produces **EGCG** (**5**).[4] A typical polyphenol fraction extracted from green tea contains **EGCG** (49%), **ECG** (14%), **EGC** (11%), **EC** (6%) and **C** (2%). These catechins are responsible for the bitter and astringent taste of green tea.[3] During the fermentation of black tea, monomeric catechins undergo 'polyphenol oxidase-catalysed oxidative polymerisation' leading to the formation of bisflavanols, theaflavins (responsible for colour and flavor), thearubigins and other oligomers.[2] Thearubigins comprise about 20% of the dry weight of black tea, whilst theaflavins comprise about 1-2%. Oolong tea, which has undergone partial fermentation, contains monomeric catechins, theaflavins and thearubigins.

Theaflavins are a group of well characterised compounds formed from the condensation reaction between a quinone derived from a simple catechin or its gallate, with a gallocatechin or its gallate.[1] These reactions afford theaflavin itself (**6**) or several possible theaflavin gallates represented by polyphenol (**7**).[1]
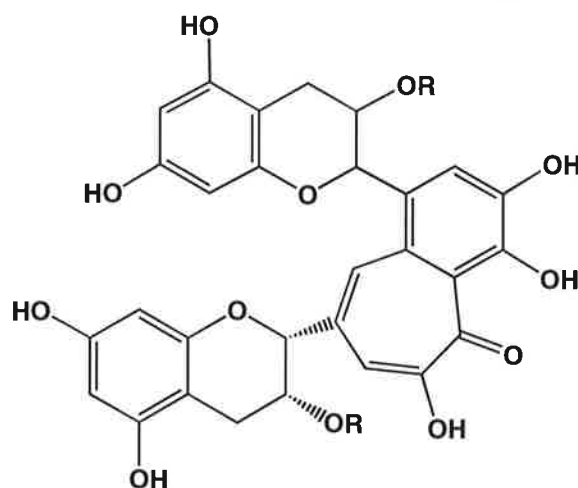
R=H (6)
R=H or Galloyl (7)

The compositions of the thearubigen components and the mechanism of their formation are not well known.[1] Thearubigens are high molecular weight species with a distribution of weights between 1000-40000, which constitute the largest mass of extractable matter in black tea.[1] The proanthocyanidin condensation polymers represented by structure (**8**) are thought to be a part of the thearubigen fraction.[1]
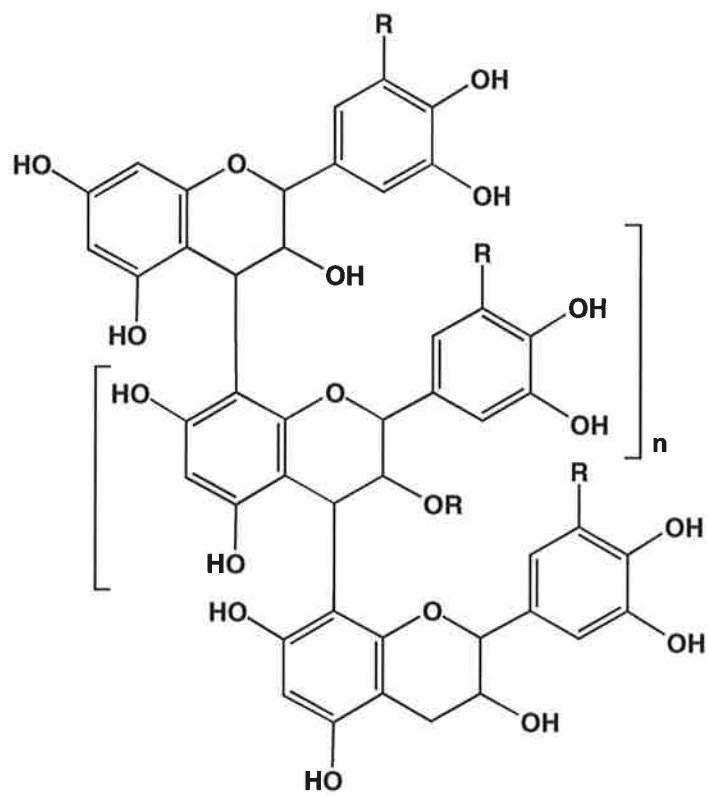
R=H or OH (8)

(II) The importance and benefits of Green tea consumption

Polyphenols are an important class of natural products. Their wide distribution in the plant kingdom ensures they are consumed in the human diet. Similarly the trend towards natural foods,[5] greater health awareness and the potential health benefits of a diet rich in polyphenols are ensuring their popularity. Many physiological functions of tea have been found,[5] which have been put to practical use by the food industry in drinks, such as canned and bottled tea drinks, which are now one of the most popular soft drinks in Japan.[6]

In recent years, the potential health benefits of tea have received increased attention. Catechins are found in traditional herbal medicines,[7] and today are probably best known for their 'antioxidant' activity.[8] This refers to their ability to react readily with active oxygen species (one-electron oxidants), resulting in powerful free-radical scavenging activity.[7] Catechins also complex Fe^{2+} which is an initiator of radical formation.[7] Active oxygen species cause cell damage, are thought to be an important cause of various diseases, and are linked to aging, inflammation, radiation damage, immunity, cataracts, arteriosclerosis and myocardial ischaemia.[9] Besides their powerful antioxidant properties, catechins are also of interest due to their physiological activities such as capillary strengthening activity and antiartherosclerotic effects.[3] Numerous other biological activities have been associated with polyphenols (of which catechins are currently a very important group)[7] such as inhibiting viral reverse transcriptase,[8] suppressing ulcer formation, and neuroprotection.[7] They have shown an anticarcinogenic and bacteriostatic effect on several organisms, causing them to be the subject of intense studies for some time.[3] Additionally, catechins have been shown to be effective in the treatment of acute viral hepatitis in various strains of mice. However, in spite of much information about catechins and their effects on animals, there is limited information available on the metabolism and pharmacokinetics of these potentially therapeutic agents in humans.[7,10] For example, it has been shown that catechins inhibit carcinogenesis, tumorigenesis and mutagenesis in animal models but as yet little research has been

directed towards their effects in humans.[8] These results may explain the increasing popularity of green tea and polyphenol preparations as dietary supplements, in spite of the fact that a lot of work remains to be performed on their absorption and bioavailability in humans.

(III)   A novel radioenzymatic assay for detecting Green Tea Catechins.

There is ample evidence for the presence of catechins in tea and in animal blood plasma models,[8,10] but limited information describing the absorption, pharmocokinetics and metabolism of these therapeutic agents in humans.[10] One of the reasons for this is that there are a lack of assays with suitable sensitivity to enable the analysis of individual tea catechins in human blood after the consumption of green or black tea.[11]

The most sensitive method to date for assaying catechins in plasma is HPLC in conjunction with specialised electrochemical detection systems.[11] The limit of detection for this system is 0.5-1.5 ng/ml for epicatechin and derivatives. Recently capillary electrophoresis using a separation buffer has been shown to have a limit of detection for each catechin of <20 ppm,[12] yet to date, this method has not been refined to determine catechin content in human blood plasma samples.

A prototypical radioenzymatic assay has been developed at the CSIRO Division of Human Nutrition for measurement of tea catechins using (+)-catechin (1) as the trial compound. Specifically, the procedure involves the transfer of a tritium labeled methyl group from *S*-adenosylmethionine (*SAM) to the 3' oxygen (determined by NOE difference experiments)[13] of catechin. The reaction is catalysed by the enzyme catechol *O*-methyl transferase (COMT) (obtained from mammalian liver) as illustrated below (Scheme 1).
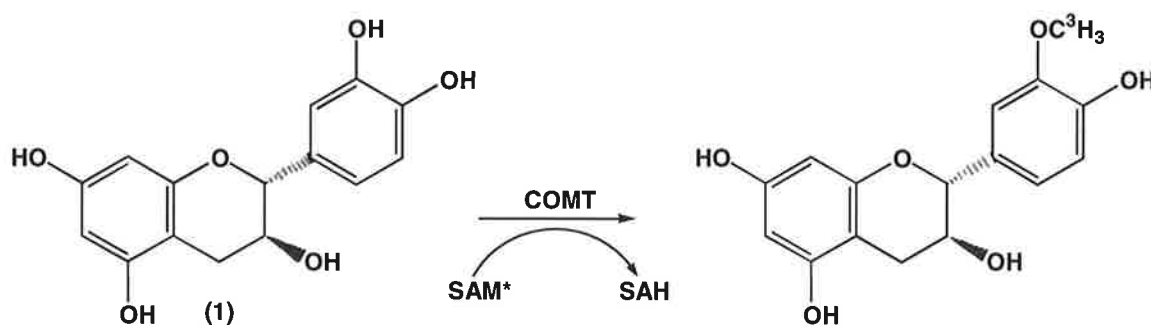

Scheme 1

The *O*-methyl catechin formed is easily extracted from the plasma using ethyl acetate, and purified by HPLC or thin layer chromatography (t.l.c). The purification step is facilitated by the addition of a non-radioactive 3' *O*-methyl catechin as a carrier. This assists in the recovery of the radioactive material from the HPLC ('peak shape' was improved)[13] and aids in the running of the t.l.c fractions from the initial purification step prior to HPLC. Subsequent measurements of the tritium content of the key fractions give a direct measurement of the initial catechin concentration. To date, the reaction has been conducted using rat plasma with added (+)-catechin (**1**). As little as 50 pg of catechin has been assayed which is a sensitivity ten times greater than that reported using HPLC with EC detection.[11]

This novel assay requires substantial amounts of pure catechins to use for firstly; optimising and expanding the preliminary experiments[13] and secondly, as carriers of the radioactive catechin in conjunction with t.l.c or HPLC purification.

The current aims for this project are to provide a convenient synthesis of the tea catechins **EC** (**2**), **EGC** (**3**), **ECG** (**4**) and **EGCG** (**5**) for the CSIRO Division of Human Nutrition. They will be used at a later stage to refine the novel assay for trialing in human plasma and assess its capacity to measure all of the tea catechins.

There are a number of ways of obtaining green tea catechins. Firstly they can be extracted directly from the tea leaves and purified using methods that have evolved over the years. T.l.c and preparative chromatography were some of the first methods used for detecting and isolating tea catechins.[3] These methods were superceded by gas liquid chromatography (GLC), liquid chromatography, and HPLC methods that now provide accurate and easy quantitative analysis.[3]

Secondly, individual catechins (or more complex structures) may be obtained by transforming simple catechins into the desired structure. This is sometimes the method of choice when a particular catechin molecule is readily available. Using this method, the bisgallate (**9**) was obtained from (+)-catechin (**1**).[7] The bisgallate (**9**) has been found to inhibit the growth of several human breast cancer cell lines.[7]
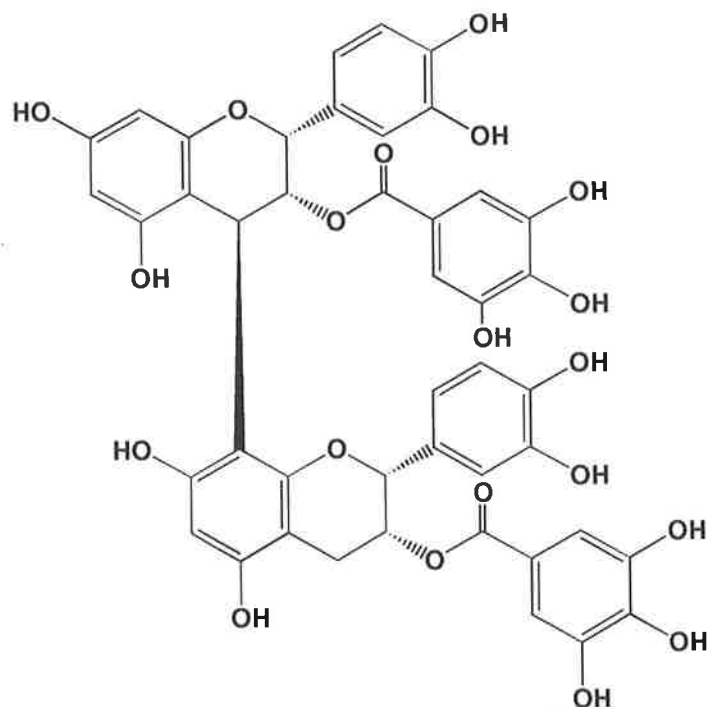
(9)

Direct synthesis is a convenient means of obtaining the required catechin molecules. It offers the advantage of minimal purification in comparison to that which is required when the catechins are extracted from tea. Synthesis also allows for the collection of larger quantities of the required catechins, an achievement that cannot be accomplished by extracting the catechins from tea leaves. Presently there are a number of syntheses directed at the formation of either one or two of the catechin molecules, with most designed to give ($\pm$)-catechin derivatives rather than the epi forms.[7,14,15] Surprisingly, there are currently no syntheses designed to produce all four of the required catechin molecules **EC (2)**, **EGC (3)**, **ECG (4)**, and **EGCG (5)**.

In order to obtain the required 'epi' green tea catechins, the three methods discussed; extraction, transformation and direct synthesis will be investigated and evaluated.

Chapter 2: Current extraction and purification procedures of Green Tea.

(I) Introduction

The requirement for authentic samples of **EC (2)**, **EGC (3)**, **ECG (4)**, and **EGCG (5)** has led to the investigation of techniques to obtain these samples directly from green tea. In addition authentic samples of n.m.r purity were needed as an identification reference for the catechin synthesis, as discussed in Chapter 1. These samples are required to elucidate the sometimes contradictory data available and to allow for quick and easy analysis of the synthetically produced catechins.

Current separation procedures for **EC (2)**, **EGC (3)**, **ECG (4)**, and **EGCG (5)** rely on chromatography. Many methods of firstly extracting the tea then purifying the extracts are available, each with their own benefits and drawbacks.[16-18] Most extractions involved the formation of a polyphenol fraction from the tea by macerating it in an aqueous alcoholic solution then, after removing the alcoholic solvent, extraction into a solvent such as ethyl acetate or chloroform.[16] Purification of the polyphenol fraction has developed over the years. Some of the earlier work has involved the use of paper chromatography and 2-D t.l.c using cellulose layers.[3] These methods were however time consuming and involved problems in quantification. Gas liquid chromatography was introduced to overcome these disadvantages, followed thereafter by liquid chromatography. Liquid chromatography was first employed for the preparative isolation of flavanols from green tea.[3] Generally the polyphenol fraction was partially purified using Sephadex LH-20 or silica columns prior to analysis. This led to the introduction of reverse phase HPLC, reducing the sample clean up to a minimum. These separations usually were carried out using a gradient elution system, such as acetic acid-methanol-water.[3] HPLC systems however are still limited in that they require complex mobile phases and they fail in some instances to provide clean separation of the analytes from each other.[8] In particular these methods fail to address the larger preparative separation of

individual catechins from green tea. There have also been reports of the separation of individual catechins using column chromatography.[19,20]

(II)   Results and Discussion

The extraction of green tea to obtain individual catechins in their pure form was attempted using many different solvent systems and forms of column chromatography. The best results were obtained when the catechins were extracted using aqueous ethanol from the tea leaves (10 g) and purified using a sequential combination of sephadex LH-20 (ethanol), silica and preparative liquid chromatography (p.l.c). The individual catechins were seen clearly by t.l.c on silica plates using chloroform/methanol/acetic acid (76:19:5) as the solvent system. However, no matter the loading weight of the crude sample, p.l.c could not separate the samples cleanly due to their similar   Rf values. Small (~10 mg) slightly impure samples of **EC (2)**, **EGC (3)**, **ECG (4)**, and **EGCG (5)** were obtained that were clearly identified as these catechins by their ^{1}H n.m.r spectra after comparison with literature data.[6]

Other extraction techniques described in the literature, relied on repeated purification by chromatography and/or purification by HPLC to give the catechins in a pure form.[21,22] However, these processes yielded the individual catechins in small amounts, and thus, were not a practical means for obtaining substantial amounts of catechins.

(III)   Conclusions

The extraction of Green Tea to give samples of **EC (2)**, **EGC (3)**, **ECG (4)**, and **EGCG (5)** by chromatography was tedious and time consuming.   Small, impure samples were obtained which gave sufficient data (^{1}H n.m.r) for each catechin, but only for reference purposes.   Other ways of obtaining the required epicatechins will be investigated such as transformation of existing catechin molecules and synthesis. This may allow larger, pure amounts of the catechins to be obtained.

Chapter 3: The manipulation of (+)-catechin to form epicatechins.

(I) Introduction

As (+)-catechin (**1**) is commercially cheap compared to the other catechins, and being readily available, an attractive approach to forming **EC** (**2**) lay in inverting the stereochemistry at position-3 of (+)-catechin (**1**) which is outlined in Figure 2. In theory this methodology will allow the generation of the epi series of catechins from a precursor with the *trans* stereochemistry at positions-2 and -3, such as gallocatechin and catechin gallate which will give **EGC** (**3**) and **ECG** (**4**) respectively.
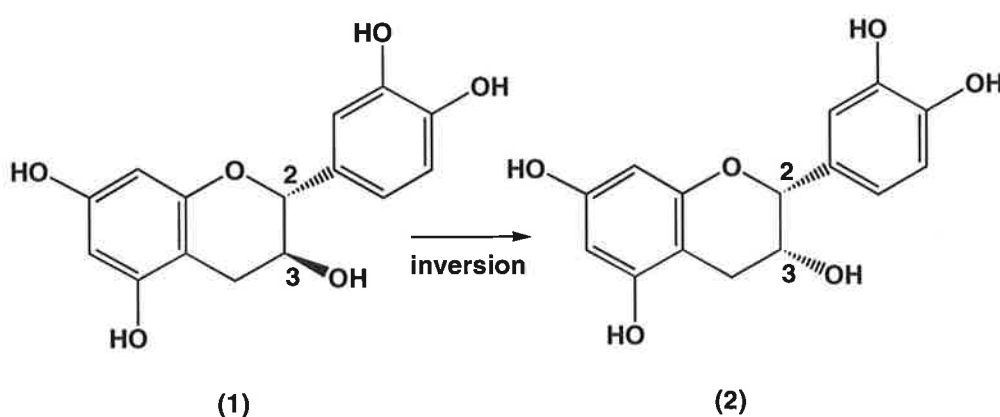
Figure 2: The inversion at position-3 of (+)-catechin (**1**), to give EC (**2**).

The Mitsunobu reaction has been used extensively to transform various natural products, such as steroids, nucleosides, glycerols and carbohydrates.[23] The reaction proceeds under mild neutral conditions and exhibits stereospecificity, functional group selectivity and regioselectivity.[23] This reaction involves an alcohol reacting with a carboxylic acid in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) at room temperature, furnishing carboxylate esters in 34-90% yield.[23] The stereochemically significant feature of this reaction is that it

proceeds with virtually complete inversion of the configuration of the initial alcohol. Hydrolysis of the product ester gives the inverted alcohol.
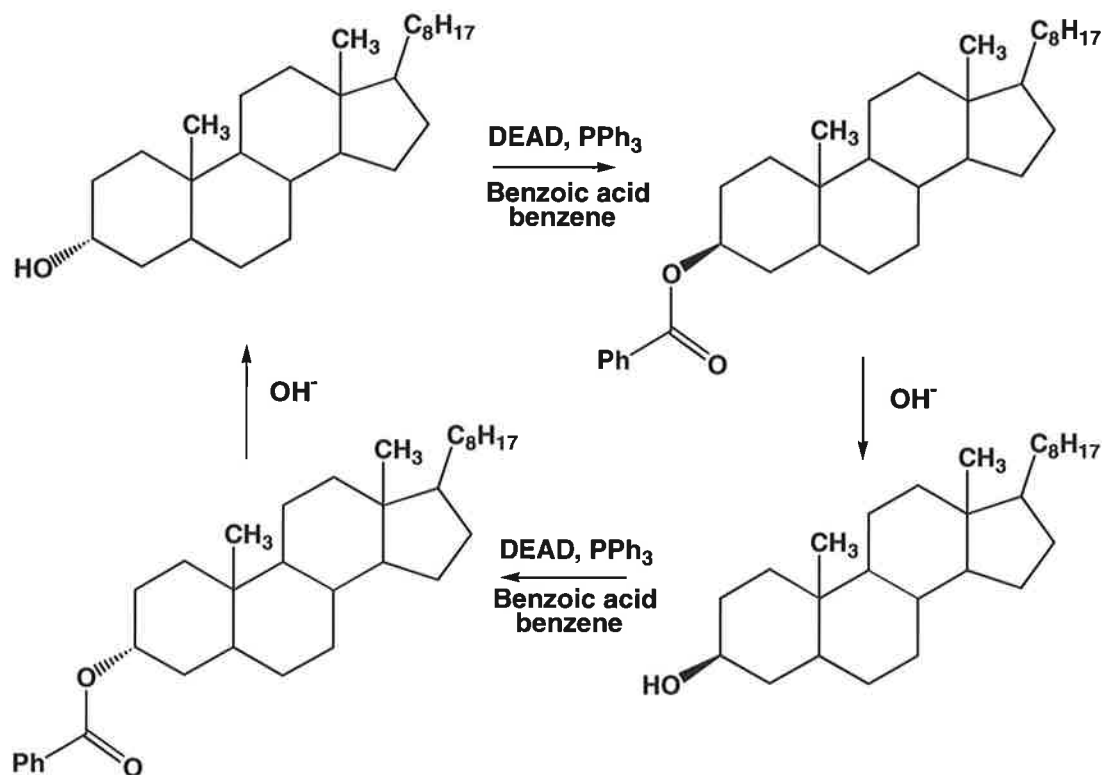
Scheme 2

Scheme 2 illustrates the stereochemical significance of the Mitsunobu reaction, which can be used to give an inverted ester, and on hydrolysis, an inverted alcohol.

The Mitsunobu reaction can additionally be used to alkylate phenols and heterocyclic compounds, esterify phosphoric esters, cause intramolecular dehydration and prepare carbonates.[23]

An obvious application of the Mitsunobu reaction would be to transform (+)-catechin (**1**) to it's 'epi' form and as a bonus, gain the gallate ester **ECG** (**4**) in the process, as outlined in Scheme 3.
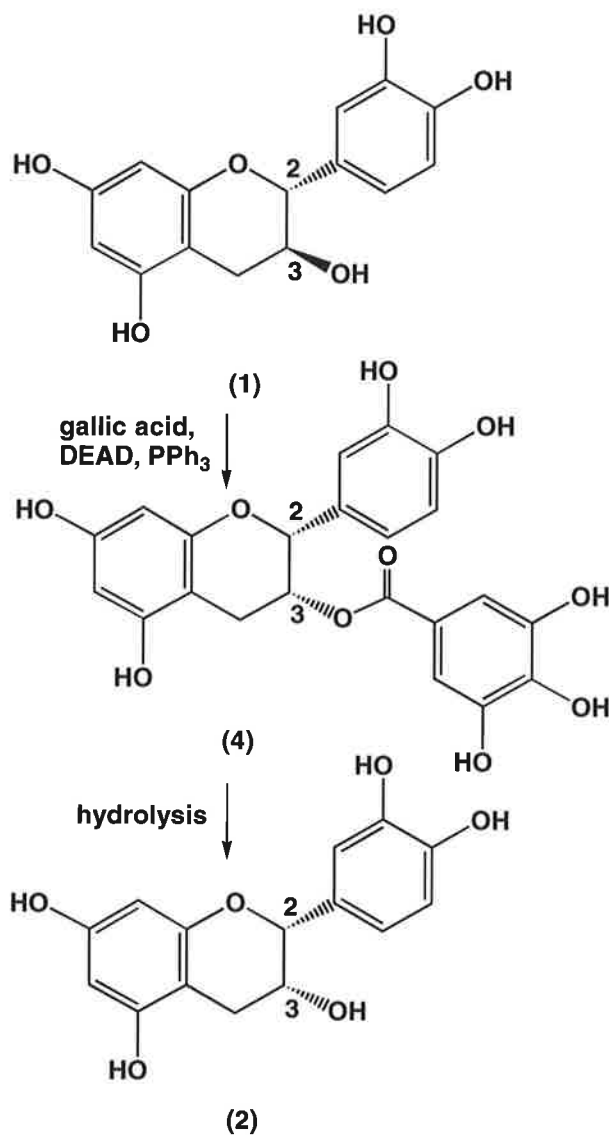
Scheme 3

The Scheme 3 shows how the formation of **(-)-ECG** (**4**) may be achieved using Mitsunobu conditions and gallic acid. The gallate (**4**) may then be hydrolysed to give **(-)-EC** (**2**). The Mitsunobu reaction required the protection of the catechin phenolic groups, as they may have the potential to participate in the reaction.

Catechins contain four phenolic groups, which can be protected as ethers or esters. Formation of cyclic acetals and ketals, such as methylenedioxy, acetonide, cyclohexylidenedioxy, diphenylmethylenedixoy or cyclic esters such as cyclic carbonates, selectively protects the two ortho (3' and 4') hydroxy groups in the presence of the two isolated phenol groups (5 and 7).[24]

The methylenedioxy group is often present in natural products and is formed easily by reaction of a catechol group with dichloro- or dibromomethane in high yields.[24] This protective group has the advantage that it is stable to many reagents but leads to the disadvantage of it being hard to remove, requiring the use of reagents such as aluminum tribromide.[24] Acetonides are easily formed (acetone/catalyst) and can be cleaved by mild acid hydrolysis. Acetonides have been widely used in the protection of adjacent hydroxyl groups in carbohydrates, as well as 1,3-diols.[25] The cyclohexylidene ketal is prepared simply from cyclohexanone under acid catalysis. It is slightly more stable than the acetonide and thus requires stronger acid conditions for hydrolysis.[24] This derivative has been used to protect myo-inositol in high yields.[26] The diphenylmethylene ketal is prepared from dichlorodiphenylmethane in moderate yields. It is easily hydrolysed under acidic conditions. Cyclic carbonates have been used to a limited extent only. They are prepared from chloroformates but are readily cleaved under mild conditions such as heating in water.[24] They have been used widely to protect carbohydrates and to block nucleosides that undergo mild reactions, which will not cause cleavage.[27]

The potential for the phenolic groups in the A- and B-ring to react under the Mitunobu conditions, such as the possibility of quinone formation in the B-ring, requires that these groups be protected. Differential protection is advantageous in that it allows for selective deprotection and thus greater manipulation of the catechin molecule. The reason for selectively protecting catechin relates to the assay where synthetic 3' or 4', or 3',4'-O-methylated derivatives are used to aid in the recovery of the tritiated samples, by acting as carriers in the purification steps (Chapter 1). The selective deprotection of the catechol moiety of (**10**), then methylation to give (**11**) may allow a simple route to obtaining these derivatives (Scheme 4). The phenolic protecting groups on carbons 5 and 7 (A ring) may then be removed at a later stage as outlined, to give the methylated species (**12**).
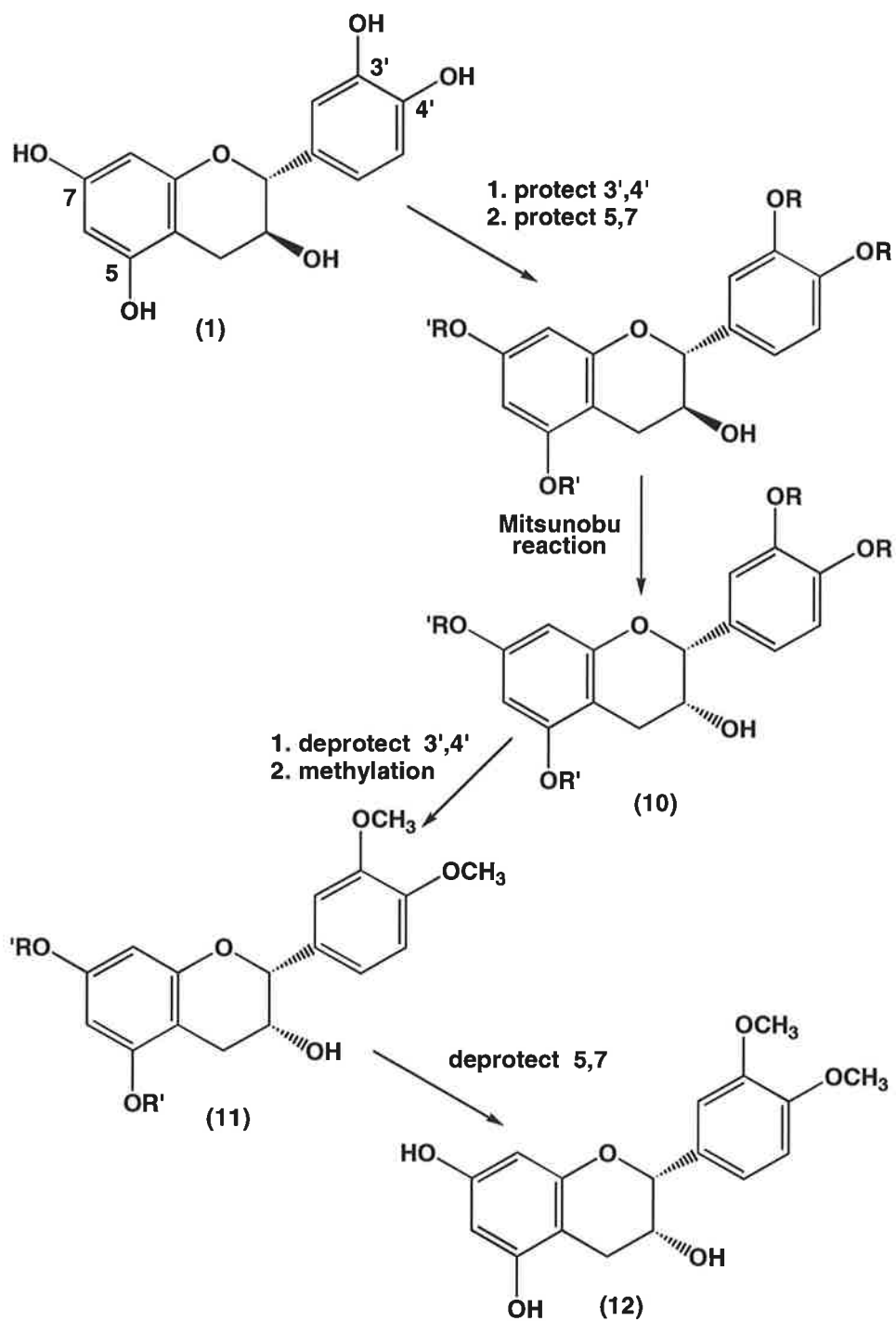
Scheme 4

(II) Results and Discussion

The selective protection of the catechol moiety of (+)-catechin (**1**) (as discussed in Section I) was attempted using a variety of ether and ester protection groups.

It was found that the protection of the catechol group as a methyl ene acetal using potassium fluoride and dichloromethane gave multiple, unidentifiable products. When the reaction was repeated using dibromomethane, which has a higher boiling point, there was no noticeable improvement of the reaction results. This suggested that protection of the catechin system under these conditions was not going to occur.

The protection of the catechol moiety as an acetonide derivative was investigated extensively. The acetonide system can be added and removed using a variety of different reagents and conditions that have the advantage of being relatively mild.[24] Reacting (+)-catechin (**1**) in the presence of 2,2-dimethoxypropane and *p*-toluenesulfonic acid yielded (+)-catechin (**1**) and a complex mixture when analysed by [1]H n.m.r spectroscopy. The addition of acetone to this reaction mixture is another method of generating acetonides,[24] however this gave similar mixtures. Replacing *p*-toluenesulfonic acid with D-camphor-10-sulfonic acid[28] gave similar results. Omitting the acid and adding molecular sieves to the reaction still resulted in a complex product mixture. However, in a reproducible reaction, stirring a solution of (+)-catechin (**1**) in acetone containing iodine for one hour, gave a unique four ring species, 7',7'-dimethyl-5-hydroxy-*trans*-pubeschin (**13**), in 53% yield.
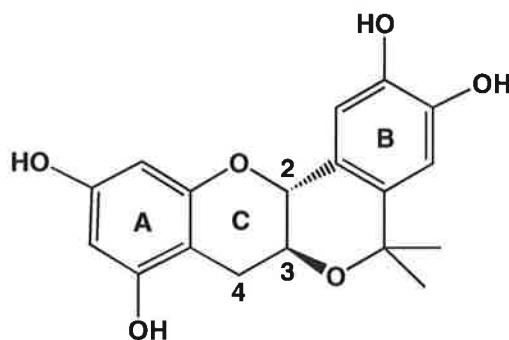
(13)

This product showed only four phenolic signals in its ^{1}H n.m.r spectrum (δ: 7.56, 8.07, 8.41, 8.48), which were removed by shaking with D_2O, but there was no alcoholic OH signal suggesting that the hydroxyl group at C3 had been removed or converted into something different. The spectrum also showed an absence of a B-ring proton at ~δ6.80 suggesting ring alkylation at carbon 6'. The presence of two three-proton singlets at δ1.51 and δ1.52 implied the incorporation of two methyl groups into the molecule. This was also confirmed in the ^{13}C n.m.r spectrum which showed three new signals at δ28.6, 32.1 (Me x 2) and 76.1 (C7'). The stereochemistry at carbon 2 and 3 was thought to be that of starting (+)-catechin as the protons at carbons 2 and 3 showed similar splitting patterns with *trans* diaxial coupling (J=9.3 Hz). Furthermore, the protons at position-4 had a similar splitting pattern to (+)-catechin (**1**); δ2.51 ($J_{4ax,3}$=10.5, $J_{4ax,4eq}$=15.6 Hz) and 3.02 ($J_{4eq,3}$=6.0, $J_{4eq,4ax}$=15.6 Hz). However, in (-)-**EC** these protons appear as an AB quartet at δ2.73, 2.85 (J=17.1 Hz, A part d with J=4. 1Hz).[6] A DEPT (180) experiment showed that the carbon at position-6'(δ124.98) had lost a proton and possibly become a quaternary carbon, which is consistent with the structure (**13**).

This 4-ring molecule (**13**) has been obtained previously by irradiation of a solution of (+)-catechin in moist acetone containing carbon tetrabromide,[29] and has been identified as a novel peltogynoid.[30] (+)-7',7'-Dimethyl-5-hydroxy-2R,3S-*trans*-pubeschin (**13**) was also isolated when the carbon tetrabromide reaction was conducted in anhydrous acetone without irradiation, but the formation of this product was inhibited by the addition of solid sodium bicarbonate to the reaction mixture.[29] This indicated that the reaction was a simple acid catalysed reaction between the flavan-3-ol and acetone, the hydrobromic acid being generated from the action of a bromine atom on an active hydrogen of the acetone.[29] In this case the acid generated was thought to be hydroiodic acid. Van Der Westhuizen and co-workers suggest that the reaction proceeds by either nucleophilic attack of the hydroxy group onto the acetone species to give (**A**) or electrophilic attack at carbon-6' in the B-ring, to give (**B**).[29] These two intermediates may then be converted into the 4-ringed species (**13**) by attack of the tertiary alcohol, assisted in both cases by delocalisation of charge on the B-ring.

(A)   (B)
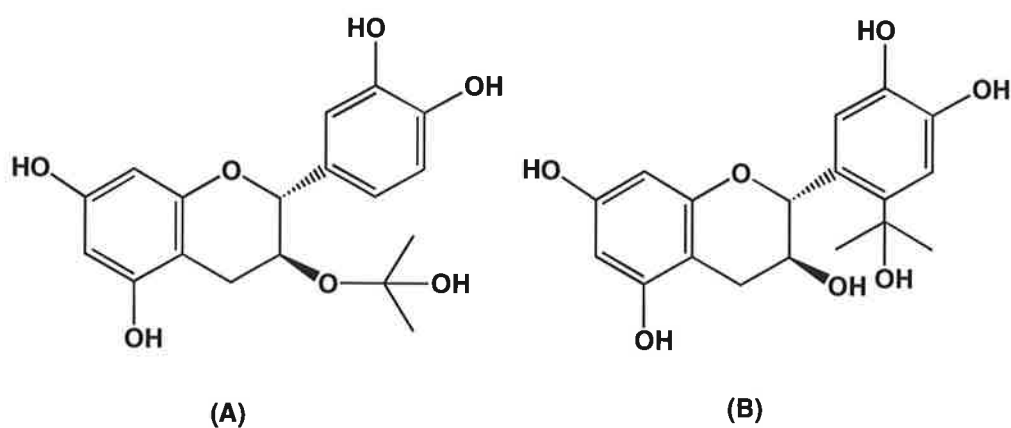
Reaction of dimethoxypropane, acetone, dimethylformamide and pyridinium *p*-toluenesulfonate at 0° C yielded the same 4-ring species (**13**) in a 39% yield. In this case the carbonyl group of the acetone or the methoxy groups of dimethoxypropane may have been protonated. This might have led to an acid catalysed reaction with the flavan-3-ol as described previously.

Protecting the catechol phenol groups using a cyclohexylidene ketal was attempted using firstly cyclohexanone, *p*-toluenesulfonic acid and alumina. The reaction gave only a complex mix of products, none of which were identifiable. The reaction was then attempted under Dean-Stark conditions, using cyclohexanone, *p*-toluenesulfonic acid, toluene, dimethylformamide resulting in 7'-cyclohexyl-5-hydroxy-*trans*-pubeschin (**14**) in a 51% yield.
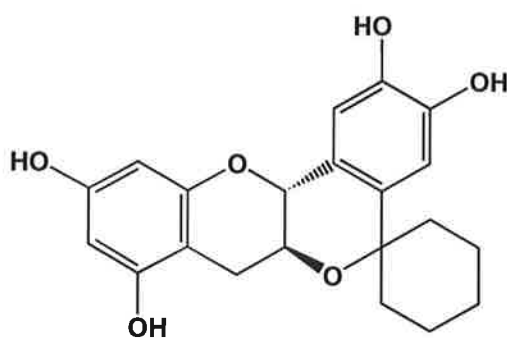
(14)

The four ring species was spectroscopically similar to the derivative (**13**), in that it showed four phenol groups (no alcoholic OH) and a absence of one B-ring proton at carbon 6' in the ^{1}H n.m.r spectrum, suggesting ring substitution at this position.

The selective protection of catechin and epicatechin has been reported by Ferreira and co-workers.[a] This involved the use of benzyl carbonates, the regioselectivity of which was facilitated by the marked differences in the pKa values of the phenolic hydroxyl groups and the ability of the o-dihydroxy functionality of the pyrocatechol B-ring to form borate complexes.[a] However, in our hands this method gave multiple products as indicated by t.l.c with small amounts of material being obtained after chromatography, none of which could be identified as the required protected derivative. Repeating this reaction gave no improved results.

a)   Van Dyke, M. S.; Steynberg, J. P.; Steynberg, P. J.; Ferreira, D. *Tetrahedron Lett.* **1990**, *31*, 2643-2646.

Additionally this molecule showed a multiplet at δ1.4-2.0 corresponding to the ten protons of the cyclohexyl group. A molecular ion of *m/z* 370 was obtained in the mass spectrum, suggesting that this product had indeed formed.

The same product, but in a poorer yield (18%) was obtained by repeating this reaction, but without azeotropic distillation of the water.

The reported ease of preparation of diphenylmethylene ketals warranted their investigation.[24] The reaction of (+)-catechin (1) with neat dichlorodiphenylmethane led to complex products as indicated by [1]H n.m.r spectroscopy and t.l.c analysis. A similar result was obtained when (+)-catechin (1) was heated with dichlorodiphenylsilane. Thus protection using an ester group rather than an ether group was pursued. Even though cyclic carbonates are very labile, their formation was investigated. When 1,1'-carbonyldiimadazole was heated with (+)-catechin (1) in toluene, a complex product mixture was obtained as indicated by [1]H n.m.r spectroscopy. This was again the case using benzyl chloroformate and a buffered solvent system, when trying to form a benzoyl carbonate. See opposite.

The protection of the phenolic groups of (+)-catechin (1) could be accomplished (non-selectively) by protecting all four as their methyl ethers. This was easily achieved by heating with methyl iodide and potassium carbonate to afford a white, stable crystalline derivative in 53%. Spectral data was consistent with literature values.[31] The methoxy groups were chosen due to their ease of formation and their simple n.m.r spectra compared to using benzyl ethers as protecting groups. A drawback to using methoxy groups is the difficulty of their removal. However, it was more important to gain reaction methodology and a clear outline of what was happening, rather than spend time on benzylation reactions of catechin phenols, which have been shown to be tedious and proceed with low yields.[7] Once the reaction was optimised, protecting groups that are more easily removed, such as benzyl groups, may be utilised.

The Mitsunobu reaction was undertaken upon (+)-catechin tetramethylether (15) as depicted in Table 1 below.

Table 1: The Mitsunobu reactions of a number of carboxylic acids with (+)-catechin tetramethyl ether (15), triphenylphosphine and DEAD.

Entry	Acid	Solvent & temperature	Time (h)	Product
1a	Gallic	THF/room temp.	24	Unreacted
1b	Gallic	1,4-dioxane/ Δ	2	Unreacted
2a	Benzoic	THF/room temp.	18	Unreacted
2b	Benzoic	THF/room temp.	47	Unreacted & multiple products
2c	Benzoic	Benzene/room temp.	30	Unreacted
2d	Benzoic	1,4-dioxane/ Δ	10	Unreacted & multiple products
3	Formic	THF/room temp	48	Elimination (16) & formate (17)
4	Acetic	Benzene/room temp. →60° C	24 (RT) 48 (60°C)	Unreacted & multiple products

Reacting (+)-catechin tetramethylether (**15**) under Mitsunobu conditions (DEAD/PPh₃) with gallic acid in THF or under harsher conditions (refluxing in 1,4-dioxane), returned the starting catechin ether (**15**) (Table 1, entry 1). This may be due to the Mitsunobu reagents reacting preferentially with the 3,4,5-hydroxy groups of the gallic acid, to form complex product mixtures, suggesting that the hydroxy groups of the gallic acid may need to be protected.

When the reaction was conducted using an acid that did not contain any extra phenolic groups, such as benzoic acid, starting materials were still recovered (Table 1, entry 2a). However reacting the protected catechin molecule for a longer time in THF at room temperature (Table 1, entry 2b), gave multiple products as indicated by t.l.c and the presence of many peaks in the ^{1}H n.m.r spectrum.

Changing the solvent to benzene (Table 1, entry 2c) did not improve the outcome, and still returned starting material from the reaction. Reaction in refluxing 1,4-dioxane (Table 1, entry 2d) consumed all starting material, but gave a complex product mixture by [1]H n.m.r, whose components could not be identified.

Changing the acidic component from benzoic acid to the more acidic formic acid gave, even at room temperature in THF, two products (Table 1, entry 3).
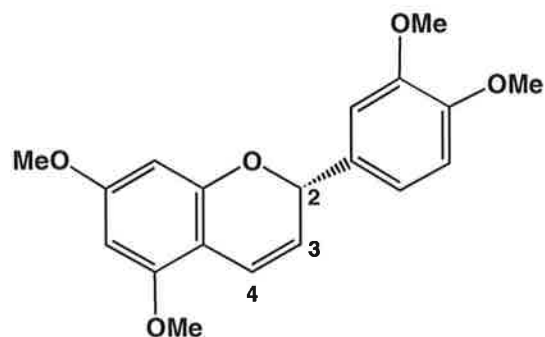
(16)

The first product (16) was obtained as a yellow solid in 25% yield which was distinguished from starting material by the protons at postions-2 and -3, as they now appeared as a dd at $\delta 5.77$ (J=1.8, 3.3 Hz) and a dd at $\delta 5.59$ (J=3.3, 9.9 Hz) respectively, consistent with literature data.[32] The proton at position-4 appeared as a dd at $\delta 6.80$ (J=1.8, 9.9 Hz). This was different to the two protons at position-4 in the starting material, which appeared at $\delta 2.51$ ($J_{4ax,3}$=10.5, $J_{4ax,4eq}$=15.6 Hz) and 3.02 ($J_{4eq,3}$=6.0, $J_{4eq,4ax}$=15.6 Hz). A molecular ion at m/z 328 in the mass spectrum indicated the structure (16) had formed.

The second product was identified as the required formate (17), which was isolated as a yellow oil in 14% yield.
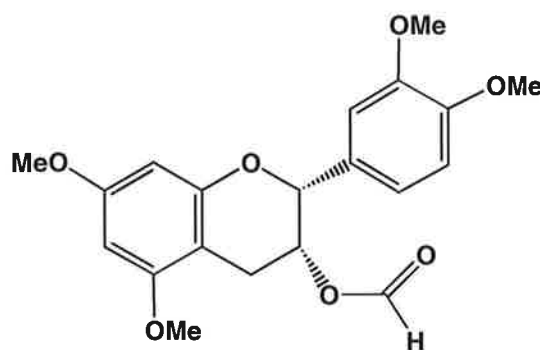
(17)

The product was identified by a singlet at δ8.10 corresponding to the formate hydrogen in the ^{1}H n.m.r spectrum. Further more, the protons at position-4 appeared as a multiplet from δ2.98-3.00 (starting material shifts: δ2.59 and 3.07) a change similar to that of (-)-**ECG** (**4**) (multiplet at δ2.92-3.03)[6] suggesting the reaction proceeded with inversion of configuration. The presence of the formate group was exemplified by a proton multiplet for position-3 at δ5.59 (starting material δ4.07). The proton at position-2 gave a broadened singlet at δ5.07 in the ^{1}H n.m.r spectrum, distinct from a doublet at δ4.66 (J=8.4 Hz) of the starting material.

When the reaction was conducted at both room temperature and at 60°C using acetic acid (Table 1, entry 4), signals due to the starting catechin ether (**15**) together with a complex mixture of signals were evident in the ^{1}H n.m.r spectrum.

The Mitsunobu reaction is thought to proceed through addition of DEAD (**18**) to triphenylphosphine giving a quaternary phosphonium salt (**19**). This salt is then protonated by the addition of an acid to give another salt (**20**), which is attacked by the alcohol to give the alkoxy-phosphonium salt (**21**). This species finally undergoes S_N2 type displacement by the counter anion to give the inverted ester (**22**) (Scheme 5).[23]

$$C_2H_5O-\overset{\overset{O}{\|}}{C}-N=N-\overset{\overset{O}{\|}}{C}-OC_2H_5 \quad + \quad Ph_3P \longrightarrow$$

(18)

$$R-\overset{\overset{O}{\|}}{C}-OH \longrightarrow$$

$$\left[C_2H_5O-\overset{\overset{O}{\|}}{C}-N-\overset{\overset{\ominus}{N}}{\underset{\overset{\oplus}{PPh_3}}{}}\overset{\overset{O}{\|}}{=}C-OC_2H_5\right]$$

(19)

$$\left[C_2H_5O-\overset{\overset{O}{\|}}{C}-\underset{\overset{\oplus}{PPh_3}}{N}-\overset{H}{N}-\overset{\overset{O}{\|}}{C}-OC_2H_5 \quad R-\overset{\overset{O}{\|}}{C}-O^{\ominus}\right] \longrightarrow$$

(20)

$$R^2\overset{\bullet\bullet}{O}H$$

$$\left[Ph_3\overset{\oplus}{P}-O-R^2 \quad R-\overset{\overset{O}{\|}}{C}-O^{\ominus}\right] \quad + \quad \left(C_2H_5O-\overset{\overset{O}{\|}}{C}-NH\right)_2 \longrightarrow$$

(21)

$$Ph_3P=O \quad + \quad R^2-O-\overset{\overset{O}{\|}}{C}-R$$

(22)
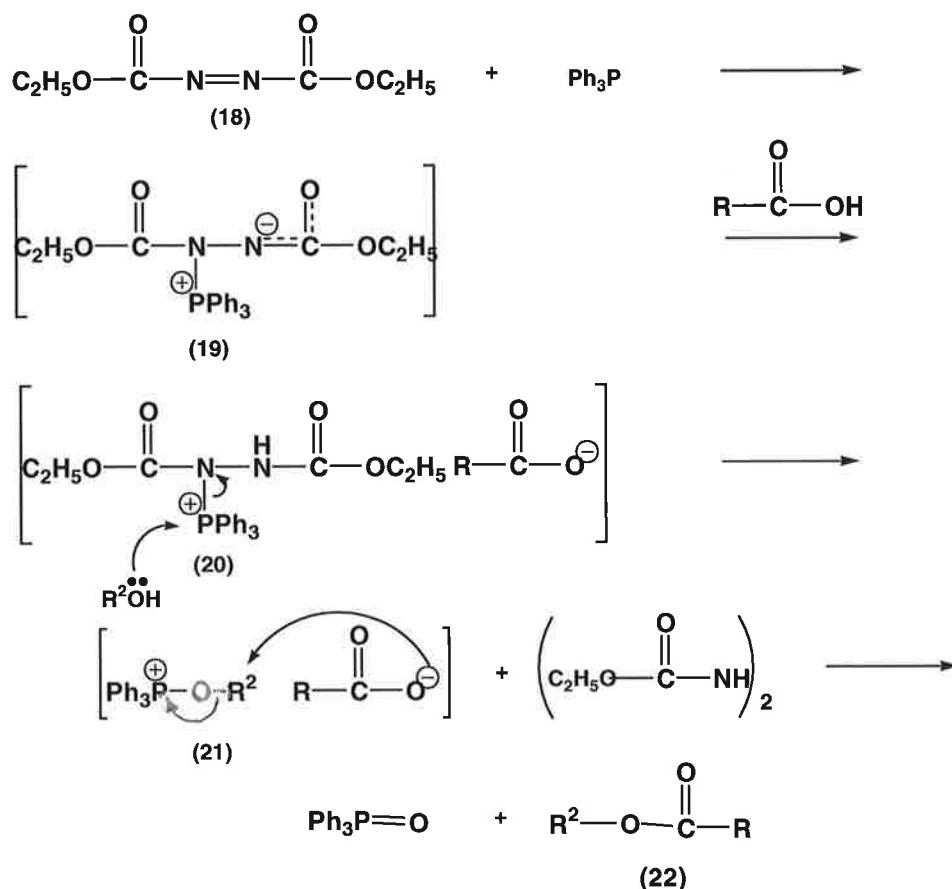
Scheme 5

It has been suggested that the nature of the counter anion derived from the acidic component and the structure of the alcohol play an important role in the reaction path.[23] Esterification of the catechin ether requires reaction at the C3 hydroxyl group. This may have been inhibited by the steric hindrance of the three bulky phenyl groups attached to the phosphorus atom in (20), interacting adversely in this region. Thus reaction may not have occurred at all or elimination may have proceeded. However, the formation of the formate ester (17) (Table 1, entry 3) suggests that attack by the alcohol upon the triphenylphosphine salt (20) did occur, indicating that steric hindrance of the phenyl groups was not inhibiting the reaction. Thus the nature of the counter ion may be the determining factor. The smaller formate anion may have been able to facilitate displacement of triphenylphosphine oxide from carbon-3 on the catechin molecule, to give the formate (17), whereas the larger counter anions such as the benzoate anion, may be too bulky to effect this transformation. This smaller anion may also facilitate elimination of the formate by removal of an adjacent hydrogen (hydrogen-2 or -4), which is more favourable than

elimination of triphenylphosphine oxide (through a similar means). This was because the formate (**17**) had the (-)-epicatechin geometry (which allows *trans* diaxial elimination, Figure 4) whereas the triphenylphosphine intermediate had the (+)-catechin geometry. This was evident in some Mitsunobu reactions on carbohydrate substrates, where if the hydroxyl group exists in a 1,2-diaxial arrangement with respect to the vicinal hydrogen atom, the phosphonium salt formed may undergo elimination rather than substitution.[33] Steroids also show similar trends in that the steric requirements of sterols, nucleophilicity of the attacking acidic components and reaction conditions play important roles in the success of the reaction.[23]
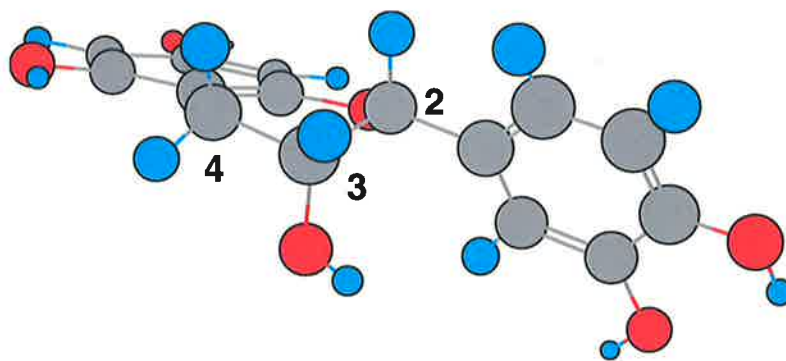

Figure 3: The optimised 3D structure (MOPAC) of (-)-EC. The *trans*-diaxial array of the epicatechin hydroxyl group at carbon-3 with respect to the hydrogen at carbon-2 and one of the hydrogens at carbon-4, is clearly shown.

(III) Conclusions

Catechin was protected successfully as its tetramethyl ether, rather than having its phenolic groups differentially protected. This was found to be difficult and gave alternative products, such as the 4-ring species (**13**) rather than the required derivatives.

Esterifying the C3 hydroxyl group with inversion of configuration *via* the Mitsunobu reaction did not give the required ester. This method mainly returned starting catechin, except when using formic acid, where the formate (**17**) and the elimination product (**16**) were evident. These results suggested that (+)-catechin tetramethyl ether (**15**) and the combination of Mitsunobu reagents used, produced (in most cases) too much steric hindrance for the desired reaction to proceed. Thus another means of transforming (+)-catechin (**1**) to **EC** (**2**) and eventually the other epicatechin derivatives, will be investigated.

Chapter 4: The formation of Epicatechin and Epicatechin gallate precursors

(I)   Introduction

Due to the failure of the Mitsunobu reaction, an alternative method for inverting the stereochemistry of the alcohol group at position-3 (C-ring) of a (+)-catechin derivative was investigated. Again (+)-catechin (**1**) was utilised due to its ready availability and low price. This new method involved the oxidation of the alcohol of a (+)-catechin derivative at position-3 and then the stereoselective reduction of the carbonyl group to give an **EC** derivative. The formation of an **EC** derivative would allow the generation of an **ECG** derivative by esterification. During the course of this work, a similar method outlining the oxidation of a (+)-catechin derivative was published.[7] This method was used to aid in the investigation of the oxidation step, in part by reproducing the results obtained by Tuckmantel and co-workers.[7]

The first step of this method was the oxidation of (+)-catechin tetramethyl ether (**15**). Oxidising reagents are an essential part of modern organic synthesis,[34] and over the years, oxidising reagents have been developed to display higher selectivity and functional group tolerance. This has aided in the preparation of complex target molecules.[34]

The oxidation of alcohols has changed dramatically from using the harsh basic or acidic chromium reagents of the past to milder more selective procedures.[34] Such procedures include catalytic oxidants such as ruthenium tetroxide and tetrapropylammonium perruthenate, which undergo reduction in neutral media at room temperature.[34,35] Oxidations involving reagents on solid supports, such as

silver carbonate on celite also provide neutral conditions, oxidise an array of compounds and eliminate undesired side reactions.[36] Sodium hypochlorite in acetic acid represents another oxidant that is both cheap and rapid. This reagent has been used to oxidise similar molecules to catechin, such as borneol to camphor on a preparative scale in excellent yields.[37] However, ring chlorination of the (+)-catechin derivative (15) may be a problem when using this reagent.

Dimethylsulfoxide (DMSO) is one of the most studied solvents and reagents in organic synthesis.[38] The first use of activated DMSO as an oxidising agent was by Kornblum and co-workers,[39] and since then a variety of procedures using DMSO with various electrophilic 'activators' have been subsequently developed and reviewed.[39] Many DMSO activators exist, including acetic anhydride and sulfur trioxide-pyridine which both react with DMSO at room temperature. Trifluoroacetic anhydride, halogens and oxalyl chloride react with DMSO at temperatures well below room temperature due to the unstable nature of their intermediates.[38] This allows the generation, handling and control, and trapping of highly reactive intermediates. Oxalyl chloride was found to be a superior DMSO activator by Mancuso and Swern.[38] Quantitative yields were obtained at -60° C, irrespective of steric factors of the alcohol, and competing side reactions were minimal. Alternatively the widely used Moffatt procedure involves reaction of an alcohol, dicyclohexylcarbodiimide (DCC) and an acid at room temperature, furnishing a ketone under very mild conditions. This reaction has been used to oxidise sensitive alcohols contained within alkaloids and carbohydrates.[39]. It was found that the reaction was not inhibited by bulky substitutents surrounding the alcohol and was independent of the DMSO activator.[40]

Oxidation is a useful tool for converting flavan derivatives with alcohol groups in the heterocyclic ring to other products.[41] Ample evidence exists for the oxidation of flavan-3,4-diols to flavanones, but not for the oxidation of flavan-3-ols.[41] The oxidation of flavan-3-ols to 3-oxoflavans is a process which still remains virtually unknown.[42] The little literature available reveals that 3-oxoflavans have been synthesised, but with difficulty.[43] By applying the Pftizner-Moffatt oxidation

procedure, Clark-Lewis and co-workers[42,43] obtained 5,7,3',4'-tetramethoxy-3-oxoflavan (**23**) in about 28% yield, accompanied by the side product, 3-methylthiomethoxyflav-3-ene (**24**).

(**23**)　　　　　(**24**)
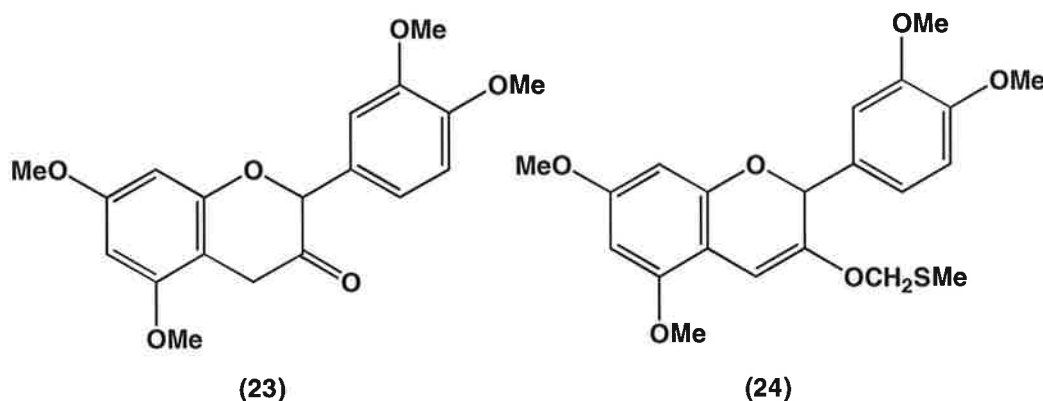
Ruthenium tetroxide gave the ketone (**23**) in low yields of 5%,[43] as did the combination of DMSO with acetic anhydride.[41]

There are many reagents available for stereospecific reduction of carbonyl groups to alcohols. Hydride transfer reagents are commonly used as reducing agents in organic synthesis; the two reagents most frequently used are lithium aluminum hydride and sodium borohydride. Of the two, sodium borohydride is milder and shows more selectivity,[44] but gives mixtures of (+)-catechin (**1**) and (-)-epicatechin (**2**) when reducing 3-oxoflavan.[42] To attenuate the vigorous reducing power of lithium aluminium hydride, one or more of its hydrogen atoms can be replaced by an alkoxy group. An example is lithium tri-*t*-butoxyaluminium hydride, which exhibits increased stereoselectivity in the reduction of ketones to alcohols.[44] Another reagent that shows modified reactivity because of its steric bulk is di-isobutylaluminium hydride (DIBAL-H). Since the aluminium atom is tri-coordinate, it acts as a Lewis acid and coordinates to the oxygen of the ketone group before it is reduced.[44] Alternatively a Lewis acid can be added to a reducing agent, causing the same effect. For instance, cerium chloride in the presence of sodium borohydride has been found to reduce the carbonyl group of a number of optically active cyclopentenone ethers with high diastereoselectivity.[45] One of these ethers (**25**) (Scheme 6), when reduced under these conditions gave the *cis* product (**26**) in greater that 95% whilst the *trans* product (**27**) was obtained in less than 5%.
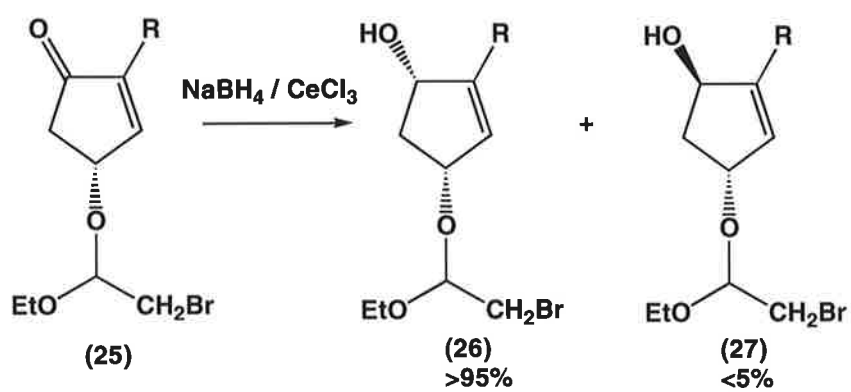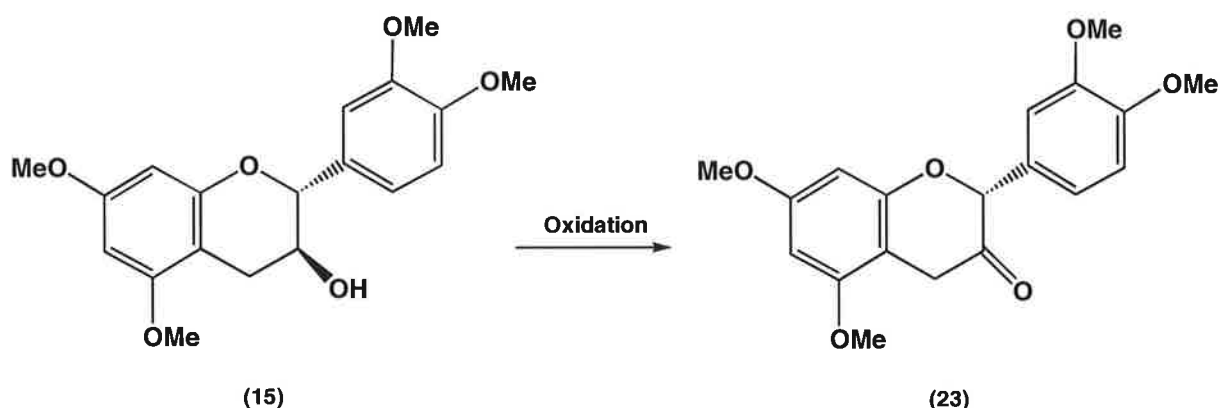
Scheme 6[45]

R=5,5-dimethyl-1,3-dioxan-2-yl

(II)   Results and Discussion

The oxidation of (+)-catechin tetramethyl ether (**15**) to the corresponding ketone (**23**) (Scheme 7) was attempted using an extensive array of oxidants as depicted in Table 2.

Scheme 7.

(+)-Catechin tetramethyl ether (**15**) was used in preference to (+)-catechin (**1**) as it was thought that the unprotected phenolic groups may oxidise to some extent in the reaction. Secondly, the use of (+)-catechin tetramethyl ether (**15**) was preferred over that of other protected species (such as the benzyl ether), as it was readily available and gave an ^{1}H n.m.r spectrum that was easy to interpret.

Table 2. Reagents and conditions for the oxidation of

(+)-catechin tetramethyl ether (15).

Entry	Reagents*	Time (h)	Temp. (°C)	Product
1	CrO_3, ether, H_2O	24	Ambient	Starting material
2a	Jones reagent, acetone	18	Ambient	Multiple products
2b	"	0.5	"	Starting material +degradation
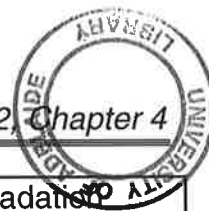
3a	PCC, NaOAc, CH_2Cl_2	0.5	Ambient	Degradation
3b	PCC, CH_2Cl_2	"	"	"
4a	Ag_2CO_3, celite, toluene	21	110	Starting material
4b	Ag_2CO_3, celite, $(CH_2)_2Cl_2$	4	146	"
5a	$PdCl_2$, K_2CO_3, CCl_4	24	76	Starting material
5b	$PdCl_2$, NaOAc, Acetone, O_2	3	Ambient	Starting material + complex mixture
6a	$Pb(OAc)_4$, CH_2Cl_2	2	Ambient	Complex mixture
6b	$Pb(OAc)_4$, AcOH, H_2O	22	119	Starting material + acetate (19%)
7a	Cl_2/thioanisole, CCl_4, Hunig's base	2.5	-25	Starting material
7b	Cl_2/thioanisole, CCl_4, Et_3N	"	"	"
8	Br_2/$CHCl_3$, NaOH, $NaHCO_3$	2	-4	Complex mixture
9	NaOCl, AcOH	17	Ambient	Starting material
10a	TPAP, NMO, CH_2Cl_2, 4Å sieves	1	Ambient	Starting material
10b	"	17	"	Multiple products
11a	*t*-BuOK, cyclohexanone, toluene	0.5	110	Starting material
11b	Aluminum isopropoxide, cyclohexanone, toluene	0.5	110	Starting material + required ketone (1%)
11c	Aluminum isopropoxide, acetone, benzene	21	80	Starting material + unidentifiable
12	RuO_4, $NaIO_4$, CCl_4	0.75	Ambient	Required ketone (5%) + starting material

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13	DMSO, Ac$_2$O	52	Ambient	Starting material + acetate (29) (41%)
14	DMSO, TFAA, CH$_2$Cl$_2$, Et$_3$N	1	-50 → ambient	Starting material
15a	DMSO, (COCl)$_2$, CH$_2$Cl$_2$, Et$_3$N	0.25	-60	Multiple products
15b	"	18	-50 → ambient	Degradation
16	DMSO, DCC, py-TFA	21	-5 → ambient	Starting material + ketone (23) (27%)
17	Me$_2$S/NCS, toluene, Hunig's base	20	-25 → ambient	Starting material + ketone (23) (13%)
18	Dess-Martin periodinane, moist-CH$_2$Cl$_2$	3	Ambient → 40	Ketone (23) (38%)

*References for the oxidation reactions are cited in the experimental section.

Out of the 22 different procedures summarised in Table 2, only five yielded the desired ketone (23).

The ketone (23) was identified by an absorbance at 1731 cm^{-1} in the infrared spectrum. Further evidence was the formation of an AB quartet for the two protons at position-4, at δ3.50, 3.57 (J=21.6 Hz) in the ^{1}H n.m.r spectrum, distinct from signals at δ2.60 (dd, J=9.6, 16.5 Hz) and 3.08 (dd, J=5.1, 16.5 Hz) of the starting alcohol. The proton at position-2 now showed a singlet at δ5.28, different from a doublet at δ4.66 (J=8.4 Hz) in the starting material. A multiplet at δ4.07 in the ^{1}H n.m.r spectrum of the starting alcohol, could not be seen in the spectrum of the ketone (23). Furthermore, the ^{13}C n.m.r spectrum now gave a signal at δ205.52, indicating a carbonyl group.

Using Oppenauer conditions (Table 2, entry 11b) (Aluminum isopropoxide, cyclohexanone, toluene) (+)-catechin tetramethyl ether (**15**) was partially oxidised, giving the ketone (**23**) in a low yield (1%) after chromatography. This was the first time this ketone was obtained under these conditions, even though a similar system, hepta-*O*-methylprocyanidin A$_2$ (**28**), has been oxidised under modified Oppenauer conditions in moderate yields.[46]
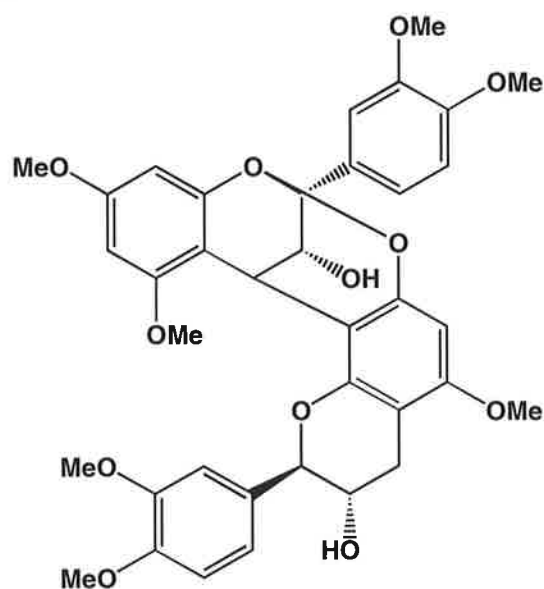

(**28**)

Using different conditions (Table 2, entries 11a and 11c), the Oppenauer oxidation still gave back mainly starting materials.

A combination of sodium metaperiodate under ruthenium tetroxide catalysis gave the required ketone in 5% yield (Table 2, entry 12). This result is in accord with the findings of Clark-Lewis and co-workers, who obtained similar yields for the ketone (**23**) using the ruthenium tetroxide methodology.[43]

The use of the Pftizner-Moffatt procedure to oxidise (+)-catechin tetramethyl ether (**15**) has also been described by Clark-Lewis and co-workers, providing the ketone (**23**) as a crystalline solid in 28% yield.[42] Using this procedure the ketone (**23**) was obtained in similar yields of 27% (Table 2, entry 16). The ketone tended to develop a pink colouration on storage, but was however stable as shown by t.l.c and ^{1}H n.m.r analysis. Increased time and the use of excess oxidant did not afford greater yields of the ketone nor increased consumption of starting ether (**15**). Clark-Lewis and

co-workers blamed their low yields on the generation of 3-methylthiomethoxyflav-3-ene derivatives such as (24), which formed in competition with the ketone.[43] There was no evidence at all of these species in our reaction mixture. The attempted oxidation of (+)-catechin tetramethyl ether (15) using DMSO with acetic anhydride as an activator (Table 2, entry 13) afforded the 3',4',5,7-tetramethyl ether acetate (29) of (+)-catechin in 41% yield. However, when (-)-epicatechin tetramethyl ether was oxidised using this methodology, the ketone was obtained in moderate yields (30%).[41] Other attempts at using this oxidation combination on protected catechin species have given the same adverse result.[7,42] Using more reactive DMSO activators such as trifluoroacetic anhydride (Table 2, entry 14) and oxalyl chloride (Table 2, entry 15), at low temperatures, gave starting material or complex product mixtures (many spots by t.l.c) respectively. The fact that oxalyl chloride reacts to give something other than starting material (Table 2, entry 15) is in accordance with its ability to react at low temperatures irrespective of steric factors associated with the alcohol.[40] Multiple products were evident by t.l.c, none of which appeared to correspond to the required ketone (23).

DMSO oxidations proceed with the reaction of a nucleophilic species such as an alcohol, with an activated DMSO reagent.[38] This gives the alkoxysulfonium salt (30), which upon addition of base forms the methyl-carbanion or ylide (31) which then collapses to carbonyl and dimethylsulfide by an intermolecular hydrogen transfer (Scheme 8, route A).[40]
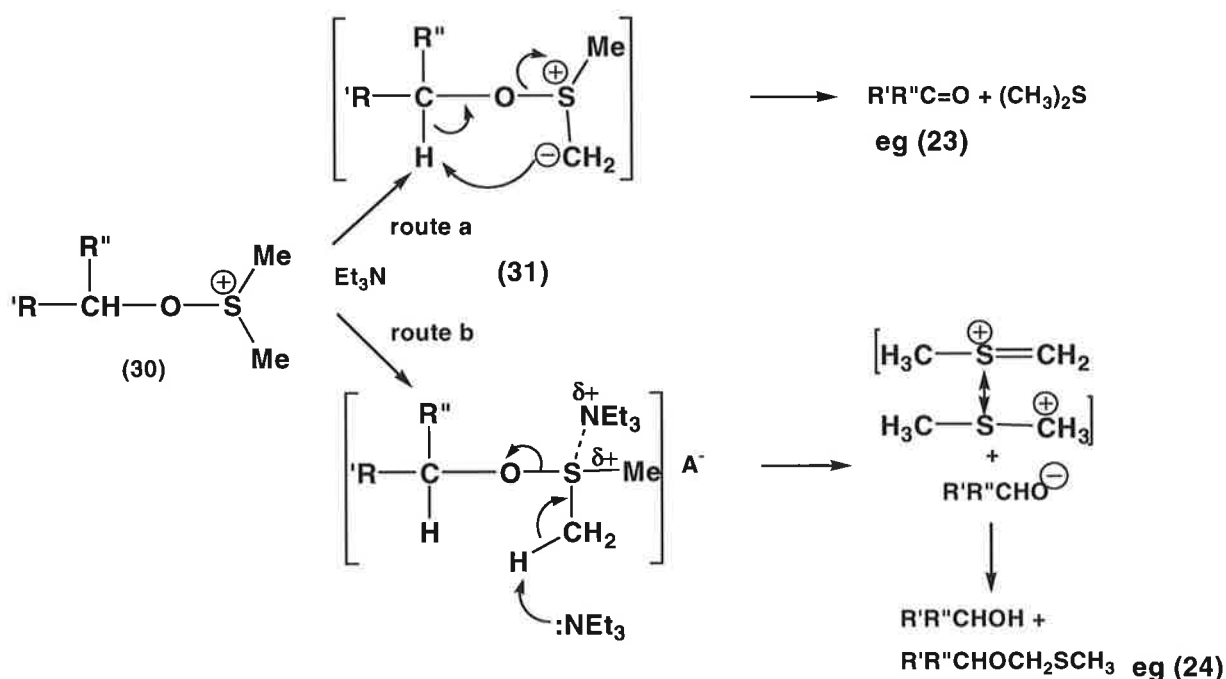
Scheme 8.[40]

However, ylide (**31**) may also collapse to a methyl methylenesulfonium ion and an alkoxide ion (Scheme 8, route b).[40] The alkoxide ion can either remove a proton from the system to form an alcohol (starting material) or recombine with the methyl methylenesulfonium ion to give an alkyl methylthiomethyl ether,[40] an example of which was 3-methylthiomethoxyflav-3-ene (**24**) obtained by Clark-Lewis and co-workers.[43] The recovery of starting catechin ether (**15**) in the DMSO oxidations may be due to what has just been described for the alkoxide ion (Scheme 8, route b). Another reason for the recovery of starting alcohol may be a result of steric factors preventing the alcohol from forming the alkoxysulfonium salt (**30**). This may lead to reaction elsewhere in the molecule resulting in the formation of complex reaction mixtures (Table 2, entry 15).[39]

A similar reaction to the DMSO oxidations is the oxidation using dimethyl sulfide-*N*-chlorosuccinimide complex. This affords the alkoxysulfonium salt (**30**) (Scheme 8), which is then cleaved using bases such as triethylamine or diisopropylethylamine, as outlined. The ketone (**23**) was obtained using this method (Table 2, entry 17), but in slightly lower yields (13%) than the Pftizner-Moffatt procedure.

Whilst this work was in progress, the results of a study by Tuckmantel *et al* concerning the oxidation of catechin tetrabenzyl ether appeared in the literature.[7] This work suggests the best method of obtaining the tetrabenzyl ether protected ketone is through using the Dess-Martin periodinane, giving crude yields of 90%.[7] The Dess-Martin periodinane has become increasingly popular for the oxidation of alcohols to aldehydes and ketones when other reagents fail. This is largely due to the fact that hypervalent iodine compounds are selective, mild and avoid the use of excessive reaction times, difficult work-up procedures and the need for large excesses of the oxidant.[47]

This approach had not yet been investigated and it was attempted in the hope of reproducing their results. The oxidation reaction was undertaken upon (+)-catechin tetramethyl ether (**15**) giving the ketone (**23**) in 38% isolated yield (Table 2, entry 18). Product loss due to chromatography may explain the lower yield compared to Tuckmantel and co-workers, who stated a crude yield of 90% for the tetrabenzyl ether protected ketone.[7]

The only other product to be identified from the oxidation reactions was the tetramethyl ether acetate (**29**) of (+)-catechin (Table 2, entry 6b). The acetate was obtained in 19% yield. It was not known whether the acetate (**29**) existed in the epi configuration or the configuration of the starting (+)-catechin ether (**15**). To investigate this, the acetate was hydrolysed to give (+)-catechin tetramethyl ether (**15**). This suggested the acetate had not formed with inversion of configuration at carbon-3, implying formation by an acid catalysed esterification reaction with acetic acid.

In summation, the oxidation methods that were moderately successful for the preparation of (+)-catechin tetramethyl ether (**15**), such as ruthenium tetroxide/sodium metaperiodate, Pfitner-Moffatt and Dess-Martin periodinane, were mild and designed for sensitive substrates. These results were not surprising as the literature has suggested that the oxidation of catechin molecules was difficult,[7,43] and has only occurred using a few reagents in moderate yields.[42,43] Oxidation using harsher acidic or basic reagents/conditions tended to lead to product degradation.

With a reasonable amount of the ketone (23) in hand, attention was then turned to reducing it stereoselectively to give an epicatechin derivative (32) (Scheme 9).
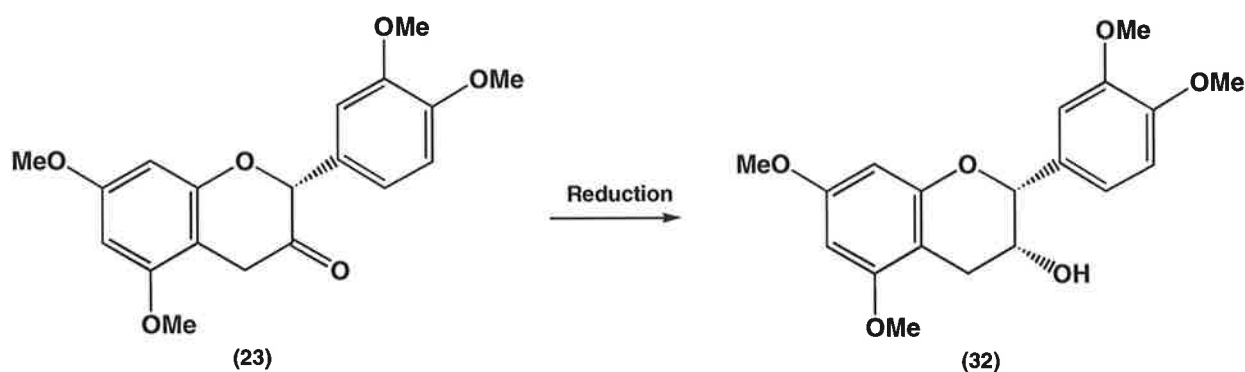
Scheme 9

Table 3, Reagents and additives used for the reduction of 5,7,3',4'-tetramethoxy-3-oxoflavan (23).

Entry	Reagent (eq.)	Additive (eq.)	*trans/cis*[*]	Yield- *trans/cis* (%)
1	NaBH₄ (5)	-	1:1.3	61
2	NaBH₄ (4)	CeCl₃ (1)	1:3	59
3	NaBH₄ (5)	CeCl₃ (1)	1:4	58
4	NaBH₄ (5)	CeCl₃ (2.2)	1:6	46
5	NaBH₄ (5)	CeCl₃ (5)	1:7	45
6	LiBH(s-Bu)₃ (1.3)	LiBr (5.2)	1:99[§]	33[†]

* Ratio determined by ^{1}H n.m.r, † Isolated yield of *cis* isomer, § no catechin observed

The results obtained using sodium borohydride in the presence of cerium chloride (a mild reducing mixture) are outlined (Table 3, entries 2-5). Cerium chloride acts as a Lewis acid and coordinates with the ketone of the 3-oxoflavan (23) prior to reduction. The hydride ion should then attack the less hindered β-face selectively giving an epicatechin derivative (32). Without the addition of cerium chloride, reduction using excess sodium borohydride was poorly selective giving a 1:1.3 ratio (^{1}H n.m.r) of (15) to (32), both isomers being isolated together in 61% yield after purification (Table 3, entry 1). The two isomers (15) and (32) could not be separated

by chromatography as they possessed the same Rf value irrespective of the running solvents.

Epicatechin tetramethyl ether (**32**) was distinguished from the starting ketone (**23**) by the disappearance of the carbonyl absorption at 1732 cm^{-1} in the infrared spectrum. A new signal (multiplet) in the ^{1}H n.m.r spectrum at $\delta 4.27$ was evident, attributed to the proton at postion-3 of the C-ring. The carbon at this position showed a signal in the ^{13}C n.m.r at $\delta 67.08$. The protons at position-4 of the C-ring showed an ABX pattern, the AB portion at $\delta 2.87$, 2.95 ($J=17.5$ Hz). This signal was different to the starting ketone (**23**), which displayed an ABq at $\delta 3.50$, 3.57 ($J=21.6$ Hz) for these protons.

The **EC** derivative (**32**) showed differences in the splitting pattern of the protons at positions-2 and -4, compared to the (+)-catechin derivative (**15**). This suggested the newly formed derivative had the required epi stereochemistry. The proton at position-3 appeared as a mulitplet in both cases. The proton at position-2 in the **EC** derivative (**32**) appeared as a singlet at $\delta 4.96$, whereas it appeared as a doublet at $\delta 4.66$ ($J=8.4$ Hz) in the (+)-catechin derivative (**15**). Additionally, the protons at position-4 in the **EC** derivative (**32**) showed an AB splitting pattern (of an ABX system) as just described, different from that of (+)-catechin tetramethyl ether (**15**), which showed signals for these protons at $\delta 2.59$ (dd, $J=9.6$, 15.9 Hz) and 3.08 (dd, $J=6.0$, 15.9 Hz).

Decreasing the amount of reducing agent and adding one equivalent of cerium chloride improved the selectivity of the reduction to a 1:3 ratio of the *trans* to *cis* isomers (Table 3, entry 2). The yield of the two isomers was however slightly lower (59%). Using five equivalents of sodium borohydride in (Table 3, entry 3) increased the selectivity and recovery yield of the *cis* and *trans* isomers slightly. Increasing the amount of cerium chloride to 2.2 equivalents further increased the selectivity of the reaction (Table 3, entry 4), but gave a lower isolated yield (46%) of the two isomers. Increasing the amount of cerium chloride to five equivalents resulted in a ratio of 1:7 (Table 3, entry 5), with similar yields to entry 4.

Literature that was published at the time of these investigations, suggested that using bulky L-selectride for the reduction of a 3-oxoflavan (protected as a tetrabenzyl ether) to the epicatechin derivative, proceeded with good selectivity and yield (81%).[7] This reagent was thought to exhibit selectivity in attack from the less hindered β face.[7] The reaction was trialed, giving almost exclusive formation of the required isomer (**32**) in 33% yield (Table 3, entry 6).

The reactions (Table 3, entries 1-5) gave satisfactory yields of the *cis* and *trans* catechin isomers. There appeared to be a slight decrease in the yield as the amount of CeCl$_3$ increased, possibly due to side reactions associated with more additive in the reaction mixture. However, increased amounts of CeCl$_3$ gave a better selectivity for the required *cis* isomer (**32**). The reaction (Table 3, entry 6) also gave an adequate isolated yield of the *cis* isomer (**32**), with no (+)-catechin ether (**15**) being observed in the ^{1}H n.m.r spectrum. The 33% yield was lower than the other entries but is probably comparable if the *cis* isomer was actually isolated in these cases.

On obtaining epicatechin tetramethyl ether (**32**), the next step was to esterify at the hydroxyl group at position-3 to obtain the gallate ester derivative of **EC** (**33**) as shown below.
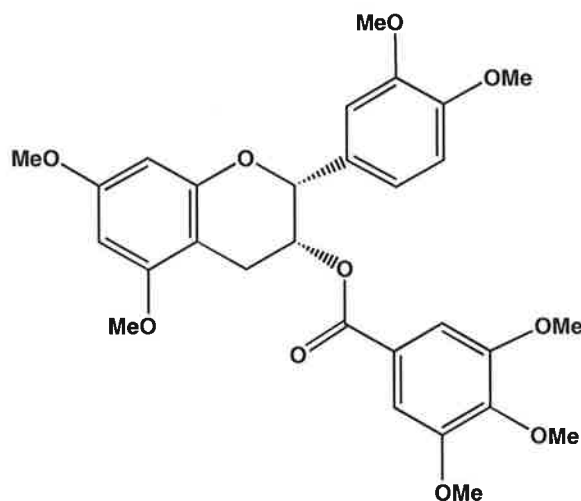

(33)

In the first instance (+)-catechin tetramethyl ether (**15**) was reacted with gallic acid in benzene using sulfuric acid as a catalyst. Refluxing this solution for 18 h resulted in baseline material by t.l.c. Performing the reaction in THF and employing

trifluoroacetic acid as the catalyst resulted in starting material being recovered. These results suggested that the esterification reaction under acid conditions was difficult to accomplish and/or that the unprotected phenol groups of gallic acid were interfering with the reaction.

Gallic acid was reacted with sodium hydroxide and methyl iodide in refluxing methanol to give 3,4,5-trimethoxybenzoic acid as a white solid in 61%. This product showed a nine-hydrogen singlet at $\delta 3.93$ in the ^{1}H n.m.r spectrum due to the three methoxy groups on the aromatic ring. It also contained a singlet at $\delta 7.29$ due to the two aromatic protons. Trimethoxybenzoyl chloride was readily obtained from this acid by refluxing in thionyl chloride for 30 min. Following a procedure for the esterification of epicatechin derivatives,[7] the acid chloride was reacted at room temperature with (+)-catechin tetramethyl ether (15) in the presence of dimethylaminopyridine (DMAP) and pyridine. This method gave complex products as well as a trace of the required protected gallate (34). Numerous multiplets appeared in the ^{1}H n.m.r spectrum ($\delta 2.00$-3.20, 4.50-7.00) as well as many signals in the methoxy region of the spectrum ($\delta 3.75$-3.93). However starting material was absent from the spectrum. A far superior esterification procedure was the reaction of the acid chloride, catechin molecule and pyridine at room temperature. This method yielded the required gallate (34) after 48 h as a pure, white solid in 27% yield. Product loss was possibly due to difficulties with recrystallisation. A molecular ion at m/z 541 indicated that the starting catechin (15) had been esterified. The gallate (34) was also identified by ^{1}H n.m.r spectroscopy which showed a two hydrogen singlet at $\delta 7.11$, indicative of the two aromatic hydrogens on the gallate group and additional methoxy signals at $\delta 3.90$ (s, 3H) and 3.84 (s, 6H). The spectrum also showed a distinctive shift of the multiplet due to the proton at position-3, to $\delta 5.49$ from $\delta 4.06$ (starting catechin derivative). The proton at position-2 gave a doublet at $\delta 5.12$, which appeared at $\delta 4.66$ in the starting material. The gallate (34) also showed a carbonyl peak at $\delta 166.70$ in the ^{13}C n.m.r spectrum.

Epicatechin tetramethyl ether (32) was reacted under the conditions described for the esterification of the 3-hydroxyflavan tetrabenzyl ether derivative.[7] These conditions (DMAP, acid chloride, pyridine) returned only starting material. The reaction of

epicatechin tetramethylether (**32**) using the conditions that were successful for the (+)-isomer (3,4,5-triemthoxybenzoyl chloride in pyridine), returned only starting material akin to the first esterification attempt. The two reactions were repeated using fresh reagents, again with no success. Finally the esterification reaction giving the heptamethyl ether of (-)-epicatechin gallate (**33**), was achieved using dicyclohexylcarbodiimide (DCC) (Scheme 10).
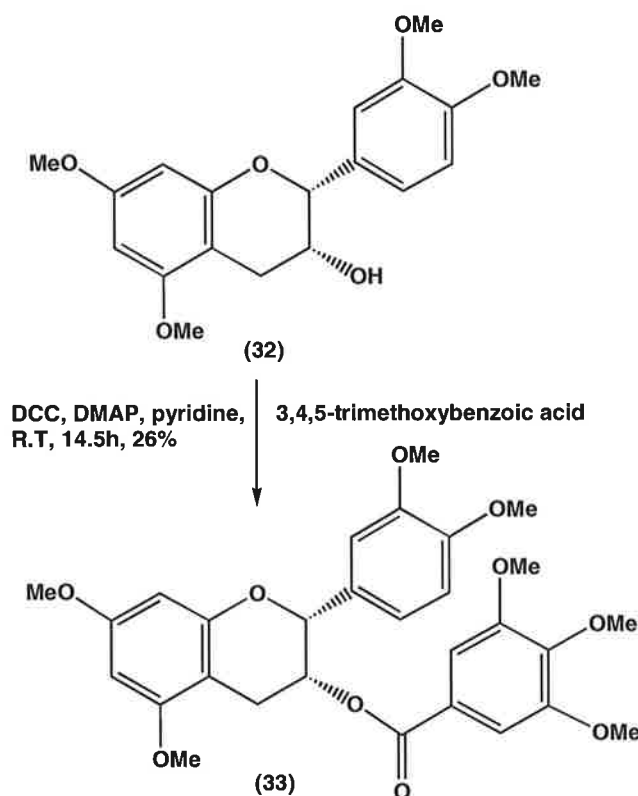
Scheme 10

This reaction was conducted at room temperature using 3,4,5-trimethoxybenzoic acid and DMAP in pyridine over 14.5 h. The required gallate (**33**) was obtained in 26% yield; the moderate yield being due to incomplete conversion of starting materials and tedious purification steps to remove DCC/DCU (dicyclohexylurea) from the product mixture.

By using DCC, reaction with the acid took place to generate a highly reactive acylating agent (**35**).

(35)
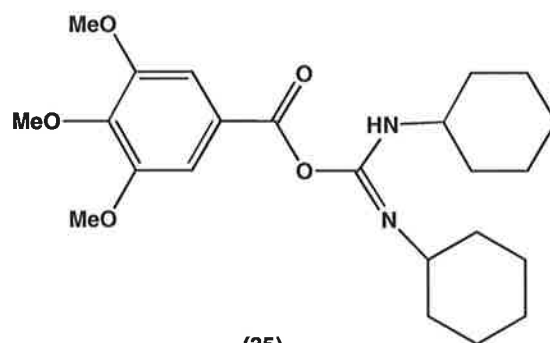
This species (**35**) must have been more reactive than the acid chlorides used in the other esterification attempts, which is why this method worked and the others failed.

(III)   Conclusions

The oxidation of (+)-catechin tetramethyl ether (**15**) was achieved using only a few methods compared to the number that were examined. The best oxidant was found to be Dess-Mertin periodinane, giving the required ketone in moderate yield. It was found that oxidants maintaining mild reaction conditions gave better results than harsher acidic reagents.

The reduction of the ketone (**23**), using stereospecific reagents such as L-selectride, gave the **EC** derivative (**32**) in moderate isolated yield. Increasing the amount of stereoselective additives gave a greater ratio of the required *cis* derivative over the *trans* derivative.

The esterification reaction of (+)-catechin tetramethylether (**15**) with 3,4,5-trimethoxybenzoyl chloride proceeded under basic conditions (pyridine). However, the epicatechin derivative (**32**) failed to react under these conditions and the esterification reaction could only be achieved using 3,4,5-trimethoxybenzoic acid with DCC and DMAP in pyridine, giving the **ECG** derivative (**33**) in moderate yield.

The reactions described in this chapter provided **EC** and **ECG** precursors easily albeit in moderate yields. However, this methodology was not suitable for forming the gallo derivatives, **EGC** and **EGCG**. This prompted the investigation of other ways of forming all of the required epi derivatives, which will be discussed in subsequent chapters.

Chapter 5: Investigation into the Synthesis of Epicatechins, Section A.

(I) Introduction

The methodology described in Chapter 4 allowed the formation of an **EC** precursor in satisfactory yield from the oxidation and stereoselective reduction of (+)-catechin (**1**). The **EC** precursor could then be esterified to furnish an **ECG** derivative. However, this method did not allow the formation of an **EGC** derivative and thus an **EGCG** derivative. Hence this chapter describes attempts to develop new syntheses of epicatechins that could be modified to produce also **EGC** (**3**) and derived systems. Within the literature, there is a distinct lack of syntheses designed specifically for forming epicatechins, especially all four of the epicatechins. Most of these syntheses give racemic catechin.

Previous Syntheses of Catechins and Epicatechins.

One of the most common ways of obtaining catechins is by the deoxygenation of flavanones using sodium cyanoborohydride (Scheme 11)[48]


(36)
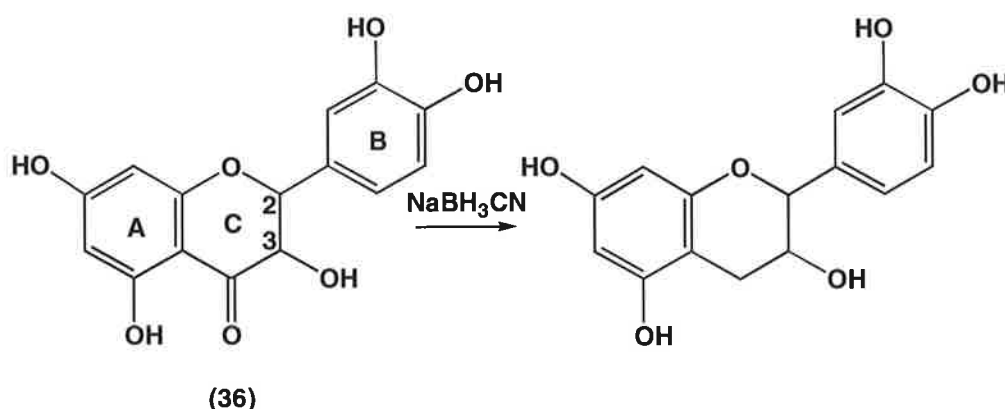
Scheme 11

In this way catechin has been obtained from the natural product dihydroquercetin (**36**) in 90% yield. The catechin formed was largely racemic (the specific rotation

showed about 70% racemisation)[48] although the *trans* geometry of the B ring and 3-hydroxyl group was well preserved. The racemisation was a possible result "of the opening of the C-ring and its reclosure before reduction of the carbonyl group had taken place".[48] The sodium cyanoborohydride reduction proceeded under conditions sufficiently mild that no protecting groups were required for the hydroxyl and phenol groups. Other methods including the sodium borohydride reduction of flavanone acetates required protecting groups, and were subject to the limitation that the 5-acetoxy substituent must be present. The sodium borohydride method furnished (±)-catechin pentaacetate in 56% yield.[49]

A similar method for obtaining (+)-catechin pentaacetate used an enantioselective epoxidation of the chalcone (**37**) and chiroptical HPLC purification of the (-)-chalcone epoxide (**38**) to the optically pure state.[14] Treatment of (**38**) (100% ee) with methanolic hydrogen chloride afforded (+)-taxifolin (**39**) which was converted into (+)-taxifolin pentaacetate (**40**). The sodium borohydride reduction as described above and subsequent acetylation gave catechin pentaacetate (**41**) in 88% yield (Scheme 12).
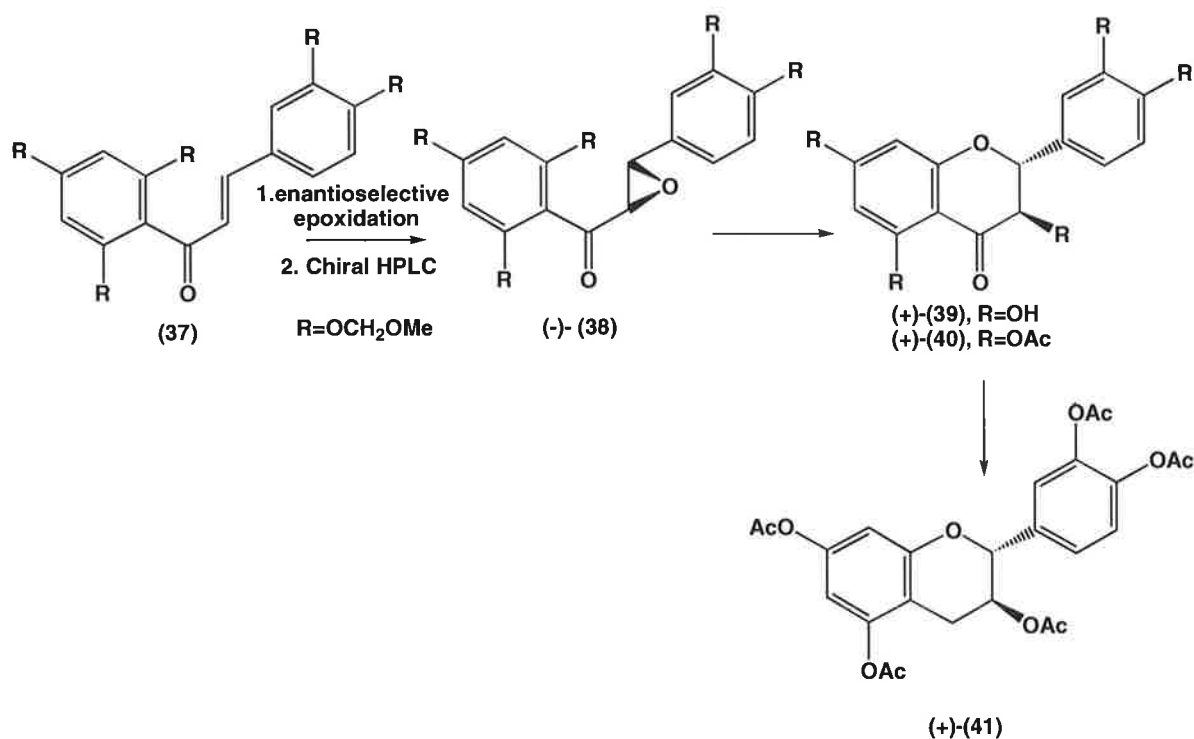
Scheme 12

The synthesis above describes the stereoselective formation of (+)-catechin pentaacetate (**41**),[14] but does not specify a synthesis for (-)-epicatechin pentaacetate, nor the generation of **ECG**, **EGC** or **EGCG** derivatives. The reduction step has the disadvantage that a 5-acetoxy substituent must be present in the flavanone. This method also uses HPLC to generate the (-)-epoxide (**38**), which then limits the scale of further reactions and the amount of product finally obtained.

The total synthesis of the regioselectively ^{13}C-labelled racemic flavan-3-ol, 4-[^{13}C]catechin (**42**), has been conducted to enable detection of catechin molecules in human biological fluids (Scheme 13).[50]
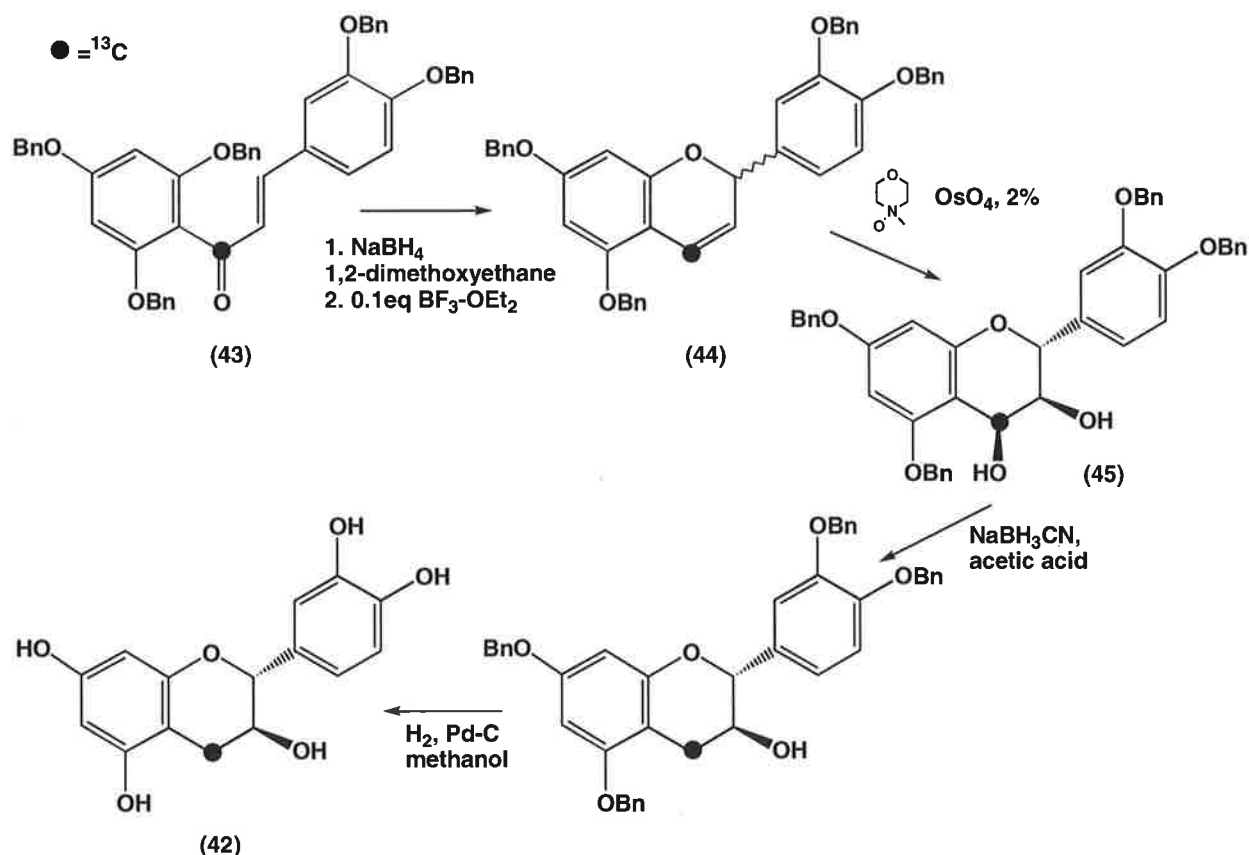
Scheme 13

Regioselectivity was achieved by borohydride reduction of (**43**) and Lewis acid cyclisation to give the racemic flavene (**44**), which was directly transformed by an osmium-catalysed dihydroxylation into (**45**), with high diastereoselectivity (the all *cis*-isomer was not observed).[50] Treatment of (**45**) with sodium cyanoborohydride followed by hydrogenolysis yielded the target racemic catechin (**42**) in 4% overall yield.

This synthesis however was not extended to form racemic epicatechin nor racemic gallocatechin, which could be utilised to form an EGC derivative using the methodology developed in Chapter 4. This synthesis of racemic catechin (Scheme 13) proceeded in ten steps, which was also a drawback.

Asymmetric dihydroxylation has also been used to provide a stereoselective approach to flavan-3-ol derivatives.[15] A series of polyoxygenated 1,3-diarylpropenes were treated with AD-mix-α or AD-mix-β in the presence of methanesulfonamide; subsequent acid-catalysed cyclisation afforded the diastereomeric pair **(29)** and **(46)**.[15] The flavan-3-ols were essentially enantiomerically pure after p.l.c.[15]

R_1-R_4=OMe

(29)   **(46)**
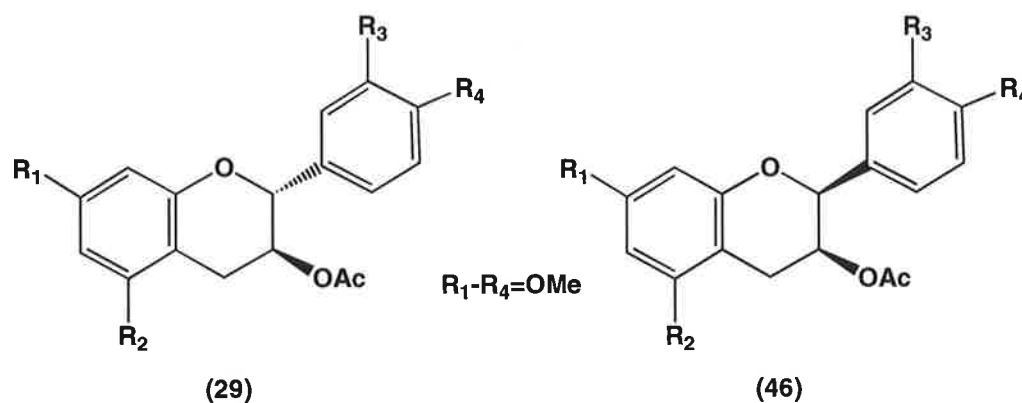
The flavanol synthesis however had the disadvantage that it required nine steps, gave a mixture of stereoisomers and was designed to produce only a small amount of the *trans* or *cis* derivatives **(29)** and **(46)** after p.l.c.

Aim, Section A.

This section of Chapter 5 will describe approaches to a new synthesis of epicatechins, which will incorporate the synthesis of epigallocatechins from 3-oxoflavan precursors. Rather than transforming (+)-catechin **(1)** into a 3-oxoflavan (Chapter 4), the synthesis of these molecules will enable the formation of molecules possessing the gallo- substitution, which will eventually be present in the B-ring, so that **EGC** and **EGCG** derivatives may be formed.

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Utilising the unique chemistry provided by Weinreb and co-workers, an approach to the formation of the ketone (**47**) was devised according to the retrosynthetic scheme outlined (Scheme 14). The non-substituted ketone (**47**) was selected as the initial target to simplify the reactions, and if viable, the required substitution in the A and B rings representative of **EC** and **EGC** would be added. Once the open chain ketone (**48**) has been obtained from a Grignard coupling reaction, the ring closure will be investigated as will the chemistry required to reduce the carbonyl group and form racemic epicatechin systems. The reduction of such carbonyl groups has been investigated previously in Chapter 4.
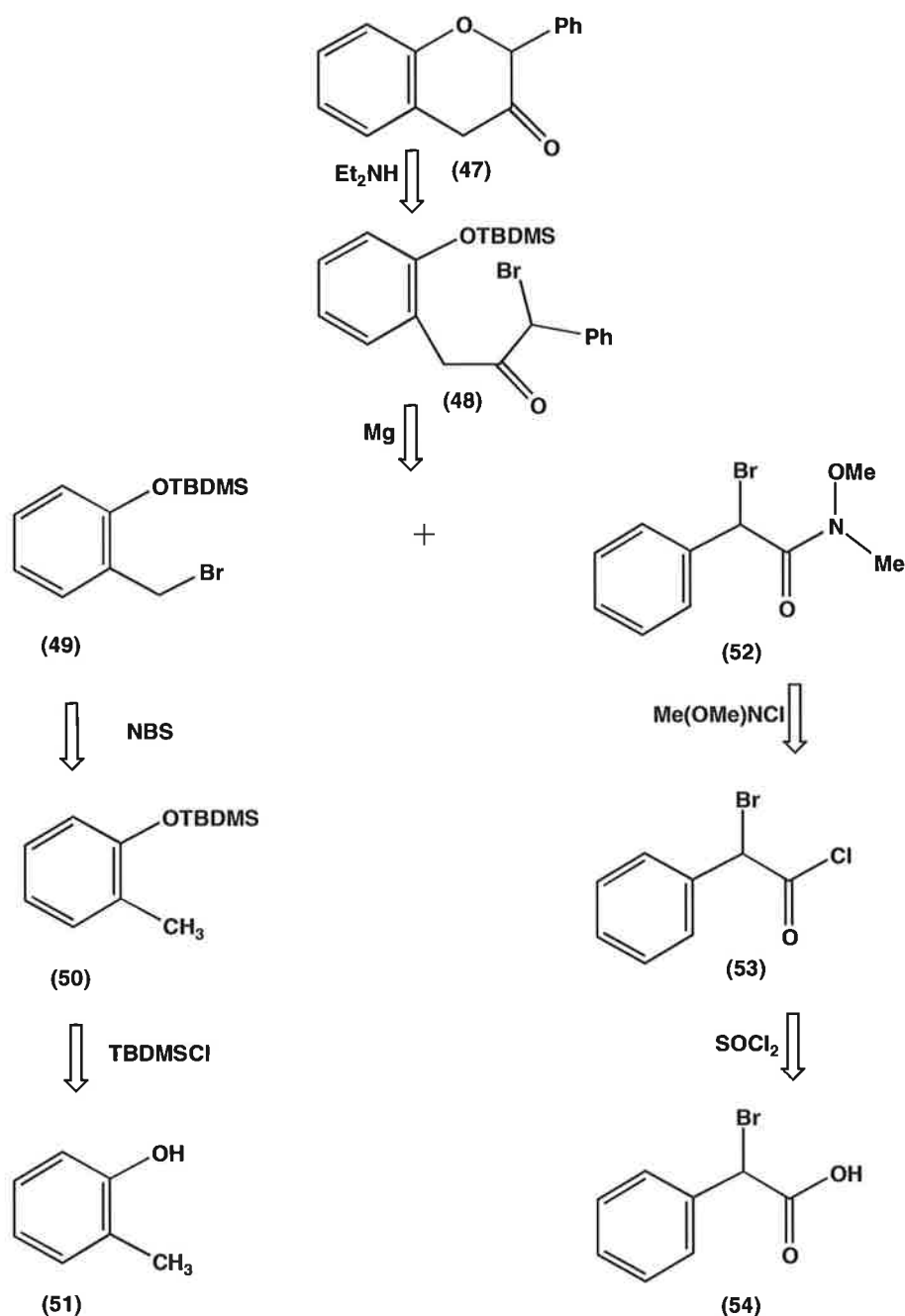
Scheme 14

The protected benzyl bromide species (**49**) may be derived from the protected cresol (**50**),[51] which can be obtained from *o*-cresol (**51**) *via* well established reaction methodology.[24] Similarly, the amide (**52**) could be generated from the α-bromo acid chloride (**53**),[52] which is derived from the acid (**54**) using standard chemistry. The generation of the ketone (**48**) may be achieved by coupling of the benzylmagnesium bromide species (**55**) and the Weinreb amide (**52**) to generate a 3-oxoflavan precursor. The presence of the bromine group on the amide may cause problems in the coupling reaction and so a protected alcohol or another good leaving group could

be an alternative if necessary. Cyclisation of the coupled species (**48**) should occur as a result of deprotection of the silyl ether using diethylamine, to give the 3-oxoflavan (**47**) quickly and efficiently.[53]

Grignard Chemistry.

Although organometallic reagents involving many different metals have found application in organic synthesis, those based on magnesium and lithium have found the widest use.[44] The synthesis of ketones from carboxylic acids (and derivatives) *via* coupling with various organometallics, has been extensively investigated over the past few decades.[52] The difficulty with this method is that the reactive nature of the Grignard and organolithium reagents tends to cause over addition to the substrate furnishing tertiary alcohols, when in fact the ketone is desired. A superior method for the acylation of various organometallics has been developed that involves the combination of *N*-methoxy-*N*-methylamides (Weinreb amides) with both Grignard or organolithium reagents, yielding ketones in high yield with no trace of tertiary alcohol.[52]

The requirements for this reaction are the preparation of the Weinreb amide and the Grignard reagent. The amides can be prepared easily from commercially available materials, but depending upon the substituents, it can be much more difficult to prepare the Grignard reagent. Two problems exist when synthesising Grignard reagents. Firstly, unreactive halides can react sluggishly with magnesium giving incomplete conversion and low yields. Secondly there has been particular difficulty with allylic or benzylic halides due to the ease of formation of the coupled 'Wurtz' product, caused by direct reaction between the halide and the reagent.[54] Thus benzylic and allylic Grignard reagents are hard to prepare or inaccessible by using classical methods such as the reaction of magnesium turnings with a benzyl or allyl halide.[55] This problem has been alleviated by a number of methods, for example using more active and reactive forms of magnesium. Magnesium powder is a more reactive form of magnesium as there is a greater surface area available for reaction. For example, high purity magnesium that has been evaporatively sublimed *in vacuo* allowed the synthesis of (**56**) where other methods failed.[54]

(56)
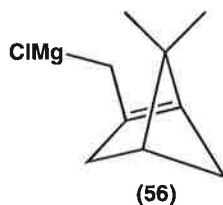
Another approach described the activation of magnesium turnings by sonication which was thought to disperse the surface bound water from the metal.[54] The dry stir method of activating magnesium has become increasingly popular due to its experimental ease and application to problematic compounds. This approach involves stirring magnesium turnings in a flask under an inert atmosphere for an extended period of time. This causes a decrease in particle size, a grey/black colouration of the metal and a deposited magnesium mirror in the flask, which acts to increase the activity of the magnesium.[54] In this manner benzyl magnesium chloride has been prepared in yields of 100%, where in the past its synthesis has been difficult due to Wurtz coupling reactions.[54] Another source of active magnesium which may be soluble depending on the solvent used, is from the reversible formation of a magnesium-anthracene complex with magnesium and a catalytic amount of anthracene.[55] In this manner benzylmagnesium chloride has been prepared in 95% yield and benzylmagnesium bromide has been prepared in 85% yield, with the formation of dibenzyl in 8% yield. The reaction of benzyl iodide gave dibenzyl in 100% yield.[55] However this method requires additional reactions (compared to normal Grignard reactions) and extra purification steps to remove unwanted anthracene.

Organocuprate Chemistry.

Organometallic reagents containing carbon-copper(I) bonds provide a class of very useful coupling reagents with organic halides.[56] However, the use of uncomplexed alkyl copper(I) reagents in coupling reactions is limited due to their rapid decomposition.[56] Formation of 1:1 "ate" complexes of these reagents with reagents such as organolithium reagents, stablises the carbon-copper(I) bond towards decomposition.[56] Whereas the behavior of copper(II) is that of a transition metal, copper(I) cannot be as clearly defined.[57] Lithium diorganocopper reagents (R_2CuLi)

(homocuprates) react cleanly, under mild conditions with a wide range of carboxylic acid chlorides to give ketones in excellent yield, as outlined in Scheme 15.[58]
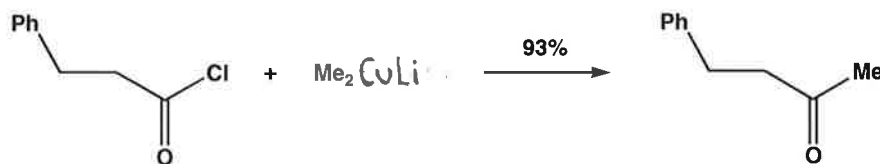
Scheme 15

Lithium dialkyl cuprates are generally prepared by adding two mole equivalents of an alkyl lithium solution to an ethereal slurry of a copper(I) salt such as copper(I)iodide, at low temperatures. Other copper complexes have been used in place of the copper salt, such as dimethylsulfide-copper(I)bromide, which has the advantage of being easily prepared, crystalline, and avoids side reactions from copper(II) compounds and other metal salt impurities in the copper(I) salts.[59]
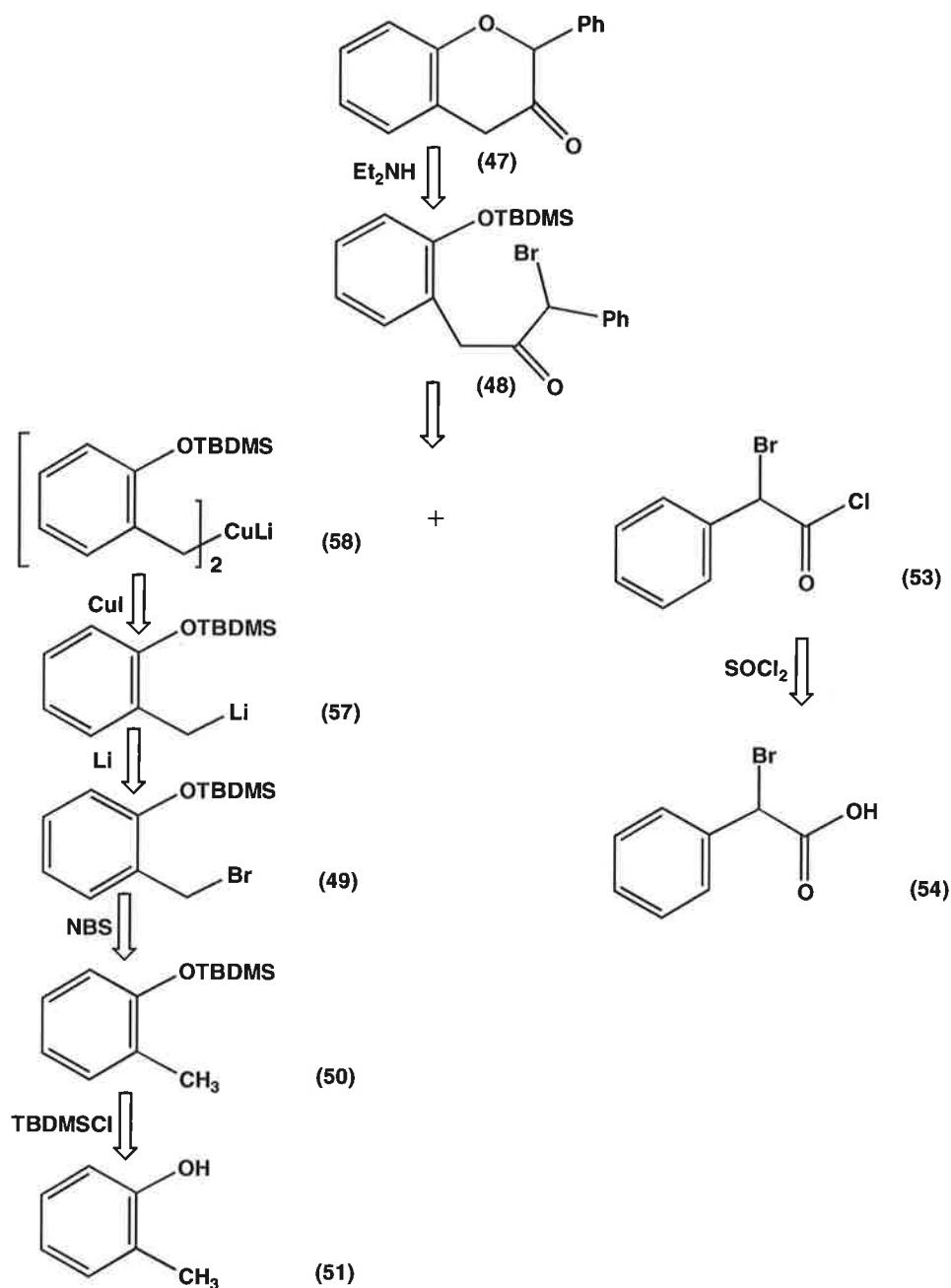
As with Grignard reagents, the organolithium reagent, if not commercially available, is prepared from lithium metal and a halide. An example of this is the preparation of benzyl lithium from benzyl chloride and lithium wire. This, as with benzylic Grignard reagents has always been troublesome due to Wurtz coupling leading to the production of dibenzyl.[60] Often the problem of poor yields is encountered when forming organolithium reagents from lithium wire and a halide.[61] This has been alleviated by reacting lithium naphthalene and an alkyl halide at low temperatures, giving high yields of the reduction products RH and RLi, in 39-99%.[61] Further work suggests that the correct combination of low temperature, addition rate, ratio of reactants and solvent combination will allow the formation of benzyl lithium in 86% without contamination from the Wurtz coupled product.[60] Another lithiation technique used for many aromatic hydrocarbons is the combination of butyl lithium with *N,N,N',N'*-tetramethylethylenediamine (TMEDA). The tertiary amine acts to increase the activity of butyl lithium, allowing metalations in excellent yield. An example of this is the lithiation of *N,N*-dimethyl-*o*-toluidine (Scheme 16).
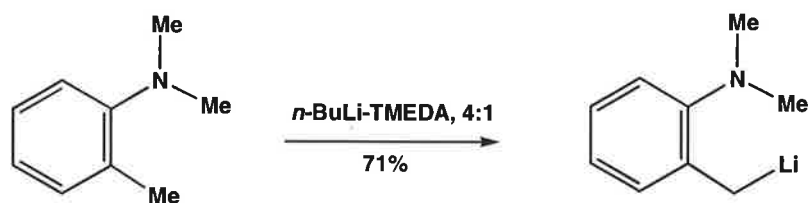
Scheme 16

Another method of generating benzyl lithium is through the cleavage of dibenzylmercury with lithium. This procedure was not ideal as it contained more than one step and utilised toxic materials.[60] The mechanism of these coupling reactions are not clear.[56]

The proposal utilising a copper coupling reaction to afford the 3-oxoflavan (**47**) is shown in Scheme 17.

Scheme 17

As with the benzyl Grignard reagent, the benzyl lithium reagent was to be prepared from the benzyl bromide species (**49**), which was obtained through bromination of a protected *o*-cresol system (**51**). The lithium di-organocuprate may be prepared from the protected benzyl lithium species (**57**) on reaction with copper(I) iodide. The bromo-ketone (**48**) should be available from the coupling of the homocuprate (**58**) with the same acid chloride that was used in the Grignard reaction scheme. Again the bromine in the acid chloride may lead to complications in the coupling reaction

and if this was the case, it could be substituted for another leaving group. The ketone **(47)** may then be obtained by facile deprotection and cyclisation of **(48)** using diethylamine.[53]

(II)   Results and Discussion

The bromination of the protected cresol (**50**) took place after the phenol group was protected using *tert*-butyldimethylsilylchloride and imidazole as outlined in Scheme 18.   The TBDMS protecting group was chosen due to its stability under Grignard reaction conditions.[24]
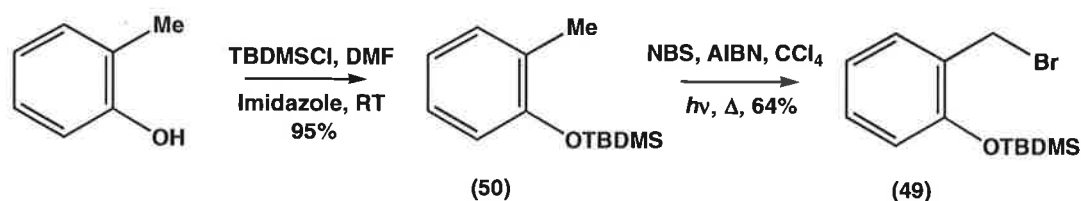
Scheme 18

The protected cresol species (**50**) was obtained as a clear oil after reaction overnight at room temperature.   The infrared spectrum of (**50**) showed the disappearance of the hydroxyl group, whilst the ^{1}H n.m.r spectrum revealed a six hydrogen singlet at $\delta 0.19$ and a nine hydrogen singlet at $\delta 0.99$ indicative of two methyl groups on the silicon atom and the *t*-butyl group adjacent to the silicon atom respectively.   The protected cresol (**50**) was easily brominated using *N*-bromosuccinimide initiated by AIBN.   The bromide was obtained as a clear, colourless oil in 64%, and was identified by a singlet at $\delta 4.53$ corresponding to the benzyl hydrogens in the ^{1}H n.m.r spectrum; the four aromatic hydrogens in the region $\delta 6.80$-7.35 and distinct molecular ions at *m/z* 301/299.   Attempts at forming the bromide (**49**) through reaction of 2-hydroxybenzyl alcohol and a brominating reagent (HBr, CBr$_4$) followed by silylation using *tert*-butyldimethylsilylchloride, proved futile.

The Weinreb amide (**52**) was readily prepared from α-bromophenylacetic acid, as outlined in Scheme 19.
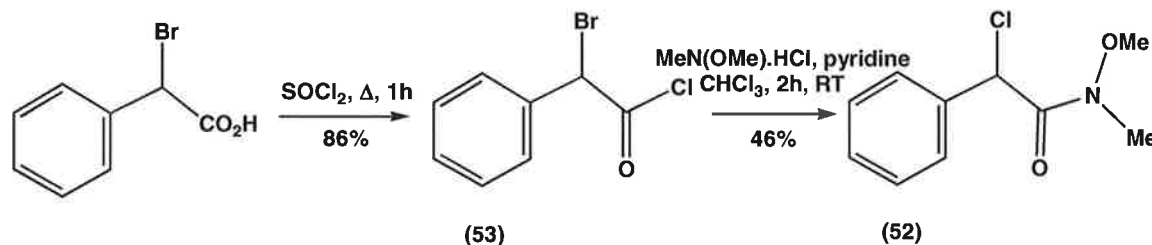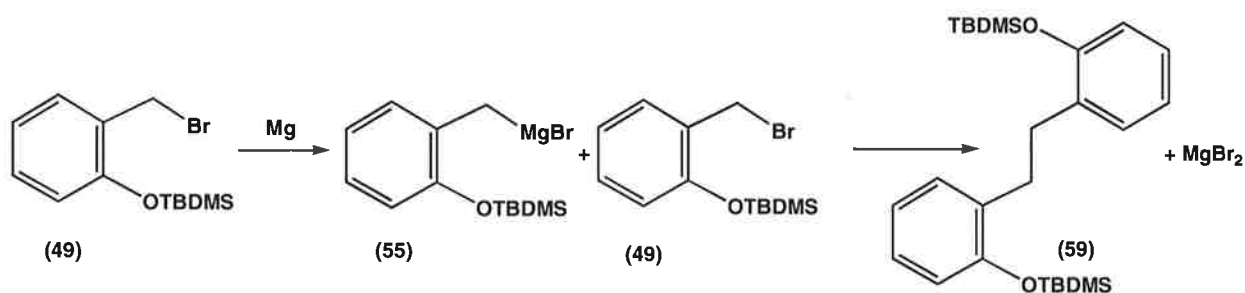
Scheme 19

The acid chloride (**53**) was obtained, using neat thionyl chloride, as a clear oil in 86% after Kugelrohr distillation. The acid chloride was reacted with commercially available *N,O*-dimethyl-hydroxylamine hydrochloride to give the Wein-reb amide (**52**) in 46%. The amide obtained contained a chlorine atom rather than a bromine atom, at the α-position; the halogen exchange may have taken place either during the formation of the acid chloride or the Weinreb amide. This exchange was evident from the mass spectrum, which showed a molecular ion at *m/z* 213/215 (3:1) and fragmentation from 125/127 (3:1) showed the loss of HCl (**36**). The ^{1}H n.m.r spectrum confirmed the presence of the amide, showing two three-hydrogen singlets at δ3.20 and 3.48, which corresponded to the methyl and methoxy group attached to the nitrogen atom, respectively. The α-hydrogen was also shifted downfield from δ5.67 to 5.92.

The coupling of the Weinreb amide (**52**) to the protected benzyl bromide species (**49**) required firstly the formation of the benzylmagnesium bromide reagent, and then secondly, reaction with the amide to give the ketone (**48**).

Magnesium turnings were activated using a catalytic amount of iodine, and a dilute solution of the benzyl bromide (**49**) in ether was added slowly over an extended period of time. High dilution procedures have been reported to give good yields of benzyl magnesium chlorides.[54] The Weinreb amide was added to the reaction, but after 17 h at room temperature the reaction was found to contain the Wurtz coupled product (**59**) (Scheme 20) in only 4%, as part of a complex mixture which also contained starting materials. This coupled product (**59**) showed a singlet at δ2.96, corresponding to the benzylic protons; these protons appeared as a singlet (2H) at δ4.53 in the benzyl bromide species (**49**).

Scheme 20

The formation of the Wurtz coupled product (**59**) (Scheme 20) is thought to proceed *via* a radical pathway.[55] The benzylic radical could potentially react with benzyl bromide (**49**) or with itself, to give the coupled species (**59**). It has been found that the available surface of active magnesium is a critical factor when considering the formation of (**55**), so that RMgBr is in competition with the magnesium surface for the benzyl bromide (**49**).[54]

Magnesium powder was used next in an attempt to avoid Wurtz coupling. The powder was activated further in an inert atmosphere by heating at >100° C for 30 min, affording a 'magnesium mirror' on the surface of the flask. The bromide (**49**) was added slowly at 0° C with high dilution. The amide was reacted over 1 h, but this time gave the coupled product in only 5.5% yield together with starting reagents. This reaction was repeated a number of times varying the dilution and reaction times, however the Wurtz product was obtained in all cases with no sign of the desired product (**48**).

In case the presence of the amide was causing the generation of the coupled product (**59**), it was substituted with benzaldehyde. Magnesium powder was again activated in an inert atmosphere over 18 h, and a catalytic amount of iodine was used. After the addition of benzaldehyde, the reaction gave a small amount of the protected cresol (**51**), a trace of the Wurtz product (**59**) and degradation products. As there was no sign of the required alcohol, it was thought the presence of the amide was not causing the formation of the Wurtz product.

Chloride was not used as the halide in these coupling reactions as it has been found to give side reactions, even though it was to a lesser degree than the benzyl

bromides.[54] Due to the formation of the undesired Wurtz product, focus was shifted towards the generation of the required ketone **(47)** through lithium organocuprate chemistry.

Lithium Organocuprate Chemistry.

Coupling *via* an acid chloride and a lithium organocuprate reagent commenced using phenylacetyl chloride as a model substrate for α-bromophenylacetyl chloride until the reaction methodology was established. This acid chloride was easily prepared from phenyl acetic acid and oxalyl chloride in dichloromethane.

The preparation of the protected benzyl lithium species **(57)** was firstly attempted using the traditional method of refluxing lithium wire with the benzyl bromide **(49)** in ether (presuming a 50% yield of the organolithium reagent).[62] Purified copper(I) iodide was added to the solution at 0° followed by phenylacetyl chloride. After 15 min reaction and work-up, Wurtz coupling was evident in the reaction mixture (15%), together with a complex mixture of products (t.l.c and ^{1}H n.m.r spectroscopy). This coupling reaction was repeated a number of times with great care, resulting in the formation of a small amount of the Wurtz product in all cases, together with starting materials.

Lithium naphthalene has been used in some cases for the generation of benzyl lithium reagents from benzyl halides that have been difficult to convert.[60] The particular solvent combination of diethyl ether-THF-hexane (4:3:1) has been found to give increased yields of the ketone and diminish the amount of Wurtz product. Lithium naphthalene was prepared accordingly (in this case presuming a 75% conversion of the organolithium reagent)[60] and the copper coupling reaction attempted using phenylacetyl chloride and the described solvent system. There was no sign of the required ketone and the residual naphthalene made the purification and identification steps difficult. No clearer results were obtained when the reaction was repeated.

The coupling reactions described so far have shown no sign of the required ketone **(48)**, even after most reactions were repeated a number of times. The direct cause

of this was hard to identify due to the reaction being multi-faceted and reliant upon conversions that cannot be proven or identified along the way.
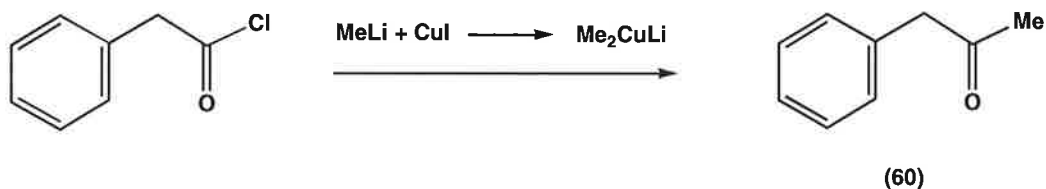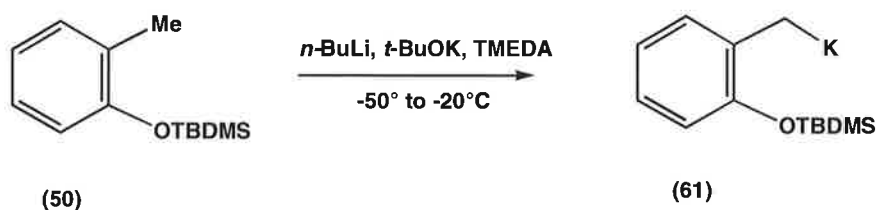

Scheme 21

The reaction of phenylacetyl chloride with the lithium dimethyl organocuprate (formed from methyl lithium), to form phenyl acetone (**60**) was investigated as a much simpler trial reaction in hope of revealing the step(s) that were causing the problems (Scheme 21).

The formation of methyl lithium was attempted in the first instance by reaction of lithium naphthalene and methyl iodide in THF at 0°C. This solution was added directly to dimethylsulfide-copper(I)bromide complex in dimethyl sulfide and ether, which has the advantage of being more stable than Cu(I)I. After the addition of phenyl acetyl chloride at -78°C, the reaction was shown to have not produced any phenyl acetone (**60**), only naphthalene, phenylacetic acid and other unidentifiable material when analysed by t.l.c and ^{1}H n.m.r spectroscopy.

The reaction (Scheme 21) was repeated using commercial methyl lithium. In this case phenyl acetone was obtained as yellow oil in 29% and was identified by a three-hydrogen singlet at $\delta 2.15$ and two-hydrogen singlet at $\delta 3.70$ α to the carbonyl group, in the ^{1}H n.m.r spectrum.[63] In phenyl acetyl chloride the methylene hydrogens appeared at $\delta 4.10$. When the lithium organocuprate was formed from commercial methyl lithium and copper iodide rather than the dimethylsulfide-copper(I)bromide complex, and reacted with phenylacetyl chloride as above, phenyl acetone (**60**) was again obtained as a yellow oil in 22%. From these results it can be deduced that the step causing the most problems in these copper-coupling reactions was the formation of the organolithium species, as two types of copper reagent have shown to give the required product when using

commercially available organolithium reagent. This problem was enhanced when synthesising benzylic lithium reagents due to their tendency to couple.

It is possible that the protected cresol (**50**) can be directly metalated using butyl lithium, potassium *t*-butoxide and TMEDA giving the benzyl organopotassium species (**61**) (Scheme 22). This type of reaction has been used previously on *O*-protected *o*-cresols to metalate the methyl group whereas using just butyl lithium-TMEDA resulted in ring-metallation.[64]

Scheme 22

The attempted formation of the organopotassium species (**61**), commenced using a 1:1 combination of butyl lithium and potassium *t*-butoxide. Such organopotassium species are known to be easily alkylated by reaction with alkyl halides.[64] Addition of phenyl acetyl chloride to the benzyl potassium reagent (**61**), gave only starting *O*-protected cresol and phenyl acetic acid. Repeating the reaction again with the addition of copper(I) iodide gave similar results. The absence of Wurtz coupled product suggests that the benzyl organopotassium species may not have been formed. Alternatively, the organopotassium species may have formed and then became protonated under the conditions described, which may account for the presence of the starting protected cresol (**50**) in the reaction mixture.

As the reactions leading to the formation of the organopotassium species gave poor results, the formation of a benzylic lithium species was attempted using the protected cresol (**50**) under similar conditions. The *ortho* protected ether may offer advantages to the generation of the benzylic lithium species as a five membered chelate may be formed. The protons on the methyl group are more acidic than the ring protons, allowing for preferential metalation.[65] The metalation was conducted using a 4:1 combination of butyl lithium and TMEDA in hexane, respectively. This combination gave a precipitate [the complex (**62**)] on standing at room temperature for 15 min.[65]
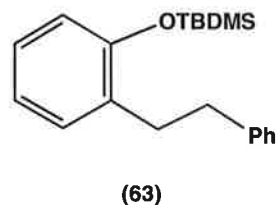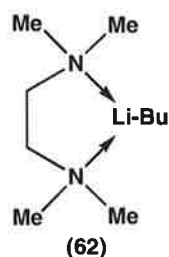
This complex has been used to increase the reactivity of the butyl lithium allowing metalation to occur more rapidly, selectively and with increased yields.[65] After the addition of the protected cresol (**50**) to the complex (**62**), the solution was stirred for 3.75 h, in which time a precipitate had formed.[65] Addition of phenylacetyl chloride and work-up yielded mainly starting cresol (**50**). The reaction was repeated giving the same results.

When the above reaction was quenched with benzyl bromide rather than phenylacetyl chloride, the starting cresol was obtained again in lesser yield than before. A significant amount of benzyl bromide was still present in the ^{1}H n.m.r spectrum, together with two new signals at $\delta 2.90$ and 2.93. These signals may be caused by the two-methylene groups of the desired product (**63**). However, due to the low yield suggested by the ^{1}H n.m.r spectrum of the crude, complex mixture, efforts were not made to isolate this potential product (**63**).

(III)   Conclusions

The formation of benzylic Grignard and organolithium species has hindered the progress of the proposed synthetic routes outlined in this chapter. In both cases the only product isolated aside from starting materials, was the coupled 'Wurtz' type product, and in small amounts. Trial reactions have shown that the copper reagents were not the cause of these disappointing results, again suggesting that the benzyl lithium formation was difficult to achieve. Thus the synthesis of the ketone (**47**), as a precursor to the catechin series, was unsuccessful using Grignard reactions with Weinreb amides and lithium diorganocuprate coupling reactions, even after a number of attempts at each reaction. As a result, other ways of synthesising the epicatechin series were attempted as described in Section B.

Chapter 5: Investigation into the Synthesis of Epicatechins, Section B.

(I)   Introduction

The synthesis of **EC** precursors, more specifically **EGC** precursors, *via* 3-oxoflavans as outlined in Section A of Chapter 5, could not be achieved. Therefore instead of forming 3-oxoflavans, the direct synthesis of racemic **EC** and **EGC** precursors was investigated, using methodology which would still allow gallo- substitution to be incorporated in the B-ring of the epicatechin molecules. Again this method aims to synthesise all the epicatechin derivatives **EC (2)**, **EGC (3)**, **ECG (4)** and **EGCG (5)** in substantial yield, which to this date has not been described in the literature.

This section of Chapter 5 describes the results from other approaches to the synthesis of epicatechin molecules (Scheme 23). Two synthetic routes were investigated that had the potential to generate racemic catechins (**Route A**) or racemic epicatechins (**Route B**). The methodology developed in Chapter 4 allowed the conversion of racemic catechin derivatives (**Route A**) to racemic epicatechin derivatives, and thus the gallate ester derivatives. The formation of racemic *trans* epoxides (**Route A**) would afford racemic catechin mixtures assuming a nucleophilic cyclisation reaction.[66,67]   Conversely, the generation of racemic *cis* epoxides (**Route B**) would allow the direct formation of racemic epicatechin derivatives, again provided the opening of the epoxide is by a S_N2 mechanism. The critical step in both these routes is the allylation of phloroglucinol or the acylation of a phloroglucinol derivative to give a *trans* or *cis* alkene, which would eventually determine whether racemic catechins or epicatechins are formed.
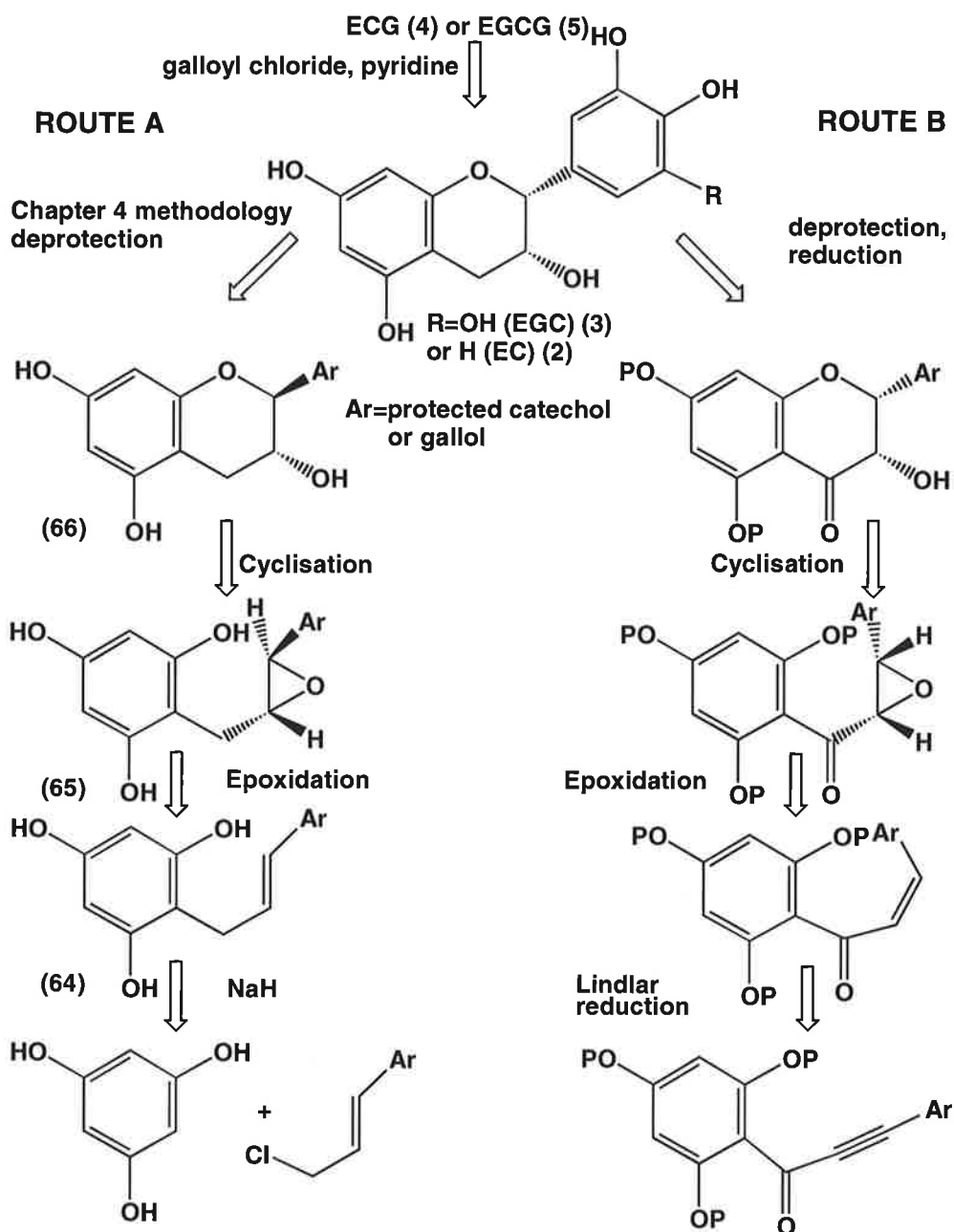
Scheme 23

Route A

A simple way of affording the *trans* alkene (**64**) may be by the allylation of phloroglucinol with cinnamyl chloride (Scheme 23), using procedures developed for similar compounds.[68] The racemic *trans* epoxide (**65**) may then be generated using a variety of epoxidation reagents, including (but not limited to) dimethyldioxirane, halohydrins and peroxyacids.[69,70] The *trans* geometry of the racemic epoxide mixture should be maintained by an S_N2 opening of the epoxide under basic conditions,[66] using a phenolate anion. The partial S_N1 nature of the intermediate

imposed by using acids may cause the formation of other undesired stereoisomers (*cis*) through generation of a carbocation,[66] complicating the reaction mixture. The racemic catechin molecules (**66**) may then be oxidised, and stereoselectively reduced (Chapter 4) to furnish the required racemic epicatechin derivatives.

The Synthesis of Allylphenols (Route A).

O-Allylation and rearrangement (Claisen Rearrangement) or direct *C*-allylation has been used to achieve the alkylation of phenolic compounds to form allylphenols.[68] The substituted allylphenols, formed from reaction with cinnamyl or crotyl chloride, can be prepared by *C*-allylation more easily than the allyl compounds without substituents in the allyl group, as the more reactive substituted allyl halides gives rise to more *C*-allylation than *O*-allylation.[68] For instance, 2-cinnamylphenol (**67**) can be made from the *C*-allylation of phenol with cinnamyl chloride in 60%.[68]

| (67) | (68) | (69) |
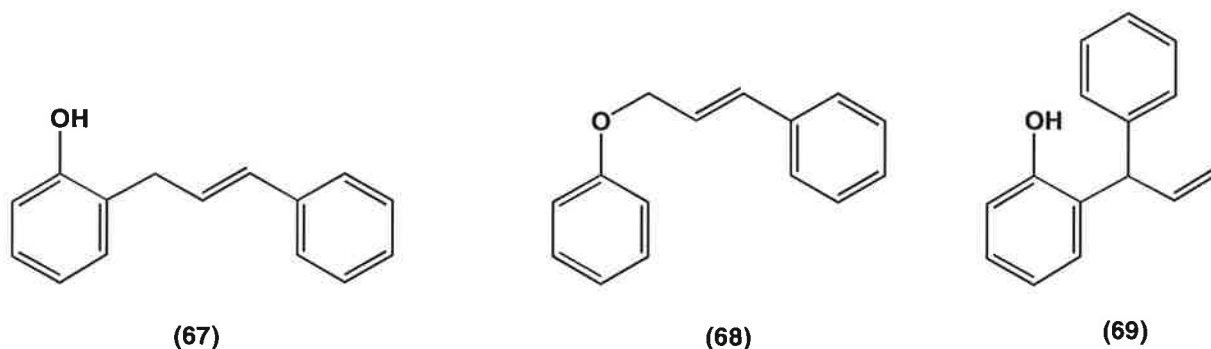
The compound (**67**) cannot be made from by the rearrangement of the γ-substituted allyl ether (**68**), as this compound yielded (**69**) by inversion.[68] Aromatic *C*-allylation reactions are an important means of generating carbon-carbon bonds and have been used with phytyl bromide in the synthesis of vitamin K.[68] As *C*-allylation predominates over *O*-allylation when using more substituted and reactive allyl halides such as cinnamyl chloride, this reaction should provide the *trans* alkene (**64**) readily.

(II)   Results and Discussion

Route A.

Attempts to form the cinnamyl phenol (**64**) commenced from the reaction of phloroglucinol with sodium hydride and cinnamyl chloride (Scheme 24). Cinnamyl chloride was used as a model to study the allylation reaction.
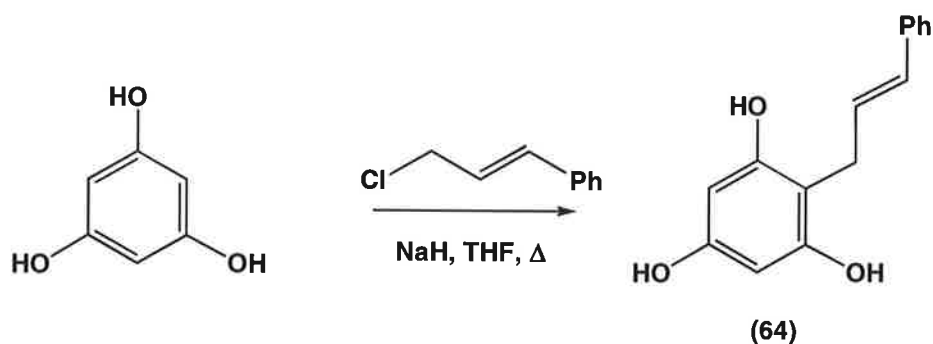
Scheme 24

The first procedure investigated was that used for the synthesis of *trans*-2-cinnamylphenol.[68]. After refluxing a solution of one equivalent of sodium hydride and cinnamyl chloride for 19 h, a yellow oil was isolated after column chromatography, that was identified as the di-adduct (**70**), in 15% yield.
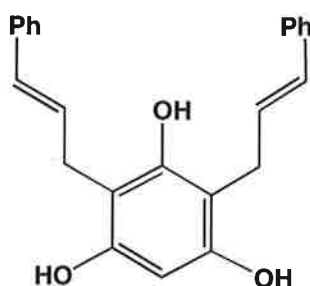
(70)

The di-adduct (**70**) was identified by a one hydrogen signal at $\delta 6.03$ in the ^{1}H n.m.r spectrum, which corresponded to the aromatic hydrogen of the phloroglucinol ring. This signal integrated to one hydrogen, not three compared to phloroglucinol, suggesting diallylation of the carbon atoms rather than the oxygen atoms. A strong molecular ion at *m/z* 358 confirmed that diallylation had occurred. The ^{1}H n.m.r

spectrum also revealed a doublet of triplets at δ6.33 with coupling of 6.3 Hz and 15.9 Hz, representing the α-hydrogen. The β-hydrogen of the alkene showed a doublet at δ6.5 (*J*=15.9 Hz), whilst the methylene protons appeared at a doublet at δ3.55 (*J*=6.3 Hz). The large coupling values of the alkene hydrogens confirmed the stereochemistry of the cinnamyl alkene group as being *trans*. The product was again confirmed as being the *C*-alkylation product rather than the *O*-alkylation product by looking at the position of the methylene carbon of the side chain in the [13]C n.m.r spectrum, which appeared at δ27.45, indicating it was attached to a carbon atom rather than oxygen.

The reaction was repeated at room temperature but gave the same mixture of products as was found for the reaction at reflux for 19 h, except in different amounts. In this case, careful t.l.c analysis revealed that the reaction contained (in order of decreasing Rf) cinnamyl chloride, the di-adduct (70), an unknown spot and phloroglucinol all in approximately the same amounts. The unknown spot was isolated by column chromatography, and tentatively assigned by [1]H n.m.r to be a mixture of either the product (71) or (72), and the required mono-adduct (64). The product (71) may have formed by *O*-allylation and Claisen rearrangement or S_N2' attack on the double bond of cinnamyl chloride, whilst the product (72) could only have formed by S_N2' attack on the double bond of cinnamyl chloride.

(71)   (72)   (64)
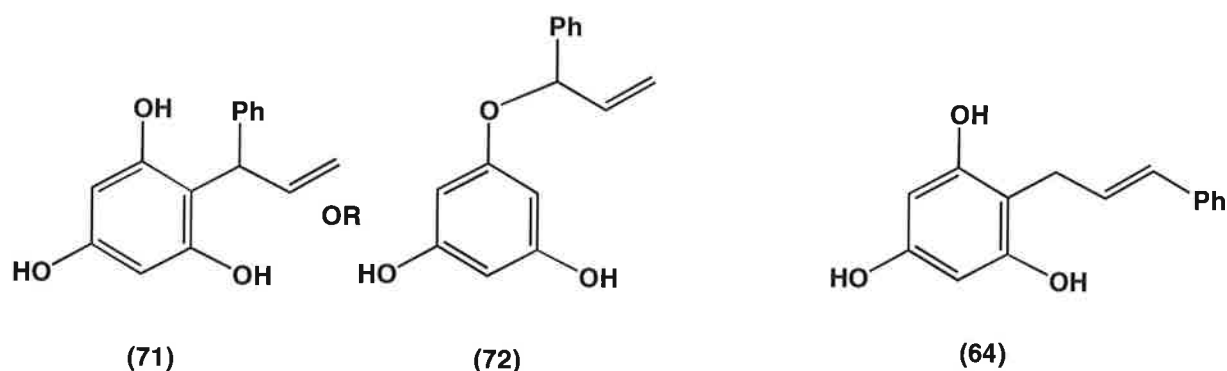
The signals in the [1]H n.m.r spectrum for (71) and (72) were hard to resolve as they were contaminated with the required *C*-allylated mono-adduct substructure (64), but did reveal a group of signals at δ5.02-5.34, which suggest terminal alkene protons. In addition a multiplet at δ6.29 was present which may be attributed to the non-terminal alkene hydrogen of the chain. The position of this multiplet in the [1]H n.m.r spectrum was not distinct enough to distinguish between the two products

(71) and (72).[71] The ^{1}H n.m.r spectrum also showed a singlet at δ5.93, suggesting two aromatic hydrogens on the substituted rings of the terminal alkene product (71) and/or (64), and possible mono-alkylation of both products. However, due to the complicated ^{1}H n.m.r spectrum, this singlet could not be used to distinguish between (71) and (72), as the spectrum may contain non-symmetrical aromatic signals indicating three protons and thus suggesting (72) over (71). The presence of a doublet at δ3.45 was attributed to the *C*-allylated product (64) by comparison with the data of the di-adduct. There appeared to be no other similar doublets in the spectrum, suggesting the absence of an *O*-allylated cinnamyl ether. The gas chromatograph trace of this fraction revealed two products of mass 242, which showed different mass losses but could not be used to identify the products further. These spectra did however suggest that the unknown product was an isomer to the *C*-allylated mono-adduct (64), however together with the combined spectral data, it was not possible to distinguish if this isomer was (71) or (72). Repeating the allylation reaction using different solvents such as THF or less than one equivalent of sodium hydride did not improve the results.

As the *C*-allylation reaction gave what was suspected to be substantial Claisen rearrangement,[68] focus was turned to preparing the cinnamyl phenol (64) from an initial reaction between phloroglucinol and (1-chloroallyl)benzene (Scheme 25).
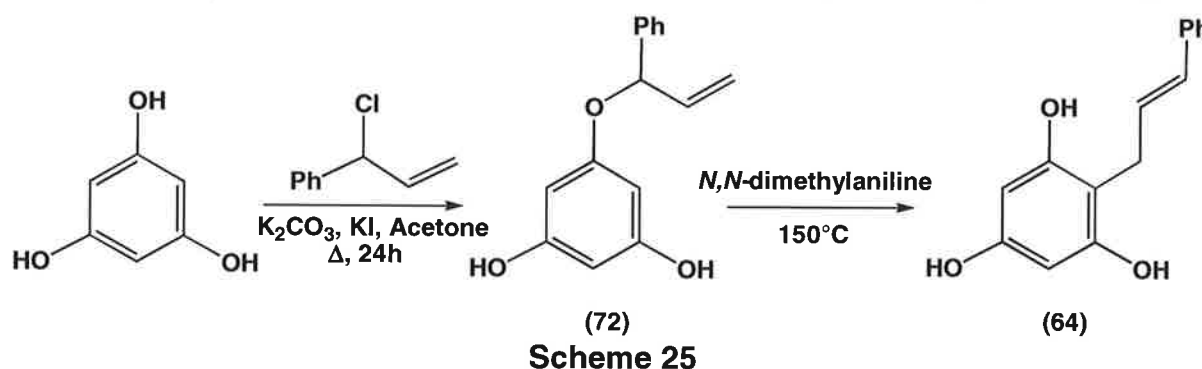
Scheme 25

(1-Chloroallyl)benzene was prepared by isomerisation and chlorination of cinnamyl alcohol using thionyl chloride in ether at $0°$C for 1 h.[72] The yellow oil obtained was used directly in the   reaction (Scheme 25), however an aliquot of the initial mixture of (1-chloroallyl)benzene was found to contain a 5:1 mix of cinnamyl chloride to (1-chloroallyl)benzene (^{1}H n.m.r). The phenol ether (72) was not purified but

heated at 150°C with *N,N*-dimethyl aniline as solvent for 4 h to give a purple oil that appeared as multiple products by t.l.c. Purification was attempted using column chromatography, yielding four fractions that were still impure, one of which contained cinnamyl chloride. These fractions all contained complex mixtures indicated by multiple signals in the ^{1}H n.m.r spectra, none of which showed the presence of the required product (**64**). The complex spectra are a possible result of side reactions caused by the use of impure (1-chloroallyl)benzene. Another reason may be that S_N2' addition to (1-chloroallyl)benzene may occur (Scheme 26) rather than direct displacement of chlorine (Scheme 25). This could then give the rearrangement product (**71**). This type of S_N2' reaction may also occur on the cinnamyl chloride impurity, further complicating the reaction mixture.
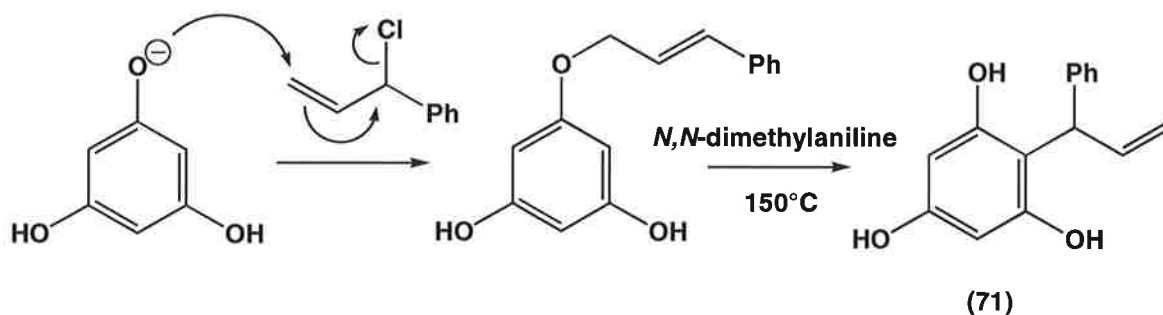
Scheme 26

These methods of forming cinnamyl phenols all resulted in unwanted products, such as the di-adduct (**70**) and complex mixtures. The mono-adduct (**64**) was only obtained in low yield in an impure fraction. These results were disappointing and it was decided that another method of synthesising epicatechin precursors should be investigated.

(III)   Introduction, Route B.

The synthesis of epicatechin precursors, especially the gallo- group of epicatechins, might also be achieved *via* the reactions outlined in **Route B** (Scheme 27). This route was now considered due to the disappointing results obtained from **Route A** (Scheme 23).
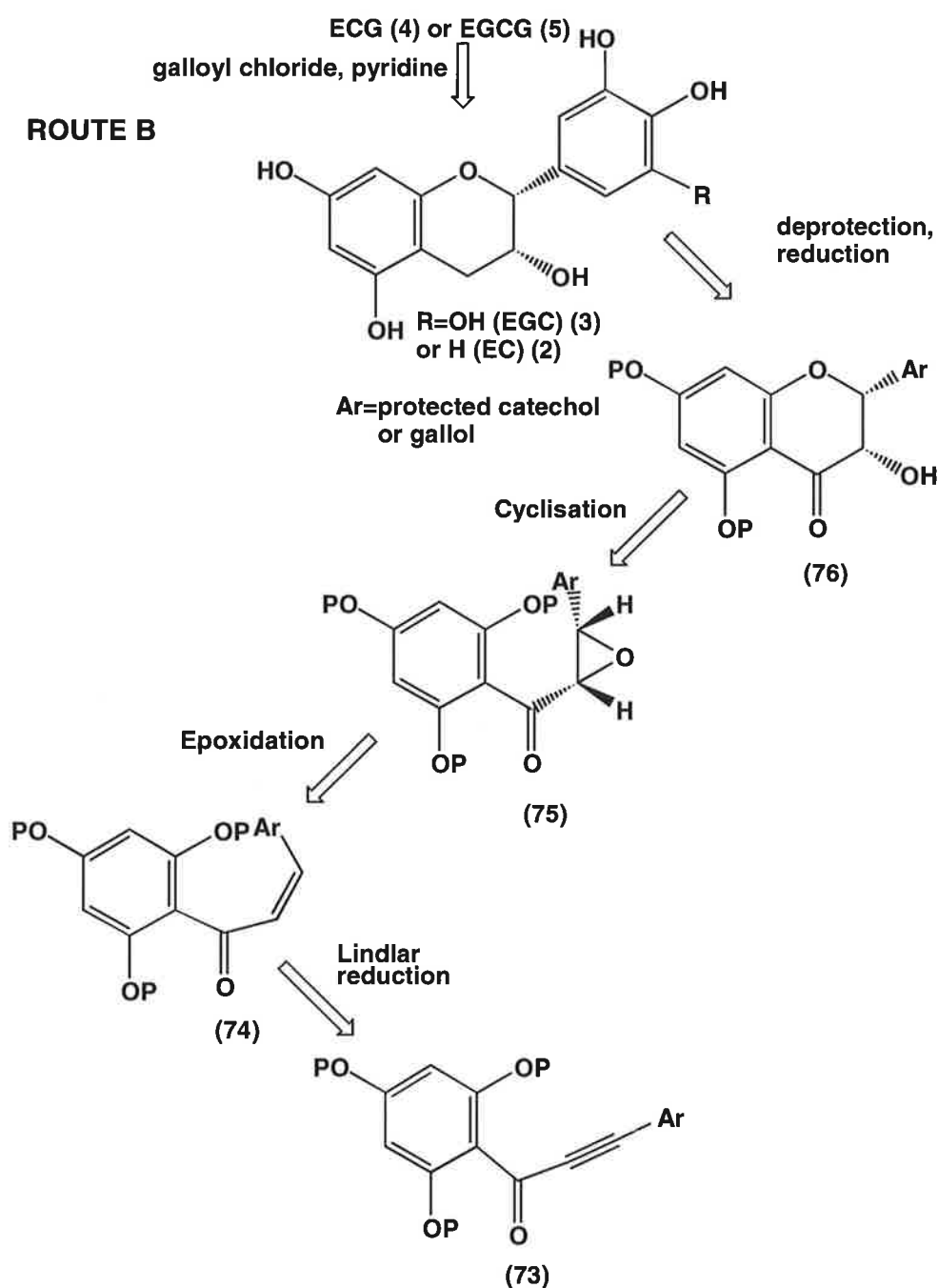
Scheme 27

Acylation reactions are one of the most common methods for preparing aryl ketones,[73] and should furnish the acetylenic ketone (73) from the reaction of a protected phloroglucinol derivative with a propiolic acid derivative. α, β-Acetylenic ketones such as (73), are valuable synthetic intermediates because of their potential conversion into a variety of different compounds.[69,74,75] In this case the acetylenic ketone (73) is of great importance as the alkyne may be partially reduced under Lindlar conditions[76] to give the *cis*-alkene (74), which is the basis for forming racemic epicatechin derivatives rather than racemic catechin derivatives (**Route A**). Thus racemic *cis* epoxides (75) may be formed from epoxidation of the alkene (74). The use of an enantioselective epoxidation reagent may aid in selectively obtaining one enantiomer.[66,77] Cyclisation and ring opening of the epoxide (75) should then give the *cis* flavanonol (76), which may then be easily reduced using sodium cyanoborohydride[48] to give the racemic epicatechin derivatives. **EC** (2) and **EGC** (3) may be obtained after deprotection of the phenolic groups, and may then be used to give **ECG** (4) and **EGCG** (5) using the esterification reaction refined in Chapter 4.

The acetylenic ketone (73) may be generated from acylation reactions using either route 1 or 2 as shown in Scheme 28.
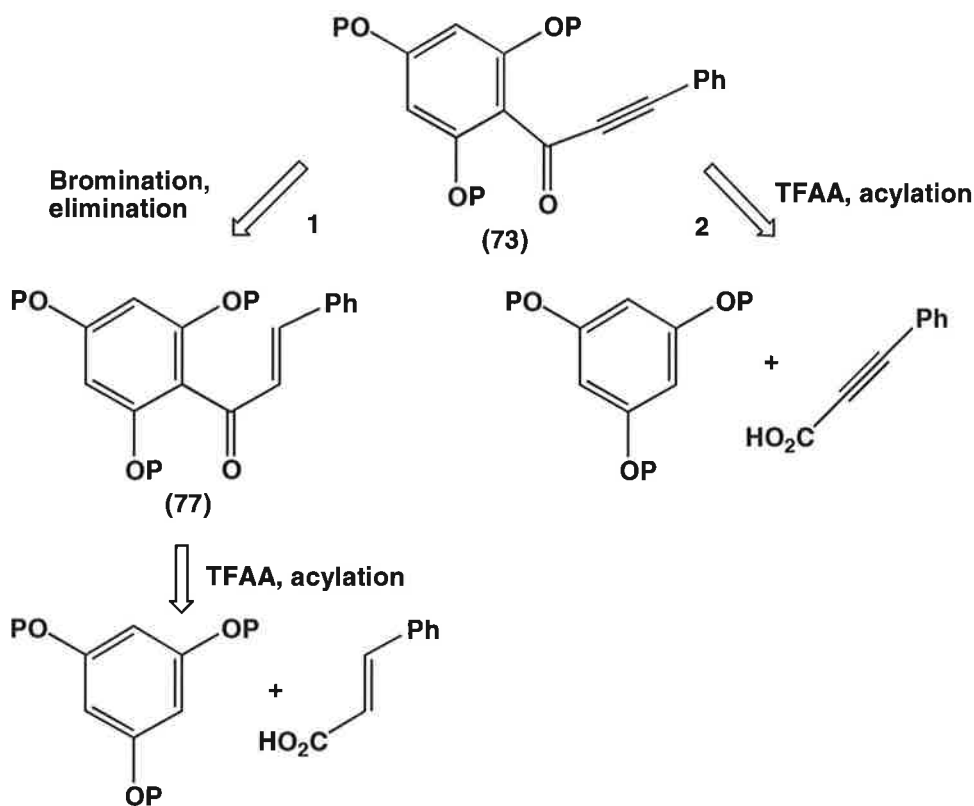
Scheme 28

The chalcone (**77**) may be synthesised by an acylation reaction between a protected phloroglucinol derivative and a substituted cinnamic acid.[50] Formation of an α, β-dibromide derivative followed by elimination of two molecules of hydrobromic acid should then give the alkyne (**73**) according to pathway 1. The alkyne (**73**) may be synthesised directly, using a similar acylation reaction with substituted phenylpropiolic acids, according to pathway 2.

Preparation of acetylenic ketones (Route B).

Acetylenic ketones have been prepared from the acylation of phenylpropioyl chloride and aluminum chloride with di- or tri-hydric phenols.[78] The reaction with anisole gave the acetylenic ketone (**78**) in 20% and a small amount of the β-chloro adduct (**79**)[78]. The adduct (**79**) was formed by the addition of hydrochloric acid (generated during the reaction) across the triple bond. Johnston and co-workers also found that as the reactivity of the aromatic compound towards electrophilic substitution increased, so to did the yields of both ketones.[78]

(78)   (79)
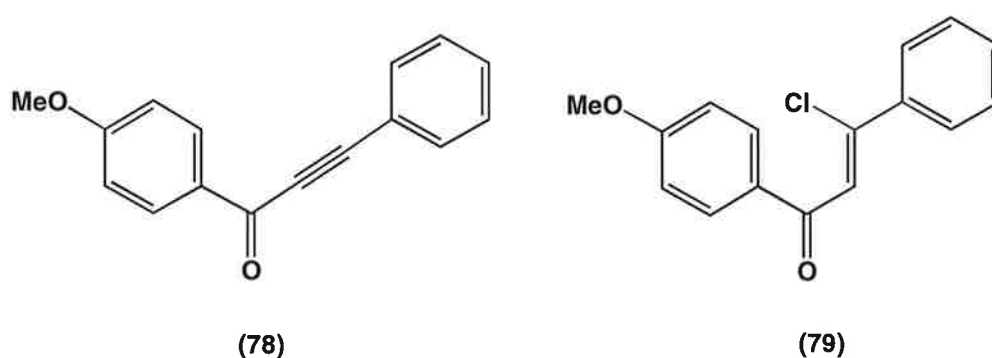
The recommended procedure for the Friedel-Crafts acylation calls for a little more than one mole of aluminum chloride per mole of acyl halide.[73,79] It has also been shown that the reaction can proceed satisfactorily with a small amount of aluminum chloride (or any catalyst) or none at all.[80] This variation required that the aromatic system be sufficiently activated and that the temperature be sufficiently high when using small amounts of catalyst, to ensure hydrochloric acid evolution is rapid and the ketone-catalyst complex can dissociate.[80]

Acid anhydrides have been used for many years to promote the condensation of carboxylic acids with aromatic compounds.[81] The interaction between the anhydride and acid forms a mixed anhydride. Phosphorus pentoxide, *o*-nitrobenzoic anhydride, monochloroacetic anhydride and most commonly trifluoroacetic anhydride have all been used to form mixed anhydrides with success.[81] The types of aromatic compounds that can be acylated by this method are limited, as the aromatic ring must be sufficiently activated, such as in phenol, furans and polyalkylbenzenes.[81]

α, β-Acetylenic ketones have been prepared by methods other than acylation, however there is limited information describing the preparation of acetylenic ketones containing phloroglucinol style substitution of the aromatic rings. For example lithium acetylide gave the acetylenic ketone (80) in 91% yield, upon condensation with 2-hydroxybenzaldehyde, followed by oxidation (Scheme 29).[82]

(80)
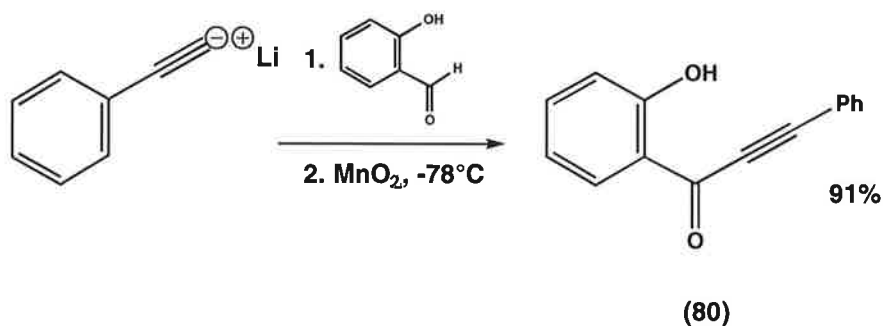
Scheme 29

A different method that allowed the incorporation of more substitution in the acetylenic ketone **(81)**, was the condensation of phenylpropiolic acid with the phenol **(82)** by means of *N,-N'*-dicyclohexylcarbodiimide using pyridine as a solvent, which gave the ketone **(83)** in 92% (Scheme 30).[83] A photo-Fries rearrangement of this compound gave the acetylenic ketone **(81)** in 30% yield.[83]

(82)   **(83)**

(81)
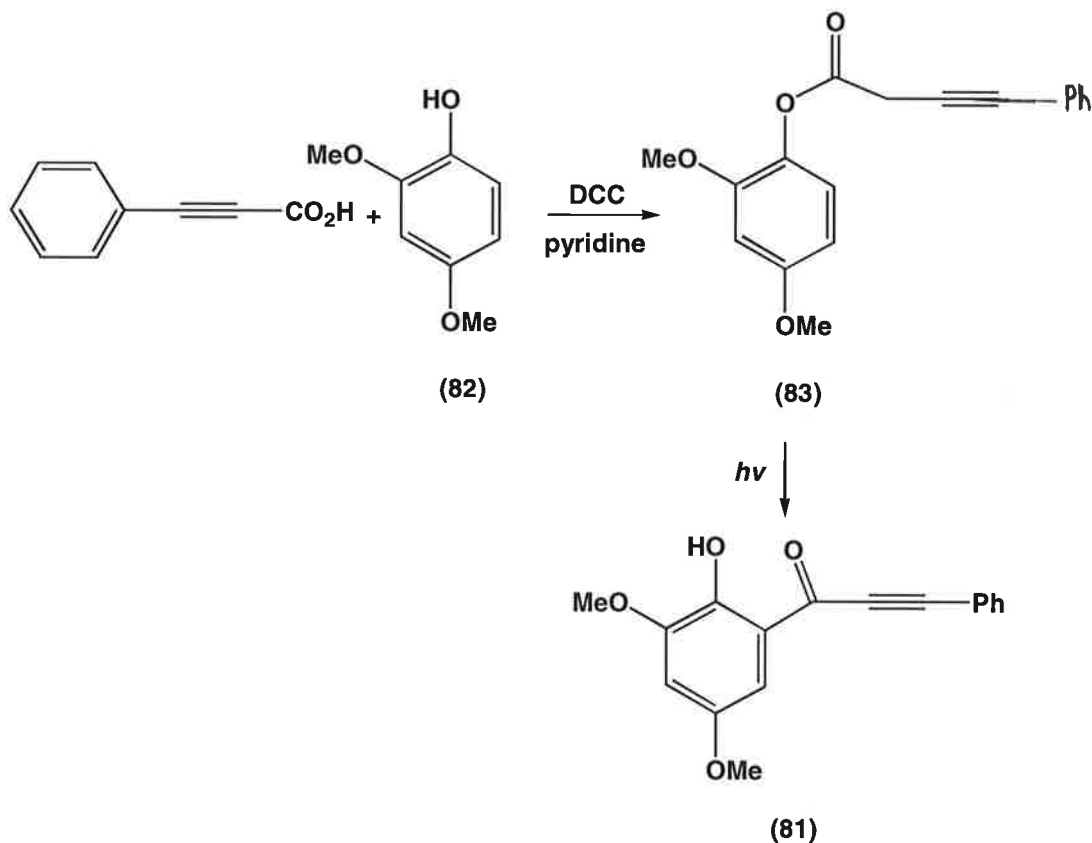
Scheme 30

Another method used to generate the ethynyl ketone **(84)** is outlined in Scheme 31.[84] This method has been used to generate substituted oxygen, sulfur, selenium and

tellurium containing acetylenic ketone derivatives,[84] but does not describe the incorporation of further aromatic substitution in the ketone (**84**).

(**84**)
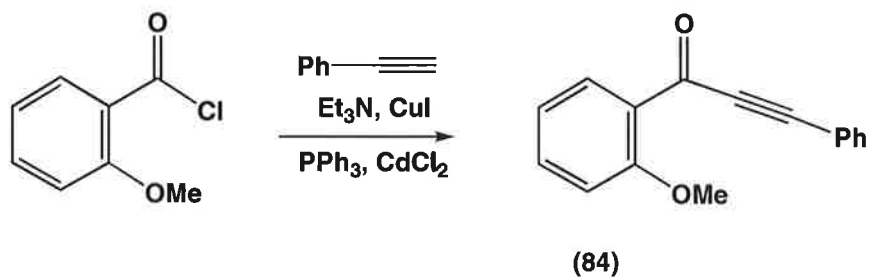
Scheme 31

(IV) Results and Discussion

Route B.

Pathway 1.

The synthesis of the acetylenic ketone (73) commenced with acylation of the readily available cinnamic acid derivatives according to pathway 1 (Scheme 28).
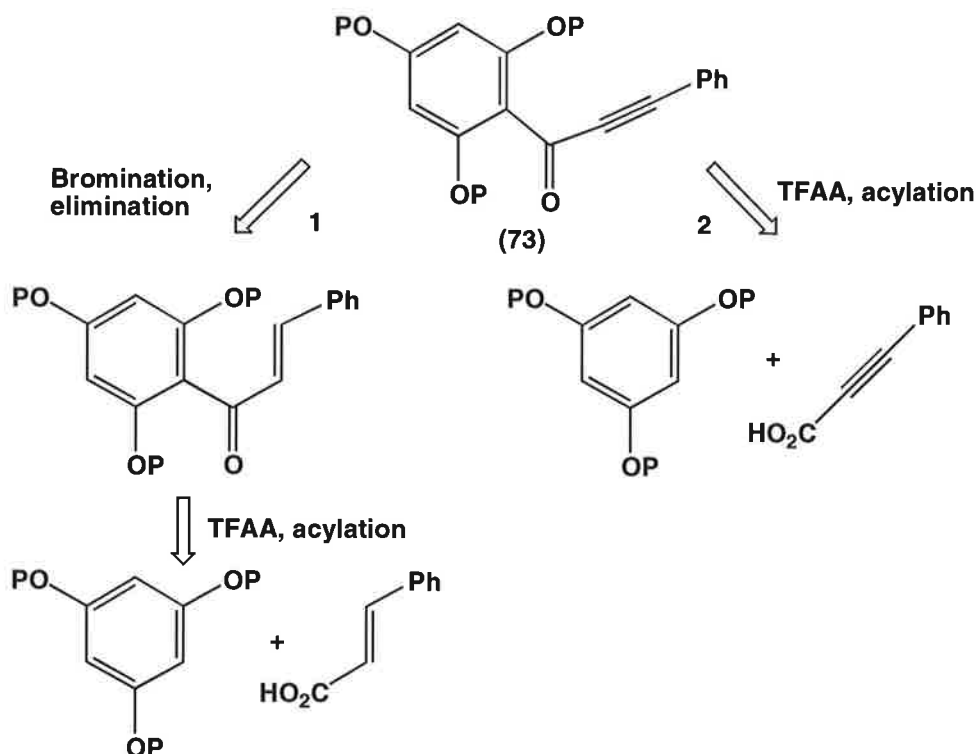
Scheme 28

Initial investigation into the acylation reactions were conducted using trimethoxybenzene due to the simplicity of its n.m.r spectrum and tribenzyloxybenzene as the benzyl groups could be cleaved (at an appropriate stage) much more readily than the methyl groups. Tribenzyloxybenzene (85) was formed from phloroglucinol using a literature procedure (Scheme 32).
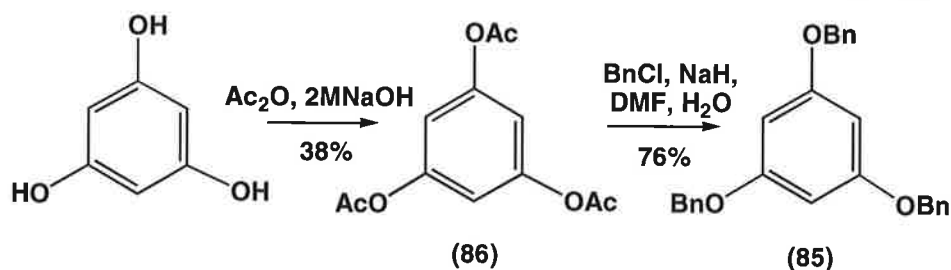
Scheme 32

Previously, attempts to directly benzylate activated rings such as phloroglucinol or systems such as catechin,[7,85] have resulted in the *O*-benzylated product being contaminated by substantial amounts of the *C*-benzylated product. In the case of phloroglucinol, this provided a product that could not be efficiently separated from the *O*-benzylated product.[85] Using acetate groups such as in the structure (**86**), helped to withdraw electron density from the aromatic ring and prevent *C*-benzylation.[85] This method is based on simultaneous benzylation with the partial hydrolysis of phloroglucinol triacetate (**86**).[85]

The acylation reactions were conducted as outlined in Scheme 33.

P=Me, 19% (**87**)
P=Bn, 32% (**88**)
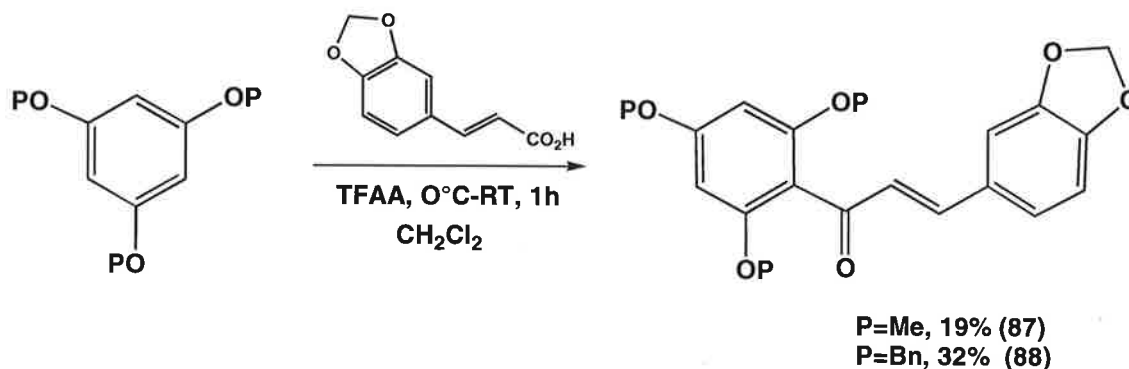
Scheme 33

Methylenedioxycinnamic acid (which can be regarded as a protected diol derivative of cinnamic acid) was used initially, because of its availability, to investigate the acylation step. The mixed anhydride formed between the acid and trifluoroacetic anhydride, was the principal acylating agent. Addition of the protected phloroglucinol to a mixture of the cinnamic acid and trifluoroacetic acid at 0°C, and stirring at room temperature for 1 h gave the required substituted chalcones (**87**) and (**88**) in 19% and 32% respectively. The yield for the trimethoxy chalcone (**87**) was low, as much

of the starting trimethoxybenzene was not consumed. The t.l.c was clearer for the benzyloxy species (**88**), but there still appeared to be a reasonable amount of starting material remaining (which was not consumed in the reaction). The formation of the trimethoxy compound (**87**) was confirmed by a molecular ion at *m/z* 342. The methoxy signals in the ^{1}H n.m.r had changed from one singlet (9H) to two singlets at δ3.76 (6H) and 3.85 (3H) suggesting that the trimethoxybenzene ring had been mono substituted. The two aromatic protons on this ring appeared as a singlet at δ6.16. The methylene protons from the methylenedioxy group gave a two-hydrogen singlet at δ5.99. The two alkene protons showed *trans* coupling of 16.1 Hz and appeared at δ6.79 (α) and 7.28 (β). The ^{13}C n.m.r spectrum showed a carbonyl signal at δ198.52. Similarly, the tribenzyloxy chalcone (**87**) showed a molecular ion at *m/z* 570 in its mass spectrum. The methylene protons of the benzyl group appeared as two singlets at δ4.96 (2H) and δ5.03 (4H) in the ^{1}H n.m.r spectrum suggesting a lowering of symmetry in the tri-substituted ring and that it had been acylated. The α-alkene proton appeared at δ6.82 (*J*=15.9 Hz) whilst the β-proton was hidden under the aromatic hydrogen multiplet (δ7.23-7.38) of the benzyl phenyl groups. The methylene protons from the methylenedioxy group appeared as a singlet at δ5.93. The carbonyl group gave a signal in the ^{13}C n.m.r spectrum at δ194.45.

Formation of a dibromide should allow a direct route to the alkyne (**89**) or (**90**), as outlined in Scheme 34. However, attempts at brominating the substituted chalcones (Scheme 34) using a variety of procedures, gave disappointing results.
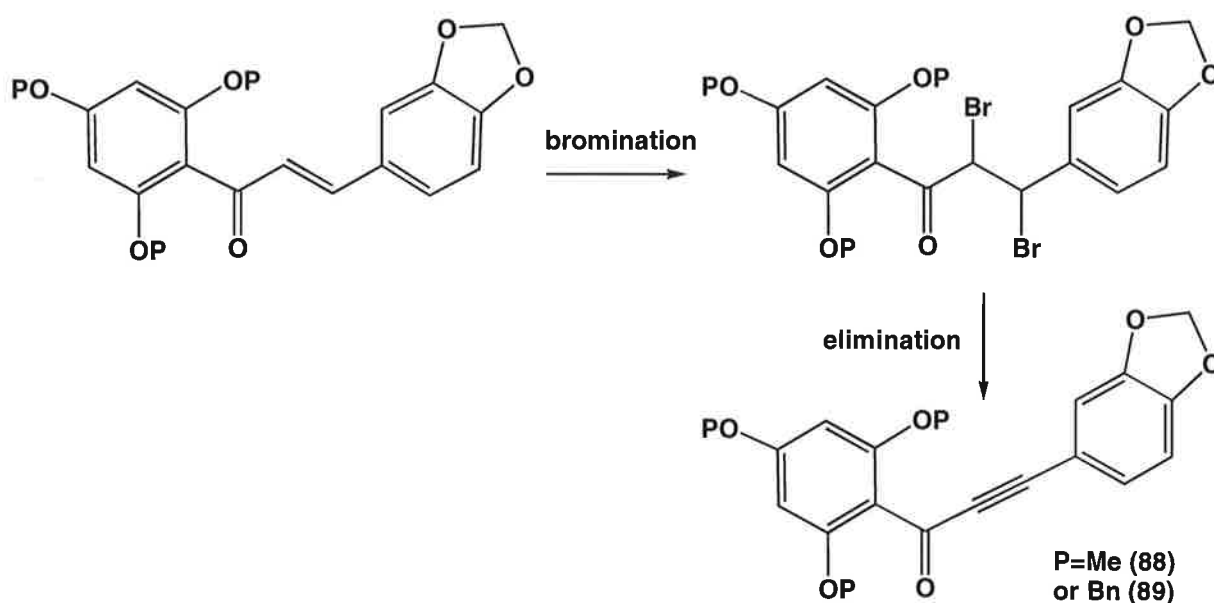
Scheme 34

The major product from a reaction of two equivalents of a bromine solution and the trimethoxy-substituted chalcone (**87**), in carbon tetrachloride at room temperature in the absence of light, was the tribromide (**91**).

(91)
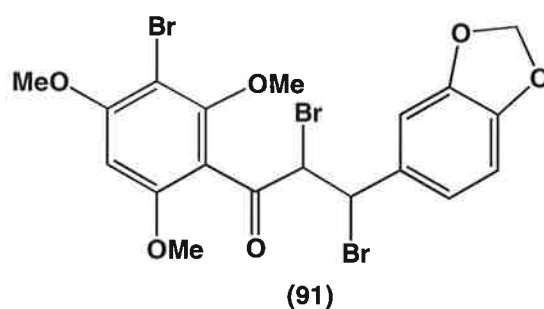
Two doublets at $\delta 5.49$ and 5.70 in the ^{1}H n.m.r spectrum, both with a coupling constant of 11.1 Hz, were assigned to the α and β protons respectively. The only aromatic hydrogen signal for the trimethoxy substituted ring was at $\delta 6.36$. The three-methoxy groups on this ring appeared at $\delta 3.93$ (3H) and 3.96 (6H), which was different to the corresponding signals of the starting chalcone (**87**) that appeared at $\delta 3.76$ (6H) and 3.85 (3H). Mass spectral analysis of the tribromide (**91**) was inconclusive. Recrystallisation of this material from ethanol gave a solid that showed signals from a new product together with the one just described. The filtrate contained only the new product, which possibly had one of the two adjacent bromine groups substituted for an ethoxy group. This suggestion was in agreement with the FAB mass spectrum, which gave strong molecular ions at m/z 545/547/549. The

^{1}H n.m.r spectrum showed ethoxy signals at δ1.06 (triplet) and 3.83 (quartet), with integration suggesting one ethoxy group. The spectrum showed one aromatic proton at δ6.35 suggesting the trimethoxy substituted aromatic ring was substituted five times, possibly with one bromine atom. The new product showed two doublets at δ4.73 and 5.02, with a coupling constant of 9.6 Hz that were likely to be the α and β protons respectively, compared to the corresponding signals at δ5.49 and 5.70 in (**91**). The methoxy protons appeared as two singlets at δ3.90 (6H) and 3.96 (3H). Further analysis of the products obtained could not be made due to decomposition as a result of further attempts at purification. Additional mass spectral analyses (FAB and GCMS) were largely inconclusive. The ethoxy-substituted product obtained in the residue was reacted with potassium-*tert*-butoxide in hope of causing elimination and forming the alkyne (**89**). This reaction however gave an extremely complex mixture of products when viewed by ^{1}H n.m.r, which showed numerous methoxy and aromatic signals.

Bromination of the chalcone (**87**) using one equivalent of bromine in acetic acid gave a product that appeared as multiple spots by t.l.c, and contained numerous methoxy signals in the ^{1}H n.m.r. The spectrum did not contain a signal at δ6.16, the value at which the aromatic protons at position-three and five appear, suggesting ring bromination had occurred. Attempts at purification of the complex product mixture were unsuccessful.

The bromination of the tribenzyloxy substituted chalcone (**88**) was attempted using a solution of bromine in carbon tetrachloride in a similar manner to that used for the trimethoxy substituted chalcone (**87**). The reaction gave many products when viewed by t.l.c and a ^{1}H n.m.r spectrum that contained many benzyl peaks suggested a complex mixture. Chromatography was unsuccessful in resolving the heterogeneous mixture.

Bromination of the tribenzyloxy substituted chalcone (**88**) using one equivalent of bromine in acetic acid gave a mixture of products (t.l.c) and a complex ^{1}H n.m.r spectrum.

The general tendency to form multiple products in most of these reactions may be due to aromatic halogenation, of either ring as well as hydrobromic acid and bromine addition to the double bond.[86] These results show that the formation of the dibromide may not be straightforward. Accordingly attention was turned to the alternate possibility involving Friedel-Crafts acylation using a substituted propiolic acid (pathway 2).

Pathway 2, Acylation reactions using a mixed anhydride formed from a propiolic acid.

P =Me (92)
P =Bn (85)   **R =H or OMe**
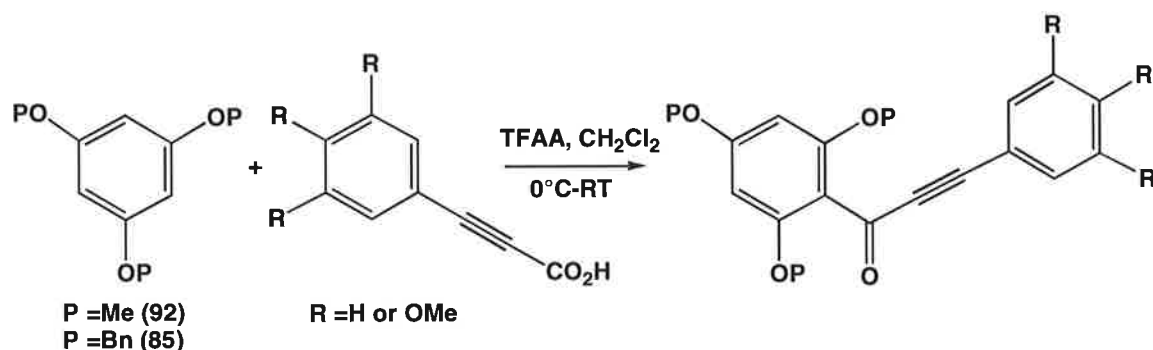
Scheme 35

The acylation of a propiolic acid derivative with an aromatic nucleus has not been described previously using a mixed anhydride (Scheme 35). The acylation of trimethoxybenzene (**92**) using phenylpropiolic acid (to establish methodology) and trifluoroacetic anhydride gave a dark purple solution instantly upon addition of the substituted benzene to a solution of the mixed anhydride at $0°C$. The reaction yielded a small amount of starting material (**92**) and the alkene (**93**) in 66% yield.

(93)
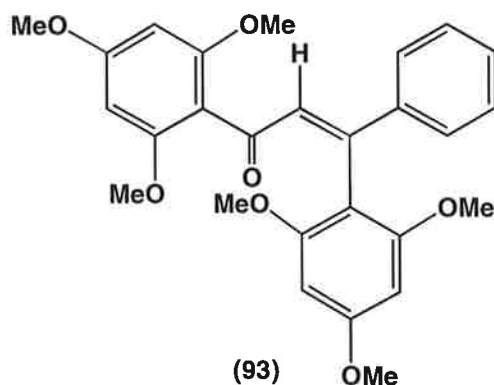
The ^1H n.m.r spectrum of the alkene (**93**) showed a one proton singlet at $\delta 6.99$ due to the α-hydrogen. Four singlets in the region $\delta 3.56$-3.78 (a total of 18 hydrogens),

supported the presence of six methoxy groups. In the ^{13}C n.m.r spectrum there were no acetylenic carbon signals in the region δ80-100, but instead there were signals at δ130.94 and δ144.38 due to the alkene α and β carbons respectively.[71] The ROESY spectrum showed correlation of the α-hydrogen to the phenyl protons, strengthening the proposed structure and stereochemistry. The α-hydrogen also showed correlation in the HMBC spectrum with the carbonyl carbon, the β-carbon (weak), the quaternary carbon on the phenyl ring, and the two quaternary carbons on the substituted methoxy rings (Table 4, figure 4). This suggested that the second trimethoxy benzene group had not added to the α-carbon of the alkene or the carbonyl group.

Table 4: 600 MHz n.m.r C-H correlations for the α-hydrogen of the chalcone (93).

Signal	^{1}H	^{13}C (HMQC)	^{13}C (HMBC)
	δH	δC	δC
α-hydrogen (alkene)	6.98	130.94	108.99 (quaternary carbon-methoxy benzene), 113.70 (quaternary carbon-methoxy benzene), 140.78 (quaternary carbon-phenyl), 144.38 (β-C), 192.39 (C=O)
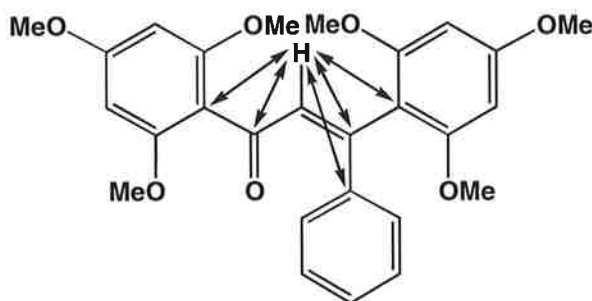
Figure 4: HMBC correlations

The second equivalent of trimethoxybenzene presumably added to the β-carbon of the initial alkyne in a Michael addition style, due to the activation of the attacking aromatic ring as a result of the three methoxy groups.

To see whether the acylation or the Michael addition reaction was affected by steric factors, tribenzyloxybenzene (**85**) was used in place of trimethoxybenzene (**92**). After the reaction was stirred for one hour at room temperature, a yellow oil was obtained upon work up in 25% yield. The only other product present in the reaction was starting material. The oil was identified as the trifluoroacetyl derivative (**94**).
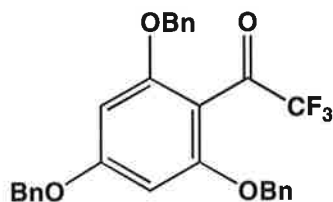
(94)

The ^{1}H n.m.r spectrum of (**94**) showed a singlet at $\delta 6.23$ (2H) suggesting that the ring was mono acylated. The ^{13}C n.m.r spectrum showed a distinct quartet at $\delta 111.13$ (J=523 Hz), and a carbonyl group at $\delta 181.12$ indicative of a trifluoroacetyl group, identifying the derivative (**94**). The reaction was repeated with different variations such as stirring the trifluoroacetic anhydride and phenylpropiolic acid together for longer or increasing the reaction time. No further products apart from the small amount of trifluoroacetyl derivative (**94**) were obtained under any of these conditions. The trifluoroacetyl derivative (**94**) may have been formed by a number of ways. The reaction between a carboxylic acid and trifluoroacetic anhydride is thought to establish the equilibria below.[87]

$$RCOOH \; + \; (CF_3CO)_2O \; \rightleftharpoons \; RCOOCOCF_3 \; + \; CF_3COOH \qquad (1)$$

$$RCOOH \; + \; RCOOCOCF_3 \; \rightleftharpoons \; (RCO)_2O \; + \; CF_3COOH \qquad (2)$$

$$(RCO)_2O \; + \; (CF_3CO)_2O \; \rightleftharpoons \; 2RCOOCOCF_3 \qquad (3)$$
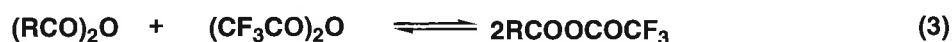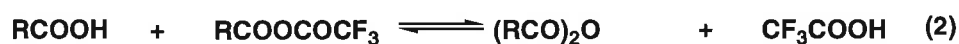
Thus the formation of the trifluoroacetyl derivative (**94**) could be from the nucleophilic attack on the trifluoroacetate carbonyl group in the mixed anhydride, represented in equation 1 and 3. Alternatively, it has been suggested that trifluoroacetylation of activated aromatic compounds occurs easily in the presence of trifluoroacetic anhydride, without the aid of a catalyst.[88] This may mean that tribenzyloxybenzene (**85**) was reacting with residual anhydride in preference to the mixed anhydride. In addition, it is noteworthy that trimethoxybenzene (**92**) overreacted in the presence of

the mixed anhydride between phenylpropiolic acid and trifluoroacetic anhydride. In the case of tribenzyloxybenzene (**85**), the reduced reactivity could be due to the steric or electronic effect of the benzyl ether groups reducing the ability of the ring to interact with the required carbonyl of the mixed anhydride. The carbonyl that is attacked in acylation reactions using mixed anhydrides, generally results in the ketone with the larger R group forming.[73] This suggests that a steric effect of the larger benzyl groups may inhibit the attack of the aromatic ring on the required carbonyl group of the mixed anhydride, and instead attack may occur on the carbonyl of the smaller trifluoroacetyl group. The general lack of reactivity of this system and the small amount of trifluoroacetyl derivative (**94**) actually obtained, suggest that the tribenzyloxy groups may also inhibit the nucleophilic attack at this carbonyl.

Further investigation of the novel Michael addition reaction.

The generation of the substituted chalcone (**93**) *via* acylation then Michael addition to the triple bond, prompted further investigation into this novel reaction. Trimethoxybenzene (**92**) was reacted with propiolic acid and trifluoroacetic anhydride at room temperature (Scheme 36).
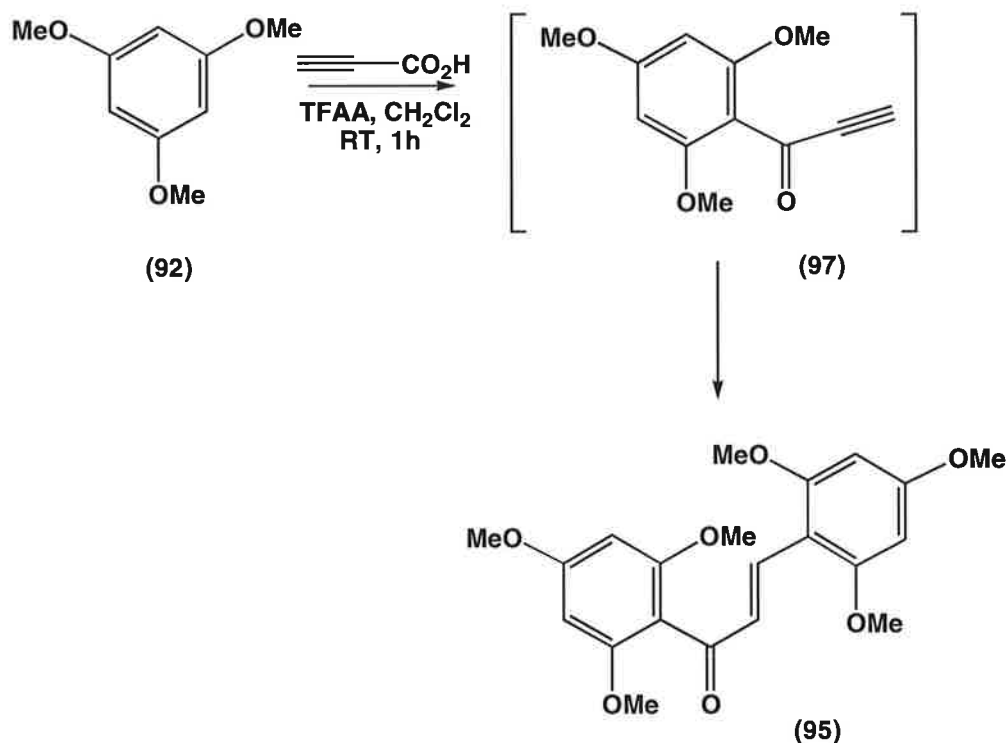
Scheme 36

As before, a methoxy substituted chalcone (**95**) was formed as yellow crystals in 10% isolated yield. The reaction mixture also contained the trifluoroacetyl derivative of trimethoxybenzene (**96**) as a white solid in 52%. The chalcone (**95**) was generated through forming the alkyne (**97**) initially, which then was attacked at the β-alkyne carbon by another equivalent of trimethoxybenzene to give the alkene (**95**). The structure and *trans* geometry of the double bond of the chalcone was confirmed by an X-ray crystal structure (Figure 5).
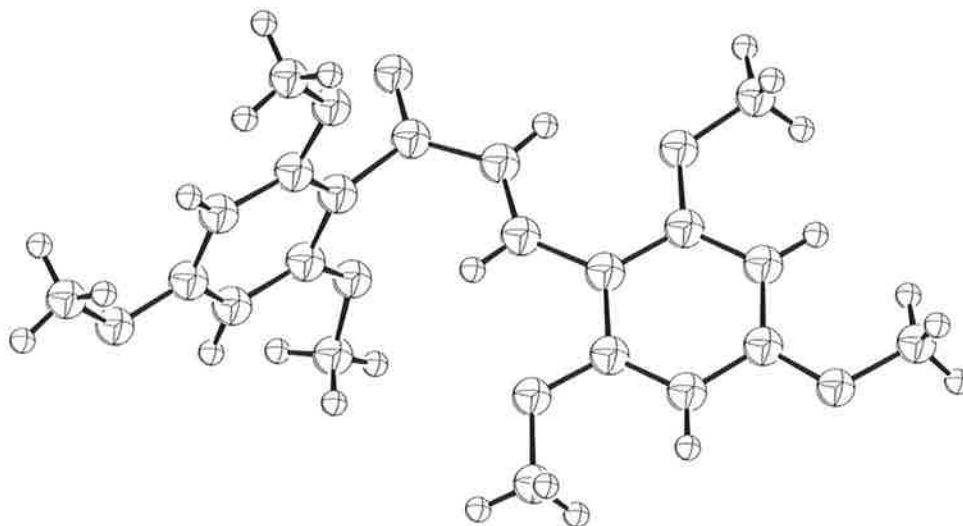
Figure 5: Crystallographic data of (**95**), $C_{21}H_{24}O_7$, triclinic, P bar 1, a =9.122(4) Å, b =15.188(4) Å, c =7.342(4) Å, α =99.74(3)°, β =96.14(4)°, γ =94.11(3)°, V =992.5(7) Å^3, Z =2, D_X =1.300 mg.m^{-3}, $R(F)$ =0.060, $R_W(F)$ =0.063.

It was hoped that by adding extra trifluoroacetic acid (10 mol%, additional to the trifluoroacetic acid generated *in situ*), the carbonyl groups of the mixed anhydride may become more polarised by protonation, so that the formation of the acylium cation is more favorable (Scheme 37).
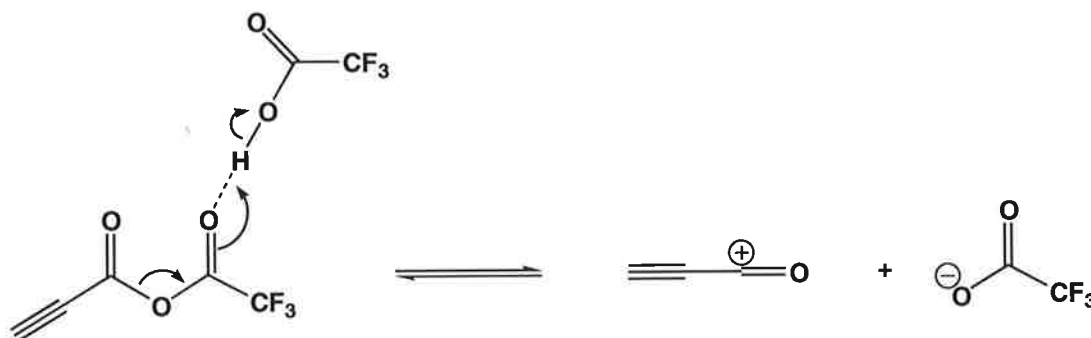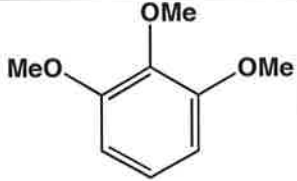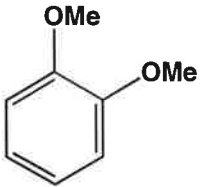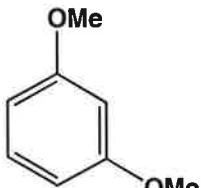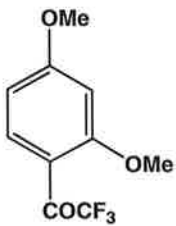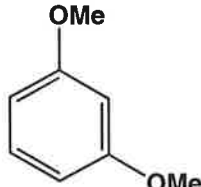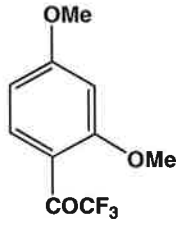
Scheme 37
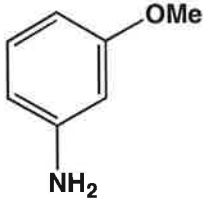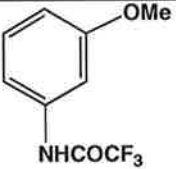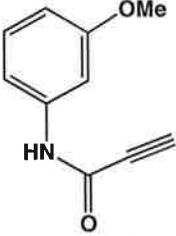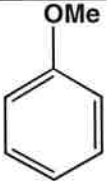
The acylium ion is thought to be the principal acylating agent, a result of a combination of the three equations already mentioned. Under these conditions, the substituted chalcone (**95**) was obtained in 15% and the trifluoroacetyl derivative (**96**) in 38% yield. These results suggest that the addition of extra trifluoroacetic acid does not cause a distinct increase in the yield of the chalcone (**95**).

The benefits of this one step acylation and spontaneous Michael addition reaction are that these two reactions occurred *in situ* within 1 h and in moderate yield compared to other multi-step chalcone syntheses, which are time consuming and give the chalcones in moderate yields.[15,70] To investigate this novel reaction further, a series of substituted benzenes were reacted with trifluoroacetic anhydride (2 eq) and propiolic acid (1 eq); the results are displayed in table 5. In particular, the scope and applicability of the reaction to form substituted chalcones, which are precursors to flavones, flavanols and aurones, quickly and efficiently was of considerable interest.

Table 5: The reaction of some substituted benzenes with propiolic acid and trifluoroacetic anhydride.

Entry	Substrate	Conditions	Solvent	Substrate :acid	Product
1a	MeO OMe OMe	0°C (addition), RT (22h)	CH_2Cl_2	1.5:1	Starting material
1b	"	0°C (addition), Δ (24h)	CH_2Cl_2	1.5:1	Starting material
1c	"	RT (addition), 50°C (7h)	-	1:1	Starting & polymeric material

2	OMe OMe (1,2-dimethoxybenzene)	0°C (addition), RT (1½h), Δ (18h)	CH_2Cl_2	1.5:1	Starting material
3a	OMe OMe (1,3-dimethoxybenzene)	0°C (addition), RT (4½h)	CH_2Cl_2	1.5:1	Starting & polymeric material, OMe OMe COCF₃ (**98**), 5%
3b	OMe OMe (1,3-dimethoxybenzene)	RT (addition), 50°C (3½h)	-	1:1	Starting & polymeric material, OMe OMe COCF₃ (**98**), 5%
4	OMe OMe (1,4-dimethoxybenzene)	RT (18h)	CH_2Cl_2	1.5:1	Starting material

| 5 | 3-methoxyaniline (OMe, NH_2) | RT (18h) | CH_2Cl_2 | 1.5:1 | $NHCOCF_3$, OMe **(99)**, 86% / HN-propynoyl, OMe, O **(100)**, 9% |
| 6 | anisole (OMe) | RT (18h) | CH_2Cl_2 | 1.5:1 | Starting material |

Chalcones were only formed from systems that were activated by three alkoxy groups, at positions 1,3 and 5 on the ring, as described previously (Scheme 36). These results suggest that 1,2,3-trimethoxybenzene (Table 5, entry 1) is not as reactive as 1,3,5-trimethoxybenzene. Methoxy groups are known to be *ortho* and *para* directing activators, so that in 1,3,5-trimethoxybenzene, each non-substituted position is activated by all of the methoxy groups. In 1,2,3-trimethoxybenzene every methoxy group does not activate each non-substituted position. However, the two positions in the ring *ortho* to the 1- and 3-methoxy groups are more activated, whilst the non-substituted position *para* to the methoxy group is less activated.

The acylation reaction of other methoxy substituted aromatic rings that were not sufficiently activated, returned only starting materials (Table 5, entries 2, 4 and 6).

The reaction of 1,3-dimethoxy benzene yielded a small amount of the trifluoroacetyl derivative **(98)** as a cream solid (Table 5, entry 3a). This was identified by a molecular ion at *m/z* 234 in the mass spectrum. The position of acylation was determined from the ^1H n.m.r spectrum which showed three aromatic signals in the downfield region from δ6-8, suggesting substitution in one part of the aromatic ring. As there were no features of symmetry in the ^1H n.m.r spectrum it was concluded

that the ring had been substituted at position-4 rather than position-2. In the product (98) the aromatic signal at position-3 of the ring, between the two methoxy groups, appeared as a doublet at $\delta6.49$ ($J=2.4$ Hz) in the ^{1}H n.m.r spectrum. The proton at position-5 of the ring appeared as a dd at $\delta6.57$ ($J=2.4$, 8.7 Hz). The proton at position-6 appeared as a doublet of quartets at $\delta7.77$ ($J=8.7$, $J_{HF}=1.2$ Hz), and was shifted downfield as a result of being adjacent to the carbonyl group at position-1 of the ring. The ^{13}C n.m.r spectrum also showed a quartet at $\delta118.17$ ($J_{CF}=377$ Hz) and a carbonyl group at $\delta167.02$, indicative of the trifluoroacetyl group. Polymeric material was also recovered from the reaction, which showed multiple, complex signals in the methoxy, alkene and aromatic region of the ^{1}H n.m.r spectrum. High molecular weight species were obtained from the LC-mass spectrum.

Repeating this reaction using a 1:1 ratio of substituted benzene to mixed anhydride and heating the solution neat to 50°C for 3.5 h gave exactly the same amount of trifluoroacetyl derivative (98) (Table 5, entry 3b). A lesser amount of starting material and a greater amount of polymeric material was identified by t.l.c, the polymeric material appeared as a smear. Attempted purification of the smeared products gave material that contained some signals in the ^{1}H n.m.r spectrum similar to those obtained in entry 3a. These results show that 1,3-dimethoxybenzene is not as activated as 1,3,5-trimethoxybenzene as the methoxy groups cannot activate all of the non-substituted sites on the ring. The *meta* position is not activated at all and the position between the two methoxy groups is likely to be too hindered for reaction to occur, which is why the acetyl derivative (98) was formed by reaction at position-4 of the ring.

The aromatic ring acylation of *m*-anisidine was attempted (Table 5, entry 5) even though it was realised that the amine was likely to participate in a nucleophilic reaction with the mixed anhydride. When the reaction was run at room temperature for 18 h, a mixture of two amides were formed, the trifluoroacetamide (99) in 86% and the propiolamide (100) in 9%. There was no sign of any ring-acylated products as the ^{1}H n.m.r spectra of both products showed four aromatic proton signals in the range $\delta6.73$-7.26. The spectra confirmed acylation on the amine, as the singlet (2H) at $\delta3.65$ in the starting material was no longer present and had been replaced by an

amide proton at δ8.91 (trifluoroacetamide) and 7.76 (propiolamide). The trifluoroacetamide showed a quartet in the ^{13}C n.m.r at δ116.00 (J_{CF} =443) and a multiplet at δ155.17 due to the carbonyl carbon. The propiolamide showed a signal at δ2.92, corresponding to the terminal alkyne hydrogen and the ^{13}C n.m.r showed two peaks at δ74.74 (β-alkyne carbon, intense) and 78.27 (α-alkyne carbon, weak). It has been noted that mixed (molecular) anhydrides favour trifluoroacetamide formation in preference to propiolamide formation.[87] To see whether aromatic ring acylation would occur using a protected amine, the mixed anhydride reaction was repeated using the trifluoroacetamide (**99**). After stirring the reaction for 2 h at room temperature, nothing but starting trifluoroacetamide was obtained. This suggested that the aromatic ring was not activated sufficiently for acylation.

Mixed Michael Addition Reactions.

As 1,3,5-trimethoxybenzene (**92**) reacts well under acylation conditions using a mixed anhydride, it was of interest to investigate whether different combinations of 1,3,5-trimethoxybenzene and 1,2,3-trimethoxybenzene may allow the formation of a product with a substitution pattern similar to **EGC** (**3**). It was expected that the initial acylation would be upon 1,3,5-trimethoxybenzene and that the excess of 1,2,3-trimethoxybenzene may add to the triple bond in Michael style, before a second equivalent of 1,3,5-trimethoxybenzene reacted. To gain an **EGC** derivative, the position *meta* to the 1- and 3-methoxy groups of 1,2,3-trimethoxybenzene needs to attack the triple bond, which is unlikely due to the positions *ortho* to the 1- and 3-methoxy groups being the most reactive. Nevertheless, the efficient generation of a substituted chalcone in this way would be very useful.

Upon addition of both trimethoxybenzenes to a solution of the mixed anhydride in dichloromethane, a purple solution formed. The reaction yielded the trifluoroacetyl product derived from 1,3,5-trimethoxybenzene (**96**), as a white solid in 11%. A second minor fraction was obtained from chromatography, appearing as a pale yellow gum. This fraction showed eight methoxy signals in its ^{1}H n.m.r, with integrations of more than three hydrogens each, indicating a complex mixture. The spectrum also showed two doublets at δ5.09 and 6.64 with coupling of 11.7 Hz and another two doublets at δ5.86 and 6.46 with coupling of 10.8 Hz, presumably alkene

signals (arising from some type of polymeric material). A multiplet appeared at δ6.05 consisting of fifteen hydrogens in total (compared to the integration of the alkene signals) which could have corresponded to the aromatic hydrogens from 1,3,5-trimethoxybenzene. LC-MS did not further separate the mixture, and gave high molecular weight species in the spectrum.

Changing the reaction conditions slightly by using 1:1 ratio of the two trimethoxybenzenes and stirring at room temperature for 2 h returned a similar combination of products. The trifluoroacetyl derivative (**97**) was obtained in higher yield (29%) than before, which may have been a result of changing the ratio of the substituted benzenes. A polymeric fraction was also obtained.

A further variation in the reaction conditions used a 1:1.5 ratio of 1,3,5- to 1,2,3-trimethoxybenzene and this time the reaction was refluxed in dichloroethane, for 2.5 h. Aside from a small amount of both starting materials, a complex mixture of products was visible by t.l.c. The reaction product was purified by chromatography to give four fractions each of which were predominately one spot by t.l.c. The highest Rf sample showed two doublets at δ7.97 and 6.17 with coupling of 10.2 Hz in the ^{1}H n.m.r spectrum, which could be attributed to *ortho* aromatic protons on a substituted 1,2,3-trimethoxybenzene substrate. The spectrum also showed two doublets at δ6.42 and 6.28 with coupling of 2.1 Hz, which are typical of two *meta* protons on a 1,2,3,5-tetrasubstituted aromatic ring, such as a 1,3,5-trimethoxybenzene ring that had been acylated. Between δ3.82 and 3.86 three singlets were observed, corresponding to the methoxy protons, with an entire integration value of fifteen hydrogens. This indicated the loss or modification of one methoxy group, and suggested that the cyclic structure (**101**) was a possibility. The limited data available was in agreement with n.m.r data for similar flavones.[89,90] The mass spectrum showed peaks above 400, but also contained a strong peak at 372, which is the molecular weight of the flavone (**101**).
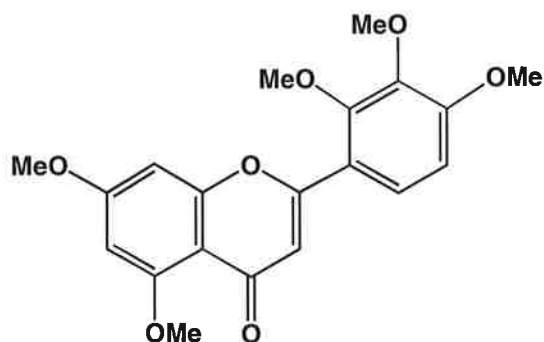
(101)

The other three fractions obtained from the column gave complex mixture of signals when viewed by ^{1}H n.m.r spectroscopy.

These results show that 1,3,5-trimethoxybenzene **(92)** is the only substrate that reacts cleanly in these acylation-Michael addition reactions, presumably due to its high level of reactivity.

Acylation reactions using a Lewis acid with an anhydride or an acid chloride.

The formation of substituted α, β-acetylenic ketones [of the general structure **(73)**] commenced using a Friedel Crafts acylation reaction in the presence of Lewis acids and either propiolic anhydrides or propiolyl chlorides due to the formation of unwanted products when the acylation reactions were conducted using a mixed anhydride.

R =OBn or OMe
R' =H, OMe, OBn

(73)
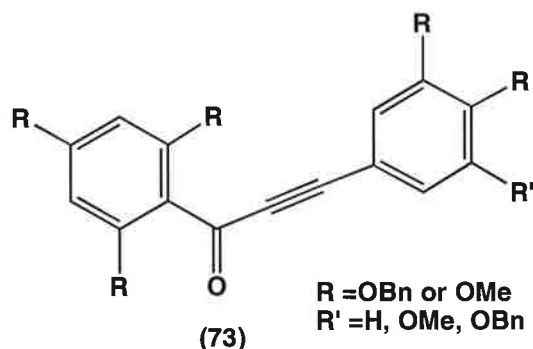
Acylation Reactions using Propiolic Anhydride.

The acylation reaction between an activated aromatic system and propiolic anhydride was first investigated using zinc chloride as the catalyst (Scheme 38).

163
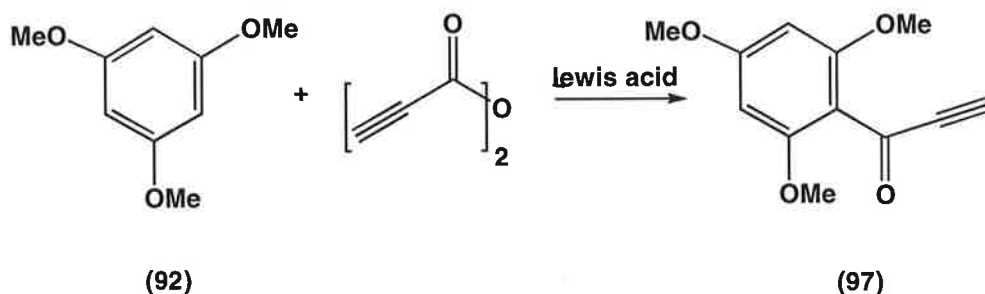
Scheme 38

Propiolic anhydride was prepared by treatment of sodium propiolate with oxalyl chloride.[91] The solution in either ether or dichloroethane was presumed to contain 95% of the anhydride and was used in subsequent reaction without further purification.[91]

When 1,3,5-trimethoxybenzene (**92**) was reacted with propiolic anhydride in a refluxing solution of dichloroethane containing two equivalents of zinc chloride, a mixture of products was formed. The reaction mixture was purified by chromatography to firstly yield 1,3,5-trimethoxybenzene (10% recovery) and the chromone (**102**) as white solid (3%).
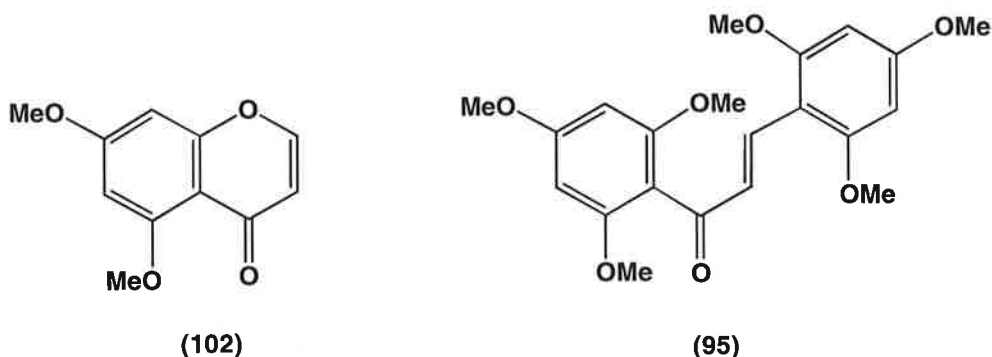
The chomone (**102**) was identified by two three-hydrogen singlets in the ^{1}H n.m.r spectrum due to the methoxy groups. The spectrum also showed two doublets at δ6.28 and 6.41 with coupling of 2.1 Hz, indicating two *meta* related aromatic hydrogens. The alkene hydrogens were observed as two doublets at δ6.15 (α) and 7.98 (β) with a coupling of 9.6 Hz. The ^{13}C n.m.r spectrum showed two methoxy carbons, the α and β carbons at δ111.65 and 139.37 respectively and the carbonyl carbon at δ193.79. This chemical shift value is typical of carbonyl groups in

conjugated chromone systems.[92] Further chromatography gave a low yield of a pale yellow solid that showed two methoxy singlets in the ^{1}H n.m.r at $\delta3.46$ and 3.80 in a 2:1 ratio respectively. The partial loss of symmetry suggests that the 1,3,5-trimethoxybenzene moiety had been substituted in one position on the ring. There was also a singlet at $\delta6.20$ (2H), suggesting the loss of one aromatic hydrogen, which is consistent with a 1,2,3,5-substitution pattern. Both ^{13}C n.m.r (extra peaks to the starting material) and mass spectrum data (many peaks with $m/z > 200$) indicated that the solid was a more complex mixture.

A later chromatographic fraction was mainly the chalcone (**95**), which was obtained as a yellow solid in 14% yield. This molecule had been previously obtained in 15% yield by acylation using the mixed anhydride formed from propiolic acid and trifluoroacetic anhydride.

The acylation reaction between 1,3-dimethoxybenzene and propiolic anhydride was attempted using zinc chloride catalysis, but only starting material was recovered from the reaction material, as indicated by t.l.c.

The required ketone (**97**) was not isolated from zinc chloride catalysed Friedel Crafts acylation with propiolic anhydride. The reaction with 1,3,5-trimethoxybenzene indicated that the acetylenic species had formed but progressed to either cyclise or compete in Michael addition reactions. The chalcone (**95**) was formed in comparable yields to acylation using trifluoroacetic anhydride.
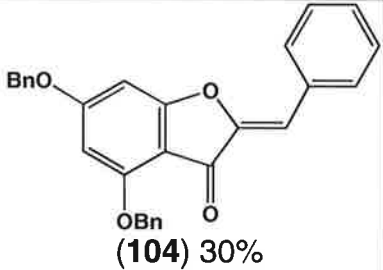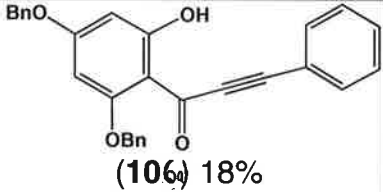
Acylation using Phenylpropioloyl Chloride and a Lewis acid.
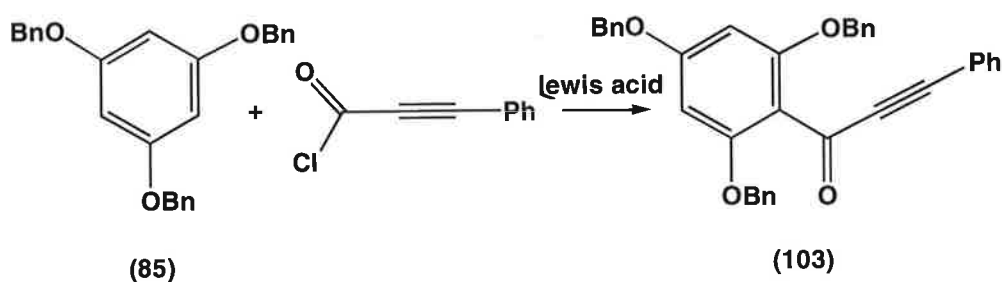
Scheme 39

The acylation reaction was attempted on 1,3,5-tribenzyloxybenzene (**85**) as outlined in Scheme 39, as this substrate failed to react under acylation conditions using a mixed anhydride. Phenylpropiolyl chloride was prepared from reaction of phenylpropiolic acid in thionyl chloride at 60°C.[78] The non-substituted acid chloride was used to gain reaction methodology in the examples described (Table 6).

Table 6: Acylation reactions using 1,3,5-tribenzyloxybenzne with phenylpropioloyl chloride and a variety of lewis acids.

1	AlCl$_3$ (stoich)	CH$_2$Cl$_2$, 40°C, 5 min	Baseline material
2	AlCl$_3$ (stoich)	CH$_2$Cl$_2$, -30°C–0°C, 1¼h	Starting material
3	FeCl$_3$ (cat)	(CH$_2$)$_2$Cl$_2$, Δ, 1½h	(**104**) 30%
4	FeCl$_3$ (stoich)	(CH$_2$)$_2$Cl$_2$, Δ, 1½h	Baseline material
5	ZnCl$_2$ (cat)	(CH$_2$)$_2$Cl$_2$, Δ, 1h	(**106**) 18%
6	ZnCl$_2$ (stoich)	(CH$_2$)$_2$Cl$_2$, Δ, 1h	Complex mixture

The investigation commenced using a stoichiometric amount of aluminum chloride as catalyst in dichloromethane at 50°C. These conditions appeared to be too harsh, as only baseline material was visible by t.l.c after 5 minutes. It was presumed that the benzyl ethers on the phloroglucinol derivative were deprotected under these conditions, presumably leading to more side reactions. This may also be caused by the use of a vigorous catalyst (high Lewis acidity) with a highly activated, polybenzyloxy aromatic ring. Johnston and co-workers had noted previously that the reaction of stoichiometric amounts of aluminum chloride with phenylpropiolyl chloride and anisole, gave the required acetylenic ketone with only a small amount of impurities,[78] suggesting that the high reactivity of 1,3,5-trimethoxybenzene may have caused the unwanted side reactions. The reaction was repeated at sub zero temperatures (Table 6, entry 2) in hope of preventing product degradation. The lower temperatures proved to inhibit the reaction, returning only starting materials.

The acylation reaction was attempted using a Lewis acid of lesser strength in hope of gaining better results. Ferric chloride was used in stoichiometric and catalytic amounts (Table 6, entries 3 and 4). It has been shown that Friedel-Crafts acylation reactions upon activated aromatic nuclei can occur using a trace of catalyst.[80] Using a stoichiometric amount of catalyst (Table 6, entry 4) in refluxing dichloroethane for 1.5 h gave only baseline material indicating product degradation. Thus the use of ferric chloride instead of aluminum chloride did not alleviate the problem of degradation. However, the use of a trace amount of catalyst provided dramatically different results (Table 6, entry 3). Using exactly the same conditions as entry 4, bright yellow crystals were obtained after chromatography in 30%, which were identified as the aurone (**104**) by x-ray crystallographic analysis (Figure 6).
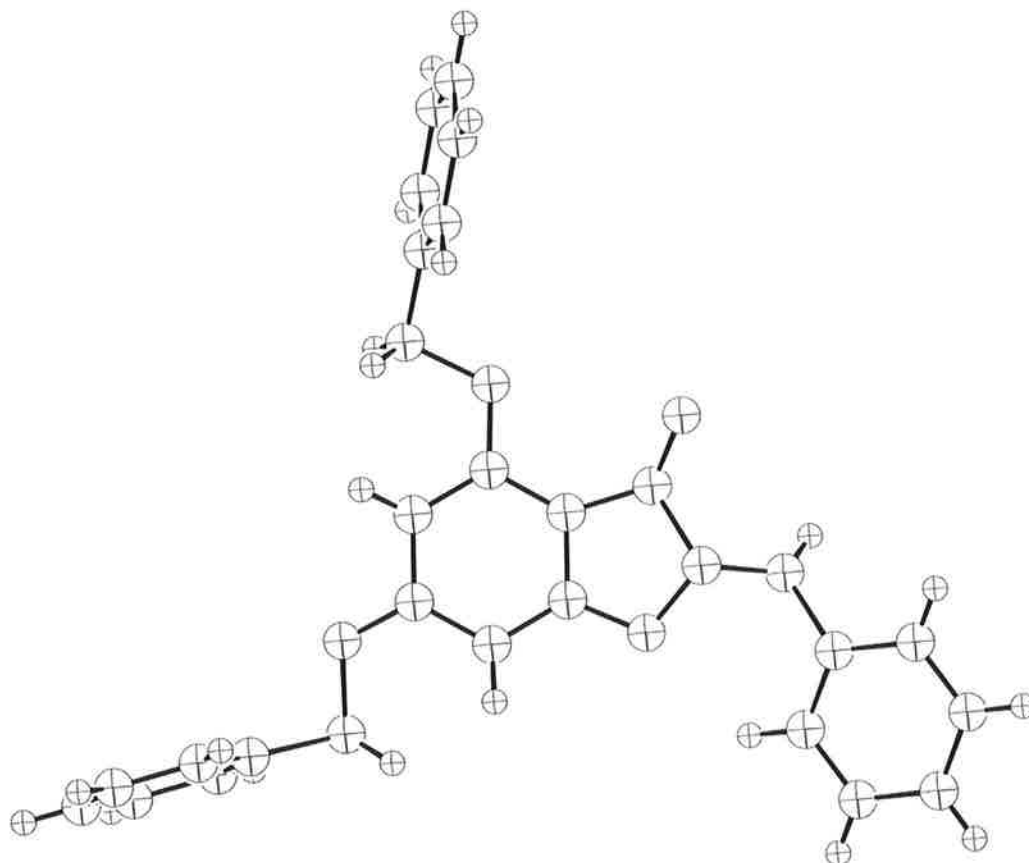
Figure 6: Crystallographic data of (**104**), $C_{29}H_{22}O_4$, monoclinic, $P2_1$, $a = 12.946(7)$ Å, $b = 6.759(4)$ Å, $c = 13.51(2)$ Å, $\beta = 111.95(7)°$, $V = 1096(2)$ Å^3, $Z = 2$, $D_X = 1.316$ mg.m^{-3}, $R(F) = 0.110$, $R_W(F) = 0.089$.

(104)
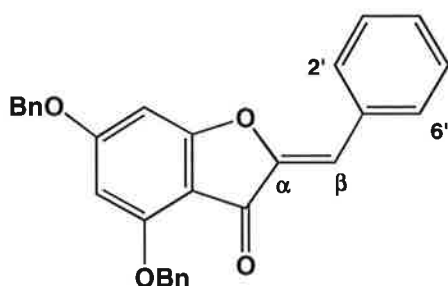
The ^{1}H n.m.r spectrum of (104) revealed two, two hydrogen singlets at $\delta 5.09$ and 5.28 of the benzyl groups. ^{13}C n.m.r showed two signals at $\delta 71.17$ and 71.49, which corresponded to the methylene carbons of the benzyl groups. There were two aromatic hydrogen signals in the ^{1}H n.m.r spectrum, at $\delta 6.22$ and 6.44 that appeared as doublets with *meta* coupling of 1.4 Hz, as expected for the A-ring. A singlet at $\delta 6.75$ was due to the olefinic (β) proton. For further discussion of aurone stereochemistry, refer to the cyclisation section later on in this chapter.

A likely explanation for the formation for the aurone (104) is that the required acylation occurred, followed by attack of the benzyloxy oxygen at the α-position of the triple bond (5-*exo*-dig cyclisation). This would give the intermediate (105) leading to the (*Z*)-aurone (Scheme 40).
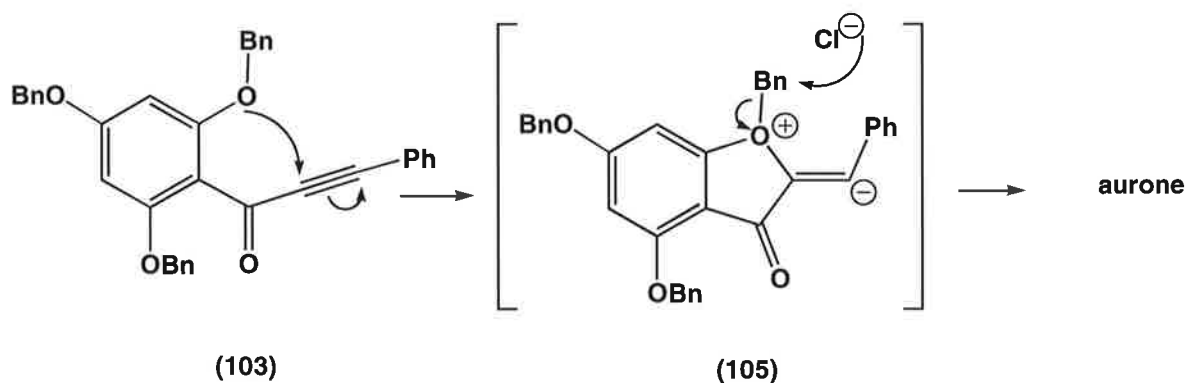
Scheme 40

Although it is not clear whether the benzyl group is cleaved before or after cyclisation, a likely mechanism is shown in Scheme 40. The chloride ion is formed from either ferric chloride or the hydrogen chloride generated by the reaction.

This type of selective dealkylation has also been described by Solladie and co-workers using boron trifluoride diethyl etherate.[b]

b)   Solladie, G.; Gehrold, N.; Maignan, J. *Eur. J. Org. Chem.* **1999**, 2309-2314.

Alternatively, deprotection may have occurred before cyclisation and involved an interaction between the Lewis acid, the carbonyl oxygen and one of the benzyloxy oxygens, to give the complex (106). This theory assumes that acylation of the aromatic ring occurred before deprotection of the benzyl ether.
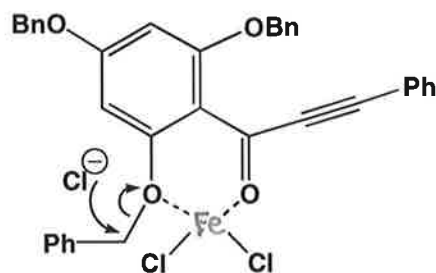
(106)

The benzyl oxygen presumably became polarised by the coordinated ferricchloride, thus allowing for a nucleophile, such as chloride ion to attack the benzylic carbon atom, which results in cleavage of the group. In similar 1,3,5-tribenzyloxychalcone systems, it was suggested[50] that the coordination between the ketone, Lewis acid (titanium chloride) and the ether oxygen caused the selective removal of one benzyl group.[50] See opposite.

The use of either aluminum chloride or ferric chloride seemed to cause over activity in the acylation reaction, as polymeric material was obtained. It was hoped that these problems could be overcome by using a much less acidic Lewis acid such as zinc chloride. When the acylation reaction was conducted using zinc chloride (Table 6, entries 5 and 6), the   acetylenic ketone (106a) was obtained as yellow crystals in 18%. The structure of (106a) was confirmed unequivocally by x-ray crystallography (Figure 7).
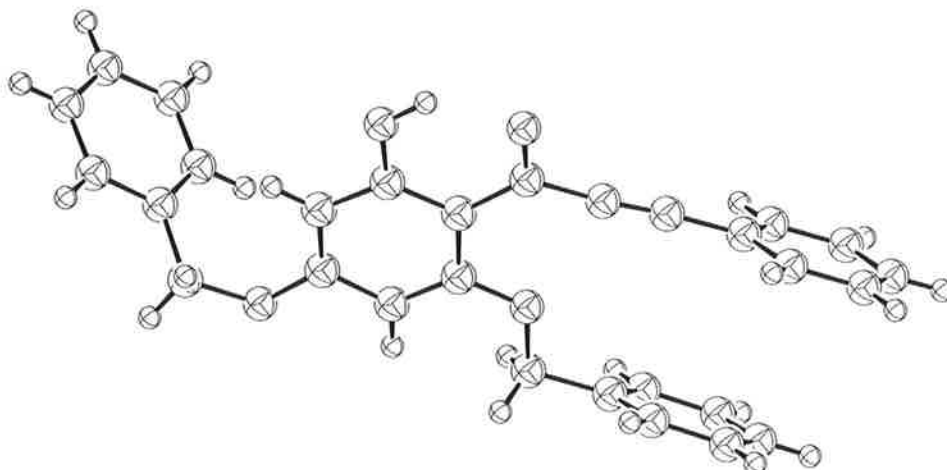
Figure 7: Crystallographic data of (**10**6*q*), $C_{29}H_{22}O_4$, triclinic, *P* bar 1, *a* =10.795(3) Å, *b* =12.877(5) Å, *c* =7.877(2) Å, α =97.20(3)°, β =96.21(2)°, γ =84.00(2)°, *V* =1075.4(5) Å^3, *Z* =2, D_X =1.342 mg.m^{-3}, *R(F)* =0.066, R_W*(F)* =0.046.

The acetylenic ketone (**10**6*q*) showed two singlets in the ^{1}H n.m.r spectrum for each of the benzyl groups at δ5.07 and 5.09. The ^{13}C n.m.r spectrum also showed two signals for these carbons at δ71.10 and 71.85. The two *meta* aromatic protons appeared as two doublets (*J*=2.2 Hz), at δ6.09 and 6.16 in the ^{1}H n.m.r spectrum. The α and β alkyne carbon signals appeared at δ96.17 and 91.01 respectively in the ^{13}C n.m.r spectrum. The carbonyl signal appeared at δ178.42.

An advantage of this reaction was the removal of one of the benzyl groups adjacent to the acyl group, which suggested that deprotection of the intermediate (**106**) occurred prior to cyclisation (Table 6, entry 5).

When the acylation reaction was catalysed by a stoichiometric amount of zinc chloride, the reaction products were more complex (t.l.c). Attempted purification by chromatography was unsuccessful.

These reactions have revealed some unique chemistry. The use of zinc chloride catalysis generated a molecule perfectly set up for cyclisation reactions. Cyclisation also occurred in a one-pot reaction using ferric chloride, a stronger Lewis acid to give the aurone (**104**) in good yield. Aurones are generally synthesised from a multi-step

sequence, which involves the condensation between a substituted benzofuranone and benzaldehyde. The benzofuranone has to be prepared prior to the reaction.[93] For this reason it was of interest to investigate these acylation reactions further, particularly with added substitution in the phenyl ring. It is also of interest to investigate whether the cyclisation of the acetylenic ketones could be directed to form flavone structures rather than aurones.

Acylation using substituted phenylpropioloyl chlorides.

A variety of substituted phenylpropiolyl chlorides were synthesised from substituted phenylpropiolic acids or from sodium salts of acids, by reaction with thionyl chloride. Sodium salts were used to minimise the amount of hydrochloric acid present in the reaction mixture, which may add to the triple bond of the acid chloride or to the triple bond of the acylated product.[78]
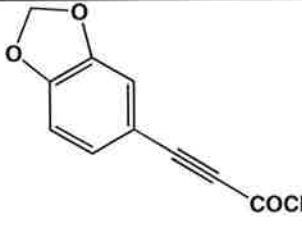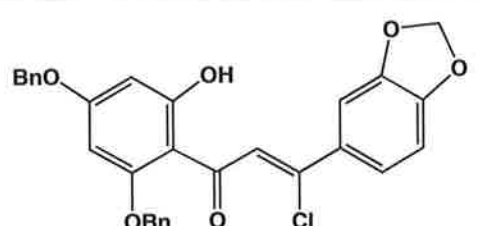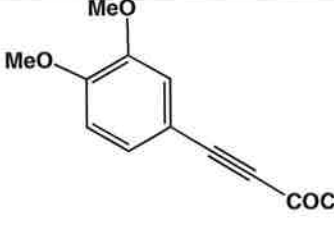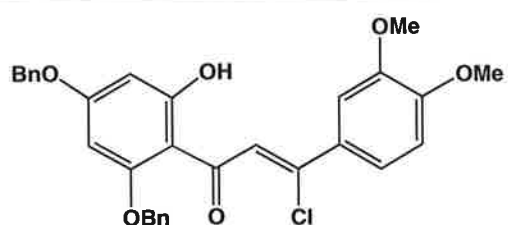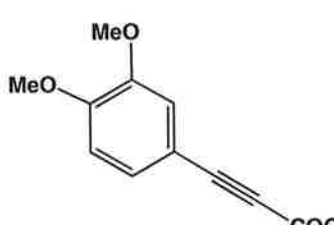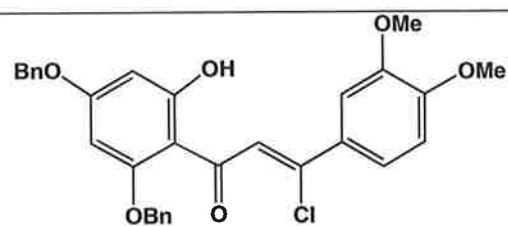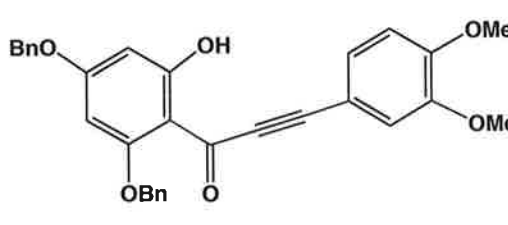
The acylation reaction proceeded according to the conditions described (Scheme 41), using substituted acid chlorides which should allow the incorporation of the appropriate substitution in the B-ring for the formation of **EC** and **EGC** precursors (**Route B**).
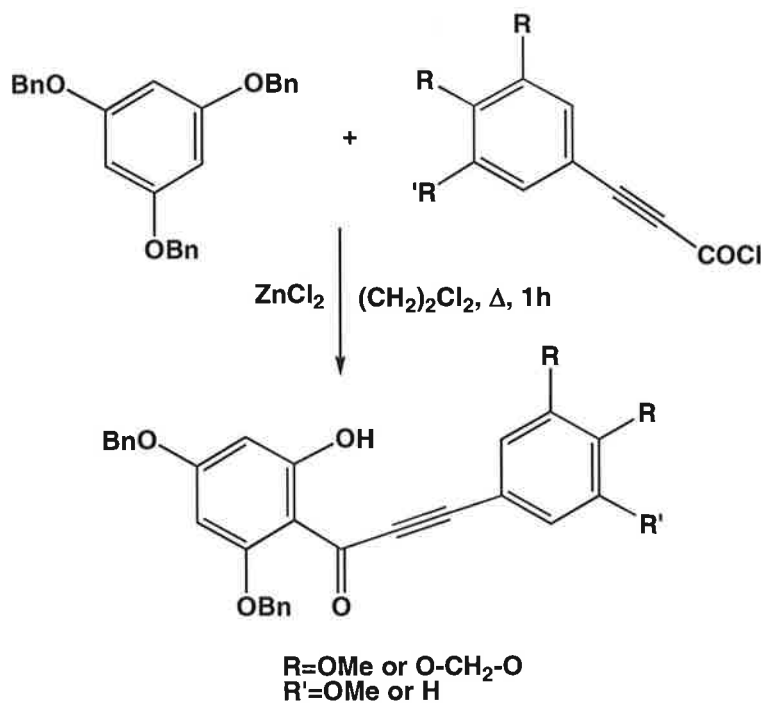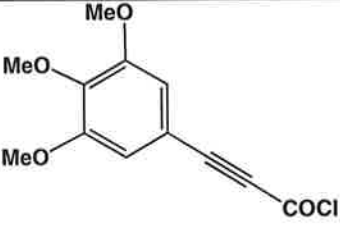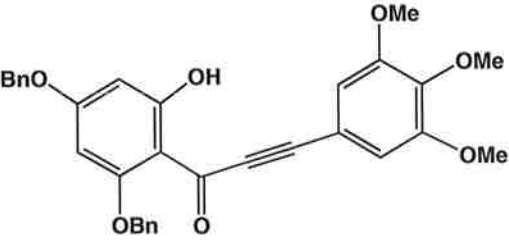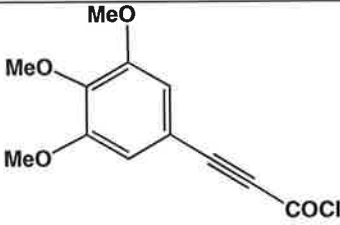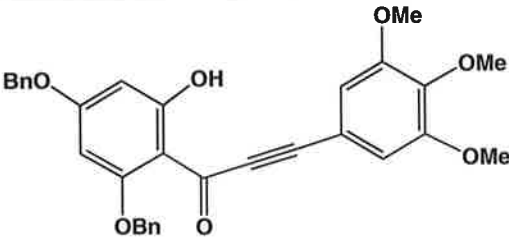
Scheme 41

Substituted acid chlorides were reacted with 0.16 mol% of zinc chloride per acid chloride and 1,3,5-tribenzyloxybenzene in refluxing dichloroethane. These conditions had previously been found to yield acetylenic ketones (Table 6), and the same conditions were investigated in attempt to generate the substituted derivatives required. These reactions are summarised in Table 7.

Table 7: The Acylation of 1,3,5-tribenzyloxybenzene (85) with some substituted, aromatic acid chlorides.

Entry	Acid Chloride	Product	% Yield
1	prepared from acid	(107)	14
2a	prepared from acid	(108)	57
2b	prepared from Na salt	(108) + (109)	5 (alkene), 13 (alkyne)

3a	prepared from Na salt	**(110)**	30
3b	prepared from acid	**(110)**	34

The structure of the hydrogen chloride adduct (**107**) (Table 7, entry 1) was determined from its crystal structure (Figure 8).
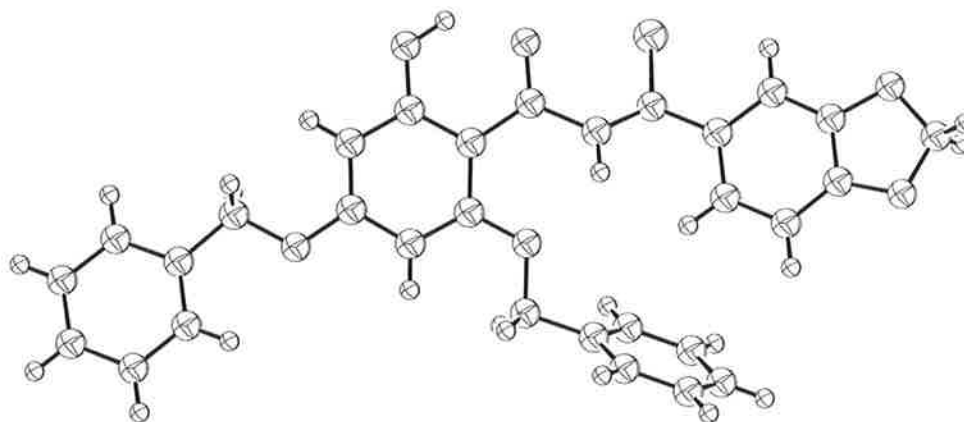
Figure 8: Crystallographic data of (**107**), $C_{30}H_{23}O_6Cl$, orthorhombic, $P2_12_12_1$, a =17.17(1) Å, b =19.346(4) Å, c =14.525(4) Å, V =4824(3) Å^3, Z =8, D_X =1.187 mg.m^{-3}, $R(F)$ =0.048, $R_W(F)$ =0.053.

The structures of the acetylenic ketones and the other hydrogen chloride adducts were determined from their spectral data, as well as by comparison with the data obtained for the hydrogen chloride adduct (**107**). All of the products showed only two

benzyl groups determined by two, two proton singlets in the ^{1}H n.m.r spectra in the region δ4.89-5.15, and only two signals for benzyl methylene carbons in the ^{13}C n.m.r spectra. The expected aromatic signals were observed in all cases. The α-hydrogen of (107) and (108) showed proton crosspeaks to the carbonyl carbon, the β-carbon and C1' using HMBC experiments (600 MHz) (Figure 9, table 8).

Table 8: 600 MHz Data for the α-hydrogen from two β-chlorochalcones.
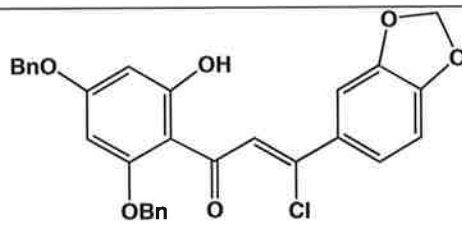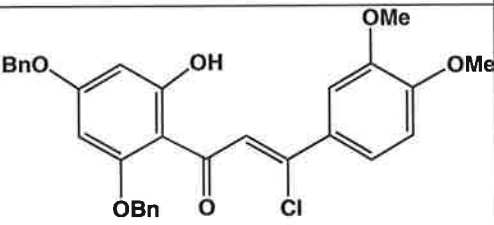
Compound	^{1}H δH	^{13}C (HMQC) δC	^{13}C (HMBC) δC
(107)	7.30 (α-H)	125.41	131.83 (C1'), 139.47 (C-β), 192.12 (C=O)
(108)	7.40 (α-H)	124.93	130.29 (C1'), 139.98 (C-β), 192.08 (C=O)

Figure 9: HMBC correlations.

R=-O-CH$_2$-O-
or OMe
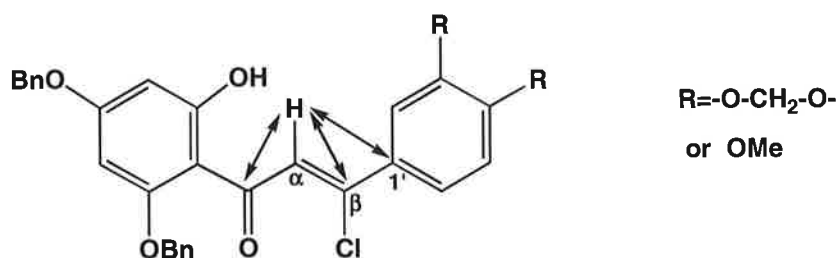
In the ^{13}C n.m.r spectrum of (109) (Table 7, entry 2b), the α, β-alkynyl carbons were visible at δ97.42 and 90.29 respectively, and the carbonyl carbon at δ178.39. The carbonyl group appeared more down field at δ192 for both hydrogenchloride adducts (107) and (108) compared to the value for the acetylenic ketone (109).

Another distinct difference between the two types of products was that the α-carbon was at approximately δ125 for the hydrogen chloride adducts and the β-carbon was at δ140, a noticeable difference compared to the values stated above for the respective α, β-alkynyl carbons of (**109**). The 600 MHz data showed an HMQC correlation of the α-hydrogen to the α-carbon and HMBC correlations of the α-hydrogen with the carbon at position-1', the β-carbon and the carbonyl carbon (Figure 9, table 8).

In all of these reactions some of the 1,3,5-trimethoxybenzene was recovered at the end of the reaction which indicated that it could be profitable to further investigate and optimise these reactions.

There seemed to be no correlation between what product was formed (acetylenic ketone *versus* hydrogen chloride adduct) and the way the acid chloride was formed. Time however, did not permit a study of the factors that favoured hydrogen chloride addition. The formation of β-chlorochalcones has been reported previously in similar acylation reactions involving triple bonds.[78]

From these results it is evident that the acylation/deprotection reaction can be extended to form substituted acetylenic ketones or hydrogen chloride adducts in moderate yields. The slight differences in relation to what product was formed, was more likely to be due to a combination of factors such as the presence of substitution (or not) on the acid chloride rather than the way the acid chloride was formed. This method has much scope for further investigation particularly for its potential to generate epicatechin precursors. Other methods of forming the β-chlorochalcones are from the opening of chalcone epoxides using Vilsmeier reagent (dimethyl formamide, phosphorus oxychloride)[94] but the compounds (**107**) and (**108**) (Table 7, entries 1 and 2) derived from phloroglucinol derivatives have not been described in the literature. Substituted acetylenic ketones derived from phloroglucinol derivatives, such as (**109**) and (**110**) (Table 7, entries 2b and 3) have also been neglected in the literature; however one method that gave similar compounds required three steps and proceeded in low yields.[83]

Cyclisation Reactions.

As a consequence of the *in situ* cyclisation of the acetylenic ketone (10%) to give the aurone (**104**) (Table 7, entry 3), it was of considerable interest to investigate methodology by which the cyclisation of the acetylenic ketone (10%) to the flavone (**111**) could be achieved (**Route C,** Scheme 42).

Route C
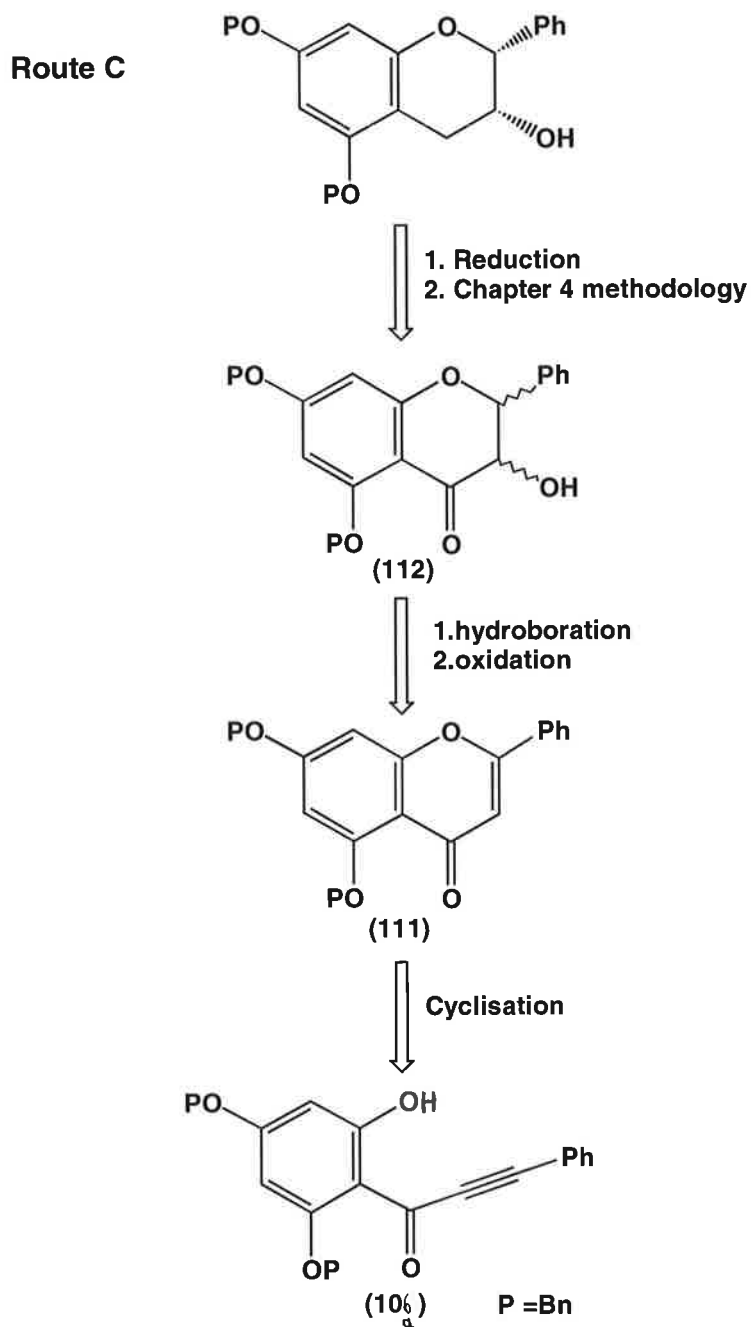
Scheme 42

The cyclisation of acetylenic ketones to give flavones has been described previously.[53,74,83,95-98] Once formed the double bond of the flavone may easily be converted to a *trans* flavanonol (112) using boron reagents followed by oxidation (Scheme 42).[99-101] The carbonyl group of the flavanonol (112) can then be easily removed as described previously[48] (**Route B**), to give a racemic mixture of catechins that may then be converted to their epi form using methodology described in Chapter 4. This route would allow the generation of **EC** and **EGC** precursors using

177

the substituted acetylenic ketones (**109**) and (**110**). **EC** and **EGC** precursors may then be esterified to afford **ECG** and **EGCG** precursors respectively (Chapter 4).

The cyclisation of phenolic acetylenic ketones, involving nucleophilic attack at the triple bond, remains less clear cut than for the analogous ring closures in tetrahedral or trigonal systems.[74,102] Recent *ab initio* calculations have revealed that the transition state energies in 5-*exo*- and 6-*endo-digonal* cyclisations using phenoxide ion are very close.[103] This suggests that it may be difficult to gain complete selectivity for either flavone or aurone formation. Furthermore, similar *ab initio* calculations support the proposal of obtuse approach angles, rather than acute approach angles for digonal systems as proposed by Baldwin, and hence favor the 5-*exo*-dig cyclisation mode.[96] The experimental data, however, confirms that both types of ring closures are allowed processes.[96] In contrast to the cyclisation of *o*-hydroxy chalcones, the related cyclisation of aryl α, β-acetylenic carbonyl compounds have hardly been documented.[74] Further studies on the cyclisation of α, β-acetylenic ketones have shown that the cyclisation conditions play an important role in determining which product is isolated.[103] Cyclisation of the acetylenic ketone using potassium carbonate in refluxing acetone is reported to favour the 6-*endo*-dig ring closure to give the flavone (**113**) with a small amount of 5-*exo*-dig derived product (**114**) also being formed.[74]
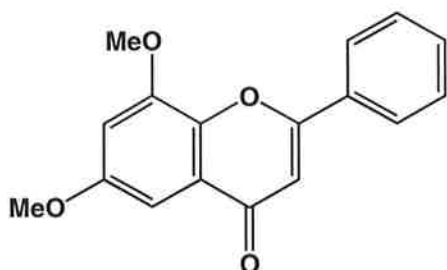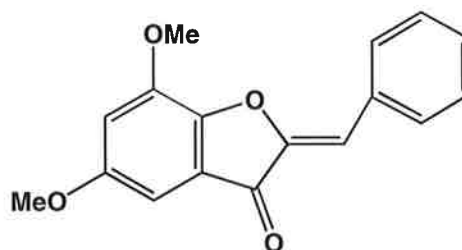
(113)   (114)

The flavone (**113**) was expected to be the preferred product as β-carbons in α, β-acetylenic carbonyl compounds are typically vulnerable to nucleophilic attack.[74] However, different results were reported when the cyclisation was performed in an ethanolic solution of sodium ethoxide; in this case the reaction proceeded much more rapidly (than the reaction with potassium carbonate in acetone), and gave a 5 *exo*-dig

closure and hence the aurone (**114**) as the preferred product.[74] A similar effect was note by Garcia and co-workers when using potassium carbonate in ethanol.[74] Garcia and co-workers proposed a mechanism to account for these results which suggested that the flavone was formed by a step-wise conjugate addition of the phenolate anion to the triple bond; the formation of (**115**) being favoured over the alternate carbanion (**116**).[74]
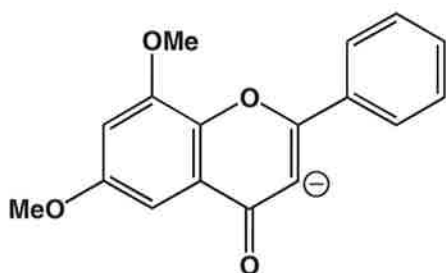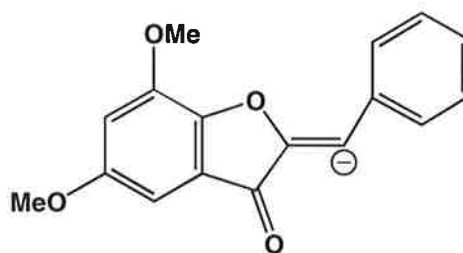
(**115**)   (**116**)

However, the anion (**116**) was thought to be generated by kinetically controlled attack by the phenolate anion at the α-carbonyl carbon.[74] This anion and subsequently the aurone (**114**) are formed when this less stable anion (**116**) is captured, which was more likely to occur in protic solvents such as ethanol.[74] Other results have revealed that *o*-hydroxyphenyl-α, β-acetylenic ketones can be cyclised under acidic conditions (30% hydrobromic acid/acetic acid,[84] and *p*-toluenesulfonic acid[96]) to give flavones in moderate yield.

Cyclisation reactions using non-substituted precursors.
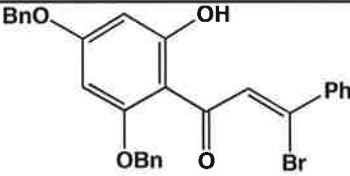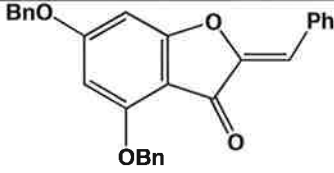
The cyclisation of the novel acetylenic ketones was attempted firstly using the un-substituted phenyl derivative (**106xi**) as a model compound, in hope of forming the flavone (**111**) (Scheme 43).

(106a)   (111)
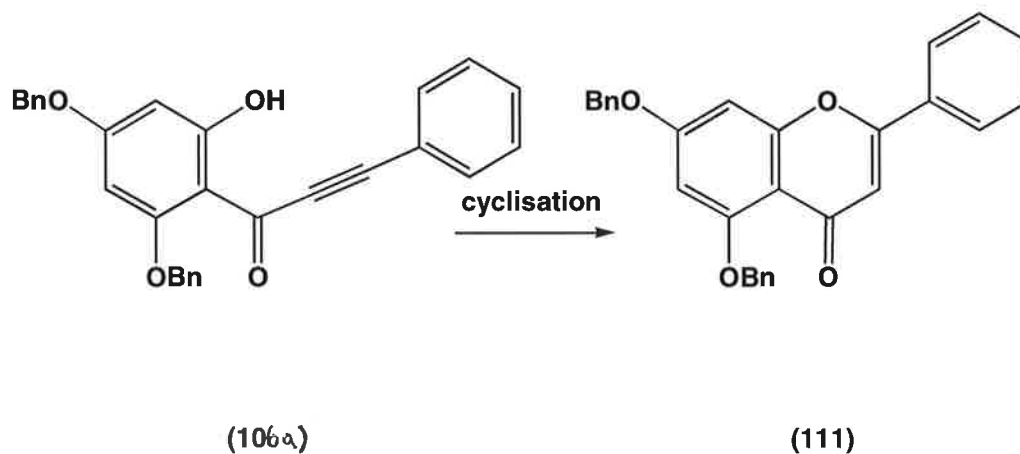
Scheme 43

Table 9: Products from the ring closure reaction of the acetylenic ketone (103).

Entry	Conditions	Product
1	1.5eq. K_2CO_3, acetone, Δ, 2.5h	 (104) 42% (isolated)
2a	1.2eq. K_2CO_3, d_6-acetone, RT, 23h, n.m.r	 (104) + (*E*)-isomer (**117**) (2:1-^{1}H n.m.r)
2b	1.2eq. K_2CO_3, acetone, RT, 2h	 (104) + (*E*)-isomer (**117**) (32:1-^{1}H n.m.r)
3	TFA, d_6-benzene, RT, 1h, n.m.r	Starting material

4	4N HBr, 1,4-dioxane, 65°C, 3.5h	 **(118)** + ring brominated product [**(119)** or **(120)**] (1:2-^{1}H n.m.r)
5	*p*-TsOH (cat), CH$_2$Cl$_2$, Δ, 23h	Starting material
6	Et$_2$NH, EtOH, Δ, 24h	 **(104)** 64% + (*E*)-isomer 12% (isolated)

The treatment of (106a) under basic conditions (potassium carbonate in refluxing acetone, Table 9, entry 1) gave only the aurone **(104)** in 42% yield. The procedure used was similar to that of Garcia and co-workers who claimed that cyclisation under these conditions using similar molecules gave predominately flavones.[74] The aurone was identified by comparison with spectral data and a crystal structure obtained previously (Figure 6). One feature of the ^{1}H n.m.r spectrum may be used to distinguish aurones from flavones. The 2',6'-phenyl hydrogens are shifted down-field in aurones (*Z* and *E*), compared to flavones, due to the deshielding anisotropic effect of the carbonyl group (*E*-aurones) and the lone pair of electrons on the ring oxygen (*Z*-aurones), on these protons.[93] This anisotropic effect over rides the shielding of the 2',6'-protons caused by resonance associated with the ring oxygen. In flavones the 2',6'-protons cannot be shielded by resonance as charge can only by localised on the α-carbon (or in the carbonyl group). These protons are not effected by anisotropy as described before, and thus have no distinctive downfield shift. For a range of aurones, these protons appeared between δ7.76-8.22 of the ^{1}H n.m.r spectrum,[93] which was in agreement with the two proton multiplet obtained for the (*Z*)-aurone **(104)** at δ7.85. Aurones can also be distinguished from flavones by ^{13}C n.m.r spectroscopy using differences in the δ values of the central three carbon

unit (alkene carbons and carbonyl carbon), employing a range of values formulated from many aurones and flavones.[104] Another means of determining aurone from flavone is by UV-vis spectroscopy.[105] In general, aurones show absorbencies at a higher wavelength than flavones.[105]

To confirm the flavone was not being formed first and converted to aurone, the reaction was followed by ^{1}H n.m.r (Table 9, entry 2) using d_6-acetone at room temperature. The aurone was the only product observed when the reaction was monitored over 1 h. The β-proton of the aurone was not visible in the spectrum probably due to deuteration. When the spectrum was monitored for 23 h using the same conditions, the spectrum still showed peaks due mainly to the (Z)-aurone by comparison with the ^{1}H n.m.r spectrum obtained previously for the aurone (**104**), for which the stereochemistry was determined by x-ray crystallography (Figure 6). Hastings and co-workers have discovered that the (Z)- and (E)-aurones, such as (**104**) and (**117**) could be distinguished by ^{1}H n.m.r spectroscopy using both the differences in the shifts of the β-hydrogens and the 2' and 6' hydrogens of the phenyl ring.[93] The β-hydrogen shift alone, did not unambiguously determine the stereochemistry of the double bond.

(Z)-(**104**)   (E)-(**117**)
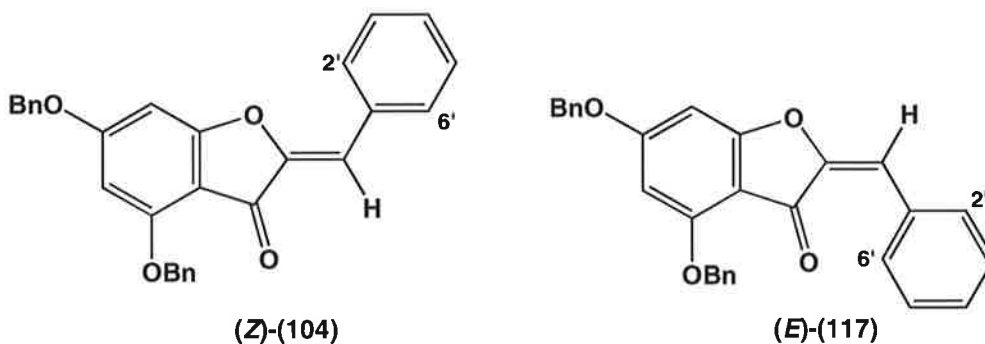
The resonance effect caused by the ring oxygen (mesomeric effect) meant that the β-hydrogens are shielded in both (Z) and (E)-aurones,[93] however it was reported that if the hydrogen was *trans* to the oxygen atom (*ie. Z*), it would appear upfield in the ^{1}H n.m.r spectrum than if it were in the *cis* (*ie. E*) arrangement.[93] Additionally, the β-hydrogens are de-shielded by the anisotropic effect of the carbonyl group in Z-aurones and the lone pair of electrons on the ring oxygen in E-aurones.[93] The combination of the resonance and the anisotropic effect means that the shift of the β-hydrogen in Z-aurones is more upfield than in E-aurones.[93] Similarly, the 2'- and

6'-phenyl protons are shielded by resonance from the ring oxygen in both isomers however, the anisotropic deshielding caused by the carbonyl in the (*E*)-aurone such as (**117**), means that the 2', 6'-protons in (*E*)-aurones appear more downfield than in (*Z*)-aurones.[93] The infrared absorption between 1800-1500 cm^{-1} was found to be characteristic and distinguish between the two aurone isomers.[93] By comparison with the published IR data, the (*Z*)-stereochemistry of the aurone (**104**) was inferred.

Hastings and co-workers have suggested that the (*Z*)-aurone is the more stable of the two aurone isomers.[93] Another minor product from the ^{1}H n.m.r reaction using d$_6$-acetone (Table 9, entry 2) in a 2:1 ratio with the (*Z*)-aurone was also evident in the spectrum after 23 h. This product showed similar signals to the (*Z*)-aurone. The ^{1}H n.m.r spectrum showed another two hydrogen multiplet at δ8.22-8.26 due to de-shielding of the 2' and 6' phenyl hydrogens which was most likely due to the (*E*)-isomer (**117**), as the signals were more downfield than the corresponding signals from the (*Z*)-isomer. As discussed previously, the flavone would not give the same de-shielded signals for the 2' and 6' phenyl hydrogens. The cyclisation reaction was repeated using non-deuterated acetone (Table 9, entry 2b) for clarity. After 2 h, the reaction showed mainly (*Z*)-aurone (**104**), but also a trace of (*E*)-aurone (**117**) in a ratio of 32:1 according to the crude ^{1}H n.m.r spectrum. The β-hydrogens were visible in this spectrum at δ6.77 and 6.81 for (*Z*)- and (*E*)-isomers respectively. The downfield shift of δ6.81 compared to the shift of the β-hydrogen for the (*Z*)-aurone was in agreement with the rationale proposed by Hastings and co-workers, as discussed previously. (*E*)-Aurones can be obtained by photo-isomerisation of (*Z*) aurones in high yield,[93] which was most likely to be the cause of isomerisation [the n.m.r sample (Table 9, entry 2a) was left on a bench (in the presence of light) for 23 h, resulting in a greater potential for isomerisation].

The cyclisation reactions of the acetylenic ketone (**106a**)have shown that the use of basic conditions for ring closure results in the aurone (**104**), which Garcia and co-workers suggest is through a kinetically controlled attack by the phenolate oxygen at the α-carbon of the triple bond.[74] It has also been noted that aurone formation, instead of flavone formation, was only observed in acetylenic ketone systems containing an aromatic group attached to the triple bond,[106] similar to our case. This

and a combination of other factors led Sakamoto and co-workers to propose a radical intermediate that led to the formation of the undesired aurones. However the addition of radical traps to their experiments did not diminish aurone formation.[106] The mechanism of aurone formation is complicated,[74,103,106] but it has been suggested that in the absence of a proton source, (phenolic hydrogen, protic solvent), flavone formation should be universal. Thus, the presence of proton sources, such as the phenolic hydrogen and maybe water, may explain why aurone was formed rather than flavone. As these results (aurone formation rather than flavone) were in stark contrast to what has been found by others,[74,96,97] the cyclisation reaction was attempted using acidic conditions.

It was expected that by using acidic conditions for ring closure, protonation of the carbonyl group would occur allowing for preferential attack at the β-acetylenic carbon by the phenolic group, as a result of the positive charge at this position caused by conjugation.[106] Alvaro and co-workers have also noted that flavone formation can also be accomplished under acidic conditions.[96] However, when the reaction of the acetylenic ketone (106a) was conducted in d_6-benzene using trifluoroacetic acid and following by [1]H n.m.r, only starting materials were observed after 1 h at room temperature (Table 9, entry 3). Heating this mixture at reflux for ten minutes and then re-running the spectrum, still led to the recovery of starting materials.

The cyclisation of an acetylenic ketone to a flavone using hydrobromic acid in 1,4-dioxane has been described by Obrecht and co-workers (Table 9, entry 4).[98] Hydrobromic acid was thought to add across the triple bond, giving a bromo-chalcone with the bromine group at the β-position of the double bond.[98] Nucleophilic attack of the phenolate group then displaced the bromine group to give the required flavone by an addition/elimination sequence. Using Obrecht and co-worker's conditions, the reaction of the acetylenic ketone (106a) gave what appeared to be the β-bromochalcone (**118**) (Table 9, entry 4) together with a possible ring brominated product, in a ratio of 1:2 respectively according to the crude [1]H n.m.r spectrum. The spectrum showed no distinctive phenyl 2',6'-hydrogen signals of the aurone, and t.l.c showed the absence of starting alkyne. Evidence for the bromochalcone structure (**118**) was the presence of two benzyloxy groups, indicated

by two, two hydrogen singlets that appeared at $\delta 5.07$ and 5.11. The ^{1}H n.m.r spectrum also showed two doublets at $\delta 6.14$ and 6.22 of 2.1 Hz, which were indicative of the 3- and 5-ring hydrogens and suggested that the ring had not been additionally substituted by a bromine atom. The α-proton of the double bond was presumed to be contained in the aromatic region of the spectrum ($\sim \delta 7.03$), hidden by a multiplet from $\delta 6.15$-7.51. The major product [(**119**) or (**120**)] in the spectrum was thought to have bromine substitution in the ring as indicated by a one hydrogen singlet at $\delta 6.15$, indicative of either the 3- or 5-ring proton. The two methylene benzyloxy groups appeared at $\delta 4.99$ and 5.10, shifted further apart than the starting material, a possible response to the bromine substituent. From the data available, it could not be determined if the triple bond of (**119**) or (**120**) had undergone hydrobromic acid addition. No further characterisation of these products was made due to the small amount of sample obtained.

(**119**) R =H, R' =Br
(**120**) R =Br, R' =H
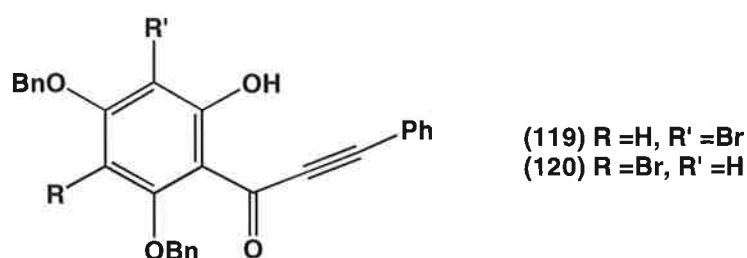
Alvaro and co-workers have shown that the cyclisation of acetylenic ketones such as (**121**), occurs under both basic and acidic conditions (Scheme 44) and gives the chromone (**122**) in quantitative yield.[96]

(**121**)   (**122**)
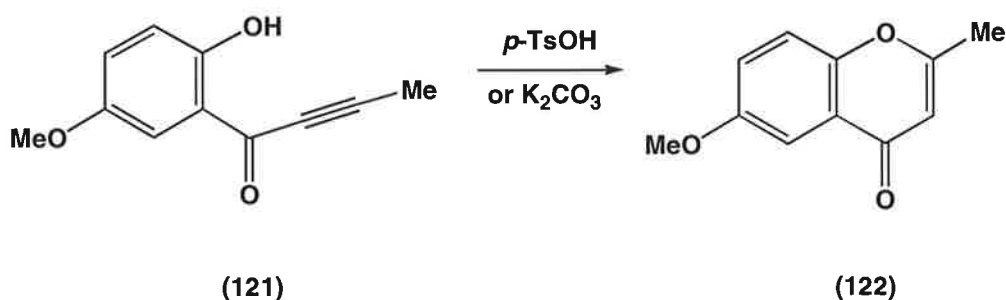
Scheme 44

Hence the cyclisation of the phenyl substituted acetylenic ketone (**106a**) was attempted using a catalytic amount of *p*-toluenesulfonic acid in refluxing dichloromethane for 23 h (Table 9, entry 5). After 30 min the reaction showed only starting material by t.l.c. It has been suggested that a radical mechanism may cause

aurone formation,[106] therefore a small amount of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction in hope of alleviating this problem. After 23 h in the presence of both *p*-toluenesulfonic acid and TEMPO, the initial acetylenic ketone was the only material isolated. The lack of reactivity of the acetylenic ketone (**106a**)using acidic conditions compared to (**121**) was surprising.

Bhat and co-workers have shown that enaminoketones derived from acetylenic ketones, cyclise to flavones *via* an addition/elimination process in one step.[53] This methodology is outlined using the acetylenic ketone (**106a**)in Scheme 45.

(106a)

(123)

(111)
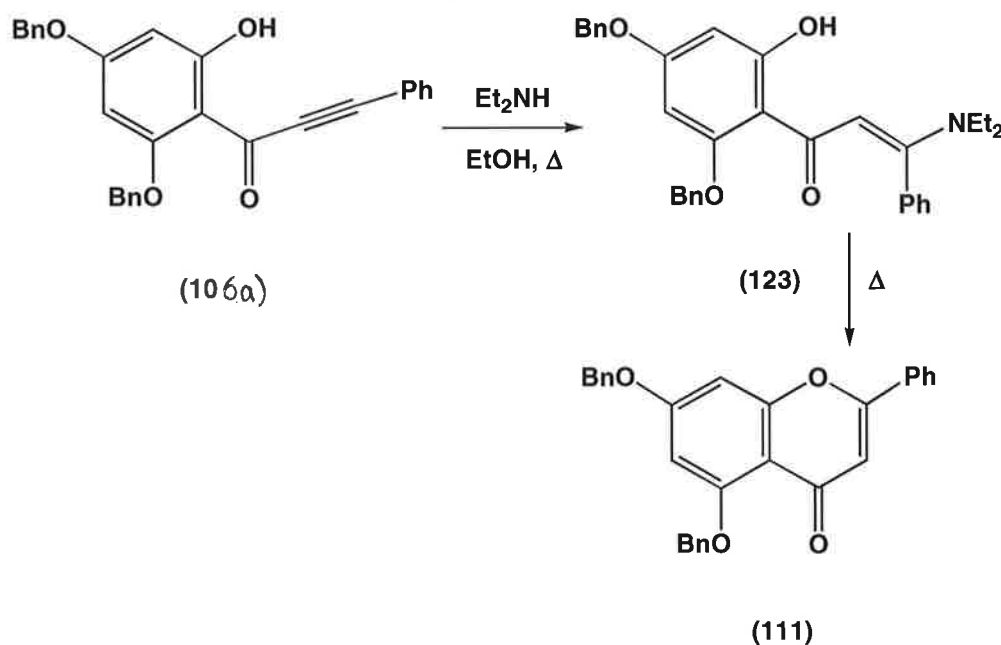
Scheme 45

Hence the reaction was conducted (Table 9, entry 6), in a refluxing solution of diethylamine and ethanol over 24 h, but gave only the (*Z*)-aurone (**104**) in 64%, together with a small amount of the (*E*)-aurone (**117**). Two examples in the literature involve cyclisation of an acetylenic ketone where the phenolic group was initially protected.[53,106] During reaction in diethylamine, the protected phenol became deprotected, the phenolate anion then attacked the enaminoketone such as (**123**) to give a flavone.[53] Another example claimed that cyclisation of an acetylenic ketone containing an unprotected phenol in diethylamine, gave exclusively flavone.[95] This result was in contrast to the results obtained (Table 9, entry 6). It can be postulated that aurone formation was a result of proton abstraction from the phenol (**106a**)by diethylamine, to give the phenolate anion, which attacked the α-carbon of the triple

bond. This was similar to the results obtained (Table 9, entries 1 and 2) using basic conditions (potassium carbonate in refluxing acetone) to effect cyclisation. As the aurone (**104**) was obtained from the reaction rather than the flavone (**111**), deprotonation of the phenol then cyclisation must have occurred faster than the addition of diethylamine to the triple bond. Protection of the phenol group, then reaction in diethylamine may be a way of alleviating this problem. The literature indicated that in most cases the cyclisation of an acetylenic ketone to yield a flavone via an enaminoketone intermediate proceeded when the phenol was protected rather than in its free form.[53,106]

Protection of the phenol group.

The protection of the phenol with a trimethylsilyl group was first attempted using standard conditions (Scheme 46).[24]

(10**6**a)

(**104**)
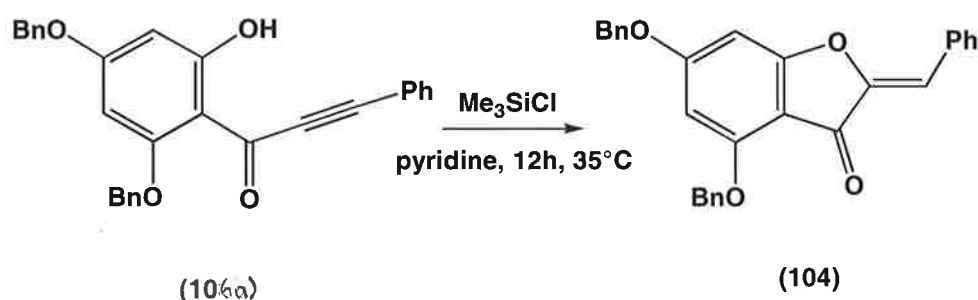
Scheme 46

Surprisingly the product was the (*Z*)-aurone (**104**) in 55%. The aurone formation rather than the silyl ether formation may have been a result of the phenolate anion attacking the triple bond in preference to or more quickly than its reaction with trimethylsilyl chloride. In some cases, reaction of systems similar to that of the acetylenic ketone (10**6**a) with a tertiary amine has led to aurone formation.[95] Thus this method was not investigated further, nevertheless it could be a useful alternative for the formation of an aurone (and needs to be investigated further).

Another way to protect the phenol group was as the *tert*-butyldimethylsilyl ether (TBDMS). This silyl group is more robust than the trimethylsilyl group and was hoped to be a better choice. *tert*-Butyldimethylsilyl triflate was thought to be a superior reagent than *tert*-Butyldimethylsilyl chloride as it has been used for the protection of unreactive secondary alcohols and tertiary alcohols where other reagents have

failed.[107] This reagent is also very reactive, especially at low temperatures, which was advantageous in our case. The reaction proceeded using 2,6-lutidine as base in CH$_2$Cl$_2$ with addition of the triflate[107] at -20°C. After stirring at room temperature for 1 h, a pale yellow solid was obtained that had a much higher Rf value than that of the starting alkyne or the aurone when analysed by t.l.c. The ^{1}H n.m.r spectrum showed two singlets at δ0.30 (6H) and 1.15 (9H) indicating the presence of a *t*-butyldimethylsilyl (TBDMS) group. The two aromatic protons on the substituted ring appeared as two doublets at δ6.28 and 6.48, with *meta* coupling of 2.0 Hz. These signals in the starting phenol appeared at δ6.07 and 6.16 (J=2.5 Hz). This information suggested that (**124**) had formed, and the product was used in the cyclisation reaction without further purification.
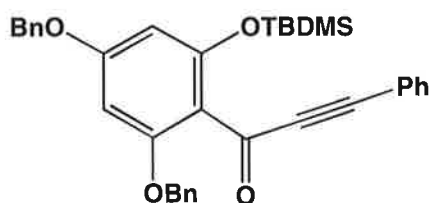
(**124**)

Bhat and co-workers had shown that the conversion of TBDMS-protected phenol containing alkynones to enaminoketones and subsequent cyclisation, could be effected in a single step using 10 equivalents of diethylamine in refluxing ethanol over 48 h.[53] When (**124**) was refluxed for 24 h in the presence of diethylamine, a single product was isolated from the reaction mixture. T.l.c showed a much lower Rf than the silyl ether (**124**), suggesting the molecule had been deprotected, which was confirmed by ^{1}H n.m.r spectroscopy. The ^{1}H n.m.r spectrum appeared different to both the starting alkyne (**106a**)and the aurone (**104**). However, as the spectrum still contained ethyl peaks indicative of the non-cyclised enaminoketone intermediate (δ2.88-3.10, 3.66-3.92), and a one hydrogen singlet at δ5.64 in the spectrum indicative of the α-hydrogen implying the structure (**123**), it was refluxed again in diethylamine for a further 24 h. Upon work-up, two other products were evident in the reaction mixture (t.l.c, ^{1}H n.m.r) together with the signals from the possible intermediate (**123**) initially obtained. None of the signals in the ^{1}H n.m.r spectrum of the mixture corresponded to those of the aurone (**104**) (however the spectrum of the mixture was complex). By considering the integration values of the signals, it was

evident which signals corresponded to the two new products. One compound contained an α-proton at δ6.68 (singlet) and two doublets at δ6.67 and 6.51 (*J*=2.1 Hz) corresponding to the two protons contained on the substituted aromatic ring. The methylene signals from the protons on the benzyl groups appeared at δ5.29 and 5.13. The other product contained an α-proton signal at δ6.38 and two doublets at 6.11 and 6.10 (*J*=2.4 Hz) (aromatic ring protons). The benzyl signals appeared as two singlets at δ5.06 and 5.01. Either one of these products may be the required flavone as they both contain signals expected for the desired flavone. Individual components of the mixture were unable to be obtained by chromatography.

The cyclisation reaction of the phenyl acetylenic ketone (**106a**) under basic or acidic conditions gave either unwanted products or starting material respectively. When the phenol of (**106a**) was protected, in this case as a TBDMS-ether, deprotection and cyclisation gave product mixtures including possibly the enaminoketone intermediate (**123**), which could not be cleanly separated. As the required epicatechin structures contain substitution in the phenyl ring, attention was turned to cyclisation reactions involving these types of precursors. It was also hoped that electron-donating substitution in these molecules might allow the formation of flavones through direct methods that did not work for the non-substituted acetylenic ketone (**106a**).

Cyclisation reactions using substituted precursors.

The cyclisation of substituted acetylenic ketones commenced with reactions using the trimethoxysubstituted molecule (**110**); the products expected were either the aurone (**125**) (or its *E*-isomer), the flavone (**126**) or a combination of all (Scheme 47).

(110)

cyclisation

(125)

OR

(126)
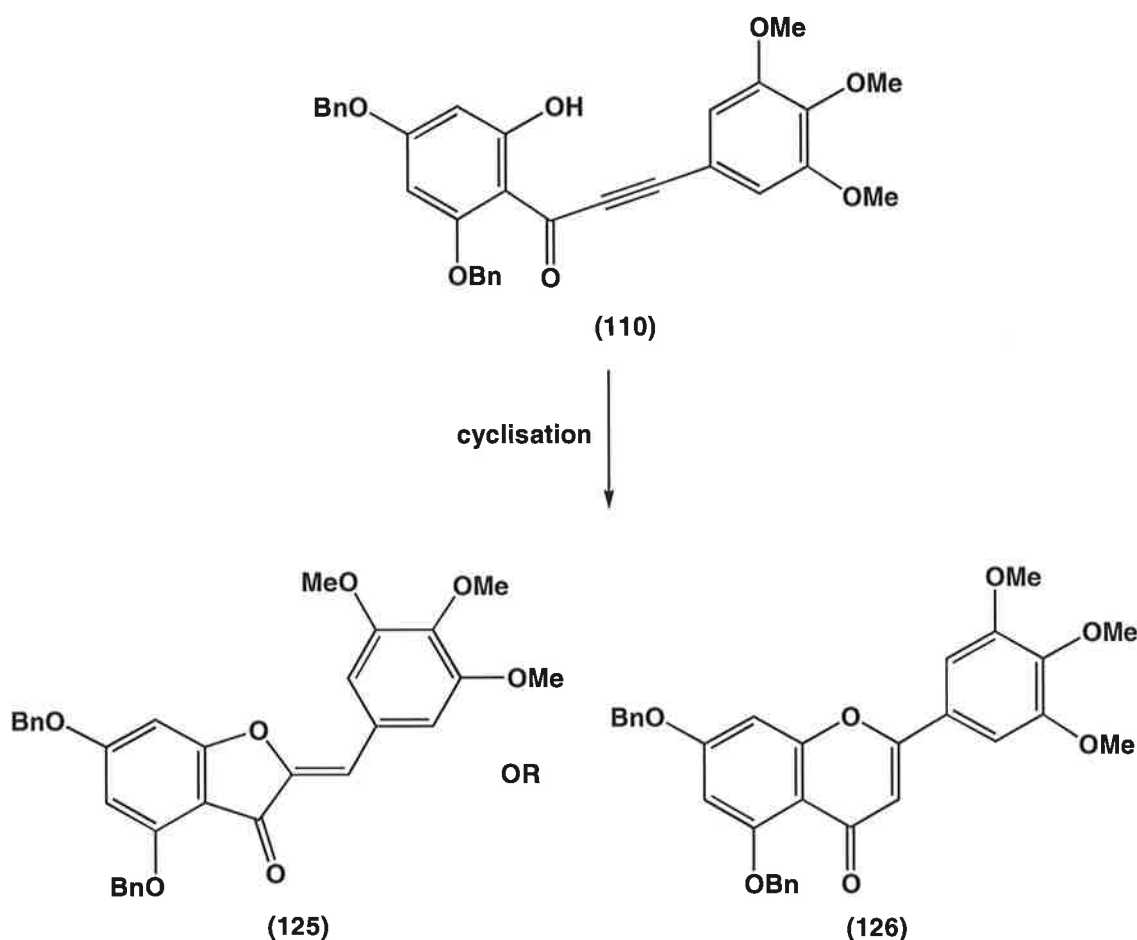
Scheme 47

Table 10: Cyclisation reactions of the 3,4,5-trimethoxy substituted acetylenic ketone (110).

Entry	Conditions	Product
1	1.5eq K_2CO_3, acetone, Δ, 40 min	(Z)-Aurone (125) (quantitative)
2	Trifluoroacetic acid, 50°C, 1½ h	Complex mixture
3	Diethylamine, ethanol, Δ, 24 h	(Z)-Aurone (125), 20%
4	KF, 18-crown-6, DMF, ambient temp., 2 h	(Z)-Aurone (125) (major) + unknown by-product (minor)

Refluxing a solution of the acetylenic ketone (110) with potassium carbonate in acetone (Table 10, entry 1),[74,83,96] led to the formation of aurone (125) in quantitative yield. The mass spectrum of the aurone gave a strong molecular ion at *m/z* 524. The (Z)-aurone (125) was identified by n.m.r spectra [similar to that of the previously obtained (Z)-aurone (104)]. The ^{1}H n.m.r spectrum showed the three methoxy groups at δ3.91 (one group) and 3.94 (two groups). The benzyl methylene

protons showed two signals at δ5.10 and 5.28 confirming that there were still only two benzyloxy groups present in the molecule. The two aromatic protons adjacent to the benzyloxy groups on the substituted ring, at δ6.24 and 6.43 coupled to each other with a coupling constant of 1.5 Hz. The distinctive upfield shift of the β-proton of the olefinic group appeared at δ6.69, similar to that of the aurone (**104**), was due to shielding by resonance as discussed previously. The two aromatic protons on the trimethoxy ring appeared as a singlet at δ7.13, a downfield shift from δ6.52 in the starting material, consistent with aurone shifts found previously.[93] Aurone formation was similar to that found using the un-substituted phenyl-acetylenic ketone (**10(a)**), showing that the substitution of the three methoxy groups on the ring had caused no preference for attack at the β-carbonyl carbon, over attack at the α-carbon.

When (**110**) was treated with trifluoroacetic acid at 50°C for 1.5 h (Table 10, entry 2), a complex mixture of products was evident by n.m.r and t.l.c, none of which were identified as starting material.

The cyclisation (Table 10, entry 3) was conducted using similar methodology for the un-substituted phenyl derivative, where the free phenol remained unprotected. The reaction proceeded in a refluxing ethanolic solution of diethylamine over 24 h. The reaction gave a yellow solid in 20% that was identified as the (Z)-aurone (**125**).

Stirring a solution of the acetylenic ketone (**110**) in DMF containing 18-crown-6 and potassium fluoride (Table 10, entry 4), gave a crude product that contained mainly the aurone (**125**) in its [1]H n.m.r spectrum, by comparison with data previously obtained (Table 10, entry 1). Three small signals were visible near the baseline at δ6.14 and 6.34 (doublets, J=1.5 Hz) and at δ6.62 (singlet), that were different from the aurone (**125**) or the acetylenic ketone (**110**). The other signals from this potential product were obscured by the signals of the aurone (**125**), however the three visible signals may possibly be from either the (E)-aurone or the required flavone (**126**). The reaction mixture was not purified further as the [1]H n.m.r spectrum showed that the (Z)-aurone (**125**) was the major product of the reaction, and the unknown was present in a much smaller quantity. From these cyclisation reactions it was obvious that the extra trimethoxy substitution of the aromatic ring did not aid in the generation

of the flavone structure and that the aurone was obtained as the primary product. Aurone formation may be due to the small scale of these reactions, thus increasing the effect of protic materials such as water on the cyclisation reactions. Unfortunately time and an absence of starting materials did not permit further investigation into the cyclisation of these acetylenic ketones in the absence of a proton source. These conditions may be generated by protecting the free phenol group of an acetylenic ketone as a silyl ether, then reacting the protected molecule under the conditions described (Table 10, entry 4), which has been successful for other acetylenic ketones that were prone to aurone formation rather than flavone formation.[103] The assignment of a number of reported flavones may need to be clarified, since in many cases, the structures described are not justified and the data provided does not rule out the corresponding aurones as the products. This may mean that flavone formation is not as facile as suggested in the literature.[74,83,95,98]

β-Chlorochalcones may also be potential flavone precursors, similar to the enaminoketone[53] and bromochalcone[98] intermediates mentioned previously. Hence it was of interest to examine the potential for the phenoxide anion to add, in a 1,4 manner to the β-chloro α, β-unsaturated system of (**108**). Reaction of the phenol (**108**) with sodium hydride in dichloroethane (Scheme 48) for 30 min, showed that one product was obtained in quantitative yield with no starting material evident (t.l.c). The mass spectrum of this material showed a strong molecular ion at *m/z* 494, suggesting the aurone (**127**) or flavone (**128**) had been formed. Additional spectral data was needed to distinguish between the two potential products.

(108)

NaH, Cl(CH)₂Cl, Δ

(128) OR **(127)**
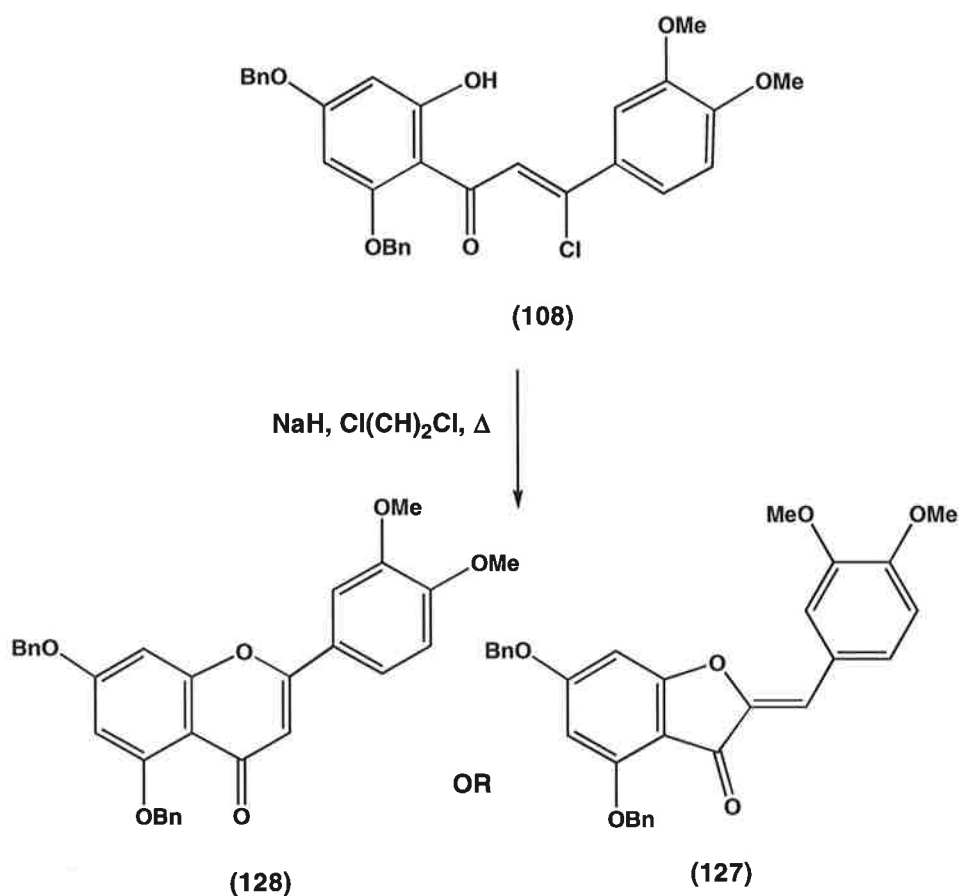
Scheme 48

Ultra-violet visible spectra were run on two aurones that had been previously obtained **(104)** and **(125)** as well as the unknown product. The aurone **(104)** had been identified unequivocally by x-ray crystallography (Figure 6).

(104) **(125)**
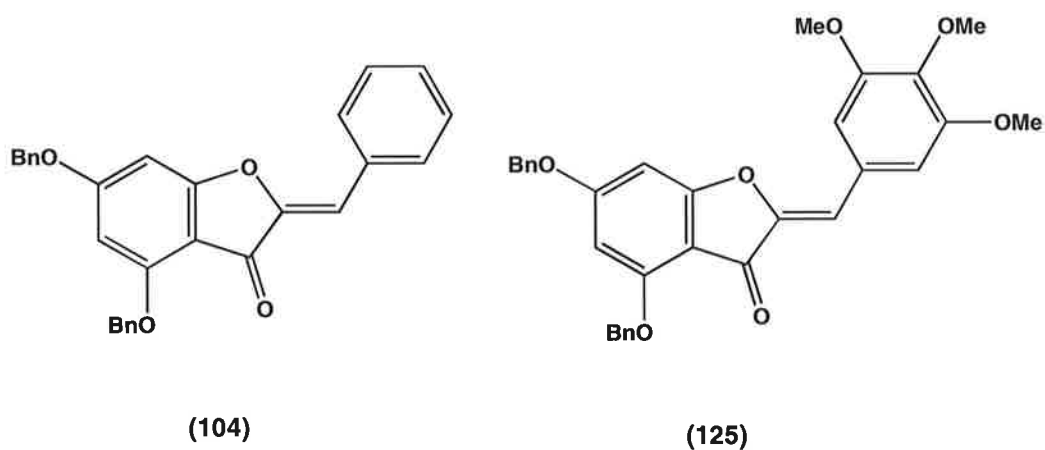
The UV-spectra of the two aurones and the unknown all showed a very strong absorbance below 300 nm. The only other band visible was at λ_{max} 367 for the

non-substituted aurone (**104**), λ$_{max}$ 384 for the trimethoxy substituted aurone (**125**) and at λ$_{max}$ 397 for the dimethoxy substituted unknown. However, for more than one hundred similarly substituted flavones, the UV spectra showed no absorbances above λ$_{max}$ 354.[105] Furthermore, a comparison of 6,8-dimethylflavone with 5,7-dimethylaurone gave bands at λ$_{max}$ 300 and 380 respectively,[74] suggesting that the unknown was the aurone (**127**).

600 MHz n.m.r spectroscopy data was used to further distinguish between the aurone (**127**) and the flavone (**128**).

Table 11: 600 MHz correlations for the proton at position-3 of the flavone (128) or the aurone (127) with specific carbon atoms.

Compound	^{1}H	^{13}C (HMQC)	^{13}C (HMBC)
	δH	δC	δC*
Flavone (**128**)	6.66 (α-H)	111.21	113.64 (C2') **4**, 125.27 (C6') **4**, 125.56 (C1') **3**, 146.89 (C2) **2**, 149.00 (C3') **5**, 180.35 (C=O) **2**.
Aurone (**127**)	6.66 (α-H)	111.21	113.64 (C2') **3**, 125.27 (C6') **3**, 125.56 (C1') **2**, 146.89 (C2) **2**, 149.00 (C3') **4**, 180.35 (C=O) **3**.

* Bold numbers refer to $^nJ_{CH}$ where n = the number of bonds over which the coupling interaction is observed.
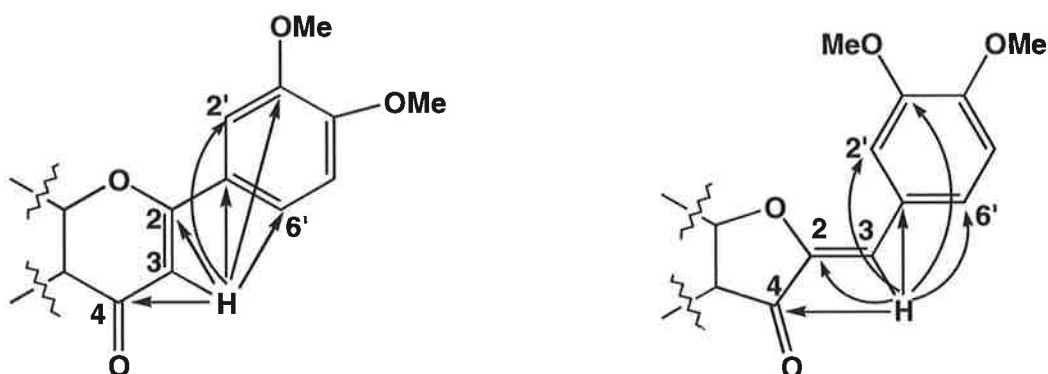
Figure 10: 600 MHz HMBC correlation of the proton at postion-3 of the flavone and aurone respectively, to the designated carbon atoms.

The data outlined in Table 11, suggested that the product obtained in the cyclisation reaction was more likely to be aurone than flavone due to the number of bonds over which the interaction of the proton at position-3 occurred with specific carbon atoms shown in Figure 10. $^{n}J_{CH}$ (n =2, or 3) are typically observed.[71] If the product was the aurone (**127**) the values (Table 11) of the proton at position-3 to the carbons listed would be n =2,3 or 4, whilst if the product was the flavone (**128**), these values would be n =2,3,4 or 5 which are a more unacceptable range. More specifically the $^{n}J_{CH}$ values for the HMBC correlation between the proton at position-3 and the carbons at postions-2' and –6' have a n =3 for the aurone, which is a more agreeable value than n =4 of the flavone,[71] especially since the cross peak gave a strong signal in the spectrum, loosely suggesting that the product formed was the aurone (**127**) rather than the flavone (**128**).

Further experimental data was needed to confirm the identity of the product formed in the cyclisation reaction (Scheme 48). The ^{13}C n.m.r spectra of a wide variety of flavanoids and related compounds have been reported by Pelter and co-workers.[104] A range of chemical shifts were formulated for the central three-carbon unit of a wide variety of flavones (**129**) and aurones (**130**).[104]
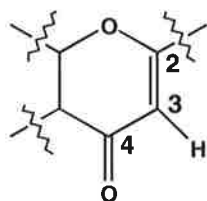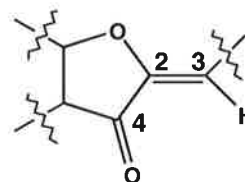
(129) (130)

Table 12: The ^{13}C n.m.r chemical shifts of the three carbon unit from a range of literature flavones and aurones,[104] together with the unknown obtained from the cyclisation reaction (Scheme 48).

Molecule	δC2	δC3	δC4 (C=O)
Flavones	160.5-163.2	104.7-111.8	176.3-178.3
Aurones	146.1-147.7	111.6-111.9	182.5-182.7
Unknown (Scheme 48)	146.88	111.21	180.35

This data again suggests that the unknown product is more likely to be aurone than flavone, especially when comparing the chemical shift for the carbon at position-2, which appears to be the distinguishing feature of flavones from aurones.

The reaction of the dimethoxy substituted acetylenic ketone (**109**), using the conditions that gave quantitative conversion of the trimethoxy substituted acetylenic ketone (**110**) to aurone (**125**) (potassium carbonate in refluxing acetone), afforded a product in quantitative yield that possessed an ^{1}H n.m.r spectrum identical to that obtained from the cyclisation of the dimethoxy substituted β-chlorochalcone (**108**). This reaction, the UV experiments, the 600 MHz n.m.r data and the ^{13}C n.m.r spectra and all suggest that the unknown product was the aurone (**127**).
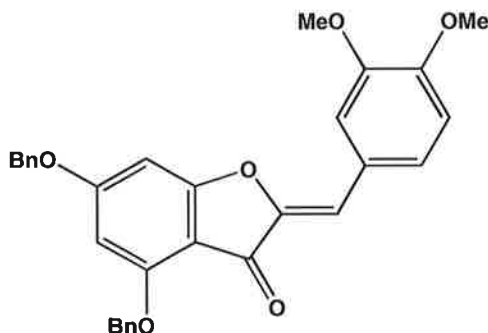
(**127**)

The formation of the aurone is likely to be a result of the elimination of hydrogen chloride from the double bond of the adduct (**108**), giving the acetylenic ketone (**109**), which then cyclised to the aurone (**127**) as described previously in the chapter.

In an attempt to alleviate the preferable loss of hydrogen chloride from the adduct (**108**) so that direct cyclisation of the phenolate anion may occur, the reaction was performed in excess triethylamine, a milder base. After refluxing in dichloroethane for 2 h, the reaction still contained starting material as well as another product (t.l.c). The new product was identified by ^{1}H n.m.r spectroscopy as the aurone, which was contained in the crude mixture with the starting adduct (**127**), in a ratio of 1:2 respectively.

(V)   Conclusions

The results described in this section show that neither **Route A** nor **Route B** was suitable for the preparation of epicatechins due to problems encountered with the allylation and acylation reactions.   A suitable route to dialkyl substituted phloroglucinols was discovered using allylation reactions outlined in **Route A**. **Route B** described the acylation of protected phloroglucinol systems with substituted arylpropiolic acids, which gave novel chalcone structures in which another phloroglucinol system had added to the initial acylation adduct.   By altering the acylation conditions, aurones can be generated in one step by the acylation of a phloroglucinol derivative, using an acid chloride and ferric chloride.   When this reaction was catalysed by zinc chloride a range of substituted acetylenic ketones and/or their hydrogen chloride adducts were formed in moderate yields, an advantage of this reaction being that the deprotection of one of the three benzyloxy groups had occurred *in situ*, creating molecules that could be cyclised directly.   In all cases cyclisation using a wide variety of conditions (**Route C**), gave aurones in good to excellent yields.   Further research is required on the cyclisation reaction to see whether pH and solvents differences may control the direction of cyclisation.

Chapter 6:   Experimental

General.

Melting points were determined on a Kofler hot-stage micro-melting point apparatus equipped with a Reichart microscope and are uncorrected.

Elemental analysis was performed at the University of Otago, New Zealand. High-resolution accurate mass spectra were performed by the University of Tasmania mass spectrometric service.

Ultraviolet-visible (UV-Vis) spectra were recorded on a Varian Cary 300 Bio UV-Visible Spectrophotometer as solutions in methanol in quartz cells.

Infrared spectra were recorded on a Hitachi 270-30 spectrometer, or a Perkin Elmer Spectrum BX, or a ATI Mattson Genesis FTIR as nujol mulls or liquid films between sodium chloride plates.

^1H n.m.r and ^{13}C n.m.r spectra were recorded on a Varian Gemini-200 (200.13 and 50.32 MHz, respectively) spectrometer or a Varian Gemini-2000 (300.13 and 74.47 MHz, respectively) spectrometer or a Varian Inova (599.95 and 150.87 MHz, respectively) spectrometer.   Spectra were obtained for solutions in $CDCl_3$ [tetramethylsilane (δ_H 0.00 for $SiMe_4$) and $CDCl_3$ (δ_C 77.77) as internal standards] at 25°C, or in $CDCl_3$ containing either d_6-DMSO or d_6-Acetone [tetramethylsilane (δ_H 0.00 for $SiMe_4$) and $CDCl_3$ (δ_C 77.77) as internal standards] at 25°C. J values are expressed in Hz.   Chemical shifts are quoted on the δ-scale in parts per million (ppm), followed by multiplicity, coupling constant(s) and assignment. The following abbreviations have been used in reporting spectra data: s, singlet; d, doublet;

t, triplet; q, quartet, m, multiplet; broad b. A range is give when describing multiplets of well defined boundaries.

Electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded at 70 ev on a Vacuum Generators ZAB 2HF mass spectrometer. LC-Q and GC-Q mass spectra were recorded on Finnigan mass spectrometers.

Flash chromatography was performed on Silica Gel 60, 230-400 mesh (Merck) or Sephadex LH-20 (Pharmacia) were stated. Thin layer chromatography was performed on either aluminium backed Silica Gel 60 plates (Merck) or Aluminium oxide 150 plates (Merck) and were visualised by UV light (254 nm) or by staining with either potassium permanganate dip [potassium permanganate (3 g) and potassium carbonate (20 g) dissolved in aqueous sodium hydroxide solution (5%, 5 ml) and water (100 ml)] or vanillin dip [vanillin (3 g) dissolved in ethanol (100 ml) containing sulfuric acid (0.5 ml)].

Solvents and general reagents were purified and dried using standard laboratory procedures,[108] and stored under an atmosphere of nitrogen. All organic extracts were dried over either anhydrous sodium sulfate or anhydrous magnesium sulfate. All reactions were conducted under an atmosphere of nitrogen, unless otherwise stated.

The following reagents were prepared according to published procedures: pyridinium p-toluenesulfonate,[109] pyridinium chlorochromate,[44] aluminum isopropoxide,[110] Dess-Martin periodinane,[111] and tert-butyldimethylsilyl triflate.[107]

Part 2, Chapter 2.

Extraction and isolation of Catechins from Green Tea leaves.[20]

Green tea leaves (Butterfly brand) (10 g) were ground to a fine powder and macerated with an aqueous solution of ethanol (1:1) (25 ml x 4). The ethanol was removed under reduced pressure and the remaining aqueous layer extracted with ethyl acetate (25 ml x 4). The brown solution was dried ($MgSO_4$) and concentrated to give a pale brown solid (1.47 g, 14.7% by weight of the original amount of tea). A sample of this fraction (0.40 g) was passed through a Sephadex LH-20 column (95% ethanol). The fractions containing similar Rf values by t.l.c were combined to give three separate fractions that were concentrated under reduced pressure. The last fraction (3) off the column contained mainly **EGCG (5)**, by comparison of spectral data.[6] Separate chromatography (silica, chloroform/methanol/formic acid, 76:19:5) of the other two fractions gave material which was further purified by p.l.c using the same solvent systems. From the original fraction one, slightly impure catechin (**1**) and **EC (2)** were obtained. Fraction two yielded samples of **EC (2)**, **ECG (4)**, **EGC (3)** and **EGCG (5)**. [1]H n.m.r analysis ($CDCl_3/d_6$-DMSO) showed peaks consistent with literature values for each of the catechins.[6]

Part 2, Chapter 3.

Protection of 3',4'-OH's.

Attempted formation of the acetonide.

(+)-Catechin (**1**) (0.20 g, 0.69 mmol) was added to a solution of *p*-toluenesulfonic acid (0.14 g, 1.30 mmol) dissolved in 2,2-dimethoxypropane (1.5 ml) and stirred for 20 h. The orange solution was neutralised with Amberlite resin (IRA-410) and filtered. A yellow gum was obtained on concentration of the filtrate, which afforded a pale pink solid and yellow oil after chromatograhy (silica, CH_2Cl_2, ethyl acetate, acetic acid, 60:40:0.5). The solid was identified as (+)-catechin (**1**), whilst the liquid showed multiple, complex signals by [1]H n.m.r.

Attempt 2.

(+)-Catechin (**1**) (0.20 g, 0.69 mmol) was suspended in acetone (10 ml), to which was added 2,2-dimethoxypropane (0.65 g, 6.26 mmol) and then *p*-toluenesulfonic acid (0.03 g, 0.17 mmol). The bright yellow solution was stirred for 17 h, then neutralised with Amberlite resin (IRA-400) over 3 h. The mixture was filtered and concentrated to give a pale yellow solid. Purification by chromatography (silica, 60% ethyl acetate in CH_2Cl_2) gave three products which all showed complex spectra (^1H n.m.r, ^{13}C n.m.r, IR and MS), none of which showed any sign of the required product.

Attempt 3.

(+)-Catechin (**1**) (0.20 g, 0.69 mmol) was dissolved in 2,2-dimethoxypropane (0.65 g, 6.26 mmol), to which was added D-camphor-10-sulfonic acid (0.01 g, 0.05 mmol) and the solution was then stirred for 18 h. The resulting mixture appeared cloudy and was diluted with ethyl acetate (20 ml) and washed with saturated $NaHCO_3$ (20 ml) and brine (20 ml). The solution was dried (Na_2CO_3) and concentrated to yield a white foam. Recrystallisation (heptane/ethyl acetate) gave a white solid that appeared as two products by t.l.c analysis (60% ethyl acetate in CH_2Cl_2). These products gave multiple, complex signals when analysed by n.m.r spectroscopy.

Attempt 4.

(+)-Catechin (**1**) (0.10 g, 0.34 mmol) was added dropwise to a stirred solution of iodine (9.00 mg, 0.04 mmol) in acetone (5 ml). After stirring at room temperature for 1 h, the iodine was destroyed with an aqueous solution of sodium hydroxide (0.1M) (4 ml). The resulting solution was extracted with chloroform (15 ml) and ethyl acetate (15 ml). The separate organic extracts were washed with water (20 ml) and dried over Na_2SO_4. The ethyl acetate fraction contained a single product by t.l.c. (Rf=0.3, MeOH/CHCl$_3$ 1:4) and was concentrated under reduced pressure to give 7',7'-dimethyl-5-hydroxy-*trans*-pubeschin (**13**) as a yellow gum (0.06 g, 53%). v_{max}(nujol): 3180 (OH), 1598 (C=C), 1142 (C-O-C) cm^{-1}. ^1H n.m.r (300 MHz, CDCl$_3$/d$_6$-DMSO) δ: 1.51 [s, 3H, Me], 1.52 [s, 3H, Me], 2.51 [dd, 1H, 10.5, 15.6 Hz, C(4)H-ax.], 3.02 [dd, 1H, 6.0, 15.6 Hz, C(4)H-eq], 3.87 [m, 1H, C(3)H], 4.52 [d, 1H, 9.3 Hz, C(2)H], 5.99 [s, 1H, C(8)H], 6.08 [s, 1H, C(6)H], 6.59 [s, 1H, C(5')H],

7.13 [s, 1H, C(2')H], 7.56, 8.07, 8.41, 8.48 [bs x 4, 4H, OH x 4]. D_2O shake removed only the peaks at δ: 7.56, 8.07, 8.41 and 8.48. ^{13}C n.m.r (75.47 MHz, $CDCl_3/d_6$-DMSO) δ: 27.49 [C4], 28.64, 32.10 [Me x 2], 67.00 [C3], 73.57 [C2], 76.06 [C7'], 95.53 [C8], 96.56 [C6], 100.72 [C4a], 112.29 [C2',C5'], 124.98 [C6'], 135.05 [C1'], 143.73 [C3'], 144.77 [C4'], 156.12 [C8a], 156.83 [C5], 156.98 [C7]. *m/z* 331 (MH$^+$, 28%), 316 (36), 192 (40), 177 (23), 139 (7). This data was consistent with that of the literature.[29]

To aid in identification, 7',7'-dimethyl-5-hydroxy-*trans*-pubeschin (13) (0.02 g, 0.05 mmol) was stirred at room temperature in acetic anhydride (1 ml) and a drop of pyridine. After 36 h the solvents were removed under reduced pressure, giving the pure tetra-*O*-acetyl derivative (0.02 g, 75%). ^1H n.m.r (300 MHz, CDCl$_3$) δ: 1.54 [s, 6H, Me x 2], 2.25, 2.27, 2.30, 2.32 [s x 4, 12H, Ac x 4], 2.64 [dd, 1H, 10.6, 15.6 Hz, C(7)H-ax.], 2.99 [dd, 1H, 5.8, 15.6 Hz, C(7)H-eq.], 3.95 [m, 1H, C(3)H], 4.68 [dd, 1H, 1.0, 9.0 Hz, C(2)H], 6.55 [d, 1H, 2.5 Hz, C(8)H], 6.68 [d, 1H, 2.5 Hz, C(6)H], 6.94 [s, 1H, C(5')H], 7.49 [s, 1H, C(2')H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 21.27 [Me x 4-Ac], 27.32 [C4], 28.39 [Me], 32.05 [Me], 65.98 [C3], 73.54 [C2], 76.83 [C7'], 108.68 [C8], 109.42 [C6], 112.62 [C4a], 120.87, 121.02 [C2' and C5'], 131.49 [C6'], 141.40 [C1], 141.67 [C3'], 142.35 [C4'], 150.33 [C5,7], 155.72 [C8a], 168.72, 168.87, 169.06, 169.49 [C=O x 4]. *m/z* 499 (MH$^+$, 24%), 457 (100), 414 (10), 397 (20), 355 (12), 283 (4), 246 (3), 221 (5), 205 (5). This data was consistent with that reported in the literature.[29]

Attempt 5.

A mixture of (+)-catechin (1) (0.10 g, 3.45 mmol) and 2,2-dimethoxypropane (0.09 g, 0.86 mmol) in DMF (5 ml) containing acetone (0.5 ml), was stirred with pyridinium *p*-toluenesulfonate[109] (6.00 mg, 0.02 mmol) for 24 h at 0°C. The reaction was warmed to room temperature and additional 2,2-dimethoxypropane (0.1 ml) was added every 24 h for 72 h. The solution was then heated at reflux for 48 h. Upon cooling the reaction was diluted with water (5 ml), extracted with ethyl acetate (10 ml x 2), washed with a saturated solution of $NaHCO_3$ (5 ml) and dried over K_2CO_3. Purification by chromatography (silica, 20% methanol in chloroform) gave catechin

(0.02 g, 20%) and 7',7'-dimethyl-5-hydroxy-*trans*-pubeschin (**13**) (0.44 g, 39%) Rf=0.38 (20% methanol in chloroform). Spectral data was consistent with the previous results.

Attempt 6.

(+)-Catechin (**1**) (0.10 g, 0.34 mmol) was added to a solution of dimethoxypropane (0.85 g, 8.10 mmol), acetone (1 ml), toluene (1 ml) and 4Å molecular sieves (0.20 g). The solution was heated for at reflux for 120 h after which it was concentrated under reduced pressure. The crude product smeared when run on t.l.c plates and showed multiple, complex signals by ^{1}H n.m.r.

Attempted formation of an oxasilole.

(+)-Catechin (**1**) (0.20 g, 0.69 mmol) and 1-hydroxybenzotriazole (9.0 mg, 0.06 mmol) were suspended in acetonitrile (3 ml), to which was added triethylamine (0.35 g, 3.40 mmol) and lastly dichlorodiphenylsilane (0.19 g, 0.76 mmol). The solution was stirred at 65°C for 2 h and then cooled to room temperature. The white precipitate was filtered off and the filtrate retained. The concentrated gum was suspended in ethyl acetate (20 ml) and washed with water (20 ml), saturated $NaHCO_3$ (20 ml) and brine solution (20 ml). The solution was dried (Na_2CO_3) and concentrated to give a product that showed numerous phenyl signals and little or no catechin signals by ^{1}H n.m.r and ^{13}C n.m.r spectroscopy.

Attempted formation of a cyclohexylidene acetal, attempt 1.

To a stirred solution of CH_2Cl_2 (7 ml), cyclohexanone (0.0 7g, 0.7 mmol) and *p*-toluenesulfonic acid (0.03 g, 0.14 mmol) was added (+)-catechin (**1**) (0.20 g, 0.69 mmol) and alumina (7 g). The reaction was stirred for 96 h after which the solvent was removed by distillation and the residue washed with ethanol. The concentrated filtrate revealed a complex mixture of products (^{1}H n.m.r).

Attempt 2.

A solution of (+)-catechin (**1**) (0.20 g, 0.69 mmol), *p*-toluenesulfonic acid (0.5 ml of a 10% solution in DMF), cyclohexanone (1.04 g, 0.01 mol) in toluene (3 ml) and DMF (4.30 ml) were reacted under Dean-Stark conditions for 5 h. Additional *p*-toluenesulfonic acid (4 x 0.5 ml of 10% solution) was added to the reaction every 30 min. The reaction was then stirred at room temperature for 72 h and the solvent removed *via* distillation under reduced pressure. Preparative t.l.c (silica, 60% ethyl acetate in dichloromethane) gave a pale yellow gum (0.13 g, 51%), that was identified as 7'-cyclohexyl-5-hydroxy-*trans*-pubeschin (**14**). Found *m/z* 370.14153. Calcd for $C_{21}H_{22}O_6$: 370.14162. ν_{max}(nujol): 3183 (OH), 1602 (C=C), 1140 (C-O) cm^{-1}. ^{1}H n.m.r (600 MHz, CDCl$_3$/d$_6$-DMSO) δ: 1.4-2.0 [m, 10H, cyclohexyl], 2.43 [dd, 1H, 10.5 Hz, 15.6 Hz, C(4)H-ax.], 2.90 [dd, 1H, 6.0 Hz, 15.6 Hz, C(4)H-eq.], 3.65 [m, 1H, C(3)H], 4.37 [d, 1H, C(2)H], 5.85 [d, 1H, 2.4 Hz, C(8)H], 5.95 [d, 1H, 2.4 Hz, C(6)H], 6.49 [s, 1H, C(5')H], 6.99 [s, 1H, C(2')H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$/d$_6$-DMSO) δ: 21.37 [C(9', 11')], 25.52 [C(10')], 27.09 [C(4)], 34.84 [C(8', 12')], 65.68 [C(3)], 73.22 [C(2)], 75.89 [C(7')], 94.96 [C(6)], 96.04 [C(8)], 101.55 [C(4a)], 112.01 [C(2',5')], 124.82 [C(1')], 134.89 [C(6')], 143.51 [C(3')], 144.42 [C(4')], 155.68 [C(8a)], 156.55 [C(5,7)]. *m/z* 370 (M$^+$, 21%), 253 (50), 202 (37), 139 (11), 83 (100), 43 (95).

Attempt 3.

(+)-Catechin (**1**) (0.50 g, 1.70 mmol), *p*-toluenesulfonic acid (0.40 ml of a 10% solution in DMF), cyclohexanone (2.60 g, 26.5 mmol), toluene (0.7 ml) and DMF (3 ml) were added together and heated at reflux for 23 h. The solvents were removed *via* distillation and the residue purified by chromatography (silica, 60% ethyl acetate in CH$_2$Cl$_2$) to give 7'-cyclohexyl-5-hydroxy-*trans*-pubeschin (**14**) (0.09 g, 18%) and catechin (0.13 g, 26%). The spectra for (**14**) was consistent with that reported above.

Attempted formation of a diphenylmethylene acetal.

(+)-Catechin (1) (0.10 g, 0.34 mmol) was dissolved in dichlorodiphenylmethane (0.09 g, 0.37 mmol) and heated to 170°C for 10 min, in which time the mixture turned dark brown. The dichlorodiphenylmethane was distilled off resulting in a black gum which showed no identifiable signals by ^{1}H n.m.r.

Attempted formation of a cyclic carbonate.

A solution of (+)-catechin (1) (0.10 g, 0.34 mmol), 1,1'-carbonyldiimadazole (0.22 g, 1.38 mmol) in toluene (5 ml) was heated at reflux for 24 h. The resulting solution that contained black lumps, was diluted with ethyl acetate (20 ml), washed with water (20 ml x 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue chromatographed (silica, 20% MeOH in $CHCl_3$) to give a product that contained multiple, complex signals by ^{1}H n.m.r.

Attempted formation of a methylenedioxy acetal, attempt 1.

(+)-Catechin (1) (0.10 g, 0.34 mmol), potassium fluoride (0.10 g, 1.70 mmol), DMF (1 g) and CH_2Cl_2 (0.03 g, 0.38 mmol) were shaken together for 2 min. The resulting pale pink solution was then heated at 120°C for 18 h, after which it was extracted with ethyl acetate (10 ml) and washed with water (10ml x 4) followed by an aqueous sodium hydroxide solution (0.1M) (10 ml). The solution was dried over Na_2SO_4 and the solvent removed under reduced pressure giving a yellow oil that appeared as multiple, smeared products by t.l.c, which showed the presence of catechin by ^{1}H n.m.r.

Attempt 2.

(+)-Catechin (1) (0.10 g, 0.34 mmol), potassium fluoride (0.25 g, 4.30 mmol), DMF (1 g) and CH_2Br_2 (0.26 g, 1.50 mmol) were maintained at 120°C for 5 h. The dark red solution was then taken to room temperature and stirred for 12 h. The solution was extracted with ethyl acetate (20 ml), washed with water (20 ml) and dried (Na_2SO_4). T.l.c at this stage showed only baseline material.

Attempted formation of an aryl benzyl carbonate.

Sodium hydroxide (0.50 g) and boric acid (1.00 g) were dissolved in water (50 ml) at room temperature, to which was added catechin (1) (0.10 g, 0.35 mmol) and the pH

adjusted to 9 using concentrated hydrochloric acid. Benzyl chloroformate (0.12 g, 0.69 mmol) was added to the borate buffer over 30 min, and the mixture was then stirred at room temperature for 1.25 h. The mixture was acidified with hydrochloric acid (3M), then extracted with ethyl acetate (20 ml x 2). The dried (Na_2SO_4) extracts were concentrated under reduced pressure by three-quarters, followed by the addition of ether (10 ml). The resulting precipitate was discarded and the filtrate again concentrated to give a yellow oil. Purification by chromatography [silica, hexane (40 ml), followed by 50% ethyl acetate in hexane] yielded a yellow oil that showed complex signals in it's [1]H.n.m.r.

Catechin tetramethyl ether (15).

Catechin (1) (0.10 g, 0.35 mmol), potassium carbonate (0.19 g, 1.38 mmol), methyl iodide (0.19 g, 1.37 mmol) and acetone (3 ml) were refluxed for 20 h. The solution was then filtered and half the solvent was evaporated in a stream of nitrogen. An aqueous solution of sodium hydroxide (1M) was added to the concentrated solution until a precipitate formed, and the solution was then filtered. Recrystallisation (methanol) yielded the title compound (15) as a white solid (0.06 g, 53%). M.p: 139-140°C, (lit: 143-144°C).[31] ν_{max}(nujol): 3532 (OH), 1617 (C=C) and 1142 (C-O) cm^{-1}. [1]H n.m.r (300 MHz, $CDCl_3$) δ: 2.59 [dd, 1H, 9.3, 15.9 Hz, C(4)H-ax.], 3.07 [dd, 5.4, 15.9 Hz, C(4)H-eq.], 3.76, 3.81 [s x 2, 6H, OCH_3 B-ring], 3.90 [s, 6H, OCH_3 A-ring], 4.07 [m, 1H, C(3)H], 4.66 [d, 1H, 8.4 Hz, C(2)H], 6.11 [s, 1H, C(8)H], 6.14 [s, 1H, C(6)H], 6.89-7.02 [m, 3H, C(2',5',6')H]. [13]C n.m.r (75.47 MHz, $CDCl_3$) δ: 28.34 [C4], 56.04-56.67 [OCH_3 x 4], 68.96 [C3], 82.48 [C2], 92.63 [C8], 93.76 [C6], 102.38 [C4a], 110.74 [C5'], 112.01 [C2'], 120.62 [C6'], 131.98 [C1'], 150.10 [C3', C4'], 155.98 [C8a], 159.45 [C5], 160.44 [C7]. *m/z* 346 (M$^+$, 19%), 195 (3), 167 (100), 151 (18), 137 (12), 109 (9), 77(13), 69 (15), 41 (17). Spectral data was consistent with that reported in the literature.[31]

Mitsunobu Reactions.

General procedure:

Catechin tetramethyl ether (15) and triphenylphosphine (1.1-1.5eq.) were dissolved in a solvent, to which was added diethyl azodicarboxylate (DEAD) (1.1-1.5eq.) and the acidic component (1-1.5eq.) at room temperature. The solvent was removed

after the appropriate reaction time and the residue subjected to chromatography (silica, 50% ethyl acetate in hexane).

Table 1.

Entry 1a.

Catechin tetramethyl ether (**15**) (10 mg, 0.03 mmol), triphenylphosphine (8.0 mg, 0.03 mmol), DEAD (6.0 mg, 0.03 mmol) and gallic acid (5.0 mg, 0.03 mmol) were stirred in THF (1 ml) for 24 h, in which time the mixture appeared dark brown. T.l.c analysis revealed only starting materials.

Entry 1b.

The above reaction was repeated in 1,4-dioxane at reflux over 2 h. T.l.c analysis showed only starting catechin.

Entry 2a.

Catechin tetramethylether (**15**) (10 mg, 0.03 mmol), triphenylphosphine (10 mg, 0.04 mmol), benzoic acid (4.0 mg, 0.03 mmol) and DEAD (8.0 mg, 0.04 mmol) were stirred in THF (5 ml) for 18 h. The mixture remained a yellow colour during this time. The reaction mixture appeared to contain only starting catechin according to ^{1}H n.m.r analysis.

Entry 2b.

The reaction was carried out as in entry 2a, except that the solution was stirred for 47 h. Work up and chromatography yielded mainly starting catechin ether (**15**) together with complex signals (^{1}H n.m.r).

Entry 2c.

Catechin tetramethyl ether (**15**) (10 mg, 0.03 mmol), triphenylphosphine (10 mg, 0.04 mmol), DEAD (8.0 mg, 0.04 mmol) and benzoic acid (5.0 mg, 0.04 mmol) were dissolved in benzene (2 ml) and stirred for 30 h. The yellow solution gradually turned colourless. Crude ^{1}H.n.m.r analysis showed only starting catechin.

Entry 2d.

The reaction was repeated at reflux over 10 h in 1,4-dioxane. The initial yellow solution became colourless almost instantly, however no starting catechin ether (**15**) was consumed.

Entry 3.

Catechin tetramethyl ether (**15**) (10 mg, 0.03 mmol), triphenylphosphine (8.0 mg, 0.03 mmol), formic acid (1.0 mg, 0.03 mmol) and DEAD (5.0 mg, 0.03 mmol) were dissolved in THF (2 ml) and stirred for 48 h. The clear, colourless oil yielded two new products after chromatography, the first being (2*S*)-2-(3,4,dimethoxyphenyl)-5,7-dimethoxy-2*H*-chromene (**16**), (2.3 mg, 25%). M.p: 110-112°C, (lit: 119°C).[32] Rf=0.6 (50% ethyl acetate in hexane). v_{max}(nujol): 1620 (C=C), 1598 (C=C) 1116 (C-O), 722 (C=C) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.74, 3.81 [s x 2, 6H, OMe-C3',4'], 3.89 [s, 6H, OMe-5,7], 5.59 [dd, 1H, 3.3, 9.9 Hz, C(3)H], 5.77 [dd, 1H, 1.8, 3.3 Hz, C(2)H], 6.03 [m, 2H, C(6,8)H], 6.80 [dd, 1H, 1.8, 9.9 Hz, C(4)H], 6.81 [m, 1H, C(5')H], 6.99 [m, 2H, C(2',6')H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 56.04-56.61 [Me x 4], 71.54 [C2], 92.59 [C8], 94.55 [C6], 101.66 [C4a], 111.39 [C2'], 111.81 [C5'], 119.72 [C4], 120.52 [C6'], 127.89 [C3], 134.58 [C1'], 152,01 [C3',4'], 169.05 [C8a], 161.99 [C5], 162.37 [C7]. *m/z* 328 (M$^+$, 26%), 277 (27), 208 (9), 182 (98), 165 (73), 137 (31), 111 (32), 77 (73), 44 (100).

The second product was identified as (2*R*,3*R*)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-3,4-dihydro-2*H*-3-chromenyl formate (**17**), (1.6 mg, 14%), Rf=0.54 (50% ethyl acetate in hexane). ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 2.98-3.00 [m, 2H, C(4)H], 3.74 [s, 6H, OMe x 2], 3.88 [s, 3H, OMe], 3.91 [s, 3H, OMe], 5.07 [s, 1H, C(2)H], 5.59 [m, 1H, C(3)H], 6.12 [d, 1H, 1.8 Hz, C(8)H], 6.23 [d, 1H, 1.8 Hz, C(6)H], 6.86-7.04 [m ,3H, C(2',5',6')H], 8.01 [s, 1H, formate-H]. The small amount of product made further analysis difficult.

Entry 4.

Catechin tetramethyl ether (**15**) (30 mg, 0.09 mmol), triphenyphosphine (30 mg, 0.10 mmol) and acetic acid (6.0 mg, 0.10 mmol) were dissolved in benzene (5 ml). DEAD (20 mg, 0.10 mmol) was added, causing the reaction mixture to become colourless. The reaction was stirred for 18 h, affording starting materials when

analysed by t.l.c. The reaction mixture remained unchanged even when heated at 60°C for 48 h.

Part 2, Chapter 4.

Oxidation of Catechin tetramethyl ether (15).

Table 2.

Entry 1, Chromium trioxide.[44]

Catechin tetramethyl ether (15) (10 mg, 0.03 mmol) was dissolved in ether (5 ml) and cooled to 0°C. A solution of chromium trioxide (3.5 mg, 0.03 mmol) in water (5 ml) was added dropwise over 7 min. T.l.c. analysis (50% ethyl acetate in hexane) revealed only starting material after 24 h.

Entry 2a, Jones Reagent.

Jones reagent[44] (0.20 ml) was added dropwise to a stirred solution of catechin tetramethylether (15) (0.01 g, 0.03 mmol) in acetone (3 ml) and stirred at room temperature for 18 h. The acetone was removed under reduced pressure and the residue diluted with ether (5 ml) and washed with water (5 ml). The organic extracts were dried (Na_2SO_4) and the solvent was removed, yielding a complex mixture by t.l.c (50% ethyl acetate in hexane) and n.m.r (^1H and ^{13}C).

Entry 2b, Jones Reagent.

Catechin tetramethyl ether (15) (0.01 g, 0.03 mmol) was dissolved in acetone (1 ml) to which Jones reagent (0.1 ml) was added dropwise. After stirring at room temperature for 30 min, the acetone was removed using a stream of N_2 gas. Ether (1 ml) was added to the dark brown solution and an aqueous solution of sodium hydroxide (2M) was added until the reaction mixture was at pH 12. The solution was extracted with ether (10 ml x 3) and the combined ether extracts were washed with brine solution (10 ml). The ether extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude ^1H n.m.r spectrum showed starting catechin ether (15) and other products containing multiple signals.

Repeating this reaction using more Jones reagent (2 ml) and longer reaction times (2 h) gave base line material [t.l.c (50% ethyl acetate in hexane)].

Entry 3a, Pyridinium chlorochromate (PCC).[44]

Catechin tetramethylether (15) (40 mg, 0.11 mmol), PCC (50 mg, 0.24 mmol) and sodium acetate (40 mg, 0.05 mmol) were suspended in CH_2Cl_2 (1 ml) and stirred at ambient temperature for 30 min. T.l.c analysis (50% hexane in ethyl acetate) revealed baseline material. This reaction was repeated in the absence of sodium acetate, for 48 h, again giving baseline material (entry 3b), suggesting product decomposition.

Entry 4a, Fetizon's reagent.[44]

A suspension of catechin tetramethylether (15) (0.01 g, 0.03 mmol) and Fetizon's reagent (0.10 g, 0.20 mmol) in toluene (2 ml) was refluxed for 21 h. T.l.c analysis (50% ethyl acetate in hexane) showed the presence of only starting material.

Entry 4b.

The reaction (entry 4a) was repeated using 1,2-dichloroethane as the solvent and the oxidant was added dropwise to a solution of the catechin ether (15). The reaction was heated at reflux for 4 h and the dark grey solution was filtered through a pad of florisil giving a yellow solid upon solvent evaporation (reduced pressure). The solid was identified as starting material by ^1H n.m.r and t.l.c analysis (50% ethyl acetate in hexane).

Entry 5a, CCl₄/palladium(II) chloride.[112]

Catechin tetramethyl ether (15) (20 mg, 0.06 mmol), potassium carbonate (8.0 mg, 0.06 mmol), palladium(II) chloride (0.1 mg, 0.6 µmol) and CCl_4 (0.5 ml) were refluxed for 24 h. The salts were removed by filtration and the concentrated residue was purified by chromatography (silica, 50% ethyl acetate in hexane) affording the required ketone (23) (0.1 mg, 0.5%) (see further on for spectra) and starting catechin ether.

Entry 5b, Oxygen/palladium(II) chloride.[113]

Catechin tetramethyl ether (**15**) (20 mg, 0.06 mmol), palladium(II) chloride (0.1 mg, 0.6 μmol), sodium acetate (2.0 mg, 0.03 mmol) and acetone (17 ml) were combined. Oxygen was bubbled through the reaction mixture for 3 h. After the removal of acetone, the brown solid was resuspended in $CHCl_3$ (5 ml) and washed successively with a 2M aqueous solution of sodium hydroxide (3 ml) and water (5 ml). The dried solution (Na_2SO_4) was concentrated to give a brown gum that contained mainly starting catechin ether, as well as a complex mixture of products (n.m.r).

Entry 6a, Lead tetraacetate.

Catechin tetramethyl ether (**15**) (0.01 g, 0.03 mmol) was cooled in CH_2Cl_2 (1 ml) to 0°C. Purified, white $Pb(OAc)_4$ (0.02 g, 0.04 mmol) was added and the solution stirred at room temperature for 2 h. The reaction was filtered and the filtrate concentrated to give two products when viewed by t.l.c. The ^1H n.m.r spectrum showed multiple methoxy signals ($\delta 3.60$-4.00), many aromatic signals and other broad peaks, nothing of which could be attributed to the required product (ketone).

Entry 6b, Lead tetraacetate.[114]

Catechin tetramethyl ether (**15**) (0.01 g, 0.03 mmol) was dissolved in a solution of lead tetraacetate (0.02 g, 0.05 mmol) in acetic acid (10 ml) and water (0.32 ml). The reaction was left at reflux for 22 h, and then stirred at room temperature for a further 17 h. The brown solution was poured onto crushed ice, and the reaction flask washed out with ether (20 ml). The solution was extracted and the organic layer washed with fresh iron (II) sulfate solution (15 ml), aqueous Na_2CO_3 solution (10 ml) and dried over Na_2SO_4. Chromatography of the concentrated solution (50% hexane in ethyl acetate), gave two products; starting catechin ether and (2*R*,3*S*)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-3,4-dihydro-2*H*-3-chromenylacetate (**29**) (2.1 mg, 19%), as a pale, yellow oil. v_{max}(nujol): 1720 (C=O, acetate), 1115 (C-O). ^1H n.m.r (200 MHz, $CDCl_3$) δ: 1.96 [s, 3H, CH_3], 2.67 [dd, 1H, 6.6, 16.8 Hz, C(4)H-ax.], 2.91 [dd, 5.4, 16.8 Hz, C(4)H-eq.], 3.77 [s, 6H, OMe], 3.86 [s, 3H, OMe], 3.87 [s, 3H, OMe], 5.02 [d, 1H, 6.6 Hz, C(2)H], 5.35 [dt, 1.2, 6.6 Hz, C(3)H], 6.09 [d, 1H, 2.2 Hz, C(8)H], 6.17 [d, 1H, 2.2 Hz, C(6)H], 6.81-6.95 [m, 3H, C(2',5',6')H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 21.67 [Me-acetate], 24.72 [C4], 56.32-56.78 [OMe x 4], 69.81

[C3], 79.05 [C2], 92.54 [C8], 93.76 [C6], 101.45 [C4a], 110.42 [C5'], 111.77 [C2'], 119.91 [C6'], 131.06 [C1'], 149.68 [C4', C3'], 155.54 [C8a], 159.28 [C5], 160.56 [C7], 170.92 [C=O]. *m/z* 387 (M^+, 3%), 327 (84), 297 (10), 286 (2), 180 (45), 137 (12), 101 (38), 72 (40), 43 (100). Data was consistent with literature values.[115]

Hydrolysis of the Acetate (29).

2-(3,4-Dimethoxyphenyl)-5,7-dimethoxy-3,4-dihydro-2*H*-3-chromenylacetate **(29)** (2.10 mg, 6.0×10^{-3} mmol) was added to a mixture of potassium carbonate (1.5 mg, 0.01 mmol) in methanol (0.7 ml) and water (0.3 ml). The solution was heated at reflux for 30 min, then cooled. The methanol was removed using a stream of N_2 gas, and the remaining solution diluted with water (5 ml) and extracted with CH_2Cl_2 (5 ml x 2). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, to give a white solid in quantitative yield, that was identical by spectral analysis to (+)-catechin tetramethyl ether **(15)**.

Entry 7a, Cl₂/thioanisole.[116]

Concentrated hydrochloric acid (5 ml) was dropped onto excess potassium permaganate generating chlorine gas, which was bubbled through carbon tetrachloride (1.5 ml), for 15 min. The carbon tetrachloride solution was taken to -10° C, to which thioanisole (0.10 g, 0.83 mmol) was added and a small amount of white precipitate evolved. The reaction was cooled to -25° C, at which stage catechin tetramethyl ether **(15)** (0.02 g, 0.06 mmol) was added in CH_2Cl_2 (2 ml). The solution was stirred at -25° C for 2.5 h, and then a solution of *N,N*-diisopropylethylamine (0.21 g,1.66 mmol) in CH_2Cl_2 (2 ml) was added dropwise. The cooling bath was removed and after 5 min, ether (5ml) was added to the reaction. The organic layer was washed with ice cold 1% aqueous hydrochloric acid (5 ml). Concentration of the dried (Na_2SO_4) extracts produced a white solid that was identified as starting catechin (t.l.c, n.m.r). The reaction was repeated using triethylamine (entry 7b) (0.17 g, 1.66 mmol) instead of *N,N*-diisopropylethylamine, again giving starting catechin ether.

Entry 8, Bromine oxidation.[117]

Catechin tetramethyl ether (**15**) (20 mg, 0.06 mmol) was added to a mixture of sodium hydroxide (70 mg) and $NaHCO_3$ (28 mg) in water (3 ml), which was then cooled to -2°C - -4°C. Bromine (9.0 mg, 0.06 mmol) in chloroform (0.50 ml) was added dropwise over 30 min, and the reaction was left to stir at -4°C for 2 h. The reaction was diluted with water (2 ml) and acidified until it appeared red in colour, using an aqueous solution of hydrochloric acid (1 M). After stirring at room temperature for 1 h, the organic layer was extracted and washed successively with water (2 ml), diluted $NaHCO_3$ solution (2 ml), and water (2 ml). A yellow solid was obtained after concentration of the dried (Na_2SO_4) organic layer, which contained no traces of the starting catechin ether (t.l.c). Chromatography (silica, 50% ethyl acetate in hexane) gave three fractions, each showing complex signals in their ^1H n.m.r spectra.

Entry 9, Sodium hypochlorite.[37]

Catechin tetramethyl ether (**15**) (0.02 g, 0.06 mmol) was dissolved in acetic acid (1 ml) to which a 10% aqueous solution of sodium hypochlorite (0.05 ml, 0.07 mmol) was added dropwise, causing the formation of a precipitate and an orange colouration of the solution. After 4 h stirring, additional sodium hypochlorite solution (0.1 ml) was added. A saturated aqueous solution of $Na_2S_2O_5$ was added after 17 h, until the reaction mixture appeared colourless. Brine solution (5 ml) was added and the aqueous mixture was extracted with ether (5 ml x 2). The ether layer was washed with a 1M aqueous sodium hydroxide solution (5 ml) and the aqueous phase extracted again with more ether (5 ml). The combined ether layers were dried (Na_2SO_4) and concentrated to give only catechin tetramethyl ether.

Entries 10a and 10b, Tetrapropylammonium perruthenate (TPAP).[34]

TPAP (1 crystal, approx. ~0.05 mg, 0.02 mmol) was added to catechin tetramethyl ether (**15**) (10 mg, 0.29 mmol), *N*-methylmorpholine *N*-oxide (5.0 mg, 0.43 mmol) and powdered 4Å molecular sieves (14 mg) in CH_2Cl_2 (0.5 ml). The solution was stirred at room temperature for 1 h; in which time t.l.c analysis showed only starting materials. The same amounts of TPAP/NMO were again added and the reaction left for 17 h. The reaction mixture was filtered through a pad of silica, eluted with CH_2Cl_2

(2 ml) giving a yellow gum after solvent evaporation. The gum consisted of multiple products when analyses by t.l.c, and n.m.r spectroscopy showed a complex mixture of signals.

Entry 11a, Oppenauer oxidation.[110]

Potassium *t*-butoxide (0.8 mg, 7.0×10^{-3} mmol) was added to a mixture of catechin tetramethyl ether (**15**) (10 mg, 0.03 mmol), cyclohexanone (60 mg, 0.57 mmol) and toluene (20 ml) at reflux. After removing the solvent the resulting orange oil was dissolved in ether (10 ml) and washed with a 2N aqueous H_2SO_4 solution (10 ml), a 40% aqueous $Na_2S_2O_5$ solution (10 ml) and water (15 ml). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica, 50% hexane in ethyl acetate) gave one fraction, which was identified as starting catechin ether.

Entry 11b, Oppenauer oxidation.

To a mixture of cyclohexanone (0.11 g, 1.17 mmol) and toluene (7 ml) containing catechin tetramethyl ether (**15**) (0.02 g, 0.06 mmol) at reflux was added aluminium isopropoxide[110] diluted in toluene (3 ml). The solvents were removed *via* distillation giving a yellow solid, which was diluted with water (5 ml) containing a trace of acetic acid (0.1 ml). The solution was steam distilled and the resulting yellow solid was dissolved in chloroform (10 ml) and washed with an aqueous sodium hydroxide solution (1M, 10 ml), a 40% aqueous $Na_2S_2O_5$ solution (5 ml) and water (7 ml). The dried organic layer (Na_2SO_4) was concentrated to give a pale yellow oil which was subjected to p.l.c (silica, 50% ethyl acetate in hexane) giving 5,7,3',4'-tetramethoxy-3-oxoflavan (**23**) (0.7 mg, 1%) and mainly starting catechin ether. Spectra for the ketone were consistent with that of entry 16.

Entry 11c.

Catechin tetramethyl ether (**15**) (0.02 g, 0.06 mmol), aluminum isopropoxide (0.04 g, 0.17 mmol), acetone (0.07 g, 1.20 mmol) and benzene (10 ml) were heated at reflux for 21 h. After cooling to room temperature, the reaction mixture was washed with a 1 M hydrochloric acid solution (5 ml x 2) and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. T.l.c analysis showed multiple products

including starting catechin. N.m.r spectroscopy showed multiple signals indicating a complex mixture.

Entry 12, Ruthenium tetroxide.[35]

Into a separating funnel was placed a saturated aqueous solution of sodium metaperiodide (2.5 ml) and a 0.022 M ruthenium tetroxide solution[35] (1.5 ml). Catechin tetramethyl ether (15) (0.02 g, 0.06 mmol) was dissolved in carbon tetrachloride (2.5 ml) and added in portions to the funnel. The funnel was shaken after every addition, until the black colour of the ruthenium dioxide disappeared. This procedure was repeated numerous times with the addition of fresh sodium metaperiodide solution (5 ml), until all the catechin ether had been consumed (t.l.c). The carbon tetrachloride layer was separated and the remaining ruthenium tetroxide destroyed by addition of 2-propanol (1 ml) to this layer. The precipitated ruthenium dioxide was filtered off and the yellow solution concentrated under reduced pressure. P.l.c (50% ethyl acetate in hexane) gave the required ketone (23) (1.0 mg, 5%) as well as starting catechin ether.

Entry 13, Swern oxidation.[118]

Catechin tetramethyl ether (15) (0.02 g, 0.06 mmol) was dissolved in DMSO (0.5 ml) to which was added acetic anhydride (0.12 g, 1.16 mmol). The mixture was stirred for 52 h, then diluted with ethanol (5 ml) and stirred a further 1 h. Water was added to the mixture (2 ml), followed by 43% ammonia solution (2 ml). Most of the ethanol was removed using a stream of N_2 gas, and the remaining solution extracted with chloroform (5 ml x 2). The organic layer was washed with water (2 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica, 50% ethylacetate in hexane) gave two products; starting catechin ether and (2R,3S)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-3,4-dihydro-2H-3-chromenylacetate (29) as a colourless gum (8.7 mg, 41%). Spectral data was consistent with that obtained previously (entry 6b).

Entry 14, Swern oxidation.[119]

A solution of DMSO (0.02 g, 0.03 mmol) and CH_2Cl_2 (5 ml) were cooled to -50°C using a dry ice/acetone bath. Trifluoroacetic anhydride (TFAA) (0.05 g, 0.22 mmol),

diluted in CH_2Cl_2 (2.5 ml), was added drop wise to the cooled solution over 10 min. A solution of catechin tetramethylether (**15**) (0.05 g, 0.10 mmol) in CH_2Cl_2 (5 ml) was added to this solution over 10 min, and the mixture was stirred at -50°C for 40 min. The reaction was warmed to room temperature and stirred for 1 h. Triethylamine (0.04 g, 0.09 mol) was added dropwise over 10 min, and the reaction was then washed successively with dilute aqueous solutions of H_2SO_4 (5 ml), K_2CO_3 (5 ml) and water (5 ml). The organic solution was dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a yellow gum, which consisted of catechin tetramethyl ether.

Entry 15a, Swern Oxidation.[40]

A solution of oxalyl chloride (4.0 mg, 0.04 mmol) in CH_2Cl_2 (1 ml) was cooled to -60°C, and DMSO (5.0 mg, 0.07 mmol) diluted with CH_2Cl_2 (0.5 ml) was added dropwise over 5 min. Stirring was continued at -60°C for 10 min followed by the addition of catechin tetramethyl ether (**15**) (10 mg, 0.03 mmol) dissolved in CH_2Cl_2 (1 ml) over 5 min. The reaction was stirred for 15 min and triethylamine (20 mg, 0.14 mmol) was added over 5 min whilst the mixture remained at -60°C. The cooling bath was removed causing the reaction to become pink in colour. Water (2 ml) was added causing a colour change to yellow. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (5 ml). The combined organic phases were dried (Na_2SO_4), and concentrated under reduced pressure. T.l.c (50% ethyl acetate in hexane) and n.m.r analysis revealed the presence of complex, multiple products, none of which appeared to be starting material.

Entry 15b, Swern Oxidation.[38]

A mixture of CH_2Cl_2 (1 ml) and oxalyl chloride (0.09 g, 0.19 mmol) was cooled to -50°C, to which was added DMSO (0.03 g, 0.42 mmol) diluted in CH_2Cl_2 (1 ml). The reaction was stirred for 2 min. Catechin tetramethyl ether (**15**) (0.03 g, 0.09 mmol) was dissolved in CH_2Cl_2 (1 ml) and added to the reaction mixture within 5 min. Stirring was continued for 15 min, followed by the addition of triethylamine (0.04 g, 0.43 mmol); the reaction was then allowed to warm to room temperature. Stirring was continued for 18 h, and water was added to the mixture (5 ml). The aqueous layer was re-extracted with CH_2Cl_2 (5 ml x 2) and the organic layers were washed

with an aqueous saturated solution of sodium chloride (5 ml). The mixture upon drying (Na$_2$SO$_4$) and concentration yielded baseline material by t.l.c (50% ethyl acetate in hexane), suggesting product degradation. The ^{1}H n.m.r spectrum showed complex signals.

Entry 16, Pfitzner and Moffat variation of the Swern oxidation, (+)-5,7,3',4'-tetramethoxy-3-oxoflavan (23).[42]

A solution of pyridine (10 mg, 0.14 mmol) and trifluoroacetic acid (8.0 mg, 0.07 mmol) in benzene (1 ml) was added to catechin tetramethyl ether (15) (50 mg, 0.14 mmol) dissolved in DMSO (0.21 ml) and benzene (1 ml). Molten dicyclohexylcarbodiimide (90 mg, 0.43 mmol) was added to the stirred solution at 5°C and the reaction was then left for 21 h at room temperature. Ether (2 ml) was added, followed by a solution of oxalic acid (40 mg, 0.43 mmol) in methanol (1 ml), causing a colour change from yellow to pale pink. Water (5 ml) was added after 30 min and the solution was filtered to remove most of the dicyclohexylurea (DCU). The organic layer was washed with a 5% aqueous solution of sodium hydrogen carbonate (5 ml x 2), water (5 ml x 2), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The dark red gum was chromatographed (silica, 50% solution of hexane in ethyl acetate) to give yellow oil which slowly solidified. Recrystallisation (hexane/ethyl acetate, 3:1) gave the title compound as a white solid (10 mg, 27%). M.p: 106-107°C, (lit: 112.5-113°C).[42] Anal. Calc. for C$_{19}$H$_{20}$O$_6$: C, 66.27; H, 5.85. Found: C, 66.13; H, 5.79%. Found *m/z* 344.1250. Calcd for C$_{19}$H$_{20}$O$_6$: 344.1259. ν_{max}(nujol): 1731 (C=O). ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.50, 3.57 [ABq, 2H, 21.6 Hz, C(H)4], 3.81 [s, 6H, OMe], 3.97 [s, 3H, OMe], 3.99 [s, 3H, OMe], 5.29 [s, 1H, C(2)H], 6.19 [d, 1H, 2.1 Hz, C(8)H], 6.31 [d, 1H, 2.4 Hz, C(6)H], 6.90 [m, 3H, C(2',5',6')H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 34.32 [C4], 56.17, 56.59 [OMe x 4], 83.93 [C2], 93.86 [C8], 97.19 [C6], 101.54 [C4a], 110.54 [C5'], 111.82 [C2'], 120.60 [C6'], 128.88 [C1'], 149.56, 149.71 [C3', C4'], 153.43 [C8a], 157.86 [C5], 161.09 [C7], 205.52 [C=O]. *m/z* 344 (M$^+$, 34%), 316 (100), 301 (24), 178 (44), 163 (15), 135 (31), 111 (17), 95 (18), 69 (60).

Entry 17, *N*-chlorosuccinimide/dimethylsulfide.

Dimethylsulfide (0.02 g, 0.32 mmol) was added to a stirred solution of *N*-chlorosuccinimide (0.04 g, 0.26 mmol) in toluene (1 ml) at 0°C. The reaction was taken to -25°C, after which a solution of catechin tetramethyl ether (15) (0.02 g, 0.06 mol) was added. After 2 h at this temperature diisopropylethylamine (0.08 g, 0.52 mmol) in pentane (0.2 ml) was added and the mixture taken to room temperature, and left stirring for 18 h. The yellow reaction was diluted with ether (5 ml) and washed successively with cold 1 M hydrochloric acid solution (5 ml x 2) then cold water (5 ml x 2). After drying (Na_2SO_4), the concentrated solution was chromatographed (silica, 50% ethyl acetate in hexane) to give two main products; starting catechin ether and 5,7,3',4'-tetramethoxy-3-oxoflavan (23) as a cream solid (2.5 mg, 13%). Spectral data was consistent with entry 16.

Entry 18, Dess-Martin Periodinane Oxidation.[7]

To a solution of catechin tetramethyl ether (15) (0.40 g, 1.15 mmol) dissolved in CH_2Cl_2 (3 ml) at room temperature, was added Dess-Martin periodinane[111] (0.54 g, 1.27 mmol) all at once. Water saturated CH_2Cl_2 (0.22 ml) was added over 10 min and the turbid orange solution was stirred for 1 h. Additional periodinane (0.10 g) and water saturated CH_2Cl_2 (0.05 ml) was added and the solution refluxed for another 2 h. Saturated $NaHCO_3$ solution (5 ml) was added to the amber reaction mixture followed by $Na_2S_2O_3.5H_2O$ (2.0 g) in water (20 ml). The solution was extracted with CH_2Cl_2 (10 ml x 2) and dried (Na_2SO_4). The pale yellow oil was subjected to chromatography (silica, 10% ethyl acetate in chloroform) giving 5,7,3',4'-tetramethoxy-3-oxoflavan (23) as a pale yellow solid. Recrystallisation (MeOH) yielded a white solid (0.15 g, 38%). M.p: 105-106°C, (lit: 112.5-113°C).[42] Spectral data was consistent with entry 16.

Table 3, Epicatechin tetramethyl ether (32).

Entry 1, General method.

5,7,3',4'-Tetramethoxy-3-oxoflavan (23) (0.01 g, 0.03 mmol) was dissolved in methanol (1 ml) and cooled to 0°C. Sodium borohydride (5.50 mg, 0.15 mmol) was added all at once to the cooled mixture and stirred at this temperature for 1 h. Iced water (5 ml) was added to the reaction, and the methanol was removed under a

stream of N_2 gas. The aqueous mixture was extracted with ether (5 ml x 2) and the ether extracts were washed with brine solution. The dried (Na_2SO_4) organic extracts were concentrated under reduced pressure to give a yellow gum that was purified by p.l.c (silica, 50% ethyl acetate in hexane) to give as a white solid epicatechin tetramethyl ether (**32**) (6 mg, 61%). M.p: 141-142°C, (lit: 144-145°C).[42] Anal. Calc. for $C_{19}H_{22}O_6$: C, 65.86; H, 6.40. Found: C, 65.78; H, 6.57%. Found *m/z* 346.14142. Calcd for $C_{19}H_{22}O_6$: 346.14162. ν_{max}(nujol): 3520 (OH), 1618 (C=C), 1142, 1114 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 2.87, 2.95 [AB portion of an ABX system, 2H, J_{AB}=17.5 Hz, C(H)4], 3.77 [s, 3H, OMe], 3.79 [s, 3H, OMe], 3.89 [s, 3H, OMe], 3.92 [s, 3H, OMe], 4.23 [X portion of ABX, 1H, C(H)3], 4.96 [bs, 1H, C(H)2], 6.11[d, 1H, 2.5 Hz, C(8)H], 6.20 [s, 1H, 2.5 Hz, C(6)H], 6.91 [d, 1H, 8.4 Hz, C(4')H], 7.03-7.09 [m, 2H, 1.8, 8.4 Hz, C(1',5')H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 28.10 [C4], 56.01 [OMe], 56.10 [OMe], 56.62 [OMe x 2], 67.08 [C3], 80.15 [C2], 92.85 [C8], 94.03 [C6], 100.96 [C4a], 110.40 [C5'], 111.93 [C2'], 119.33 [C6'], 131.55 [C1'], 149.55-149.82 [C3', C4'], 155.90 [C8a], 159.93 [C5], 160.36 [C7]. *m/z* 346 (M$^+$, 39%), 180 (28), 167 (100), 137 (10), 109 (8), 77 (5).

Entry 2.

The reaction was carried out as stated in entry 1, except that cerium chloride (7 mg, 0.03 mmol) was added to the reaction prior to the sodium borohydride. Epicatechin tetramethyl ether (**32**) and (+)-catechin tetramethyl ether (**15**) were obtained as a white solid (6 mg, 59%) in a ratio of 3:1 respectively.

Entry 3.

The reaction was carried out as stated, with the use of cerium chloride (7.0 mg, 0.03 mmol) and sodium borohydride (5.5 mg, 1.50 mmol). Epicatechin tetramethyl ether (**32**) and (+)-catechin tetramethyl ether (**15**) were obtained as a white solid (6.0 mg, 58%) in a ratio of 4:1 respectively.

Entry 4.

(+)-5,7,3',4'-Tetramethoxy-3-oxoflavan (**23**) (6.0 mg, 0.02 mmol) was dissolved in methanol (1 ml), to which was added cerium chloride (9.0 mg, 0.04 mmol) followed by sodium borohydride (3.0 mg, 0.09 mmol) at 0°C. After 1.5 h the reaction was

worked up as stated in entry 1, yielding epicatechin tetramethyl ether (**32**) and (+)-catechin tetramethyl ether (**15**) (2.7 mg, 46%) in a ratio of 6:1 respectively.

Entry 5.

The reaction was conducted as stated in entry 2, changing the amount of cerium chloride used (40 mg, 0.14 mmol) and the reaction time (2 h). After the usual work up procedure epicatechin tetramethyl ether (**32**) and (+)-catechin tetramethyl ether (**15**) were obtained (4.0 mg, 45%) in a 7:1 ratio respectively.

Entry 6.[7]

Anhydrous lithium bromide (0.08 g, 0.91 mmol) was dissolved in THF (1 ml), and cooled using an ice bath. Lithium tri-*sec*-butylborohydride (L-Selectride®) (1M solution, 0.23 ml, 0.24 mmol) in THF was added dropwise and the reaction solution was cooled further to -78° C. The ketone (**23**) (0.06 g, 0.17 mmol) dissolved in THF (1 ml) was added slowly over 30 min, and the combined solution stirred at the same temperature for 2 h. The cold bath was removed and a 2M aqueous sodium hydroxide solution was added (1.5 ml). The reaction flask was placed in a water bath at room temperature and a mixture of 35% aqueous hydrogen peroxide (0.5 ml) and ethanol (1.5 ml) was added dropwise within 2 h. The reaction was stirred in the water bath for 18 h, after which the product was found to have partially crystallised. Chloroform was added to the mixture, and the phases were separated. The aqueous layer was extracted with chloroform (5 ml), and the combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a yellow solid (0.06 g). Recrystallisation (methanol) afforded epicatechin tetramethyl ether (**32**) as a cream coloured solid that was dried *in vacuo* (0.02 g, 33%). M.p: 141-142° C, (lit: 144-145° C).[42]

Esterification Reactions.

Attempt 1.

Gallic acid (5.0 mg, 0.03 mmol) was dissolved in sulfuric acid (0.5 ml) and added to a stirred solution of (+)-catechin tetramethylether (**15**) (10 mg, 0.03 mmol) in benzene (1 ml). The reaction was heated at reflux for 18 h, cooled, and diluted with water (2 ml). The organic layer was separated and washed with an aqueous solution of

NaHCO$_3$ (2 ml), and then water (2 ml). The dried (Na$_2$SO$_4$) extracts were concentrated under reduced pressure yielding a brown oil that consisted of mainly baseline material when viewed by t.l.c (50% ethyl acetate in hexane).

Attempt 2.

The above reaction was repeated, except that benzene was replaced by THF and that sulfuric acid was replaced by trifluoroacetic acid. The reaction was heated at reflux for 3 h. T.l.c analysis showed mainly starting materials and a trace of another product at a higher Rf. Chromatography (silica, 50% ethyl acetate in hexane) gave the top spot as a yellow gum (1.5 mg) which gave complex signals when viewed by ^{1}H n.m.r.

3,4,5-Trimethoxybenzoic acid.[120]

Gallic acid (2.00 g, 0.01 mol) was dissolved in a 1M aqueous solution of sodium hydroxide (10 ml) to which was added ethanol (20 ml) and methyl iodide (9.81 g, 0.07 mol) and heated to reflux. A 5M aqueous solution of sodium hydroxide (12 ml) was added over 90 min, and the solution heated for a further 1.5 h. A 40% aqueous potassium hydroxide solution (4 ml) was added to the hot reaction mixture and heating was continued for 1 h. The solution became dark red in colour within this time. The cooled reaction mixture was acidified using a 1M aqueous solution of hydrochloric acid and extracted with CH$_2$Cl$_2$ (15 ml x 2). The organic extracts were then washed with a 2M aqueous solution of sodium hydroxide (10 ml). The aqueous layer was reacidified (conc. HCl) and extracted with CH$_2$Cl$_2$ (20 ml x 3). Evaporation of the dried (Na$_2$SO$_4$) organic layer gave a yellow solid that was recrystallised (methanol) to give 3,4,5-trimethoxybenzoic acid as a white solid (1.54 g, 61%). M.p: 166-170°C, (lit: 168-171°C).[Aldrich, 1997 #185] v_{max}(nujol): 3200-2400 (O-H), 1682 (C=O), 1586 (C=C), 1123 (C-O) cm^{-1} ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.93 [s, 9H, OMe], 7.39 [s, 2H, C(2,6)H], 8.09 [CO$_2$H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 56.94 [OMe-C3,5], 61.63 [OMe-C4], 108.16 [C2,6], 124.77 [C1], 143.74 [C4], 153.67 [C3,5], 172.30 [C=O]. *m/z* 212 (M$^+$, 100%), 195 (39), 169 (16), 141 (15), 109 (3), 95 (2). N.m.r spectra were consistent with the literature.[63]

3,4,5-Trimethoxybenzoyl chloride.

1,3,5-trimethoxybenzoic acid was added to excess thionyl chloride and heated for 30 min. After a period of time, the excess thionyl chloride was distilled from the reaction, under reduced pressure towards the end. An off white solid was obtained that was used without further purification.

Esterification of catechin tetramethyl ether (15), attempt 3.[7]

Catechin tetramethyl ether (0.06 g, 0.16 mmol) was added to pyridine (1 ml), followed by 3,4,5-trimethoxybenzoyl chloride (0.10 g, 0.43 mmol) then dimethylaminopyridine (0.02 g, 0.14 mmol). The reaction was left stirring in a closed flask for 45 h, water (1 ml) was added and the reaction stirred again for 5.5 h. Ice and a 5% aqueous solution of hydrochloric acid (5 ml) were added and the product extracted into CH_2Cl_2 (7 ml x 2). The organic phases were washed with brine (5 ml) and dried over Na_2SO_4. Concentration gave a pale yellow gum (0.03 g) that showed a minute amount of the required ester (see next experiment for spectra) but consisted mainly of an unknown product, when analysed by t.l.c and n.m.r spectroscopy. The ^{1}H n.m.r spectrum of the unknown showed many multiplets in the regions $\delta2.71$-3.20 and 4.50-6.20. The product also contained additional aromatic signals in the region $\delta6.80$-7.20.

Attempt 4, 5,7,3',4'-tetra-*O*-methyl-3-*O*-(3,4,5-tri-*O*-methylgalloyl)catechin (34).

Catechin tetramethyl ether (15) (0.25 g, 0.72 mmol), 3,4,5-trimethoxybenzoylchloride (0.20 g, 0.87 mmol) and pyridine were stirred at room temperature for 48 h. The yellow solution was diluted with ethyl acetate (40 ml), then washed with a 2M aqueous solution of hydrochloric acid (20 ml x 3) followed by water (20 ml). The solution was dried over Na_2SO_4 then concentrated under reduced pressure to give a pale yellow solid. Recrystallisation (ethanol) yielded the title compound as an off white solid (0.11 g, 27%). M.p: 75-76°C. Anal. Calc. for $C_{29}H_{32}O_{10}$: C, 64.44; H, 5.97. Found: C, 64.15; H, 6.10%. v_{max}(nujol): 2839 (C-OMe), 1719 (C=O), 1593 (C=C), 1502 (C=C) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 2.80 [dd, 1H, 7.5, 16.5 Hz, C(4)H-ax.], 3.17 [dd, 1H, 5.4, 16.5 Hz, C(4)H-eq.], 3.78-3.90 [s x 7, 21H, OMe] 5.10 [d, 1H, 7.2 Hz, C(2)H], 5.49 [m, 1H, C(3)H], 6.11 [d, 1H, 2.4 Hz, C(8)H], 6.19 [d, 1H, 2.4 Hz, C(6)H], 6.82 [d, 1H, 8.4 Hz, C(5')H], 6.95 [dd, 1H, 1.8 Hz, C(2')H],

7.00 [dd, 1H, 1.8, 8.4 Hz, C(6')H], 7.11 [s, 2H, C(2",6")H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 25.65 [C4], 56.06-56.89 [OMe x 6], 61.56 [OMe-C4"], 71.01 [C3], 79.53 [C2], 92.61 [C8], 93.78 [C6], 101.64 [C4a], 107.64 [C2",C6"], 110.50 [C5'], 111.74 [C2'], 120.23 [C6'], 125.69 [C1"], 131.04 [C1'], 143.97 [C4"], 149.80 [C3',C4'], 152.72 [C3",C5"], 155.79 [C8a], 159.84 [C5], 160.60 [C7], 166.70 [C=O]. *m/z* 541 (MH$^+$, 4%), 509 (1), 447 (2), 411 (1), 369 (1), 329 (100), 298 (9), 227 (1), 195 (34), 167 (19).

5,7,3',4'-Tetra-*O*-methyl-3-*O*-(3,4,5-tri-*O*-methylgalloyl)epicatechin (33),
Attempt 1.

Epicatechin tetramethyl ether (**32**) (1.8 mg, 0.05 mmol) was stirred in pyridine (1 ml) and 3,4,5-trimethoxybenzoylchloride (1.4 mg, 0.06 mmol) was added at room temperature. The reaction was left for 48 h and then diluted with ethyl acetate (40 ml). The solution was washed with a 2M aqueous solution of hydrochloric acid (30 ml x 2) and water (10 ml). The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a white solid that appeared as epicatechin tetramethyl ether (**32**) by comparison with the ^{1}H n.m.r spectrum of the starting material.

Attempt 2.

3,4,5-Trimethoxybenzoic acid (0.03 g, 0.14 mmol, 2.5 eq) was stirred in DMF (1.25 µl) and CH$_2$Cl$_2$ (1 ml). Oxalyl chloride (0.04 g, 0.29 mmol) was added to this solution which bubbled slightly. The reaction was stirred for 50 min under a calcium chloride drying tube, the solvents were evaporated and the residue dried *in vacuo*. A solution of epicatechin tetramethyl ether (**32**) (0.02 g, 0.06 mmol) in pyridine (1 ml) was added directly to the crude acid chloride followed by dimethoxyaminopyridine (DMAP) (0.02 g, 0.14 mmol) and the mixture stirred at room temperature in a closed flask for 4 h. Water (17 µl) was added and the reaction stirred for an additional 1.5 h. A 5% aqueous solution of hydrochloric acid (20 ml) was then added and the product extracted into CH$_2$Cl$_2$ (15 ml x 3) and dried over Na$_2$SO$_4$. Concentration under reduced pressure gave a white solid, which was identified as epicatechin tetramethylether (**32**) by spectral comparison with the starting material.

Attempt 3.

Epicatechin tetramethyl ether (**32**) (0.09 g, 0.25 mmol), 3,4,5-trimethoxybenzoic acid (50 mg, 0.25 mmol), dicyclohexylcarbodiimide (60 mg, 0.28 mmol) and DMAP (3.0 mg, 2.50×10^{-2} mmol) were suspended in CH_2Cl_2 (5 ml) and stirred at room temperature for 14.5 h. The solution was then filtered and the solvent removed under reduced pressure. Ether (10 ml) was added to the residue and the resulting suspension was filtered to remove excess dicyclohexylurea (DCU). The ethereal layer was washed with water (10 ml x 4) and dried over Na_2SO_4. The pale yellow gum was purified twice by flash chromatography (silica, 60% hexane in ethyl acetate) to give 5,7,3',4'-Tetra-*O*-methyl-3-*O*-(3,4,5-tri-*O*-methylgalloyl)epicatechin (**33**) as a colourless gum (0.03 g, 26%). Found *m/z* 540.19738. Calcd for $C_{29}H_{32}O_{10}$: 540.19952. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 2.92 [d, 2H, 3.6 Hz, C(4)H], 3.73-3.87 [s x 7, 21H, OMe], 5.13 [s, 1H, C(2)H], 5.63 [m, 1H, C(3)H], 6.11 [d, 1H, 2.1 Hz, C(8)H], 6.24 [d, 1H, 2.1 Hz, C(6)H], 6.82 [d, 1H, 9.0 Hz, C(5')H], 7.02 [d, 1H, 1.8 Hz, C(2')H], 7.03 [dd, 1H, 1.8, 9.0 Hz, C(6')H], 7.17 [s, 2H, C(2'',6'')H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 33.01 [C4], 56.08-57.06 [OMe x 6], 61.54 [OMe-C4''], 69.56 [C3], 79.14 [C2], 92.53 [C8], 93.96 [C6], 100.89 [C4a], 108.08 [C2'',6''], 110.65 [C5'], 111.64 [C2'], 119.72 [C6'], 125.81 [C1''], 131.16 [C1'], 144.84 [C4''], 149.54 [C3',4'], 153.54, 153.96 [C3'',4''], 155.13 [C8a], 159.58 [C5], 160.43 [C7], 165.90 [C=O]. *m/z:* 540 (M$^+$, 4%), 418 (4), 328 (100), 297 (13), 237 (10), 195 (69), 167 (20).

Chapter 5, section A, Grignard and organocuprate reactions.

Bromination of 2-hydroxybenzylalcohol

Attempt 1[121]

A mixture of 2-hydroxybenzylalcohol (0.89 g, 7.17 mmol) and an aqueous solution of hydrobromic acid (48%) (40 ml) was stirred at room temperature for 24 h. Cold H_2O (10 ml) was added causing a pink precipitate to form, which was removed by filtration. The solid was insoluble in most solvents. T.l.c analysis of the solid using ethyl acetate as the elutant, showed only baseline material, suggesting possible polymerisation.

Attempt 2

A solution of the alcohol (0.50 g, 4.03 mmol) in ether was cooled to 0°C. Freshly distilled PBr_3 (0.50 g, 1.80 mmol) was added drop wise and the reaction was then warmed to room temperature. After stirring for 18 h, the mixture was poured onto ice and the organic layer was washed with water (20 ml), followed by 10% Na_2CO_3 (10 ml) and then dried (Na_2SO_4). T.l.c and n.m.r analysis revealed a complex mixture of products.

Attempt 3[122]

A solution of the alcohol (0.30 g, 2.40 mmol) in ether (5 ml) containing CBr_4 (0.14 g, 2.60 mmol) and PPh_3 (0.68 g, 2.60 mmol) was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue chromatographed (silica, 50% ethyl acetate in hexane), giving only starting material.

Attempt 4[123]

PPh_3 (0.63 g, 2.40 mmol) in THF (5 ml) was added drop wise to a stirred solution of *N*-bromosuccinimide in THF (10 ml), causing a precipitate to form and a colour change from orange to pink. To this solution was added the alcohol (0.30 g, 2.40 mmol) in THF (5 ml), and stirring was continued for 3 h, in which time most of the solid had disappeared. The solution was then refluxed for 30 min, and the THF removed from the brown mixture. The oil was then diluted with ether (10 ml), washed with H_2O (10 ml) and dried (Na_2SO_4). T.l.c and n.m.r spectroscopy revealed the presence of starting materials in a complex mixture.

2-(*tert*-Butyldimethylsiloxy)toluene (50).[124]

Imidazole (1.56 g, 23.0 mmol) was added to a solution of *o*-cresol (1.00 g, 9.20 mmol) and *tert*-butyldimethylchlorosilane (1.65 g, 12.0 mmol) in dry DMF (10 ml). The mixture was stirred overnight and the pale green solution was diluted with 5% $NaHCO_3$ (5 ml) and extracted with hexane (4 x 15 ml). The extracts were washed with water and dried (Na_2SO_4), to yield the title compound as a colourless, clear oil (1.96 g, 95%). v_{max}(nujol): 1601 (C=C), 1255 ($SiMe_2$), 1046 (Si-O), 838

(SiMe$_2$), 704 (Si-O) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$/d$_6$-DMSO) δ: 0.19 [s, 6H], 0.99 [s, 9H], 2.19[s, 3H], 6.72-6.84, 6.99-7.10 [m x 2, 4H, Ar-H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: -3.49 [Si-Me$_2$], 17.51 [Me], 18.97[q, t-Bu], 26.49 [Me t-Bu], 119.22 [C5], 121.70 [C1], 127.27 [C4], 129.57 [C1], 131.65 [C5], 154.59 [C1]. *m/z* 222 (M$^+$, 20%), 165 (100), 91(25).

2-(*tert*-Butyldimethylsiloxy)benzyl bromide (49).[51]

To a solution of 2-(*tert*-Butyldimethylsiloxy)toluene (50) (0.50 g, 2.24 mmol) and CCl$_4$ (5 ml) was added *N*-bromosuccinimide (0.44 g, 2.47 mmol), and the solution was brought to reflux by use of an incandescent light. AIBN (5.60 mg, 0.03 mmol) was added and the solution refluxed for a further 10 min. The reaction was brought to room temperature and filtered. The organic layer was washed with water (10 ml) and dried (Na$_2$SO$_4$), to give an orange oil. Kugelrohr distillation (175° C/0.05 torr) afforded the benzyl bromide (49) as clear, colourless oil (0.43 g, 64%). ν_{max}(nujol): 1601 (C=C), 1260 (SiMe$_2$), 1007 (Si-O), 705 (Si-C), 607 (C-Br) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 0.29 [s, 6H, Si-Me$_2$], 1.05 [s, 9H, *t*-Me], 4.53 [s, 2H, CH$_2$], 6.80 [dd, 1H, 1.2, 8.1Hz, C(3)H], 6.91 [ddd, 1H, 1.2, 7.2, 7.5Hz, C(5)H], 7.17 [ddd, 1H, 1.8, 7.5, 8.1Hz, C(4)H], 7.33 [dd, 1H, 1.8, 7.2Hz, C(6)H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: -3.49 [Si-Me$_2$], 18.99 [q, t-Bu], 26.5 [Me, t-Bu], 29.94 [CH$_2$], 119.36 [C5], 121.98 [C3], 129.15 [C1], 130.57 [C6], 131.92 [C4], 154.61 [C2]. *m/z* 301/299 (M$^+$, 4%), 245/243 (100), 221(18), 165 (54), 149 (36), 121 (2), 91 (16), 73 (28), 57 (49).

α-Bromophenylacetyl chloride (53).

α-Bromophenylacetic acid (3.00 g, 0.01 mol) was added to freshly distilled thionyl chloride (2.48 g, 0.02 mol), and the solution was heated to reflux for 1 h. The excess thionyl chloride was distilled off to give pale brown oil. Kugelrohr distillation (100° C/0.05 torr) gave α-bromophenylacetyl chloride (53) as a clear, colourless oil (2.00 g, 86%). ν_{max}(nujol): 1802 (Cl-C=O), 691.41 (C-Br) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 5.67 [s, 1H, α-H], 7.40-7.50 [m, 5H, Ar-H]. ^{13}C n.m.r (75.47 MHz,

CDCl$_3$) δ: 55.54 [C-Br], 129.57 [C3,5], 130.03 [C2,6], 130.80 [C4], 134.10 [C1], 165.34 [C=O].

N-Methoxy,*N*-methyl, α-chlorophenylacetamide (52) .[52]

α-Bromophenylacetyl chloride **(53)** (1.00 g, 4.30 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (0.46 g, 4.70 mmol) were dissolved in chloroform (40 ml) and cooled to 0°C. Pyridine (0.75 g, 9.40 mmol) was added and the reaction was stirred at room temperature for 2 h. The chloroform was removed from the mixture and the oil diluted in ether and CH$_2$Cl$_2$ (20 ml, 1:1). The organic solution was washed with a brine solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Chromatography (silica, 50% ethyl acetate in hexane) yielded the top fraction as a yellow oil (0.42 g, 46%), that was identified as the title amide **(52)**. Anal. Calc. for C$_{10}$H$_{12}$NO$_2$Cl: C, 56.32; H, 5.68; N, 6.57. Found: C, 54.26; H, 5.64; N, 6.18%. Found *m/z* 213.05545. Calcd for C$_{10}$H$_{12}$NO$_2$Cl: 213.00556. ν$_{max}$(nujol): 1673 (C=O), 1176 (C-O), 998 (N-O), 738 (C-Cl) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.22 [s, 3H, Me], 3.57 [s, 3H, OMe], 5.92 [s, 1H, α-H], 7.34 [m, 3H, C(3,4,5)H], 7.56-7.57 [m, 2H, C(2,6)H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 33.47 [Me], 57.81 [α-C], 62.08 [OMe], 128.97 [C4,5], 129.55 [C2,6], 129.70 [C4], 137.27 [C1], 167.59 [C=O]. *m/z*: 215/213 (M$^+$, 8%), 184/182 (5), 152/150 (17), 127/125 (100), 89 (24).

Grignard Reactions.

Activation by iodine.

Magnesium (50 mg, 2.20 mmol) and iodine (1 mg) were stirred vigorously in ether (2 ml) at room temperature. 2-(*tert*-Butyldimethylsiloxy)benzyl bromide **(49)** (80 mg, 0.26 mmol) in ether (2 ml) was added to the magnesium solution over 45 min, causing the iodine colour to disappear. The reaction was cooled to 0°C and the Weinreb amide (70 mg, 0.27 mmol) was added in a solution of ether (1 ml). Upon addition of the amide, the reaction mixture became cloudy, and after 30 min at this temperature, starting materials had not been consumed (t.l.c). After stirring at ambient temperature for 17 h, the reaction was again cooled to 0°C and poured onto

5% aqueous hydrochloric acid in ethanol (20 ml). The cool solution was partitioned between brine (10 ml) and a mixture of ether and CH_2Cl_2 (10 ml, 1:1). The organic extracts were separated and dried (Na_2SO_4), yielding a yellow oil after concentration. The oil consisted of mainly amide (52), but also revealed the presence of a lesser amount of the Wurtz coupled product, *tert*-butyl[2-(2-{[1-(*tert*butyl)-1,1-dimethylsilyl]oxy}phenethyl)phenoxy]dimethylsilane (59), (5.90 mg, 4%). Found *m/z* 442.27440. Calcd for $C_{26}H_{42}Si_2O_2$: 442.27231. v_{max}(nujol): 1605 (C=C), 1263 (SiMe_2), 1020 (Si-O), 705 (Si-C) cm^{-1}. ^{1}H n.m.r (200 MHz, $CDCl_3$) δ: 0.31 [s, 12H, Si-Me_2 x 2], 1.12 [s, 18H, *t*-Me], 2.96 [s, 4H, CH_2 x 2], 6.87-6.97 [m, 4H, Ar-H], 7.08-7.19 [m, 4H, Ar-H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: -3.38 [Si-Me_2], 18.98 [q, *t*-Bu], 26.46 [Me, *t*-Bu], 31.27 [CH_2 x 2], 119.09 [C4], 121.58 [C6], 127.32 [C3], 130.78 [C5], 133.43 [C2], 154.29 [C1]. *m/z*: 443 (MH$^+$, 2%), 387 (10), 357 (32), 313 (54), 222 (58), 91 (100).

Reaction using magnesium powder.

Magnesium powder (0.05 g, 2.06 mmol) was heated in a flask using a heat gun whilst been stirred rapidly for 30 min. A slight magnesium mirror was observed on the inside surface of the flask. Ether (1 ml) was run over the powder and the mixture was cooled to 0°C. 2-(*tert*-Butyldimethylsiloxy)benzyl bromide (49) (0.12 g, 0.41 mmol) in ether (2 ml) was added slowly to the reaction over 30 min and the solution maintained at 0°C for 2 h. After filtering off the solids, the reaction was again taken to 0°C and a solution of the amide (0.09 g, 0.37 mmol) in ether (4 ml) was added dropwise and stirred for 1 h, causing the formation of a white precipitate. A 5% solution of aqueous hydrochloric acid in ethanol (5 ml) was added at 0°C, after which the mixture was partitioned between ether and CH_2Cl_2 (25 ml, 1:1). The organic layer was dried (Na_2SO_4). Evaporation of the solvent gave a white solid contained in a yellow oil. Crude analysis (n.mr, t.l.c) showed mostly starting amide, together with a complex mixture of products. P.l.c (silica, 50% ethyl acetate in hexane) yielded a pale yellow oil of higher Rf than the original amide, which was identified as the Wurtz-coupled product, *tert*-butyl[2-(2-{[1-(*tert*butyl)-1,1-dimethylsilyl]oxy}phenethyl)phenoxy]dimethylsilane (59) (0.01 g, 5.5%).

Grignard reaction using benzaldehyde.

Magnesium powder (0.01 g, 0.40 mmol) was stirred for 18 h in an inert atmosphere of N_2. Iodine (1.00 mg) and THF (1 ml) were added to the magnesium and the combined solution cooled to 0°C. 2-(*tert*-Butyldimethylsiloxy)benzyl bromide **(49)** (0.10 g, 0.33 mmol) in THF (1 ml) was added over 30 min, and the reaction was left stirring at 0°C for 3 h. Benzaldehyde (0.04 g, 0.33 mmol) in THF (1 ml) was added to the cool reaction and stirred at this temperature for 30 min. The solution was poured onto ice containing a 15% solution of sulfuric acid (2 ml), and extracted with ether (5 ml x 3). A yellow oil was obtained after concentrating the dried extracts (Na_2SO_4) that contained a small amount of protected cresol **(50)** and largely baseline material when viewed by t.l.c (20% ethyl acetate in hexane). Crude ^{1}H n.m.r analysis confirmed the presence of the protected cresol **(50)** as well as showing a trace of the Wurtz product **(59)** as well as a complex mixture of alkyl and aromatic signals, none of which could be identified.

Organoncuprate chemistry.

General reaction.[125]

Lithium wire (0.01 g, 1.50 mmol) was added to ether (1 ml), followed by the majority of 2-(*tert*-butyldimethylsiloxy)benzyl bromide **(49)** (0.20 g, 0.66 mmol). The reaction was heated to reflux for 10 min, until a pale brown colour was evident in the suspension. The rest of the bromide was added and the reaction was again heated at reflux for 4 days. The solution upon cooling was filtered under N_2, and the filtrate used with out further purification. Dry, purified cuprous iodide (0.03 g, 0.16 mmol)[108] was suspended in ether (2 ml) and cooled to 0°C. The organolithium reagent (0.08 g, 0.33 mmol) in ether was added and the reaction stirred for 5 min. A cool solution of phenyl acetyl chloride (0.17 g, 1.10 mmol) in ether (5 ml), synthesised from phenyl acetic acid and oxalyl chloride, was added and stirred for 15 min. Methanol (0.5 ml) was added and the reaction warmed to room temperature. The solution was poured into to a cool 1M hydrochloric acid solution (5 ml) and extracted with ether (10 ml x 2). Upon concentration of the dried ether extracts (Na_2SO_4), an orange/pink oil was obtained. P.l.c (silica, 40% ethyl acetate in hexane) gave the

coupled-Wurtz product (**59**) (0.02 g, 15%) and other complex products (^{1}H n.m.r spectroscopy).

Lithium naphthalene.[61]

Naphthalene (0.17 g, 1.32 mmol) was dissolved in THF (2.2 ml), to which was added lithium wire (8.0 mg, 1.10 mmol) under a stream of N_2 gas. The reaction mixture was cooled to 0°C, and after 5 min the solution had turned dark green in colour. The mixture was stirred for a further 30 min at 0°C until all the lithium wire had been consumed. The organolithium reagent (0.14 g, 0.83 mmol) was used directly in the next reaction. To this solution was added hexane (2 ml) and ether (8 ml) and the mixture cooled to -95°C. 2-(*tert*-Butyldimethylsiloxy)benzyl bromide (**49**) (0.10 g, 0.33 mol) diluted in ether (6 ml), THF (4.5 ml) and hexane (1.5 ml) was added to the cooled organolithium reagent and stirred for 15 min. The solution was then added *via* cannula to a separate flask containing purified cuprous iodide (0.03 g, 0.16 mmol). The reaction was warmed to -78°C, and a solution of phenyl acetyl chloride (0.42 g, 0.83 mmol) in ether (2 ml) was added. After stirring for 1.5 h, methanol (1 ml) was added. The yellow solution was then poured onto a cold, saturated, aqueous solution of ammonium chloride (5 ml). The organic layer was removed and the aqueous layer extracted with ether (10 ml). The combined organic extracts were dried ($CaCl_2$) to give a yellow oil after concentration. Analysis (t.l.c, n.m.r spectroscopy) showed no sign of the required coupled product in the complex mixture.

Trial reaction, attempt 1; formation of 1-phenyl acetone (60).[58]

Naphthalene (2.00 g, 15.6 mmol) was added to a dry flask followed by THF (30 ml) and lithium metal (0.10 g, 15.6 mmol). The solution was stirred at 0°C until the lithium had dissolved (1.5 h), resulting in a dark green colour of the lithium naphthalenide species. Methyl iodide (1.99 g, 14.0 mmol) in THF (4 ml) was added dropwise until the green colour of the radical anion just disappeared. Methyl lithium solution in THF was added directly to a solution of dimethylsulfide cuprous(I)bromide (1.08 g, 5.25 mmol) in dimethylsulfide (6 ml) and ether (6 ml). Phenyl acetyl chloride (0.22 g, 1.40 mmol) in ether (1 ml) was added to the organocuprate solution at -78°C, and stirred at this temperature for 1 h. After this time a yellow precipitate was

present in the reaction mixture. The reaction was quenched by the addition of methanol (2 ml), and the reaction poured onto a mixture of saturated ammonium chloride solution and ammonia solution (pH 8, 10 ml), then partitioned between ether (10 ml). The ether layer was washed with a 5% ammonia solution (5 ml x 3) or until the blue colour of the copper species was removed and a yellow solution remained. The solution was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The bulk of the naphthalene was precipitated off using ethanol, and the filtrate concentrated to give a solid that consisted of a complex mixture, part of which were identified as naphthalene and phenyl acetic acid by ^1H n.m.r spectroscopy.

Attempt 2.

Dimethylsulfide cuprous(I)bromide (0.19 g, 0.92 mmol) was dissolved in ether (2 ml) containing dimethylsulfide (2 ml). A 1.45 M solution of methyl lithium-lithium bromide complex (0.04 g, 1.69 mmol) was added until the last of the initially formed yellow precipitate just dissolved to form a yellow solution. The solution was cooled to -78°C and phenyl acetyl chloride (0.05 g, 0.31 mmol) added, causing the solution to become orange in colour. After 15 min, methanol (0.11 ml) was added, followed by a mixture of saturated ammonium chloride solution containing ammonia solution (pH 8, 4 ml), all at -78°C. Extra ether (5 ml) was added to the reaction and the organic layer separated and dried (Na_2SO_4). Upon solvent concentration, a yellow oil was obtained that was identified as 1-phenyl acetone (**60**) (0.01 g, 29%). v_{max}(film): 1710 (C=O), 1608 (C=C) cm^{-1}. ^1H n.m.r (200 MHz, CDCl$_3$) δ: 2.15 [s, 3H, Me], 3.70 [s, 2H, CH$_2$], 7.19-7.39 [m, 5H, Ar-H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 29.91 [CH$_2$], 51.74 [Me], 127.76 [C4], 129.46 [C3, C5], 130.08 [C2, C6], 134.99 [C1], 191.76 [C=O].

Attempt 3.

A 1.45 M methyl lithium-lithium bromide complex in ether (0.07 g, 3.15 mmol) was added to cuprous iodide (0.30 g, 1.58 mmol) suspended in ether (4 ml) at 0°C. After stirring for 10 min the solution was cooled to -78°C and phenyl acetyl chloride (0.08 g, 0.53 mmol) added. After stirring for 15 min, methanol (0.23 ml, 5.70 mmol) was added followed by a solution of ammonium chloride and ammonia solution (pH 8, 6 ml). The reaction mixture was partitioned between ether (5 ml), separated and the organic layer dried over Na_2SO_4. Concentration of the solvent yielded a

yellow oil (0.02 g, 22%) that showed spectra consistent with that of phenyl acetone (**60**).

Organopotassium reaction, without cuprous iodide.

N,N,N',N'-Tetramethylethylenediamine (TMEDA) (0.10 g, 0.90 mmol) was added to a solution of 2.5 M butyl lithium (titrated using diphenylacetic acid)[126] (0.36 ml, 0.90 mmol) in hexane. The mixture was cooled to -50°C and a solution of 2-(*tert*-Butyldimethylsiloxy)toluene (**50**) (0.20 g, 0.90 mmol) in hexane (3 ml) was added over 5 mins, whilst maintaining the reaction at -20°C. Potassium *tert*-butoxide (0.11 g, 0.90 mmol) was added portionwise over 5 min, after which.the reaction was stirred at -20°C for 2 h. The solution was warmed to 10°C and THF was added (0.4 ml). On cooling to -78°C, a solution of phenyl acetyl chloride (0.14 g, 0.90 mmol) in ether (2 ml) was added and stirred for 15 min. Methanol (0.05 g, 1.65 mmol) was added without changing the temperature of the reaction, followed by iced water (4 ml) and then ether (5 ml). The organic layer was separated and the aqueous phase extracted with ether (5 ml x 2). The combined ether extracts were washed with a saturated ammonia solution, dried (Na_2SO_4) and concentrated to give yellow oil. Crude ^{1}H n.m.r showed peaks consistent with that of phenyl acetic acid and the starting siloxy ether (**50**).

Organopotassium reaction, with cuprous iodide.

N,N,N',N'-Tetramethylethylenediamine (TMEDA) (0.10 g, 0.90 mmol) was added to a solution of 2.5 M butyl lithium (0.36 ml, 0.90 mmol) in hexane. The mixture was cooled to -50°C and a solution of *o*-(*tert*-butyldimethylsiloxy)toluene (**50**) (0.20 g, 0.90 mmol) in hexane (3 ml) was added over 5 mins, whilst maintaining the reaction at -20°C. Potassium *tert*-butoxide (0.11 g, 0.90 mmol) was added portionwise over 5 min, after which the reaction was stirred at -20°C for 2 h. The solution was warmed to 10°C and THF was added (0.13 ml). Cuprous iodide (0.09 g, 0.45 mmol) was suspended in ether (1 ml) and cooled to 0°C. The organopotassium reagent was added directly to the cooled copper suspension using a cannula, resulting in the generation of a dark green solution. The reaction was stirred at 0°C for 10 min before being cooled to -78°C. Phenyl acetyl chloride (0.02 g, 0.15 mmol) was added to the cooled solution and stirred for 15 min. Methanol was added (0.50 g, 1.65

mmol), followed by an aqueous ammonium chloride/ammonia solution (pH 8, 5 ml), and ether (10 ml). The dried ether extract (Na_2SO_4) was concentrated under reduced pressure to give a brown oil, that appeared by crude ^1H n.m.r to consist of products similar to what was obtained from the reaction without cuprous iodide.

Organolithium formation using butyl lithium.

TMEDA (0.04 g, 0.33 mmol) was added to a dropping funnel, together with hexane (1.2 ml) and a 2.5 M solution of *n*-butyl lithium in hexane (0.54 ml, 1.3 mmol). The combined mixture was left to stand for 10 min, in which time a white precipitate formed. 2-(*tert*-Butyldimethylsiloxy)toluene (**50**) (0.20 g, 0.89 mmol) was diluted in hexane (6 ml), and the lithium suspension was added dropwise from the funnel to this mixture. After stirring at room temperature for 4 h, the reaction appeared yellow and to contain a precipitate. Phenyl acetyl chloride (0.07 g, 0.45 mmol) was diluted in hexane (1 ml) and added to the yellow mixture, generating more precipitate that dissolved after 5 min, to give a dark red solution. After stirring a room temperature for 2 h, water (3 ml) was added to the reaction, the hexane layer separated and the aqueous phase extracted with more hexane (5 ml). The combined hexane solutions were washed with a saturated solution of ammonium chloride (5 ml) and dried over Na_2SO_4.

This reaction was repeated exchanging phenyl acetyl chloride for benzyl bromide (0.31 g, 1.80 mmol). The work up proceeded as stated above.

Both reactions showed signs of starting cresol (**50**) and a small amount of phenyl acetic acid or benzyl alcohol when viewed by t.l.c or ^1H.n.m.r spectroscopy.

Chapter 5, section B.

Route A: Claisen rearrangements.

First reaction.[68]

Phloroglucinol (0.30 g, 2.88 mmol) was dissolved in THF (2 ml) to which was added sodium hydride (0.06 g, 2.83 mmol) and treated with cinnamyl chloride (0.36 g, 2.83 mmol) in THF (0.5 ml). The reaction was heated at reflux for 19 h, then cooled.

Water was added to the solution (5 ml) and the layers separated. The THF layer was distilled (under reduced pressure toward the end), and the residue was treated with Claisen's alkali; consisting of potassium hydroxide (3.5 g) dissolved in water (2.5 ml) and diluted with methanol (10 ml). The combined solution was extracted with hexane (10 ml x 2) to remove the neutral material. The alkaline solution was acidified with a solution of hydrochloric acid (2M) and extracted with ether (10 ml). The ether layer was dried (Na_2SO_4) and concentrated under reduced pressure giving brown oil. T.l.c showed four spots. Chromatography (silica, 50% ethyl acetate in hexane) yielded a yellow oil (Rf=0.55) (0.15 g, 15%), that was identified as the di-alkylated species, *2,4-di[(E)-3-phenyl-2-propenyl]-1,3,5-benzenetriol* **(70)**. Found *m/z* 358.1561. Calcd for $C_{24}H_{22}O_3$: 358.1568. ν_{max}(nujol): 3431 (OH), 1620 (C=C) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.55 [d, 4H, 1.5 Hz, CH$_2$], 5.33 [bs, 2H, OH], 6.03 [s, 1H, Ar-H], 6.33 [dt, 2H, 6.3, 15.9 Hz, α-H], 6.50 [d, 2H, 15.9 Hz, β-H], 7.16-7.35 [m, 10H, Ar-H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 27.04 [CH$_2$], 96.93 [C6], 105.69 [C2,4], 126.91 [C,2',6' x 2], 127.98 [CH$_2$-<u>CH</u>=CH- x 2], 128.68 [CH$_2$-CH=<u>CH</u>- x 2], 129.17 [C3',5' x 2], 131.66 [C4' x 2], 137.67 [C1' x 2], 154.20 [C1,5], 154.98 [C3]. *m/z* 358 (M$^+$, 55%), 267 (100), 254 (63), 241 (22), 163 (68).

The reaction was repeated as described above, except that the solution was cooled to 0°C, before the addition of cinnamyl chloride then stirred at room temperature for 24 h. T.l.c showed the presence of four spots; cinnamyl chloride, the diadduct **(70)** isolated in the above reaction, an unknown and phloroglucinol, in order of decreasing Rf. The Rf values of these compounds were consistent with what was found in the above reaction. All the spots appeared in a similar amount. The unknown fraction was identified as a mixture of the *O*-alkylated claisen product, 2-(1-phenylallyl)-1,3,5-benzenetriol **(71)** or the S$_N$2' addition product 5-[(1-phenylallyl)oxy]-1,3-benzenediol **(72)** and the required mono-adduct, 2,-[(*E*)-3-phenyl-2-propenyl]-1,3,5-benzenetriol **(64)** appearing as a yellow oil (0.05 g). The two products appeared in a 1:1 ratio (n.m.r). ν_{max}(nujol): 3081 (C=C), 3430 (OH), 1620 (C=C) cm^{-1}. ^{1}H n.m.r (200 MHz, CDCl$_3$) δ: 3.45 [d, 2H, 5.6 Hz, CH$_2$, C-alkylated], 5.02 [m, 1H, terminal alkene-H, Claisen], 5.11 [m, 1H, terminal, alkene-H, Claisen], 5.43 [m, 1H, C(1)H-allyl, Claisen], 5.93 [s, 4H, C(2,4)H-Ar, Claisen and C-alkylated], 6.23 [m, 1H, alkene-H, Claisen], 6.33 [dt, 2H, 6.3, 15.9 Hz,

α-H], 6.50 [d, 2H, 15.9 Hz, β-H], 7.12-7.33 [m, 10H, Ar-H, Claisen and C-alkylated].

m/z (71 or 72): 242 (M^+, 100%), 227 (83), 199 (81), 149 (34), 69 (79).

(1-Chloroallyl)benzene.[72]

A solution of cinnamyl alcohol (1.00 g, 7.47 mmol) in ether (75 ml) was cooled to 0° C. To this solution was added thionyl chloride (1.77 g, 0.02 mol) in ether (75 ml) over 40 min, then the solution was stirred at room temperature for 1 h. Solvent evaporation gave pale yellow oil that was used directly in the next reaction. ^{1}H n.m.r showed the presence of cinnamyl chloride and (1-chloroallyl)benzene in a ratio of 5:1. v_{max}(nujol): 3083 ($C=CH_2$), 1677 (C=C), 911.98 ($C=CH_2$), 693 (C-Cl) cm^{-1}. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 5.21[d, 1H, 9.3 Hz, H-β], 5.25 [d, 1H, 16.8 Hz, H-β], 5.43 [d, 1h, 7.2 Hz, C(1)H], 6.18 [m, 1H, H-α], 7.31 [m, 5H, Ar-H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 64.69 [C1], 117.54 [CH=$\underline{C}H_2$], 123.33 [C2',6'], 128.00 [C4'], 128.87 [C3',5'], 136.50 [$\underline{C}H=CH_2$], 138.37 [C1'].

Claisen rearrangement using (1-chloroallyl)benzene.[127]

Phloroglucinol (0.50 g, 3.96 mmol), potassium carbonate (0.55 g, 3.96 mmol), potassium iodide (0.23 g, 1.36 mmol), (1-chloroallyl)benzene (0.60 g, 3.96 mmol) and acetone (25 ml) were heated at reflux for 24 h, after which the solution appeared yellow in colour, and was filtered and evaporated under reduced pressure. The orange residue was diluted in *N,N*-dimethylaniline (2 ml)and heated to 150° C for 4 h, giving a dark purple solution. The cooled solution was shaken with an aqueous 2M hydrochloric acid solution and ice (15 ml), then extracted with chloroform (15 ml x 2). Solvent evaporation gave brown oil, which was added to hexane (5 ml) and stirred. Brown oil remained at the bottom of the flask from which was decanted a yellow hexane fraction. T.l.c analysis of the brown oil showed multiple smeared products. These products could not be identified or obtained in purity after chromatography (silica, 50% ethyl acetate in hexane).

Route B: Acylation reactions.

Using cinnamic acid derivatives.[50]

(*E*)-3-(1,3-benzodioxol-5-yl)-1-(2,3,6-trimethoxyphenyl)-2-propen-1-one (87).

Freshly distilled trifluoroacetic anhydride (1.08 g, 5.15 mmol) was added to a solution of 3,4-methylenedioxy cinnamic acid (0.50 g, 2.60 mmol) in CH_2Cl_2 (5 ml) and stirred for 10 min. The solution was cooled to 0°C and 1,3,5-trimethoxybenzene (0.43 g, 2.60 mmol) dissolved in CH_2Cl_2 (2.5 ml) was added dropwise causing an instant dark purple colour. The solution was stirred at room temperature for 1 h, after which a saturated solution of $NaHCO_3$ (3 ml) was added and stirred until the reaction turned yellow in colour. The solution was extracted with CH_2Cl_2 (5 ml x 2), and the combined extracts dried over Na_2SO_4. The required compound; (*E*)-3-(1,3-benzodioxol-5-yl)-1-(2,4,6-trimethoxyphenyl)-2-propen-1-one (**87**) was obtained as a yellow gum (0.17 g, 19%). Anal. Calc. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.38. Found: C, 66.60; H, 5.51%. Found *m/z* 342.1089. Calcd for $C_{19}H_{18}O_6$: 342.1103. v_{max}(nujol): 2730 ($O-CH_2-O$), 1640 (C=C), 1590 (C=O), 1150 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 3.76 [s, 6H, C(2,6)OMe], 3.85 [s, 3H, C(4)OMe], 5.99 [s, 2H, methylene], 6.16 [s, 2H, C(3,5)H], 6.79 [d, 1H, 16.1 Hz, H-α], 6.80 [d, 1H, 8.1 Hz, C(5')H], 6.98 [dd, 1H, 1.8, 8.1 Hz, C(6')H], 7.05 [d, 1H, 1.8 Hz, C(2')H], 7.28 [d, 1H, 16.1 Hz, H-β]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 55.99 [OMe (4)], 56.49 [OMe (2,6)], 91.40 [C3,5], 101.26 [methylene], 107.36 [C2'], 109.07 [C5'], 112.62 [C1], 125.32 [C6'], 127.93 [C-α], 130.07 [C1'], 144.52 [C-β], 148.89 [C3'], 150.17 [C4'], 157.90 [C2,6], 162.96 [C4], 198.52 [C=O]. *m/z* 342 (M$^+$, 10%), 316 (74), 195 (69), 135 (38), 84 (88), 69 (70), 45 (100).

Bromination of (*E*)-3-(1,3-benzodioxol-5-yl)-1-(2,3,6-trimethoxyphenyl)-2-propen-1-one (87).[128]

Attempt 1.

(*E*)-3-(1,3-Benzodioxol-5-yl)-1-(2,3,6-trimethoxyphenyl)-2-propen-1-one (**87**) (0.10 g, 3.05 mmol) was dissolved in carbon tetrachloride (30 ml), to which was added a 0.708 M solution of bromine in carbon tetrachloride (0.94 ml, 0.66 mmol). The reaction was left stirring in the dark for 13 h, and the solvent was removed to give a

grey, foamy solid, that appeared mainly as the 3-brominated-tribromide (91). M.p: 64-67°C. [1]H n.m.r (300 MHz, CDCl$_3$) δ: 3.94 [s, 3H, OMe-4], 3.96 [s, 6H, OMe x 2-2,6], 5.49 [d, 1H, 11.1 Hz, α-H], 5.70 [d, 1H, 11.1 Hz, β-H], 5.99 [s, 2H, O-CH$_2$-O], 6.36 [s, 1H, C(3 or 5)H], 6.77 [d, 1H, 7.8 Hz, C(5)H], 6.89 [dd, 1H, 2.1, 7.8 Hz, C(6)H], 6.91 [d, 2.1 Hz, C(2)H]. [13]C n.m.r (75.47 MHz, CDCl$_3$) δ: 49.37 [C-β], 54.42 [C-α], 56.41, 56.73 [OMe x 2], 64.16 [OMe-4], 92.80 [C5 or C3], 99.68 [O-CH$_2$-O], 108.55 [C2',5'], 116.62 [C1], 123.00 [C6'], 132.60 [C1'], 148.66, 148.79 [C3',4'], 158.35 [C4], 159.48 [C6], 160.56 [C2], 190.67 [C=O].

Recrystallisation of the tri-bromo compound in ethanol gave a solid that contained the tri-bromo compound and another product, in a 2:1 ratio ([1]H n.m.r). The filtrate contained mainly the new product, which possible had one of the two adjacent bromine groups substituted for an ethoxy group. [1]H n.m.r (200 MHz, CDCl$_3$) δ: 1.06 [t, 3H, 7.0 Hz, EtO], 3.81 [q, 2H, 7.0 Hz, EtO], 3.89 [s, 6H, OMe-2,6], 3.96 [s, 3H, OMe-4], 4.73 [d, 1H, 9.8 Hz, α-H], 5.03 [d, 1H, 9.8 Hz, β-H], 5.97 [s, 2H, O-CH$_2$-O], 6.36 [s, 1H, C(3 or 5)H], 6.78 [d, 1H, 11.7 Hz, C(5)H], 6.87 [dd, 1.6, 11.7 Hz, C(6)H], 6.93 [d, 1H, 1.6 Hz, C(2)H]. m/z: 545/547/549 (M$^+$, 20%), 467 (5), 423/421 (7), 276/274 (62), 197 (13), 182 (100), 155 (89), 89 (30). Mass spectral data (FAB and GCMS) appeared inconclusive in determining the structure of the tribromide product (91). Additional attempts of purifying both products (chromatography) caused product decomposition, determined by [1]H n.m.r and t.l.c.

Treating the possible ethoxy substituted dibromide (0.08 g), with potassium-*tert*-butoxide (0.11 g, 0.98 mmol) in a solution of THF (15 ml), for 1 h at room temperature gave a dark brown mixture. This was partitioned between a brine solution (5ml) and hexane (5ml). The aqueous phase was re extracted with hexane, and the organic phases were combined. The dried (Na$_2$SO$_4$), concentrated solution appeared as multiple spots by t.l.c. N.m.r analysis revealed a complex mixture of signals, none of which could be identified, even as starting material.

Attempt 2, Acetic acid bromination.

(*E*)-3-(1,3-Benzodioxol-5-yl)-1-(2,3,6-trimethoxyphenyl)-2-propen-1-one (87) (0.16 g, 0.47 mmol) was dissolved in acetic acid (1 ml), and bromine (0.08 g, 0.47 mmol) was added dropwise over 30 min. The brown solution was poured onto ice water (3 ml)

and filtered to give a cream solid. Chromatography (silica, 50% ethyl acetate in hexane) resulted in a foamy, yellow solid (0.02 g, M.p: 60-63° C) that was still impure and showed complex signals when analysed by [1]H.n.m.r.

1,3,5-Tribenzyloxy benzene (85).[85]

Phloroglucinol (0.30 g, 2.40 mmol) was added to a 2M aqueous solution of sodium hydroxide (1.8 ml) containing ice (2.5 g). Acetic anhydride (0.38 g, 3.80 mmol) was added and the flask shaken for 2 min. The white solid was filtered off and recrystallised from water giving 1,3,5-triacetoxy benzene (**86**) as a white solid (7.60 g, 38%). M.p: 100-102° C, (lit: 98-100° C).[131] ν_{max}(nujol): 1764 (C=O), 1601 (C=C), 1188 (C-O) cm^{-1}. [1]H n.m.r (300 MHz, CDCl$_3$) δ: 2.26 [s, 9H, Me], 6.84 [s, 3H, C(2,4,6)H]. [13]C n.m.r (75.47 MHz, CDCl$_3$) δ: 21.55 [Me x 3], 113.34 [C2,4,6], 151.68 [C1,3,5], 169.15 [C=O x 3]. *m/z* 252 (M$^+$, 7%), 210 (24), 168 (38), 126 (100), 43 (76).

1,3,5-Triacetoxy benzene (**86**) (2.00 g, 7.94 mmol), benzyl chloride (3.62 g, 0.03 mol), sodium hydride (1.38 g, 0.06 mol) suspended in DMF (40 ml) and cooled to 0° C. Water (0.43 g, 0.02 mol) was added dropwise over 10 min causing the white solution to turn yellow. After stirring at room temperature for 2 h the solution was diluted with ethyl acetate (20 ml) and washed with water (20 ml) then brine solution (20 ml). Solvent evaporation under reduced pressure yielded a cream solid that was recrystallised (methanol) to give a white solid. The solid was washed with hexane (20 ml) and dried under vacuum, giving 1,3,5-tribenzyloxybenzene (**85**) (2.40 g, 76%). M.p.: 93-94° C, (lit: 93-94° C).[129] ν_{max}(nujol): 1612 (C=O), 1594 (C=C), 1164 (C-O) cm^{-1}. [1]H n.m.r (300 MHz, CDCl$_3$) δ: 4.99 [s, 6H, CH$_2$], 6.27 [s, 3H, C(2,4,6)H], 7.32-7.43 [m, 15H, Ar-H]. [13]C n.m.r (75.47 MHz, CDCl$_3$) δ: 70.79 [CH$_2$ x 3], 95.61 [C2,4,6], 128.24 [C2',6' x 3], 128.67 [C4'], 129.26 [C3',5'], 137.77 [C1'], 161.34 [C1,3,5]. *m/z* 397 (MH$^+$, 18%), 345 (3), 307 (2), 257 (10), 214 (4), 182 (7), 149 (6), 129 (8), 91 (100).

Acylation using 1,3,5-tribenzyloxybenzene.

(*E*)-3-(1,3-Benzodioxyl-5-yl)-1-[2,4,6-tri(benzyloxy)phenyl]-2-propen-1-one (88).

Methylenedioxycinnamic acid (0.10 g, 0.51 mmol) and trifluoroacetic anhydride (0.21 g, 1.01 mmol) were stirred in CH_2Cl_2 (1 ml) for 10 min, then cooled to 0°C. 1,3,5-Tribenzyloxybenzene (85) (0.30 g, 0.76mmol) was added in CH_2Cl_2 (2.5 ml), and the reaction stirred over 1 h at 0°C. A saturated solution of $NaHCO_3$ (5 ml) was added to the cool, orange solution which became much paler. The aqueous solution was extracted with CH_2Cl_2 (5 ml x 2), and the combined extracts dried over Na_2SO_4. Solvent evaporation gave a brown gum, which was purified *via* chromatography (silica, 20% ethyl acetate in hexane) yielding a yellow solid that was identified as (*E*)-3-(1,3-Benzodioxyl-5-yl)-1-[2,4,6-tri(benzyloxy)phenyl]-2-propen-1-one (88), (0.09 g, 32%). M.p: 40-41°C. Found *m/z* 570.2032. Calcd for $C_{37}H_{30}O_6$: 570.2042. v_{max}(nujol): 2726 (O-CH_2-O), 1641 (C=C), 1582 (C=O), 1153 (C-O) cm^{-1}. ^{1}H n.m.r (300MHz, CDCl₃) δ: 4.96 [s, 2H, CH_2-4Bn], 5.03 [s, 4H, CH_2-2,6Bn], 5.93 [s,2H, methylene], 6.26 [s, 2H, C(3,5)H], 6.77 [d, 1H, 8.1 Hz, C(H)5'], 6.82 [d, 1H, 15.9 Hz, H-α], 6.91 [dd, 1H, 1.8, 8.1 Hz, C(H)6'], 6.98 [d, 1H, 1.8 Hz, C(H)2'], 7.23-7.38 [m, 16H, H-β, Ar-H]. ^{13}C n.m.r (75.47 MHz, CDCl₃) δ: 70.93 [CH_2-4Bn], 71.08 [CH_2-2,6Bn], 94.39 [C3,4], 102.13 [O-CH_2-O], 107.45 [C2'], 109.09 [C5'], 114.01 [C1], 125.31 [C6'], 127.62-129.29 [C2",3",4",6",C-α], 130.09 [C1'], 137.10 [C1"-4Bn], 137.27 [C1"-2,6Bn], 144.82 [C-β], 148.93 [C2,6], 161.83 [C4], 194.45 [C=O]. *m/z* 570 (M⁺, 16%), 552 (3), 479 (5), 424 (2), 389 (4), 345 (2), 269 (4), 237 (33), 207 (3), 175 (9), 135 (4), 91 (100), 65 (10).

Bromination of (*E*)-3-(1,3-benzodioxyl-5-yl)-1-[2,4,6-tri(benzyloxy)phenyl]-2-propen-1-one (88).

(*E*)-3-(1,3-Benzodioxyl-5-yl)-1-[2,4,6-tri(benzyloxy)phenyl]-2-propen-1-one (88) (0.05 g, 0.09 mmol) was dissolved in carbon tetrachloride (15 ml) and cooled to 0°C. Bromine (0.03 g, 0.19 mmol) in carbon tetrachloride (0.27 ml) was added whilst the reaction mixture was protected from the light. The reaction was stirred at room temperature for 18 h then the solvent was removed *via* a stream of N_2 gas. Brown oil

resulted that appeared as multiple spots by t.l.c analysis; none of which could be purified or identified even after chromatography.

Bromination using acetic acid.

(*E*)-3-(1,3-Benzodioxyl-5-yl)-1-[2,4,6-tri(benzyloxy)phenyl]-2-propen-1-one **(88)** (0.05 g, 0.09 mmol) was dissolved in acetic acid (10 ml) and treated with an acetic acid solution (5 ml) containing bromine (0.01 g, 0.09 mmol) at 0°C. The reaction was stirred overnight at room temperature, and the orange/brown solution was poured onto ice water (15 ml). The bright pink precipitate was filtered off and washed with hexane (5 ml). This solid appeared as a multiple, smeared products by t.l.c, and gave a complex ^{1}H n.m.r spectrum.

Acylation reactions using phenyl propiolic acid and trifluoroacetic anhydride.

Trifluoroacetic anhydride (0.49 g, 2.34 mmol) added to a solution of phenyl propiolic acid (0.17 g, 1.17 mmol) in CH_2Cl_2 (1.7 ml). The solution was cooled to 0°C, to which was added 1,3,5-trimethoxybenzene **(92)** (0.30 g, 1.78 mmol) in CH_2Cl_2 (1.8 ml). After stirring at room temperature for 1 h, a saturated aqueous solution of $NaHCO_3$ (5 ml) was added to the dark purple reaction mixture and stirred until it became yellow in colour. The solution was extracted with CH_2Cl_2 (5 ml x 2) and dried over Na_2SO_4. After concentration under reduced pressure, the purple oil was chromatographed (silica, 50% ethyl acetate in hexane) to give (*Z*)-3-phenyl-1,3-di(2,4,6-trimethoxyphenyl)-2-propen-1-one **(93)** as a beige solid (0.02 g, 66%). M.p: 167-170°C. Rf=0.27. Found *m/z* 464.1834. Calcd for $C_{27}H_{28}O_7$: 464.1834. v_{max}(nujol): 1590 (C=O), 1130 (C-O), 831(C=C) cm^{-1}. ^{1}H n.m.r (600 MHz, CDCl$_3$) δ: 3.56 [s, 6H, 2,6-OMe], 3.66 [s, 6H, 2',6'-OMe], 3.75 [s, 3H, 4'-OMe], 3.78 [s, 3H, 4-OMe], 5.86 [s, 2H, C(3',5')H], 5.93 [s, 2H, C(3,5)H], 6.98 [s, 1H, H-α], 7.25 [m, 3H, C(3",4",5")H], 7.35 [m, 2H, C(2",6")H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 55.03 [OMe x 6], 89.99 [C3,5 x 2], 108.99 [C1'], 113.70 [C1], 126.91 [C2",6"], 128.07 [C3",5"], 128.32 [C4"], 130.94 [C-α], 140.78 [C1"], 144.38 [C-β], 158.08 [C2,6], 158.47 [C2',6'], 160.97 [C4], 161.70 [C4'], 194.23 [C=O]. *m/z* 464 (M$^+$, 7%), 433 (100), 417 (5), 375 (3), 341 (6), 297 (3), 255 (3), 195 (12), 151 (2), 91 (4).

The reaction was conducted as stated above, except that 1,3,5-tribenzyloxybenzene (**94**) (0.30 g, 0.76 mmol) was used instead of 1,3,5-trimethoxybenzene. The quantity of other reagents was scaled accordingly. Yellow oil was obtained from the reaction after chromatography (silica, 20% ethyl acetate in hexane), that appeared as the only major product apart from starting material. This was identified as 2,2,2-trifluoro-1-[2,4,6-tri(benzyloxy)phenyl]-1-ethanone (**94**) (0.12 g, 25%). Rf=0.50. Anal. Calc. for $C_{29}H_{23}F_3O_4$: C, 70.73; H, 4.71. Found: C, 70.73; H, 4.78%. v_{max}(nujol): 1714 (C=O), 1606 (C=C), 1339 (C-F), 1159 (C-O), 696 (C-F) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 4.96 [s, 2H, CH$_2$-4Bn], 5.03 [s, 4H, CH$_2$-2,6-Bn], 6.23 [s, 2H, C(3,4)H], 7.34-7.38 [m, 15H, Ar-Bn]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 71.03 [CH$_2$-4Bn], 71.40 [CH$_2$-2,6Bn], 93.86 [C3,4], 111.13 [q, 523Hz, CF$_3$], 118.19 [C1], 127.69-129.37 [C2'-6'], 136.46 [C1'-2,6Bn], 136.58 [C1'-4Bn], 159.84 [C2,6], 164.14 [C4], 181.12 [C=O]. *m/z* 493 (M$^+$, 30%), 424 (21), 402 (4), 314 (0.2), 272 (0.3), 257 (0.2), 211 (0.2), 182 (3), 126 (4), 91 (100).

Michael addition reactions.

(*E*)-1,3-Di(2,4,6-trimethoxyphenyl)-2-propen-1-one (95); general procedure.

1,3,5-trimethoxybenzene (0.30 g, 1.78 mmol) was added all at once to a solution of trifluoroacetic anhydride (0.56 g, 2.70 mmol) and propiolic acid (0.12 g, 1.78 mmol). The solution went dark red instantly, and was stirred at room temperature for 3 h. Saturated aqueous NaHCO$_3$ solution (5 ml) was added to the purple reaction, which was stirred until it appeared yellow in colour. The solution was extracted with CH$_2$Cl$_2$ (10 ml x 2), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Purification using chromatography (silica, 50% ethyl acetate in hexane) gave 2,2,2-trifluoro-1-(2,4,6-trimethoxyphenyl)-1-ethanone (**96**) (0.24 g, 52%), as a white solid. M.p: 58-59°C, (lit: 59-60°C).^{130} Rf=0.73. v_{max}(nujol): 1720 (C=O), 1606 (C=C), 1340 (C-F), 737 (C-F) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.80 [s, 6H, OMe-C2,6], 3.84 [s, 3H, OMe-C4], 6.12 [s, 2H, C(3,5)H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 55.22 [OMe-C4], 55.61 [OMe-C2,6], 90.37 [C3,5], 105.24 [m, C1], 115.04 [q, 438Hz, CF$_3$], 160.37 [C2,6], 164.73 [C4], 180.23 [m, C=O]. *m/z* 264 (M$^+$, 19%), 249 (1), 221 (1), 195 (100), 165 (2), 152 (10), 109 (3).

(E)-1,3-Di(2,4,6-trimethoxyphenyl)-2-propen-1-one (**95**) was obtained as a yellow solid (66.50 mg, 10%). Rf=0.27. M.p: 151-152°C. Anal. Calc. for $C_{21}H_{24}O_7$:

C, 64.94; H, 6.23. Found: C, 65.02; H, 6.45%. Found *m/z* 388.15334. Calcd for C$_{21}$H$_{24}$O$_7$: 388.15219. ν$_{max}$(nujol): 1626 (C=O), 1602 (C=C), 1120 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.75 [s, 6H, OMe-C2,6], 3.81 [s, 6H, OMe-C2',6'], 3.83 [s, 3H, OMe-C4], 3.85 [s, 3H, OMe-C4'], 6.08 [s, 2H, C(3',5')H], 6.15 [s, 2H, C(3,5)H], 7.29 [d, 1H, 16.2Hz, H-α], 7.79 [d, 1H, 16.2Hz, H-β]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 55.96-56.56 [OMe x 6], 91.21 [C3,5], 91.54 [C3',5'], 107.15 [C1'], 113.51 [C1], 129.90 [Cα], 137.01 [Cβ], 159.29 [C2',6'], 162.04 [C2,6], 162.47 [C4'], 163.55 [C4], 189.96 [C=O]. *m/z* 388 (M$^+$, 22%), 357 (40), 195 (78), 91 (100), 68 (24).

The reaction above was repeated as stated, with the addition of trifluoroacetic acid (0.02 g, 0.18 mmol) at the beginning of the reaction. Upon work up, 2,2,2-trifluoro-1-(2,4,6-trimethoxyphenyl)-1-ethanone (**96**) (0.18 g, 38%) and (*E*)-1,3-di(2,4,6-trimethoxyphenyl)-2-propen-1-one (**95**) (0.11 g, 15%) were obtained.

Table 5, Double addition reactions, following the general procedure (see above).

Entry 1a.

1,2,3-Trimethoxybenzene (0.30 g, 1.78 mmol) was reacted with TFAA (0.50 g, 2.83 mmol) and propiolic acid (0.08 g, 1.19 mmol) as described. The reaction was stirred at room temperature for 22 h, in this time turning pale pink. N.m.r and t.l.c showed only 1,2,3-trimethoxybenzene.

Entry 1b.

1,2,3-Trimethoxybenzene (0.20 g, 1.19 mmol) was reacted as stated with TFAA (0.33 g, 1.59 mmol) and propiolic acid (0.05 g, 0.79 mmol), except that the TFAA and the acid were heated at reflux for 30 min, then cooled before the addition of the substituted benzene. The entire reaction was heated at reflux for 24 h, still giving only 1,2,3-trimethoxybenzene.

Entry 1c.

1,2,3-Trimethoxybenzene (0.20 g, 1.19 mmol) was added to a solution of TFAA (0,37 g, 1.18 mmol) and propiolic acid (0.08 g, 1.19 mmol) at room temperature, with

out the use of any solvents. The reaction was left stirring at 50°C and appeared dark blue in colour after 7 h. Purification by chromatography (silica, 20% ethyl acetate in hexane) gave 1,2,3-trimethoxybenzene and a minor amount of polymeric material. The polymeric material showed numerous signals from δ3.68-3.00 in the ^{1}H n.m.r spectrum as well as signals at δ5.97, 6.74, 6.84, 8.08 that had coupling constants of 12.2 Hz and 16.2 Hz.

Entry 2.

Veratrole (0.30 g, 2.19 mmol) was reacted with TFAA (0.61 g, 2.92 mmol) and propiolic acid (0.10 g, 1.46 mmol) as described. After stirring for 1.5 h at room temperature, the reaction showed no colour change. The reaction was then taken to reflux for 18 h; giving a brown solution. Work up showed that no starting material had been consumed.

Entry 3a.

1,3-Dimethoxybenzene (0.30 g, 2.19 mmol) was added to TFAA (0.61 g, 2.90 mmol) and propiolic acid (0.10 g, 1.46 mmol) as outlined. After stirring at room temperature for 4.5 h, the reaction appeared dark purple in colour. Chromatography (silica, 20% ethyl acetate in hexane) gave mainly 1,3-dimethoxybenzene, a small amount of unknown material and 2,2,2-trifluoro-1-(2,4-dimethoxyphenyl)-1-ethanone (**98**) (0.02 g, 5%). M.p: 47-49°C, (lit: 48-52°C).[131] v_{max}(nujol): 1703 (C=O), 1605 (C=C), 1286 (C-F), 1165 (C-O), 721 (C-F) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.89 [s, 3H, OMe], 3.91 [s, 3H, OMe], 6.48 [d, 1H, 2.4 Hz, C(3)H], 6.57 [dd, 2.4, 8.7 Hz, C(5)H], 7.77 [dq, J_{HF}=1.2, J=8.7 Hz, C(6)H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 56.39, 56.56 [OMe x 2], 99.41 [C3], 106.43 [C5], 118.17 [q, 377 Hz, CF$_3$], 119.23 [C1], 134.85 [C6], 153.87 [C2,4], 167.02 [C=O]. m/z: 234 (M$^+$, 16%), 165 (100), 151 (6), 135 (4), 122 (17), 107 (10). The unknown material appeared as a smear by t.l.c at a lower Rf than the other products. The product gave a complex n.m.r and LC-MS showed multiple peaks of more than m/z 955, suggesting the material was polymeric.

Entry 3b.

m-Dimethoxybenzene (0.40 g, 2.90 mmol) was added directly to a solution of TFAA (0.92 g, 4.40 mmol) and propiolic acid (0.20 g, 2.90 mmol) at room temperature, in

the absence of additional solvents. The reaction was heated at 50°C for 3.5 h, giving a violet coloured solution. A dark green oil was obtained after work up which was purified by chromatography (silica, 40% ethyl acetate in hexane), giving the same mixture of products/polymers as described in Entry 3a. There seemed to be more starting material consumed and more polymeric products, which appeared as a smear when viewed by t.l.c.

Entry 4.

p-Dimethoxybenzene (0.30 g, 2.17 mmol) was combined with TFAA (0.61 g, 2.90 mmol) and propiolic acid (0.10 g, 1.45 mmol) as described. After stirring at room temperature for 18 h, the solution appeared the same colour as when it started. The reaction gave only *p*-dimethoxybenzene upon work up.

Entry 5.

m-Anisidine (0.30 g, 2.40 mmol) was added to a solution of TFAA (0.68 g, 3.20 mmol) and propiolic acid (0.11 g, 1.60 mmol) as stated previously. The solution was stirred at room temperature for 18 h, still remaining yellow in colour within this time. Chromatography (silica, 40% ethyl acetate in hexane) yielded two products, Rf=0.1 and Rf=0.3. The first product (Rf=0.1) was obtained as a white solid (0.03 g, 9%). M.p: 81-82°C. This was identified as *N*1-(3-methoxyphenyl)-2-propynamide (**100**). Anal. Calc. for $C_{10}H_6NO_2$: C, 68.56; H, 5.18. Found: C, 68.53; H, 5.08%. v_{max}(nujol): 3270 (alkyne-H), 3100, 3000 (NH-amide x 2), 2110 (alkyne), 1656 (C=O), 1596 (C=C), 1154 (C-O), 1047 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 2.92 [s, 1H, alkyne-H], 3.79 [s, 3H, OMe], 6.70 [dd, 1H, 2.4, 8.1 Hz, C(4)H], 7.01 [dd, 1H, 1.5, 8.1 Hz, C(6)H], 7.22 [dd, 1H, 8.1 Hz, C(5)H], 7.25 [d, 1H, 2.4 Hz, C(2)H], 7.76 [bs, 1H, NH]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 55.99 [OMe], 74.77 [alkyne, C-β], 78.27 [alkyne, C-α], 106.67 [C2], 111.65 [C4], 112.86 [C6], 130.45 [C5], .138.81 [C1], 150.39 [C=O], 160.83 [C3]. *m/z*: 175 (M$^+$, 35%), 146 (14), 132 (58), 104 (31), 53 (100).

The second product (Rf=0.22) was identified as *N*1-(3-methoxyphenyl)-2,2,2-trifluoroacetamide (**99**) (0.30g, 86%). M.p: 71-72°C, (lit: 73-74°C).[132] v_{max}(nujol): 3284, 3214, 3116 (NH-amide), 1707 (C=O), 1624 (C=C), 1289 (C-O), 1048 (C-F),

683 (C-F) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.74 [s, 3H, OMe], 6.75 [dt, 1H, 1.5, 2.4, 8.1 Hz, C(4)H], 7.12 [dd, 1H, 1.5, 8.1 Hz, C(6)H], 7.22 [dd, 1H, 8.1 Hz, C(5)H], 7.26 [d, 2.4 Hz, C(2)H], 8.92 [bs, 1H, NH]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 56.02 [OMe], 107.09 [C2], 112.86 [C4], 113.35 [C6], 116.77 [q, 443 Hz, CF$_3$], 130.73 [C5], 136.88 [C1], 155.17 [m, C=O], 160.97 [C3]. m/z: 219 (M$^+$, 100%), 150 (41), 122 (19), 107 (75), 92 (28), 77 (43).

Entry 6.

Anisole (0.30 g, 2.80 mmol) was added to a solution of TFAA (0.77 g, 3.70 mmol) and propiolic acid (0.13 g, 1.85 mmol) at room temperature. The reaction was heated at reflux for 17 h and worked up as stated previously. Anisole was the only compound obtained from the reaction.

Mixed double addition reactions.

Attempt 1.

1,3,5-Trimethoxybenzene (92) (0.30 g, 1.78 mmol) and 1,2,3-trimethoxybenzene (0.60 g, 3.57 mmol) were added to a solution of TFAA (0.49 g, 2.83 mmol) and propiolic acid (0.08 g, 1.19 mmol) as stated in the general reaction. The purple solution was stirred for 1 h, giving blue/green oil on work up. Chromatography (silica, 20% ethyl acetate in hexane) yielded the two starting benzene compounds, 2,2,2-trifluoro-1-(2,4,6-trimethoxyphenyl)-1-ethanone (96) (0.05 g, 11%) and a pale yellow gum (Rf=0.05) (0.01 g) that showed multiple methoxy signals by n.m.r (^{1}H, ^{13}C) and high molecular weights (~799) when analysed by GC-MS, suggesting polymeric material.

Attempt 2.

1,3,5-Trimethoxybenzene (94) (0.30 g, 1.78 mmol) and 1,2,3-trimethoxybenzene (0.30 g, 1.78 mmol) were added to TFAA (0.75 g, 3.57 mmol) and propiolic acid (0.12 g, 1.78 mmol) and stirred at room temperature for 2 h. Chromatography gave the same combination of starting material and products as in Entry 1. The trifluoroacetyl (96) derivative was obtained as a white solid (0.14 g, 29%).

Attempt 3.

1,3,5-Trimethoxybenzene (**94**) (0.20 g, 1.19 mmol) and 1,2,3-trimethoxybenzene (0.30 g, 1.78 mmol) were added to TFAA (0.50 g, 2.40 mmol) and propiolic acid (0.08 g, 1.19 mmol) at room temperature. TFAA and propiolic acid were stirred for 5 min prior to the addition and for 5 min after. Dichloroethane (2 ml) was added to the solution, which was heated at reflux for 2.5 h. The dark purple solution was worked up as usual giving a dark brown oil. Purification (silica, 40% ethyl acetate in hexane) gave a small amount of both starting benzenes as well as four impure fractions. The fraction with the highest Rf: ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.78-3.89 [3s, 18H, OMe], 6.11 [s, 1H], 6.17 [d, 1H, 10.2 Hz], 6.28 [d, 1H, 2.1 Hz], 6.42 [d, 1H, 2.1 Hz], 7.98 [d, 1H, 10.2 Hz]. A ^{13}C n.m.r spectrum could not be obtained due to the small amount of material. The mass spectrum gave high molecular weight species around *m/z* 556, from which no reasonable structure could be deduced. The other three fractions all appeared as complex mixtures by n.m.r spectroscopy.

Acylation reactions using Propiolic anhydride.

Propiolic anhydride.[91]

Propiolic acid (1.00 g, 0.01 mmol) was diluted in ethanol (5 ml) and added to sodium ethoxide (0.31 g, 0.01 mmol) in ethanol (15 ml). The reaction was stirred for 10 min. Sufficient ether was added to dilute the ethanol and cause the product to precipitate. The solid was collected by filtration and the residue washed twice with an ether/ethanol solution (95:1, 20 ml). The salt was heated at reflux in ethanol (10 ml) for 20 min, then filtered and dried under vacuum using a nitrogen atmosphere. Sodium propiolate was obtained as a pale brown solid in quantitative yield.

Sodium propiolate (0.20 g, 2.17 mmol) was suspended by vigorous stirring in dichloroethane (10 ml) and oxalyl chloride (0.14 g, 1.09 mmol) was added in one portion at 0°C. The ice bath was removed until gas evolution started (*ca.* 10 min) and the reaction was then again placed in the bath. After gas evolution had ceased (*ca.* 15 min), the insoluble material was filtered off and the dichloroethane solution used directly.

Acylation reaction using 1,3,5-trimethoxybenzene.

Zinc chloride (0.28 g, 2.06 mmol) was added to 1,3,5-trimethoxybenzene (0.17 g, 1.03 mmol) stirred in dichloroethane (5 ml). Propiolic anhydride (0.13 g, 1.03 mmol) in dichloroethane (10 ml) was added dropwise to the stirred solution and refluxed for 2 h. The reaction was poured onto a 1M solution of hydrochloric acid (10 ml) containing ice, and extracted with CH_2Cl_2 (10 ml x 2). The extracts were dried (Na_2SO_4) and concentrated to give a dark purple oil. Purification by chromatography (silica, 40% ethyl acetate in hexane) gave 1,3,5-trimethoxybenzene (0.02g, 10% recovery). The next fraction off the column consisted of 5,7-dimethoxychromone (**102**) Rf=0.4 (40% ethyl acetate in hexane), (6.3 mg, 3%). M.p: 132-135°C, (lit: 128-130°C).[133] Found m/z 206.05883. Calcd for $C_{11}H_{10}O_4$: 206.05790. v_{max}(nujol): 1650 (C=O), 1605 (C=C), 1210 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 3.83 [s, 3H, OMe-C7], 3.91 [s, 3H, OMe-C5], 6.15 [d, 1H, 9.6 Hz, H-3], 6.28 [d, 1H, 2.1 Hz, C(6)H], 6.42 [d, 1H, 2.1 Hz, C(8)H], 7.96 [d, 1H, 9.6 Hz, H-2]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 56.47, 56.71 [OMe x 2], 93.50 [C6], 95.51 [C8], 109.97 [C4a], 111.65 [C-3], 139.37 [C-2], 157.66 [C8a], 162.16 [C5], 164.39 [C7], 193.79 [C=O]. m/z 206 (M$^+$, 69%), 178 (100), 163 (68), 135 (49), 120 (12), 92 (18).

The reaction yielded a product that appeared to contain a substituted 1,3,5-trimethoxybenzene moiety. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 3.46 [s, 6H, OMe x 2], 3.77 [s, 3H, OMe-4 para to substitution], 6.20 [s, 2H, Ar-H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$)δ: 55.77 [OMe-4 para to substitution], 57.06 [OMe x 2], 93.63 [C3,5], 117.97 [C1-substituted], 157.44 [C4], 160.09 [C2,6]. m/z 285 (M$^+$, 12%), 271 (4), 257 (28), 235 (10), 219 (62), 193 (29), 173 (100), 167 (55), 136 (22), 121 (38), 97 (22), 83 (17), 69 (70).

(*E*)-1,3-Di(2,4,6-trimethoxyphenyl)-2-propen-1-one (**95**) (56 mg, 14%) was also isolated form the reaction as a yellow solid (see ahead for spectra), Rf=0.1, (40% ethyl acetate in hexane).

Acylation reaction using 1,3-Dimethoxybenzene.

1,3-Dimethoxybenzene (0.30 g, 2.2 mmol) was dissolved in CH_2Cl_2 (10 ml) to which was added zinc chloride (0.60 g, 0.44 mmol). Propiolic anhydride (0.20 g, 2.2 mmol) contained in ether (20 ml) was added dropwise to the stirred solution, which was then heated at reflux for 2 h. The cooled red mixture was neutralised using a saturated $NaHCO_3$ solution (10 ml) then extracted with CH_2Cl_2 (20 ml x 2). Upon drying (Na_2SO_4) the concentrated oil was purified using flash chromatography (silica, 40% ethyl acetate in hexane), yielding mainly 1,3-dimethoxybenzene and a small amount of baseline material.

Acylation reactions using phenylpropiolyl chloride and a Lewis acid, Table 6.

Phenylpropiolyl chloride was prepared by heating phenylpropiolic acid in thionyl chloride at 60°C for 3h. The excess thionyl chloride was evaporated off giving pale yellow oil that was stored in the freezer and used without further purification.

Entry 1.

Aluminium chloride (0.08 g, 0.61 mmol) and 1,3,5-tribenzyloxybenzene (**85**) (0.30 g, 0.76 mmol) was placed in a flask with CH_2Cl_2 (2 ml) and cooled to 0°C. Phenylpropiolyl chloride (0.08 g, 0.51 mmol) was added to the reaction in CH_2Cl_2 (5 ml) over 10 min, causing the mixture to turn green in colour. The reaction was heated at 50°C for 5 min, then cooled and poured onto iced water (10 ml). The solution was separated and the organic layer washed with water (4 ml), an aqueous solution of sodium hydroxide (2M) (5 ml), water (5 ml) and dried over Na_2SO_4. T.l.c analysis showed only baseline material.

Entry 2.

A solution of 1,3,5-tribenzyloxybenzene (**85**) (0.03 g, 0.76 mmol) and phenylpropiolyl chloride (0.11 g, 0.69 mmol) were dissolved in CH_2Cl_2 (15 ml) and cooled to -30°C. Aluminium chloride (0.10 g, 0.76 mmol) was added to this solution causing it to turn orange in colour. The reaction was warmed to -5°C and stirred for 1.25 h. The solution was then warmed to 0°C and poured into ice water (15 ml) and separated. The organic layer was washed with water (5 ml), an aqueous 2M solution of sodium

hydroxide (5 ml), water (5 ml) and dried over Na_2SO_4. T.l.c showed the presence of only starting materials.

4,6-di(benzyloxy)-2-[(*E*)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one (104), Entry 3.

1,3,5-Tribenzyloxybenzene (**85**) (0.03 g, 0.76 mmol), phenylpropiolyl chloride (0.11 g, 0.69 mmol) and lastly ferric chloride (0.2 mg, 1.1×10^{-3} mmol) were suspended in dichloroethane (4 ml) and heated at reflux for 1.5 h. A 10% aqueous solution of sodium hydroxide (10 ml) was added to the dark purple solution and left to stir at room temperature for 18 h. The yellow solution was separated and the aqueous layer was extracted with CH_2Cl_2 (5 ml). The organic extracts were washed with water (5 ml) and dried (Na_2SO_4). The concentrated solution yielded a dark red oil that was purified by chromatography (silica, 20% ethyl acetate in hexane) to give a yellow solid (0.03 g, 30%), that was identified as *4,6-di(benzyloxy)-2-[(Z)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one* (*104*). M.p.: 161-163°C. Rf=0.13, (20% ethyl acetate in hexane). Anal. Calc. for $C_{29}H_{22}O_4$: C, 80.17; H, 5.10. Found: C, 80.38; H, 5.16%. λ_{max} 367 (log ε 4.46). v_{max}(nujol): 1693 (C=O), 1590 (C=C), 1157 (C-O), 1086 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 5.08 [s, 2H, CH_2-6Bn], 5.25 [s, 2H, CH_2-4Bn], 6.22 [d, 1H, 1.4 Hz, C(5)H], 6.43 [d, 1H, 1.4 Hz, C(7)H], 6.76 [s, 1H, β-H], 7.15-7.49 [m, 13H, Ar-H], 7.82-7.89 [m, 2H, C(2',6')H-Ar]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 71.35 [CH_2-Bn x 2], 91.27 [C5], 95.47 [C7], 106.47 [C3a], 112.14 [C-β], 127.32-131.74 [C2'-6'Ar x 3], 133.24 [C1'Ar], 136.14, 136.65 [C1'Bn x 2], 148.55 [C-α], 157.35 [C4,6], 169.40 [C7a], 169.59 [C=O]. *m/z* 435 (MH$^+$, 12%), 345 (8), 326 (4), 268 (0.5), 238 (3), 193 (0.1), 152 (0,5), 129 (2), 91 (100), 43 (11).

Entry 4

The above reaction was repeated as stated except that a stoichiometric amount of ferric chloride (0.45 g, 2.75 mmol) was used. The reaction appeared black in colour after 1.5 h. Upon work up, dark brown oil was obtained that showed baseline material when viewed by t.l.c.

1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (106α), Entry 5.

1,3,5-Tribenzyloxybenzene (**85**) (0.20 g, 0.50 mmol), phenylpropioyl chloride (0.07 g, 0.42 mmol) and zinc chloride (1 crystal, ~0.09 mg, 0.6 μmol) were heated at reflux in dichloroethane (5 ml) for 1 h, then cooled. A saturated solution of NaHCO₃ (5 ml) was added and the red solution was extracted with CH_2Cl_2 (5 ml). The combined organic extracts were dried (Na_2SO_4) to give a dark red oil. Chromatography (silica, 20% ethyl acetate in hexane) yielded a yellow solid (0.03 g, 18%). M.p.: 121-122°C. The product was identified as *1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (106α)*, Anal. Calc. for $C_{29}H_{22}O_4$: C, 80.17; H, 5.10. Found: C, 80.10; H, 5.06%. v_{max}(nujol): 2720 (O-H), 2410 (alkyne), 1618 (C=O), 1577 (C=C), 1160 (C-O) cm⁻¹. ¹H n.m.r (300 MHz, CDCl₃) δ: 5.06 [s, 2H, CH₂-4Bn], 5.13 [s, 2H, CH₂-2Bn], 6.10 [d, 1H, 2.4 Hz, C(5)H], 6.16 [d, 1H, 2.4 Hz, C(3)H], 7.05-7.46 [m, 15H, Ar-H]. ¹³C n.m.r (75.47 MHz, CDCl₃) δ: 71.10 [CH₂-4Bn], 71.85 [CH₂-2Bn], 90.50 [C-β, alkyne], 93.45 [C5], 95.37 [C3], 96.17 [C-α, alkyne], 107.99 [C1], 121.52 [C1', phenyl], 128.32-129.41 [C2'-6'Bn x 2, C3',5'-phenyl], 130.65 [C4', phenyl], 133.35 [C2,6], 136.25, 136.35 [C1'Bn x 2], 162.47 [C6], 166.89 [C2], 168.97 [C4], 178.42 [C=O]. *m/z*: 434 (M⁺, 27%), 344 (20), 325 (4), 306 (2), 254 (3), 237 (2), 192 (2), 181 (4), 129 (3), 105 (2), 91 (100).

Entry 6.

The above reaction was repeated as outlined, except that zinc chloride (0.07 g, 0.51 mmol) was used and 1,3,5-tribenzyloxybenzene was added to a solution of the catalyst and acid chloride at 0°C. The reaction was stirred at ambient temperature for 17 h. T.l.c showed a smear and chromatography was unsuccessful at isolating any product.

Table 7, General Reaction.

Tribenzyloxybenzene (**85**), a substituted acid chloride and zinc chloride (0.16 mol%) were refluxed in dichloroethane for 1 h. In this time the reaction mixture appeared a deep, dark colour and was cooled to room temperature. A saturated solution of NaHCO₃ (10 ml) was added to the mixture, which was then extracted with CH_2Cl_2 (10 ml x 2). The extracts were dried over Na_2SO_4 and concentrated under reduced

pressure. The residue was purified using column chromatography (silica) to give the required product.

Entry   1a,   3,5-di(benzyloxy)-2-[3-(3,4,5-trimethoxyphenyl)-1-methylene-2-propynyl]phenol (110).

3,4,5-Trimethoxyphenylpropioloyl chloride.

3,4,5-Trimethoxypropiolic acid (0.80 g, 3.38 mmol) was dissolved in water (2 ml) containing sodium hydroxide (0.14 g, 3.39 mmol). The reaction was stirred until the reagents were in solution (0.5 h) and the mixture appeared yellow in colour. The water was removed under reduced pressure to give a dark red residue, which was added to thionyl chloride (4.86 g, 0.04 mol), contained in ether (15 ml). The reaction was heated at reflux for 1.5 h and then concentrated under reduced pressure to give a dark brown oil that was used without further purification.

3,4,5-Trimethoxyphenylpropioloyl   chloride   (0.11   g,   4.21   mmol), 1,3,5-tribenzyloxybenzene (0.20 g, 0.51 mmol), zinc chloride (1 crystal, ~0.09 mg, 0.6 μmol) were refluxed in dichloroethane (5 ml). The reaction yielded a brown residue that was chromatographed (silica, CH_2Cl_2) to give the title compound as a yellow solid (0.06 g, 30%). M.p: 110-115°C. Found m/z 524.18263. Calcd for $C_{32}H_{28}O_7$: 524.18344. v_{max}(nujol): 3395 (O-H), 2197 (alkyne), 1651 (C=O), 1637 (C=C), 1618 (C=C), 1577 (C=C), 1267 (OH), 1127 (C-O) cm^{-1}. ^1H n.m.r (300 MHz, $CDCl_3$) δ: 3.66 [s, 6H, OMe x 2], 3.86 [s, 3H, OMe-4'], 5.05 [s, 2H, OBn-5], 5.21 [s, 2H, OBn-3], 6.06 [d, 1H, 2.1 Hz, C(4)H], 6.16 [d, 1H, 2.1 Hz, C(6)H], 6.52 [s, 2H, C(2',6')H], 7.17-7.46 [m, 10H, Bn-H]. ^{13}C n.m.r (75.47 MHz, $CDCl_3$) δ: 56.72 [OMe-3',5'], 61.58 [OMe-4'], 71.08, 71.47 [CH_2-OBn], 89.99 [Cβ], 93.42 [C4], 95.39 [C6], 96.53 [Cα], 107.88 [C2], 110.81 [C2',6'], 116.28 [C1'], 127.50-129.37 [Ar-Bn x 2], 136.14, 136.77 [Ar-C1 x 2-Bn], 137.48 [C4'], 153.60 [C3',5'], 162.82 [C5], 166.95 [C3], 168.57 [C1], 178.27 [C=O]. m/z 524 (M^+, 58%), 493 (2), 433 (31), 384 (4), 327 (3), 282 (1), 243 (3), 193 (1), 91 (100), 65 (1).

Entry 1b, 3,5-di(benzyloxy)-2-[3-(3,4,5-trimethoxyphenyl)-1-methylene-2-propynyl]phenol (110).

3,4,5-Trimethoxyphenylpropioloyl chloride.

3,4,5-Trimethoxypropiolic acid (0.80 g, 3.38 mmol) was dissolved in thionyl chloride (2 ml) and stirred at room temperature for 20 min. The majority of thionyl chloride was removed under a steam of nitrogen gas. The residue was dissolved in benzene (1 ml) which was then removed under reduced pressure to ensure the removal of all of the thionly chloride. The yellow oil was then stored below 0°C.

3,4,5-Trimethoxyphenylpropioloyl chloride (0.13 g, 0.51 mmol), 1,3,5-tribenzyloxybenzene (0.20 g, 0.51 mmol) and zinc chloride (1 crystal ~0.01 mg, 0.8 μmol) were refluxed in dichloroethane (2 ml). The reaction gave a dark brown residue that was purified by chromatography (silica, CH_2Cl_2) to give the title compound as a yellow solid (0.09 g, 34%). The experimental data was consistent with what was obtained above. Other fractions contained complex mixtures of products.

Entry 2, 3-(1,3-benzodioxol-5-yl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-2-propen-1-one (107).

3,4-Methylenedioxypropiolic acid (1.00 g) was dissolved in thionyl chloride (3 ml) and stirred at room temperature for 3 h, in which time solution was complete. Thionyl chloride was removed under reduced pressure, the remainder removed by addition of benzene (5 ml x 2) and evaporation under reduced pressure. A bright red solid was obtained in quantitative yield.

3,4-Methylenedioxypropioloyl chloride (0.09 g, 0.42 mmol), 1,3,5-tribenzyloxybenzene (0.20 g, 0.51 mmol) and zinc chloride (1 crystal ~0.09 mg, 0.6 μmol) were refluxed in dichloroethane (5 ml). A dark brown oil was obtained that was purified by chromatography (CH_2Cl_2), to give the title compound as yellow crystals (0.03 g, 14%). Found: C, 69.90; H, 4.45%. Anal. Calc. for $C_{30}H_{23}O_6Cl$: C, 69.97; H, 4.50. v_{max}(nujol): 1624 (C=O), 1599 (C=C), 1580 (Ar), 1169 (O-C-O), 968 (C=C), 722 (C-Cl) cm^{-1}. ^1H n.m.r (600 MHz, CDCl$_3$) δ: 4.98 [s, 2H, OBn-2], 5.09 [s, 2H, OBn-4], 5.98 [s, 2H, O-CH$_2$-O], 6.13 [d, 1H, 2.4 Hz, C(3)H], 6.22 [d, 1H,

2.4 Hz, C(5)H], 6.58 [d, 1H, 7.8 Hz, C(5')H], 6.80 [dd, 1H, 1.8, 7.8 Hz, C(6')H], 6.82 [d, 1H, 1.8 Hz, C(2')H], 7.09-7.44 [m, 10H, Ar-H], 7.28 [s, 1H, α-H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 71.08 [CH$_2$-Bn4], 72.25 [CH$_2$-Bn2], 93.41 [C3], 95.77 [C5], 102.22 [O-CH$_2$-O], 107.71 [C1], 108.01 [C2'], 108.61 [C5'], 122.26 [C6'], 125.92 [C-α], 128.33-129.43 [Ar-Bn x 2], 131.81 [C1'], 135.80 [ipso-Bn2], 136.49 [ipso-Bn4], 140.14 [C-β], 148.38 [C3'], 149.72 [C4'], 162.17 [C2], 166.26 [C4], 170.93 [C6], 192.82 [C=O]. *m/z* 479 (M-Cl$^+$, 2%), 388 (29), 371 (46), 277 (2), 215 (17), 131 (7), 91 (100), 73 (45).

Entry 3a, 2-[3-(3,4,-dimethoxyphenyl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-2-propen-1-one (108).

3,5-Dimethoxyphenylpropioloyl chloride.

3,4-Dimethoxyphenylpropiolic acid (0.30 g) was dissolved in excess thionyl chloride (2 ml) and stirred at room temperature for 45 min until solution was complete. The excess thionyl chloride was removed under reduced pressure. The extract was re-dissolved in benzene (5 ml x 2) and concentrated under reduced pressure to ensure all thionyl chloride had been removed. A yellow solid was obtained in quantitative yield that was used without further purification.

3,4-Dimethoxyphenylpropioloyl chloride (0.10 g, 0.45 mmol), 1,3,5-tribenzyloxbenzene (0.18 g, 0.45 mmol) and zinc chloride (0.1 mg, 0.7 µmol) were heated in refluxing dichloroethane (5 ml). A dark red residue was obtained which gave yellow crystals after chromatography (silica, 80% ethyl acetate in hexane) and was identified as the title compound (0.14 g, 57%). M.p: 110-120° C. Found *m/z* 530.14729. Calcd for C$_{31}$H$_{27}$O$_6$Cl: 530.14960. ν_{max}(nujol): 3190 (OH), 1627 (C=O), 1580 (C=C), 1556 (C=C), 1103 (C-O), 738 (C-Cl) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.74 [s, 3H, OMe-3'], 3.94 [s, 3H, OMe-4'], 4.99 [s, 2H, CH$_2$-Bn2], 5.08 [s, 2H, CH$_2$-Bn4], 6.12 [d, 1H, 2.4 Hz, C(3)H], 6.22 [d, 1H, 2.4 Hz, C(5)H], 6.65 [d, 1H, 8.7 Hz, C(5')H], 6.91 [dd, 1H, 2.1, 8.7 Hz, C(6')H], 6.97 [d, 1H, 2.1 Hz, C(2')H], 7.07-7.42 [m, 10H, Ar-Bn], 7.41 [s, 1H, α-H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 55.76, 56.01 [OMe x 2], 70.39 [CH$_2$-Bn4], 71.44 [CH$_2$-Bn2], 92.77 [C3], 95.06 [C5], 107.71 [C1], 110.03 [C2'], 110.59 [C5'], 120.06 [C6'], 124.93 [C-α], 128.28-129.38 [Bn-Ar],

130.29 [C1'], 135.83 [ipso, Bn2], 136.45 [ipso-Bn4], 139.98 [C-β], 149.22 [C3'], 151.28 [C4'], 162.09 [C2], 166.78 [C4], 169.26 [C6], 192.73 [C=O]. *m/z* 530 (M$^+$, 2%), 495 (25), 404 (5), 314 (2), 285 (2), 243 (1), 165 (2), 91 (100), 65 (8). Other fractions obtained by chromatography showed complex mixtures (n.m.r, t.l.c).

Entry 3b, 2-[3-(3,4,-dimethoxyphenyl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-2-propen-1-one (108) and 3,5-di(benzyloxy)-2-[3-(3,4-dimethoxyphenyl)-1-methylene-2-propynyl]phenol (109).

3,4-Dimethoxyphenylpropioloyl chloride.

3,4-Dimethoxyphenylpropiolic acid (0.10 g, 0.49 mmol) was dissolved in water (0.5 ml) containing sodium hydroxide (0.02 g, 0.49 mmol). The water was then removed under reduced pressure and the solid dried on an oil pump. The brown solid was heated at reflux in a solution of thionyl chloride (0.79 g, 6.65 mmol) and ether (3 ml) for 1.5 h. The solvent was removed under reduced pressure to get a brown solid that was redissolved in benzene and concentrated again.

3,4-Dimethoxyphenylpropioloyl chloride (0.11 g, 0.49 mmol), 1,3,5-tribenzyloxbenzene (0.19 g, 0.49 mmol) and zinc chloride (1 crystal ~0.1 mg, 0.7 μmol) were heated in refluxing dichloroethane (3 ml). A dark brown residue was obtained which was purified by chromatography (CH$_2$Cl$_2$) to give two fractions. The first fraction off the column gave a yellow solid after concentration that was identified as 2-[3-(3,4,-dimethoxyphenyl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-2-propen-1-one (**108**) (21 mg, 4%) and showed spectra consistent with entry 3a. The second fraction off the column was concentrated to a yellow solid, that was identified as 3,5-di(benzyloxy)-2-[3-(3,4-dimethoxyphenyl)-1-methylene-2-propynyl]phenol (**109**) (30 mg, 13%). M.p: 140-145°C. Found *m/z* 494.17090. Calcd for C$_{31}$H$_{26}$O$_6$: 494.17292. v$_{max}$(nujol): 2181 (alkyne), 1655 (C=O), 1615, (C=C), 1580 (C=C), 1541 (C=C), 1259 (OH), 1100 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.69 [s, 3H, OMe-3'], 3.88 [s, 3H, OMe-4'], 5.06 [s, 2H, CH$_2$-Bn3], 5.19 [s, 2H, CH$_2$-Bn5], 6.08 [d, 1H, 2.1 Hz, C(4)H], 6.25 [d, 1H, 2.1 Hz, C(6)H], 6.66 [bs, 2H, C(2', 6')H], 6.82 [bs, 1H, C(5')H], 7.22-7.49 [m, 10H, Ar-H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 56.50, 56.60 [OMe x 2], 70.97 [CH$_2$-Bn3], 71.08 [CH$_2$-Bn5], 90.29 [alkyne-β], 93.53 [C4],

95.38 [C6], 97.42 [alkyne-α], 108.04 [C6], 111.48 [C2',5'], 113.46 [C1'], 116.10 [C6'], 127.57-129.40 [Ar-C], 136.36, 136.49 [ipso-Bn x 2], 149.26 [C3'], 151.93 [C4'], 162.31 [C5], 166.80 [C3], 168.84 [C1], 180.20 [C=O]. m/z 494 (M⁺, 8%), 463 (1), 403 (5), 354 (1), 297 (1), 189 (1), 155 (1), 127 (1), 91 (100), 69 (15).

Route C, Table 9, Cyclisation of 1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (10.6a).

Entry 1.

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (106a) (0.04 g, 0.01 mmol), potassium carbonate (0.02 g, 0.15 mmol) and acetone (1 ml) were heated at reflux for 2.5 h. The carbonate was removed by filtration, and the acetone solution concentrated under reduced pressure to give a yellow solid. Recrystallisation (hexane/ethyl acetate, 5:1) produced a yellow solid (0.02 g, 42%) that was identified as 4,6-di(benzyloxy)-2-[(Z)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one (104). The spectral data was consistent with that reported earlier.

Entry 2a, ¹H.n.m.r cyclisation (300 MHz, d₆-Acetone).

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (106a) (3.6 mg, 8.29 x 10⁻³ mmol), potassium carbonate (1.4 mg, 9.95 x 10⁻³ mmol) and d₆-acetone (1 ml) were mixed together in a n.m.r tube and placed immediately in the spectrometer. After 15 min the first spectrum was recorded. This showed the presence of one new compound together with the starting phenol. The new compound was identified as 4,6-di(benzyloxy)-2-[(Z)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one (104). ¹H n.m.r (600 MHz, d₆-acetone) δ: 5.32 [s, 1H, CH₂-Bn4], 5.36 [s, 1H, CH₂-Bn2], 6.53 [d, 1H, 1.8 Hz, C(3)H], 6.73 [d, 1H, 1.8 Hz, C(5)H], 7.31-7.57 [m, 13H, Ar-H], 7.94 [m, 2H, 2'+6'-Ph]. The β-hydrogen was not present in the spectrum due to possible deuteration.

The ratios of starting phenol to aurone were at 15 min: 29:1, 20 min: 1.3:1, 25 min: 1:4, 30 min: 1:16, 35 min: 1:32, 40 min: 1:213, 45 min: 1:218, 50 min: 1:226, 42h: no phenol evident. The n.m.r tube was left on the bench, in the presence of light for

23 h, after which time a spectrum was re-run. This showed the presence of another product together with the (Z)-aurone, in a ratio of 1:2 respectively. The unknown was identified as the (E)-isomer (117). ^{1}H n.m.r (600 MHz, d_6-acetone) δ: 5.26 [s, 2H, CH_2-Bn4], 5.29 [s, 2H, CH_2-Bn2], 6.49 [d, 1H, 2.1 Hz, C(3)H], 6.66 [d, 1H, 2.1 Hz, C(5)H], 7.31-7.57 [m, 13H, Ar-H], 8.22-8.26 [m, 2H, 2'+6'-Ph].

Entry 2b.

A solution of 1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (106a) (20 mg, 4.60 x 10^{-2} mmol) and potassium carbonate (7.6 mg, 5.50 x 10^{-2} mmol) in acetone (1 ml) were stirred at room temperature for 2 h. The carbonate was removed by filtration and the solution concentrated under reduced pressure. The yellow solid was identified as mainly 4,6-di(benzyloxy)-2-[(Z)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one (104). The ^{1}H n.m.r spectrum also showed the presence of the (E)-aurone (117), in a ratio of Z:E, 32:1. 4,6-Di(benzyloxy)-2-[(E)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one (117), ^{1}H n.m.r (300 MHz, CDCl₃) δ: 5.06 [s, 2H, CH_2-Bn4], 5.24 [s, 2H, CH_2-Bn2], 6.19 [d, 1H, 1.8 Hz, C(3)H], 6.29 [d, 1H, 1.8 Hz, C(5)H], 6.81 [s, 1H, β-H], 7.31-7.50 [m, 13H, Ar-H], 8.32-8.35 [m, 2H, 2'+6'-Ph]. ^{13}C n.m.r (75.47 MHz, CDCl₃) δ: 70.62 [CH_2-Bn x 2], 89.82 [C3], 95.72 [C5], 104.55 [C1], 121.56 [C-β], 126.78-128.78 [Ar], 130.86 [C2', 6'-Ph], 133.43 [C1'-Ph], 136.15, 136.77 [C1" x 2, Bn-Ar], 149.57 [C-α], 159.05 [C2, C4], 169.77 [C=O], 170.74 [C6].

Entry 3.

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (106a) (0.01 g, 2.3 x 10^{-2} mmol) was dissolved in d_6-benzene (1 ml) to which was added trifluoroacetic acid (0.5 ml). ^{1}H n.m.r (300 MHz) spectra were run every 5 min for 1 h. Within this time extra trifluoroacetic acid (0.5 ml) was added and the mixture warmed slightly. After 1 h there appeared no change to the reaction mixture.

Entry 4.[98]

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (106a) (0.01 g, 2.3 x 10^{-2} mmol) was dissolved in 1,4-dioxane (1 ml) to which was added an aqueous solution of 4N hydrobromic acid (10 ml) at room temperature. The reaction was

stirred at 65°C for 3.5 h, cooled to room temperature and diluted with ethyl acetate (8 ml). The reaction was then poured onto ice (50 g) and the aqueous phase was extracted with additional ethyl acetate (10 ml x 2). The combined organic layers were washed with brine (10 ml) and dried over Na_2SO_4. The ethyl acetate was removed under reduced pressure to give a brown oil (0.01 g). This oil showed the presence of two products by t.l.c (Rf=0.33, 0.22, 20% ethyl acetate in hexane). The top spot seemed to be the major product of the reaction. The major product was identified as (*Z*)-3-bromo-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propen-1-one (**118**) and the minor product was thought to be 1-[2,4-di(benzyloxy)-3-bromo-8-hydroxyphenyl]-3-phenyl-2-propyn-1-one (**120**). These products were in a ratio of 1:2 respectively. (Z)-3-bromo-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propen-1-one (**118**). ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 5.07 [s, 2H, CH_2-Bn4], 5.12 [s, 2H, CH_2-Bn2], 6.13 [d, 1H, 2.1Hz, C(3)H], 6.22 [d, 1H, 2.1Hz, C(5)H], 7.12-7.50 [m, 16H, Ar-H, α-H]. 1-[2,4-di(benzyloxy)-3-bromo-8-hydroxyphenyl]-3-phenyl-2-propyn-1-one (**120**). ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 4.99 [s, 2H, CH_2-Bn4], 5.10 [s, 2H, CH_2-Bn2], 6.15 [s, 1H, C(5)H], 7.14-7.52 [m, 15H, Ar-H]. The two products were not separated due to the small amount of material obtained.

Entry 5.[96]

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (**106A**) (5.0 mg, 1.15×10^{-2} mmol) was dissolved in CH_2Cl_2 (1 ml) to which was added *p*-toluenesulfonic acid (1.0 mg, 5.26×10^{-3} mmol). The reaction was heated at reflux for 30 min. In this time starting alkyne was the only product visible by t.l.c. TEMPO (0.01 mg) was added to the reaction, which was left at reflux for a further 23 h. The dark orange solution was cooled and concentrated under reduced pressure to give an orange gum. This gum appeared to be starting alkyne when analysed by ^{1}H n.m.r and t.l.c.

Entry 6.

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (**106A**) (0.02 g, 4.50×10^{-2} mmol) was dissolved in ethanol (1 ml) to which was added diethylamine (0.03 g, 4.50×10^{-2} mmol). The yellow solution was heated at reflux for 24 h. The solvents were removed under reduced pressure to give a yellow solid. Flash

chromatography (silica, CH_2Cl_2) gave 4,6-di(benzyloxy)-2-[(*Z*)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one (**104**) as a yellow solid (12 mg, 64%). 4,6-Di(benzyloxy)-2-[(*E*)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one (**117**) was also obtained from the column (2.4 mg, 12%).

Protection of 1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (106a).

Trimethylsilyl ether.

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (**106a**) (10 mg, 2.60×10^{-2} mmol) was dissolved in pyridine to which was added trimethylsilyl chloride (3.0 mg, 2.60×10^{-2} mmol) immediately. The reaction was left stirring at 35°C for 12 h. The yellow solution was diluted with ethyl acetate (3 ml) and washed successively with a 5% solution of hydrochloric acid (5 ml) and water (5 ml). The solution was dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow gum (6.1 mg, 55%) that was identified as 4,6-di(benzyloxy)-2-[(*Z*)-1-phenylmethylidene]-2,3-dihydrobenzo[b]furan-3-one (**104**).

1-(2,4-Di(benzyloxy)-6-{[1-(*tert*-butyl)-1,1-dimethylsily]oxy}phenyl)-3-phenyl-2-propyn-1-one (124).

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenyl-2-propyn-1-one (**106a**) (4.0 mg, 9.20×10^{-3} mmol) was dissolved in CH_2Cl_2 (5 ml) and cooled to -20°C. 2,6-Lutidine (2.0 mg, 1.80×10^{-2} mmol) was added to the cooled solution followed by *tert*-butyldimethylsilyl triflate (4.0 mg, 1.40×10^{-2} mmol). The yellow solution was warmed to room temperature in which time it became colourless. The mixture was stirred for 1 h, then diluted with ethyl acetate (5 ml) and water (5 ml). The organic layer was washed with a 0.3M solution of potassium hydrogen sulfate (10 ml), water (5 ml) and brine (5 ml). The organic solution was dried (Na_2SO_4) and the solvent removed under reduced pressure. A pale yellow solid was obtained (Rf=0.71) in quantitative yield. ^{1}H n.m.r (300 MHz, $CDCl_3$) δ: 0.30 [s, 6H, Si-Me], 1.15 [s, 9H, *t*-Bu-Me], 5.25 [s, 2H, CH_2-Bn4], 5.32 [s, 2H, CH_2-Bn2], 6.28 [d, 1H, 2.0 Hz, C(5)H], 6.48 [d, 1H, C(3)H], 7.47-7.17 [m, 15H, Ar-H].

Cyclisation of the triflate (124).

1-(2,4-Di(benzyloxy)-6-{[1-(*tert*-butyl)-1,1-dimethylsily]oxy}phenyl)-3-phenyl-2-propyn-1-one (**124**) (12.0 mg, 0.02 mmol), diethylamine (16.0 mg, 0.22 mmol) and ethanol (1 ml) were heated together at reflux for 22 h. The solvents were then removed under reduced pressure to give a yellow gum in quantitative yield which was identified as (*Z*)-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-(diethylamino)-3-phenyl-2-propen-1-one (**123**). ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 2.90 [m. 3H, CH$_3$-ethyl], 3.09 [m, 3H, CH$_3$-ethyl], 3.72 [q, 2H, CH$_2$-ethyl], 3.91 [m, 2H, CH$_2$-ethyl], 4.86 [s, 2H, CH$_2$-Bn4], 4.88 [s, 2H, CH$_2$-Bn2], 5.63 [s, 1H, α-H], 5.66 [d, 1H, 1.2 Hz, C(3)H], 5.84 [s, 1H, 1.2 Hz, C(5)H], 6.99-7.12 [m, 5H, Ar-H], 7.25-7.42 [m, 10H, Ar-H]. The enaminoketone (**123**) was dissolved in ethanol (2 ml) and heated at reflux for a further 24 h. The reaction was cooled and the solvent removed under reduced pressure to give a yellow gum. This gum consisted of mainly enaminoketone (**123**) and two other products in about equal amount, and at a slightly higher Rf. These products were not isolated due to them all having very similar Rf values. Product one: ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 5.00 [s, 2H, CH$_2$-Bn], 5.06 [s, 2H, CH$_2$-Bn], 6.09 [d, 1H, 2.4 Hz, C(3 or 5)H], 6.11 [d, 2.4 Hz, C(3 or 5)H], 6.38 [s, 1H, α-H], 7.20-7.54 [m, 15H, Ar-H]. Product two: ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 5,12 [s, 2H, CH$_2$-Bn], 5.25 [s, 2H, CH$_2$-Bn], 6.51 [d, 1H, 2.1 Hz, C(3 or 5)H], 6.67 [d, 1H, 2.1 Hz, C(3 or 5)H], 7.00-7.97 [m, 15H, Ar-H].

Table 10, Cyclisation reactions of 3,5-di(benzyloxy)-2-[3-(3,4,5-trimethoxyphenyl)-1-methylene-2-propynyl]phenol (110).

Entry 1, 4,6-di(benzyloxy)-2-[(*Z*)-1-(3,4,5-trimethoxyphenyl)methylidene]-2,3-dihydrobenzo[b]furan-3-one (125).

3,5-Di(benzyloxy)-2-[3-(3,4,5-trimethoxyphenyl)-1-methylene-2-propynyl]phenol (**110**) (17 mg, 0.03 mmol) was dissolved in acetone (2 ml) to which was added potassium carbonate (7.0 mg, 0.05 mmol). The reaction was heated to reflux for 40 min, cooled then filtered to remove the carbonate. The acetone was removed under reduced pressure to give *4,6-di(benzyloxy)-2-[(Z)-1-(3,4,5-trimethoxyphenyl)methylidene]-2,3-dihydrobenzo[b]furan-3-one (125)* in quantitative yield. Mp: 175-177°C. Found *m/z* 524.18302. Calcd for C$_{32}$H$_{28}$O$_7$: 524.18348. λ_{max} 384 (log ε 3.91). ν_{max}(nujol): 1700

(C=O), 1652 (C=C), 1588 (C=C), 1157 (C-O), 1083 (C-O) cm^{-1}. ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.91 [s, 3H, OMe-4'], 3.94 [s, 6H, OMe-3',5'], 5.10 [s, 2H, CH$_2$-Bn6], 5.28 [s, 2H, CH$_2$-Bn4], 6.24 [d, 1H, 1.5 Hz, C(5)H], 6.42 [d, 1H, 1.5 Hz, C(7)H], 6.69 [s, 1H, β-H], 7.13 [s, 2H, C(2',6')H], 7.30-7.49 [m, 10H, Ar-H]. ^{13}C n.m.r (75.47 MHz, CDCl$_3$) δ: 54.54 [OMe x 2], 56.94 [OMe-4'], 70.81 [CH$_2$-Bn6], 71.52 [CH$_2$-Bn4], 91.40 [C5], 97.14 [C7], 109.35 [C2',6'], 111.59 [C-β], 127.50-129.46 [Ar-C], 136.14, 136.68 [C1" x 2Bn], 140.89 [C4'], 148.10 [C-α], 153.99 [C3',5'], 159.16 [C2,4], 168.38 [C=O], 169.39 [C7a]. *m/z* 524 (M$^+$, 87%), 493 (12), 433 (73), 402 (14), 384 (30), 358 (11), 327 (15), 296 (4), 243 (15), 193 (9), 135 (2), 91 (100), 65 (13).

Entry 2.

3,5-Di(benzyloxy)-2-[3-(3,4,5-trimethoxyphenyl)-1-methylene-2-propynyl]phenol (**110**) (0.02 g, 0.04 mmol) was dissolved in trifluoroacetic acid (2 ml) and heated at 50°C for 1.5 h, in which time the solution turned dark red in colour. The reaction appeared as multiple spots by t.lc. The trifluoroacetic acid was removed under a stream of nitrogen gas, to give a dark red gum. Chromatography (silica, 60% hexane in ethyl acetate) gave a small amount of yellow gum (1.6 mg) that appeared as a complex mixture (t.l.c, n.m.r).

Entry 3.

3,5-Di(benzyloxy)-2-[3-(3,4,5-trimethoxyphenyl)-1-methylene-2-propynyl]phenol (**110**) (10 mg, 0.02 mmol) was dissolved in ethanol (1 ml) and diethylamine added (10 mg, 0.19 mmol). The yellow solution was heated at reflux for 24 h and then cooled. The solvents were removed under reduced pressure to give a yellow solid (2.0 mg, 20%) that was identified as *4,6-di(benzyloxy)-2-[(Z)-1-(3,4,5-trimethoxyphenyl)methylidene]-2,3-dihydrobenzo[b]furan-3-one (125)*. The data was consistent with that reported above.

Entry 4, 4,6-di(benzyloxy)-2-[(*Z*)-1-(3,4,5-trimethoxyphenyl)methylidene]-2,3-dihydrobenzo[b]furan-3-one (125).

3,5-Di(benzyloxy)-2-[3-(3,4,5-trimethoxyphenyl)-1-methylene-2-propynyl]phenol (**110**) (10 mg, 19 μmol) was dissolved in DMF (1 ml), to which was added 18-crown-6

(10 mg, 38 μmol) and potassium fluoride (2 mg, 38 μmol) at 0°C.[103] The solution turned from yellow to a yellow-green colour and was stirred at ambient temperature for 2 h. The mixture was diluted with a aqueous saturated solution of ammonium chloride (2 ml) and extracted with ethyl acetate (2 ml x 2). The yellow solution was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a yellow oil that appeared (^{1}H n.m.r) to contained mainly the (Z)-aurone (**125**) and a minor impurity which was not starting material (t.l.c). The by-product contained three distinct signals at δ6.14 [d, 1.5 Hz], 6.34 [d, 1.5 Hz] and 6.69 [s] which may possible be from the (E)-aurone or the required flavone (**126**). The reaction was not purified further due to the small amount of material obtained from the reaction and the small quantity of unknown present within this mixture.

Cyclisation reactions of 2-[3-(3,4,-dimethoxyphenyl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-2-propen-1-one (108).

Attempt 1, 4,6-Di(benzyloxy)-2-[(Z)-1-(3,4-dimethoxyphenyl)methylidene]-2,3-dihydrobenzo[b]furan-
3-one (127).

2-[3-(3,4-Dimethoxyphenyl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-2-propen-1-one (**108**) (10 mg, 0.02 mmol) was dissolved in dichloroethane (1 ml) and sodium hydride (washed with hexane prior to use) (0.5 mg, 0.02 mmol) added. The reaction was heated at reflux for 30 min, then cooled to room temperature and more sodium hydride was added (0.5 mg, 0.02 mmol). The reaction was stirred for 10 min and then washed with water (2 ml). The organic layer was removed, dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give   yellow crystals in quantitative yield which were identified as the title compound *4,6-di(benzyloxy)-2-[(Z)-1-(3,4-dimethoxyphenyl)methylidene]-2,3-dihydrobenzo[b]furan-3-one*   *(127)*.
M.p: 128-130°C. λ$_{max}$ 398 (log ε 4.22). ^{1}H n.m.r (300 MHz, CDCl$_3$) δ: 3.94 [s, 3H, OMe-4'], 3.97 [s, 3H, OMe-3'], 5.10 [s, 2H, CH$_2$-Bn6], 5.28 [s, 2H, CH$_2$-Bn4], 6.23 [d, 1H, 1.8 Hz, C(5)H], 6.42 [d, 1H, 1.8 Hz, C(7)H], 6.74 [s, 1H, C(3)H], 6.93 [d, 1H, 9.0 Hz, C(5')H], 7.31-7.49 [m, 12H, Ar-H, C(2',6')H]. ^{13}C n.m.r (150.87 MHz, CDCl$_3$) δ: 55.93, 55.98 [OMe x 2], 70.76, 70.84 [CH$_2$-Bn x 2], 90.60 [C7], 96.38 [C5], 106.07 [C4a], 111.13, 111.21 [C3,5'], 113.64 [C2'], 125.27 [C6'], 125.58 [C1'], 126.79-128.77

[Ar-C], 135.51 [*ipso*-Bn6], 136.05 [*ipso*-Bn4], 146.89 [C2], 149.00 [C3'], 150.39 [C4'], 158.35 [C4], 167.50 [C6], 168.61 [C7a], 180.35 [C=O]. *m/z* 494 (M$^+$, 6%), 404 (11), 314 (2), 285 (2), 256 (2), 202 (3), 151 (7), 129 (26), 91 (68), 41 (100).

Attempt 2.

2-[3-(3,4-Dimethoxyphenyl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-2-propen-1-one (**108**) (6.0 mg, 0.01 mmol) was dissolved in acetone (1 ml) to which was added anhydrous potassium carbonate (3.0 mg, 0.02 mmol). The solution was refluxed for 30 min, cooled and filtered. The yellow solution was concentrated under reduced pressure to give a yellow solid (7.0 mg, 100%) that was identified as *4,6-di(benzyloxy)-2-[(Z)-1-(3,4-dimethoxyphenyl)methylidene]-2,3-dihydrobenzo[b]furan-3-one (127)* by comparison with the ^{1}H n.m.r spectrum from above.

Attempt 3.

2-[3-(3,4-Dimethoxyphenyl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-2-propen-1-one (**108**) (0.01 g, 0.02 mmol) was dissolved in triethylamine (0.36 g, 3.58 mmol) and stirred at room temperature for 40 min in which time a bright yellow precipitate was evident in the reaction mixture. The reaction was then heated at 80°C for 30 min, then at reflux for 15 min, which did not dissolve the precipitate. Dichloroethane (1 ml) was added to the mixture, which was heated at reflux for 45 min. The solvents were distilled from the reaction under reduced pressure to give a yellow gum. This gum contained starting material (**108**) and 4,6-di(benzyloxy)-2-[(Z)-1-(3,4-dimethoxyphenyl)methylidene]-2,3-dihydrobenzo[b]furan-3-one (**127**) according to t.l.c and ^{1}H n.m.r analysis. The products appeared in a 2:1 ratio respectively according to the ^{1}H n.m.r spectrum.

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