Synthetic Approaches to Polyoxygenated Chromone and Chromanone Natural Products

A thesis presented for the

degree of

Doctor of Philosophy

by

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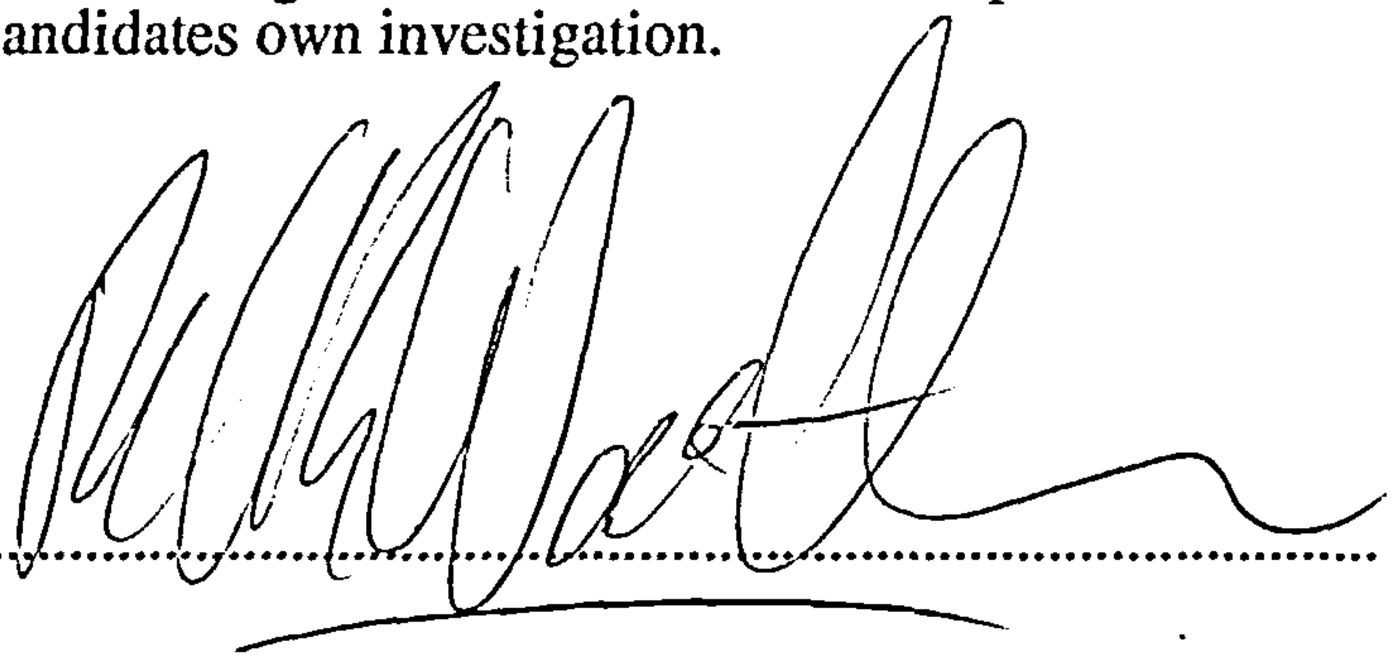
"I am not unaware that many have held and hold the opinion that events are controlled by fortune and by God in such a way that the prudence of men cannot modify them, indeed, that men have no influence whatsoever.

....Sometimes when thinking of this, I have myself inclined to this same opinion. Nonetheless, so as not to rule out our free will, I believe that it is probably true that fortune is the Arbiter of half the things we do, leaving the other half or so to be controlled by ourselves."
Niccolò Machiavelli, *Il Principe*, postulate XXV.

To all the people who've mattered.

Declaration

We the undersigned, declare that the work presented in this thesis is the result of the candidates own investigation.



Robert C.R. Wootton

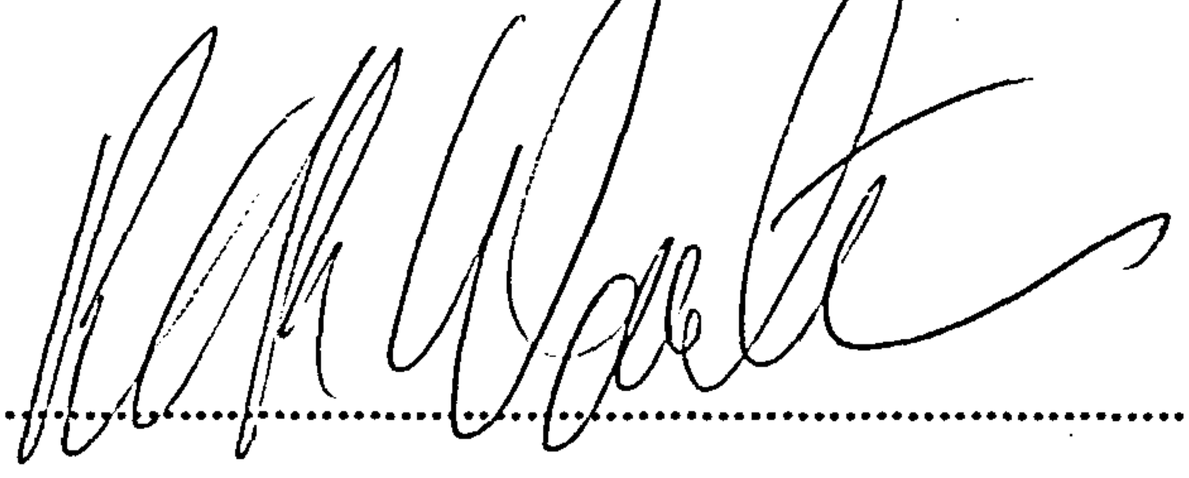
Tim Wallace

Dr. T.W. Wallace

12/04/00

Date

I declare that the work has not already been in substance for any other degree and is not being currently submitted in candidature for any other degree.



Robert C.R. Wootton

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Thankyou to everyone on the top floor, especially Colin, Angela, Christalla, Adam, Alwyn , Gill S. and Mo, none of whom allowed the sudden reappearance of a scary fridge-throwing hippy to phase them.

This thesis would not have been possible without the people at The Red House, who offered support when it was needed most, the true mark of friendship.

Abbreviations

br	broad
CI	chemical ionisation
EI	electric ionisation
d	doublet
dd	doublet of doublets
dt	doublet of triplets
g	gram(mes)
h	hours
HRMS	high resolution mass spectrometry
i.r.	infra red
m	multiplet
M	molar
MHz	megahertz
ml	millilitre(s)
mmol	millimole(s)
NMR	nuclear magnetic resonance
q	quartet
s	singlet
TLC	thin layer chromatography

Abstract

The work described in this thesis is concerned with the chemistry of polymethoxylated aromatic carbonyl compounds bearing a 2,6-dioxygenated substitution pattern, with particular regard to establishing synthetic routes to biologically active chromone and chromanone systems. Syntheses of key intermediates in the approaches to the natural products stigmatellin, baicalein and LL-D253α (and related products) were undertaken.

In chapter one the reactions of nucleophiles at the carbonyl moieties of 2,6-dioxygenated benzene carbonyl compounds are reviewed. This type of process can present special difficulties and was to prove particularly significant at various stages of the work described in subsequent chapters.

Chapter two is a review of the provenance, abundance, biosynthesis, and previous syntheses of the natural products stigmatellin, baicalein and LL-D253α, these being the targets of the synthetic work undertaken in the course of the project.

Chapter three is concerned with an approach to a fragment of the stigmatellin molecule (referred to as stigmatellin fragment A) using the Vilsmeier formylation reaction, while chapter four is concerned with an alternative approach to stigmatellin fragment A using Friedel-Crafts acylation methodology. The strategies and the results obtained are described and analysed in detail.

In chapter five a strategy for the synthesis of baicalein trimethyl ether is described and the results obtained are discussed.

CONTENTS

Chapter 1

A review of the reactions of nucleophiles at the carbonyl moieties of 2,6-dioxygenated benzene carbonyl compounds

1.1 Introduction

2,6-Dioxygenated benzene carbonyl compounds are widely found in nature, particularly, as will be seen in later chapters, in chromone and chromanone herbal and fungal metabolites. Nucleophile addition reactions at the carbonyl moieties of these compounds are a potentially potent means of synthetic elaboration. This review aims to bring to light some of the successful reactions undertaken. To avoid undue duplication the addition of sulphoxide derived carbanions to these systems will largely be dealt with in a later chapter.

This review is intended to provide a representative sample of the reactions between nucleophiles and 2,6-dioxygenated benzene carbonyl compounds at the carbonyl moiety. It is also intended to point out the limitations, if any, in the synthetic applications of these reactions. Carbanion reactions at these sites are potentially useful for chain lengthening purposes. An example is given in a later chapter where a tetramethoxypropiophenone could not be synthesised directly but could be approached *via* a nucleophile addition to a 2,3,4,6-tetramethoxybenzaldehyde.

As our research often relied upon synthetic schemes involving substitution or addition reactions at the carbonyl moiety of 2,6-dioxygenated systems we were interested in elucidating the limitations of the process. Of particular concern to us was the effect of steric hindrance by the oxo substituents in the 2 and 6 positions. Simple space-filling models suggest that the Burgi-Dunitz angles in these substrates are relatively unimpeded, but more sophisticated modelling techniques than those available to us would be required to make meaningful predictions about structure/reactivity relationships. Even with such methods empirical evidence is required in corroboration. We sought therefore to find such limitations as could be enlimbed from the literature.

The review utilises references generated in part from the Beilstein Crossfire reaction databases. Searches were generated using reaction structures with the maximum free

sites enabled. For example the general reaction for the displacement of an ester with a carbonyl species was searched using the representation shown in figure 1.1.2, where any undefined site is open to interpretation by the database. Dotted lines on the figure denote 'mappings' which define which atoms in the product are present in the reactant.

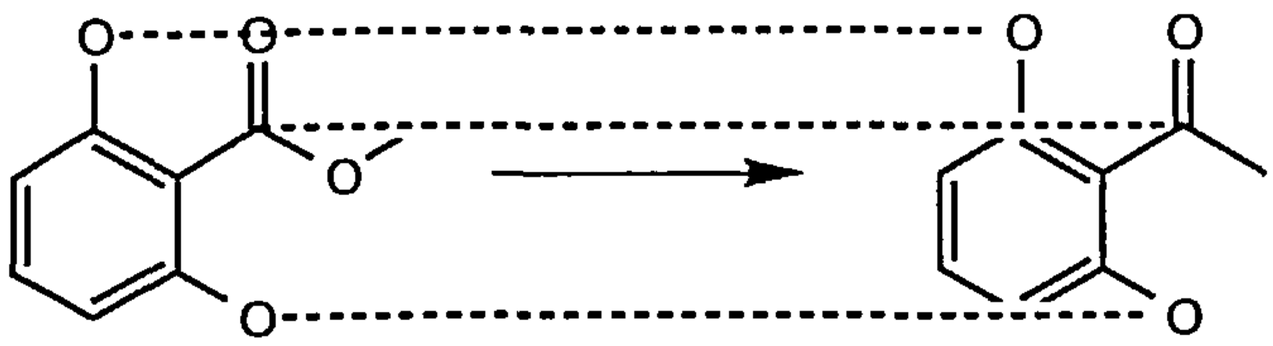


Figure 1.1.2

Each substrate was searched for nucleophiles derived from carbon, oxygen, nitrogen and sulphur. Seed references thus generated were followed up as necessary.

The review will be divided into four main sections, denoting the four main divisions of 2,6-dioxygenated substrates, *viz.* aldehydes, ketones, esters and acid chlorides and anhydrides. Each section will be further divided into differing reaction types as necessary.

1.2 Nucleophilic addition reactions at the aldehyde moiety of 2,6-dioxygenated benzaldehydes

1.2.1 Carbanion additions

Additions of carbanions to 2,6-dioxygenated benzaldehydes to give secondary alcohols have been recorded since at least 1952,[1] frequently showing good results. Both Grignard and alkali metal organometallics have been utilised. Some of the results are shown below, table 1.2.1, together with a generalised reaction scheme, figure 1.2.1.

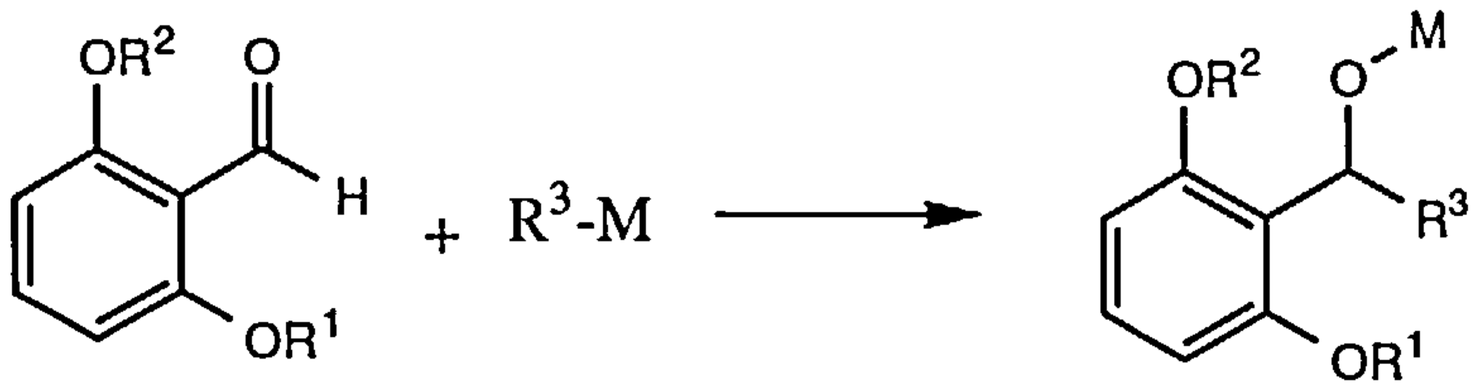
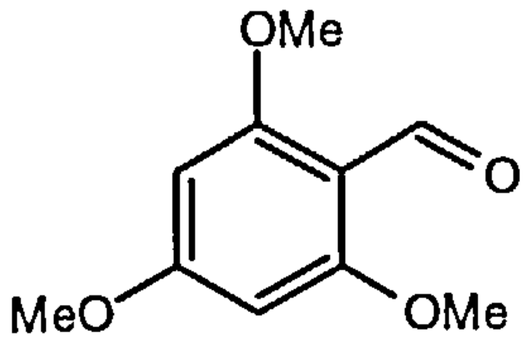


Figure 1.2.1

Substrate	R^3	M	Solvent	Yield %
1-1	Phenyl	MgBr	ether	79[2]
1-1	1-Naphthyl	MgBr	ether	90[2]
1-2	**1-4**	MgBr	THF	87[3]
1-2	**1-4**	Li	ether	89[3]
1-1	ethynyl	Na	liq. NH_3	89[4]
1-1	CH_2CN	Li	THF	87[5]
1-1	allyl	MgBr	THF	35[5]
1-3	n-$C_{14}H_{29}$	MgBr	ether/C_6H_6	62[6]
1-3	**1-5**	Na	THF	66[7]
1-1	mesityl	MgBr	ether	55[8]
1-6	methyl	MgI	ether	33[9] (di-adduct)
1-1	ethyl	MgBr	THF	60[10]
1-1	**1-7**	Li	THF/TMEDA	85[11]

Table 1.2.1



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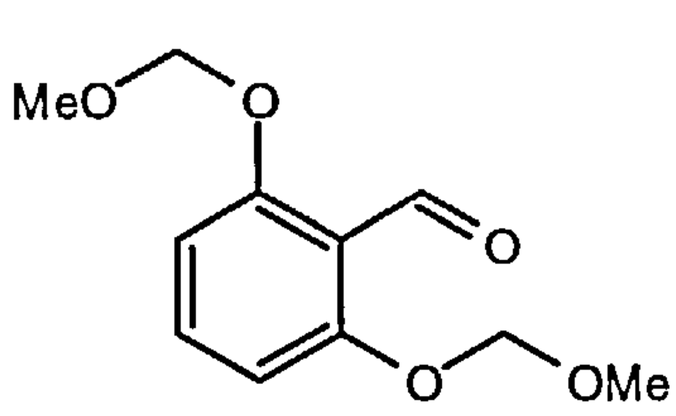

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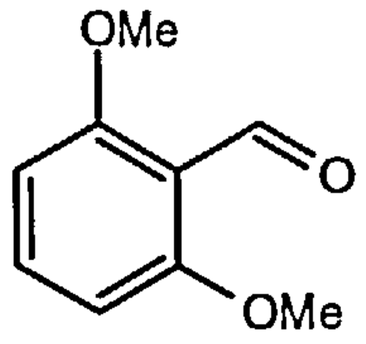

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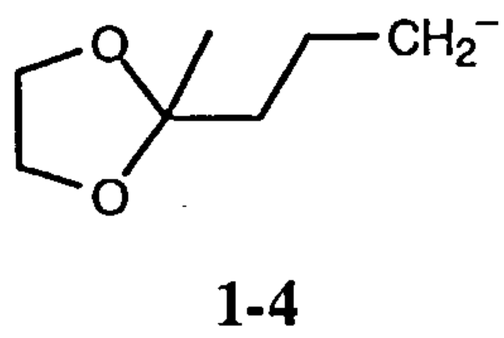

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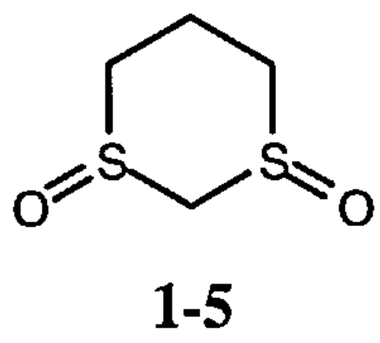

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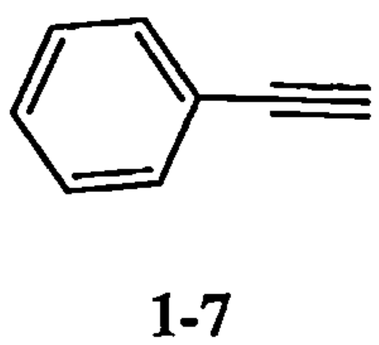

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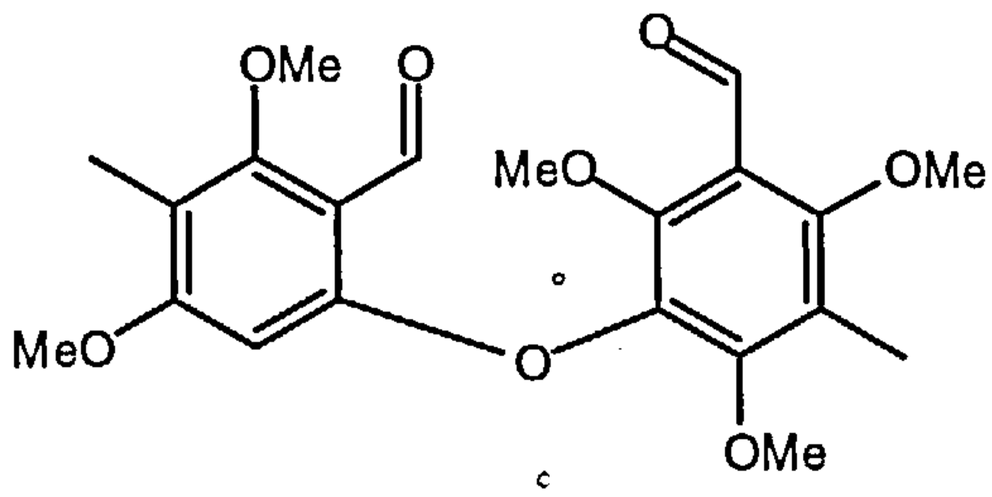


1-6

Most reactions of this form appear to function in good yield, despite the use of bulky nucleophiles. To illustrate this statement take the example of substrate **1-1**. One might expect an important factor controlling reactivity at the carbonyl group could be steric hindrance, yet the addition of a mesityl group has a yield very similar to that of an ethyl group.

Aryl groups seem to add very well regardless of size, as the first two entries show.[2] Here naphthyl is shown to add in 90% yield where phenyl adds in 79% yield, under very similar conditions.

Metal counter-ions also do not seem to be a governing factor, as lithium, magnesium and sodium are all used to good effect. It appears to be important, however to match solvent with substrate. Reaction mixtures are sometimes reported as heterogeneous[11] and chelating bases such as N,N,N',N'-tetramethylethylenediamine (TMEDA) are then added to bring the solution back to homogeneity.

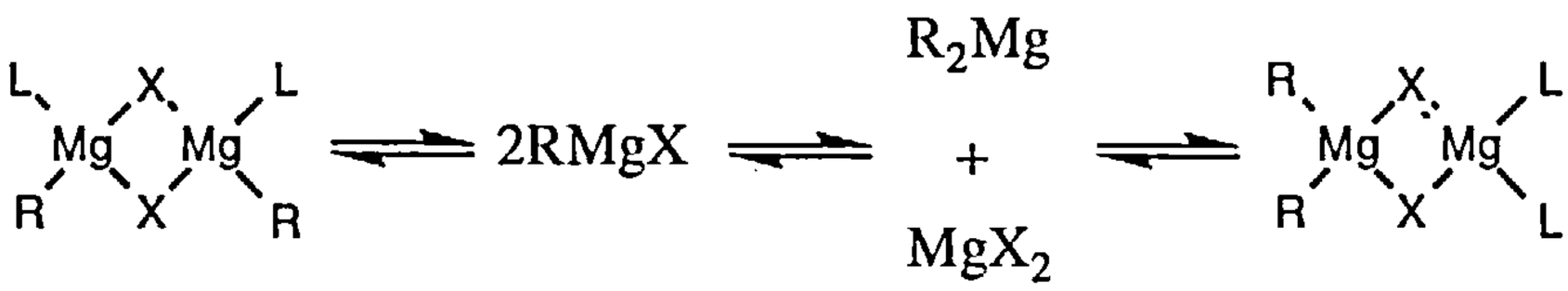
Perhaps the best way of exploring the limits of a reaction through literature studies is to focus on systems that produce non-viable results, which we will take to mean those producing yields below 40%.

All of the reactions involving lithium reagents and sodium reagents are, by this yardstick, viable. The two non-viable reactions both feature Grignard reagents, indeed the four lowest yielding reactions are all Grignard reagent based. Although it is not reasonable to base a mechanistic assumption upon yield data alone, particularly where that data is generated by several different workers, our own experience with Grignard additions to 2,6-dimethoxylated benzaldehydes may give some insight into the low yields encountered here.

Lithium reagents in solution exist in a wide variety of oligomeric lithiplexes, which can be broken up by the addition of a reagent such as TMEDA or N,N-dimethylpropyleneurea (DMPU). The allyl anion used in the addition to **1-1** is a Grignard reagent. Although Grignard reagents are often thought of as existing in the formula RMgX, this is far from the truth. The actual position is unknown but the equilibrium shown in figure 1.2.2 has been assumed to be operating.

Figure 1.2.2

This is a simplified form of the Schlenk equilibrium, shown in figure 1.2.3 below.



L=solvent molecule

Figure 1.2.3

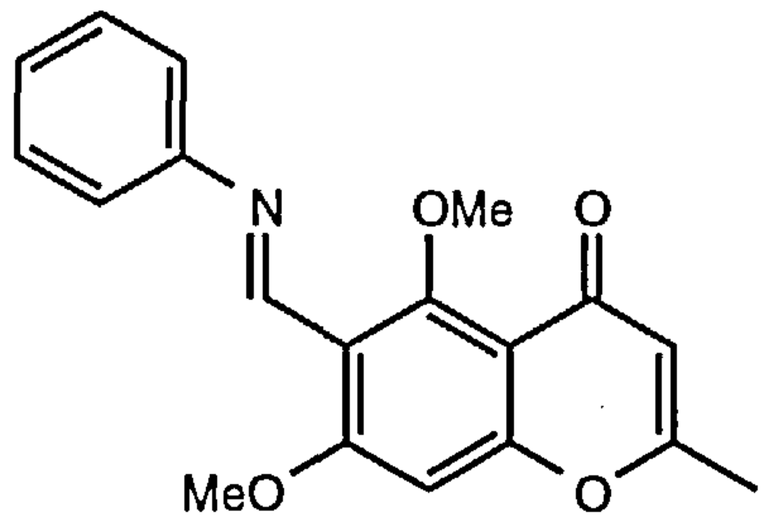
The equilibrium position varies according to substrate, with methylmagnesium bromide in ether giving spectra concordant with the right hand side of the equilibrium, and phenylmagnesium bromide giving X-ray structures concordant with the left hand side.[12] This is important because magnesium salts, particularly in etheric solution, are potent demethylating agents for aryl methyl ethers. The substrates are also known to undergo deformylation reactions (see later chapters), which are often catalysed by Lewis acids. Any demethylation or deformylation that takes place will lead to a diminution of yield. Indeed the tendency of alkyl Grignard reagents to form magnesium halide salts and dialkyl magnesium compounds in etheric solution together with the reverse tendency in aryl compounds could explain the discrepancy between the reactions of **1-1** with allyl, phenyl and naphthyl groups. This could be proved or disproved by running the reaction then accounting for 100% of the starting material in the work up. Identification of all products would point out any side reactions occurring. In our hands ethylmagnesium bromide in etheric solution proved capable of total demethylation of a tetramethoxybenzaldehyde. Etheric solvents, particularly dioxane, are known to encourage magnesium halide formation.[13]

In general then lithium reagents appear preferable to Grignard reagents with alkyl R_3 or in etheric solvents, though most addition reactions with either system are viable.

1.2.2 Other Nucleophiles

Most of the other reactions done at 2,6-dioxygenated benzaldehydes have utilised nitrogen nucleophiles. Sadly many if not all of these reactions were done as derivatisation structure proofs, so no yield is normally given. The fact that they are reported in number, however, is a good indication that they work satisfactorily. Examples of the major types, imine formation, hydrazone formation and semicarbazide formation are given below. Clearly each of these reactions must proceed through an original effective nucleophilic attack by nitrogen at the aldehyde moiety.

Imine:[14]



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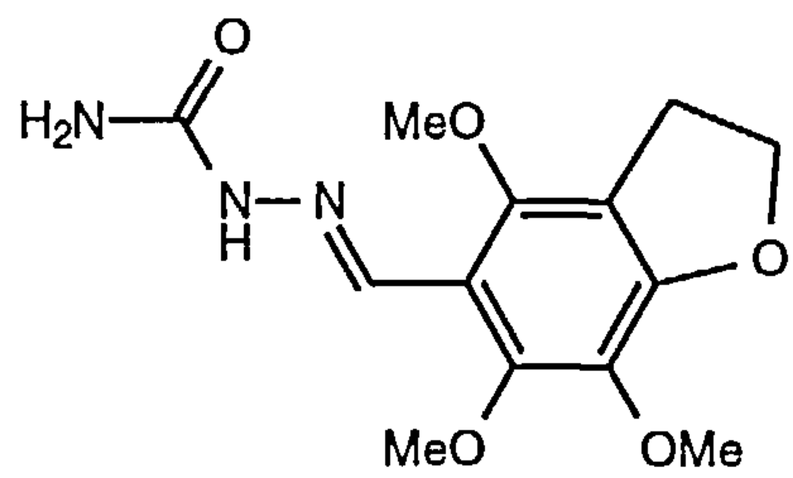
Semicarbazide:[15]



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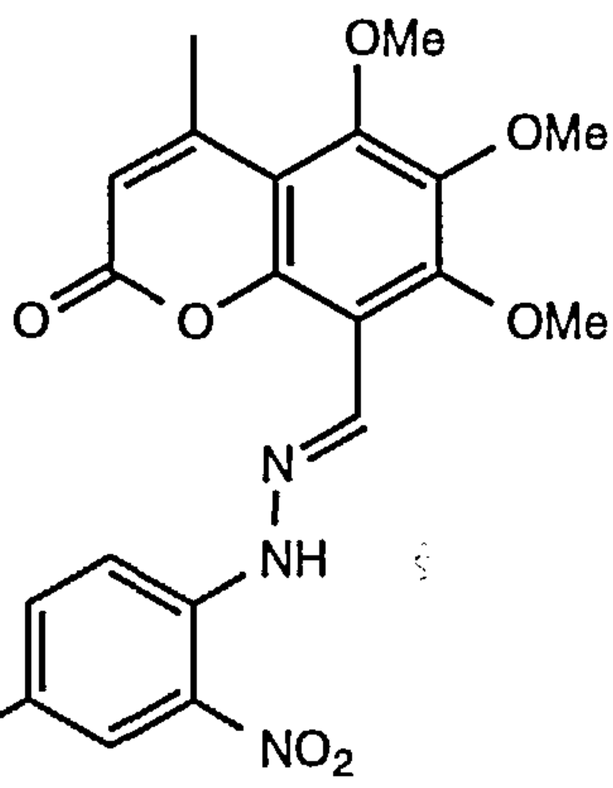
Hydrazone:[16]



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There are, however, a few other examples of nucleophile reactions that are of some interest. The first involves a sulphur ylide type of reaction using trimethylsulphonium chloride and sodium hydoxide. The general scheme of this reaction may be seen below, figure 1.2.4.

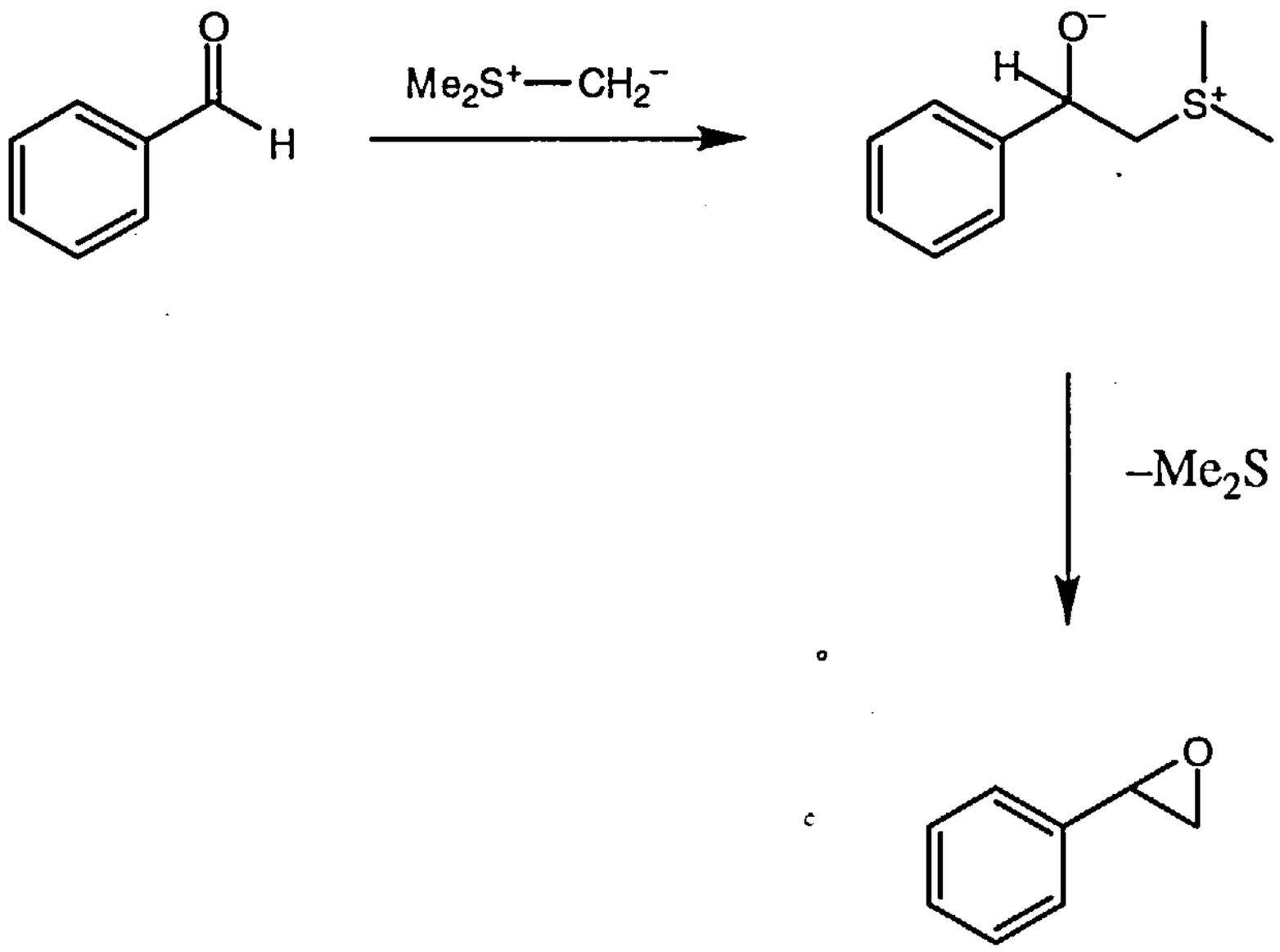
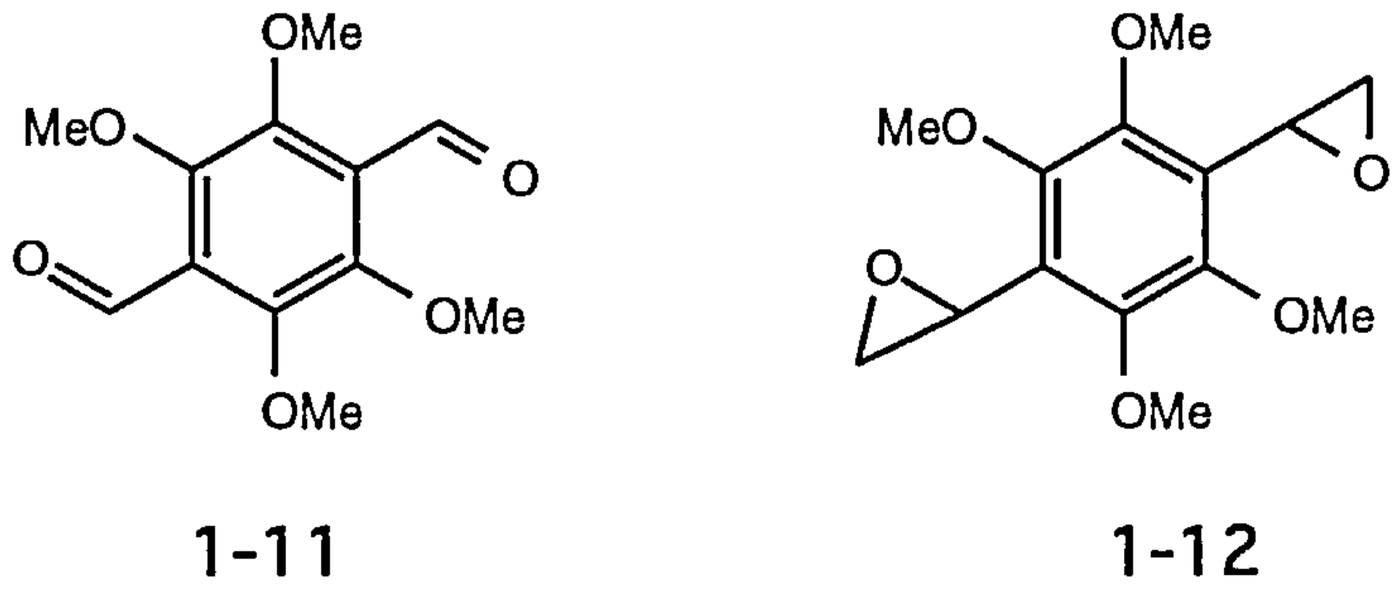


Figure 1.2.4

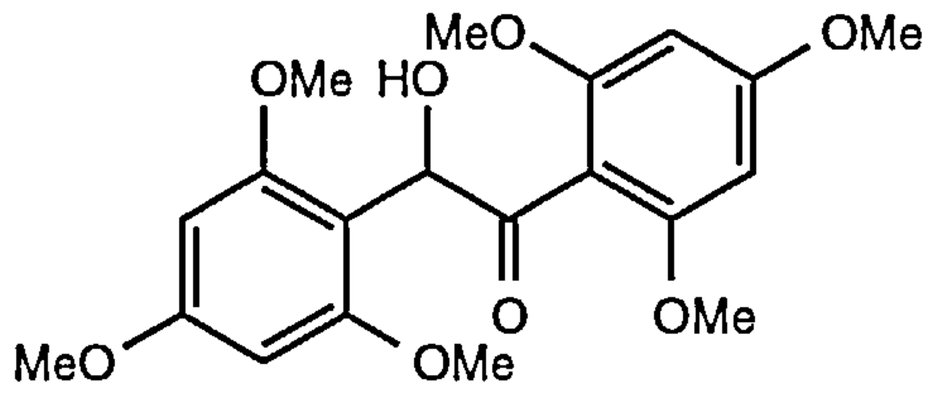
As can be seen the first step consists of a nucleophilic attack on the aldehyde. The particular aldehyde used in this case was **1-11** and the product was **1-12**, which was produced in 24% yield.[17]



1-11 1-12

Another, slightly more puzzling example is a benzoin reaction noted by Ramage *et al.*[18] The normal benzoin reaction is a coupling between two aromatic aldehyde molecules which is catalysed by cyanide ions. The first step in this process is the attack on one of the molecules by the cyanide, leading to a cyanohydrin. In the

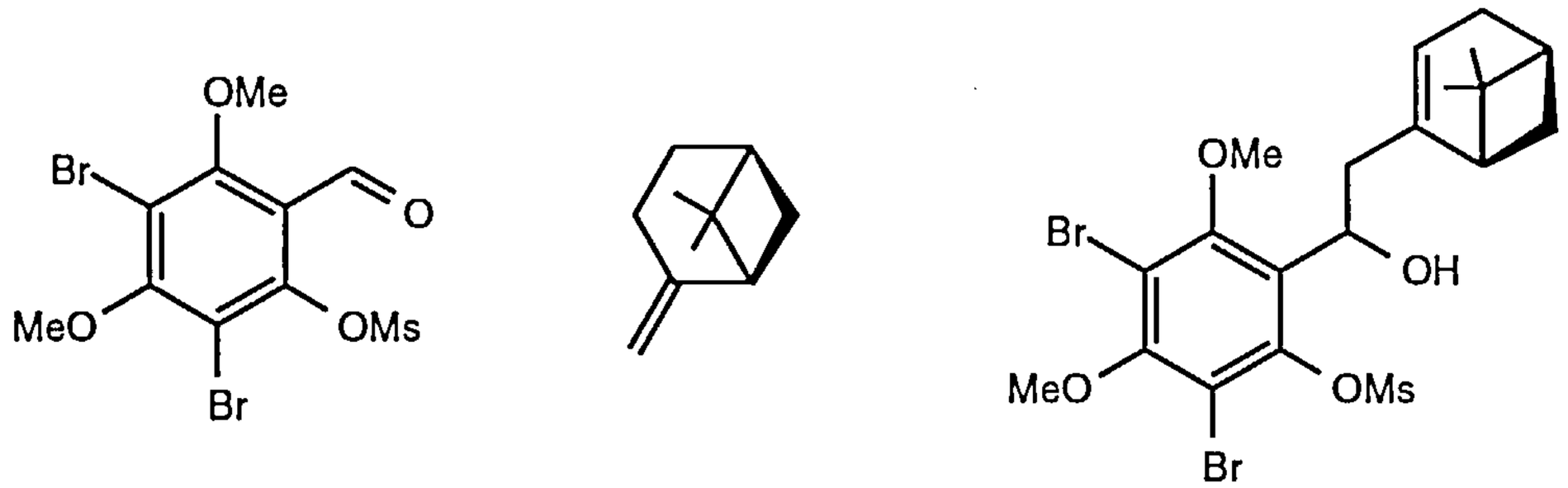
Ramage example the benzoin, **1-13**, was formed from **1-1** under the conditions which are used for a Meerwein-Ponndorf reaction (aluminium isopropoxide, isopropanol).



1-13

It is difficult to propose a mechanism for this transformation. Perhaps the sterically crowded nature of the aldehyde did not permit the normal reaction pathway to proceed, and instead the benzoin process took place using isopropoxide ions as the initial nucleophile. The steric requirements of this process would be high. The observed result awaits a more detailed mechanistic study.

The final example we shall consider is a Prins reaction. This reaction consists of the Lewis acid-catalysed addition of an olefin to an aldehyde. In the example given Majewski *et al.*[19] reacted **1-14** with 1-(S)-(-)-β-pinene, **1-15**, to gain **1-16** in 50% yield with an e.e. of 50%.



1-14 **1-15** **1-16**

The above examples show that within certain apparent practical limitations the nucleophilic addition of a variety of nucleophiles to 2,6-dimethoxylated benzaldehydes is a viable synthetic step.

1.3 Nucleophilic addition reactions at the ketone moiety of 2,6-dioxygenated aryl ketones

1.3.1 Carbanion reactions with non-cyclic 2,6-dioxygenated aryl ketones

Carbanion reactions at 2,6-dioxygenated arylketone moieties have been used to construct a wide variety of synthetic targets. The general form of the reaction is that shown below in figure 1.3.1.

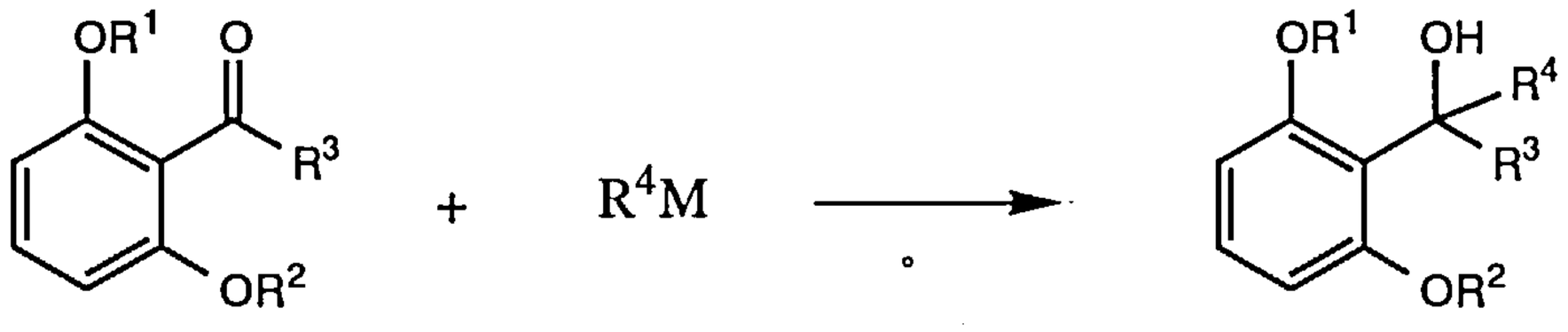
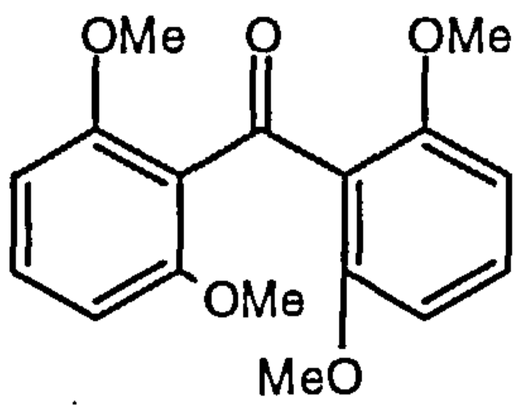


Figure 1.3.1

Substrate	R^4	M	Solvent	Yield %
1-17	**1-19**	Li	C_6H_6	80[20]
1-17	**1-20**	Li	ether	78[20]
1-21	CH_2CN	Li		95[21]
1-23	vinyl	MgBr	THF	100[22]
1-23	Me	MgI	ether/THF	93[23]
1-24	**1-25**	$CeCl_2$	THF	93[24]
1-26	Et	MgBr	THF	36[25]
1-17	**1-18**	Li	C_6H_6	65[26]
1-27	**1-28**	Li	THF	100[27]
1-29	**1-31**	Na/Li	THF	40[27]
1-29	**1-32**	Li	THF	100[27] (?)
1-33	Ph	MgBr	ether	75[28]

Table 1.3.1



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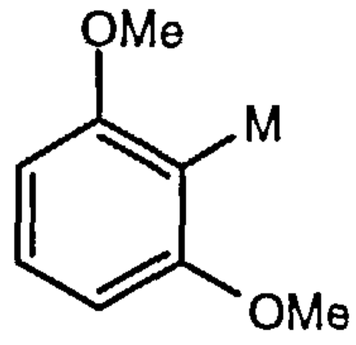

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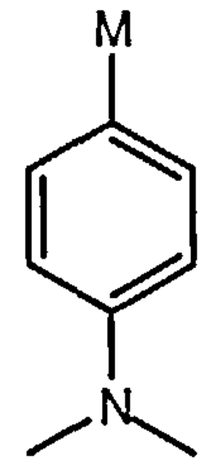

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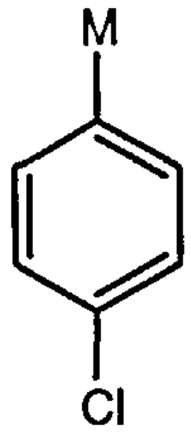

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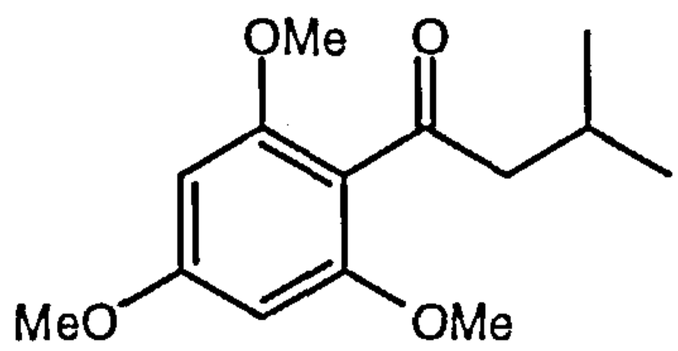

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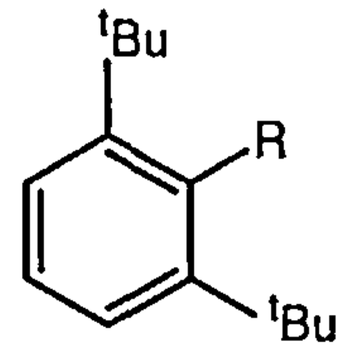

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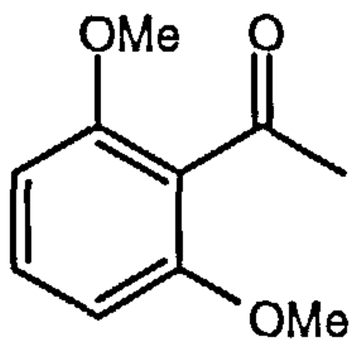

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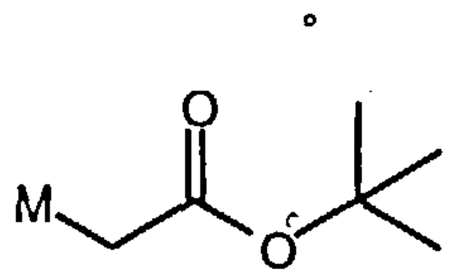

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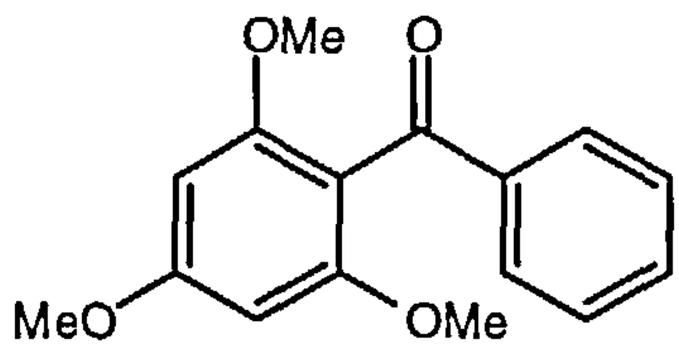

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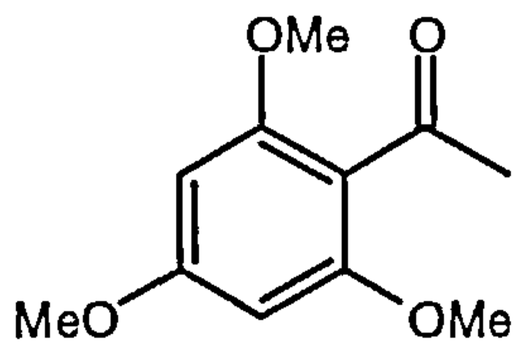

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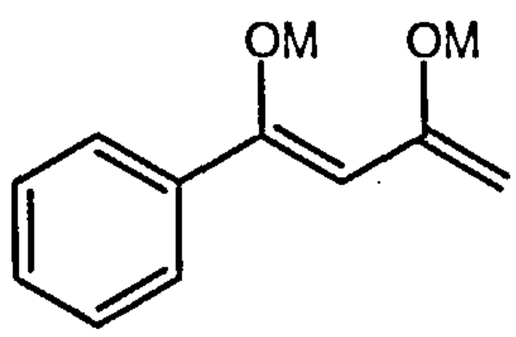
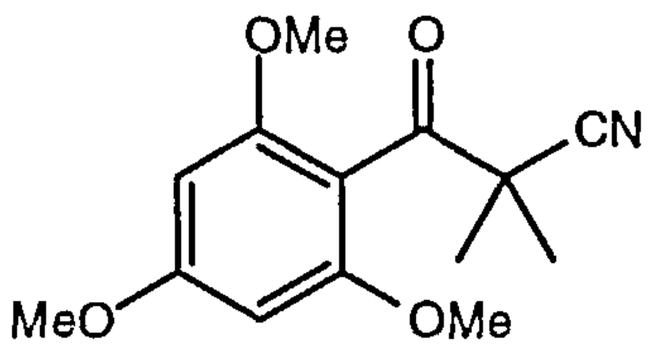


1-28



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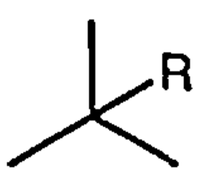

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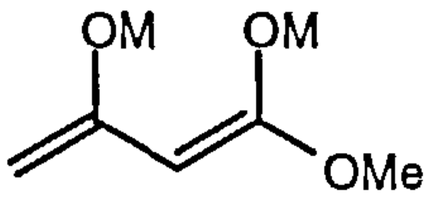
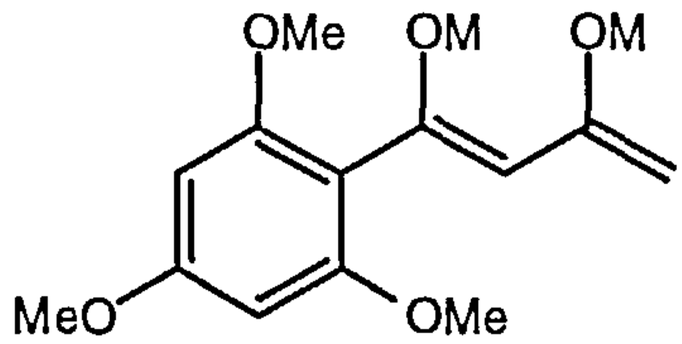


1-31



1-32

As table 1.3.1 shows, the addition of carbanions to 2,6-dioxygenated aryl ketones has been attempted on many occasions with good results. It can be seen that yields are normally high with these reactions, and that a wide range of metals can be used. The

results permit a few deductions as to the constraints that may be placed upon the reaction.

Size of attacking group (R^4)

The various reactions undertaken with substrate **1-17** permit some deductions to be made. When **1-17** was reacted with **1-19** and **1-20** the yields were very similar, 80% and 78% respectively. When **1-17** was reacted with **1-18** the yield was 65%, the reaction was still viable. Whilst **1-19** and **1-20** are very similar in size, **1-18**, being 2,6-dimethoxylated is far bulkier. This gives an indication that bulky attacking groups are only slightly, if at all disfavoured for this reaction.

Size of ketonic side chain (R^3)

Several of the substrates above have similar ring substituents yet differ in respect to R^3. Although the attacking groups vary they give some indication as to the importance of size of R^3 in determining yield in these reactions. These substrates, in apparent order of increasing size of R^3 are: **1-27, 1-21, 1-33, 1-26.** Although the attacking groups vary considerably in size, the yields (in the same order 100%, 95%, 75%, 36%) do seem to decrease with increasing hindrance. This is, of course, a rather simplistic analysis given the variance in other effects, such as electron demand of side chain, different workers producing the results *etc.* Another analysis of the data would state that yields decrease in proportion with the increasing π character of the bonds in R^3. At a first approximation, however, the steric argument is fairly sound. It would be desirable to run a series of competition reactions: make up a solution of two substrates, one substrate where R^3 = methyl, the other where R^3 = **1-22** or **1-30** with one mole of each present in solution. If one mole of Grignard reagent is then added to this solution the proportion of any products formed should give a good indication of the effect of the increasing size of R^3 on the reaction.

Schlenk equilibrium effects

The two reactions undertaken on **1-23** permit some insight into whether the variance of the yield of the addition reactions with variance of side-chain in a Grignard reagent is valid for the aryl ketone reactions. Data are limited, but it appears that both vinyl and methyl Grignards add in good yield (100% and 93% respectively). This suggests that the same strictures do not apply to ketones.

Importance of metal counterion

There are no clear trends to suggest that one counterion is more succesful than another in achieving the addition reaction. The lowest yield was again observed using a Grignard reagent, but the situation is complicated by the possibility of steric interference from R^3. Most reactions produce good yields with most counterions.

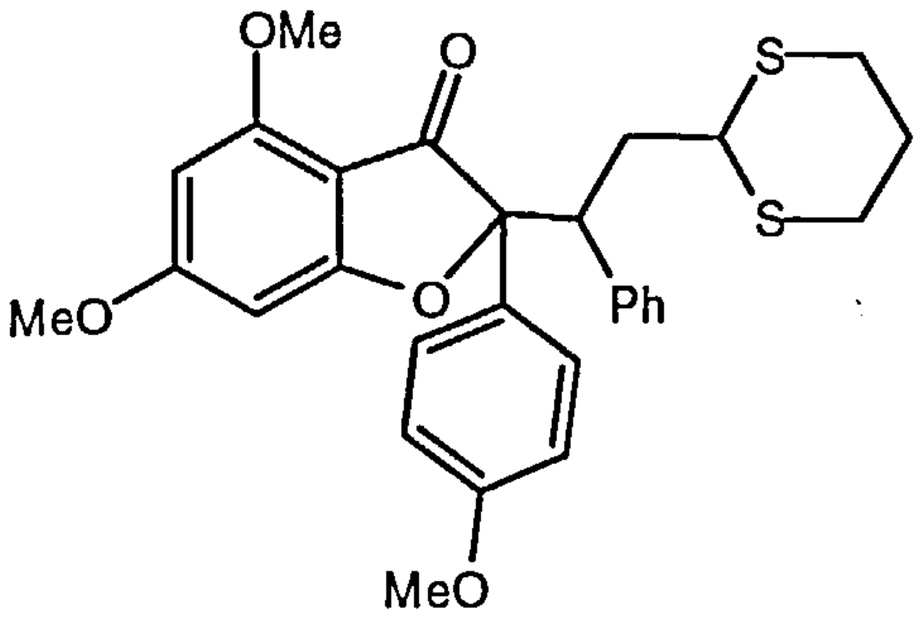
The above illustrates some of the observed trends in the nucleophile reactions of non-cyclic 2,6-dioxygenated aryl ketones.

1.3.2 Nucleophilic addition reactions of cyclic 2,6-dioxygenated aryl ketones

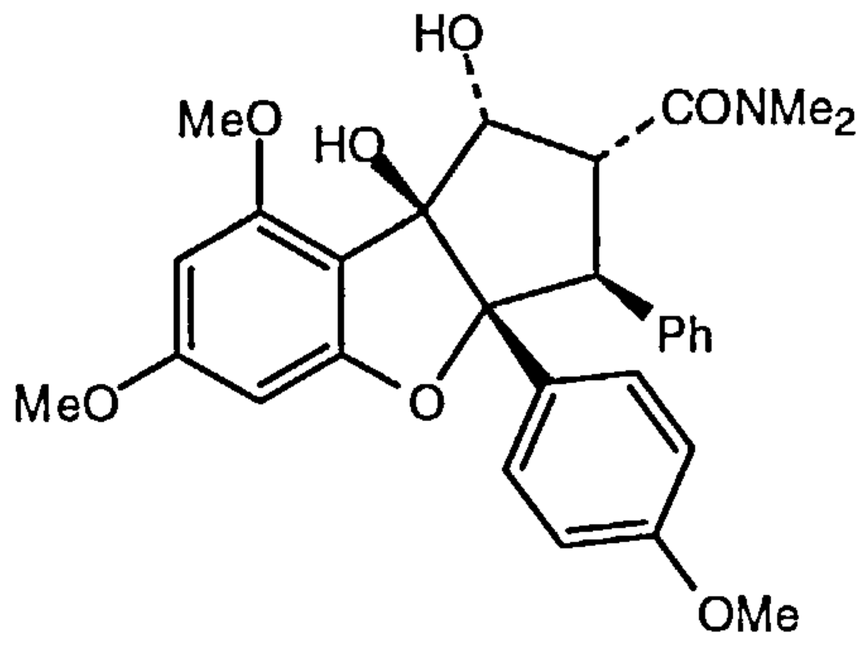
Many 2,6-dioxygenated aryl ketones exist in cyclic form as chroman-4-ones, benzofuran-3-ones and the like. Some chemistry has been done on the addition of carbanions to the carbonyl moiety of such systems.

Benzofuran-3-one additions

The substrate **1-34** has been the subject of a study by the Taylor group[29] in the course of their synthesis of rocaglamide, **1-35**.

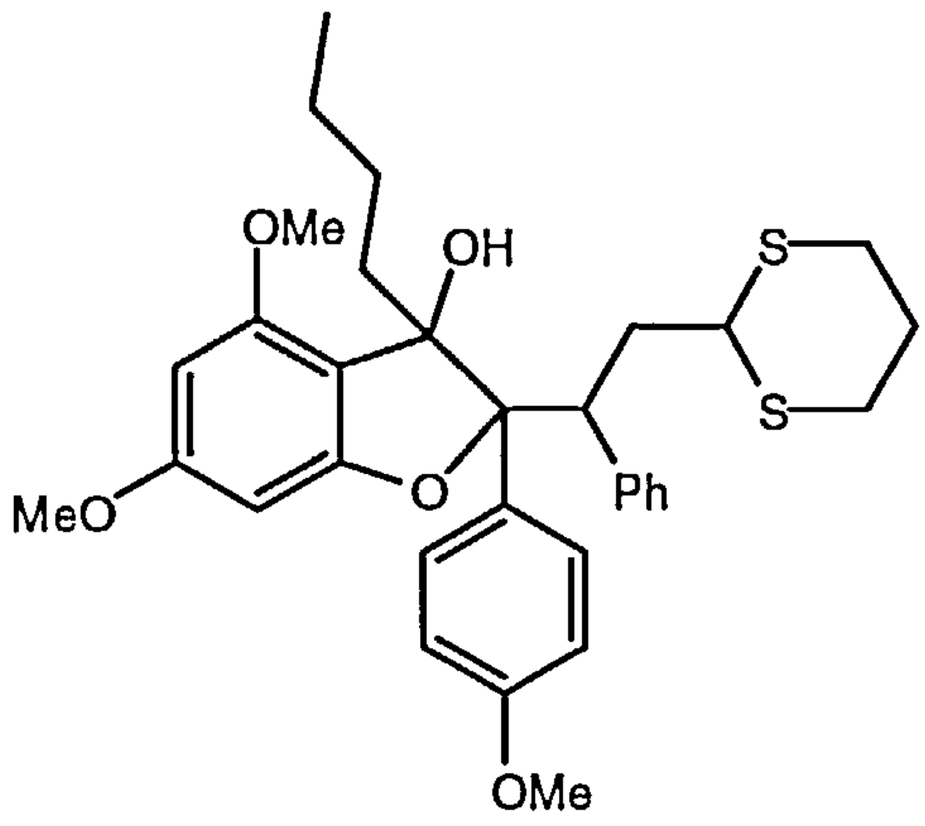


1-34

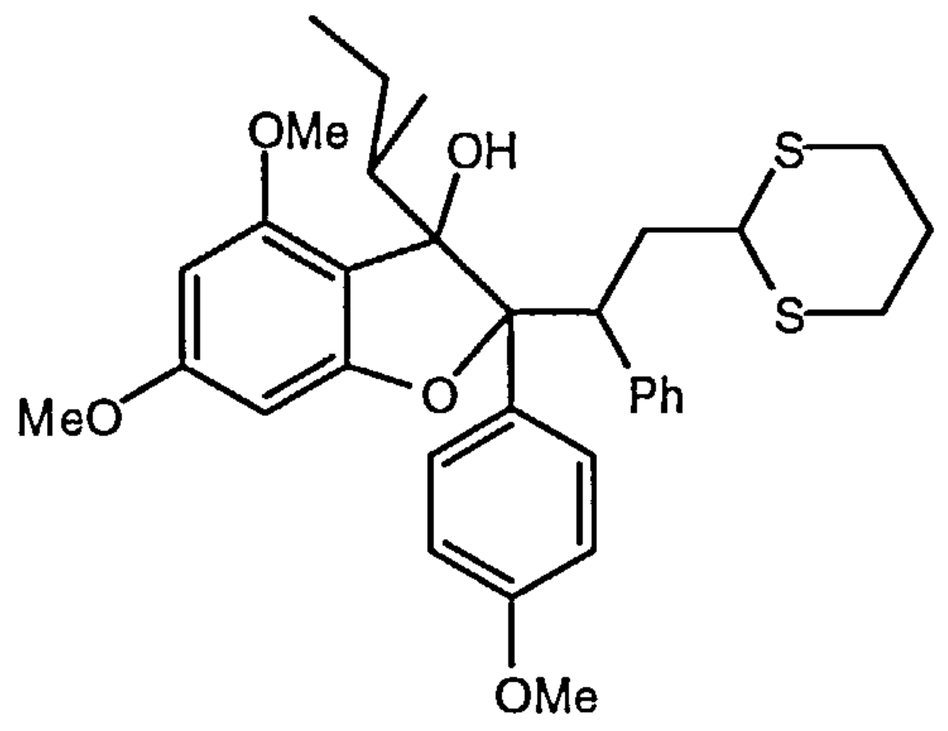


1-35

When **1-34** was treated with n-BuLi and potassium t-butoxide, so-called "complex base," it produced **1-36** in 34% yield. Without the butoxide only starting material was isolated. Similarly the reaction of **1-34** with sec-BuLi gave **1-37** in 42% yield.

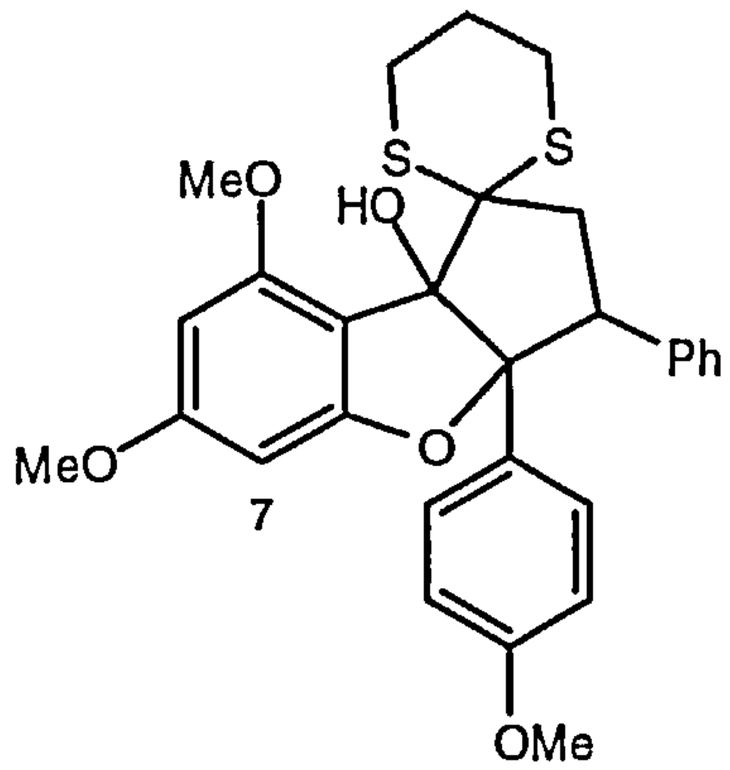


1-36



1-37

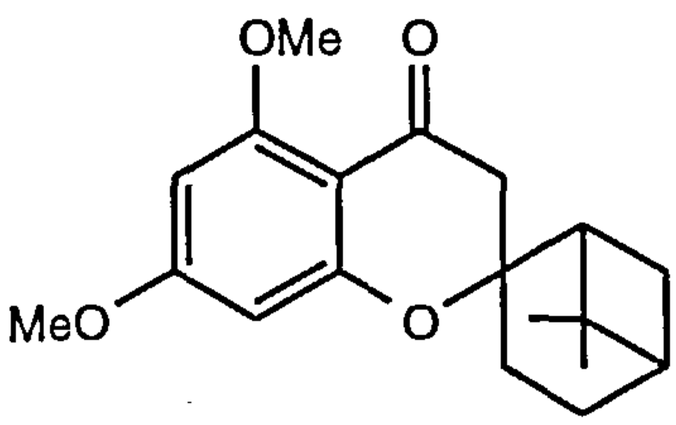
When the reactions were repeated with HMPA in the mixture and a slight excess of n- and t-butyllithium the only product was **1-38**, in 85% and 91% yields respectively. This difference in reactivity is difficult to explain. This suggests that the anion derived from deprotonating between the sulphurs of the dithioacetal forms unreactive aggregates which are broken up by the action of HMPA. Deuteration studies suggest that the initial deprotonation is at the benzofuranone C7.



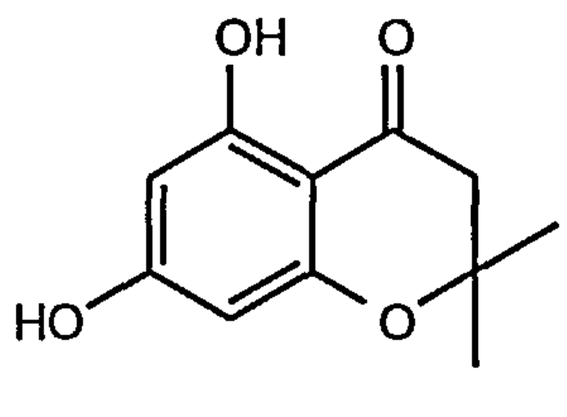
7

Chroman-4-one additions

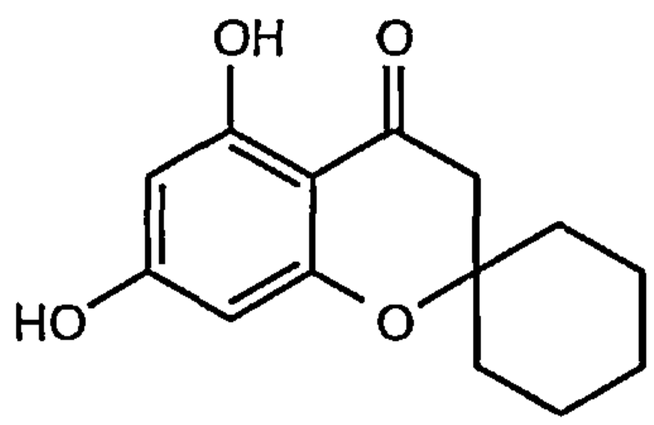
The reaction of **1-39** with isobutylmagnesium bromide in diethyl ether has been shown to proceed at more than 78% by the Majewski group.[30]



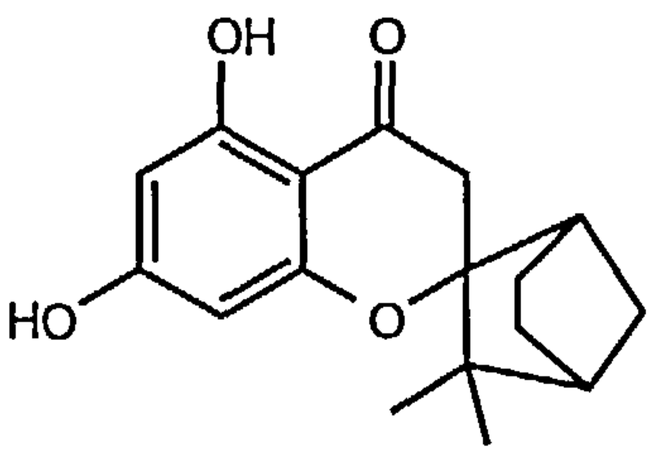
1-39



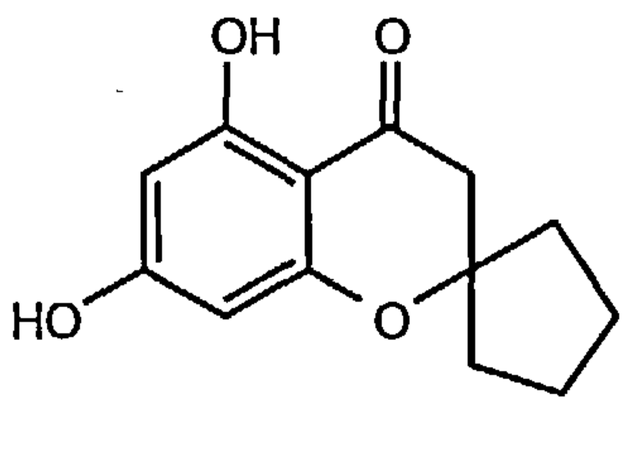
1-40



1-41



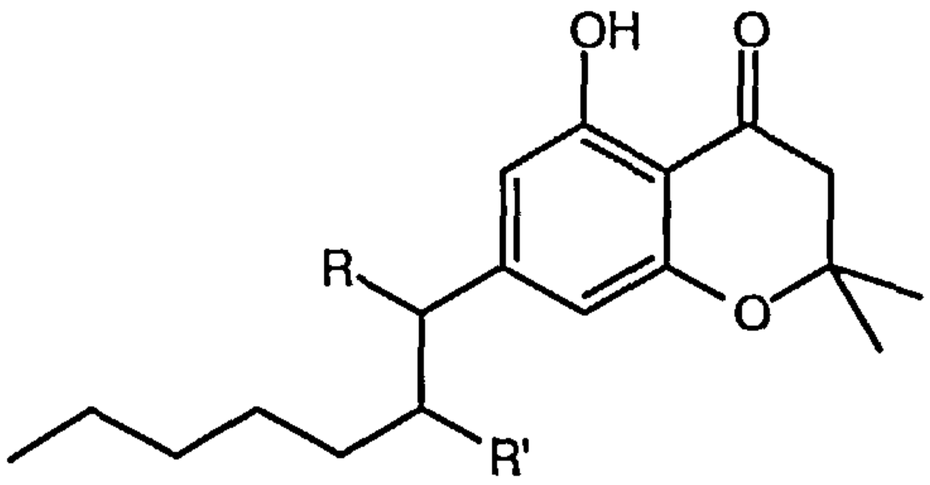
1-42



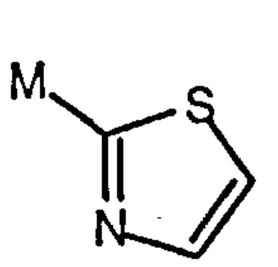
1-43

Aukrust and coworkers reacted **1-40**, **1-41**, **1-42** and **1-43** with the organozinc compound obtained from 2-methylallylbromide.[31] They achieved the expected addition products in yields of over 87%, though they did not separate these products. The zincate was produced by sonication of the bromide with zinc dust.

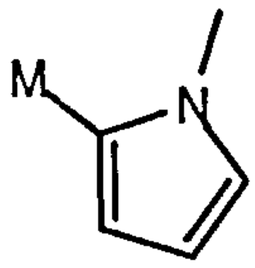
Finally Gardner *et al.* reacted **1-44**, **1-45**, and **1-46** with a wide range of metallated aromatics.[32] For a breakdown see table 1.3.2. below.



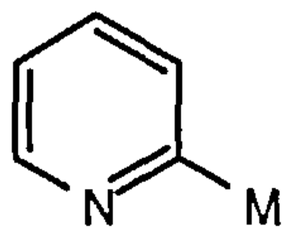
1-44 R = R' = Me
1-45 R = Me R' = H
1-46 R = R' = H



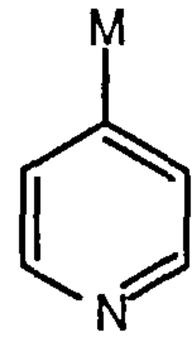
1-47



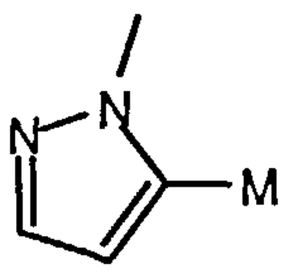
1-48



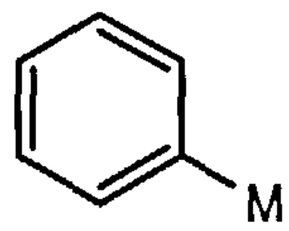
1-49



1-50



1-51



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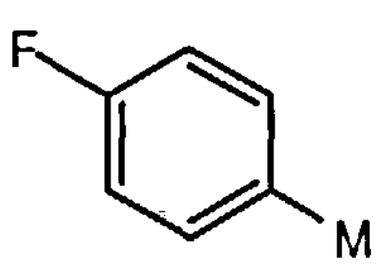
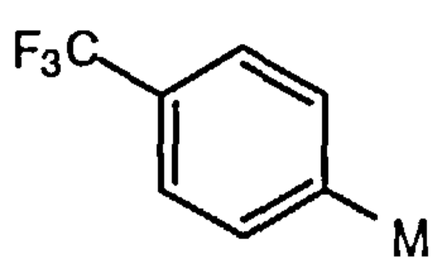


1-53



1-54

Substrate	Nucleophile	Metal	Yield (%)
1-44	**1-47**	Li	20
1-44	**1-48**	Li	50
1-45	**1-49**	Li	82
1-46	**1-49**	Li	58
1-46	**1-50**	Li	26
1-44	**1-49**	Li	40

1-44	**1-51**	Li	24
1-44	**1-52**	MgBr	52
1-44	**1-53**	MgBr	57
1-44	**1-54**	MgBr	69
1-44	**1-50**	Li	18

Table 1.3.2

These reactions proceeded in varying yields, but are difficult to analyse. Perhaps the one point of note here is that the chromone ring here has a free hydroxyl that must be deprotonated during the reaction. Though the authors have taken account of this in the amounts of metal reagent added the presence of an oxoanion near to the site of addition may be a causative factor in the low yields encountered. Our own work was expected to proceed through a nucleophilic addition to a 2-hydroxy-6-methoxybenzoate ester, therefore this points to a possible problem with the synthesis. It seems quite possible that the presence of an anion close to the reactive site could produce a diminution in yields, as electrostatic repulsion could play a role in disfavouring nucleophile approach.

The above reactions all show that the addition of nucleophiles to cyclic 2,6-dioxygenated aryl ketones is feasible, though if free hydroxyls are present more reliable results seem to be generated by zinc reagents than by other metals.

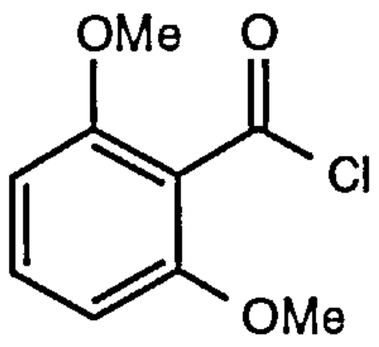
1.4 Nucleophile addition reactions at the carbonyl moiety of 2,6-dioxygenated benzoyl chlorides and benzoic anhydrides

1.4.1 Reactions with acid chlorides

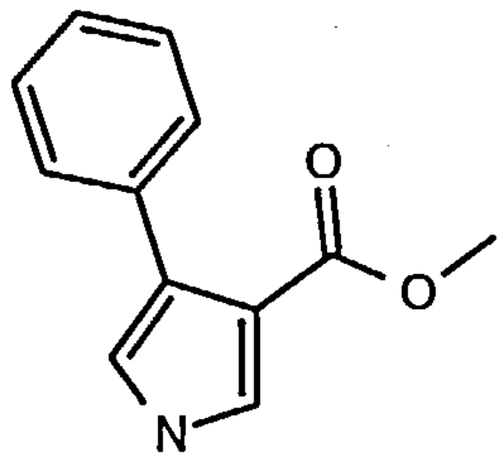
1.4.1.1 Friedel Crafts type reactions

Although the Friedel-Crafts reaction manifold is generally considered as an electrophilic attack on a benzene ring, by corollary it consists of a nucleophilic attack on the Lewis acid-activated acyl chloride by the benzene ring. Several examples of Friedel-Crafts reactions on these systems exist in the literature.

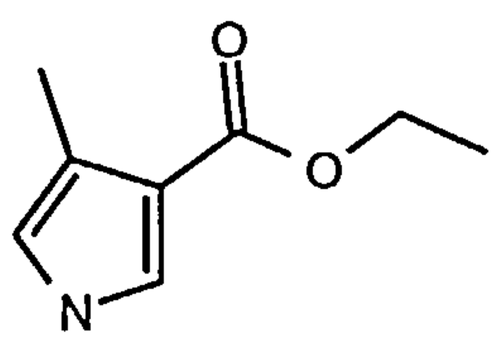
Cue and Chamberlain[33] performed tin(IV) chloride catalysed Friedel-Crafts reactions on **1-55**, using **1-56** and **1-57** as the aromatic nucleophile. These reactions proceeded in 80% and 85% respectively, giving **1-58** and **1-59**.



1-55



1-56



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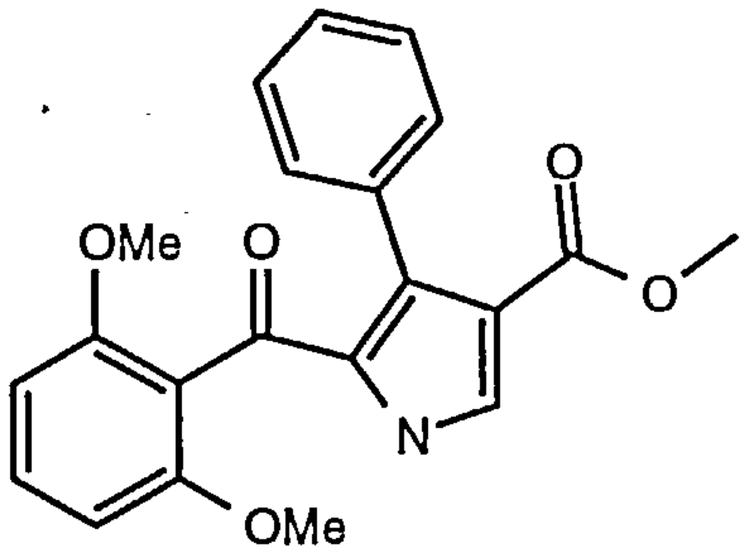
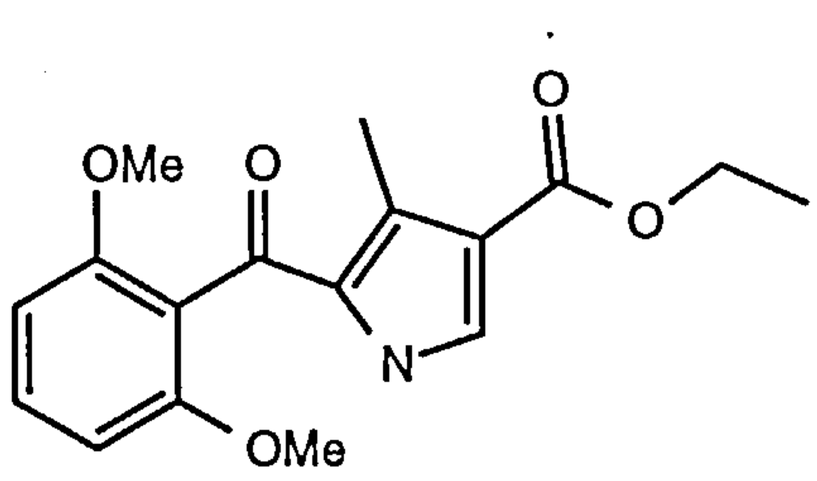
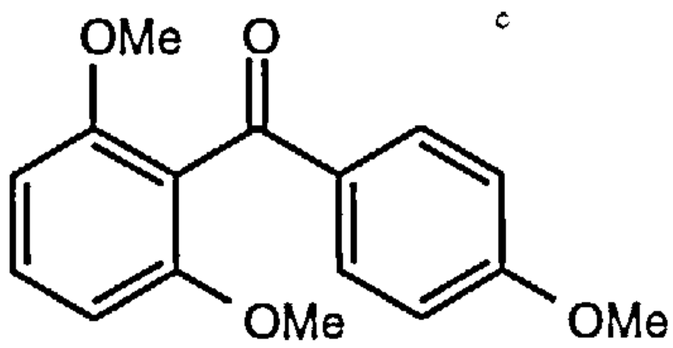


1-58



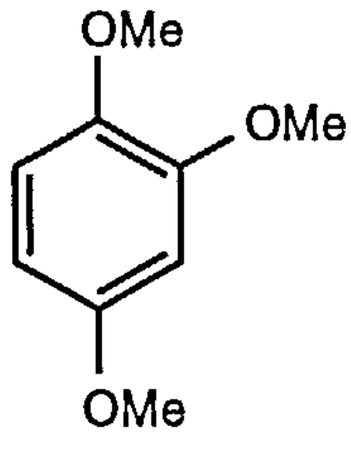
1-59



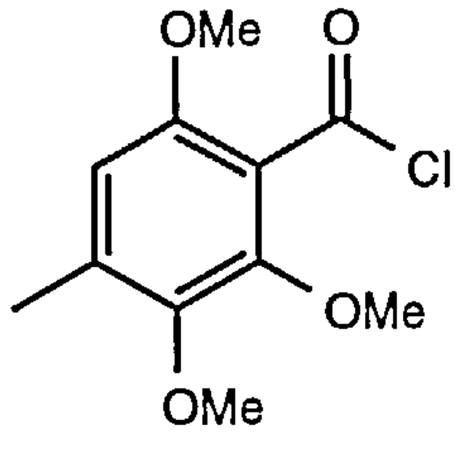
1-60

Janes *et al.*[34] reacted **1-55** with anisole to give the *para* product **1-60** in 59% yield using an aluminium trichloride catalyst in carbon disulfide.

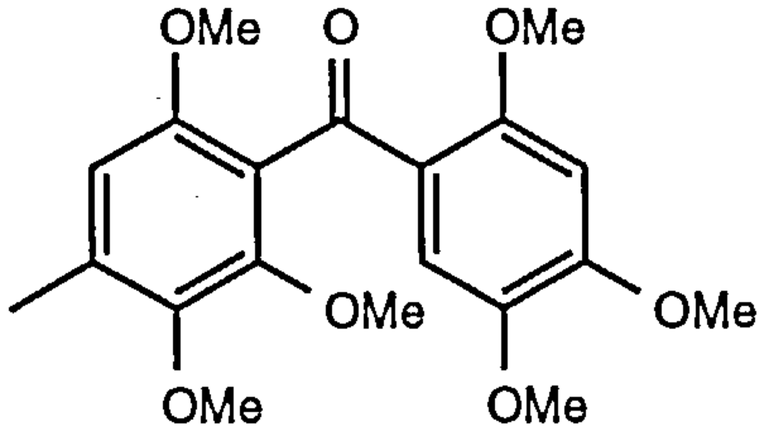
Mehta *et al.*[35] undertook the reaction of **1-61** with **1-62**, which proceeded to give a mixture of **1-63** and **1-63a** in 70% combined yield. This illustrates one of the dangers inherent in the use of Lewis acids with polymethoxylated benzene compounds, that of demethylation. In this case the demethylation led to a useful substrate, however.



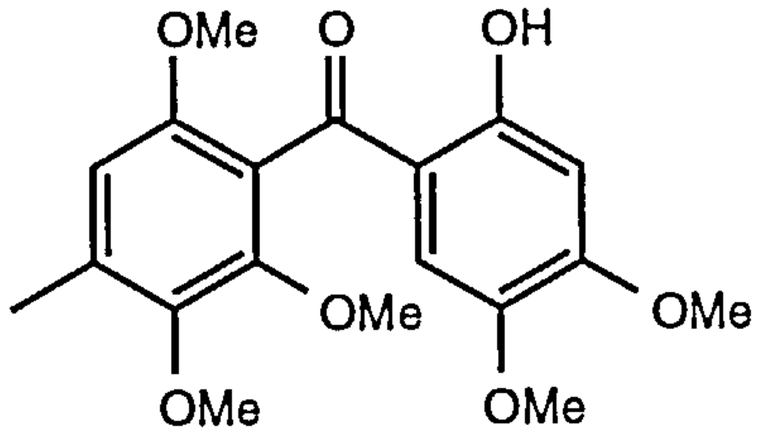
1-61



1-62

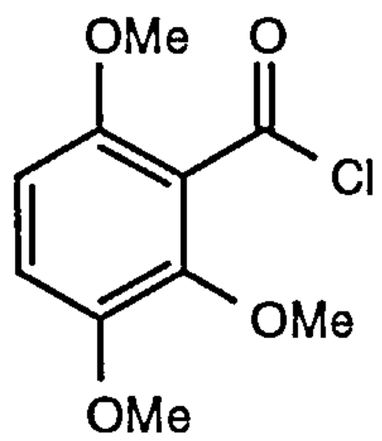


1-63

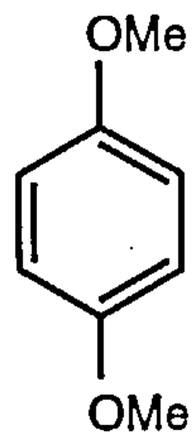


1-63a

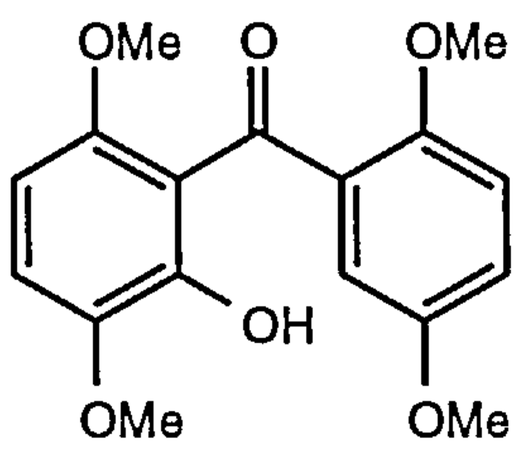
Finally Mahfouz and coworkers[36] reacted **1-64** with hydroquinone dimethyl ether **1-65** to give **1-66** in 69% yield with full *o*-demethylation.



1-64



1-65



1-66

As these examples demonstrate the Friedel-Crafts reaction is perfectly feasible with a 2,6-dioxygenated benzoyl chloride, though care must be taken over the choice of Lewis acid to avoid unwanted demethylation.

1.4.1.2 Carbanion reactions with 2,6-dioxygenated benzoyl chlorides

Several reactions of 2,6-dioxygenated benzoyl chlorides with carbanions have been reported, though yields are variable (see table 1.4.1 below). For a general reaction scheme, see figure 1.4.1 below.

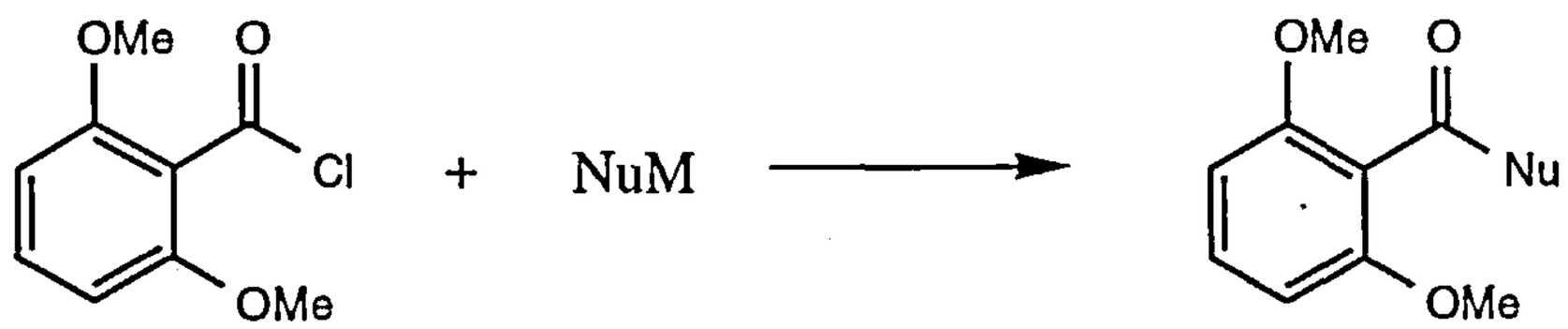
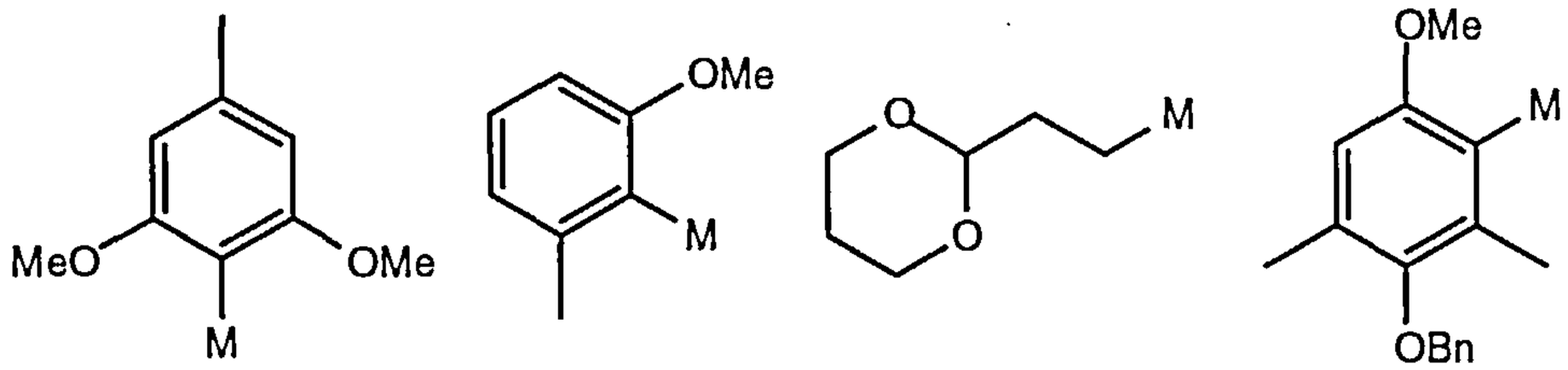


Figure 1.4.1

No.	Benzoyl chloride substituents	Nuc.	Solvent	Metal	Yield (%)
1-67	2,6-dimethoxy-3,5-dichloro	**1-68**	ether	Li	30[37]
1-69	2,3-dimethoxy-6-benzyloxy	Me	PhMe/EtOAc	ZnI	54[38]
1-70	2,6-dimethoxy-4-methyl	**1-71**	$(CH_2Br)_2$	MgBr	80[39]
1-72	2,3,5,6-tetramethoxy	Me	ether	CdCl	64[40]
1-55	2,6-dimethoxy	**1-74**	ether	Li	60[41]
1-55	2,6-dimethoxy	CN	benzene	Cu	60[42]
1-75	2,6-dimethoxy-3,5-dibromo	**1-73**	THF	MgBr	40[43]

Table 1.4.1



1-68 **1-71** **1-73** **1-74**

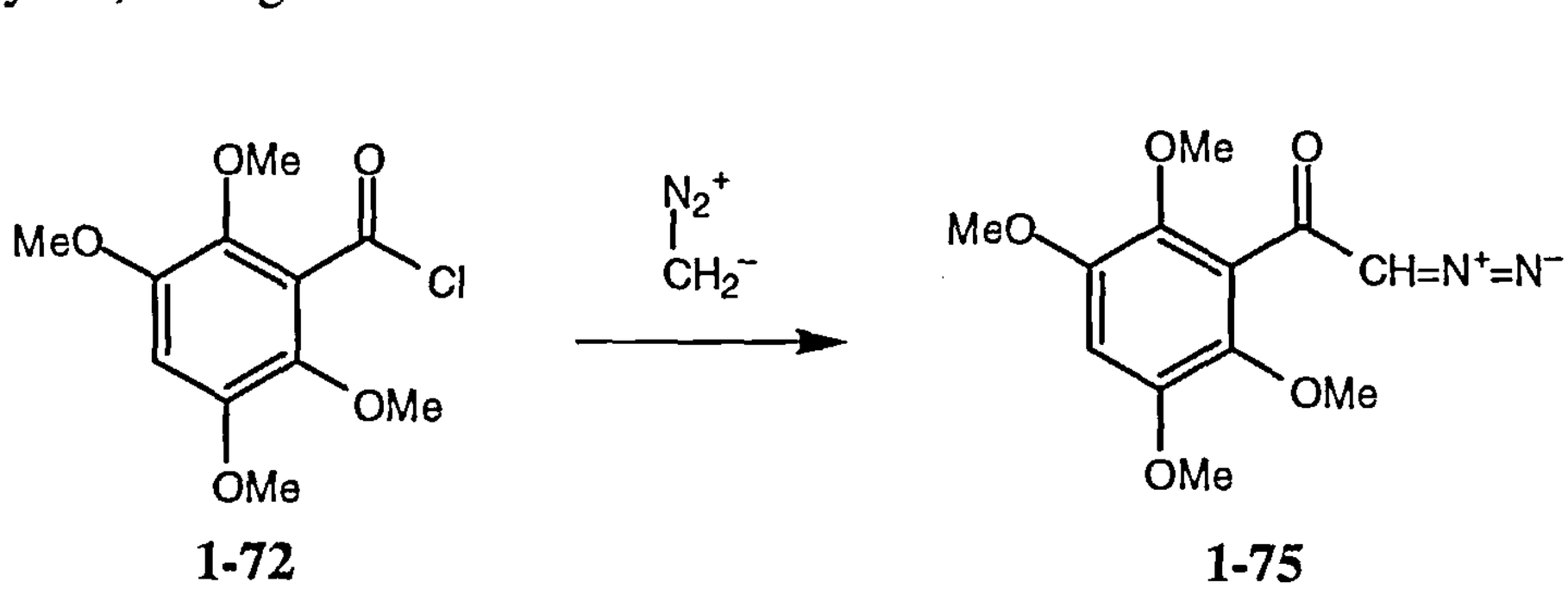
The reactions were undertaken with a variety of metal counterions and in general proceeded in reasonable yield. The lowest yield was that given by the substitution at **1-67** by **1-68**. This is perhaps to be expected as the metal reagent and the substrate are both hindered by 2,6 substituents. The metal counterions each gave reasonable

yields, the only unusual case being the cadmyl reagent. Organocadmium reagents are generally considered to give greater selectivity in substitutions where the product might lead to further reactions.[44]

All reactions gave the expected substitution. Yields seem to be independent of solvent influences.

1.4.1.3 Reactions of formally neutral nucleophiles at 2,6-dioxygenated benzoyl chlorides

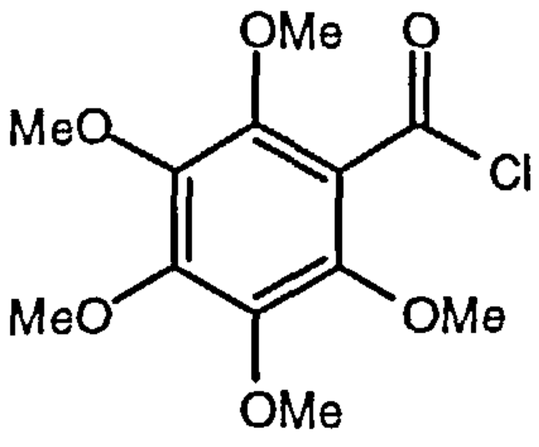
Three examples of this have been found in the literature. Two of these are preparations of diazoketones using the acyl chloride and diazomethane. The transformation of **1-72** into **1-75** was reported by the Schaefer group, without giving a yield, see figure 1.4.2.[45]



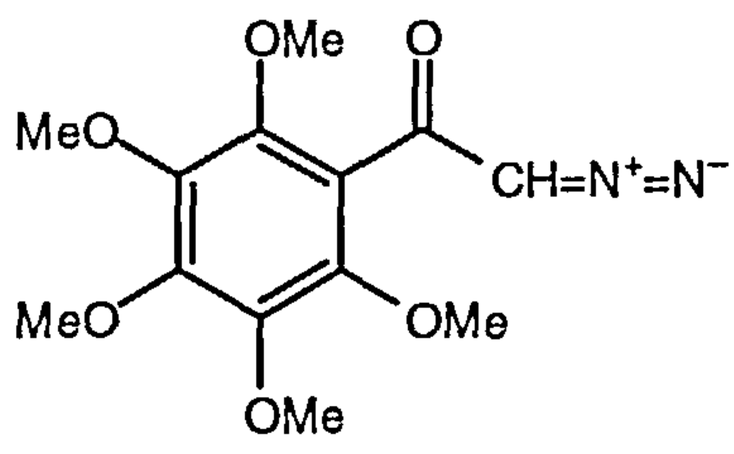
1-72 **1-75**

Figure 1.4.2

Also Dallacker and Korb[46] reported the transformation of the pentamethoxy compound **1-76** into **1-77** in 82% yield.

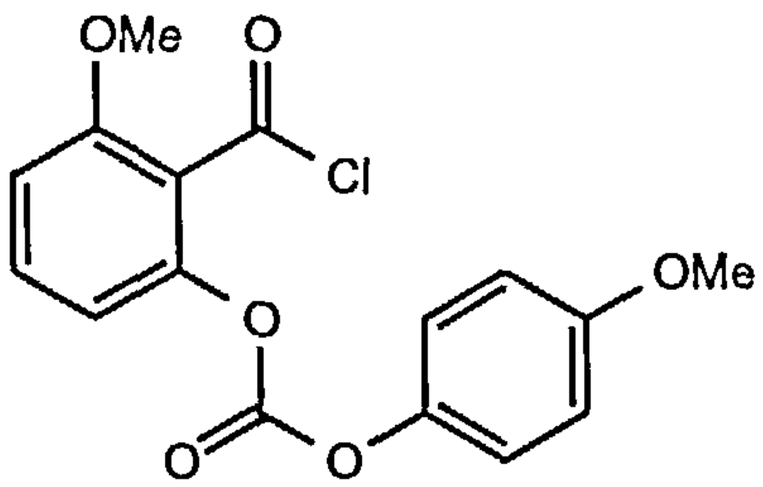


1-76

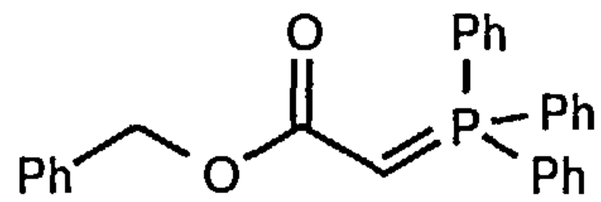


1-77

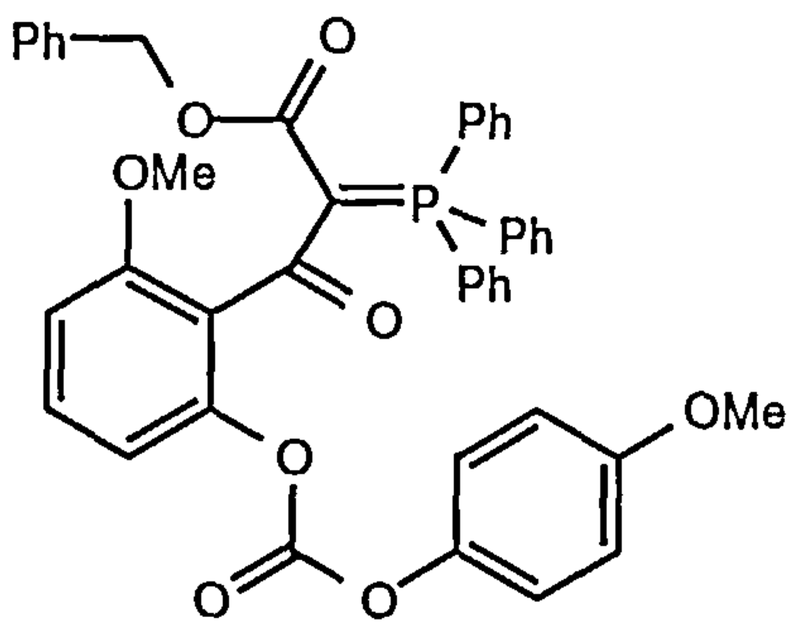
The final reaction in this section is the displacement of chlorine by a phosphorus ylide. Takeno and coworkers performed this transformation upon acyl chloride **1-78** using **1-79** as the nucleophile, to produce **1-80**.[47] No yield was given for this transformation.



1-78



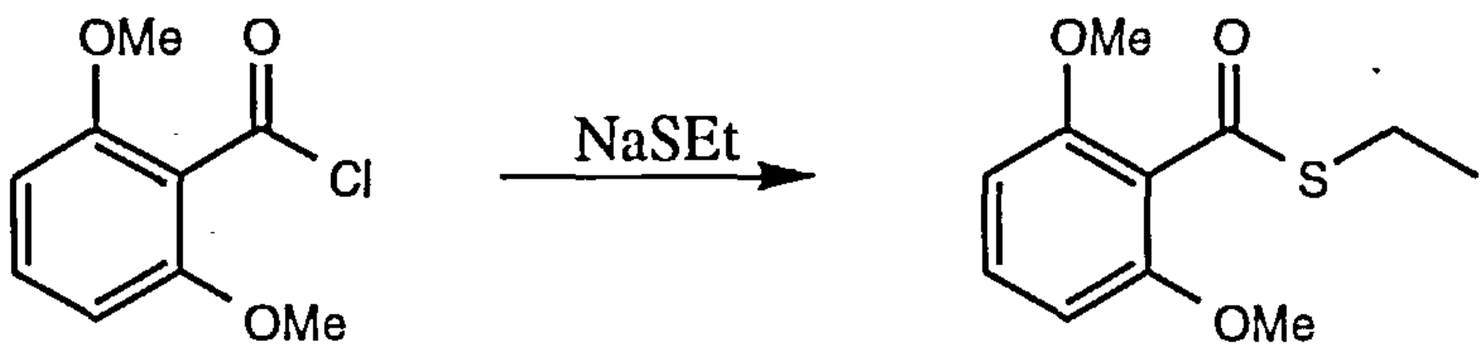
1-79



1-80

1.4.1.4 Reactions of heteroanions at 2,6-dioxygenated benzoyl chlorides

Only one reaction of this nature was uncovered in our literature search. This involved the displacement of the chloride of **1-55** with sodium thioethoxide, as shown in figure 1.4.3 below. Yields were not given for the production of the thioester **1-81**, but the synthesis of which this was a part achieved 53%.



1-55 **1-81**

Figure 1.4.3

1.4.2 Nucleophile reactions at 2,6-dioxygenated benzoic anhydrides

Our search of the literature found one paper dedicated to this subject in which a variety of chlorinated methoxybenzoic acetic anhydrides were treated with ammonia to form the corresponding amides. This paper formed part of the Maillard group's work on phloroglucinol derivatives.[48] The general form of the reaction can be seen below, figure 1.4.4.

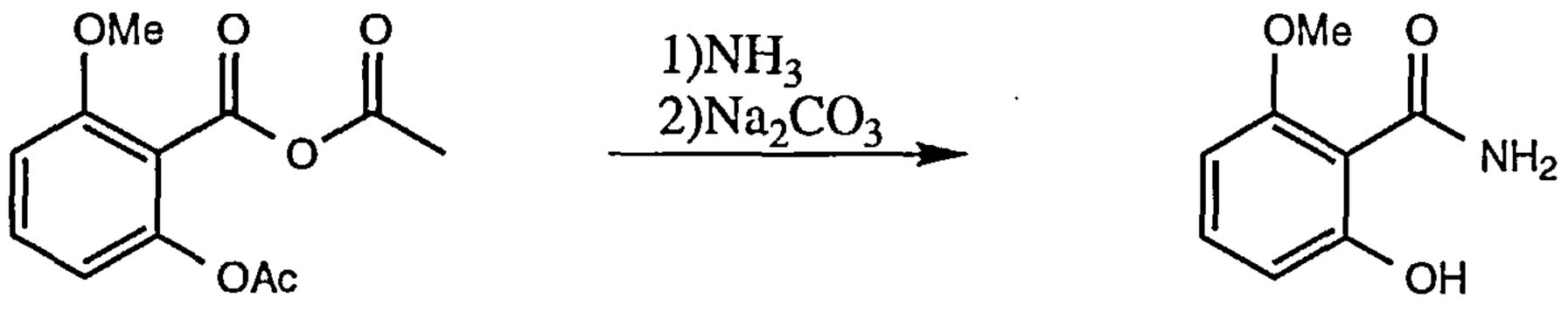
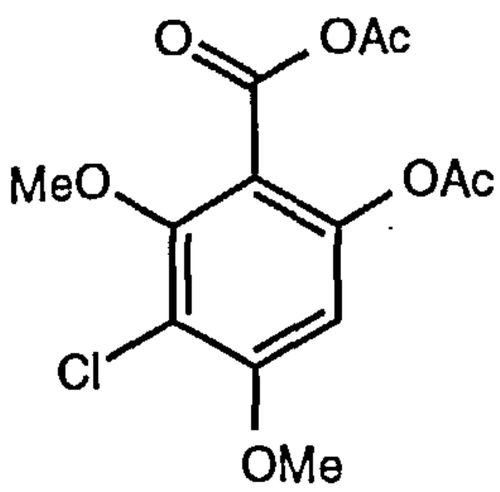
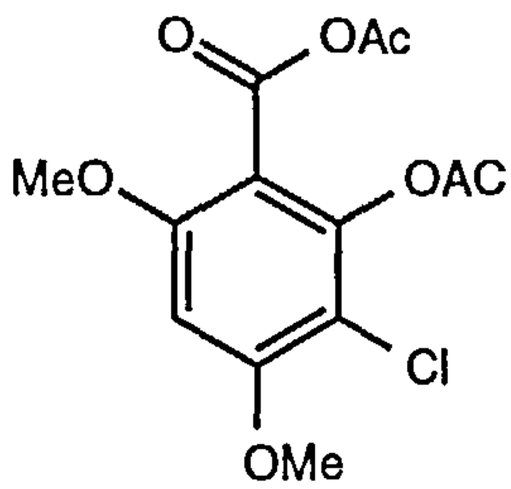


Figure 1.4.4

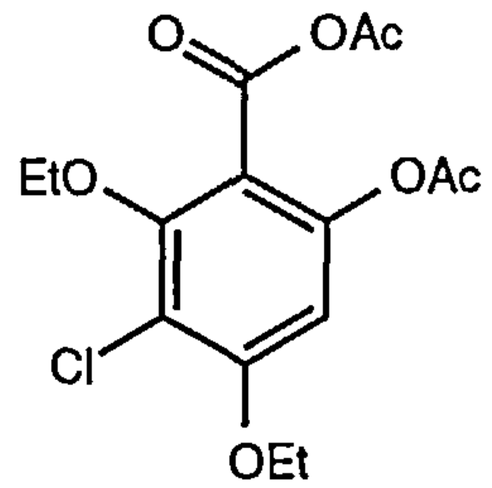
Results were varied, but on the whole succesful. For a breakdown of reactions see table 1.4.2 below.



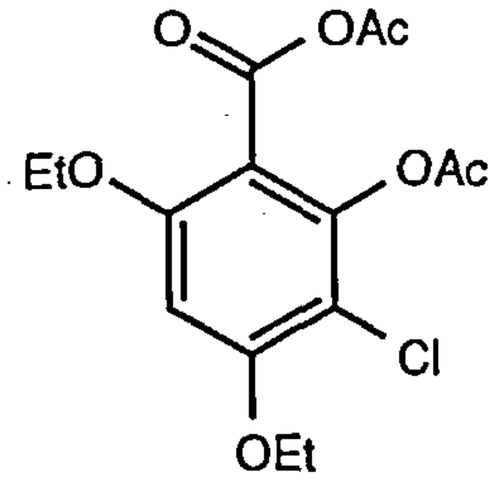
1-82



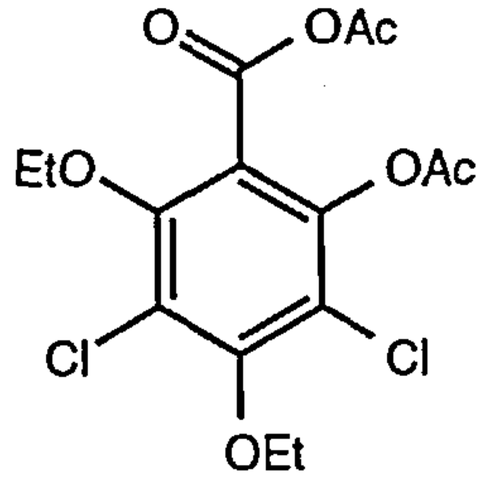
1-83



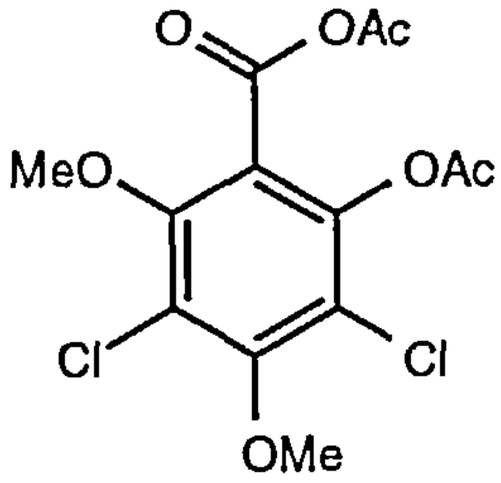
1-84



1-85



1-86



1-87

Substrate	Nucleophile	Yield (%)
1-82	NH_3	44
1-83	NH_3	64
1-84	NH_3	21
1-85	NH_3	60
1-86	NH_3	27
1-85	$NHMe_2$	41
1-85	$NHEt_2$	?
1-87	NH_3	53

Table 1.4.2

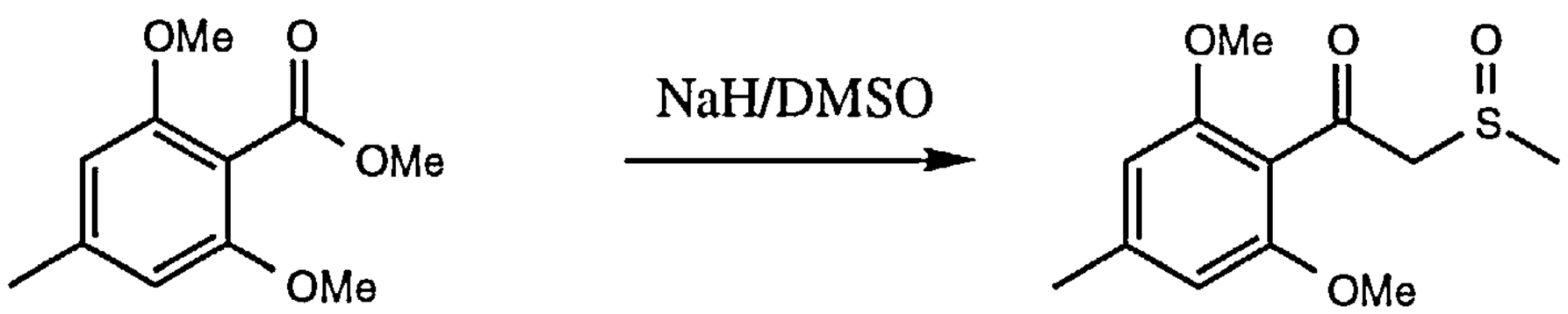
These reactions show that nucleophilic displacement at 2,6-dioxygenated benzoic acetic anhydrides is a viable reaction, though some yields are low. *Para*-chloro compounds produce smaller yields than *ortho*-chloro compounds. The effect of different ethers at the 2-position is not marked.

1.5 Nucleophile addition reactions at the carbonyl moiety of 2,6-dioxygenated benzoic esters

1.5.1 Carbanion reactions.

1.5.1.1 Intermolecular reactions.

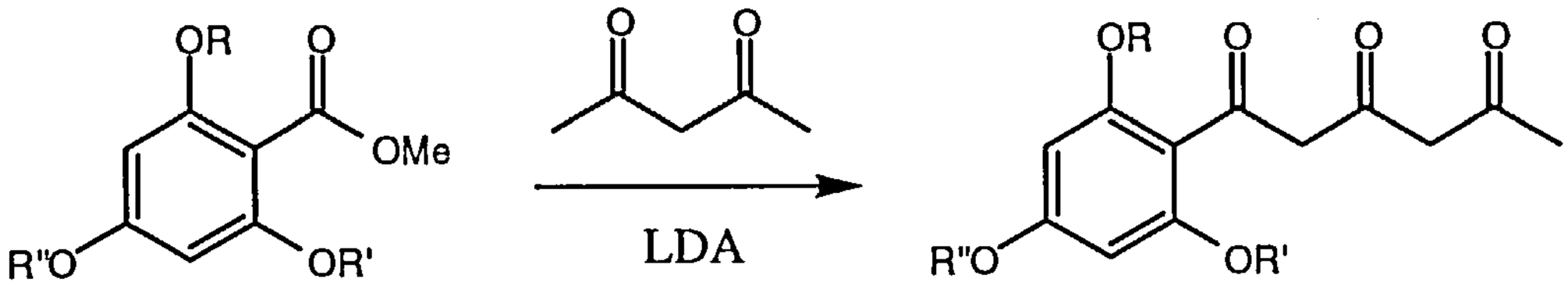
Several nucleophilic displacement reactions featuring carbanions have been reported using 2,6-dioxygenated benzoic esters as substrates. Of particular interest for our study was Mori's paper on coniochaetones A and B,[49] in which they describe the nucleophilic displacement of ester **1-88** with the sodium anion of DMSO to give the sulphoxide **1-89**, see figure 1.5.1. The reaction proceeded in 78% yield, though a six-fold excess of DMSO was used.



1-88 **1-89**

Figure 1.5.1

The Harris group carried out a series of nucleophilic displacements at 2,6-dioxygenated benzoic esters, using the lithium dianion derived from 2,4-pentanedione.[50] For a general reaction scheme see figure 1.5.2 below, and for the tabulated results of this venture see table 1.5.1.

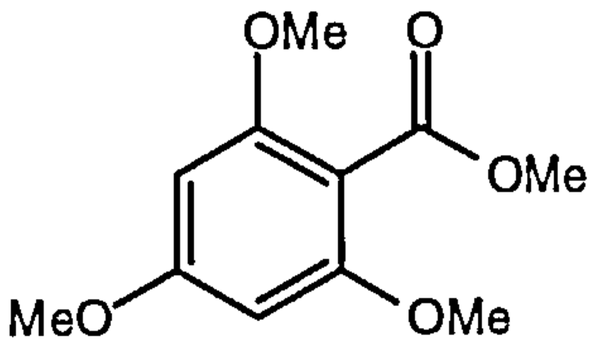


1-90 to **1-94** **1-95**

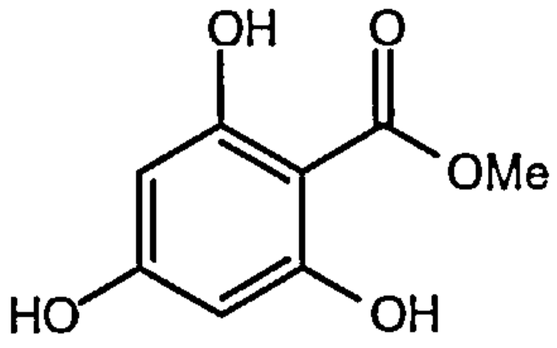
Figure 1.5.2

Substrate	Product	Yield (%)
1-90	**1-95**	61
1-91	insoluble	–
1-92	**1-96**	62
1-93	**1-95**	100
1-94	**1-95**	100

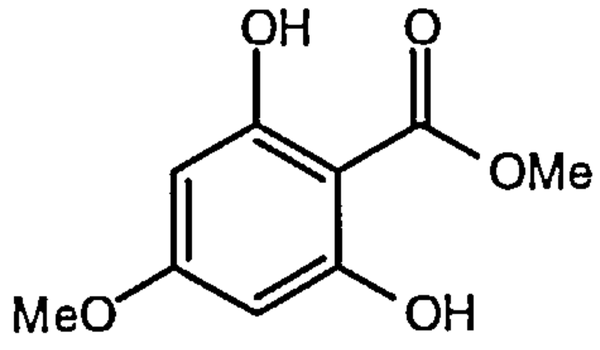
Table 1.5.1



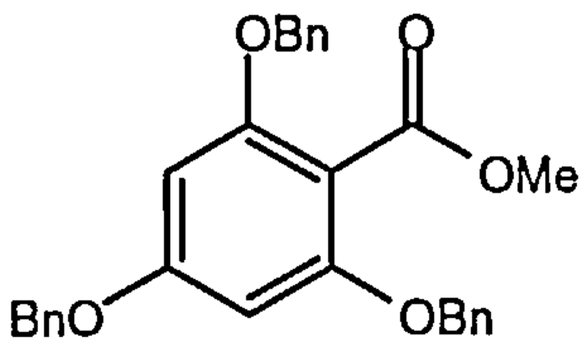
1-90



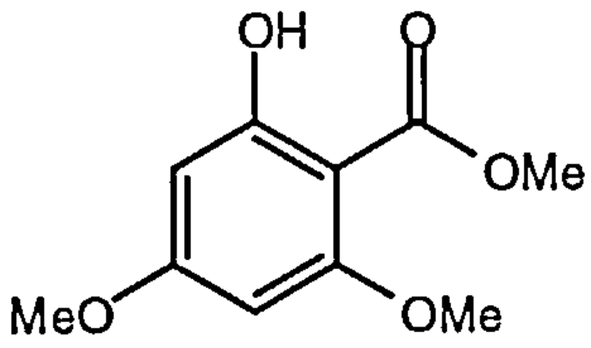
1-91



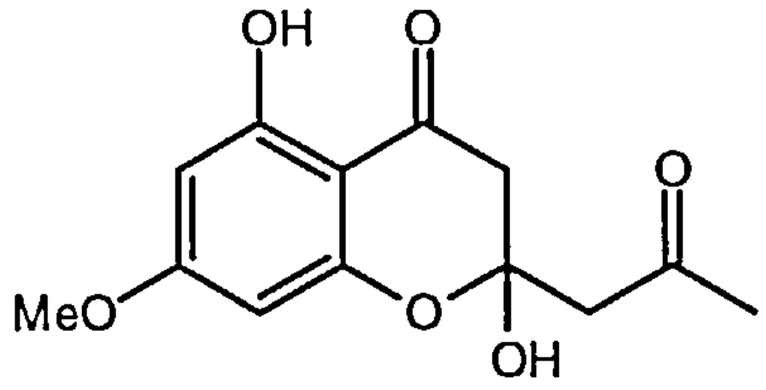
1-92



1-93



1-94



1-96

All of the reactions attempted were viable, with the exception of the substitution at **1-91** which did not proceed as the substrate formed an insoluble lithium salt on deprotonation with LDA. The reaction with **1-92** did not produce the expected product, but instead gave **1-96** in 62% yield.

1.5.1.2 Intramolecular reactions.

The anionic rearrangement of 2-halophenyl and 2-halobenzyl 2',6'-dioxygenated benzoates has been reported. The general scheme of this reaction is shown below, figure 1.5.3.

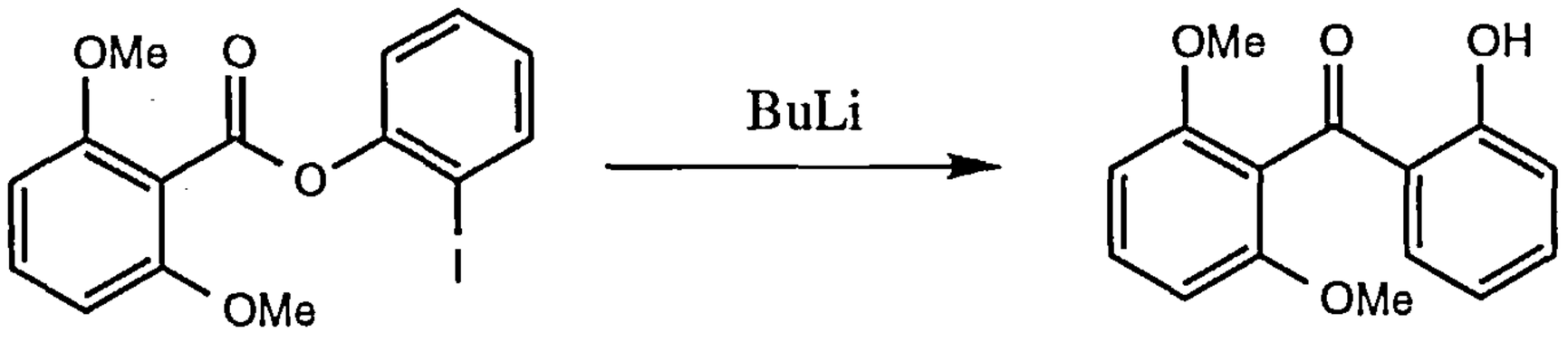
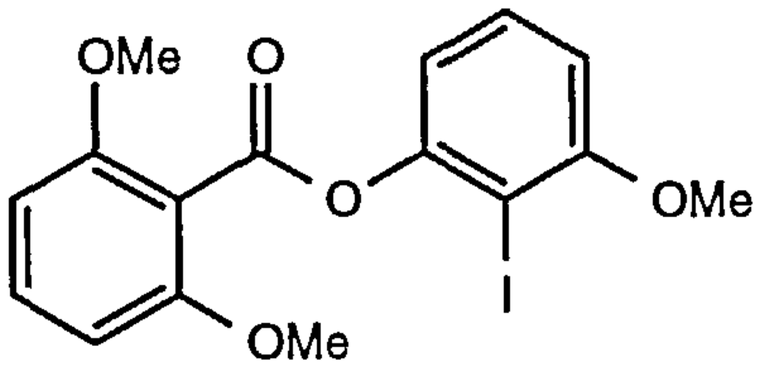
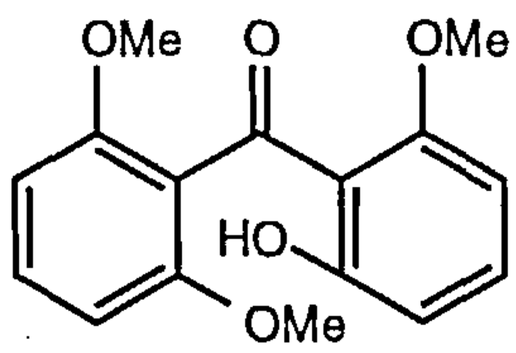


Figure 1.5.3

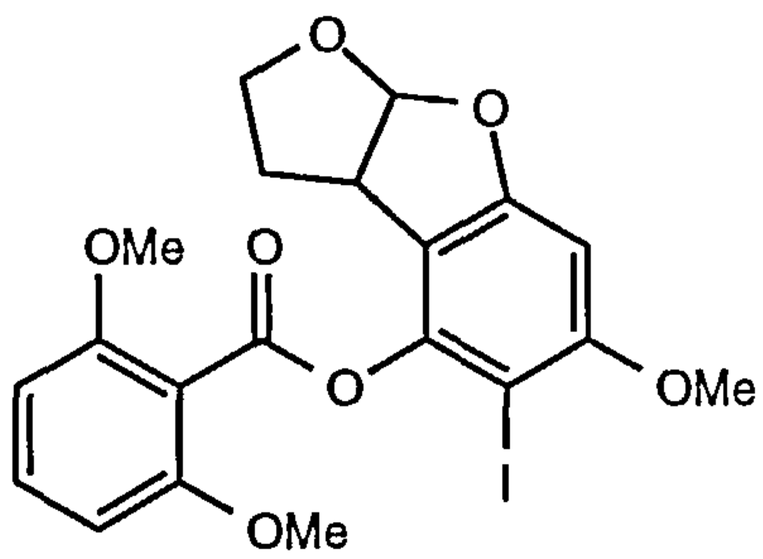
Horne and Rodrigo[51] rearranged **1-97** using butyllithium to give **1-98** in 9% yield. A similar reaction with **1-99** failed to give rearranged product.



1-97



1-98

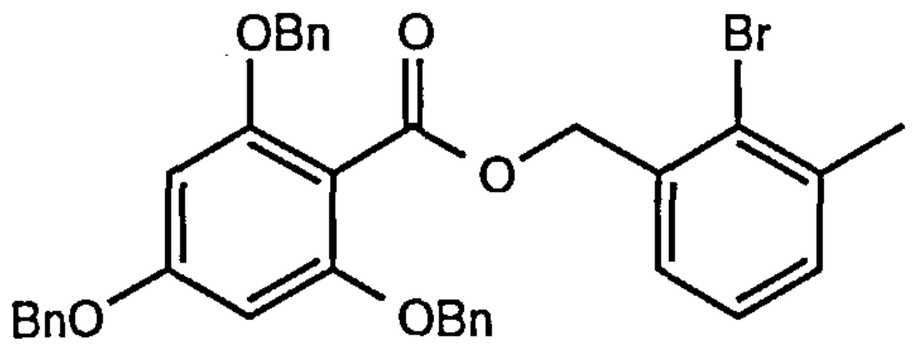


1-99

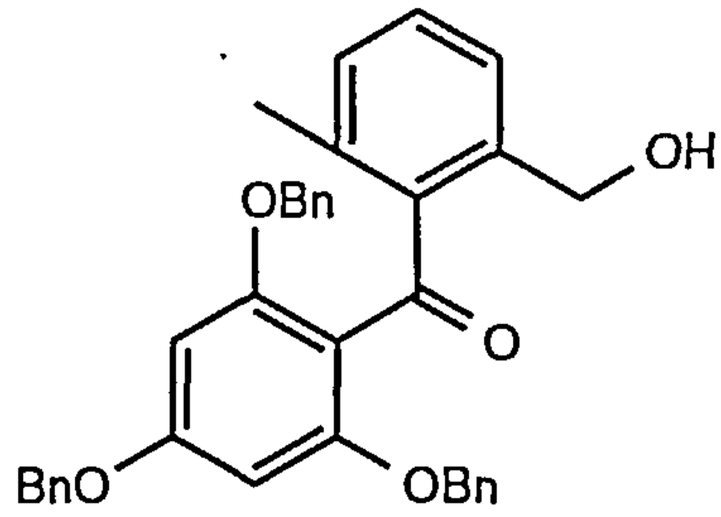
The authors of this paper suggest that the rearrangement takes place through a dimeric transition state, though crossover experiments showed the rearrangement to be solely intramolecular. The reaction functions well for 2-methoxylated species, but yields in 2,6-dimethoxylated species are low. This was attributed to the steric interactions

between the 6-methoxy moieties disrupting the dimeric complex. Lithium/iodine exchange was complete in all cases.

Lampe and coworkers rearranged **1-100** to give **1-101** in 51% yield. In this case the 2,6-dioxygenated substitution pattern does not appear to have affected the yield.[52]



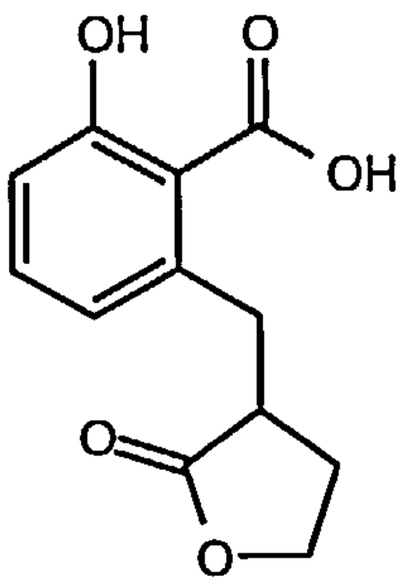
1-100



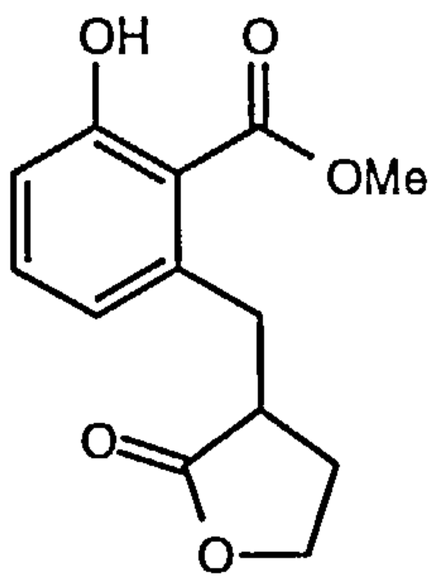
1-101

The intramolecular anionic rearrangements of 2,6-dioxygenated benzoic esters shown above are clearly more viable on benzyl systems than on phenyl ones, possibly due to a mechanistic difference: the transition state for the benzyl rearrangement is five-membered, which leads to a considerably less strained structure than the four-membered one required for the phenyl rearrangement.

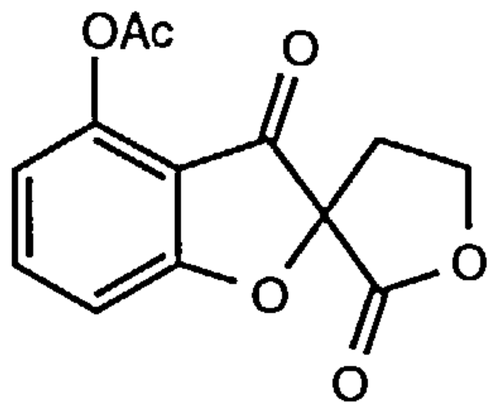
The corresponding acid **1-102** to the ester **1-103** reacted with triethylamine and acetic anhydride to give the spiro compound **1-104** in 39% yield.[53] The ester itself did not react. This was attributed to the action of electron donating groups on the ring. Similar compounds without the 6-oxygenation reacted in 35%. Compounds with acetyl functionality at C5 reacted in 47%. This would seem to substantiate the notion of inhibition/potentiation by electron demand of substituent.



1-102

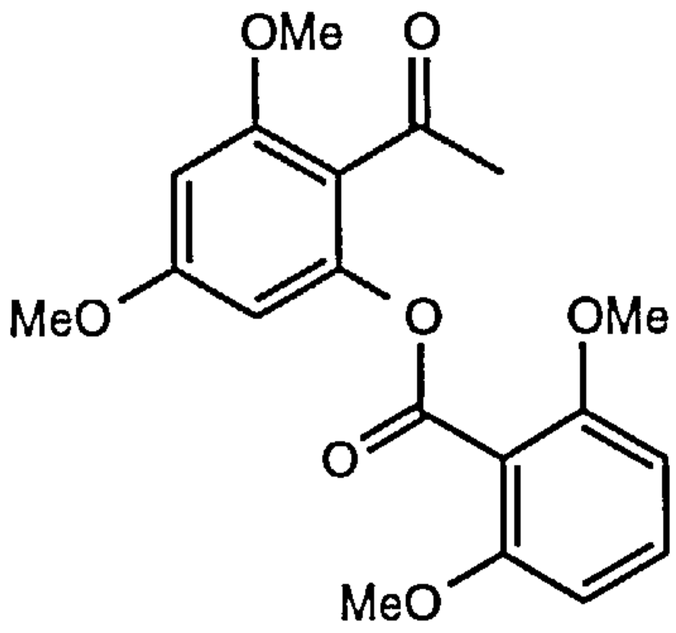


1-103

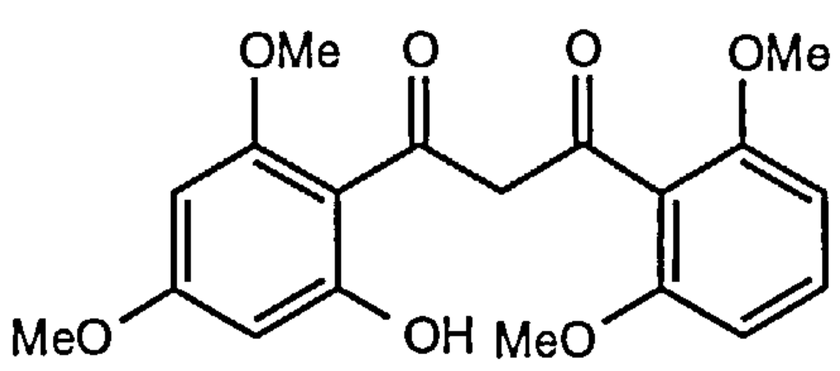


1-104

Finally in this section, an example of a Baker-Venkataraman rearrangement, where both the nucleophile migrating group and the substrate are 2,6-dioxygenated species. The phenyl benzoate**1-105** was rearranged to **1-106** in 40% yield using potassium hydroxide and pyridine.[54]



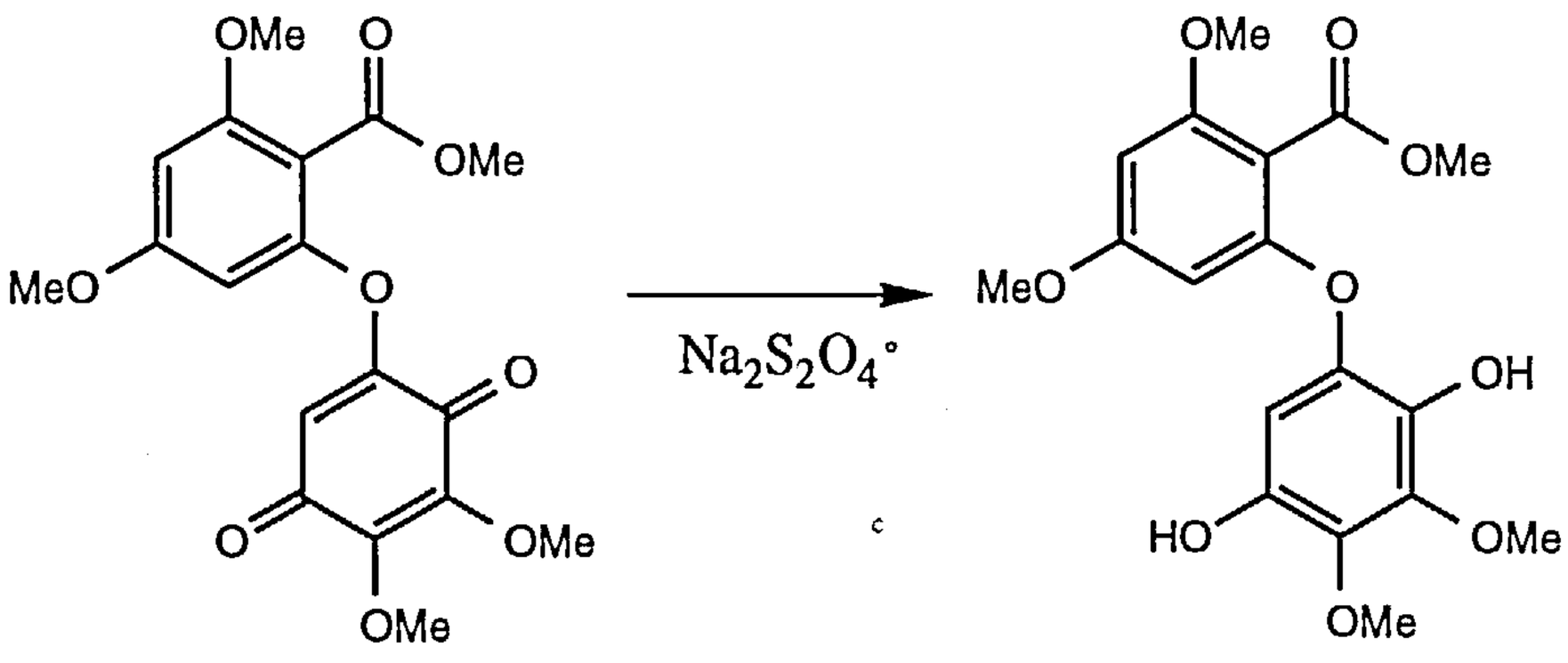
1-105



1-106

1.5.2 Acid catalysed reactions at 2,6-dioxygenated benzoate esters

Simoneau and Brassard reported a synthesis of 1,4-dihydroxyxanthones which relied upon the cyclisation of a phenyl quinone ester **1-107** to the xanthone **1-109**, *via* the hydroquinone **1-108**.[55] This was of particular interest, as the idea of protecting polyoxygenated rings as quinones has possible applications in chromone synthesis. The reaction scheme went in 68% yield, with the xanthone cyclisation proceeding in 77%.



1-107 **1-108**

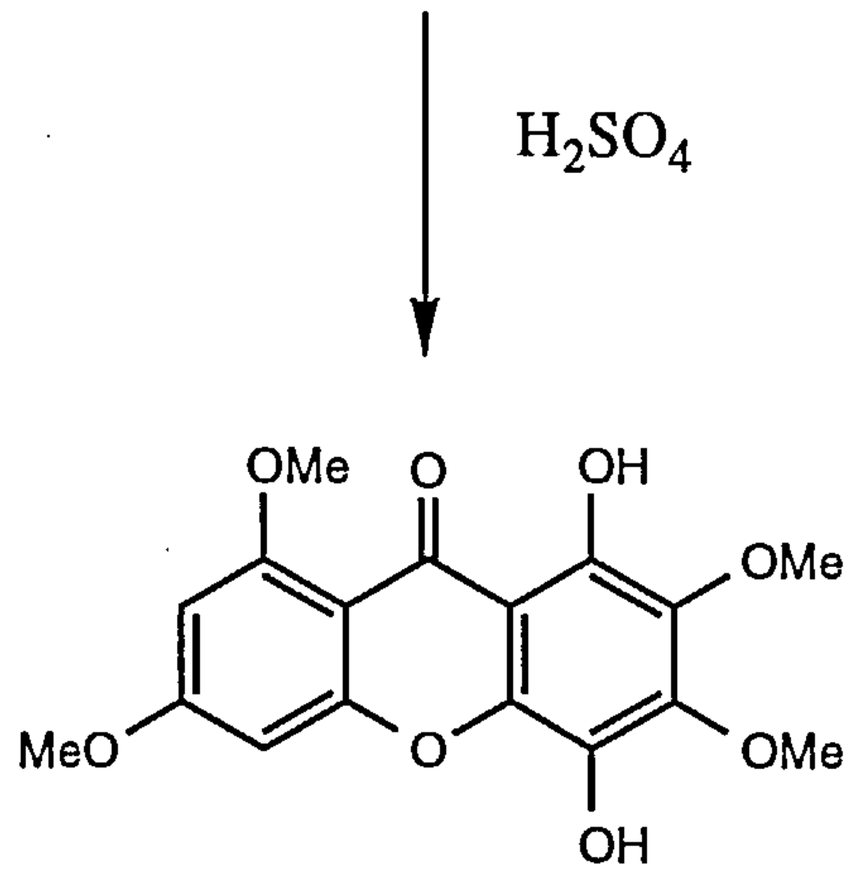
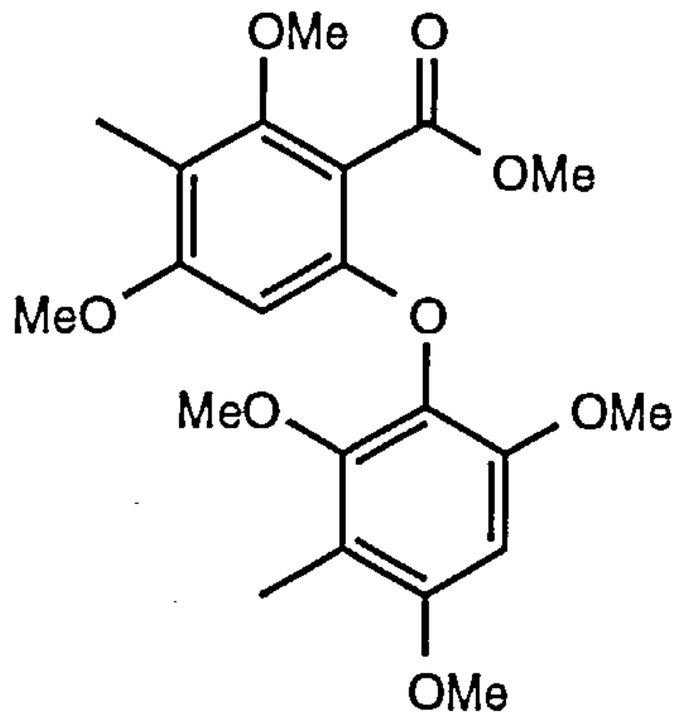


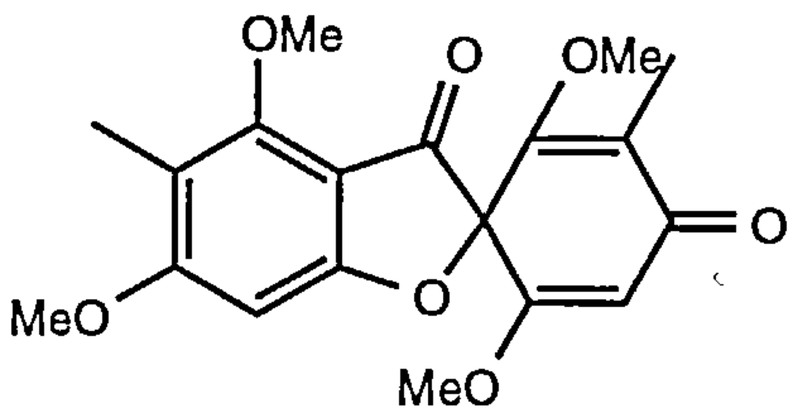
Figure 1.5.4 **1-109**

In a similar vein Sargent conducted a synthesis of grisa-2',5'-diene-3,4'-diones in which a key step was the spirocyclisation of polymethoxylated esters **1-110** and **1-112** to the corresponding dienones **1-111** and **1-113** respectively using titanium tetrachloride and hydrogen chloride.[56] The yield for **1-111** was 85% and that for **1-**

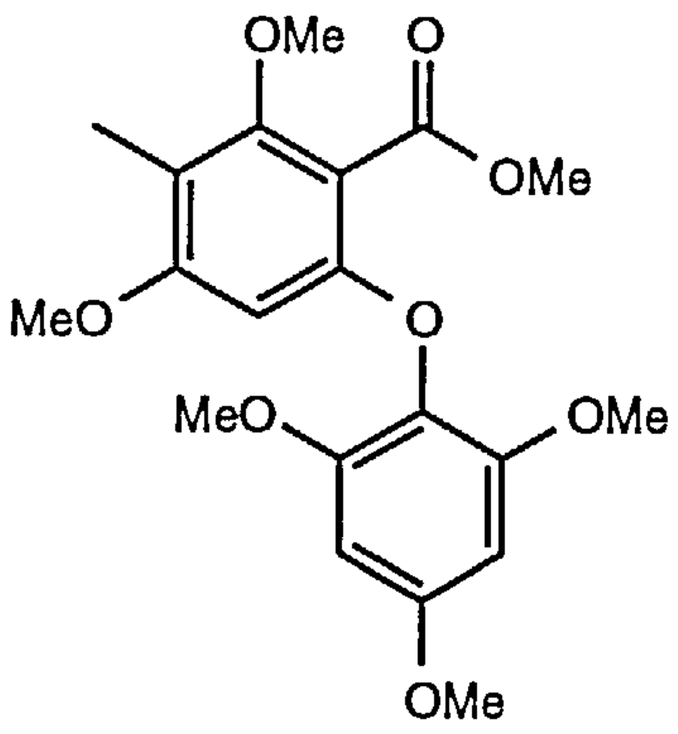
113 was 78%. An interesting feature of this reaction is that the substrate is demethylated at the same time as cyclisation.



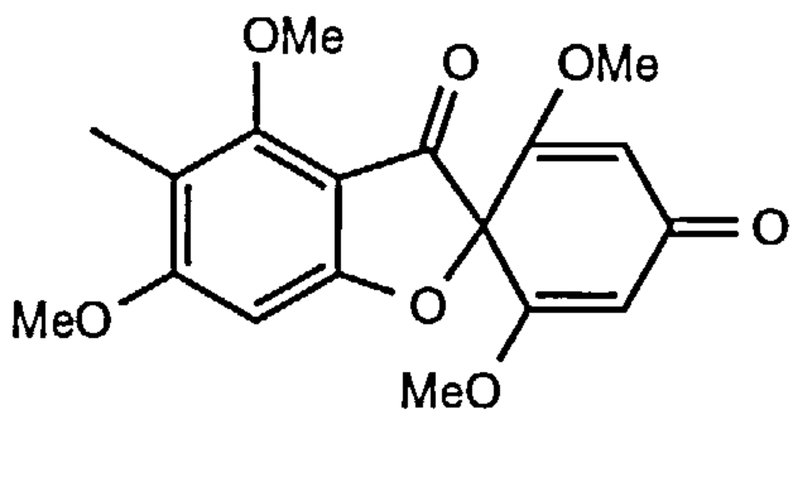
1-110



1-111

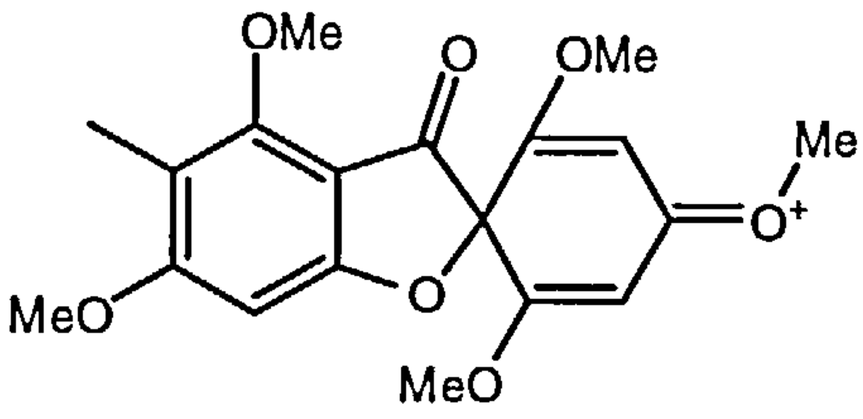


1-112



1-113

Sargent suggested a mechanism for the reaction, postulating that the first step followed an AAc1 ester cleavage pathway, followed by an attack by the ring, giving a transition state of the form **1-114.** This could then be demethylated by nucleophilic attack.



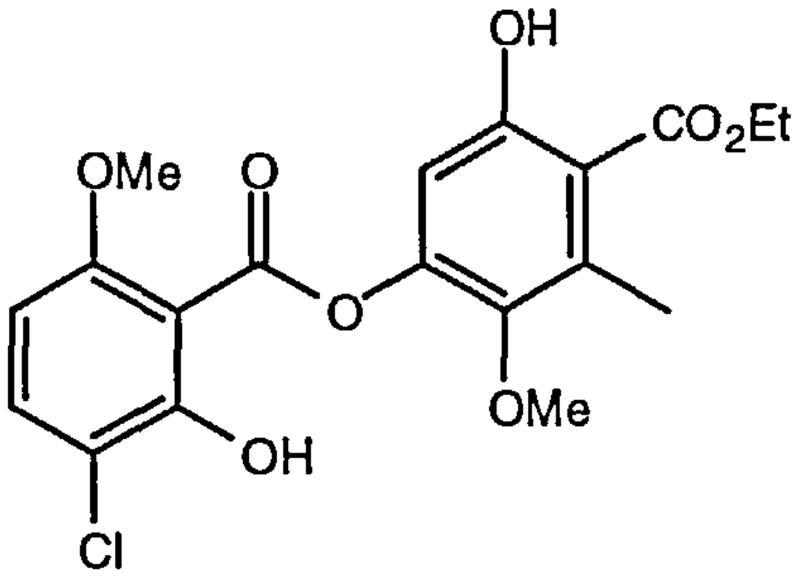
1-114

1.5.3 Heteroanion reactions at 2,6-dioxygenated benzoate esters

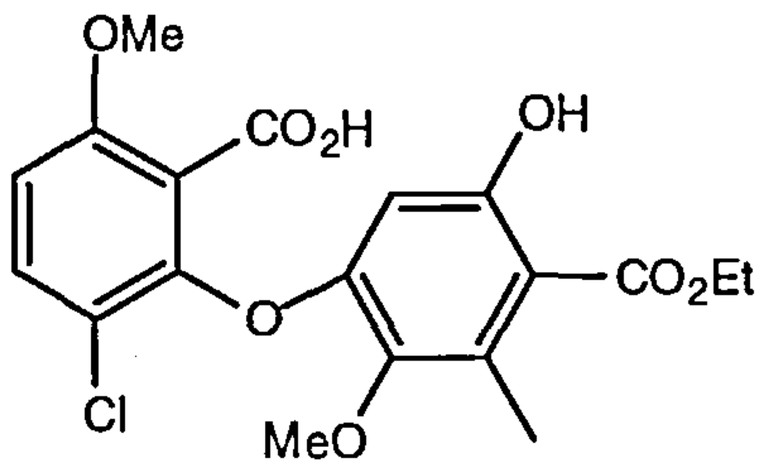
1.5.3.1 Oxoanions

Two main types of nucleophile reactions of this form have been reported, a Smiles rearrangement and transesterification.

The Smiles rearrangement of the ester **1-115** was carried out in dimethyl sulphoxide with potassium carbonate to give **1-116** in 67% yield.[57] This rearrangement effectively consists of an intramolecular nucleophilic substitution. As the carbonyl moiety is not involved in the reaction as normally written it is perhaps beyond the scope of this review, but it is included as it illustrates a possible side reaction in base-catalysed intramolecular rearrangements where an *ortho*-hydroxyl is present. As the yield suggests it is a viable reaction under relatively mild conditions.

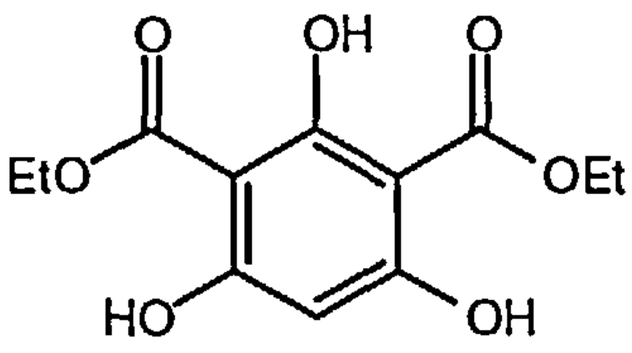


1-115

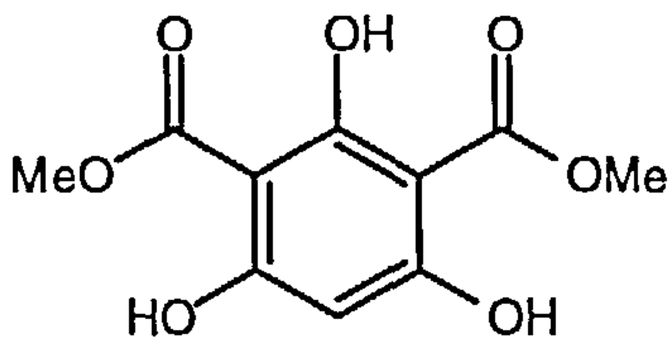


1-116

There are several examples of transesterification catalysed by base. The phloroglucinol derivative **1-117** and its equivalent methyl ester **1-118** can be interconverted in quantitative yield by refluxing in the relevant alcohol with ammonia as a catalyst.[58]



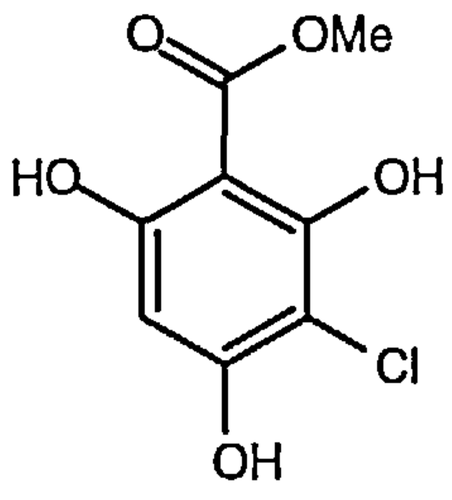
1-117



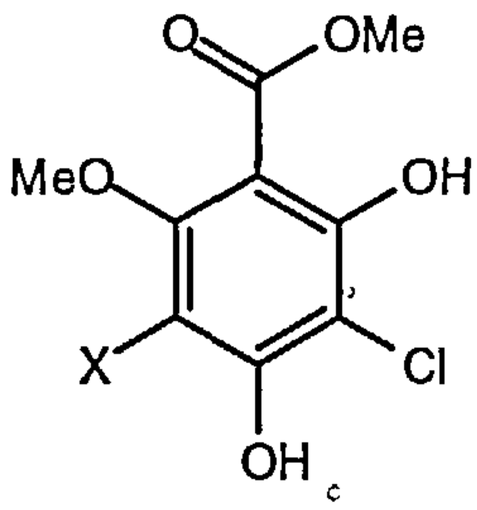
1-118

1.5.3.2 Nitrogen nucleophiles

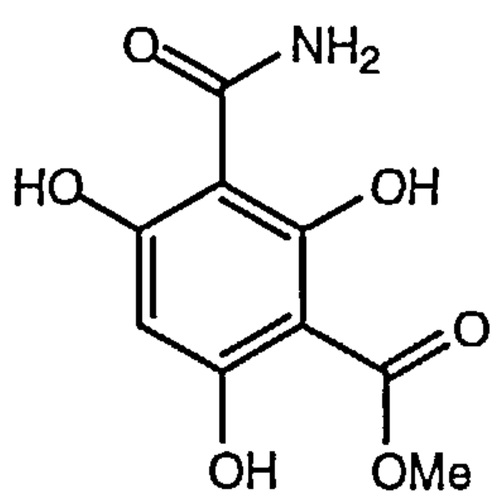
Many transformations of 2,6-dioxygenated benzoate esters into amides have been accomplished. Most of them have been achieved in aqueous ammonia. Maillard and co-workers achieved the transformation of the esters **1-119**, **1-120** and **1-121** in variable yields.[59] Leuchs transformed **1-117** into the amide ester **1-122** using strongly ammoniacal methanol,[60] and Budesinsky transformed the esters **1-123** and **1-124** into the corresponding amides.[61] Bretschneider performed a similar transformation on ester **1-125**.[62] For a breakdown see table 1.5.2 below.



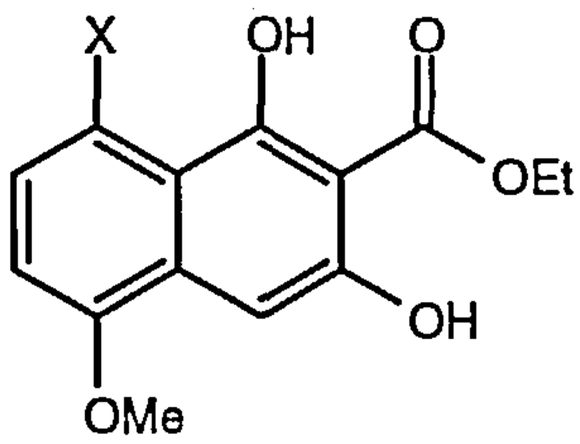
1-119



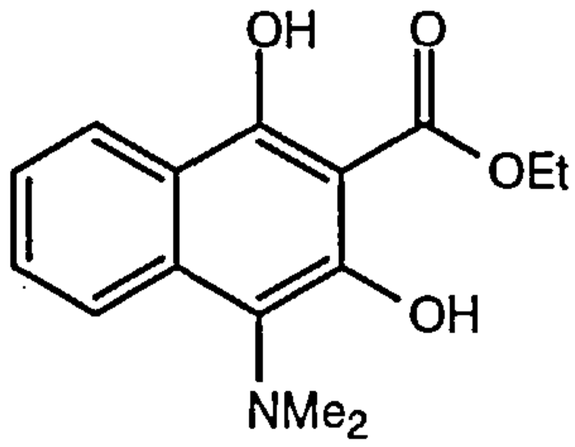
1-120 X = H
1-121 X = Cl



1-122



1-123 X = H
1-124 X = OMe



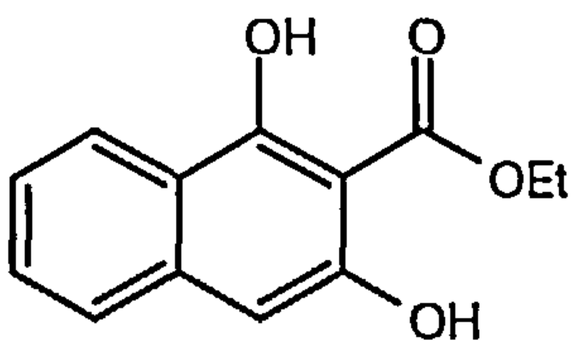
1-125

Substrate	Reactants	Yield (%)
1-119	Aqueous ammonia	55
1-120	Aqueous ammonia	15
1-121	Aqueous ammonia	73
1-117	Methanolic ammonia	100
1-123	Conc. ammonia	67
1-124	Conc. ammonia	55
1-125	liquid ammonia	66

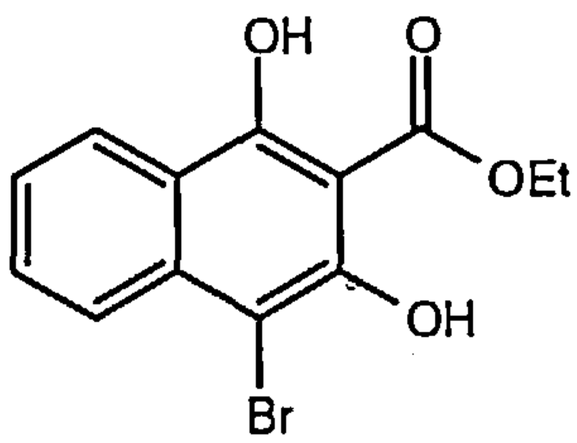
Table 1.5.2

All of the above substitutions function in fair yield, with the exception of the pentasubstituted compound **1-120**. One could speculate that in this case deactivation of the ester by the extremely electron rich ring may inhibit the reaction.

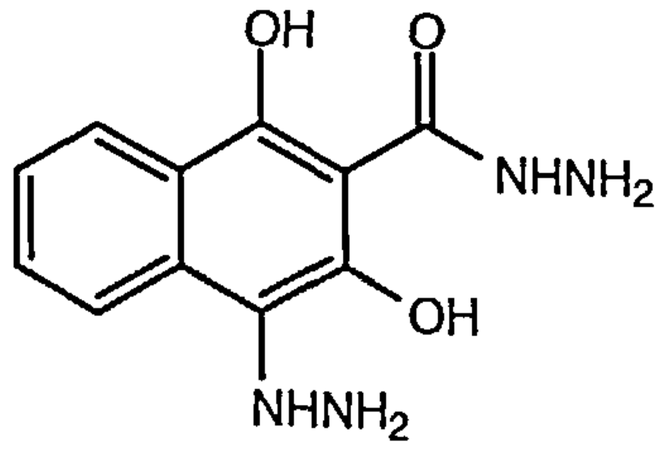
Other reactions involving nitrogen nucleophiles are exhibited by the formation of hydrazides. Bretschneider and co-workers prepared the hydrazides of **1-125** (93% yield) and **1-126** (60% yield) using hydrazine in water.[63] A similar reaction on **1-127** gave the unexpected product **1-128** in 81% yield.



1-126



1-127



1-128

1.6 Summary

Overall the reactions of nucleophiles at 2,6-dioxygenated benzene carbonyl compounds are succesful for a variety of nucleophiles in a variety of conditions. High yields can often be achieved with sterically large nucleophiles, despite the sterically crowded nature of the ring. There is some evidence that increasingly electron-rich substrates can produce lower yields, particularly in ester substitution reactions, though proper comparison is difficult without a rigorous series of experiments.

Difficulties of solubility can be experienced with the polyanions of polyhydroxy substrates.

Reactions involving heteronucleophiles are seen to work satisfactorily for the majority of substrates.

Chapter 2

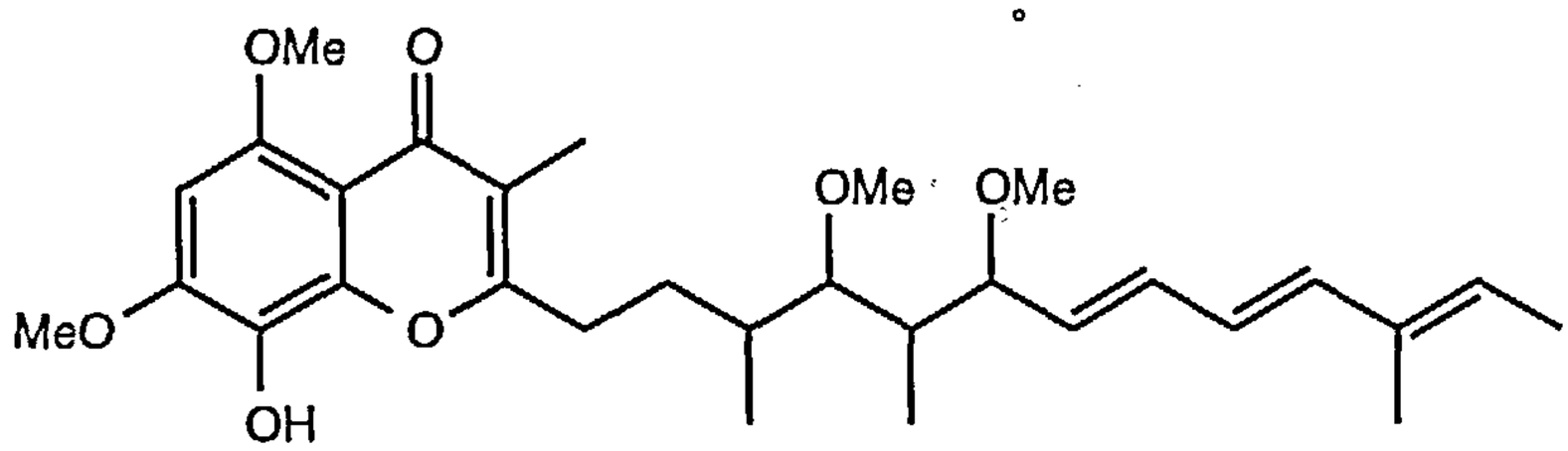
A review of the provenance, abundance, biological activity and syntheses of stigmatellin, baicalein trimethyl ether and LL-D 253a

2.1 Stigmatellin

2.1.1 Provenance of stigmatellin and some related compounds

Stigmatellin was isolated from the shake cultures of *Stigmatella Aurantiaca* strain Sga15. This is a gliding bacterium first discovered in rotting wood collected in the Siebengebirge mountains near Bonn by Dr. W. Dawid. The strain grows well in a variety of media[64] and can be stored in liquid nitrogen. The strain was found to produce two types of antibiotic, myxalamids and stigmatellin.

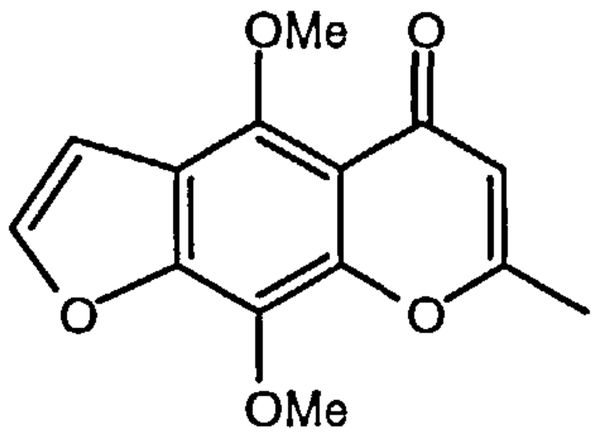
Stigmatellin **2-1** was found to have a structure as shown below; details of stereochemistry and structural elucidation will follow shortly.



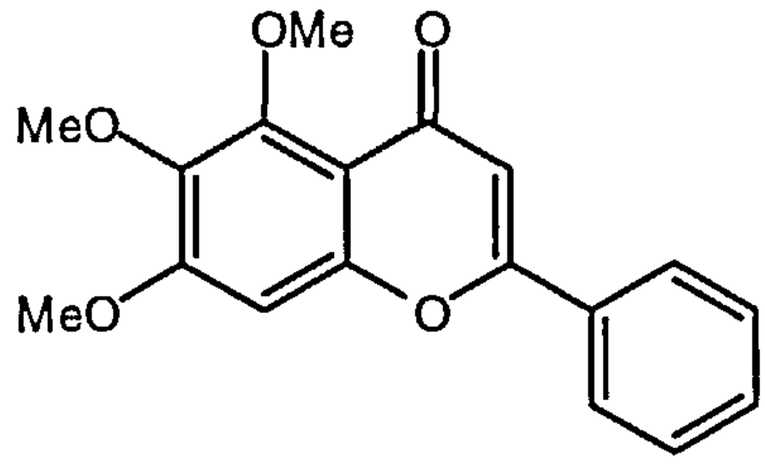
2-1

The structure of the chromone unit in stigmatellin is quite unusual in nature. A reasonably thorough search will yield very few 'relations' in the literature. Of those that can be found, perhaps the best known would be khellin **2-2**, the compound extracted from the Egyptian pseudo-papyrus *Ammi Visnaga* and mentioned in the British Pharmaceutical Codex for 1933 as effective in bronchial complaints. Although this does not contain the 3-methyl of stigmatellin, it does have a similar oxygenation pattern about the B ring.

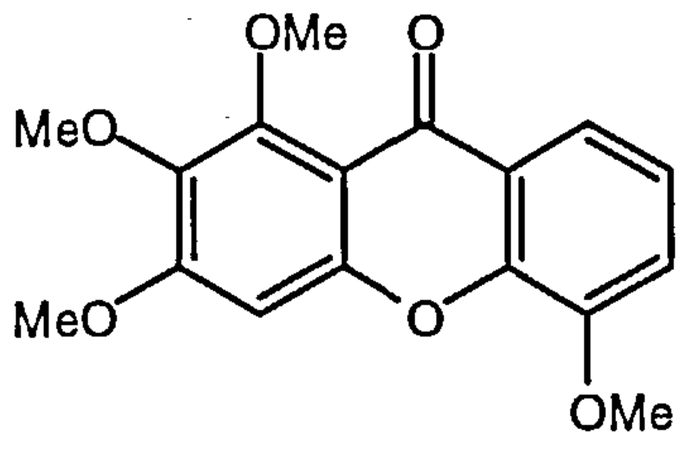
A range of compounds have a similar oxygenation pattern on the B ring with a differing fusion with the A ring, *e.g.* baicalein trimethyl ether **2-3**, the xanthone **2-4** derived from *Frasera Caroliniensis* [65] and quercetagetin **2-5**, an extract of *Tagetes Patula* [66] (the french marigold).



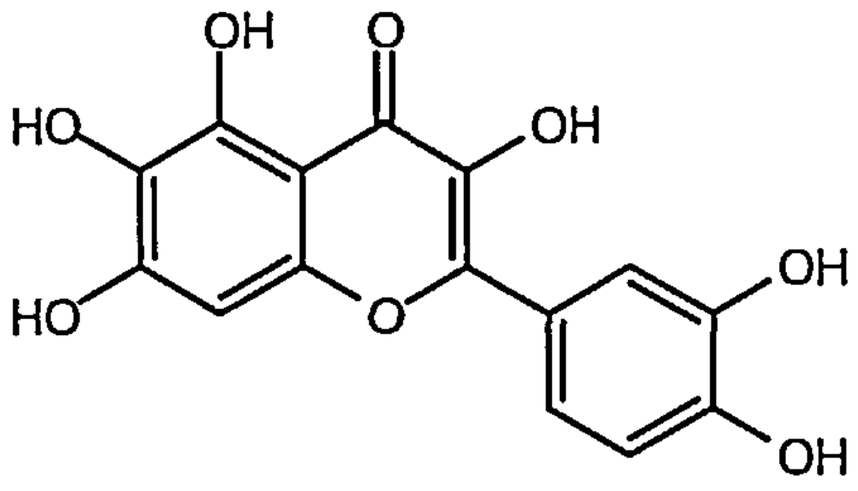
2-2



2-3



2-4



2-5

To the best of our knowledge stigmatellin has not been found in other natural sources, so a synthetic route could be valuable.

2.1.2 Biological activity of stigmatellin, its application and use

Stigmatellin was found to have strong antibiotic activity against *Saccharomyces cerevisiae* both in culture and in extract. The minimum inhibitory concentration (MIC) for stigmatellin against a variety of bacteria and fungi were measured, with some notable successes such as against *Candida albicans* (2.5 μg/ml) and *Saccharomyces cerevisiae* (0.1 μg/ml). Its function with fungi was stated as fungistatic, with cells able to reproduce after removal from doped media. Stigmatellin was found to be very toxic to animals, with an LD_{50} (mouse) of 2 mg/Kg sc.

Stigmatellin appears to interfere with respiration at the mitochondrial cytochrome bc_1 site. This was inferred from the fact that upon addition of stigmatellin all RNA and protein synthesis in the subject cells ceased and the fact that immunity to stigmatellin could be induced by the addition of glucose to organisms able to obtain energy by fermentation. The mode of action of stigmatellin seems to be similar to myxothiazole,[67] and the chromone unit seems to be responsible for it, as provided one

keeps the polarity of the side-chain similar to the natural product one can maintain activity with a variety of chains.[68] The compound was suggested as a useful probe for the study of electron transport in the cell. Stigmatellin has been used as an inhibitor of bo oxidation sites in E Coli,[69] to probe the electrostatic environment of the Q_a site in bacterial RCs.[70]

Mutations that provided immunity against stigmatellin all appear to be on the bc sites,[71] and do not necessarily provide immunity to myxothiazole.

2.1.3 Syntheses and structure elucidations

The structure **2-1** already shown was proposed by the Höfle group on the basis of extensive spectral data.[72] They also synthesised model compounds containing the chromone ring as proposed in order to test the structure and perform analyses of structure/activity correlations. We shall consider their route in detail.

The group chose as their starting material phloroglucinol dimethyl ether, which was dipropionylated using a solution of phosphorus pentoxide in phosphoric acid to give **2-6** in 41% yield. The diketone **2-6** was then submitted to a Baeyer-Villiger oxidation to yield **2-7** in 31% yield. This step is the crucial desymmetrising step; until this point the molecule had symmetry about a central mirror plane. After oxidation, **2-7** was submitted to hydrolysis to yield **2-8** (79%), which was then cyclised to the chromone using sodium acetate, acetic acid and acetic anhydride (see figure 2.1.1).

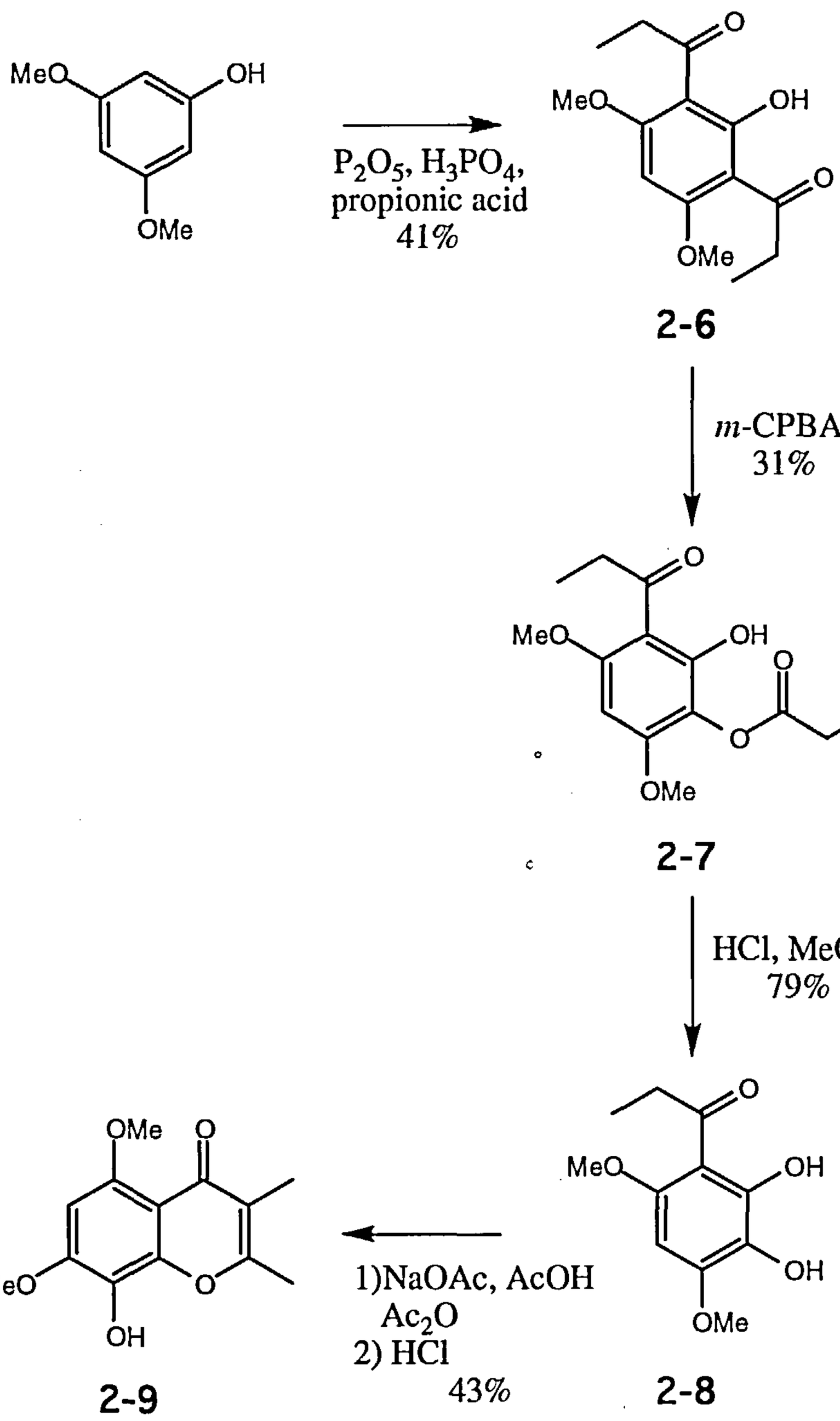
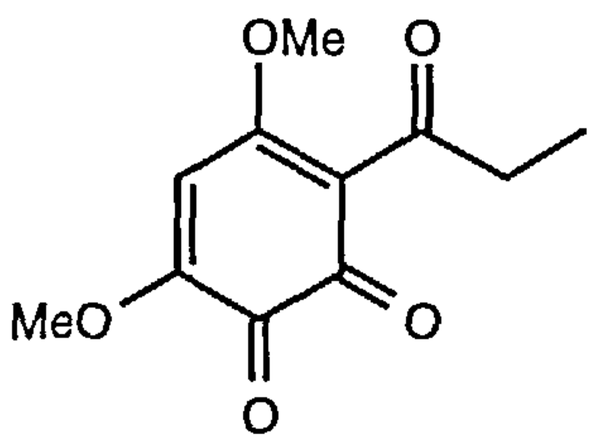


Figure 6.1.1

Perhaps the most interesting thing about this synthesis is the choice of desymmetrisation step. Faced with a total dearth of synthetic and natural intermediates with the correct substitution pattern Höfle and his coworkers chose to start with the readily accessible phloroglucinol dimethyl ether and bypass the difficulties of a controlled monoacylation and went straight for the diacylation with some success. They then chose a controlled Baeyer-Villiger oxidation to effect a functional group interchange that would lead them down to the required diol **2-8**.

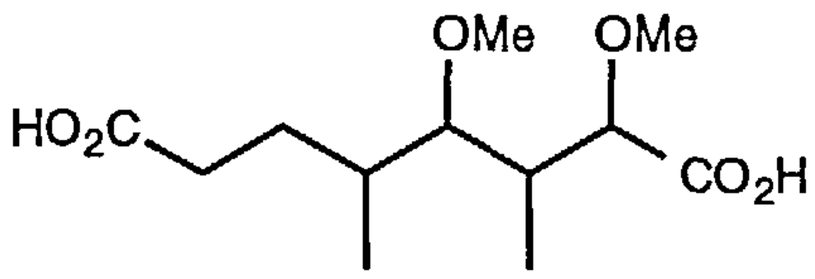
The benefit of hindsight allows us to suggest a reason why the oxidation, which normally gives high yield, gives a yield in the low thirties in this case. One would expect **2-6** to be a reasonably stable compound as far as oxidation is concerned, given that the ring has two carbonyls attached to provide stability. However **2-7** is very electron rich about the aromatic ring, and therefore susceptible to oxidation. One would expect that in the presence of a strong oxidant like *m*-CPBA quite large quantities of *ortho*- quinone **2-10** would be formed. Clearly any synthesis of stigmatellin's chromone fragment would do well to steer clear of strong oxidants.



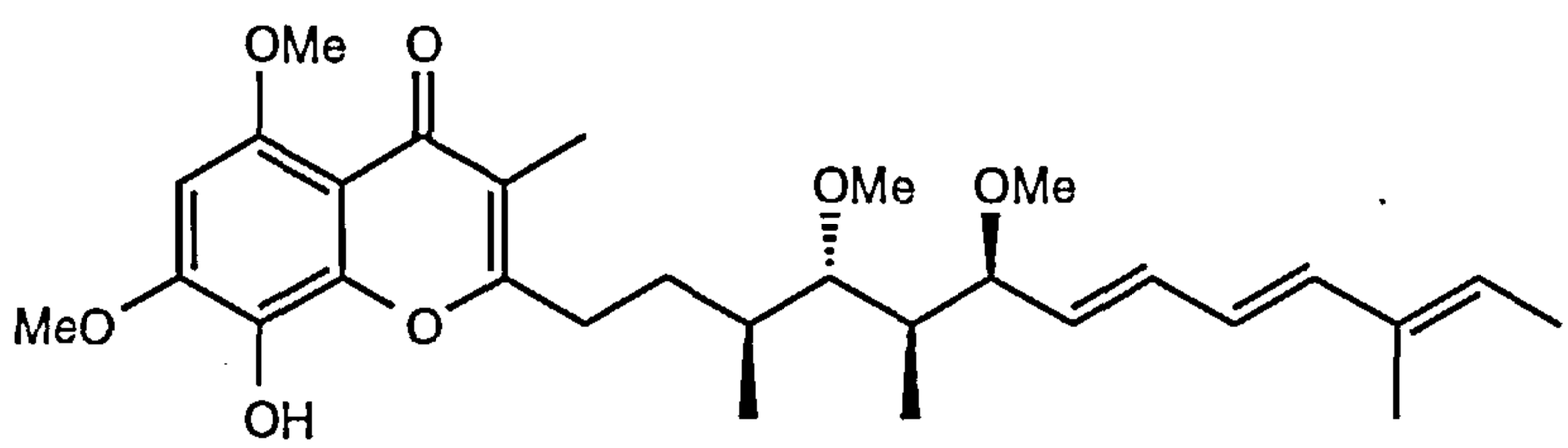
2-10

The cyclisation step is a fairly standard set of conditions for the closure of chromones. Its only limitation is that it requires large quantities of the required acyl anhydride. Should the acyl unit be complicated, as might be the case in stigmatellin analogues, this could prove a stumbling block.

The absolute configuration of the stigmatellin side-chain remained something of a problem, as no X-ray crystallograph could be taken due to difficulties with crystallisation. Enders[73] undertook a method of chemical correlation. He performed an ozonolysis on stigmatellin to isolate the chiral section of the side-chain as a diacid **2-11**, then synthesised all of the possible isomers to find out which correlated. This led to the discovery that the structure of stigmatellin was that given below, **2-1a**.



2-11

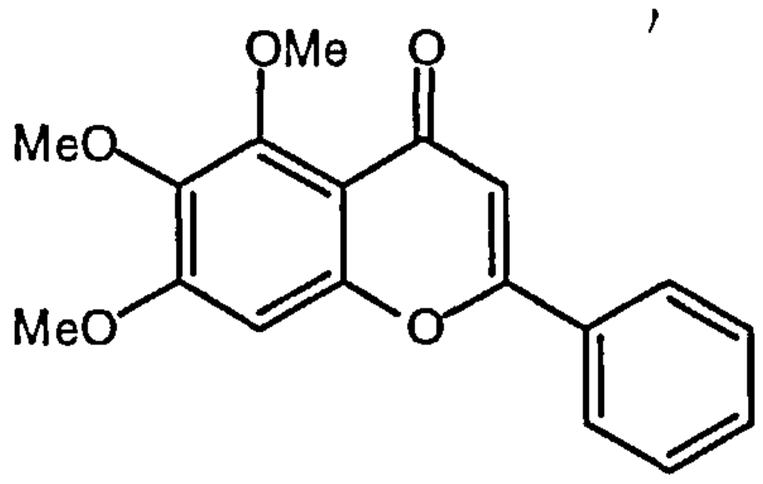


2-1a

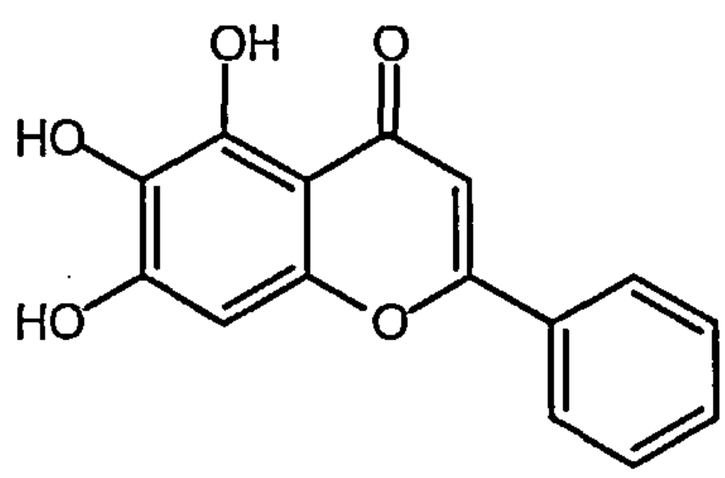
2.2 Baicalein trimethyl ether

2.2.1 Provenance of baicalein trimethyl ether and some related compounds

Baicalein trimethyl ether **2-12** is found in nature as a heartwood metabolite of trees and vines, including *Zeyhera Tuberculosa*[74] and *Popowia Cauliflora*.[75] It is one of the etheric derivatives of baicalein **2-13** which is considered to have moderate activity as an antianaphyllactic agent.[76] Baicalein itself is reasonably widespread, cropping up in, for example, Labiatae such as *Scutellaria Rivularis.*

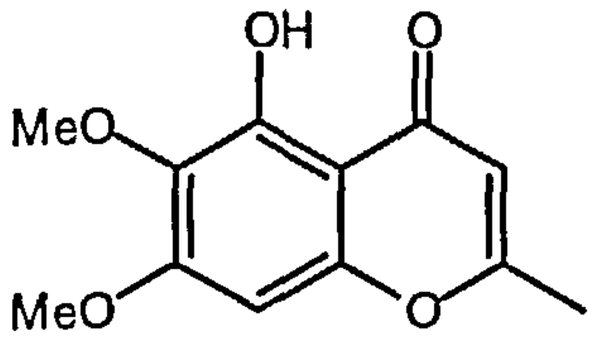


2-12

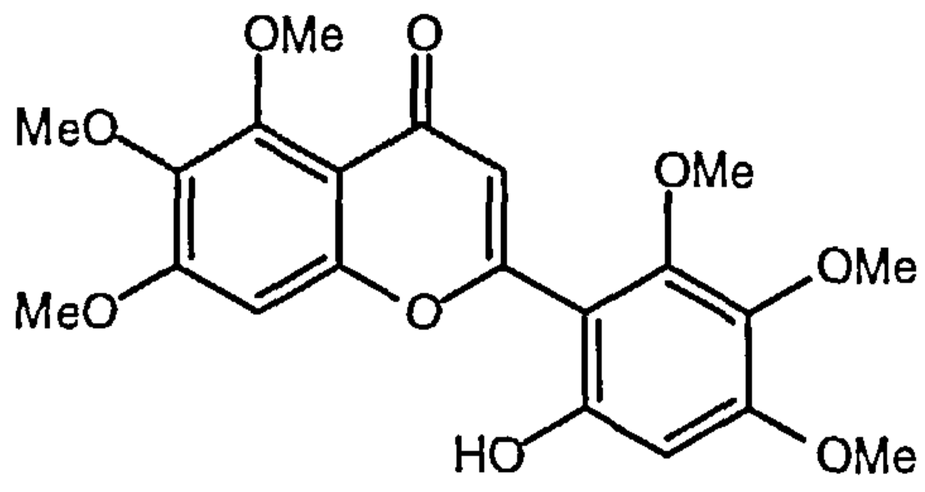


2-13

Related compounds include stellatin **2-14**,[77] and brickellin **2-15**.[78] As can be seen both have a substitution pattern similar to the baicalein group.



2-14



2-15

2.2.2 Synthesis of baicalein trimethyl ether

As will be intimated later on the synthesis of baicalein trimethyl ether is not a complex task once the ketone **2-16** has been prepared. The synthesis shown here is perhaps the first efficient synthesis. The ketone **2-16** is synthesised from 3,4,5-trimethoxyphenol using aluminium chloride and acetyl chloride in 27% yield. The benzoate **2-17** was then prepared and cyclised to baicalein trimethyl ether in 28% yield (figure 2.2.1).[79] Again one can utilise hindsight to find the flaw in the first step of this synthesis. Aluminium chloride is a very strong Lewis acid which can easily perform demethylations upon aryl methyl ethers. As the aluminium chloride is added in a ratio of 2:1 to compensate for the naked phenol in the substrate much room for mischief is left.

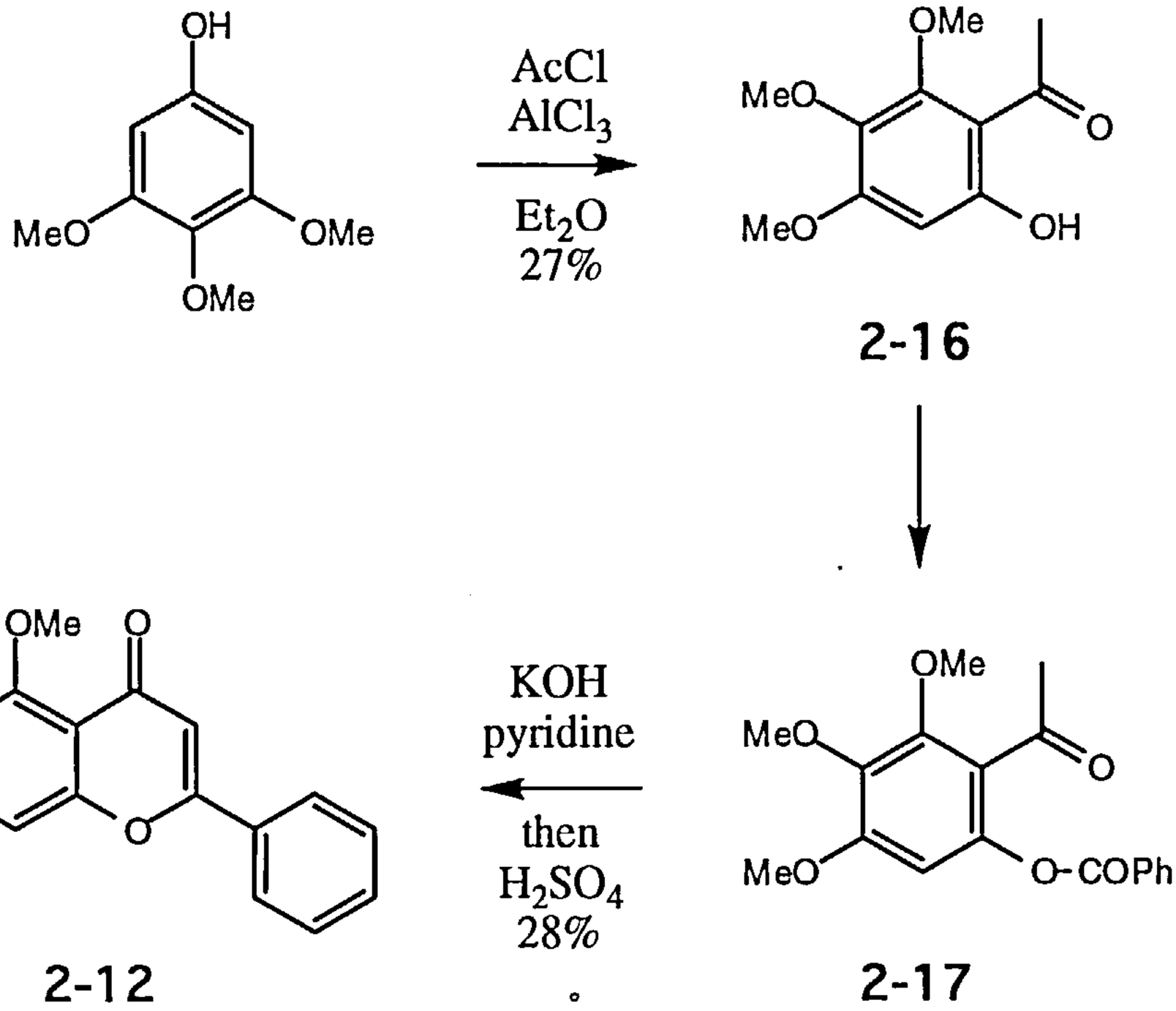


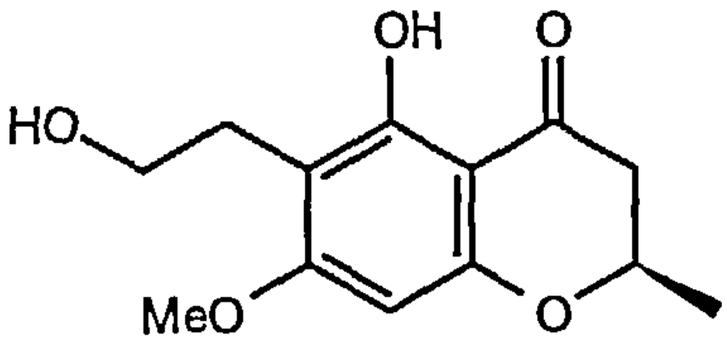
Figure 2.2.1

Added to this is the fact that in phenols Friedel-Crafts reactions are often low yielding compared to the equivalent Fries rearrangement. This synthesis is, however, a good example of a traditional chromone synthesis, and illustrates that once the substrate *o*-hydroxyketone is set up, cyclisation to the chromone is often a simple matter.

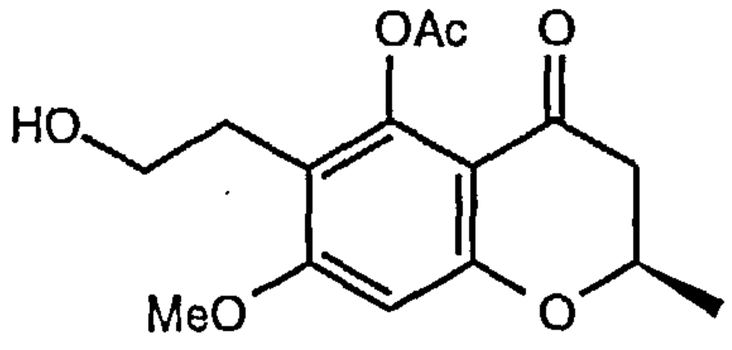
2.3 LL-D253α

2.3.1 Provenance of LL-D253α and some related compounds

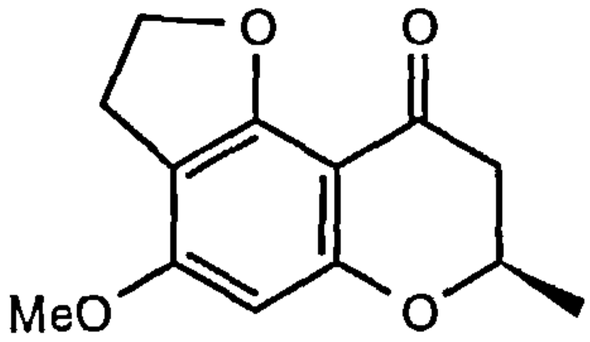
LL-D253α **2-18** was first isolated from the Lederle culture D253 by workers at the Lederle laboratories in Pearl River, New York in 1971.[80] This was a culture of *Phoma Pigmentivora*, a member of a family of arboreal fungi which are responsible for black galls on a variety of trees. The culture also produced LL-D253β **2-19** and LL-D253γ **2-20** (N.B. the structures shown are those attributed in the McGahren paper. For structure revisions *vide infra*).



2-18



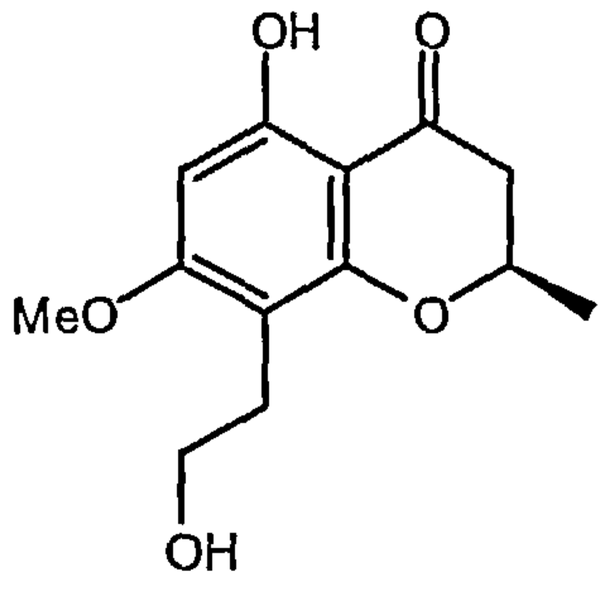
2-19



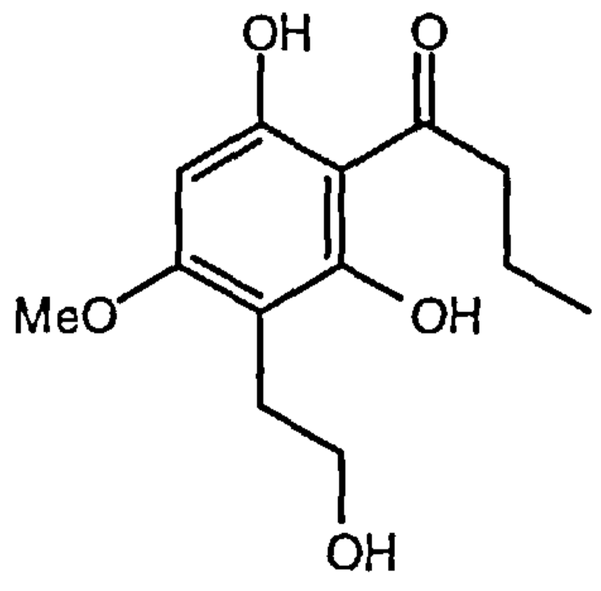
2-20

These structures were assigned on the basis of a variety of spectroscopic and chemical evidence, some of which appears to have been erroneous. Other *Phoma* species produce related compounds, one particularly interesting one being phomalone **2-21**, a fungicidal metabolite of *Phoma etheridgei*, which is a fungus frequently found on black galls of trembling aspen (*Populus tremuloides,* shiver tree) and can be assumed to have a symbiotic relationship with the tree, as phomalone shows toxicity to two major aspen pests, *Phellinus tremulae* and *Ophiostoma crassivaginata* (the aspen decay fungus and the blue strain fungus). Indeed aspen trees afflicted with black galls seem immune to attack by other fungi.[81]

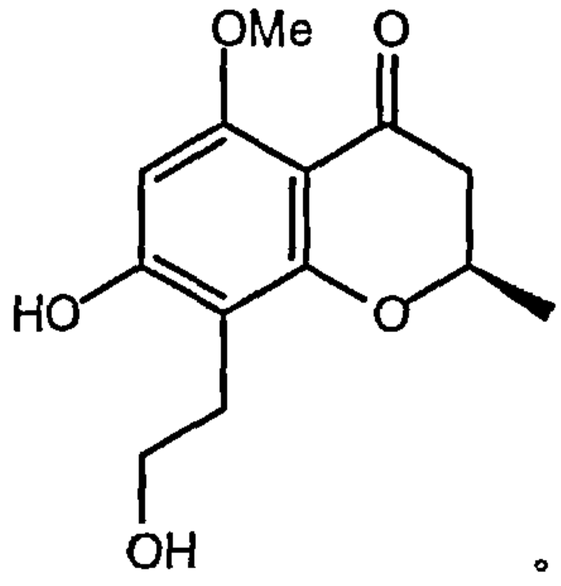
In a 1973 paper Takashi *et al.* threw some doubt on the structure of LL-D253α shown above, and suggested that given below, **2-18a**. They also isolated the compound from several other *Phoma* ssp.[82]



2-18a



2-21



2-18b

Phomalone can readily be seen to be a reductively ring opened **2-18a**. In 1984 McIntyre and Simpson reported a final structural revision of LL-D253α to **2-18b**,[83] and they went on to prove this by synthesis.

2.3.2 LL-D253α and its biosynthesis

Simpson *et al.* went on to produce a thorough paper proposing a biosynthetic pathway for LL-D253α.[84] They found that the structure appeared to be entirely polyketide, as when the fungus was grown in a medium containing labelled acetate the metabolite contained the remnants of six separate acetate groups. The postulated route for the biosynthesis of LL-D253α starts from the combination of two preformed polyketides, as shown below (figure 2.3.1).

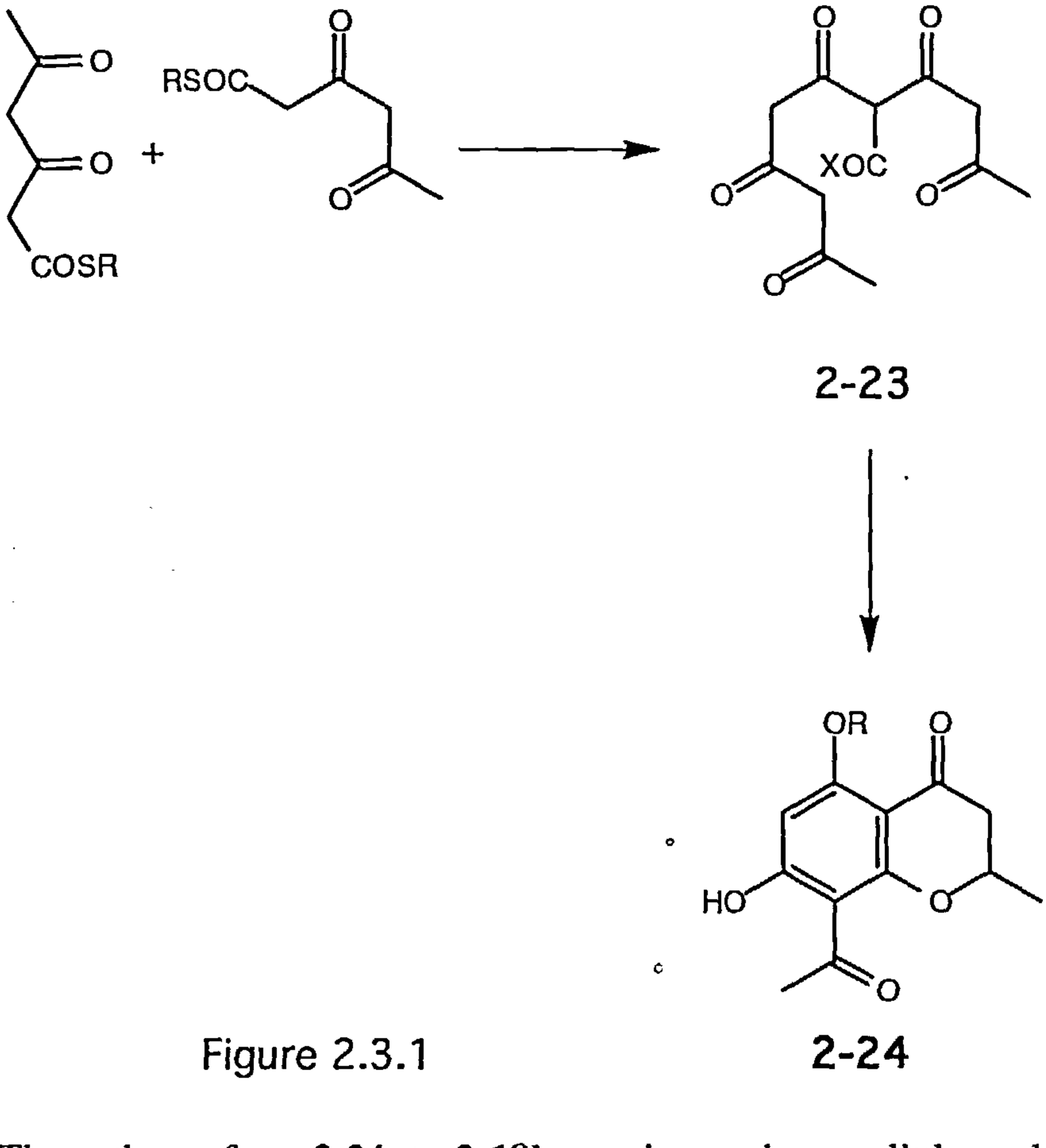


Figure 2.3.1

The pathway from **2-24** to **2-18b** remains, perhaps, a little unclear as at some stage oxygens on the pendant group seem to exchange. At any rate the 'parent' polyketide for LL-D253α seems certain to be **2-23**.

2.3.3 Synthesis of LL-D253α

Simpson et al. also published a synthesis of LL-D253α,[85] though as they give no stereochemical data, one must assume it to be racemic. In this comprehensive paper they synthesised all the likely structural contenders for LL-D253α in order to obtain structural proof. We shall concentrate only on the synthetic route leading to the final structure **2-18b**.

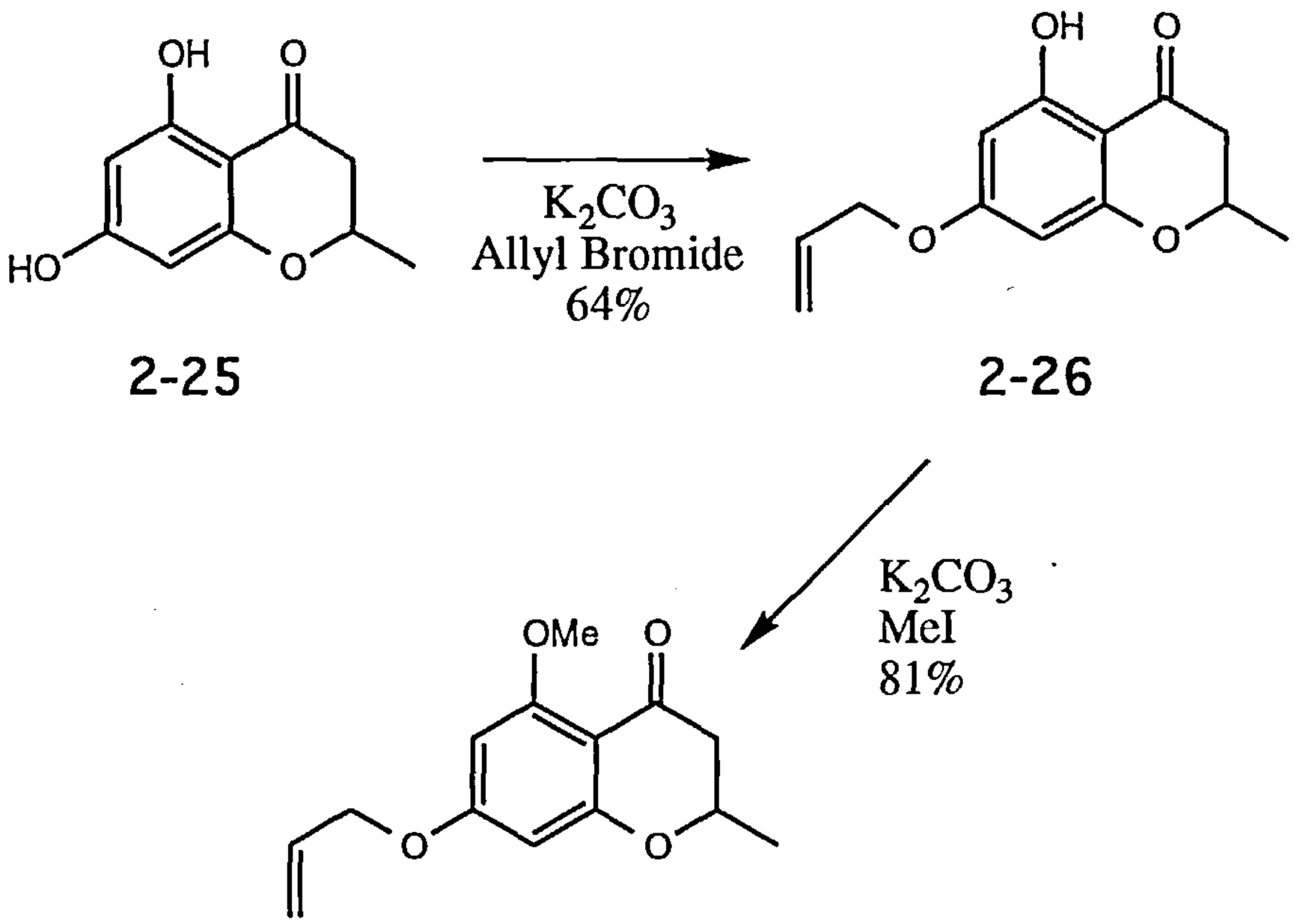
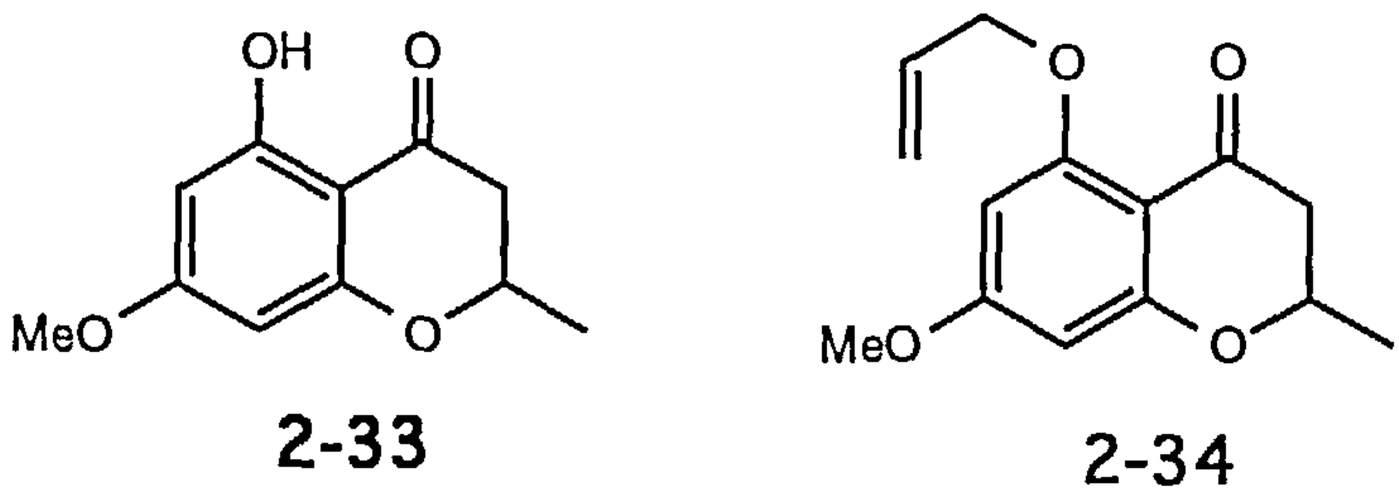


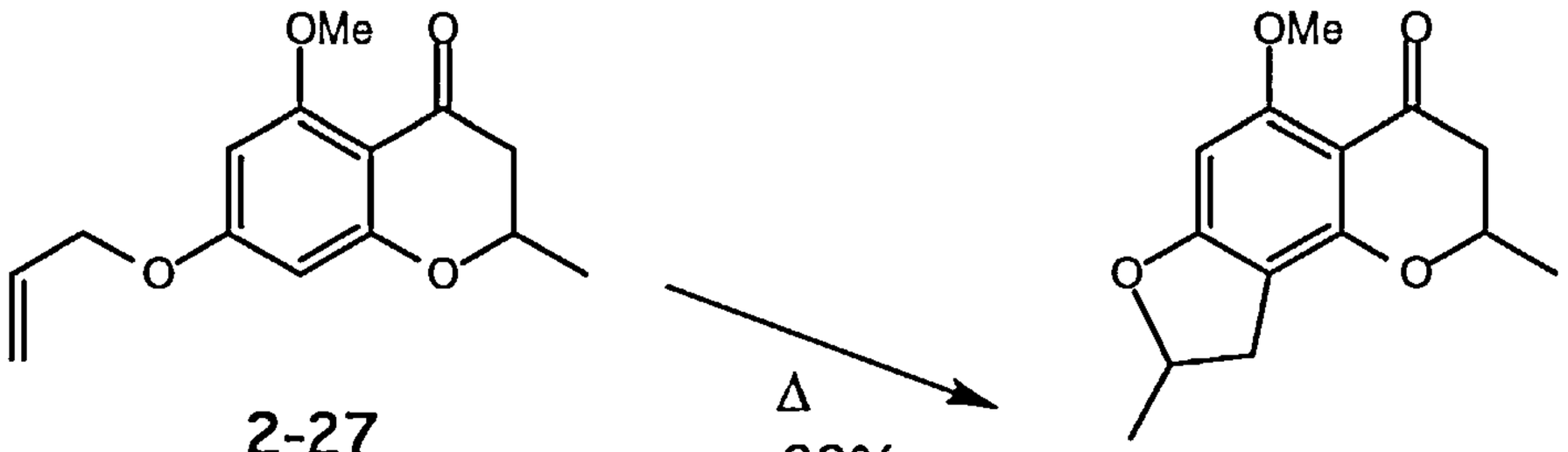
Figure 2.3.2

Simpson chose as his starting point 2-methyl-5,7-dihydroxychromanone **2-25**. This was then selectively allylated at the 7-position to give **2-26** in 64% yield. The reason for this selectivity is that the 5-hydroxyl has a strong hydrogen bond to the chromone carbonyl, and is therefore less acidic. The weakly basic allylation conditions therefore favour 7-allylation. Methylation of the vacant site then follows, to give **2-27** in 81% yield (figure 2.3.2).

The relative yields for allylation and methylation appear to be the same regardless of position. Simpson's preparation of **2-33** proceeds in 96% yield, that of **2-33** in 62% yield.



The O-allylchromanone **2-27** is then thermally rearranged to give the 8-allyl Claisen product, **2-28** (68%) and the by-product dihydrobenzofuran **2-29**. This was followed by benzyl protection of the 7-hydroxyl to give **2-30** (100%) (fig. 2.3.3).



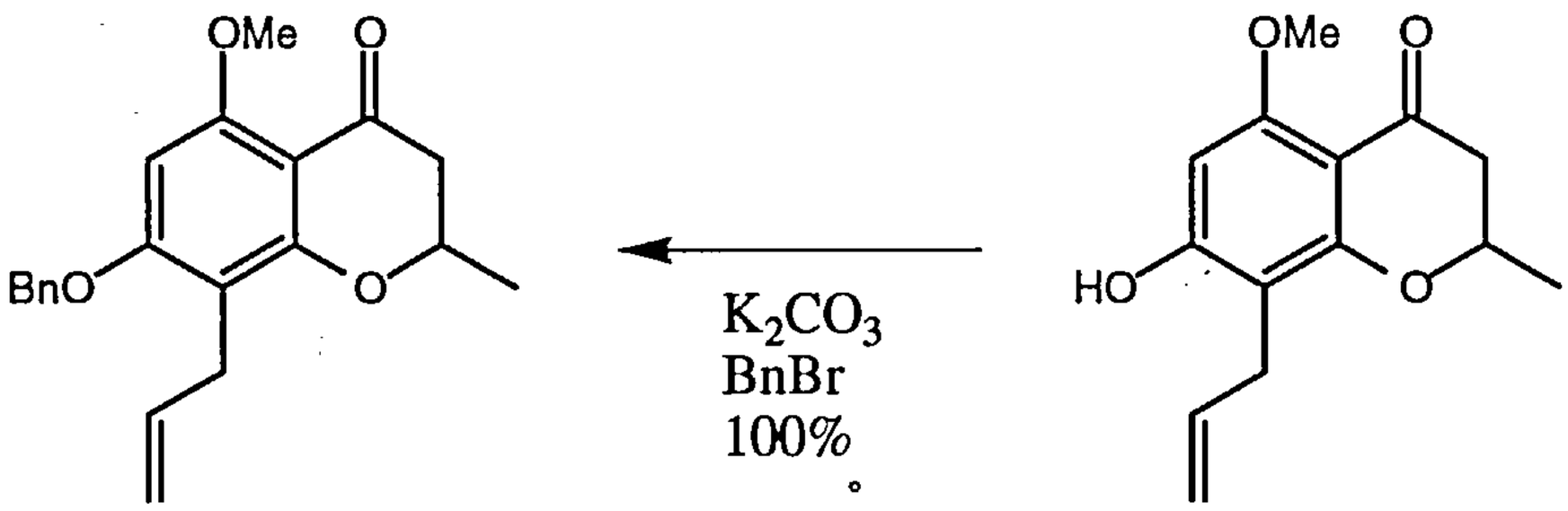
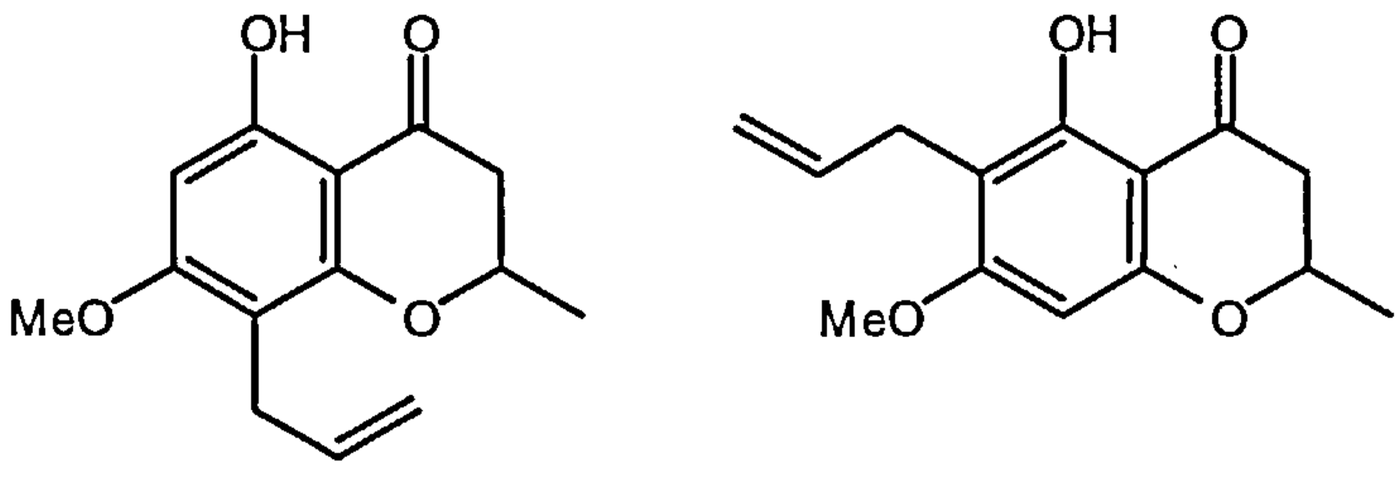


Figure 2.3.3

Simpson notes that the Claisen rearrangement of 7-allyloxychromanones has been observed to be very selective for the 8-allylchromanone product.[86] The similarly conducted rearrangement of **2-34** leads to two isomers **2-35** and **2-36** (for a discussion of the mechanism of this *para* Claisen rearrangement see chapter 6).



The allyl group of **2-30** is cleaved in a two stage process with osmium tetroxide to **2-31** in 94% yield and then periodate to give **2-32** in 25% yield. The aldehyde **2-32** is then reduced with borohydride and deprotected in 45% yield over two steps to give **2-18b**. This compound was found to be identical with the natural product (figure 2.3.4).

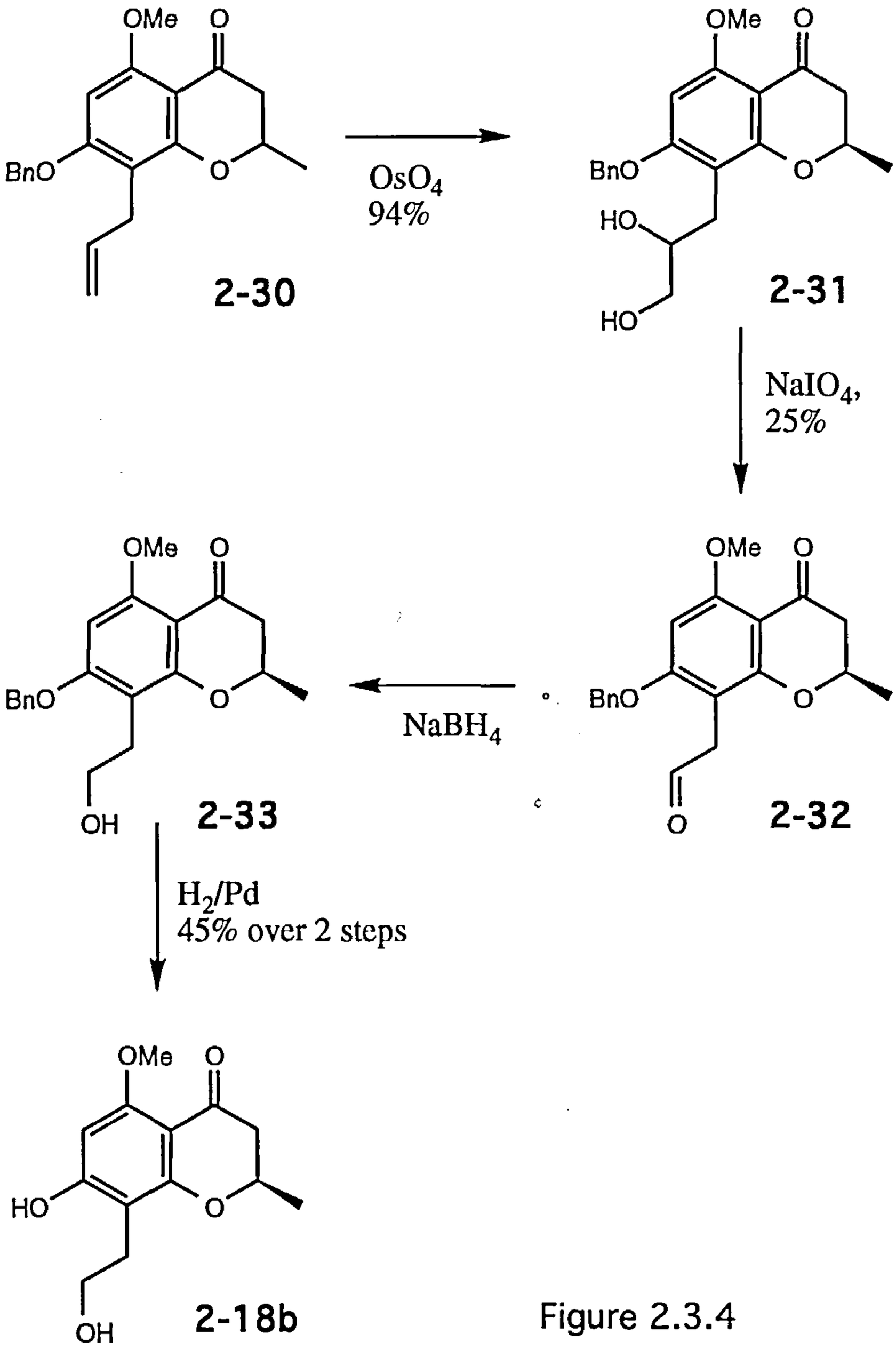
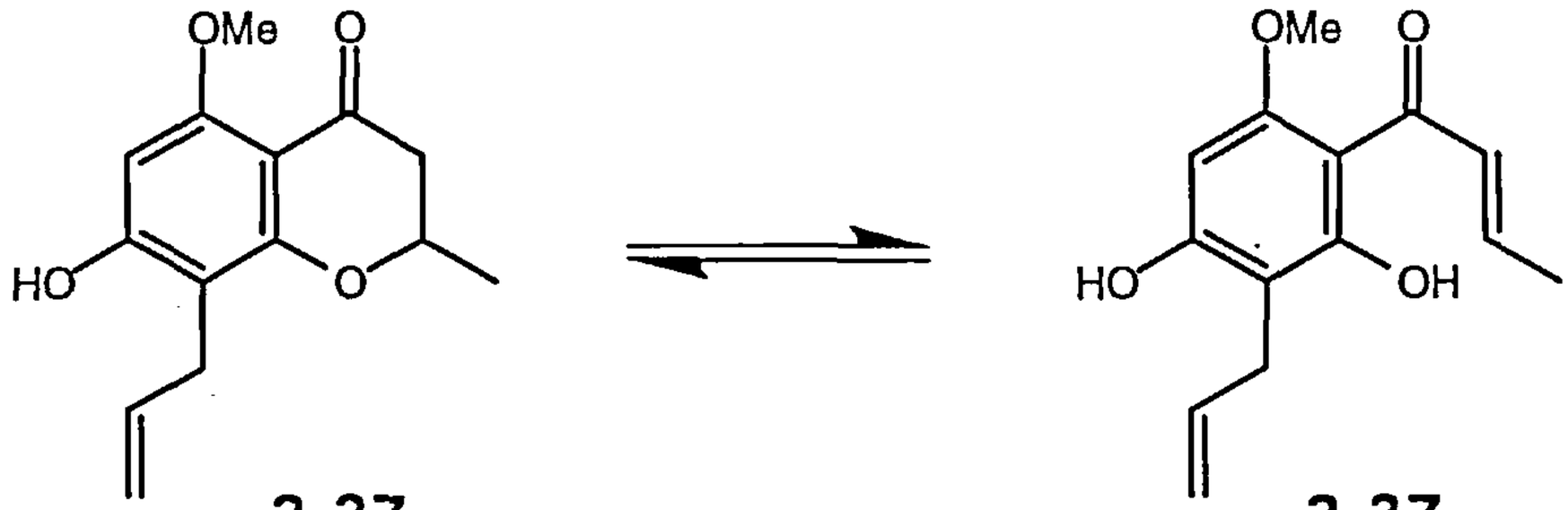


Figure 2.3.4

This synthesis is practical and relatively short. Many problems are avoided by choosing to start with the chromanone group pre-formed, but this does lead to its own conundra. The main one is that when the O-allyl compound **2-27** is subjected to strong heat in a sealed tube both **2-28** and **2-29** result. This shows that the conditions are forcing enough to lead to the addition of an alcohol to a double bond, a reaction that generally requires an acid catalyst. Another reaction that could be foreseen in these conditions is the ring opening of the chromanone to give the α,β-unsaturated butylphenyl ketone **2-37**. Assuming that an equilibrium of the type shown exists, any chirality at the chromanone 2-carbon would racemise. In fact such equilibria are

known, for example in the 2-hydroxychalcone/flavanone equilibrium,[87] though these normally require an acid catalyst. Such racemisation effects might explain why this synthesis was published as racemic.



2-27 2-37

One other notable point is that osmium tetroxide is used here in a stoichiometric manner, not as a catalytic oxidant with a co-oxidant. The Upjohn conditions for osmylation[88] have become so ubiquitous that this is noteworthy. Apparently the substrate resisted the catalytic approach, giving mainly starting material. This in itself can be counted a setback for the method, for osmium tetroxide is extremely toxic and rather expensive.

These considerations lead to the conclusion that another synthesis of LL-D253α and related compounds, preferably in a chiral non-racemic form, would be of benefit.

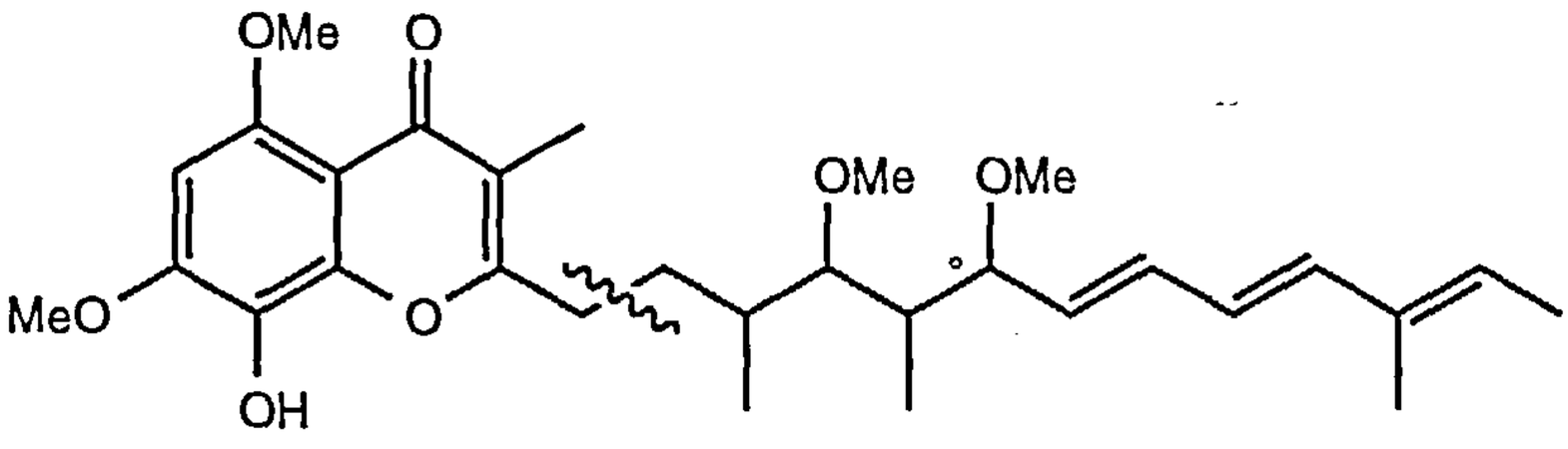
Chapter 3

Stigmatellin Fragment A: an approach via Vilsmeier formylation and standard Friedel-Crafts methodology.

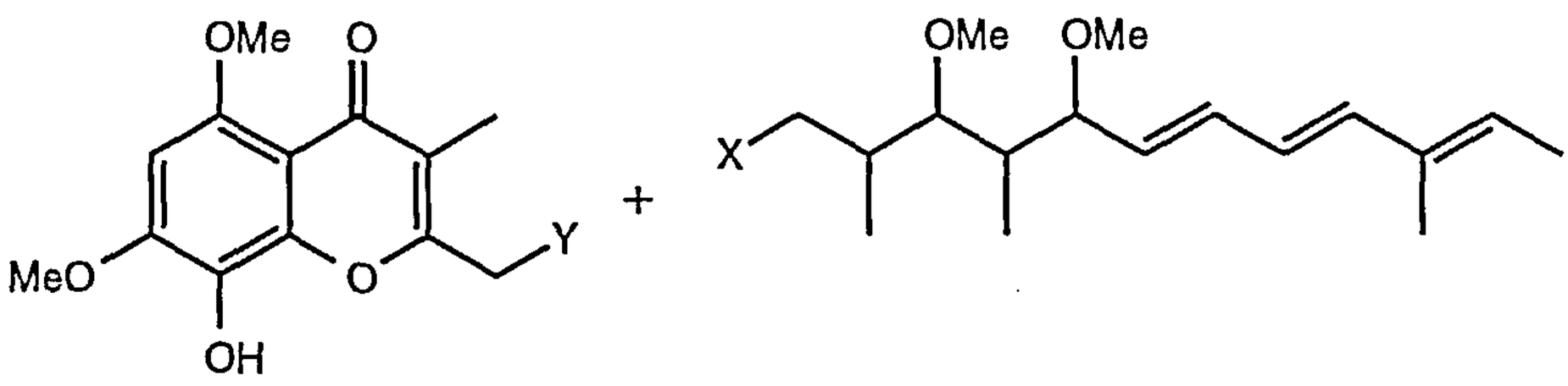
3.1 Introduction and retrosynthetic analysis

3.1.1 Introduction

Stigmatellin **3-1** is, as was discussed earlier, a large chromone metabolite of *Stigmatella Aurantiaca*, which consists of a two main subunits, a chromone ring system, **3-2** and a side chain, **3-3**. Of these two our group had the task of constructing the chromone ring system, which could later be used in coupling studies. See figure 3.1.1.



3-1



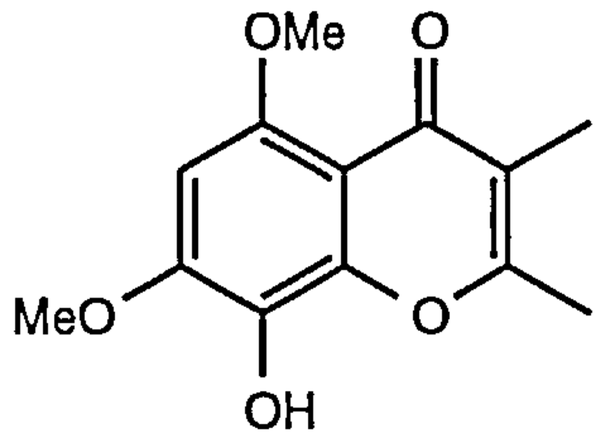
3-2 **3-3**

X,Y=notional groups to assist in coupling

Figure 3.1.1

The easiest notional group to attach in the Y position shown is a proton, as the 2-methyl protons are vinylogous to the ketone group of the chromone, and therefore

relatively acidic. This would simply require a halide or tosyl leaving group in the X position. Therefore our target was initially the chromone **3-2** below.

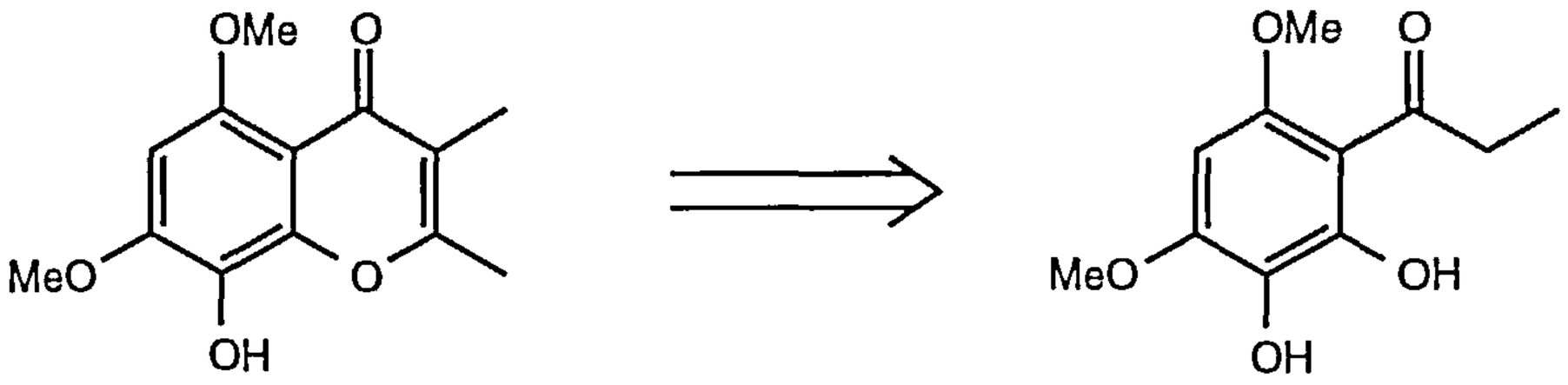


3-2

3.1.2 Retrosynthetic analysis.

Retrosynthetically this chromone subunit has several interesting features. The 2,3-dimethylchromone base skeleton has been synthesised before, both by usual methods[89] such as sodium acetate/acetic anhydride and by more rigorous and precise conditions[90] such as sodium hydride/DMSO followed by sulphuric acid. Each set of conditions has its merits. Because of the work of Höfle *et al.*,[91] we were aware that a modified version of the sodium acetate/acetic anhydride conditions could be successfully applied to this case. We felt that we should try out the Hirao methodology, which uses far less of the precursor required for the 2-substituent and therefore is easier to apply to a wide range of substrates, whilst holding the other method in reserve. Both methodologies require the same starting material, 2,3-dihydroxy-4,6-dimethoxypropiophenone, **3-4**, see figure 3.1.2. Manufacture of this key intermediate was therefore our first concern. Höfle's methodology began with a Baeyer-Villiger oxidation, but we hoped to develop an alternative synthesis that would not require such strongly oxidising conditions or the preparation of a symmetrical aryl diketone.

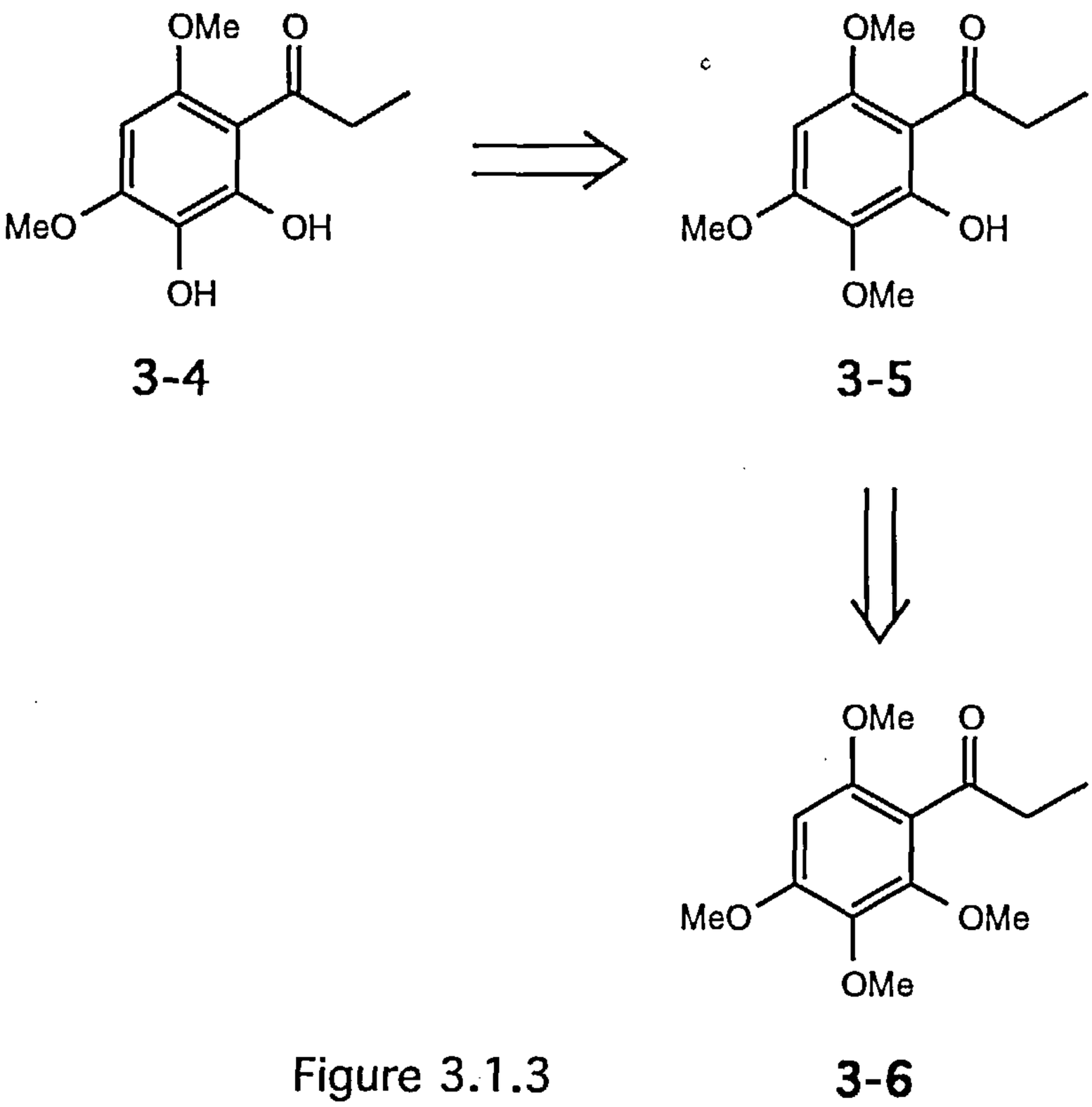
It is known that Lewis acids of various types will selectively demethylate polymethoxyacetophenones in the 2 or 6 positions. This is due to a chelation effect which will be discussed in a later chapter. A system such as **3-4** which contains several oxygenated sites and an aryl alkyl ketone could, in principle be prepared from the polymethoxy compound by a system of selective demethylation.



3-2 3-4

Figure 3.1.2

Such a scheme would have as its intermediate **3-5** and as its starting point **3-6**, see figure 3.1.3. Such a selective system of demethylation has, in fact, been proposed before.



3-4 3-5 3-6

Figure 3.1.3

Paul[92] followed reports of monocleavage of 2,3,4-trimethoxybenzaldehyde A using aluminium chloride in toluene[93] and ether[94] by doing a thorough study of the various compounds formed (figure 3.1.4 and table 3.1). He found that the major product in ether was C, particularly if a slight excess of aluminium chloride was used. To

circumvent this he used benzene as a solvent and could produce an 85% yield of B, and an 8% yield of D if the mixture was refluxed. We were interested in this result, though the necessity of using large quantities of benzene, and the low yield of D were slightly offputting. We also located two papers by the Horton group in the 1950s that showed selective 2,3-demethylation in 2,3,4-trimethoxyacetophenones using HBr/Acetic acid.[95 96] The yield for the production of 2,3-dihydroxy-4,6-dimethoxyacetophenone from 2,3,4,6-tetramethoxyacetophenone was 24% over two steps.

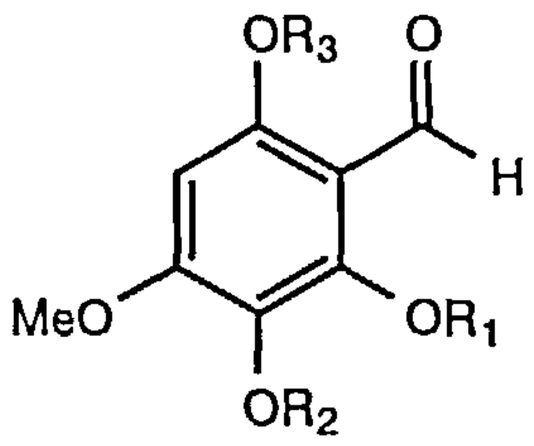


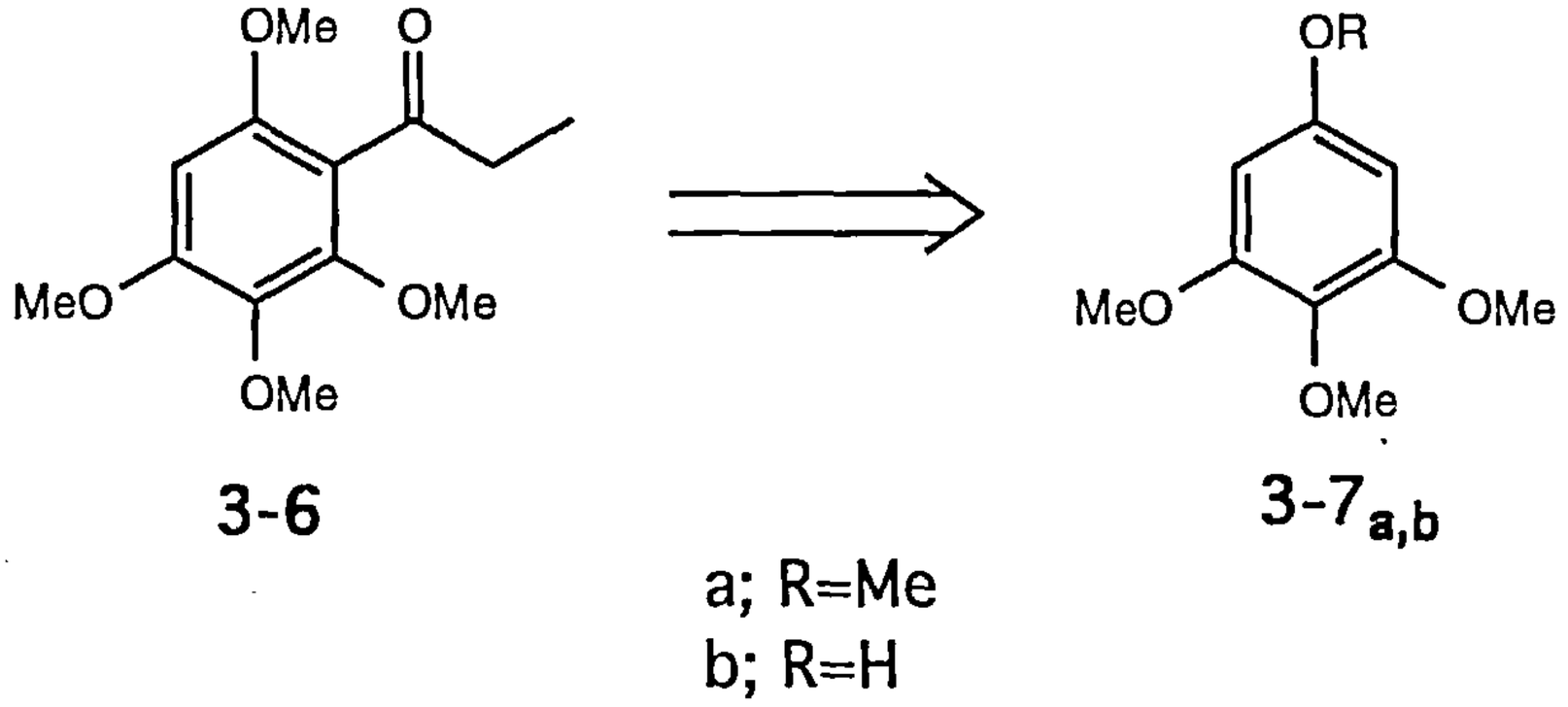
Figure 3.1.4

Compound	R_1	R_2	R_3	Yield/%
A	Me	Me	Me	n/a
B	H	Me	Me	86
C	H	Et	Me	38-55
D	H	H	Me	8

Table 3.1

This seemed quite promising, though we needed to prepare **3-6**. The possibility of a short-cut direct to **3-5** was raised by a later paper by Horton[97] which involved a boron trifluoride catalysed acylation/demethylation, but the abundance of byproducts which could be formed under slightly differing reaction conditions made us wary. We decided to try for a standard Friedel-Crafts or Fries approach to the desired propiophenone, see figure 3.1.5. We knew that many of the more usual Lewis acids, such as aluminium trichloride, boron trichloride *etc.* could demethylate our starting

ether **3-7**, so we sought alternatives. These came in the form of iodine,[98] polyphosphoric acid[99] and zinc chloride. We decided to try each of these.



3-6 3-7$_{a,b}$

a; R=Me
b; R=H

Figure 3.1.5

3.1.2.1 Friedel-Crafts route

The Friedel-Crafts reaction is an acylation of aryl groups where the aromatic ring is attacked by an externally generated electrophile. This electrophile is generated from an appropriate acylating group, often the acid chloride or anhydride, by the action of a Lewis acid. The complex thus formed may be expressed as shown below, figure 3.1.6.

The attack by the aromatic ring on this structure leads to an elimination, in this case of HCl, to rearomatise, see figure 3.1.7. The reaction normally requires an activated ring, such as toluene or chlorobenzene. Once one addition has taken place the ring is deactivated so that further additions are rarely noted.

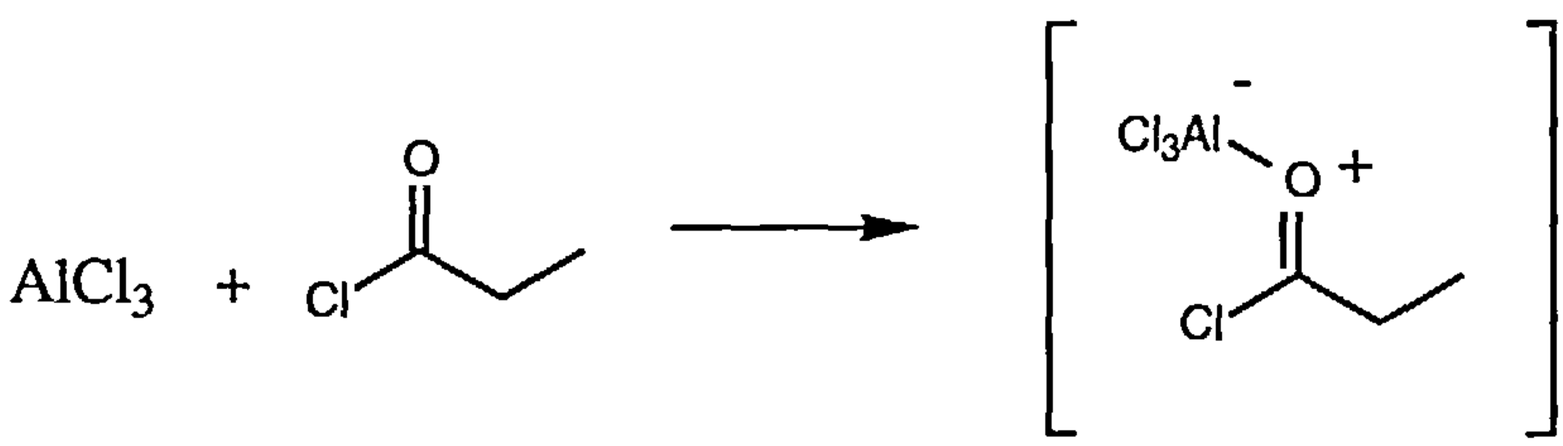


Figure 3.1.6

In our case the substrate for this reaction would be **3-7a**, which is an extremely activated compound. The dangers here lie in the possibilities of disubstitution or uncontrolled demethylation during the reaction.

The Friedel-Crafts reaction is often modified in the case of phenols to the Fries rearrangement.

3.1.2.2 Approach *via* the Fries rearrangement

The Fries rearrangement can be considered as a subset of the Friedel-Crafts reaction where the substrate and the acylating agent are one and the same molecule. The mechanism for the Fries rearrangement is given in chapter 6.

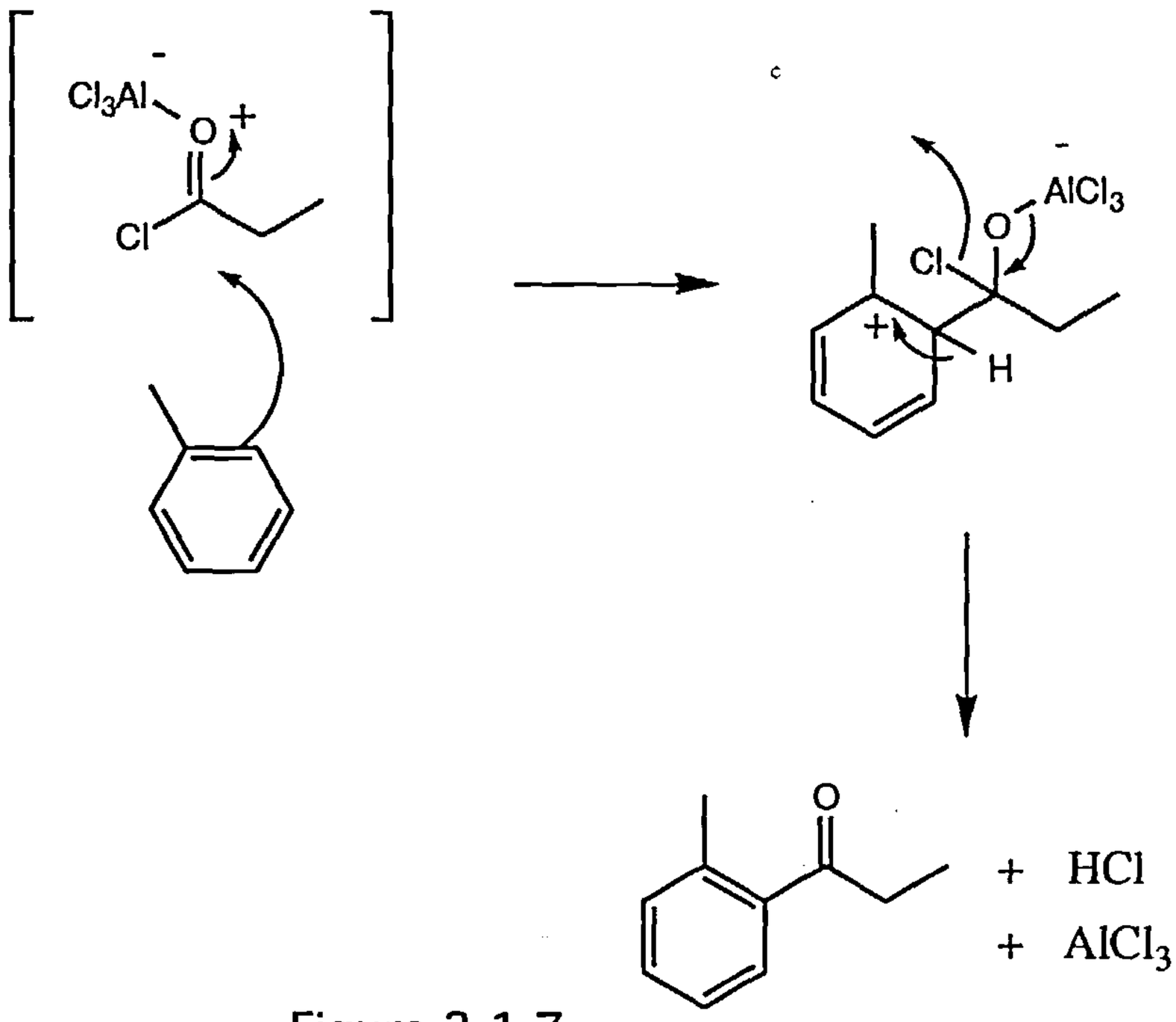


Figure 3.1.7

The rearrangement is carried out on the phenyl ester of the desired substrate, so that the route for this synthetic approach in a retrosynthetic sense appears as in figure 3.1.8. **3-7b** is acylated, then rearranged to **3-8** and methylated to give **3-6.** The starting point for this synthesis is **3-7b**, which is also the starting material for **3-7a**,

and as this compound is readily available, we therefore have our first retrosynthetic analysis.

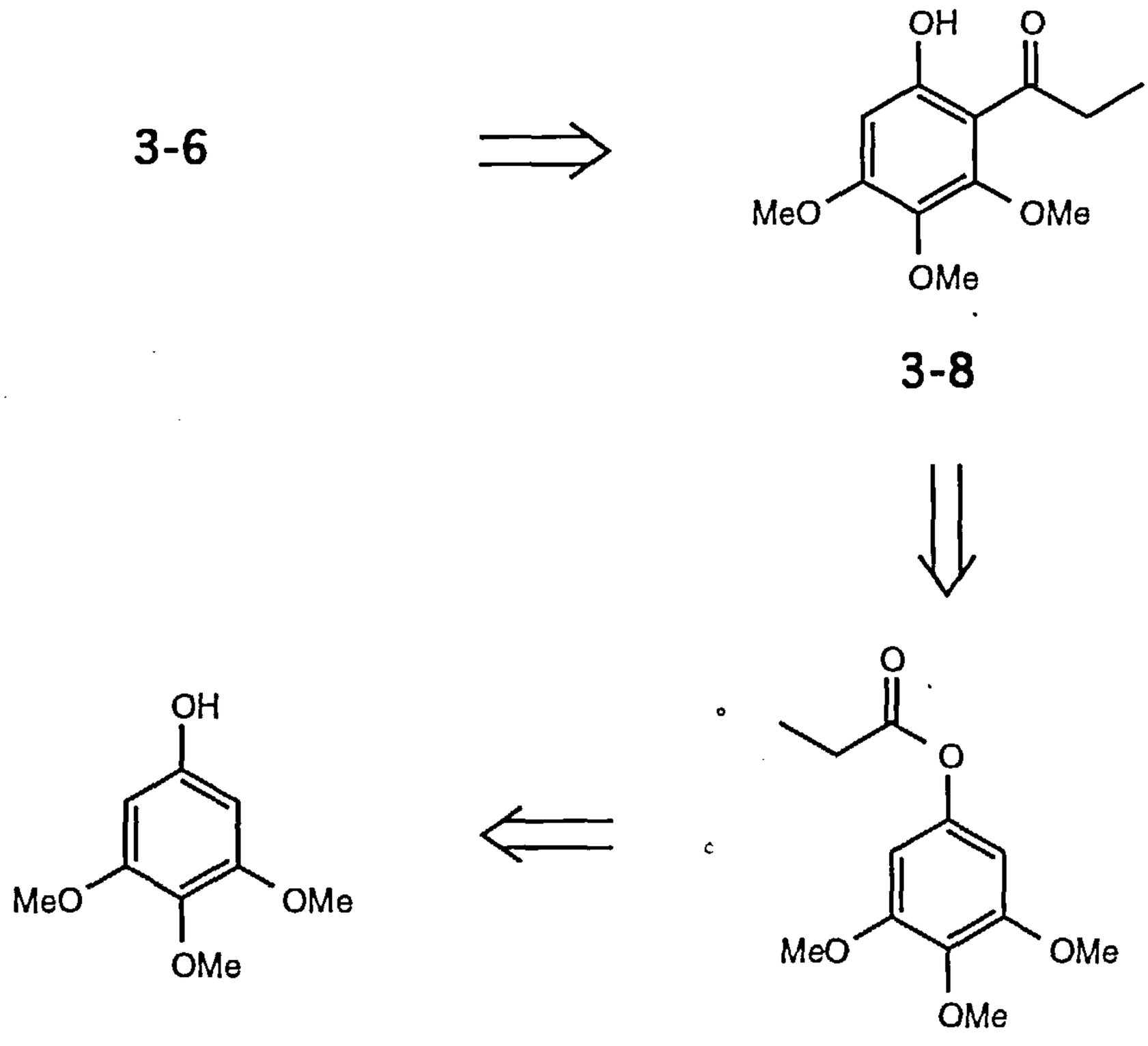
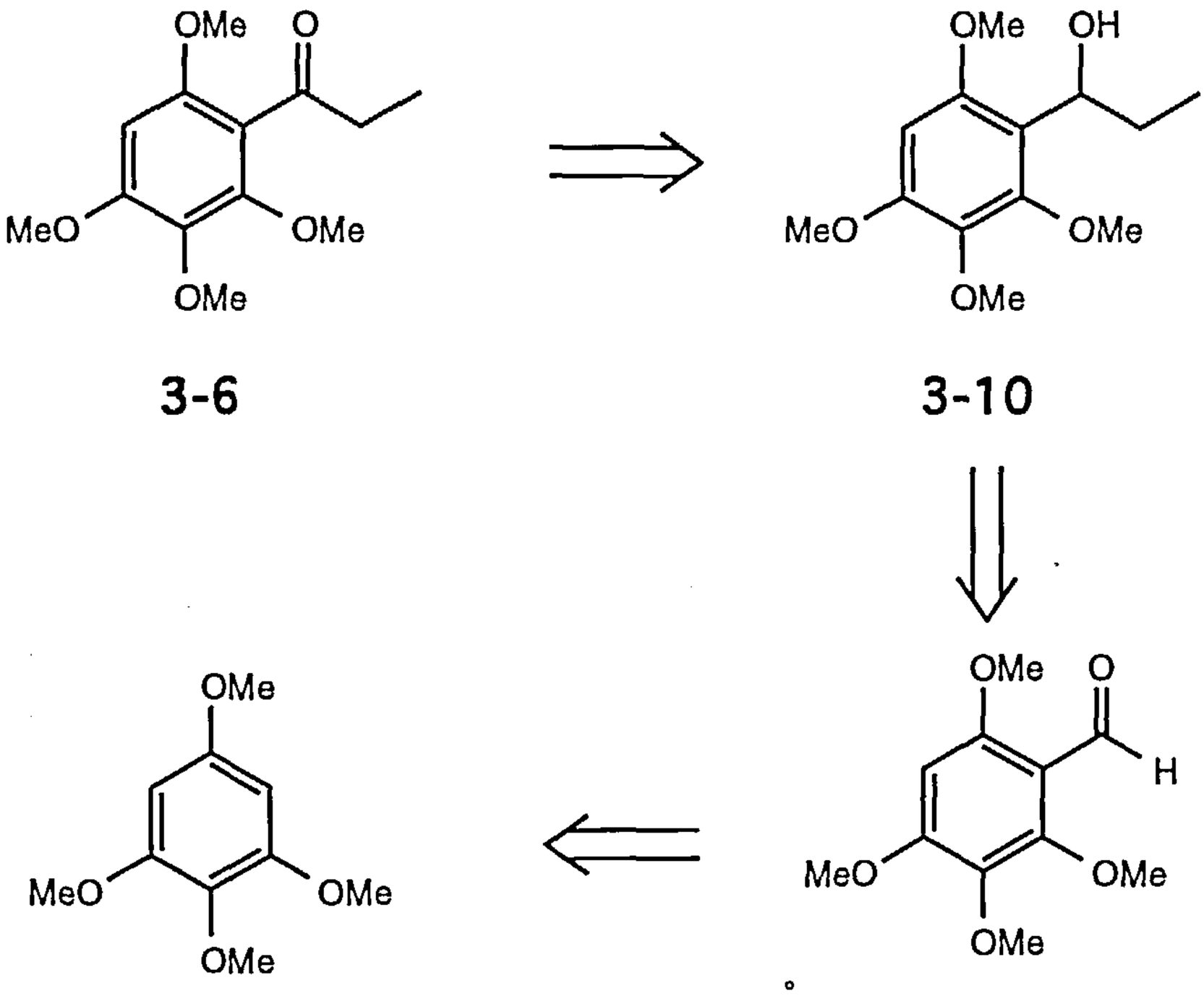


Figure 3.1.8

3.1.2.3 Approaches via formylation reactions

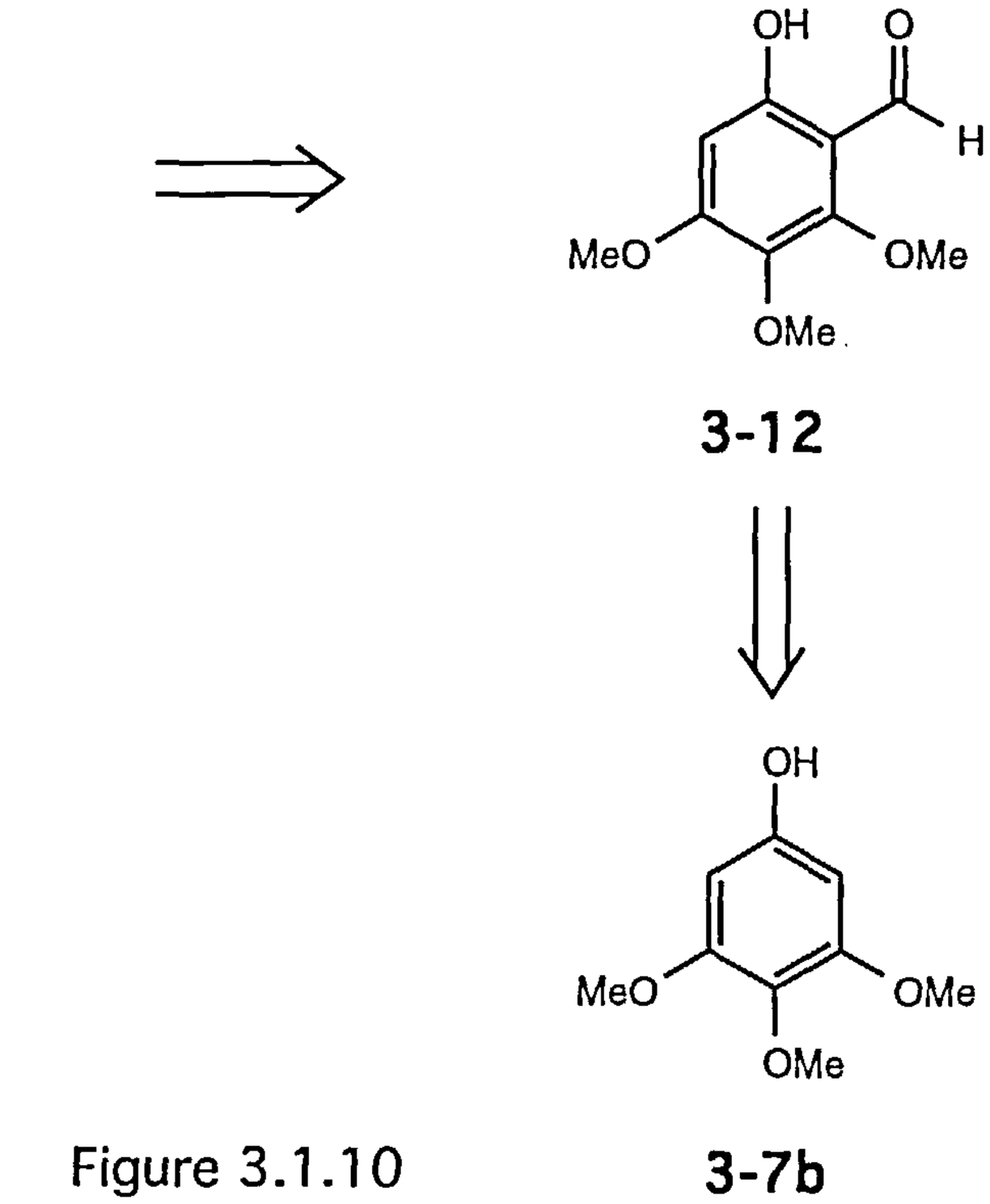
We felt it wise to have a third approach to **3-6**. To our minds it could be approached *via* the formylation of **3-7a** to give **3-11** followed by an attack by ethyl magnesium bromide to give **3-10**. Subsequent oxidation would complete the route to **3-6**, see figure 3.1.9.



3-6 3-10 3-7a 3-11

Figure 3.1.9

The danger with this synthesis lay in the fact that our substrate is inherently very susceptible to oxidation. Therefore any oxidative process would have to be specific and mild.



3-12 3-7b

Figure 3.1.10

In fact **3-11** could also be prepared from a formylation of **3-7b** followed by a methylation, see figure 3.1.10. This allows for possible differences of reactivity and stability between **3-7b** which is available commercially, and **3-7a** which is not.

It only remained, therefore, to find a suitable formylation reaction. Of the many that are available three stand out: the Vilsmeier, the Gattermann, and the Reimer-Tiemann reactions.

The Vilsmeier formylation utilises an electrophile generated by the action of phosphoryl chloride on N,N-dimethylformamide. This reaction is considered fairly general but gives best results with phenols. It has been applied to 2,6-dioxygenated systems with some success, giving an overall formylation of 80% with 3,5-dimethoxyphenol,[100] though as two isomers.

The Gattermann manifold of reactions is based around electrophiles generated from cyanides, either HCN or a metal cyanide such as zinc (ii) cyanide. The mechanism is not much researched but the electrophile is presumed to be a protonated cyanide structure of some kind. This has also been applied to the synthesis of 2,6-dioxygenated aromatic aldehydes with 2,4-dihydroxy-6-methoxybenzaldehyde being synthesised in 50% yield.[101] The drawback with this procedure is that any system involving use of metal cyanides, especially in strongly acidic media, has to be approached with caution.

The Reimer-Tiemann reaction involves the use of dichlorocarbene, generated from aqueous base and chloroform, as the electrophile. It is a powerful method for the formylation of phenols, but typically gives yields of less than 40%. An improvement in the way of a photo-induced Reimer-Tiemann reaction has been reported[102] but this was reported as giving only 20% yield with our substrate.

We decided, therefore, that the Vilsmeier formylation was the first choice. A mechanism appears below, figure 3.1.11.

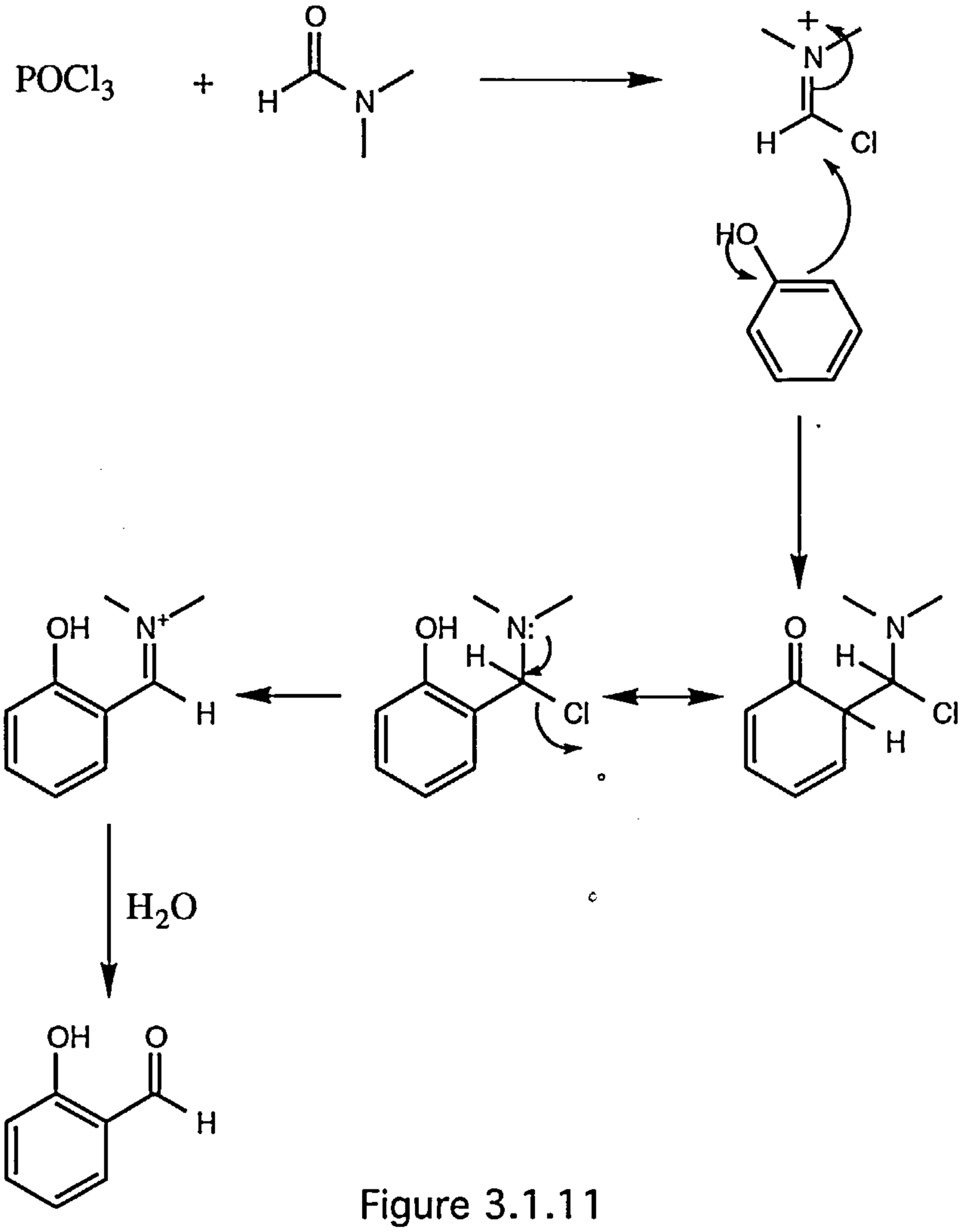
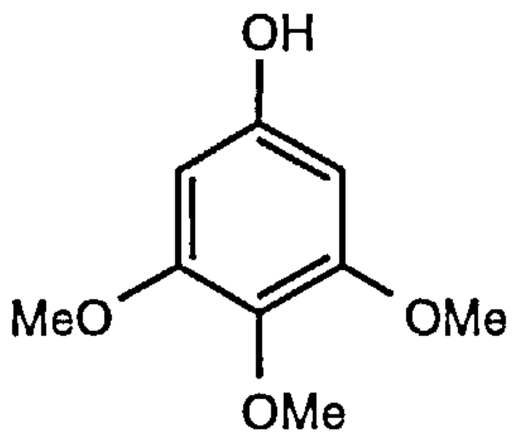


Figure 3.1.11

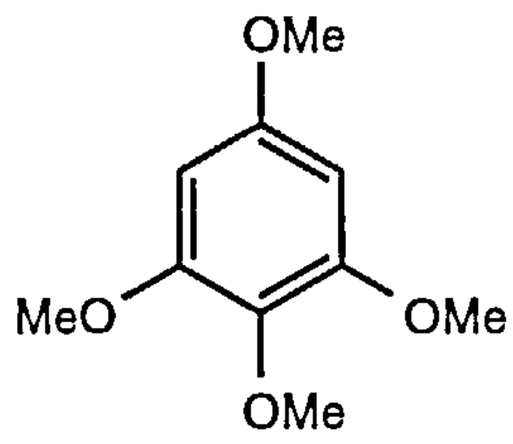
Thus with the selection of the Vilsmeier approach we had our third route to **3-6** largely sketched out. It remained to select an oxidant for the **3-10** to **3-6** transformation. We chose two possibilities, manganese(iv) oxide, which is considered specific for benzylic alcohols, and tetra-n-propylammonium perruthenate, a catalytic oxidant with N-methylmorpholine-N-oxide as the co-oxidant.[103] This latter system showed some promise due to its mildness. With this in mind we proceeded with the synthesis.

3.2 Results and discussion

3.2.1 Classical Friedel-Crafts and Fries approach.



3-7b

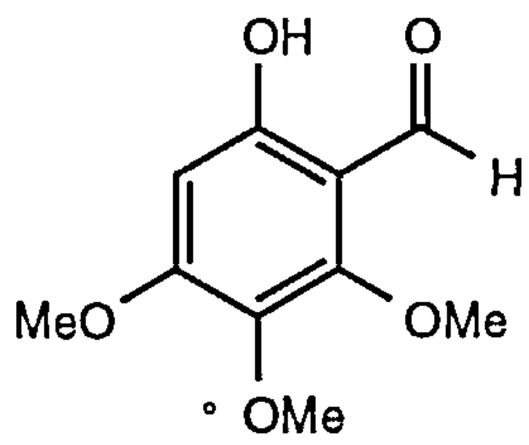


3-7a

For the Friedel-Crafts route commercially available **3-7b** had to be methylated up to **3-7a**. Methylation of **3-7b** was undertaken succesfully in acetone with dimethyl sulphate/potassium carbonate in 54% yield. The product, **3-7a** proved to be unstable in air at room temperature. This was ascribed to its polymethoxylated nature, which renders the ring extremely electron rich and opens up possibilities of undesirable spontaneous oxidations. It was felt that this compound was best used soon after synthesis. Our first attempts at Friedel-Crafts chemistry, we decided, would be acetylations rather than propionylations. This was partly due to the more ready availability of the various acetylating agents around the laboratory, partly to the simplicity of the acetyl group to NMR and partly due to the fact that more acetylations seem to have been done on our substrate than other variants. We were aware that we were searching for a compromise between power of Lewis acid catalysis and selectivity to keep the methoxy groups intact. We attempted the reaction with iodine, zinc chloride and polyphosphoric acid. The only catalyst that showed a reaction was iodine, which seemed to give uncontrolled diacetylation. This, we reasoned, was the result of the extremely active nature of the ring. The fact that iodine gave no monoacetylated product showed that the approach was unworkable. In our hands the polyphosphoric acid catalyst gave no product at all, despite the literature claims.[104] Likewise zinc chloride proved ultimately disappointing as a catalyst. We decided to abandon this area of chemistry in order to concentrate on the Vilsmeier route.

3.2.2 Vilsmeier approach to **3-6**

The Vilsmeier reaction performed on **3-7b** provided the desired product, **3-12**, in 52% yield. This compound was found to give unusual coloured solutions, particularly in dichloromethane. The very act of tipping it from one clean flask to another could change its colour from red to blue.



3-12

The compound was, however, stable to the atmospheric oxygen it encountered at room temperature. A peculiarity of the NMR spectra of *ortho*-hydroxy arylcarbonyl compounds is worth mentioning here. A strong hydrogen bond exists between the carbonyl oxygen and the phenolic hydrogen, which results in the compounds having a sharp singlet, often in the region of δH 12-15 ppm. for the hydroxyl proton. This peak is often integrable, and provides a useful tag. The same bond means that the acidic behaviour of the phenol is greatly curtailed. One could remove **3-7b** from a dichloromethane solution by extracting with 10% potassium carbonate solution. To effectively do the same to **3-12** would require 30% potassium hydroxide. Rather than attempt a methylation of this compound, therefore, which would require effective deprotonation, we attempted a formylation of **3-7a**, which proceeded in 40% yield, giving a direct route to **3-11** see figure 3.2.1. This compound did not exhibit the multicoloured behaviour of its sibling **3-12**.

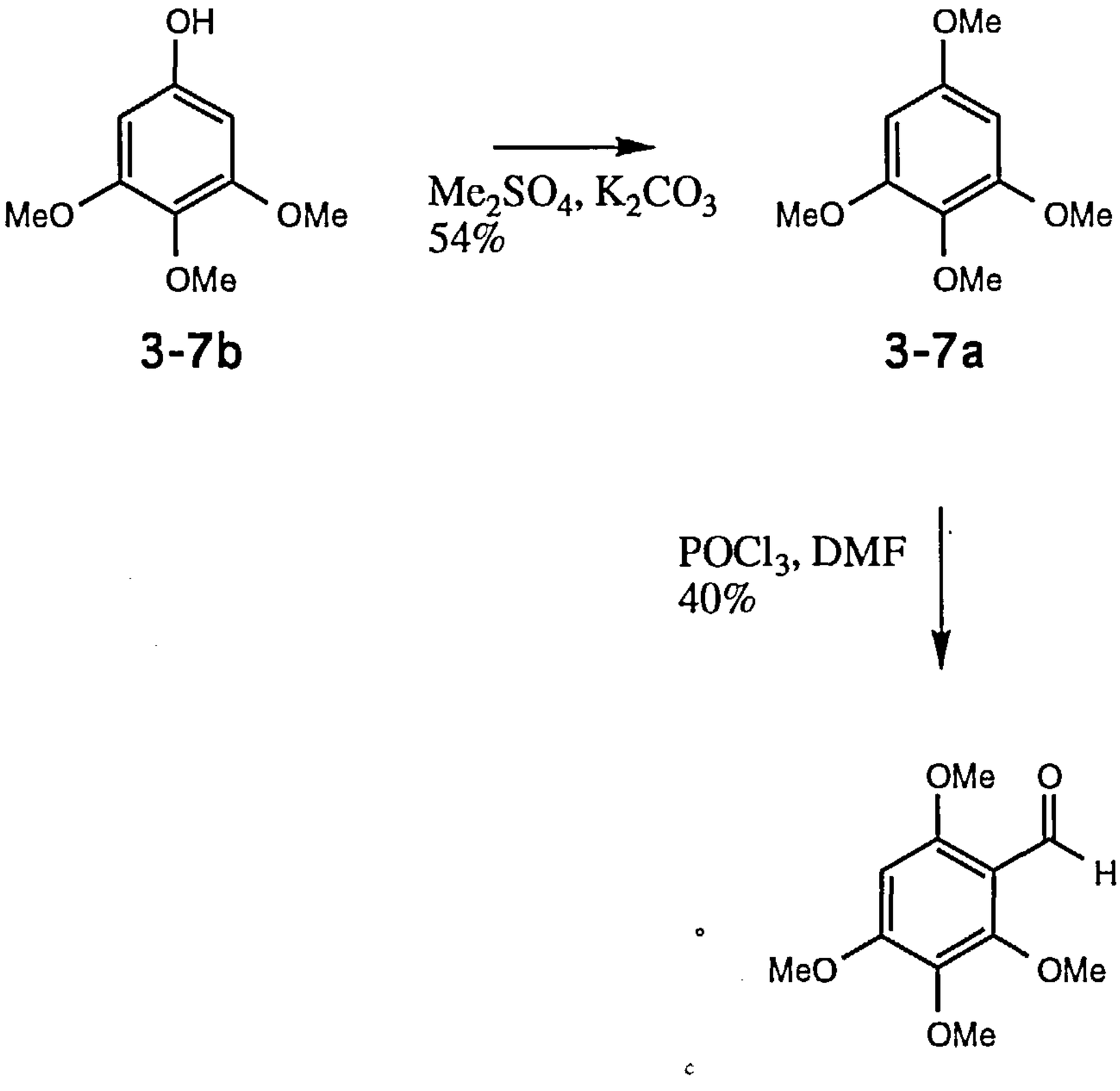


Figure 3.2.1

The aldehyde **3-11** proved to be stable to air, the carbonyl reducing the activity of the ring in comparison to **3-7a**. We therefore proceeded to attempt the nucleophilic attack with ethyl Grignard necessary to bring about the transformation to **3-10**.

The attack on **3-11** proceeded in 70% yield to give a mixture of the desired **3-10** and a variety of monodemethylated products, see figure 3.2.2. These side reactions occurred to varying extents even when using the freshest Grignard reagent. We realised that the demethylating agent would be magnesium bromide from the Grignard mixture, and that the Grignard is in an equilibrium. This can be expressed in the form:

and is temperature dependent. This greatly influences the outcome of the reaction.

The product, **3-10** itself is not very stable towards oxygen, having no carbonyl electron withdrawing group to stabilise the ring. We therefore chose to oxidise up to **3-6** in a controlled manner as soon as possible. After an abortive attempt with MnO_2 we attempted the catalytic perruthenate system, which proceeded in 54% yield from **3-10**, to give the desired **3-6**. Provided that the solution was dry and that molecular sieves were present the catalyst would achieve up to 200 cycles.

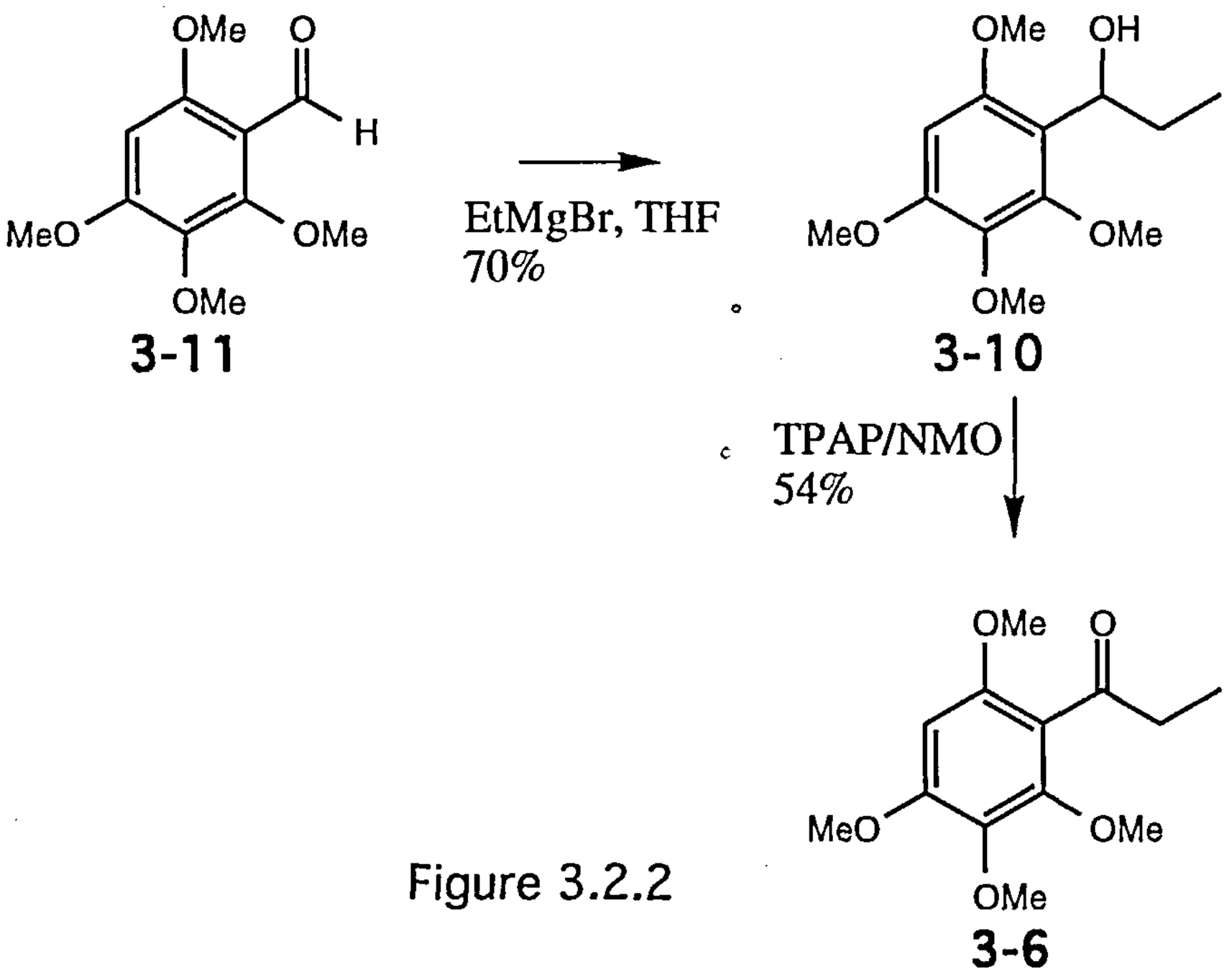


Figure 3.2.2

Thus we had a synthesis of our first stepping stone, **3-6**. It was however dependent on several unstable compounds and contained two undesirable steps, the Grignard addition which could lead to many byproducts and the Vilsmeier reaction, which could produce an amorphous mass which was difficult to separate. An attempt to run a Reimer-Tiemann reaction on our substrate led to a complex mixture of unidentified products, none of which were **3-11**. We therefore sought an alternative route to **3-6**.

Chapter 4

Stigmatellin fragment A: an approach via catalytic Fries/Friedel-Crafts chemistry

4.1 Introduction and retrosynthesis

As we have seen in the preceding chapter the difficulty in carrying out Fries or Friedel-Crafts chemistry on polymethoxylated substrates is in finding a balance between Lewis acid strength, in terms of ability to catalyse the reaction, and the tendency of a strong Lewis acid to demethylate the substrate. A further complication lies in the activity of the substrate, which may cause diacylation to occur. Traditional boron, aluminium or titanium based Lewis acids that form strong complexes to hydroxyl groups have been used in stoichiometric amounts[105, 106] and are universally demethylating agents for our substrate. Our attention was drawn to a group of Lewis acids which were stable and usable in water, formed no such strong complexes, and functioned in ratios of 1 mol%. These were the rare earth triflates. [107]

Our first use of these compounds was in the preparation of LL-D253α and baicalein trimethyl ether precursors, which will be discussed in later chapters, and experience there told us that the best approach was through a one-pot Fries type of reaction, see figure 4.1.1 below.

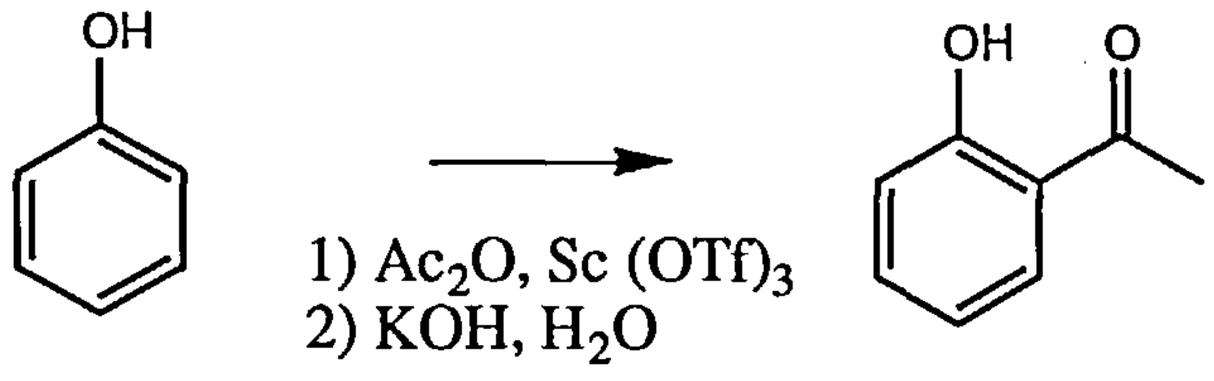
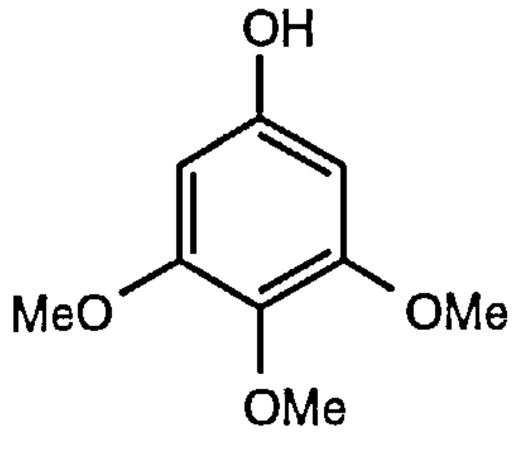
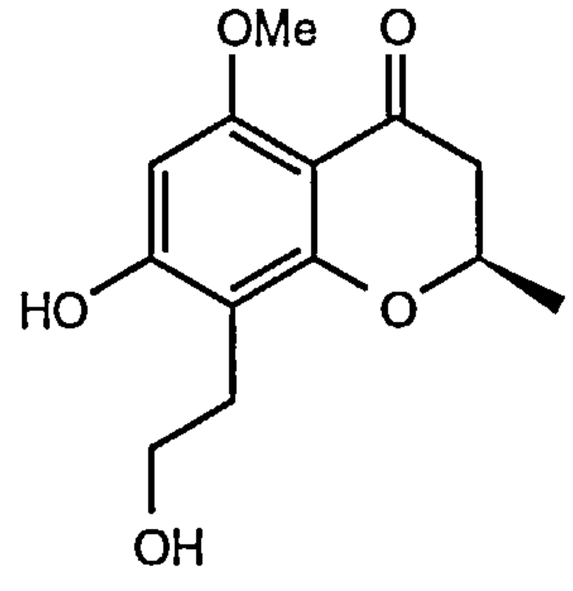


Figure 4.1.1

In our case this would be carried out upon 3,4,5-trimethoxyphenol, **3-7b**. We knew that it is necessary to treat the reaction as an equilibrium and stack it in favour of acylation with an excess of acylating agent. We were also aware that after hydrolysis the product and unreacted starting material would be easy to separate because of their differing polarities and acid/base behaviour. With this in mind we decided to proceed using propionyl chloride as the acylating agent, and scandium triflate as the Lewis acid.

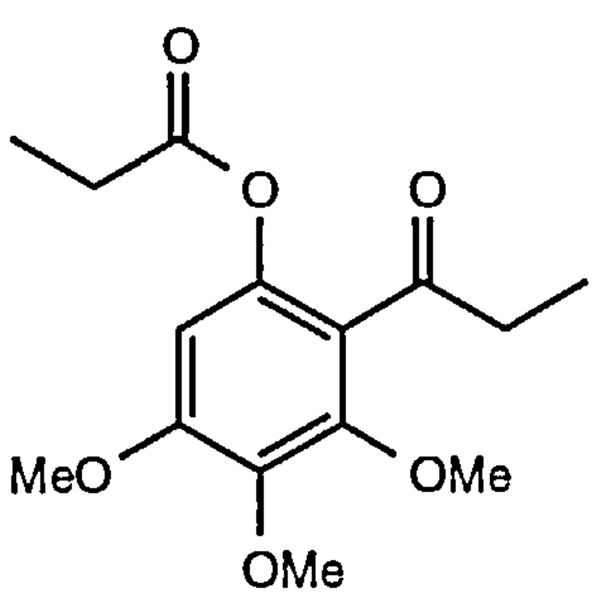


3-7b

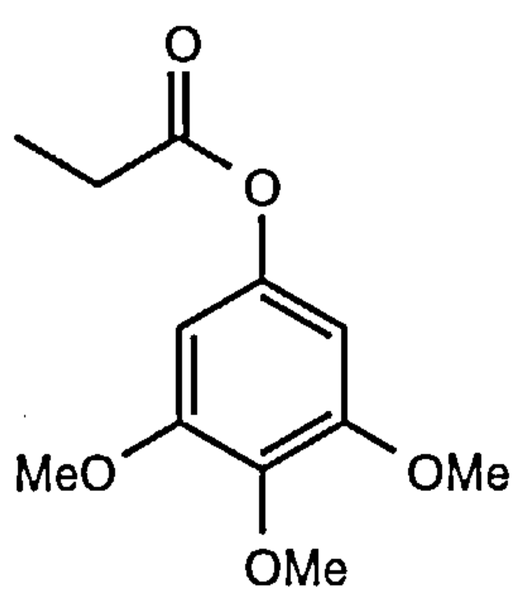


2-18b

Although *para*-Fries rearrangements, presumably through intermolecular attack, are known, in our substrate the *para* position is blocked. Also as the substrate is symmetrical it does not matter which *ortho* position the ester rearranges to. This is one of the advantages of using the selective demethylation approach.



4-1a



3-7c

The one-pot reaction system was devised in the course of our work on LL-D253α once it became clear that when a simple Fries rearrangement, which starts from the phenyl alkyl ester, was attempted with rare earth triflates on polymethoxylated substrates the only product was the phenol, not the rearranged ketone. One could circumvent this by using a large excess of acylating agent and the phenol. The system appears to be in equilibrium between the ester and the phenol, which is reasonable given that scandium triflate catalyses both esterification and ester cleavage. Empirically there also seems to be an equilibrium between the *ortho*-keto ester (e.g. **4-**

1a) and the ester (e.g. **3-7c**): the reaction in the LL-D and baicalein syntheses never went to completion despite extensive loading and prolonged reaction times.

This leaves the question of which reaction is actually happening, Fries or Friedel-Crafts. At any point there are four possible reaction routes that could take place, see figure 4.1.2. Which of these are valid is, unfortunately a question that falls outside the scope of this study.

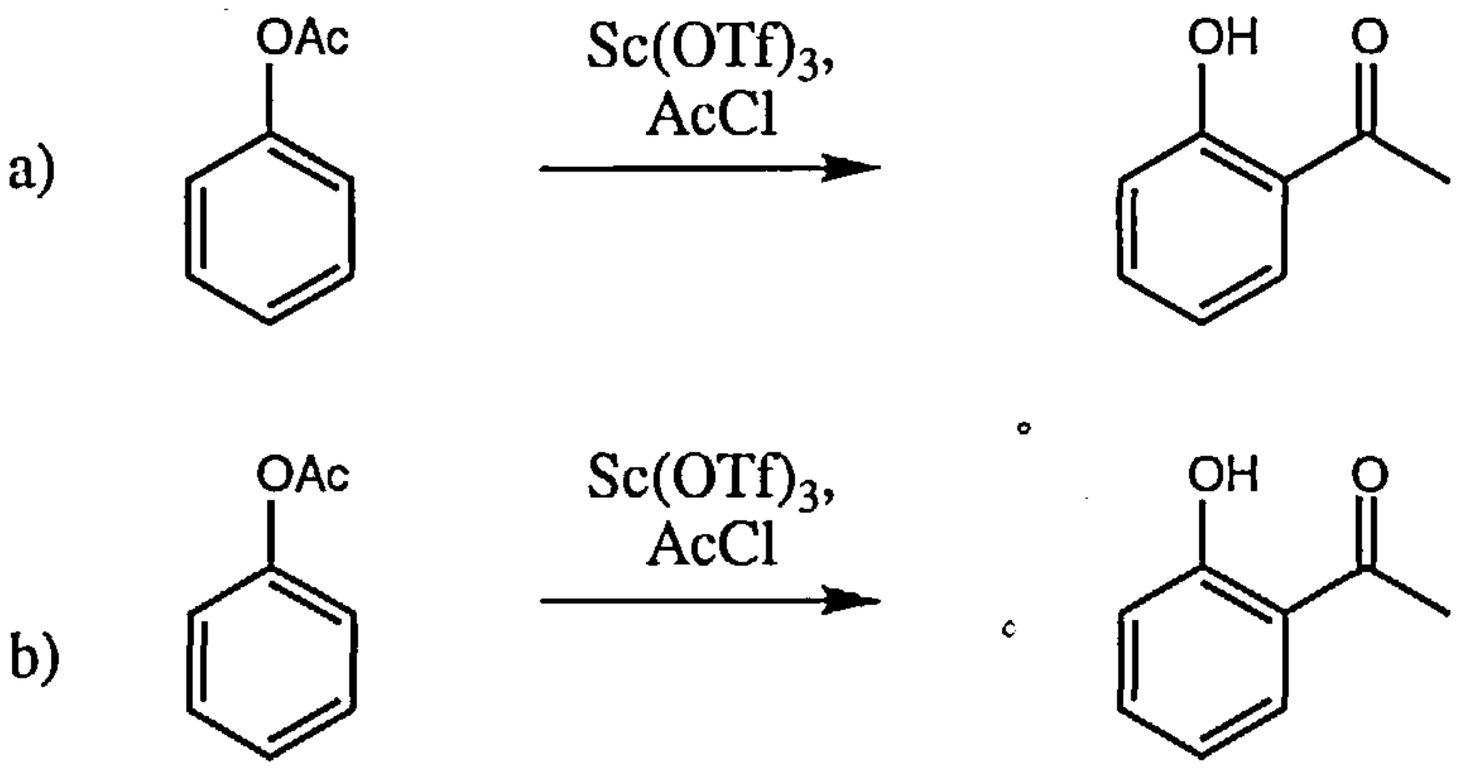
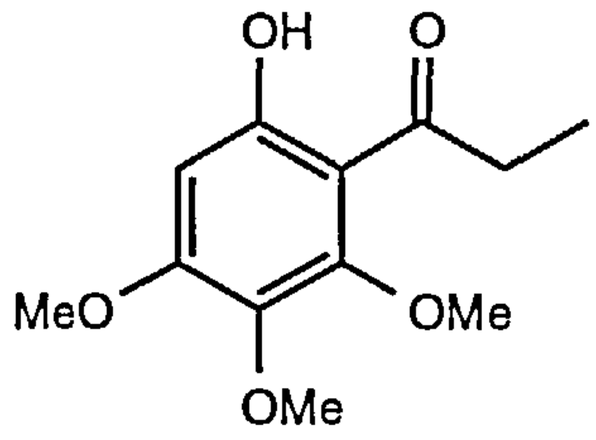


Figure 4.1.2

Methylation of the product, **3-8** of this reaction would give **3-6**.



3-8

The selective demethylation steps with hydrogen bromide in acetic acid remain the same. No mechanism for these steps was proposed in the original papers, but one has to assume that the process is similar to that for the Lewis acid catalysed reactions. The selectivity is reputedly very high. An explanation for this might lie in the folllowing structures, figure 4.1.3.

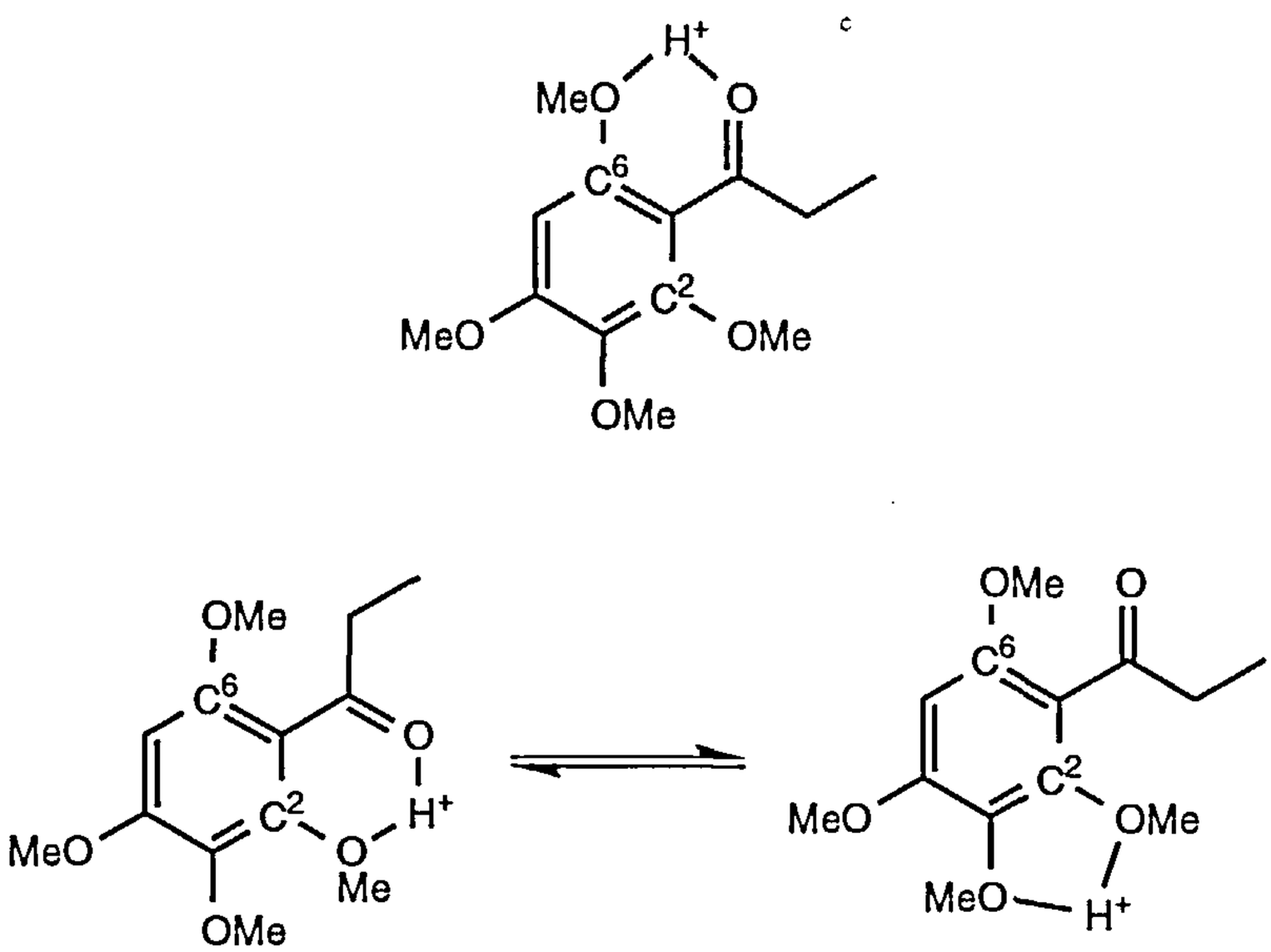
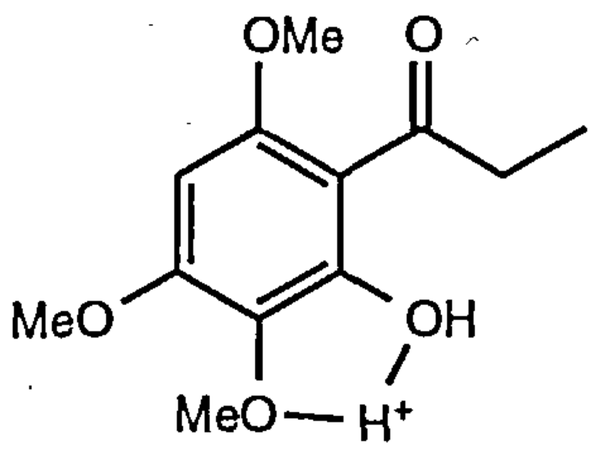


Figure 4.1.3

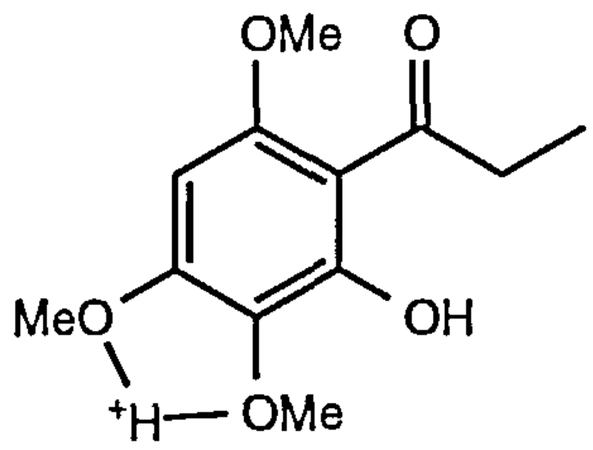
As shown, one can postulate that the protonation of the etheric oxygens can be stabilised by complexation with neighbouring groups. This was effectively the basis proposed for selective demethylations with Lewis acids, which will be discussed in a later chapter. There is only one such possible complex for protonation of the 6-

oxygen. Two are possible for the 2-oxygen. Thus the transition state required for demethylation by attack of bromide ion is more stable for the 2- than the 6- position.

The subsequent demethylation of the 3-position is explainable by a similar argument, using the hydroxyl C2-oxygen and the C4-oxygen as sites of complexation, giving intermediates such as **4-2a** and **4-2b**.



4-2a



4-2b

Given our experience with rare earth triflates, we decided to see if scandium triflate could be used as a demethylating agent. We were aware that on its own this reagent tolerates methoxy groups extremely well, but wondered if it could be persuaded to take part in a push/pull system. This type of methodology, also known as hard acid/soft base[108] has been used before , generally using boron trifluoride etherate as the acid,[109] and generally a thiol or sulphide[110] as the soft base. Aluminium halides have been used in the same way[111]. We decided to use scandium triflate as the acid and a triad of soft bases, acetate, iodide and benzyl thiol.

The cyclisation of the end product to a chromone would be undertaken *via* the Höfle methodology, though a trial would be made of the more precise Hirao system mentioned in the last chapter. Both can be considered as running through the Baker-Venkataraman rearrangement. This consists of a base catalysed transfer of the ester of an *ortho*-keto ester to the a position of the ketone. This product then cyclises and dehydrates (figure 4.1.4). This rearrangement/cyclisation system remains the most common method of chromone cyclisation.

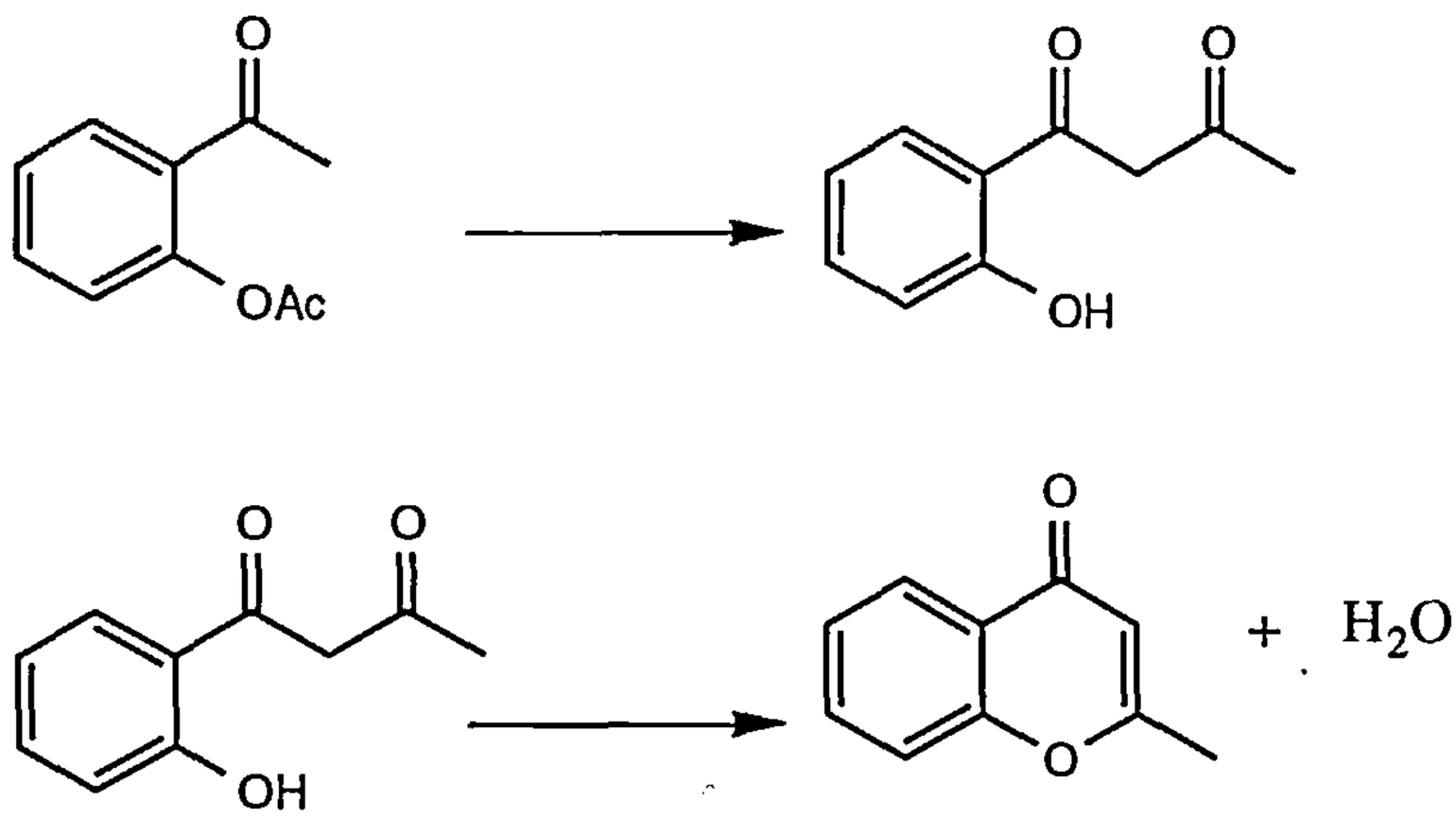


Figure 4.1.4

Some attention was paid to our proposed means of linking the two fragments of stigmatellin, and we decided to investigate the possibility of introducing a leaving group at the 2-methyl of our fragment. A paper by Rastogi[112] stated that 2-methylchromone could be brominated on the 2-methyl by N-bromosuccinimide/AIBN in fair selectivity. We decided to attempt the bromination of 2,3-dimethylchromone to investigate the possibilities for stigmatellin.

4.2 Results and discussion.

The propionylation of **3-7b** was undertaken using approximately 5 mol% of scandium triflate and a solvent system made up of a 1:1 mixture of 1,2-dichloroethane and propionyl chloride. When taken straight through hydrolysis this gave the desired product **4-1** in 16% yield (figure 4.2.1). The process also gave back the unused starting material which could be recycled, and by a simple silica filtration the catalyst could be recovered and reused. Although similar reactions have been undertaken in toluene[113] we found that this gave no transformation, possibly because the toluene was a better Friedel-Crafts substrate than **3-7b**. Though this sounds perverse given the very active nature of **3-7b** it is quite possible that steric hindrance plays a role in this.

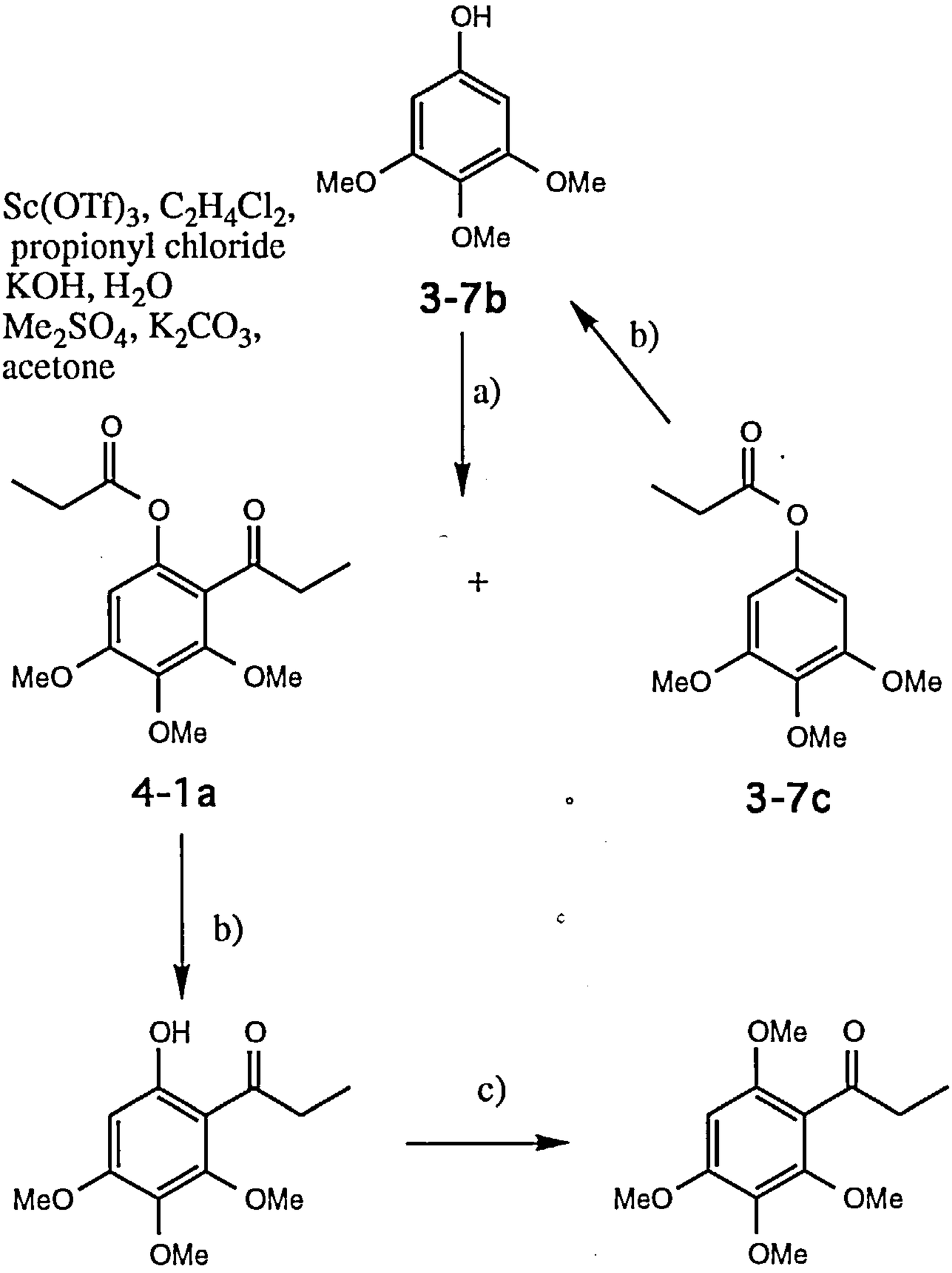


Figure 4.2.1

Methylation of **3-8** gave **3-6** in 88% yield. We therefore had our route to **3-6**, and though the first step appears to be low yielding, the recovery of starting material and catalyst, and the simplicity of the work up meant that large stocks of **3-8** could be assembled with relative alacrity.

The selective demethylation of **3-6** was undertaken with a solution of HBr in acetic acid, which was generated from acetic anhydride and aqueous HBr. The first demethylation to **4-2** was undertaken in a 6% solution of HBr and gave the desired product over one week, in 69% yield. The selectivity of this reaction was simple to

check: the desired product would give a sharp hydroxyl singlet at around 13ppm and have a spectrum differing from that of **3-8**. The second demethylation was undertaken in a 30% solution and gave a 64% yield of **4-3** in 1 day. This product was confirmed against the spectra given in the Höfle synthesis, which it matched in every significant detail (figure 4.2.2).

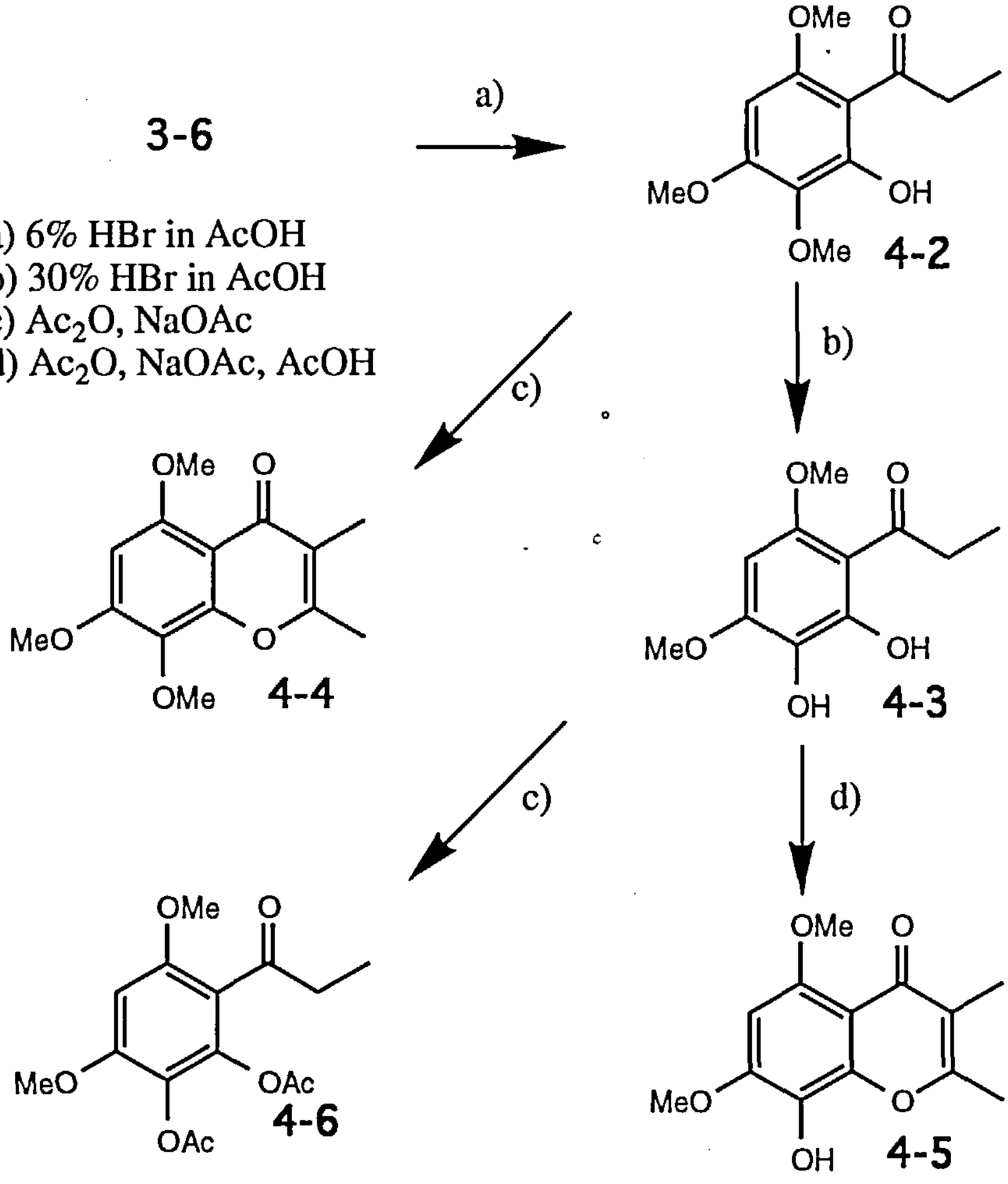


Figure 4.2.2

Our attempts to use other methodologies than the Höfle synthesis for the chromonisation of **4-3** met with little success. Even the more traditional methods using only acetic anhydride and sodium acetate were fruitless. It seems that the excess of acetic anhydride is necessary for the reaction to proceed, but only if the pH is right. Our attempt to use the simple system yielded only **4-6** after prolonged reflux. This reactive reluctance does not extend to **4-2**, however, which cyclises to **4-4** in sodium acetate/acetic anhydride, albeit in 26%. The precisely determined reaction

mixture in the Höfle system is effectively a buffer solution, which seems to allow for cyclisation to occur, giving **4-5** in 40% yield.

2-Hydroxypropiophenone could be acetylated then cyclised in several ways, including pyrolysis, and the Hirao methodology, the highest yield of **4-7** being 25% with pyrolysis. **4-7** was brominated with the AIBN/NBS mixture over a tungsten lamp, yielding only one product which, sadly, matched the spectra given in the literature[114] for 2-methyl-3-bromomethylchromone, see figure 4.2.3.

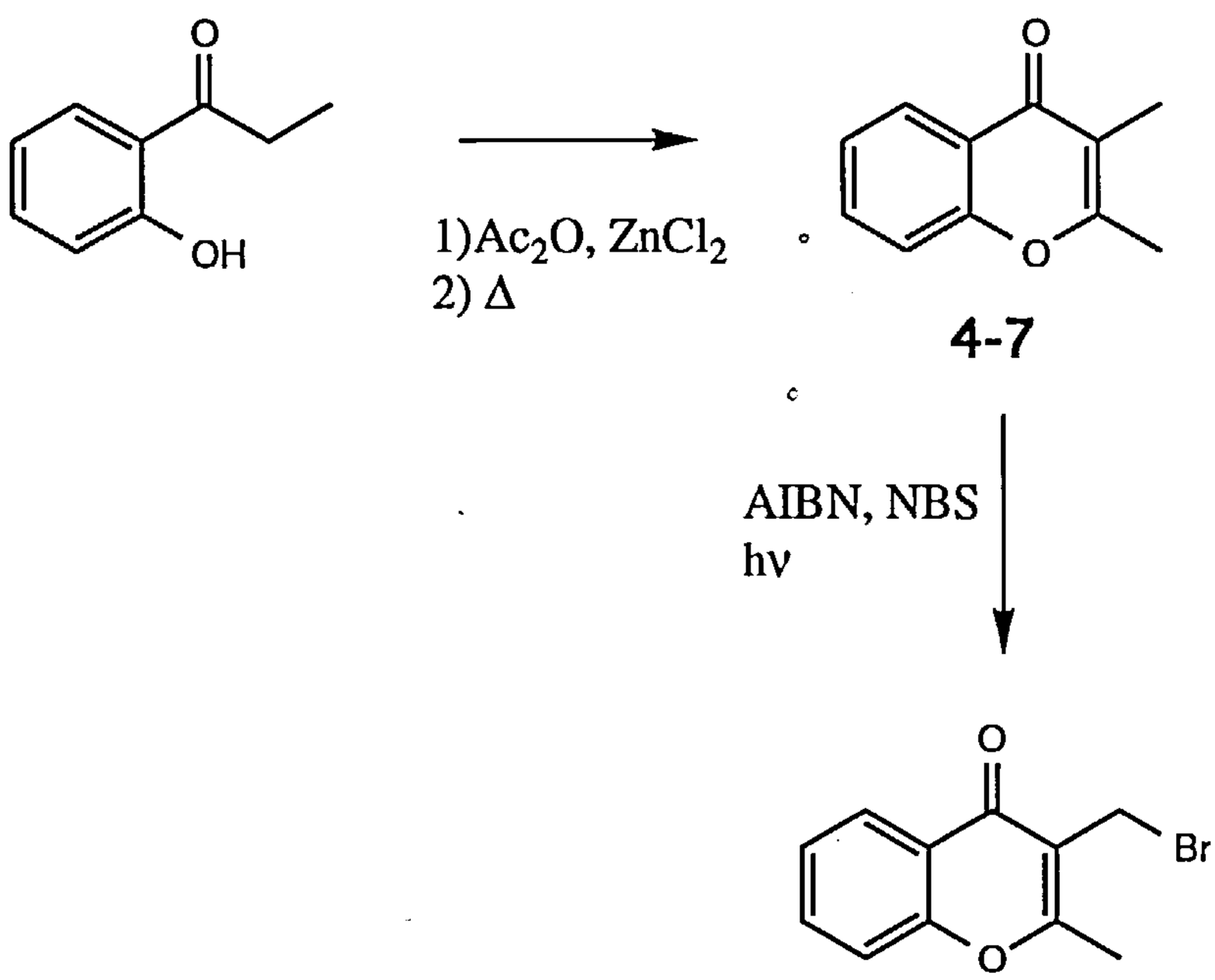
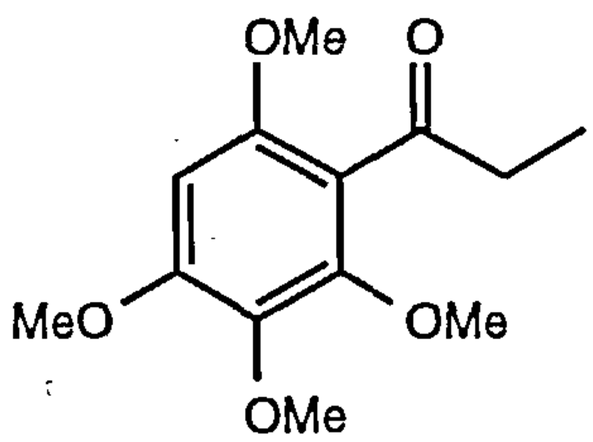


Figure 4.2.3 **4-8**

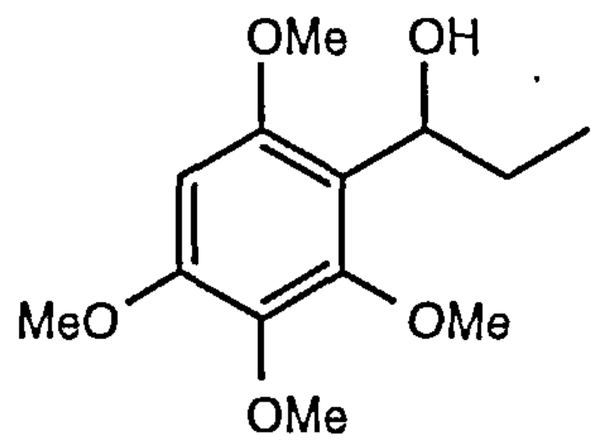
This meant that though the procedure might be useful for the creation of molecules from the iso-stigmatellin manifold it would not find instant application here. Any future coupling studies would have to be done *via* simple enolate couplings.

Finally, much difficulty was had in the synthesis of LL-D 253a precursors due to the unreactivity of a 2,6-dioxygenated benzoic ester to nucleophillic attack. We had reason during the course of our work to attempt to reduce **3-6** down to the secondary

alcohol **3-10.** All our attempts failed to produce a recognizeable product. Sodium borohydride produced no result, nor did prolonged reflux with lithium aluminium hydride. Sodium in superdry ethanol produced no result. Fearing to use any of the metal/acid methods in case of demethylation we were forced to admit that this 2,6-dioxygenated ketone was also reasonably unreactive to even quite small nucleophiles.

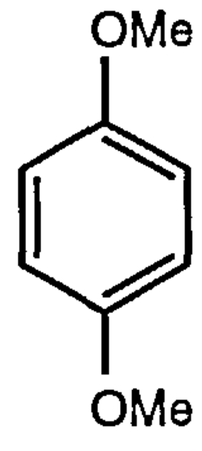


3-6

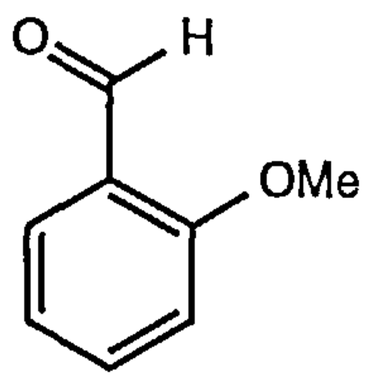


3-10

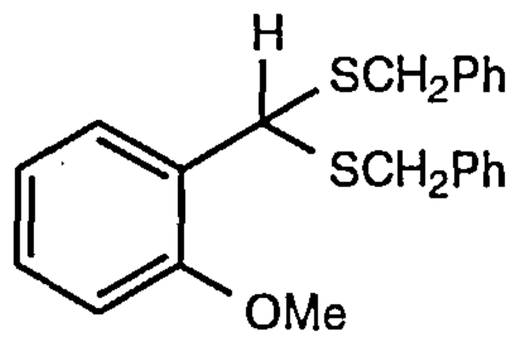
For our scandium triflate demethylation study we chose to use two substrates: 1,4-dimethoxybenzene **4-9** and *o*-anisaldehyde **4-10**. Neither of these showed any demethylation with a range of nucleophiles in DMF, but with benzylthiol as solvent and nucleophile **4-10** produced a compound giving spectra indicative of **4-11**. This appears to be a novel method of forming dithioacetals using a catalytic amount of a Lewis acid. Other methods in the literature have been stochiometric in Lewis acid.[115]



4-9



4-10



4-11

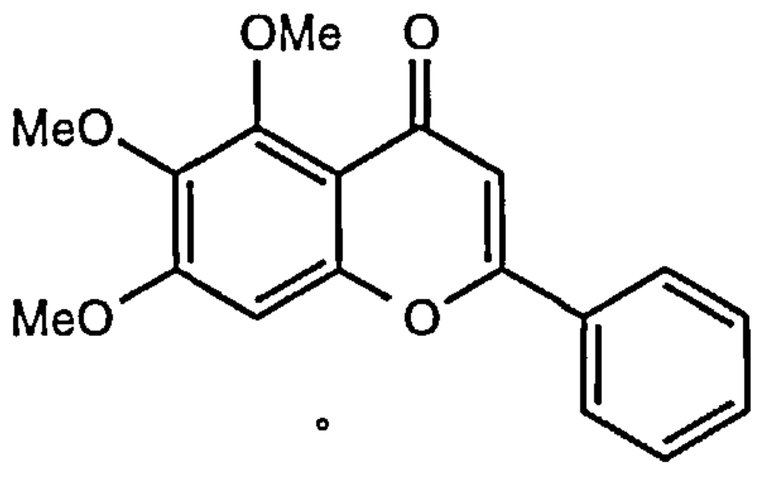
Chapter 5

Synthetic Approaches to Trimethylbaicalein

5.1 Introduction and retrosynthesis

5.1.1 Introduction

Trimethylbaicalein, **2-12**, is a flavone found in a variety of rainforest species, notably *Popowia Cauliflora* a scrambling bush (liane) indigenous to the tropical rainforest of western Africa, from Zaire to S. Nigeria.[116] The molecule itself is not a tremendous challenge to the synthetic chemist, indeed it is available from several major catalogue houses.[117]



2-12

For our purposes it is, however, an attractive target. Our work on stigmatellin fragment A required a testbed for Friedel-Crafts and Fries chemistry, particularly with a view to testing out the rare earth triflate Lewis acids. Trimethylbaicalein seemed an ideal choice: it had a similar substitution pattern to the Stigmatellin fragment **3-2**, it had been synthesised before,[118] and the flavone pattern allowed us to put to the test an observation made by a previous worker:[119] that a conjugate addition of phenyl cuprate to a chromone-3-sulphoxide will bring about a spontaneous elimination of the sulphoxide group (figure 5.1.1).

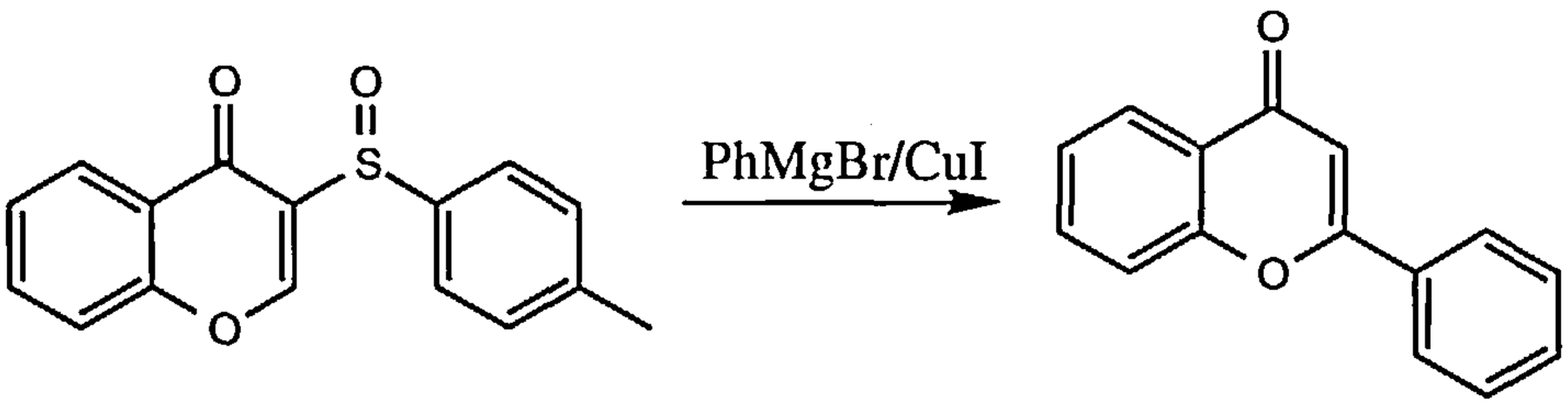
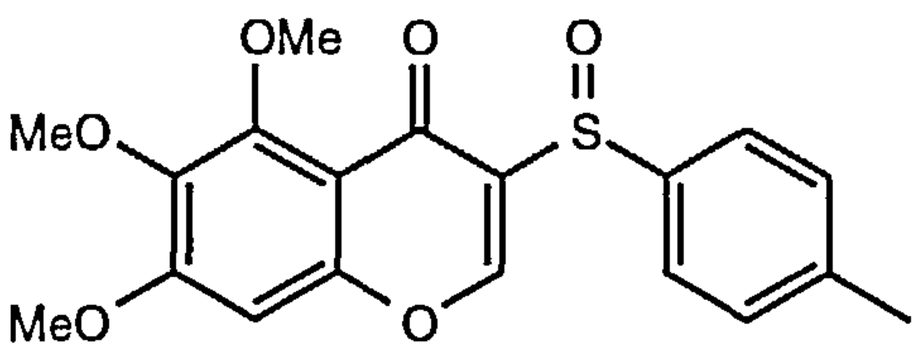


Figure 5.1.1

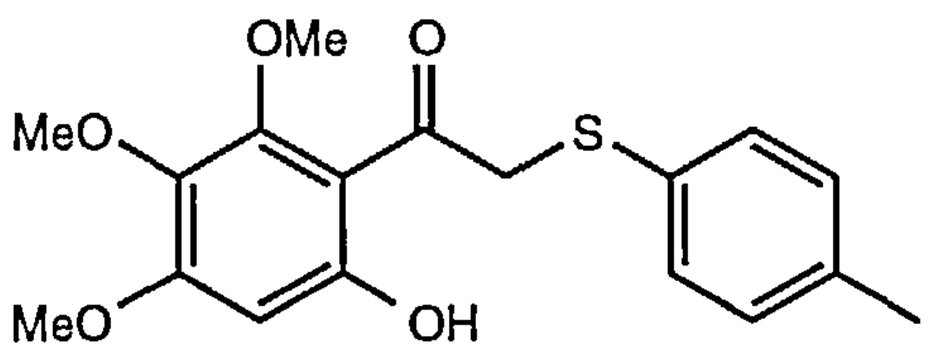
We felt that this needed investigation as the conjugate addition[120] of alkyl groups to chiral non-racemic sulphoxides has been found to be a flexible and precise approach to the synthesis of enantiomerically rich chromanones. Given the huge variety of natural flavanones, many of which show some biological activity, testing the possibility of extending the method into this wide frontier seemed sensible.

Using a chromone with the B ring substitution pattern of baicalein would enable us to use the synthesis to test many reactions, crosslinking the syntheses of stigmatellin fragment A and LL-D253α.

In order to perform any tests, however, a method of producing 3-(4-methylphenylsulphinyl)-5,6,7-trimethoxychromone, **5-2**, would need to be investigated.



5-2



5-3

Given that we fully expected our sulphoxide group to be destroyed, and its stereocentre with it, during the reaction sequence we did not feel that it was worth the effort of generating our test molecule through the enantioselective route of ester displacement (see chapter 6). Instead we decided to use the well-tried[121] method of making the β-ketosulphide **5-3** and oxidising it up to the sulphoxide, allowing us to test chiral oxidants on these systems, as well as the more normal 3-chloroperoxybenzoic acid.

To summarise, the aims with which we approached the synthesis of **5-2** and **2-12** were the following:

1) To investigate the Fries or Friedel crafts reactions of 3,4,5- trimethoxyphenol with scandium triflate catalysis.

2) To attempt to synthesise **5-2** *via* the β-ketosulphide **5-3** and to investigate the stability to oxidation of the substrate.

3) To investigate the possibility of using chiral oxidation techniques to synthesise chiral non-racemic sulphoxides of the type of **5-2**.

4) If possible to investigate the auto-elimination reaction mentioned above.

5.1.2 Retrosynthesis

As stated above our route to **5-2** passes through the β-ketosulphide **5-3**, by way of the β-keto sulphoxide **5-4** (figure 5.1.2).

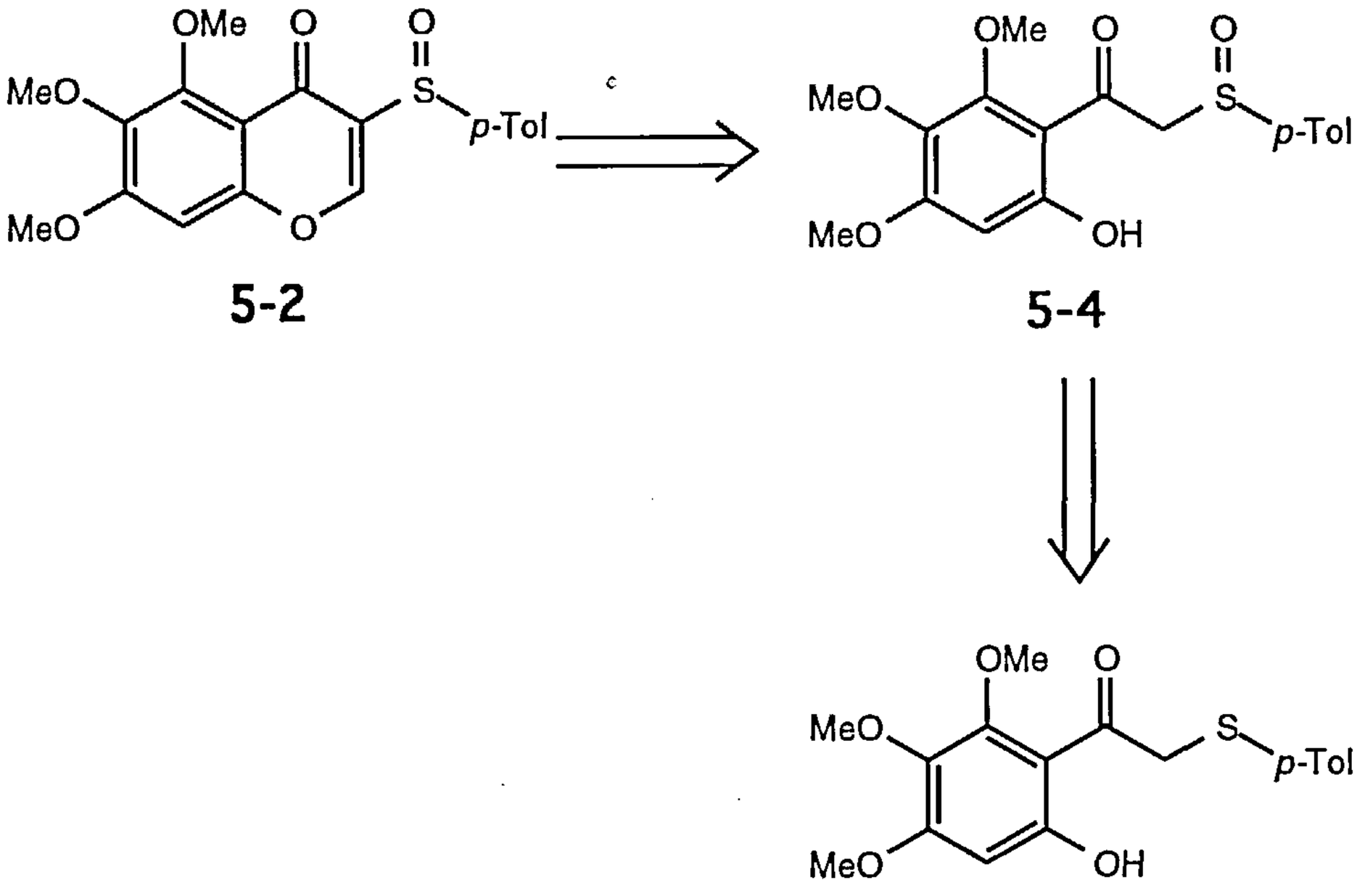


Figure 5.1.2

The thioether **5-3** itself could most readily be synthesised by a simple displacement of a leaving group, often bromide, from the α carbon of the ketone. This would require the preparation of an α-bromoketone, **5-5**. Bromination α to a ketone can be accomplished in many ways, including the use of base and bromine, [122], but one of the longest running is to use cupric bromide in either dioxane[123] or chloroform/ethyl

acetate,[124], Which is seen as being a mild yet effective method of introducing a bromine without dibromination. This would, of course, mean that our next step back in the synthesis would be the ketone **5-6**. This is an obvious product of a Fries rearrangement of 3,4,5-trimethoxyphenol, (figure 5.1.3). Hence we have our retrosynthetic scheme for **5-2** fleshed out in main. It is now necessary to consider one or two transformations in more detail.

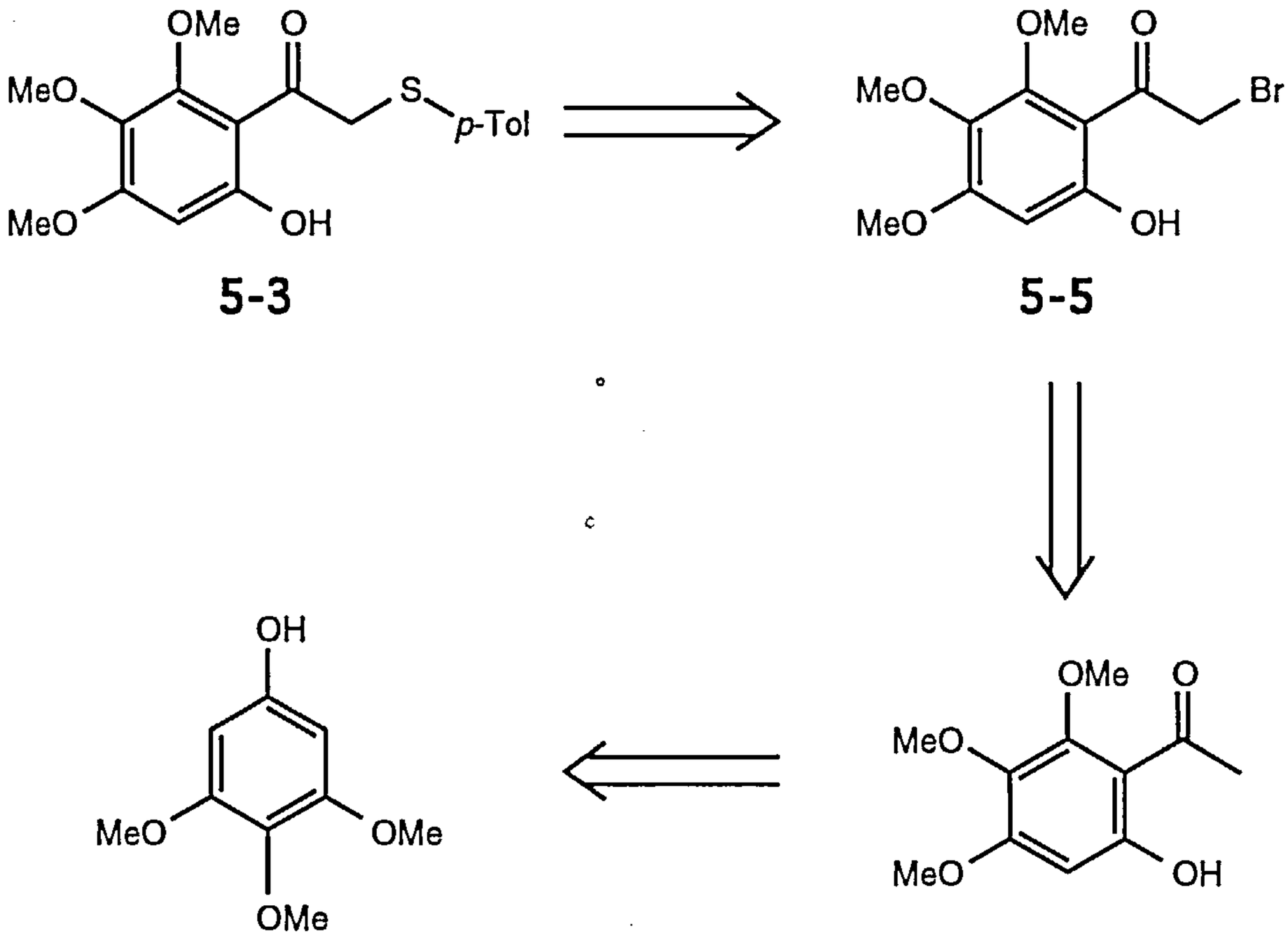


Figure 5.1.3

The oxidation step from **5-3** to **5-4** is one that could easily be problematic: the aromatic ring is very sensitive to oxidation. Although this is ameliorated somewhat by the acetyl group it is still an area of concern. We felt that it was worth attempting the oxidation using a commonly available catalyst, and also perhaps through the use of an asymmetric oxidant such as the Kagan system.[125] This would alow us to develop a methodology of approach to 2,6-dioxygenated chromanones in enantiomerically enriched form.

The other area of concern would be the cyclisation step from **5-4** to **5-2**. Our experience with stigmatellin suggested that the cyclisation step in multioxygenated systems can be very sensitive to conditions. Having two possible systems to use would therefore be an advantage. We chose Solladié's system using formylimidazole as the first as it is easy to prepare.[126] As the second we chose acetic formic anhydride[127] and sodium formate, essentially the same sort of system as used in the stigmatellin fragment A synthesis. In this system the substrate is transformed into the dianion by two equivalents of base. Formylimidazole is then added and a simple substitution takes place at the formyl carbon. Unlike the more traditional methods it seems likely that this substitution takes place directly with the enolate rather than with the phenol, (figure 5.1.4).

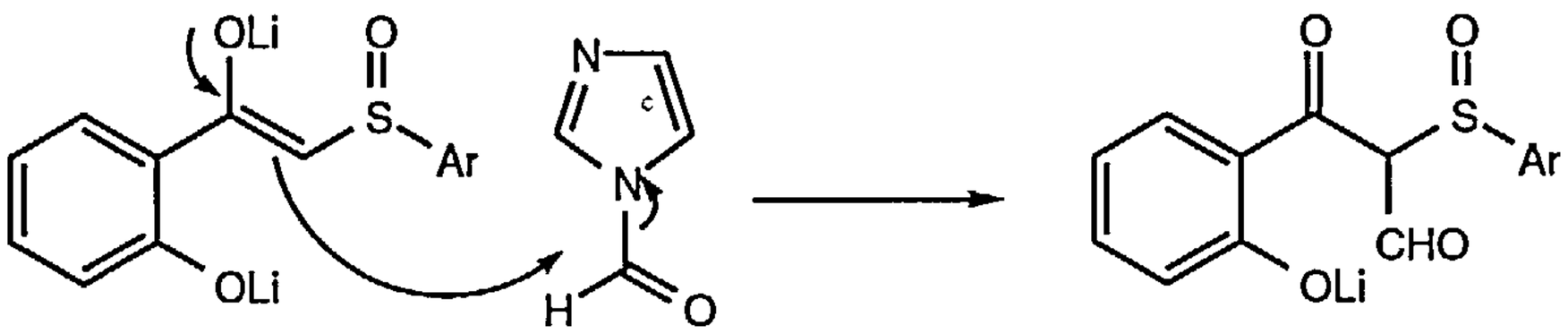


Figure 5.1.4

Therefore in this case no Baker-Venkataraman rearrangement is invoked Solladie claimed high yields (72%) for this system as opposed to low (22%) for the more traditional one. Thus the formylimidazole method was chosen for the first attempt.

5.2 Results and discussion.

The first step of the synthesis consisted of a "one pot" Fries reaction, starting from 3,4,5-trimethoxyphenol. This was attempted in several sets of conditions but the optimum was found to be running the reaction in a solvent consisting of a 6:1 mix of 1,2-dichloroethane and acetic anhydride, which resulted in a 36% yield of **5-7**. As with other "one pot" Fries setups featured in this work O-acetyl starting material **5-8** and catalyst were both recoverable from the mixture and could be reused. Initial trials using toluene as the cosolvent met with no success, possibly due to the toluene being

acetylated preferentially. Despite use of long reaction times and excesses of acetic anhydride, as well as additional amounts of scandium triflate, the proportion of rearranged **5-7** to **5-8** in the reaction mixture remained around 1:1.5. This points towards a complicating factor in the course of the reaction which has yet to be determined.

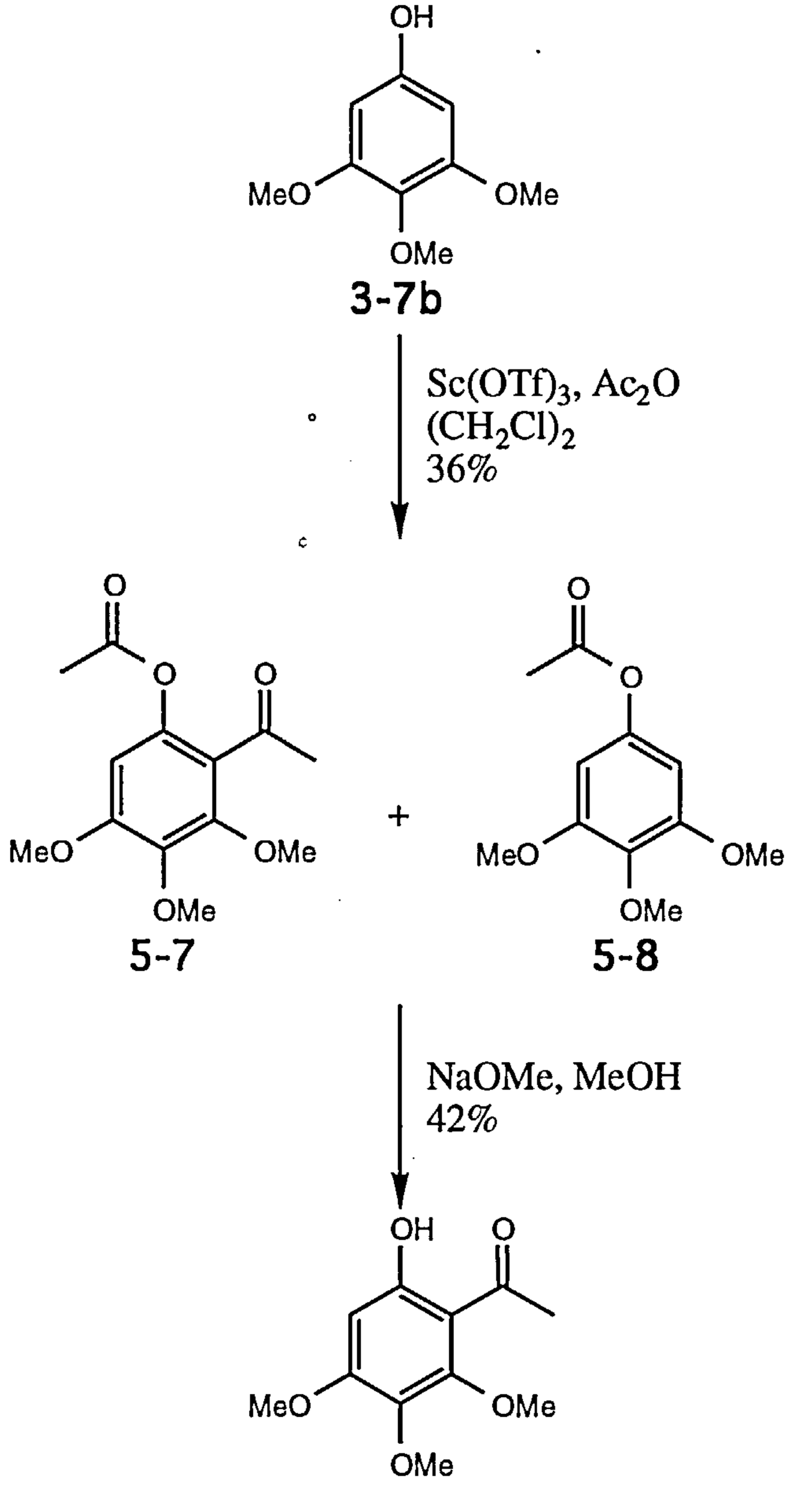
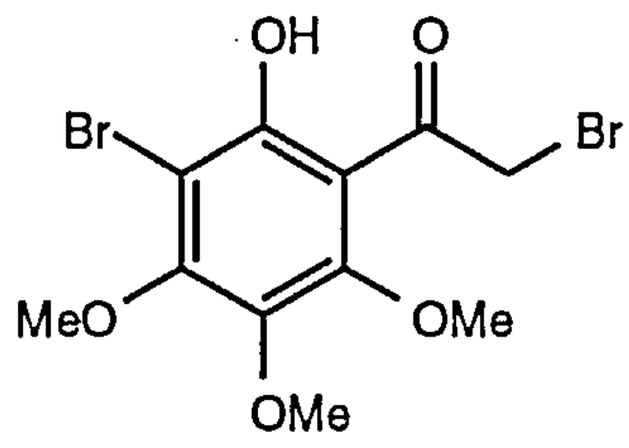


Figure 5.2.1

The hydrolysis of **5-7** to **5-6** proceeded in sodium methoxide in apparent 42% yield, though much of this loss is due to the presence of **5-8**, which is difficult to remove

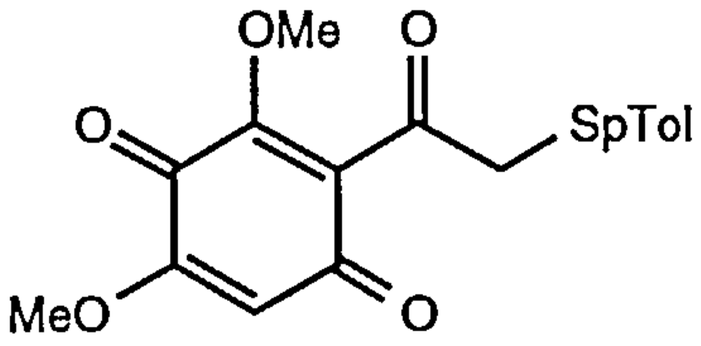
prior to hydrolysis. After hydrolysis 3,4,5-trimethoxyphenol could be removed by trituration with ether, and this became the standard practice. This is due to the large difference in polarity between the two compounds. The ketone **5-6** is, in fact largely soluble in petrol. Again, the strong hydrogen bond between the carbonyl oxygen and the phenol hydrogen decreases the acidity of the phenol and sharpens its NMR resonance signal. For an overview of the above see figure 5.2.1. This sequence confirmed that the catalytic Fries rearrangement as performed above, was a viable way to produce **5-6** in quantity.

The next step in the synthesis was the bromination α to the ketone of **5-6**. To do this we refluxed **5-6** in a 1:1 mixture of chloroform and ethyl acetate. This resulted in the desired compound **5-5** in 49% yield. It was, however, accompanied by a major impurity which could be tentatively assigned as **5-9**. The spectral evidence is unclear, however. Whatever the actual structure it is clear that this bromination is not particularly clean. It does however produce a workable amount of the desired product.

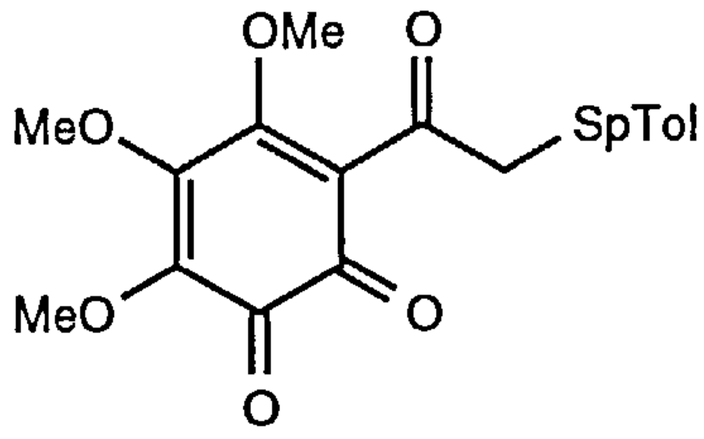


5-9

The displacement of the α bromide with sodium thiocresolate to gain **5-3** was succesful in 29% yield, though it proved difficult to separate the product from the excess of thiocresol. For an overview of this scheme see figure 5.2.2. We were now ready to proceed with the oxidation of the sulphide up to the racemic sulphoxide. Treatment of **5-3** with 3-chloroperoxybenzoic acid gave a compound giving no resonances for aromatic or hydroxyl protons. We assumed this to be the product of ring oxidation, probably an *ortho-* or *para*--quinone, such as **5-3a** or **5-3b**.



5-3a



5-3b

The compound was not characterised as it denatured over a period of some hours. This was indicative of the problems that we had experienced with *m*-CPBA during the course of this investigation, as it also denatured some LL-D 253a precursors.

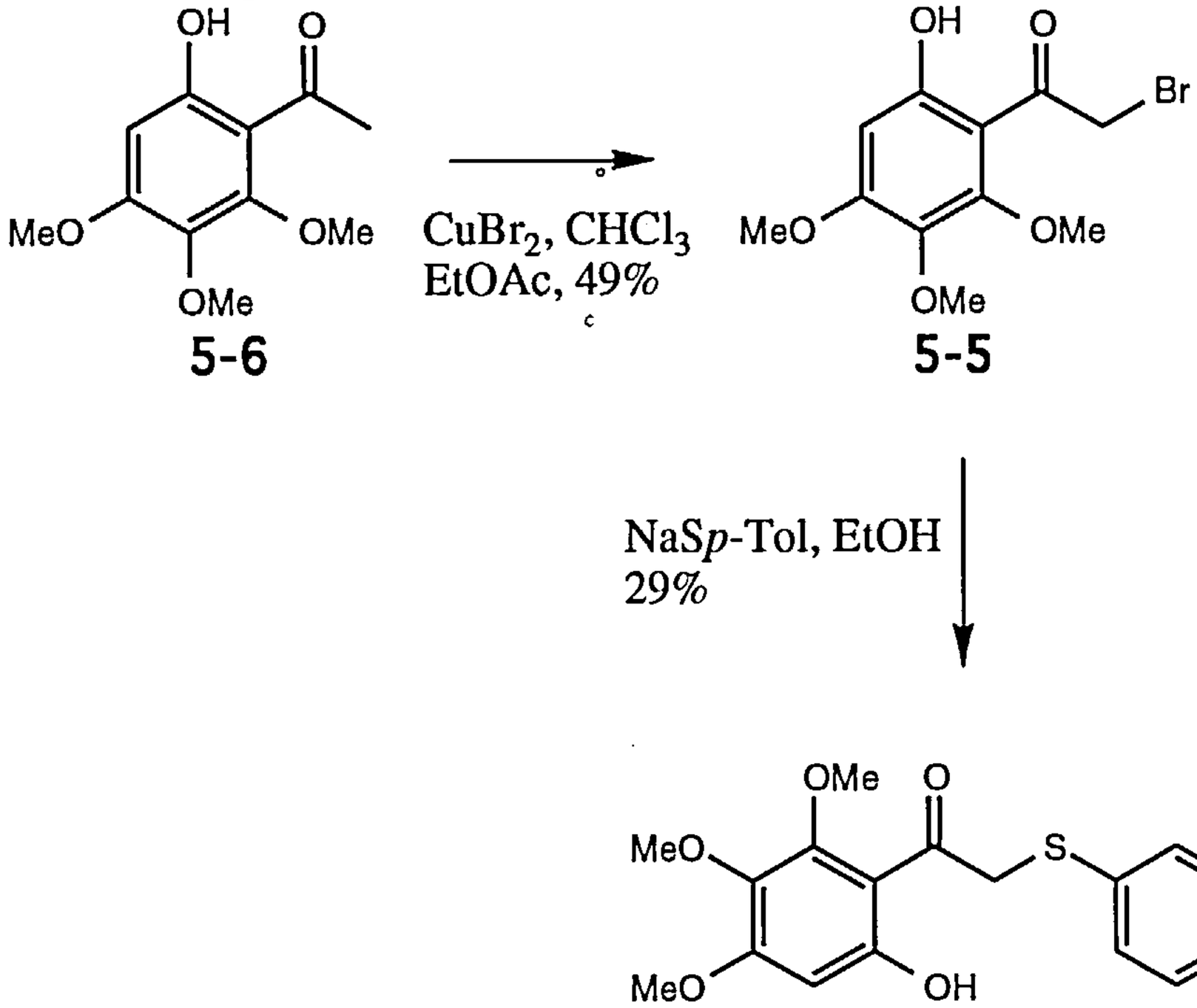


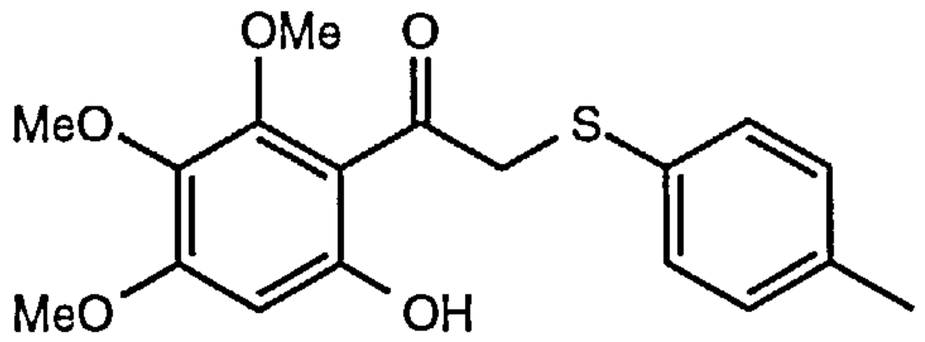
Figure 5.2.2

Obviously powerful oxidants are not well tolerated by electron rich aromatic rings, even when an easily oxidised atom like sulphur, or group, like an allyl group (see chapter 6) is on offer. This left us in something of a quandary as to the next step in this synthesis, though it did give valuable information: strong oxidants must be largely avoided in the synthesis of β–ketosulphoxides of polymethoxylated benzene rings. This information was translated to the synthesis of LL-D253α. We decided that it was necessary to alter the stability of the aromatic ring before attempting

another system of oxidation. Perhaps the most obvious way of avoiding accidental ring oxidation would be to deliberately oxidise it to the quinone ourselves. In fact this sort of oxidation is well known,[128] but synthetically useless to us. One of the main functions of this synthesis was to develop synthetic methods applicable to other substrates, specifically the LL-D253α and stigmatellin fragment A syntheses. Both of these require a specific methylation pattern, which could be difficult to regenerate once disrupted for quinone formation.

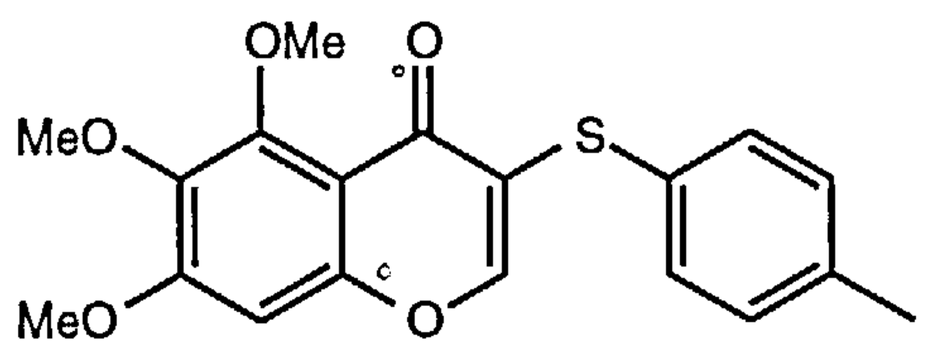
The idea that occurred to us was to cyclise **5-3** to the chromone as it stood. There was reason to believe that the chromone would be significantly more stable to oxidation than the ketone.

We attempted the cyclisation of **5-3** under the formylimidazole protocol and found that the reaction proceeded in 78% yield to give **5-10**. We elected to attempt the oxidation of this structure with a modified Kagan technique, the details of which will be discussed in the next chapter. The reasoning was two-fold. We felt that the Kagan oxidative complex would probably be more selective than a simple peracid system. We had also reached a position in the synthesis of LL-D253α precursors where we needed to investigate the potential of chiral oxidation to produce enantiomerically enriched chromone-3-sulphoxides, other methods being fraught with difficulty. Sadly, despite the pressing need all attempts at chiral oxidation of these compounds failed, in fact no transformation of **5-10** was noted at all.



5-3

formylimidazole, KH
78%



5-10

Figure 5.2.3

It would perhaps be sensible to revisit our aims for this synthetic route, to judge the success of our venture.

1) To investigate the Fries or Friedel crafts reactions of 3,4,5-trimethoxyphenol with scandium triflate catalysis.
2) To attempt to synthesise **5-2** via the β–ketosulphide **5-3** and to investigate the stability to oxidation of the substrate.
3) To investigate the possibility of using chiral oxidation techniques to synthesise **5-2**.
4) If possible to investigate the auto-elimination reaction mentioned above.

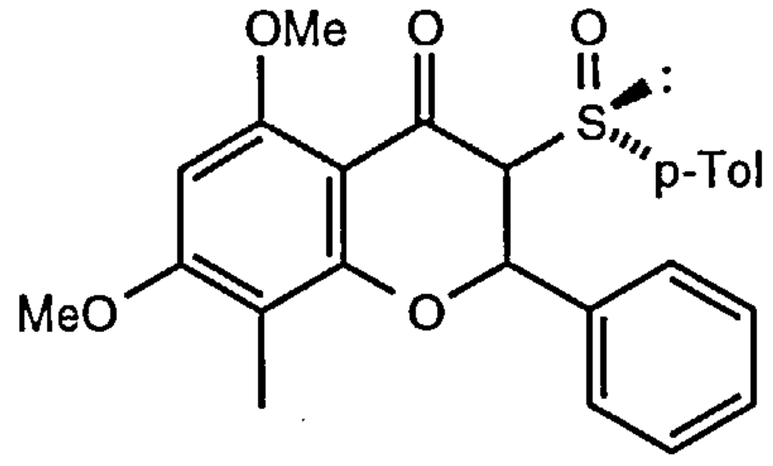
In order then.

1) This route provided a successful test bed for the catalytic "one pot" Fries methodology which was translated to stigmatellin fragment A.

2) This route confirmed our fears about the stability to oxidation of the polymethoxylated systems. We did however manage to create a novel 3-(4-methylphenylsulphinyl)-5,6,7-trimethoxychroman-2-ene-4-one, **5-10**. This proved to be more stable to oxidation than **5-3**.

3) The chiral oxidation of **5-10** was attempted with no success. The fact that starting material was returned did, however, leave open the possibility that this might be a viable route with a different oxidant.

4) Sadly we did not succeed in investigating the observed phenomenon, though it has now been observed by Solladié in **5-11**. Clearly this phenomenon will limit the uses of the conjugate addition method for the synthesis of flavanones, though by how much is still open to debate.



5-11

Chapter Six

Synthetic approaches to LL-D 253α intermediates in chiral non-racemic form and related reactions

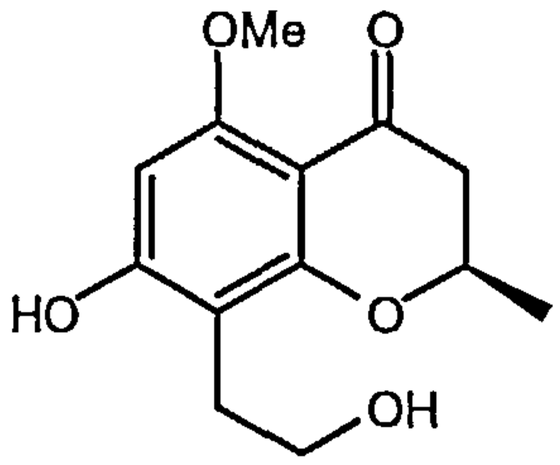
6.1 Introduction and retrosynthetic analysis

6.1.1 Introduction

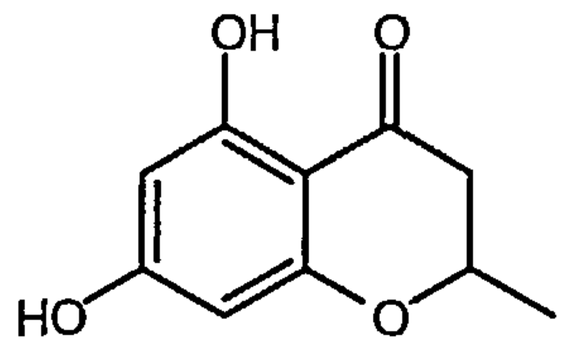
The synthesis of LL-D253α **2-18b** as elucidated by Simpson *et al.*[129] and alluded to earlier took as its starting point 5,7-dihydroxy-2-methylchroman-4-one **6-2**. This meant that the chirality of the chroman-4-one ring, centred about the 2 position, was already in place at the start of the procedure.

Simpson did not publish data regarding the optical rotation of his products, nor did he specify the chirality of his starting material, so it is to be assumed that this synthesis was racemic. Certainly the introduction of a chiral centre at the beginning of a synthesis involving such rigorous conditions as those required by a Claisen rearrangement is to give something of a hostage to fortune. We felt that a more flexible approach would be to construct the skeleton of the molecule first in the form of **6-3**, and then to introduce the 2-methyl substituent *via* a stereocontrolled 1,4-addition.

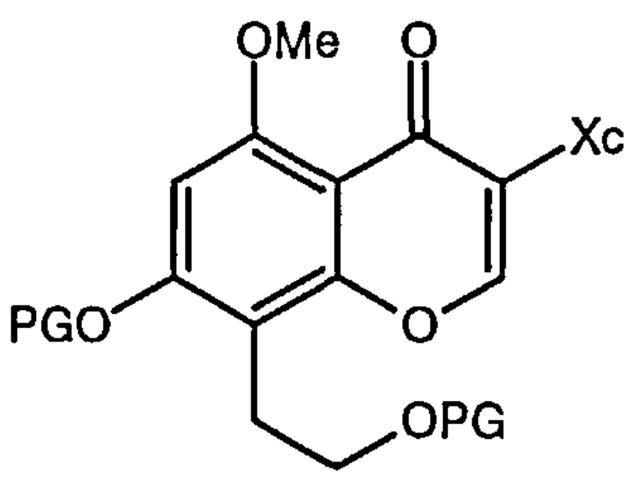
Such additions have been well documented by Wallace and Saengchantara[130] and generally give good stereoselectivity. In their work the auxiliary was a chiral sulphoxide group. Using 3-(4-methylphenylsulphinyl)chromone as a substrate they performed a conjugate addition using methyl cuprate to give chiral 2-methylchroman-4-one **6-4** in 65% yield with an enantiomeric excess of 88%. Given the success of this arrangement we decided to proceed with the retrosynthetic analysis of LL-D253α on this basis, as shown in figure 6.1.1.



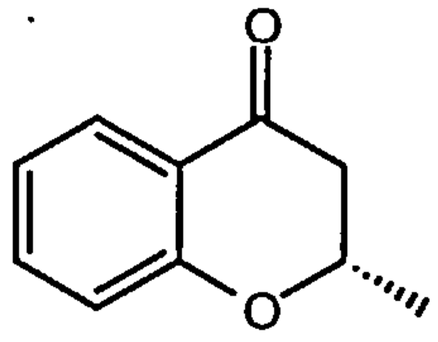
6-1



6-2



6-3



6-4

PG = protecting group
Xc = chiral auxiliary

Assuming that the Wallace methodology was to be followed as to the cyclisation of the chromone, the required precursor would be a β-ketosulphoxide **6-5**. The generation of chiral non-racemic molecules using optically active sulphoxide auxiliaries has a distinguished history in which, in recent years, the name of M. Guy Solladié plays no small part. In particular his preparations of β,δ-diketosulphoxides[131] and his demonstration of the ability of optically active sulphoxides to effect a 1,3 asymmetric induction[132] with a variety of reductants have been particularly noteworthy.

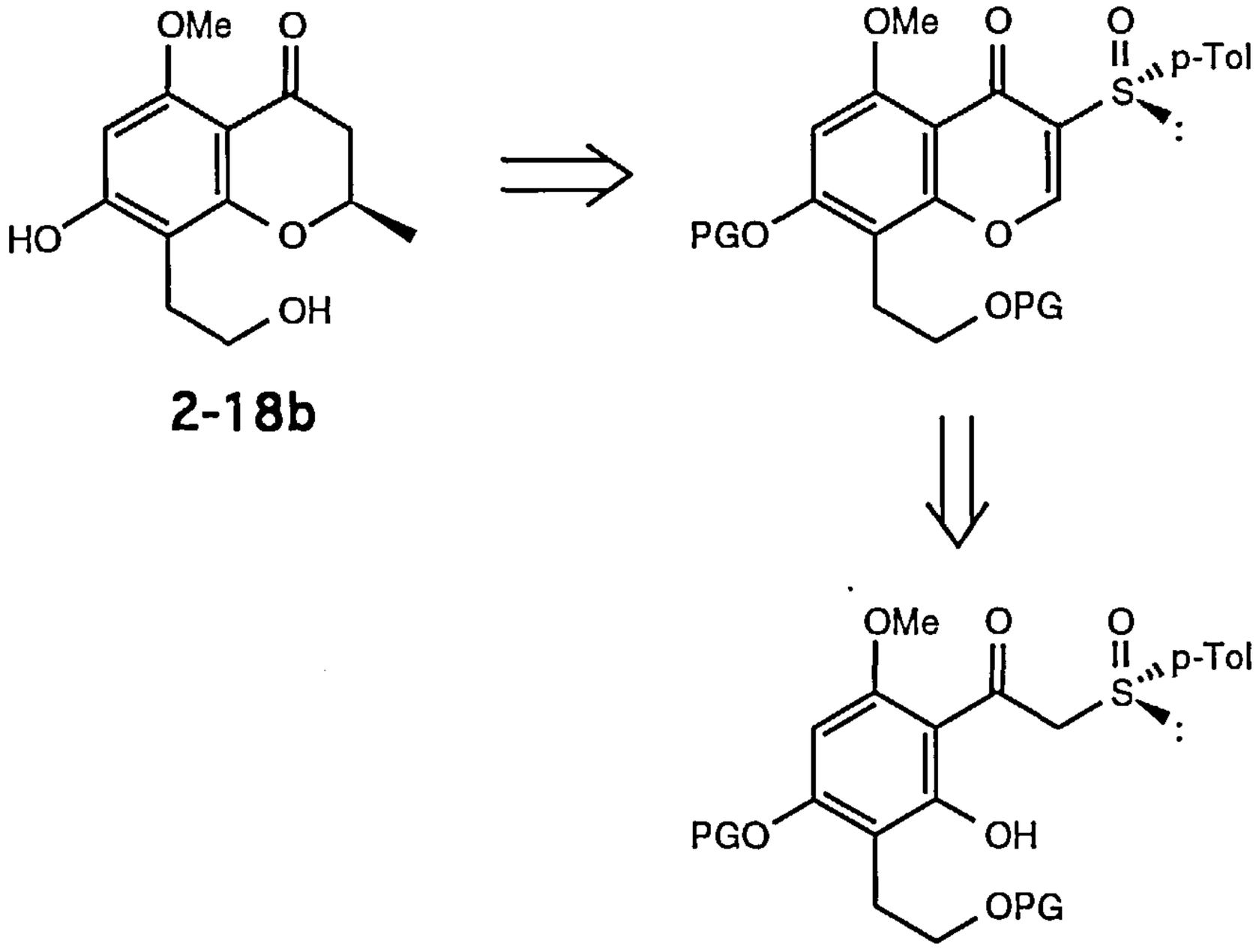


Figure 6.1.1

Most of Solladié's work has been focused upon the reactions of alkyl- or acyl-substituted β-ketosulphoxides, particularly towards reducing agents. This is typified by his syntheses of (-)-(5S,7R)-tarchanonanthuslactone[133] and haminol-1.[134] Aryl substituted β-ketosulphoxides have been generally less well explored, with the notable exception of those studied by the Wallace group, who exploited the 1,3 asymmetric induction due to the sulphoxide group to good advantage.[135] A reasonable model for the asymmetric induction of Michael-type addition to these chromone sulphoxides, and one that allows for prediction of the preferred product, is shown in figure 6.1.2.

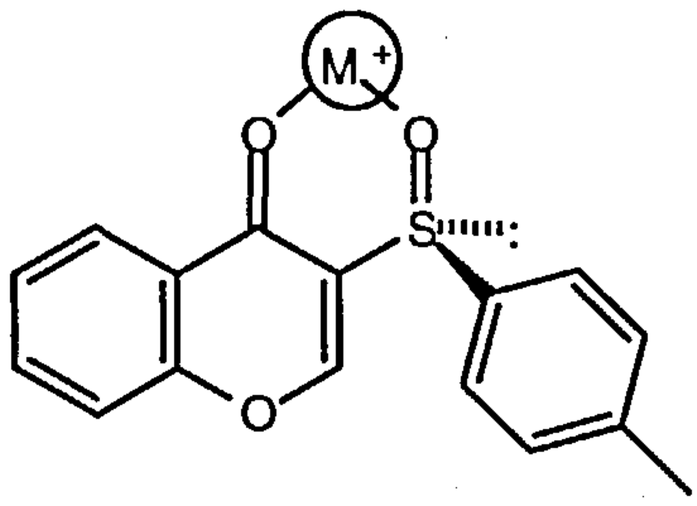
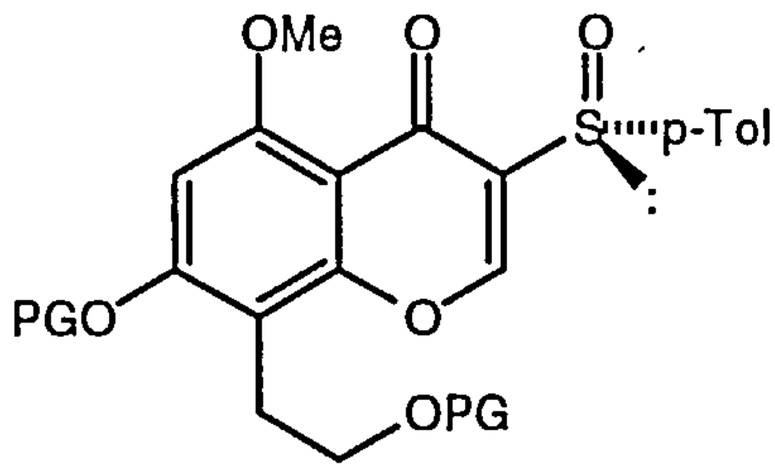


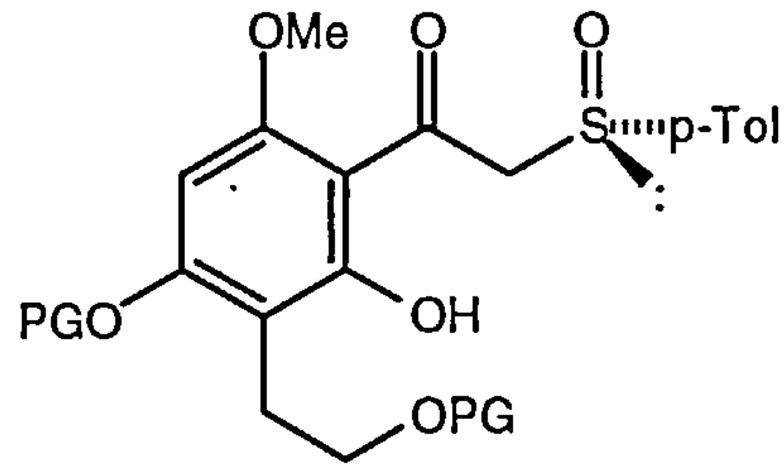
Figure 6.1.2: Chelation control of substrate conformation leads to shielding of top face of enone system.

Assuming that the metal chelates as shown to the two oxygens, attack by the nucleophile is expected on the less hindered face, that is the face shielded only by the sulphur lone pair. This would suggest that the required sulphoxide for the synthesis

of LL-D253α would be the *R*- isomer **6-6**. Stereoselective synthesis of the precursor to this isomer **6-7** would therefore be the first target in any overall asymmetric synthesis of LL-D253α.



6-6



6-7

β-Ketosulphoxides have been prepared in the past by a number of methods. These can be grouped into three major varieties; those where the sulphoxide moiety is introduced with its optical activity in place,[136] those where the sulphoxide is introduced as another group, frequently an optically active sulphinate, and the chiral centre generated *in situ via* a clean inversion[137] and those where the sulphoxide is generated by the oxidation of a thioether precursor and the correct isomer produced either by resolution or by utilising a chiral oxidant system.[138] Of these the most facile approach seemed to be the introduction of the preformed sulphoxide and the best method for this appeared to be the displacement of a suitable ester group.

6.1.2 Approach *via* ester displacement

One of the more useful attributes of the sulphoxide group is that it will increase the acidity of a proton attached to an adjacent carbon. Indeed the pKa of the methyl protons of dimethylsulphoxide is 33, giving an acidity intermediate between those of benzylic (pKa = 41) and the a protons of an ester (pKa = 25).[139] Thus a stable carbanion may be formed with which to perform a nucleophilic displacement at an ester (figure 6.1.3).

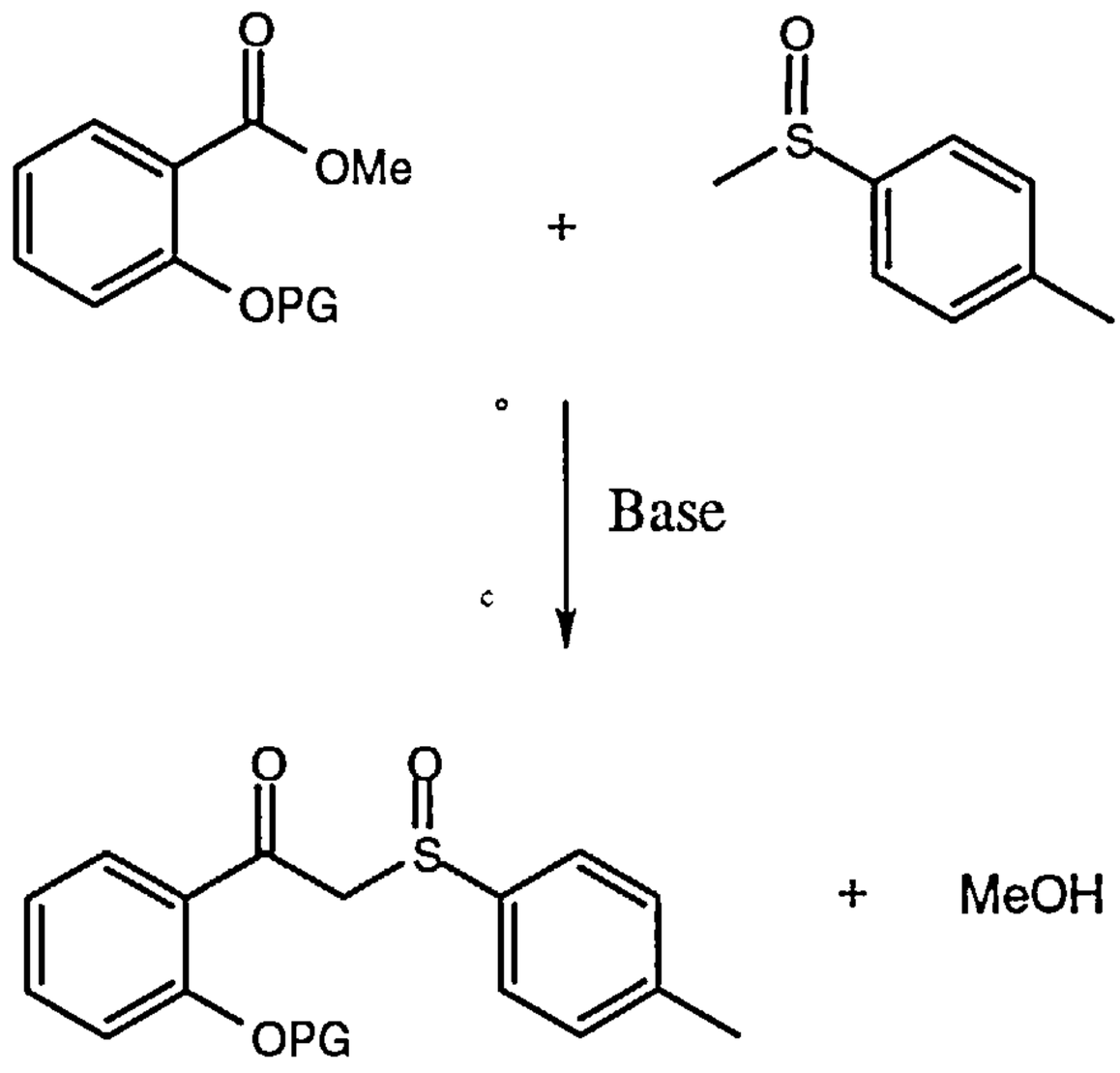
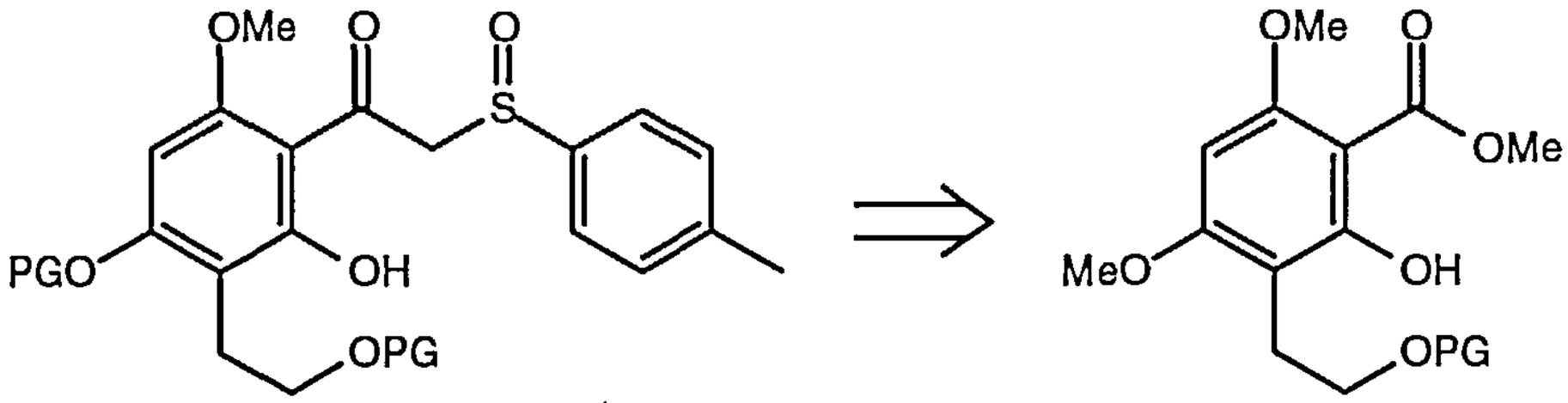


Figure 6.1.3

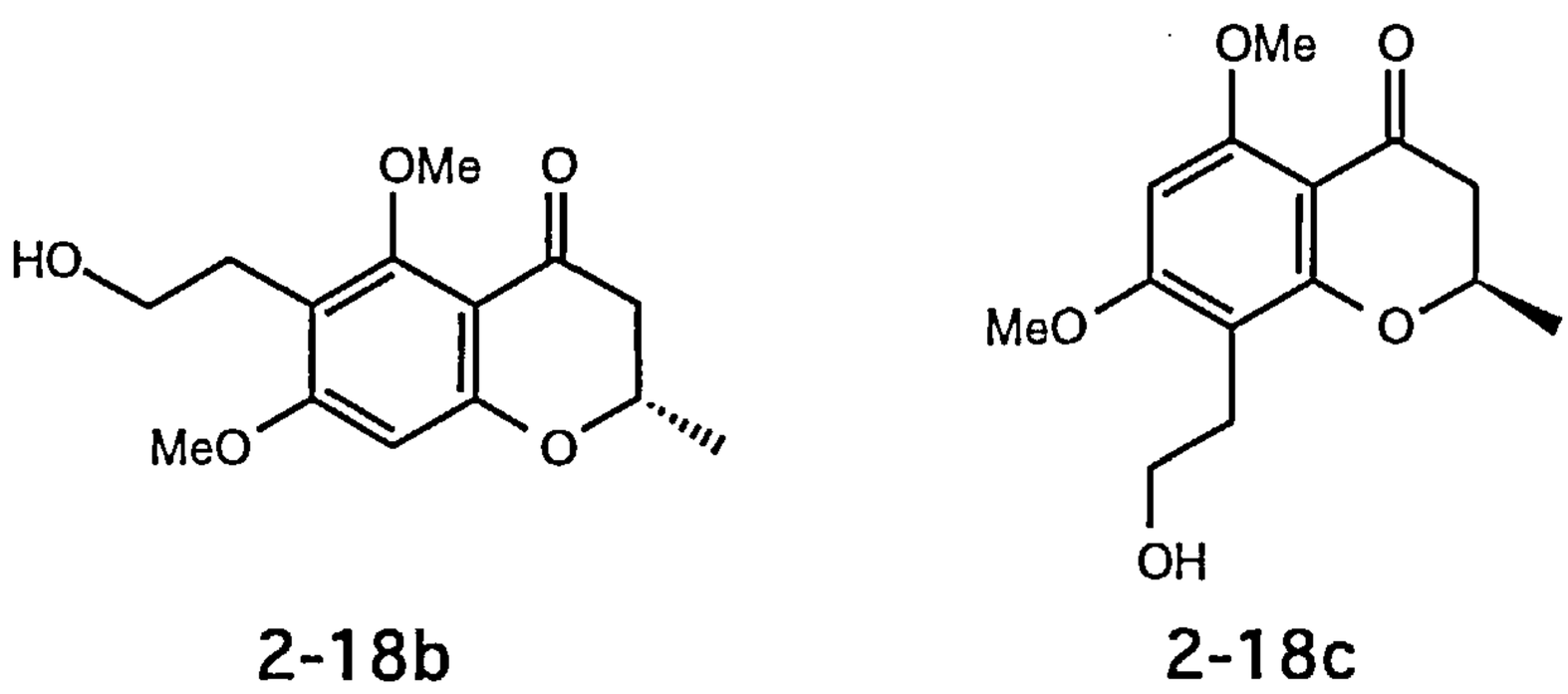
Knowledge of this transformation, and the fact that the chirality at sulphur is generally undisturbed during such a manoeuvre allows us to pursue our retrosynthetic scheme further (see figure 6.1.4). The synthetic problems that remain along this path are thus the protecting group on the phenolic oxygen of **6-8**, and the introduction of the pendant ethoxy function in protected form. In Simpson's synthesis of LL-D253α the pendant group was synthesised from an allyl group *via* Lemiuex-Johnson cleavage and reduction. The allyl group itself was introduced by a Claisen rearrangement. We saw no reason to avoid this, but worries about the stability of such an electron-rich ring system under the conditions of prolonged heat necessary to such a transformation led us to consider an alternative.



6-8 **6-8a**

Figure 6.1.4

The pendant group could be generated by the hydroboration of a vinyl ring substituent. The vinyl group itself could be synthesised in two steps from an acetyl group, which could be generated *via* Fries chemistry. This would give us two convergent approaches to the key intermediate **6-8**, allowing some room for problems to occur without jeopardising the synthesis (figure 6.1.5). We decided that the protection for the ring hydroxyl could be left as a methyl ether *pro tem* while the rest of the synthesis was elucidated. This allowed for a less complicated NMR analysis than many protecting groups would give. It also allowed us to verify our product against the natural one without deprotection. The McGahren group, who first described LL-D253α, described a methyl derivative, giving full spectral data. They assigned the structure **2-18b** (see chapter 2). In fact they must have made **2-18c**, our protected LL-D253α unit.



2-18b **2-18c**

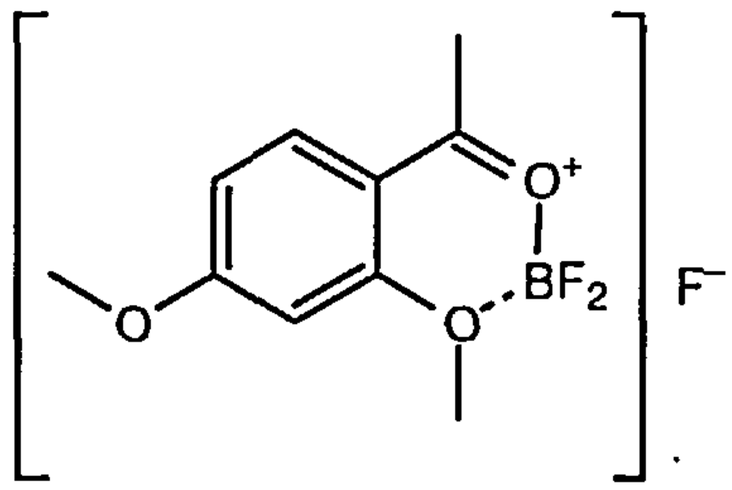
As can be seen both schemes depart from methyl 2-hydroxy-4,6-dimethoxybenzoate **6-9**. Preparation of this compound was therefore the first concern. The ready availability of 2,4,6-trihydroxybenzoic acid prompted us to adopt a

permethylation/selective demethylation approach. Directed demethylation of methyl aryl ethers adjacent to aromatic carbonyl groups is a well documented reaction. Reagents that have been used are Lewis acids such as aluminium trichloride,[140] boron trifluoride,[141] aluminium bromide[142] and magnesium iodide etherate.[143]

Figure 6.1.5

All these appear to function by chelation to the carbonyl oxygen in order to achieve the ortho direction for the demethylation, giving the proposed transition state **6-10**. Of the available reagents boron trichloride seemed to us the optimum balance between

reactivity and control. Thus we had our first approach to the critical sulphoxide intermediate.



6-10

6.1.2.1 Claisen approach to **6-8**

The Claisen approach to **6-8** relies upon the Claisen rearrangement[144] for the introduction of the carbon skeleton of the hydroxyethyl side chain. The Claisen rearrangement is a thermal, concerted, pericyclic[145] [3,3] sigmatropic rearrangement. Although, like the Cope rearrangement, its utility is largely limited by the high temperatures involved, it still finds application in synthetic circles.[146] The rearrangement proceeds *via* a dienone intermediate which rapidly tautomerises to the phenol. If anything stabilises the dienone, or interferes with the tautomerisation of the enolate[147] then a subsequent Cope rearrangement can take place leading to a *para* product. This second sequence is often known as the *para*-Claisen rearrangement (figure 6.1.6). In both cases the dienone intermediates may be trapped by Diels-Alder reactions. Many factors influence which rearrangement will take place, including substituents and solvent. As a rule of thumb polar solvents produce predominantly *ortho* products. The amount of selectivity shown in different solvents can vary quite considerably, making this an important factor.[148]

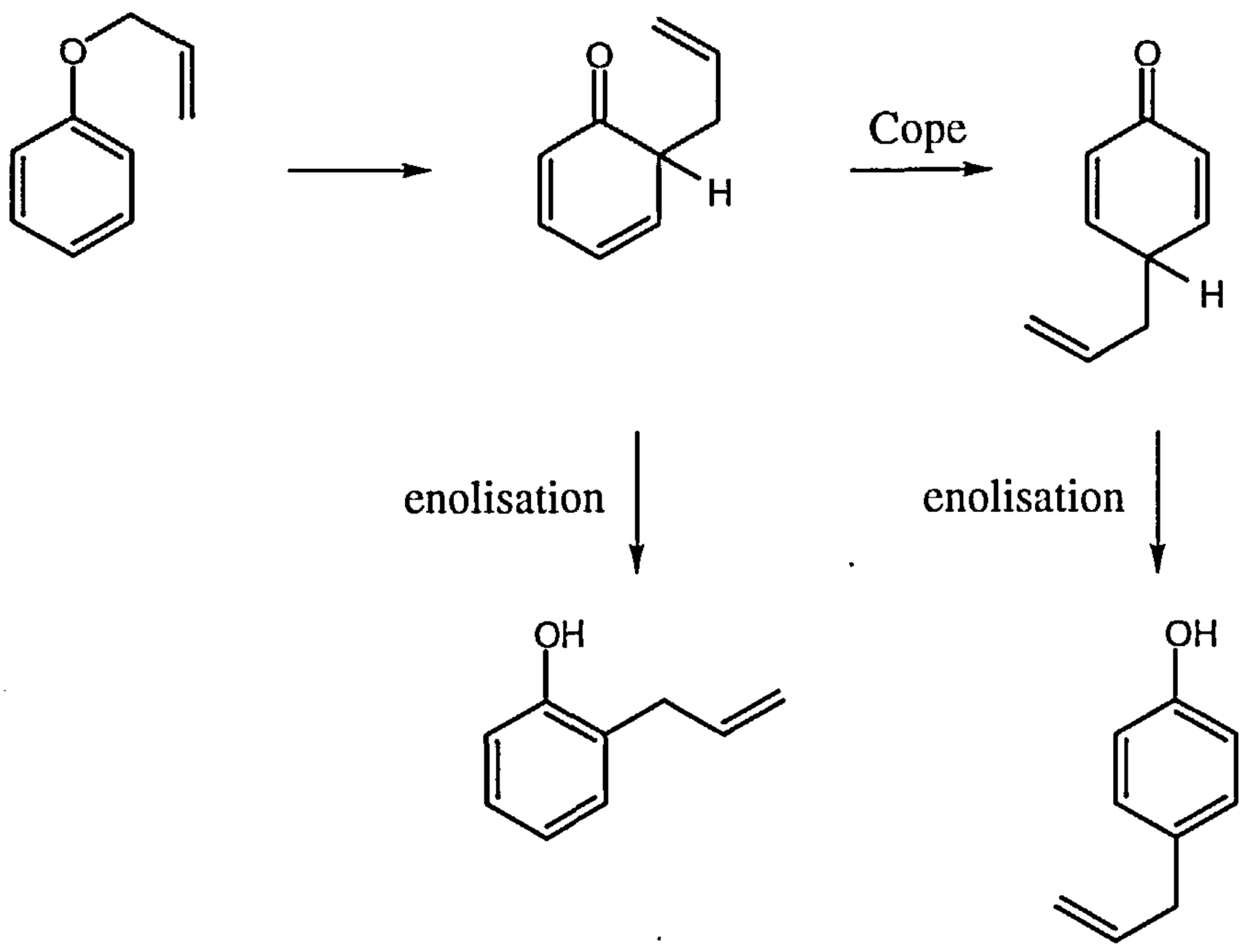
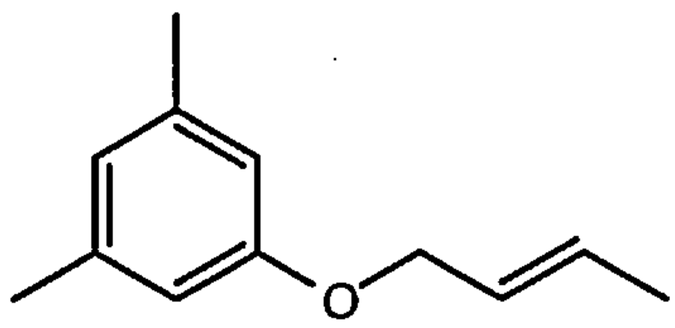


Figure 6.1.6

Changing solvent from decalin to N,N$_c$-dimethylformamide changed the *ortho:para* ratio of the rearrangement of **6-11** from 38:42 to 91:1.5. This can be explained by the ability of the polar solvents to facilitate the enolisation and restore aromaticity. Rapid enolisation removes the opportunity for further rearrangement.



6-11

Generally the *para*-Claisen rearrangement is unusual for unsubstituted allyl groups migrating to vacant *ortho* positions. Nevertheless when using the rearrangement it is probably good practice to be sure of which isomer is generated. For an approach to LL-D252α, after the generation of the *o*-allylphenol it would, at some point, become necessary to cleave the allyl double bond to gain the required chain length. This could be done by ozonolysis, but we shied away from such a harsh oxidant when a gentler alternative was at hand. The method of Lemieux and Johnson[149] can be undertaken in a variety of conditions and generally seems reliable. Subsequent selective reduction of the aldehyde would yield the desired group.

6.1.2.2 Fries approach to **6-8**

Our second proposed approach to LL-D253α was *via* a Fries rearrangement. The Fries rearrangement can be considered as an outgrowth of Friedel-Crafts chemistry. Similar Lewis acid catalysts, such as $AlCl_3$[150,151] and $FeCl_3$[152] are involved, although photo-induced Fries reactions are also known.[153] The Fries rearrangement consists of the migration of an acyl group from the phenolic oxygen of a phenyl ester to a ring carbon, in either the *ortho* or slightly more unusually the *para* positions. The rearrangement has been quoted as being intramolecular, intermolecular or both, and the results of crossover reactions seem to indicate that the mechanism is dependant on individual circumstances.[154] What seems certain is that the first step in the reaction is the formation of an associative complex between the carbonyl oxygen and the Lewis acid. This is followed by a nucleophilic attack on the carbonyl centre by the aromatic ring, and the collapse of the intermediate liberating a proton. Using traditional Lewis acids it is necessary to use at least equimolar quantities of the Lewis acid as the phenol thus formed will sequester the catalyst (figure 6.1.7). Another problem with these more venerable Friedel-Crafts catalysts is that, as may be remembered, they are potent, though selective, demethylating agents. Though syntheses do exist where demethylation, esterification and Fries rearrangement are undertaken as a 'one-pot' process[155] these seem to give rise to unusual products. The photo-Fries reaction allows rearrangement of rings with *meta*-directing substituents, but often gives rise to larger percentages of *para* products.

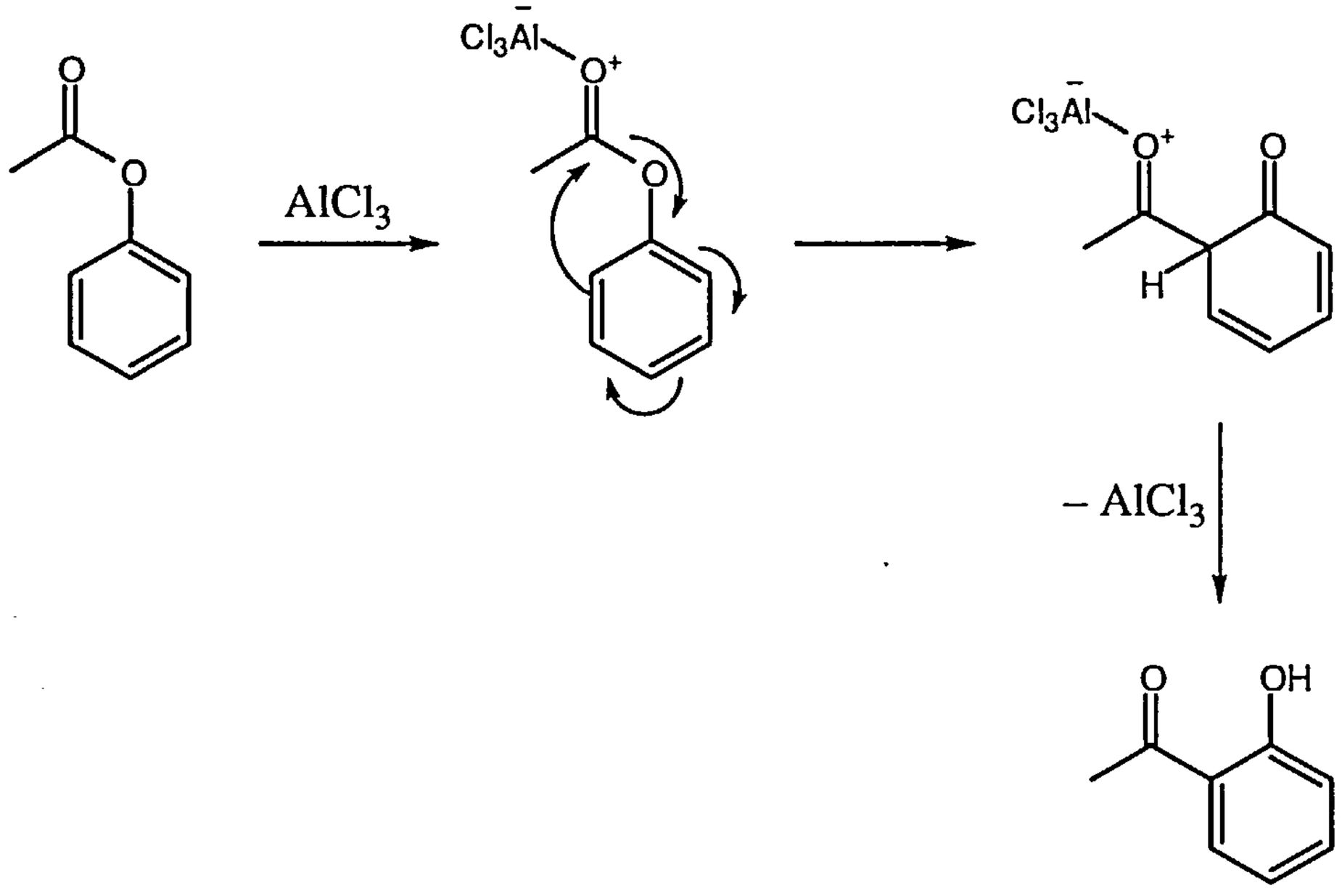


Figure 6.1.7

A new group of catalysts for the Fries rearrangement were put forward in 1995 — the rare earth triflates.[156] These were shown to be efficient catalysts of the Fries reaction in naphthyl systems, the Friedel-Crafts reaction[157] and the intermolecular carbonyl-ene reaction,[158] and to be active in the presence of free hydroxyl groups. They are not associated with demethylations and are often recyclable. We decided that a trial on electron rich phenolic systems was required. The acyl group thus introduced could be reduced selectively with, say, sodium borohydride then eliminated with DBU to give the desired vinyl group. Thus the outlines of both initial syntheses of **6-8** were posited.

6.1.3 Approaches via enolate chemistry

Sulphoxides have been prepared in chiral non-racemic form by the use of enolate ions of 1,3-diketones and similar compounds, as alluded to above. This chemistry is based on the displacement of menthol from an enantiopure menthyl sulphinate. This displacement seems to follow an SN2 mechanism. It results, at any rate, in the clean inversion of the stereocentre at sulphur. This is a development of the reaction by which chiral non-racemic methyl *p*-tolyl sulphoxide is prepared, the copper-catalysed displacement of menthol from menthyl *p*-tolylsulphinate by a methyl organometallic

compound.[159] The displacement by enolates has a long history[160] but has not been applied to aryl methyl ketone substrates with much success. We decided to keep this in reserve in case of failure of the first two syntheses. A retrosynthetic plan for this approach would be essentially similar to the preceding ones with only the nature of the ring carbonyl group being different. We decided that the Claisen variant of this synthesis should be pursued first, as it would give the least ambiguous NMR spectra for judging the course of reaction. The scheme is outlined below in figure 6.1.8. Due to the lack of clear evidence of the stereoselectivity of the displacement by simple phenyl enolates it was decided that a simpler enolate should be used as a trial molecule. We decided to use 2-hydroxy-5-methylacetophenone **6-12**, as its sulphoxide had already been synthesised unambiguously both by us and a co-worker *via* ester displacement,[161] so that assessment of product purity would be relatively straightforward.

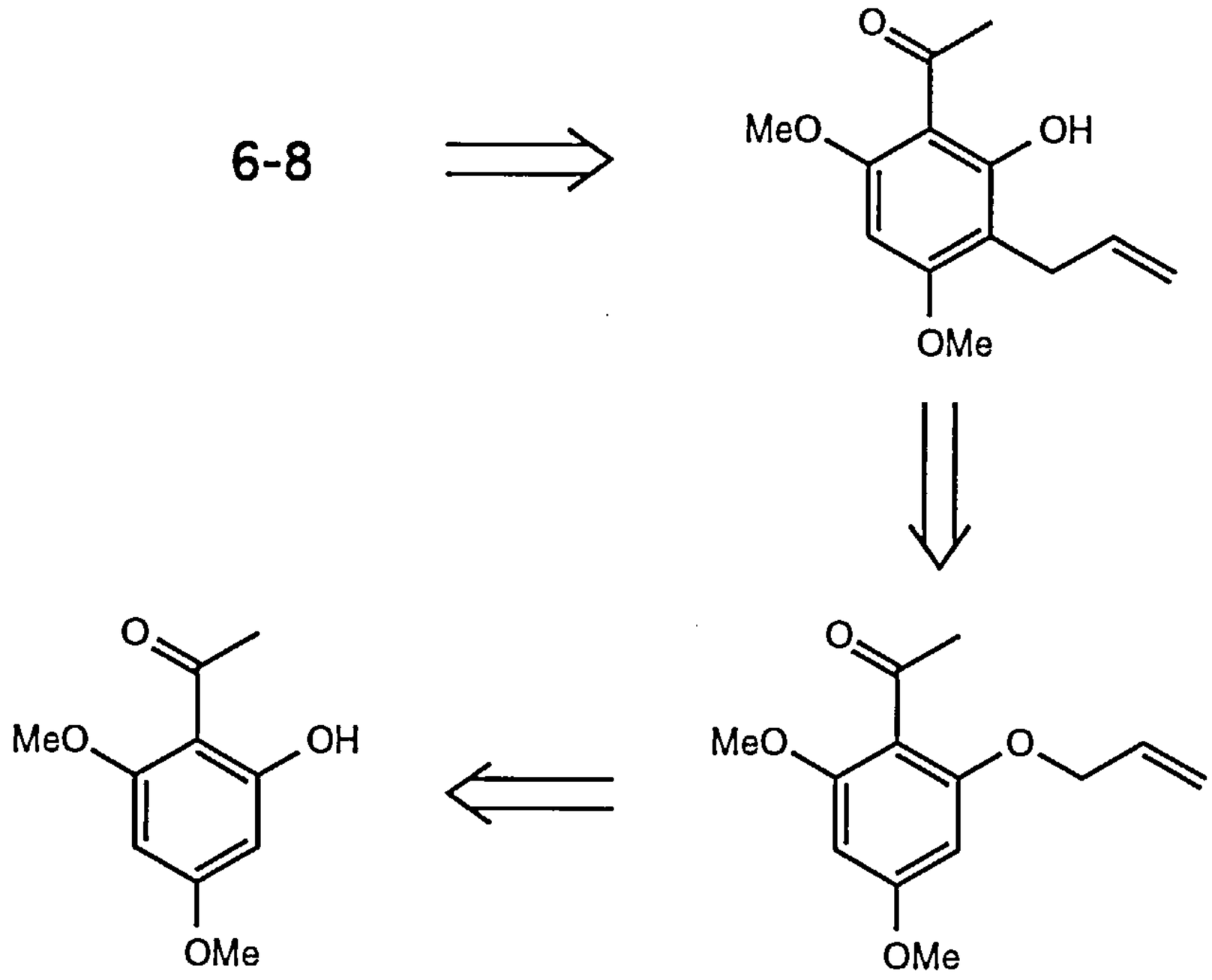
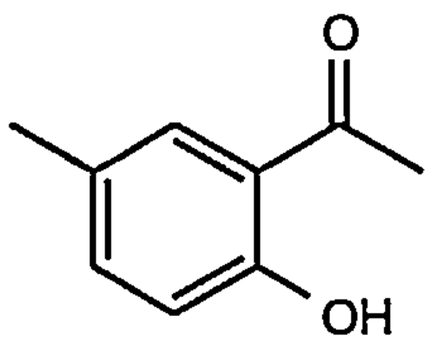


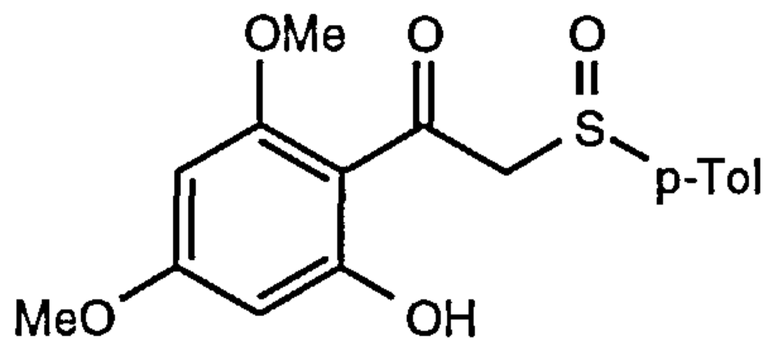
Figure 6.1.8

Previous work in our group had suggested that it was not necessary to protect the *ortho* hydroxyl of similar compounds when performing ester displacement so we assumed that one could leave it unprotected for this reaction as well. Thus two

equivalents of base would be needed for the reaction, one to deprotonate the phenol and one to deprotonate the ketone. We anticipated that it might be necessary to use a base such as lithium diisopropylamide but also anticipated that potassium hydride or potassium hexamethyldisilylamide might be utilised, and are certainly more convenient. Finally we considered that a secondary model compound might be the potential pinocembrin precursor **6-13**, which had been the subject of undergraduate projects in our group.



6-12

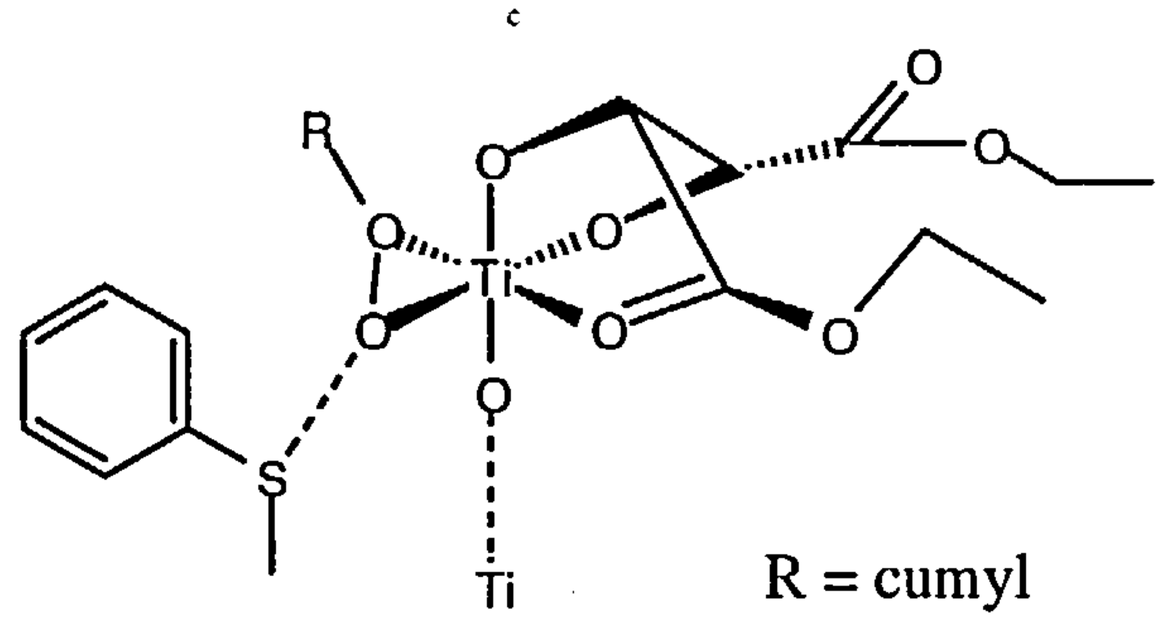


6-13

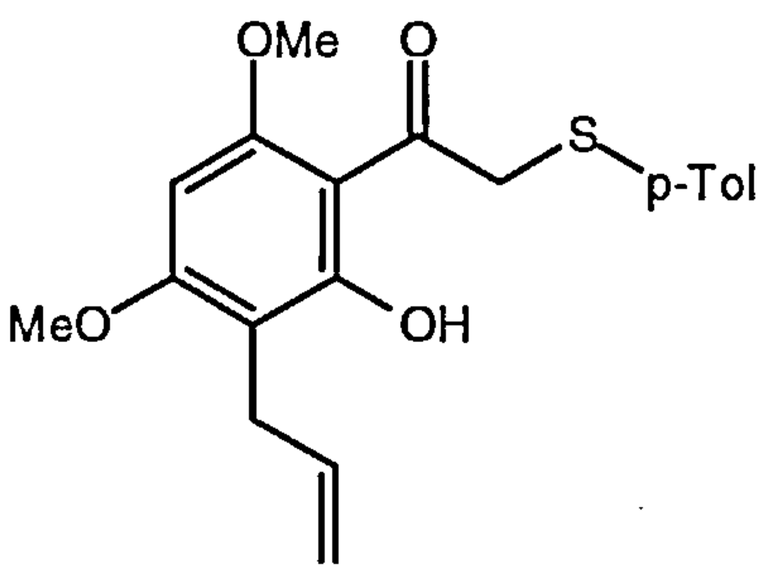
6.1.4 Oxidative approach to **6-8**

The preparation of sulphoxides by the oxidation of thioethers has long been a method of preparing sulphoxides in racemic form.[162] Reagents used have included hydrogen peroxide (both alone and with catalysts), peracids, hypochlorite, ozone, oxygen and nitric acid. Our own experience showed *m*-CPBA to be a reliable system.[163] In recent years the advent of several systems for the chiral oxidation of thioethers began to make this a viable option for the synthesis of chiral non-racemic sulphoxides. Many systems are potentially viable. Enzymatic systems have been known to produce good results, particularly when utilised as a microbial or fungal ferment. Examples of the latter are *Helminthosporium* sp. NRRL4671 and *Mortierella isabellina* NRRL1757,[164] both of which will oxidise methyl *p*-tolyl sulphide to the sulphoxide as an enantiopure compound, but with opposite selectivity. Such methods are limited in scope, as the more symmetric the system the less the selectivity of oxidation. Stoichiometric oxidants did not appeal to us due to the expense involved in procuring such a large quantity of enantiomerically enriched reagents. Catalytic systems were therefore sought. Many exist,[165] and of the plethora of examples we looked specifically at two groups which seemed to show good results for a wide range

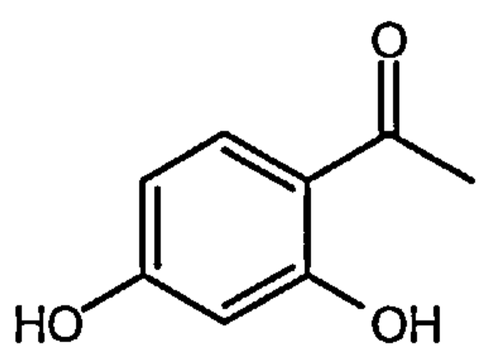
of substrates. These were the chiral manganese salen complexes,[166] which achieved e.e. values in the range 74-92%, and the Sharpless/Kagan/Modena system based upon titanium tartrate complexes,[167] of which the Kagan/Modena oxidant is titanium isopropoxide/diethyl tartrate doped with isopropanol in a 1:4:4 ratio. We chose this partly for its reliability and partly for the detailed instructions contained in Kagan's breathtakingly precise methodology paper.[168] This system is postulated as working through the formation of the complex **6-14** and is quite robust, though it shows less selectivity for aryl/aryl thioethers. In order to take advantage of this oxidant we would need to construct a basic thioether skeleton **6-15**. The synthetic approach to this could be made *via* a simple SN2 displacement of a halogen a to a carbonyl with the anion of 4-methylphenylthiol. Therefore we could use a similar approach to the main carbon skeleton as that outlined in the section above.



6-14



6-15



6-16

Here it becomes more urgent to use the Claisen route over the Fries, for as well as NMR advantages the Claisen route appeared to offer simplicity; we would not have to worry about brominating only one of two identical acetyl groups.

Bromination α to a carbonyl can be attempted in many ways.[169] Reaction with bromine in basic medium is often used but we were wary of using this reagent for two reasons. Firstly our ring substrate is easily oxidised, and the presence of a halogen in zero state could lead to unwanted reactions, secondly the allyl side-chain is a good protecting unit for our desired alcohol moiety and the halogen would not be compatible with it. Our attention was drawn to the use of cupric bromide as a selective and mild brominating agent for methyl ketones.[170] The system has been used in DMF,[171] dioxane[172] and ethyl acetate/chloroform.[173] As this latter system was used in the quantitative bromination of 2',4'-dihydroxyacetophenone **6-16** it seemed to be the best on offer, especially as the use of the dioxane system was seen to produce unwanted side reactions.[174] The retrosynthetic plan for this route is shown in figure 6.1.9.

6-15

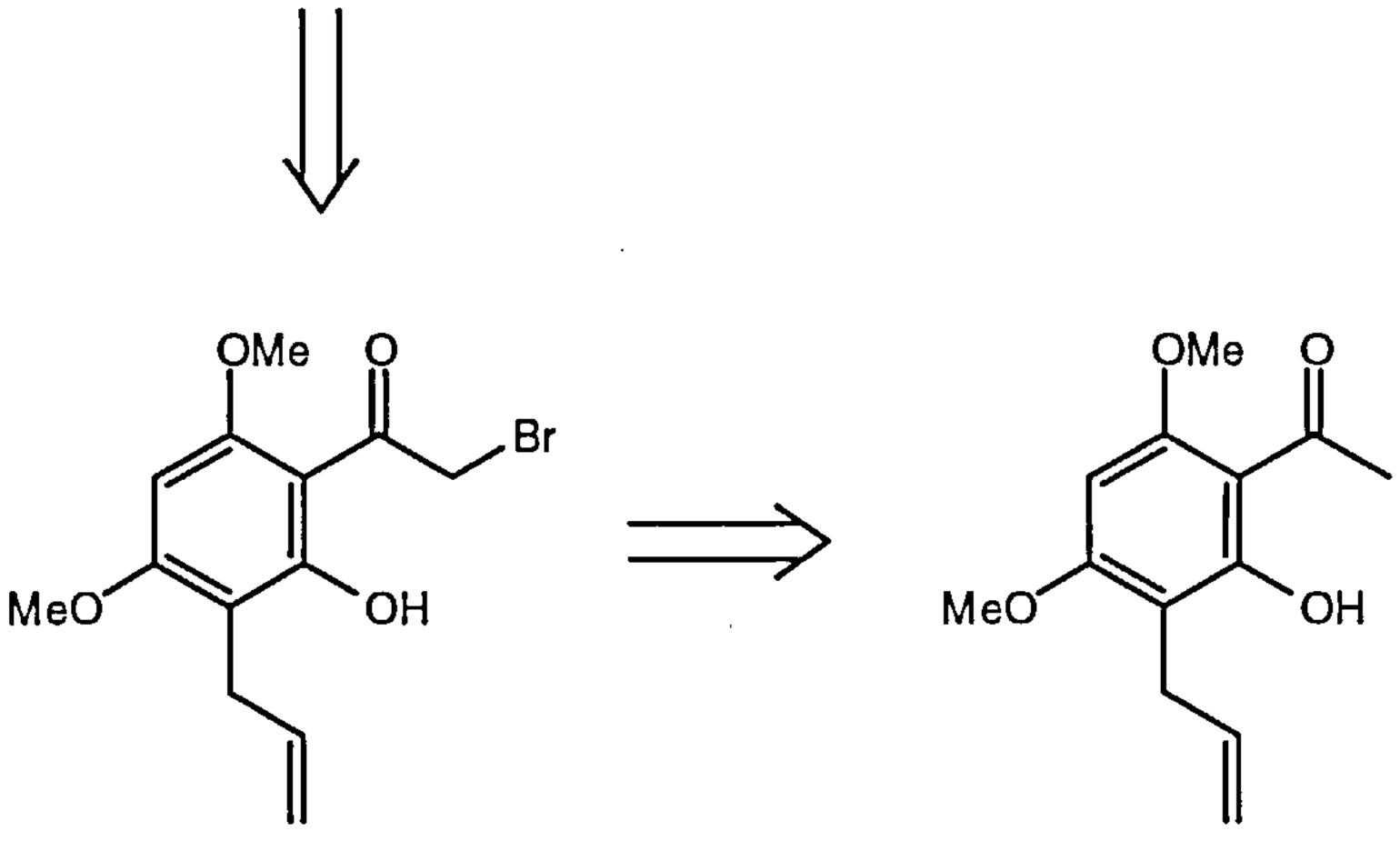


Figure 6.1.9

6.1.5 Approach to **6-8** via aldehydes

In a recent paper[175] Solladié put forward an alternative method of synthesis of chiral non-racemic sulphoxides with particular reference to those attached to 2,6-dioxygenated benzene rings. In this method the methyl *p*-tolyl sulphoxide anion is generated and then reacted with the desired substrate which is in the form of a benzaldehyde. The resultant β-hydroxysulphoxide, as a mixture of diastereomers, is then oxidised to give the target β-ketosulphoxide. This method appeared robust and efficient, and we drew up the following retrosynthetic scheme (figure 6.1.10).

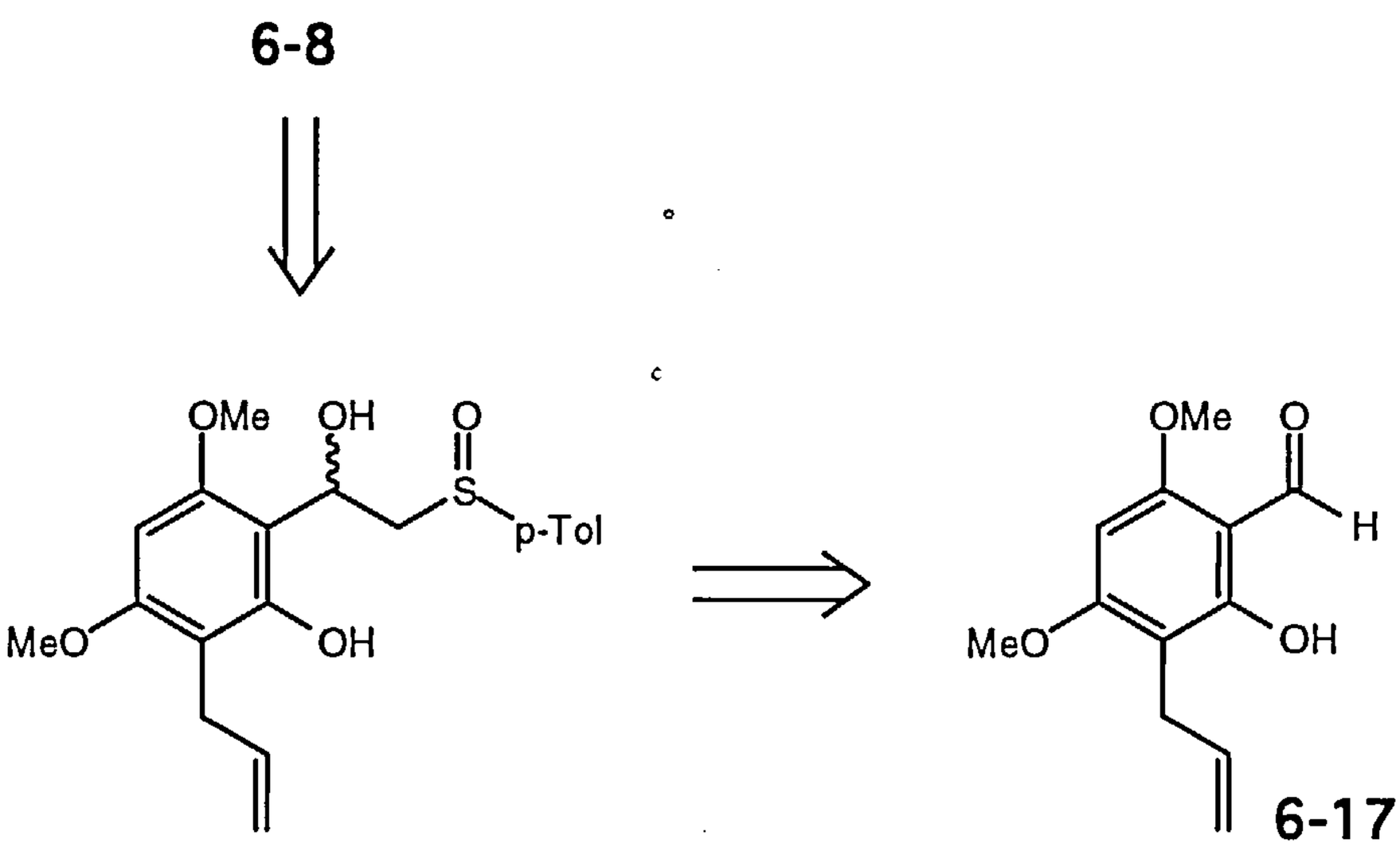


Figure 6.1.10

The aldehyde **6-17** could, in principle, be prepared in effectively the same way as the ketone precursor with the difference of starting from 2,4,6-trimethoxybenzaldehyde (figure 6.1.11).

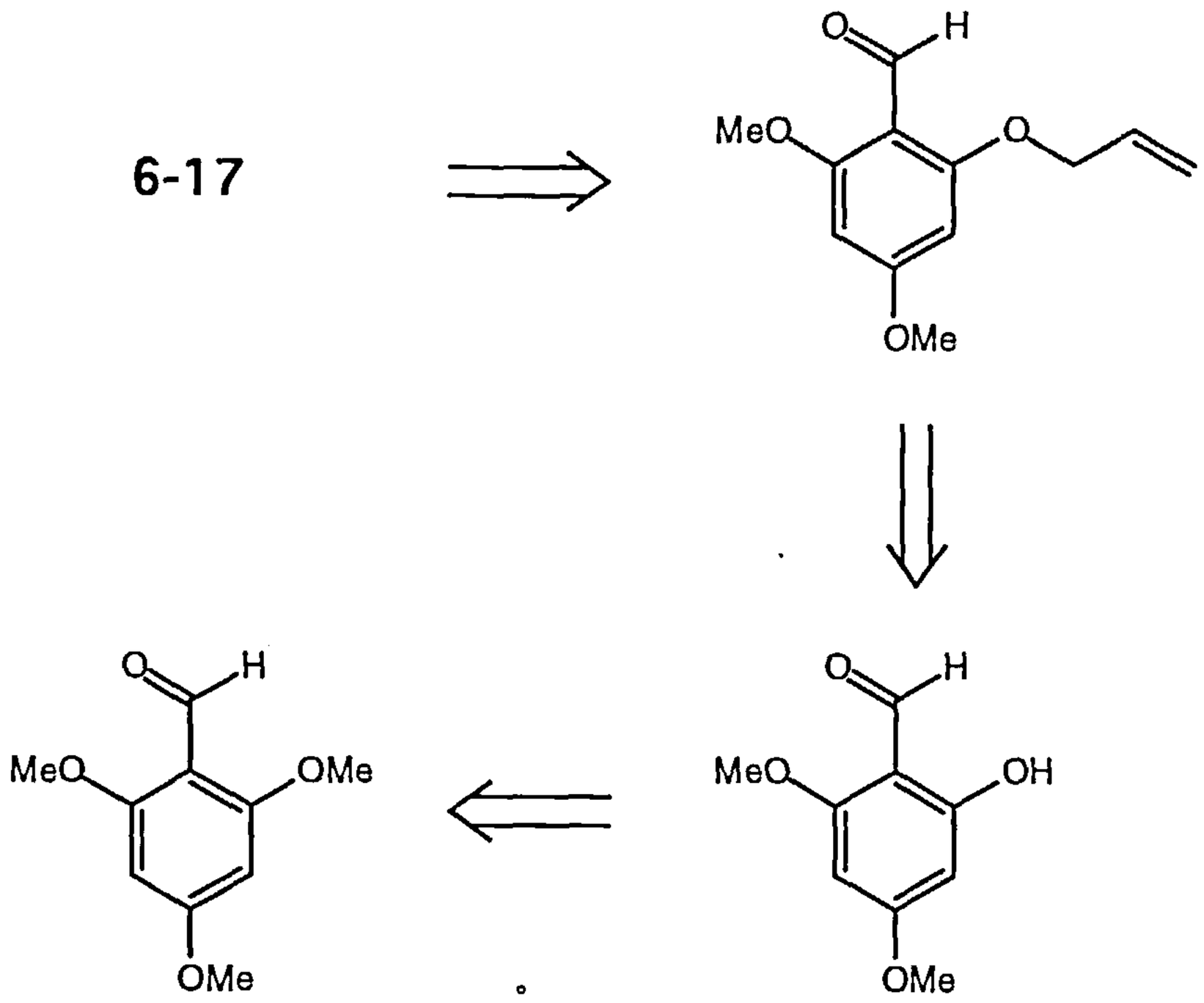


Figure 6.1.11

Solladié also included a mild method of formylating and cyclising the sulphoxide to a chromone using N-formylimidazole generated *in situ*. We decided to keep this in reserve.

6.2 Results and discussion

6.2.1 Approaches *via* methyl ester

6.2.1.1 Claisen Approach

The first section of this approach proceeded according to figure 6.2.1. Both reactions went in moderate yield without incident. The final hydroxydimethoxy ester can be purchased from Aldrich but its preparation is simple and cost-effective.

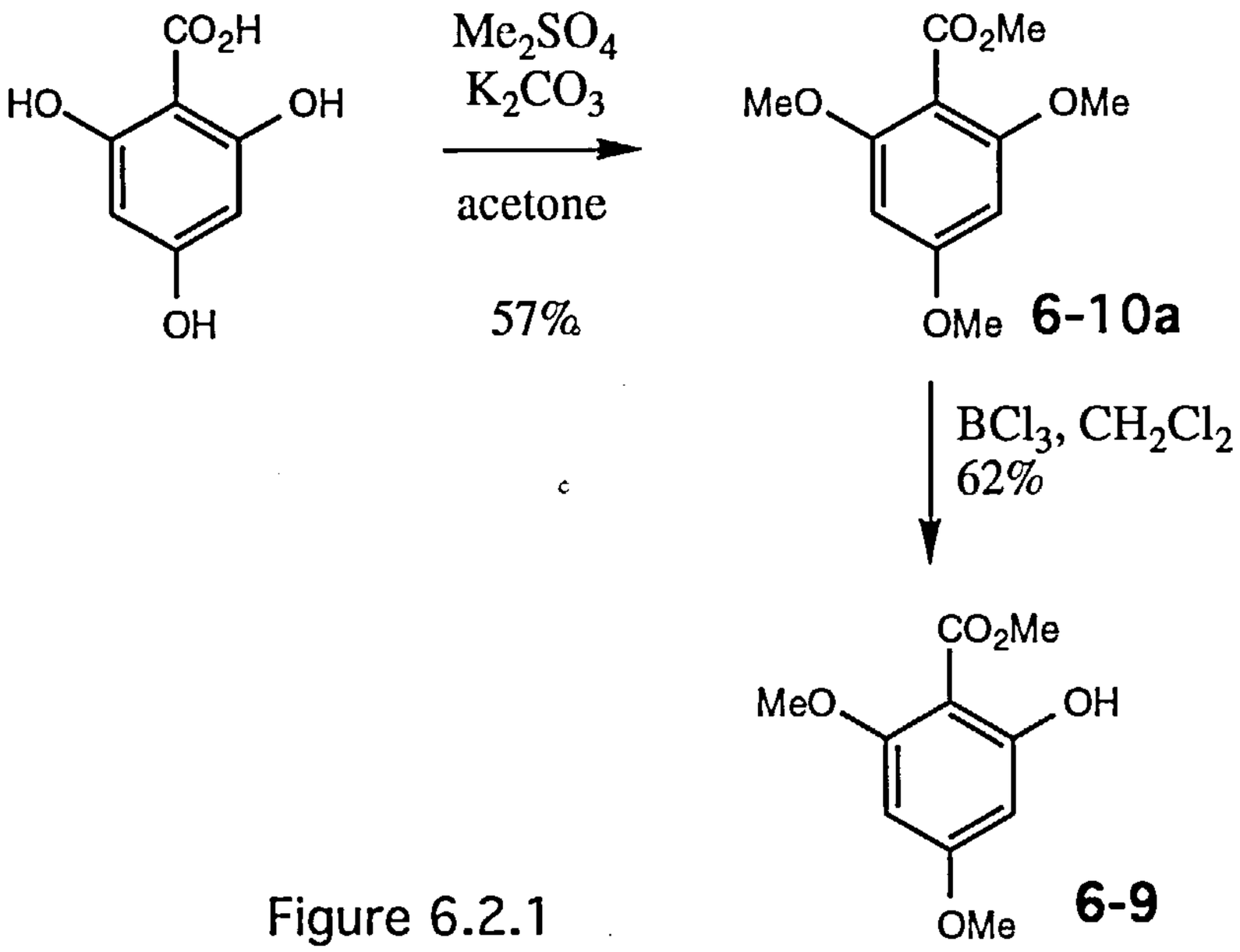


Figure 6.2.1

The mechanism of the methylation is essentially the same as that of the Williamson ether synthesis. It was found that the best results were obtained by use of an excess of both potassium carbonate and dimethyl sulphate. The mechanism of the selective demethylation is somewhat more involved. As has been mentioned above the first step is an association between the Lewis acid and the carbonyl oxygen. The subsequent association between the ether oxygen and the Lewis acid is therefore limited to the *ortho* ethers as the effective concentration of these must be much higher. Displacement of the phenol by chloride then takes place. The selectivity of this reaction is very high. This, and the fact that the ester does not seem to be demethylated led to the assumption that chelation to a carbonyl oxygen is the first step and a rapid one (figure 6.2.2). Allylation of the monohydroxy product proceeded without incident to give a yield of 76%, although this was of necessity crude, as the

product was difficult to separate on silica and when distilled underwent rearrangement.

The Claisen rearrangement was at first undertaken in a variety of solvents, such as dichlorobenzene and 80-120° petroleum ether. No transformation was observed under these conditions, even after prolonged reflux. Given that the product was a liquid with a high boiling point we determined that the best course was to reflux the neat compound under argon at around 200°C. At the end of 12h the flask was seen to be full of fine white needles, and the transformation was found to have taken place essentially quantitatively.

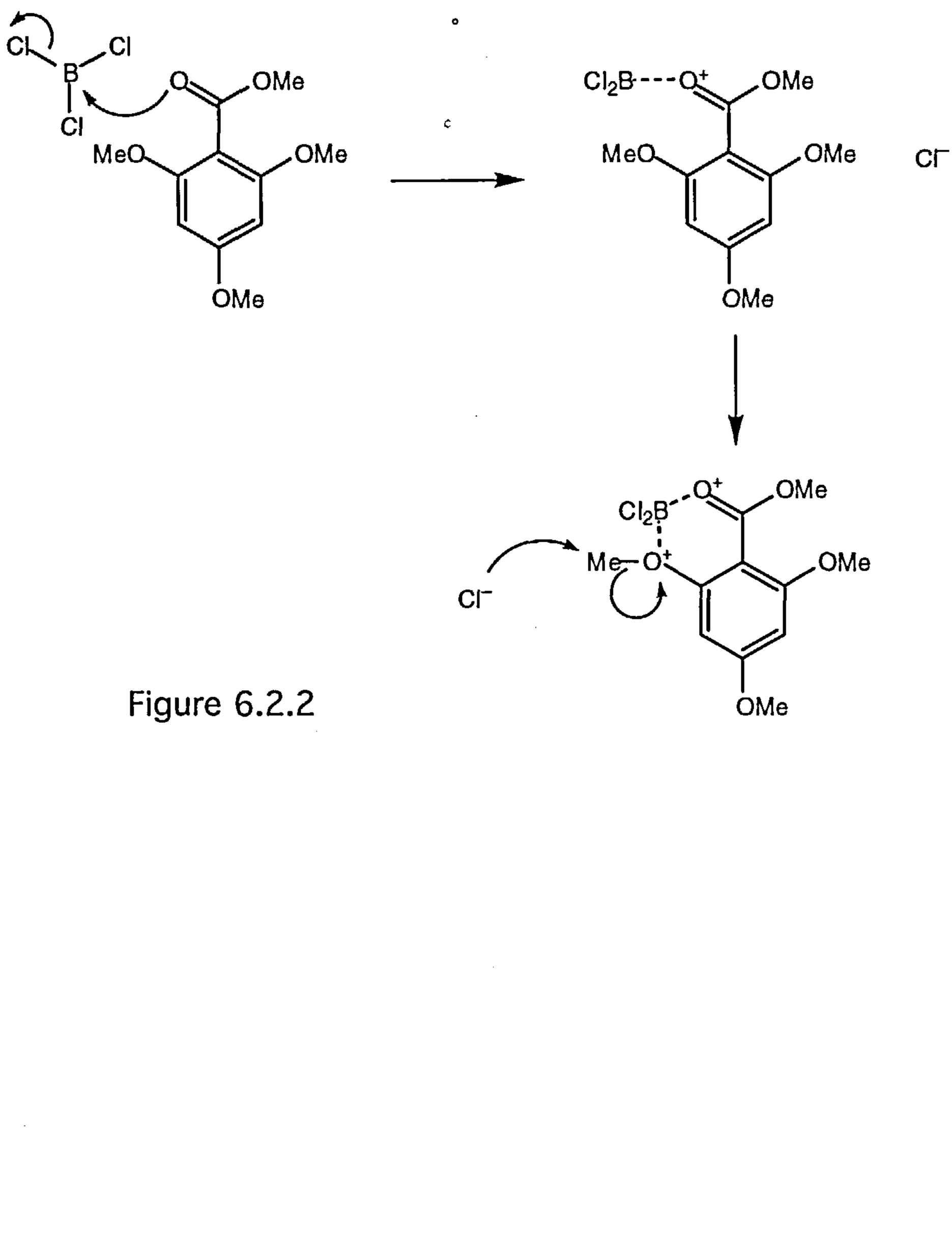
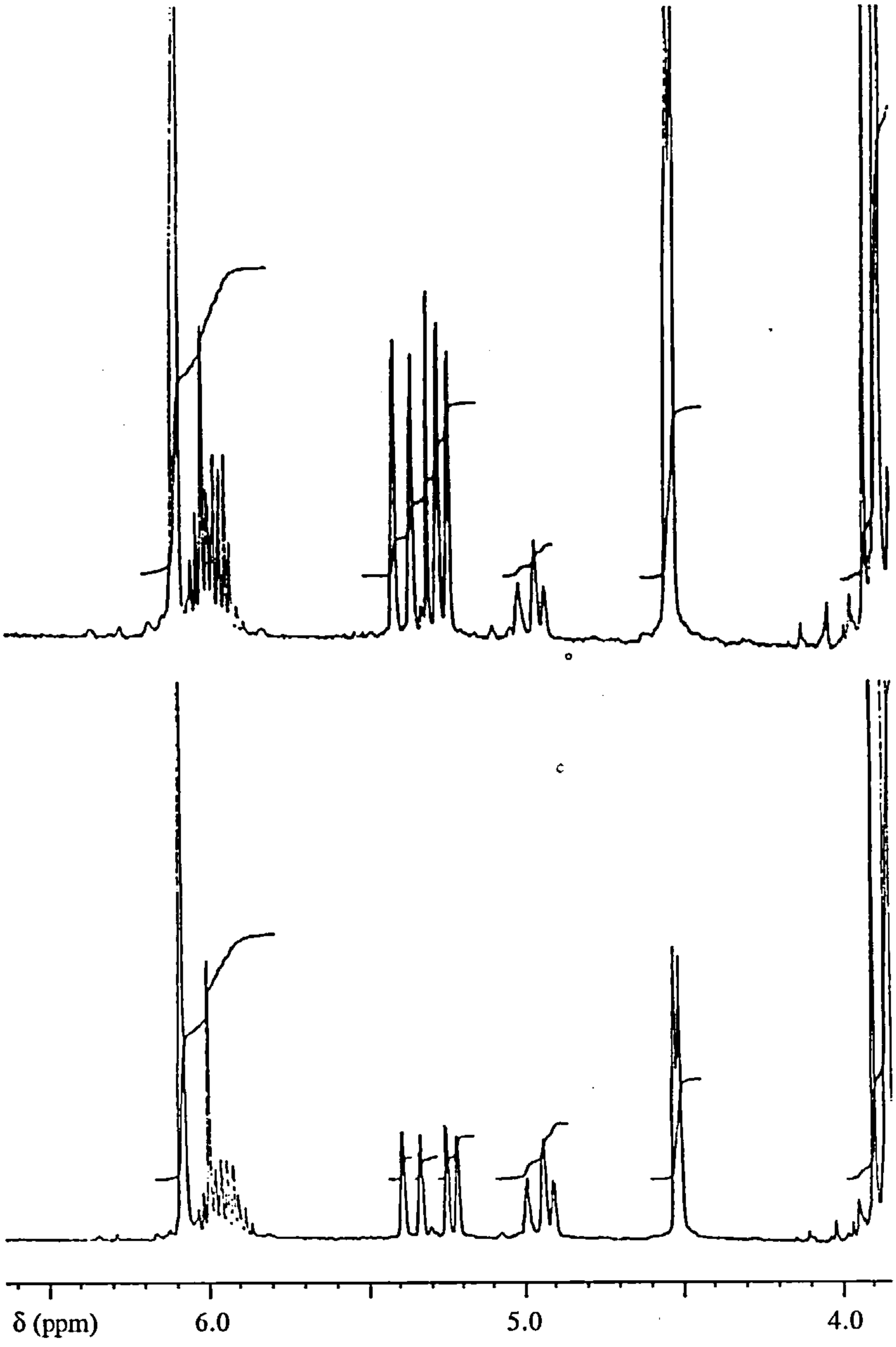


Figure 6.2.2

Progress of Claisen rearrangement monitored by NMR spectra



As can be seen from the spectra above the rearrangement is easy to follow by its ^{1}H NMR spectrum. The two spectra shown are of aliquots extracted after 2 h (upper line) and 6 h. (lower line). The clearest markers are the growth of the multiplet centred at δ 4.95 ppm and the diminution of the group of multiplets at δ 5.1-5.5 ppm.

This completed the first stage of the synthesis of the methyl ester precursor of **6-8** (figure 6.2.3). However, given the possibility of a *para*-Claisen rearrangement having taken place we decided to try to verify the structure of our product.

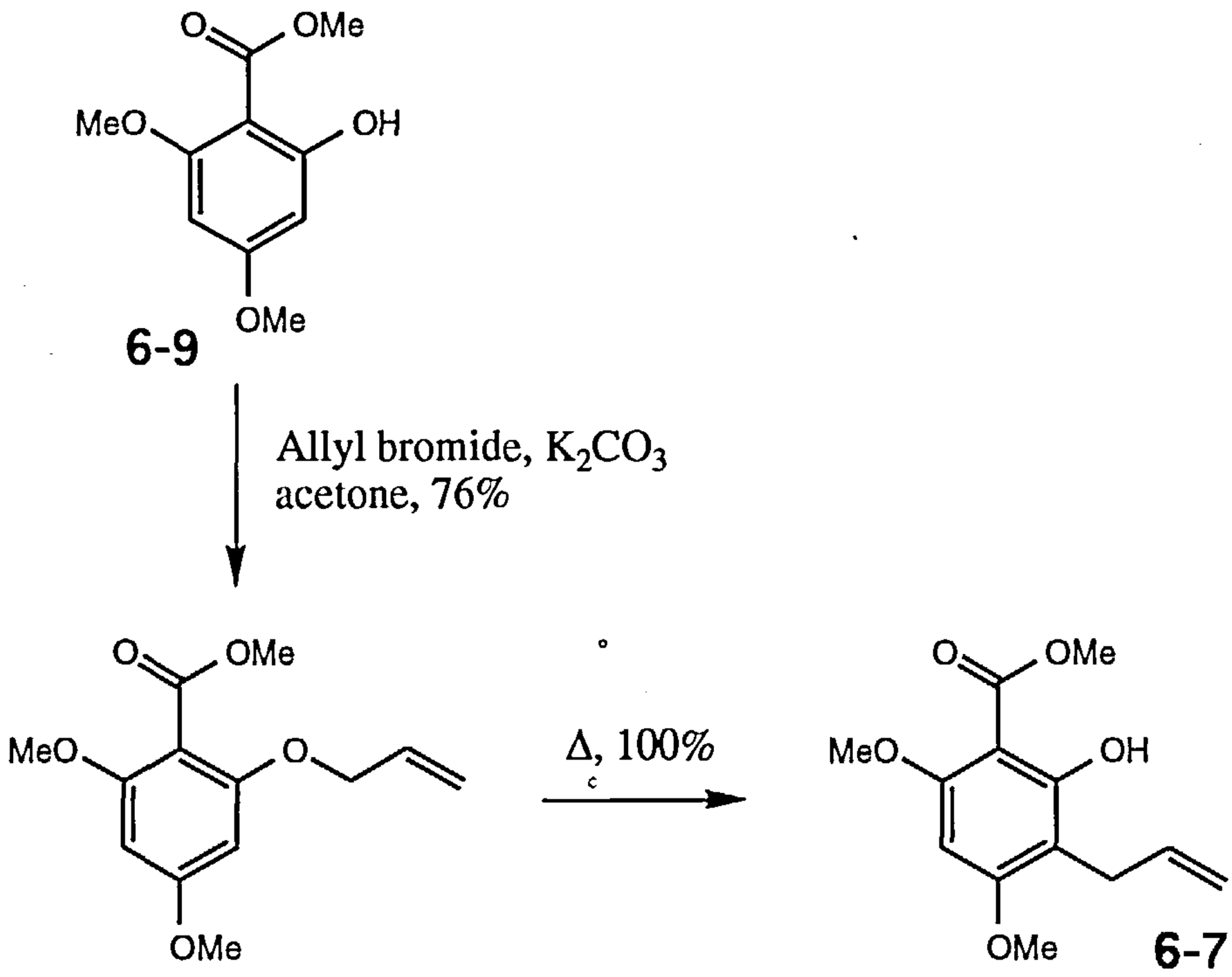


Figure 6.2.3

It was reasoned that the clearest way of ascertaining if the reaction had gone in an *ortho* or a *para* sense was to undertake a reaction between the hydroxyl group and the double bond intramolecularly. Obviously if a reaction of this type could take place the rearrangement must be *ortho*. With this in mind we postulated the oxidation of the allyl double bond to the corresponding epoxide and utilising the hydroxyl group as an internal nucleophile, a scheme shown in figure 6.2.4.

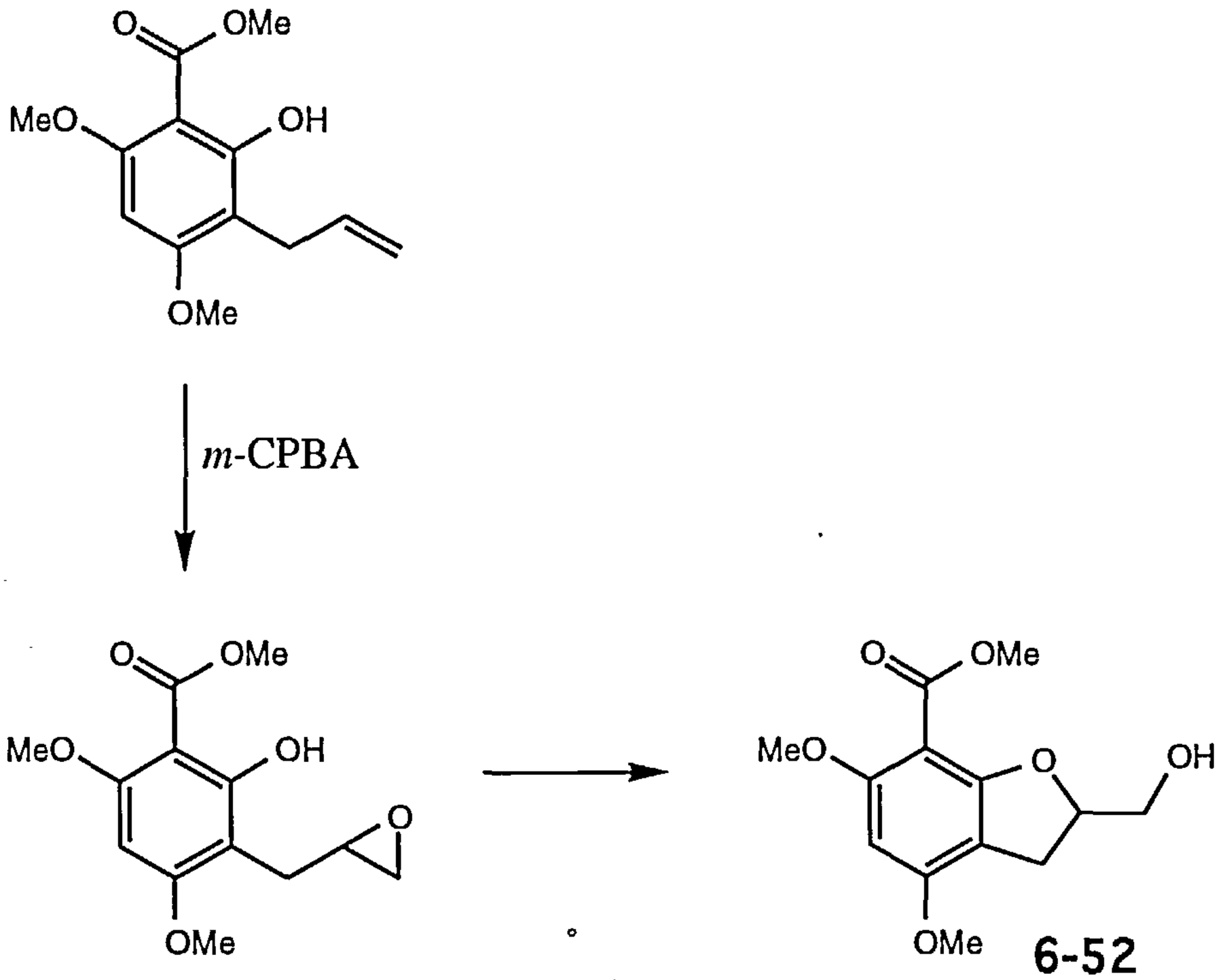
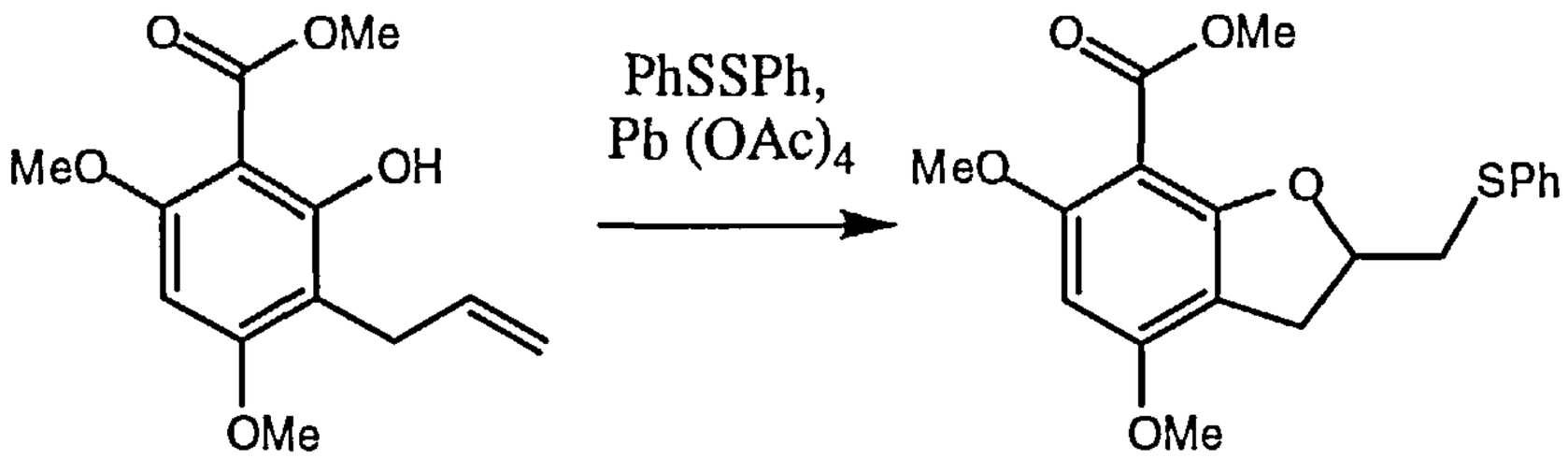
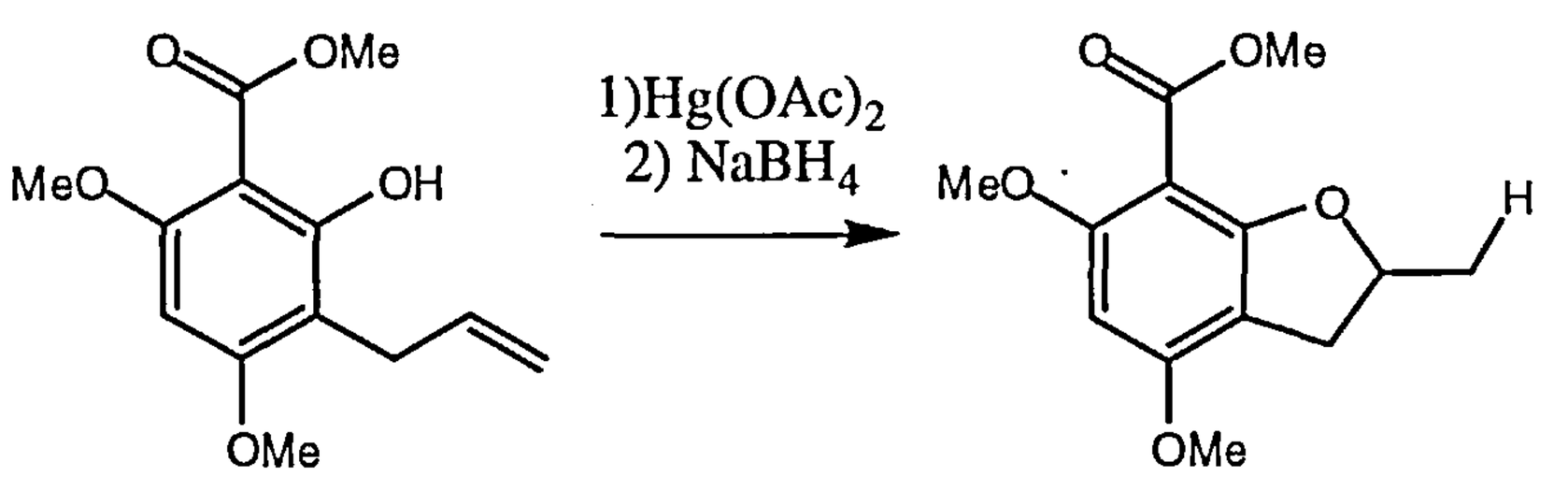


Figure 6.2.4

Such reactions have been successfully undertaken before.[176] Our attempts with 3-chloroperoxybenzoic acid to achieve this transformation led to a complex NMR spectrum that did not correspond to the desired product, as it showed no aromatic protons. The compound was not fully characterised but we theorised that it was the result of oxidation of the ring to a quinone rather than attack on the allyl double bond. With this setback we reconsidered our strategy. We put forward several reactions that can proceed, or be modelled as proceeding, *via* a cyclic electrophilic state such as an epoxide. From these we selected sulphenylation, oxymercuration and iodination as good examples. These would give the products shown in figure 6.2.5.





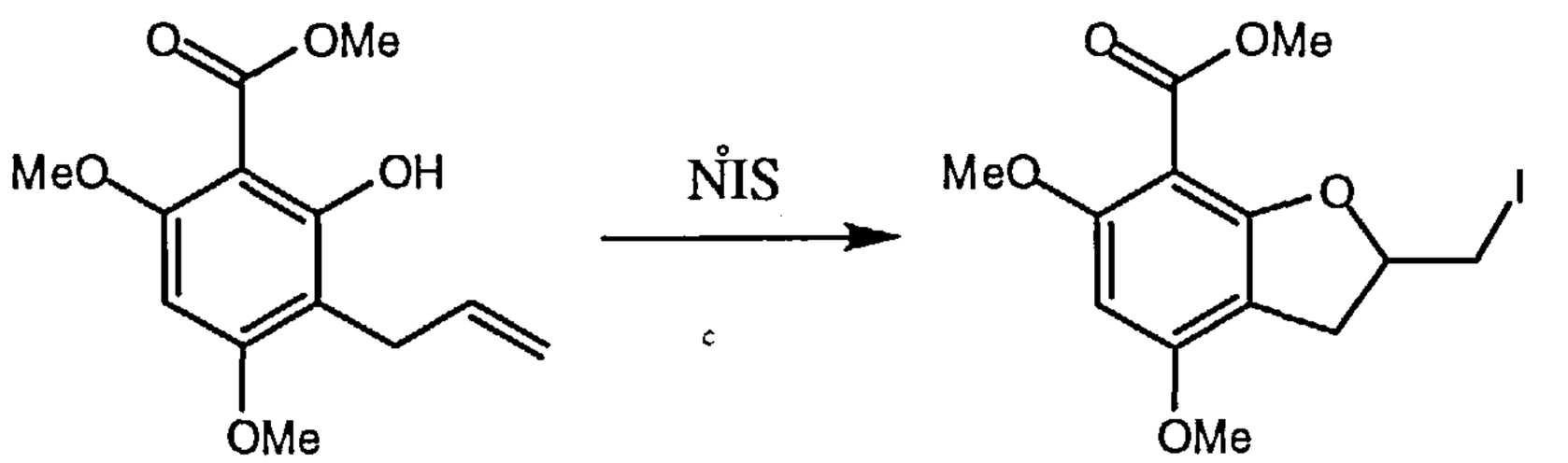
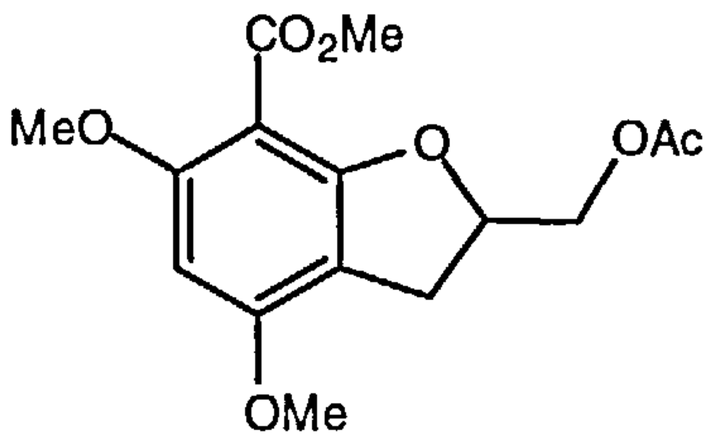
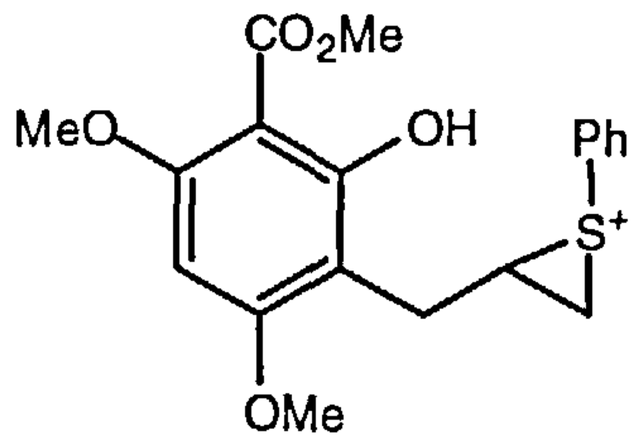


Figure 6.2.5

These three reactions were attempted. The sulphenylation reaction was originally supposed to work with trifluoroacetic acid acting as a nucleophile. As our substrate contained its own nucleophile we omitted this reagent. The compound we isolated presented something of a puzzle. It was present in 41% yield, yet contained no 'normal' aromatic protons. The rest of the spectrum was much as expected, with the addition of a 3H singlet at δH 2.02 ppm. This, and the mass spectrum containing MH^+ at 311 led to the structural assignment **6-18**.



6-18



6-19

To understand this it is necessary to look at the proposed mechanism for the reaction. In Trost's paper on the original form of the reaction he states that the reaction behaves as though ArS^+ were formed, leading to the formation of an episulfonium ion, **6-19**, or equivalent. Clearly in our case we were failing to activate the diphenyl disulphide. This could be because of the difference in reactivity between lead tetracetate and the lead tetra(trifluoroacetate) formed in the original. Thus our reaction did not use the diphenyl disulphide at all, a fact confirmed by running the reaction again with only the lead salt and achieving a similar compound in 49% yield. This is analogous to a reaction that occurs with allyl alcohols,[177] though other workers have had difficulty extending the reaction to phenolic systems.[178] It is possible that the reaction proceeds *via* a radical mechanism, such as the tentative one below (figure 6.2.6). Given that this product gave a positive result for our structural check we were satisfied, though we would prefer more proof. So we proceeded through another of our proposed probe reactions, oxymercuration.

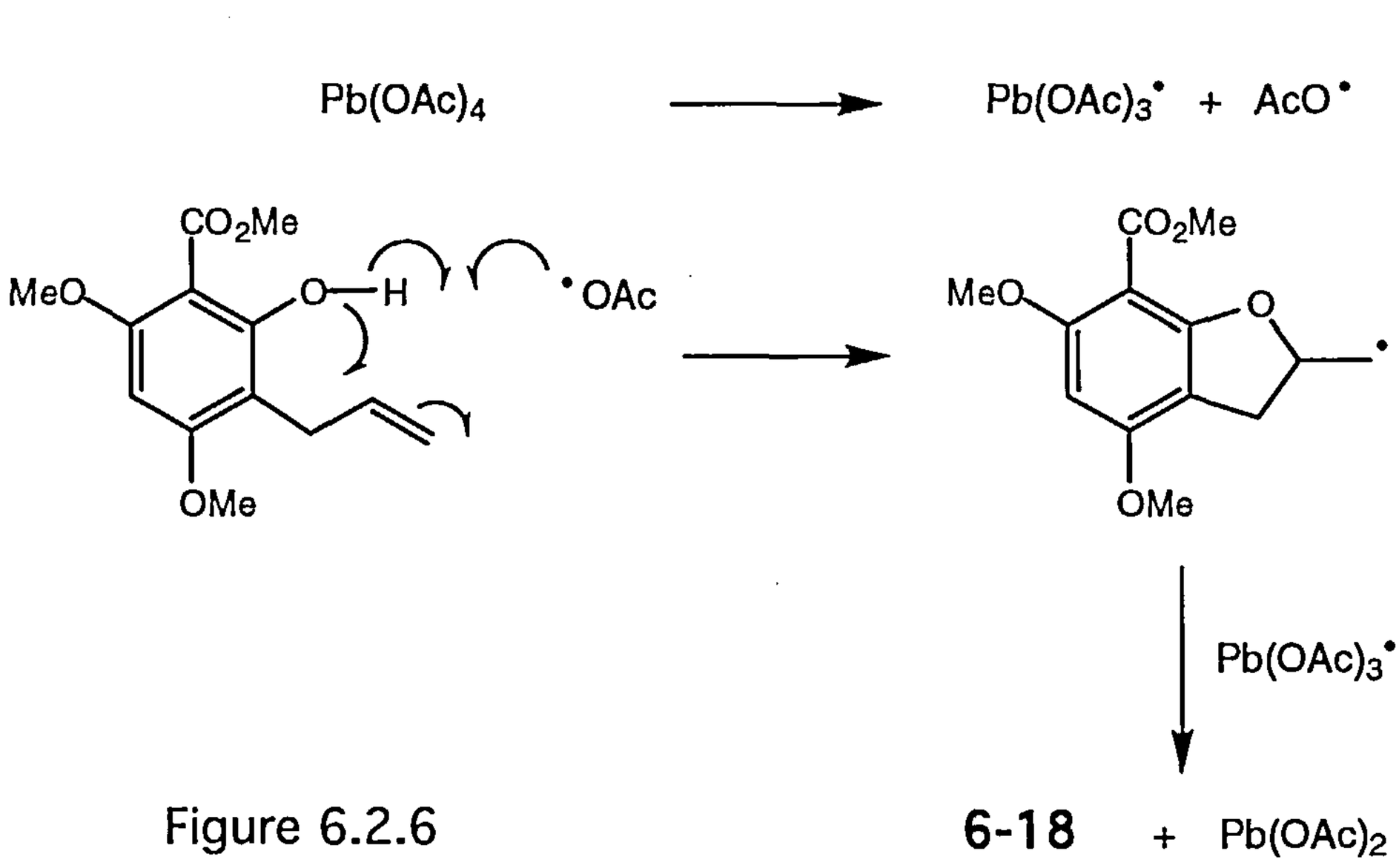


Figure 6.2.6 **6-18** + $Pb(OAc)_2$

Oxymercuration is a selective way of adding the components of water across a double bond in a Markovnikov sense. The reaction can be seen as proceeding through a cyclic mercurinium ion, which is collapsed by nucleophilic attack on the most substituted end of the group. The selectivity of the reaction can be explained by considering the equilibrium between cyclic and acyclic cationic states. A secondary

carbocation is more stable than a primary, leading to a selection of the product engendered by the nucleophile attacking this form (figure 6.2.7).

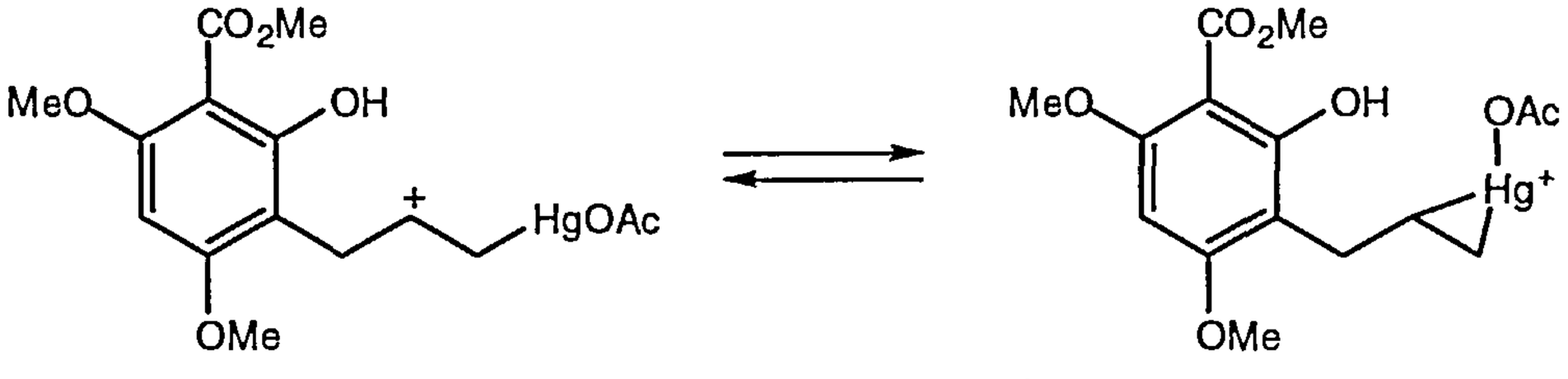
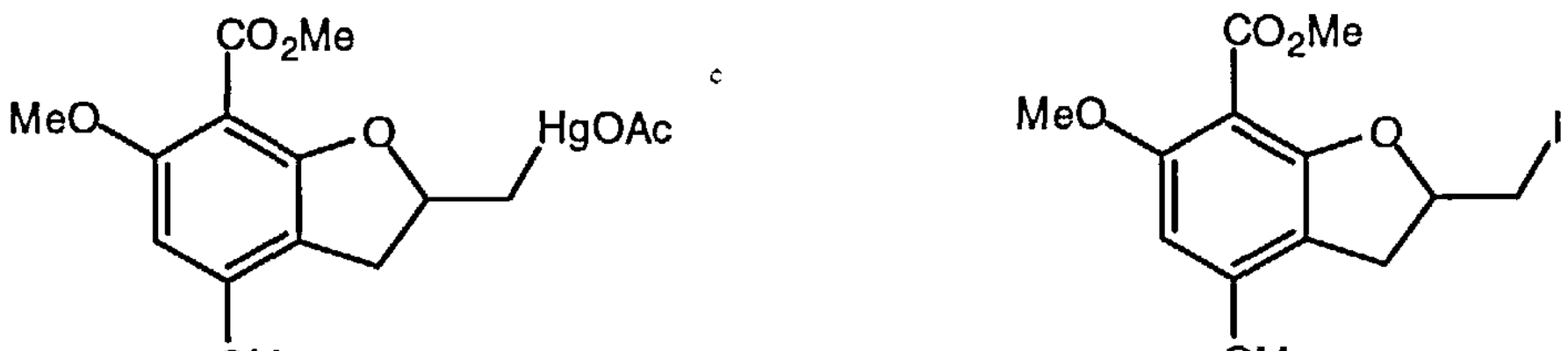


Figure 6.2.7

Using our substrate we are again in the position of using the phenol as an internal nucleophile, to create a mercuromethyl dihydrobenzofuran **6-20.** This form of reaction has been documented before.[179]

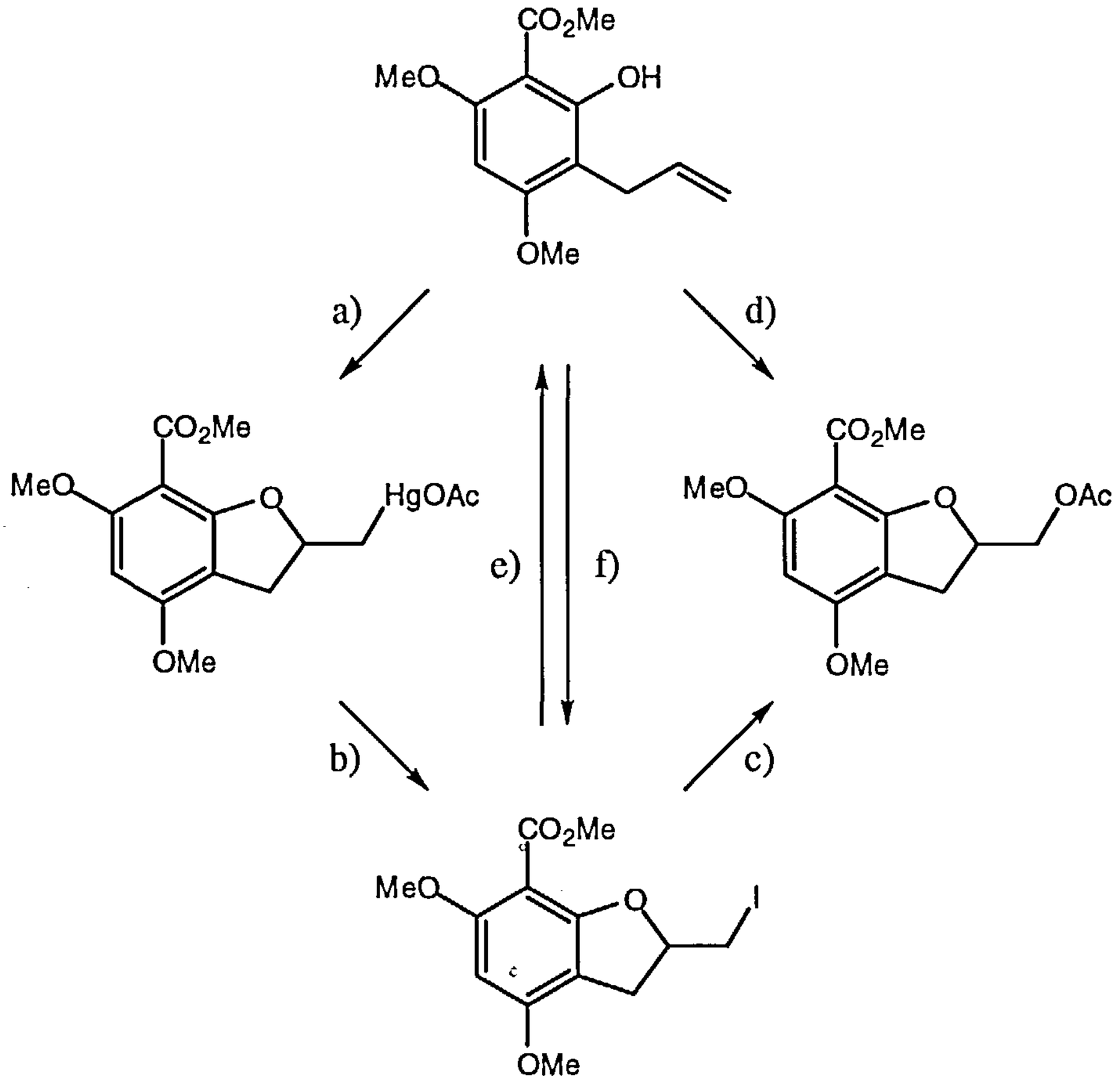


6-20 **6-21**

In fact we found that this reaction proceeded in 46% yield over three hours at room temperature. The presence of the expected five-membered ring was inferred by the lack of a resonance peak for the phenolic proton and the presence of a reasonably well defined splitting pattern for the furan protons, with values of J at 5 Hz and 13 Hz, according quite well with the results of Lethbridge *et al.* One would expect a six-membered ring, for example, to have a far less well defined spectrum. Generally demercuration is accomplished with sodium borohydride, though the Lethbridge group found that there was some decomposition of product back to the alkene. In our hands our product decayed to alkene in the presence of sodium borohydride with no isolable demercurated product. This decomposition is assumed to be a radical process, given that the demercuration is radical in nature.[180] The discrepancy between our result and those obtained by Lethbridge *et al.* leads to the inference that the terminal radical generated on our substrate is far less stable than those generated

on an unsubstituted substrate such as that employed by Lethbridge. We sought methods of demercuration that did not involve borohydride or radical processes. Although work has been done on modifying the borohydride demercuration by trapping radicals with molecular oxygen,[181] we decided to use the method favoured by Adams in his paper on dihydrobenzofuran formation *via* oxymercuration.[182] This involved treatment with potassium iodide and iodine in water, and led to formation of the iodomethyl dihydrobenzofuran **6-21** in 52% yield. This compound could itself be decomposed photochemically back to the original alkene. It could also be used in a reaction similar to the Woodward/Prevost reaction,[183] using silver acetate and acetic acid to substitute acetate for iodine giving a product identical to **6-18** (32%).

Our final reaction in this series was to react the allyl compound with N-iodosuccinimide. This resulted in a compound giving NMR and TLC data in accordance with **6-21.** The above series of reactions is summarised in figure 6.2.8.



a) $Hg(OAc)_2$, H_2O; b) KI, I_2, H_2O; c) AgOAc, AcOH; d) $Pb(OAc)_4$, CH_2Cl_2; e) hν; f) NIS

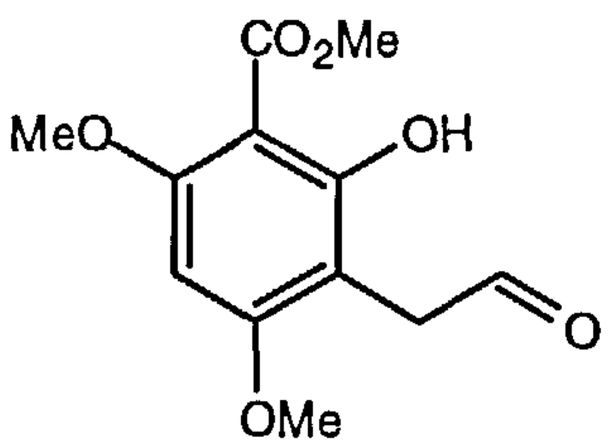
Figure 6.2.8

Taken individually these reactions might leave some doubt as to the structure of the products. Taken as an interchangeable group of products the evidence is convincing that the Claisen rearrangement does indeed lead to the expected *ortho* product.

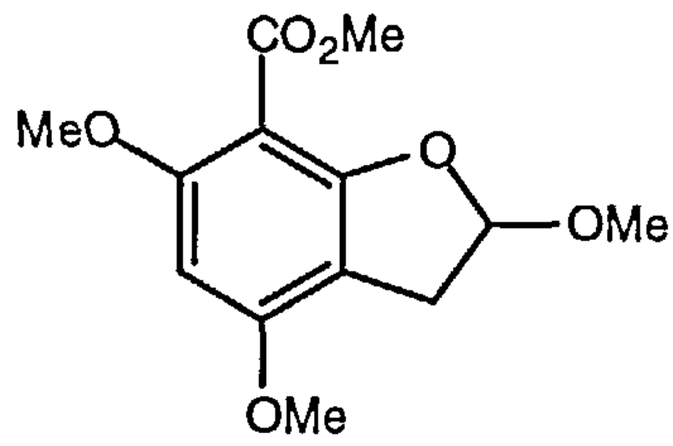
Having satisfied ourselves as to the structure of our compound we proceeded to attempt the ester substitution. Repeated and varied attempts at this reaction met with failure. Even the somewhat drastic measure of running the reaction in a 1:1 mixture of THF and DMPU (N,N-dimethylpropyleneurea) resulted in only a trace of product, and a great difficulty in removing the solvent. During one of these reactions we split the deprotonated sulphoxide solution in two, using one half to attempt the reaction and quenching the other with methyl iodide. This produced a sample of ethyl *p*-tolyl sulphoxide. Thus we knew that we were forming the anion, it was simply not

reacting. The transformation was essentially synthetically useless. We believe that this is due to the 2,6 substituents shielding the approach angles to the ester moiety. Indeed modelling work has suggested that carbonyl centres attached to 2,6-dioxygenated benzene rings are extremely well protected from nucleophilic attack.

Whilst we had the allyl ester in hand we attempted the Lemieux-Johnson cleavage on the allyl group, which proceeded in 48% yield in a THF/water system. As this stage is when the ring is perhaps most prone to oxidation we felt this proved the mildness and utility of this reaction. Utilising an ion exchange resin as an easily removable solid-phase acid catalyst we were able to transform the aldehyde **6-22** into the methyl protected lactol **6-23**, but found the latter compound to be too unstable to react further.



6-22



6-23

This was a setback, as we had hoped that the lactol form would provide a negation of the buttress effect of the allyl group on the 2-hydroxyl, allowing for a nucleophilic attack.

6.2.1.2 Approach via the Fries rearrangement

The catalytic Fries rearrangement as discussed above is a convenient method of introducing an acetyl group into a phenolic ring. Following Kobayashi's work we attempted a transformation of **6-9** in the classic manner (figure 6.2.9). First we prepared the acetate **6-24**, then submitted it to the conditions mentioned by Kobayashi (10mol% catalyst, toluene as solvent). The result was a reasonable (71%) yield of **6-9**.

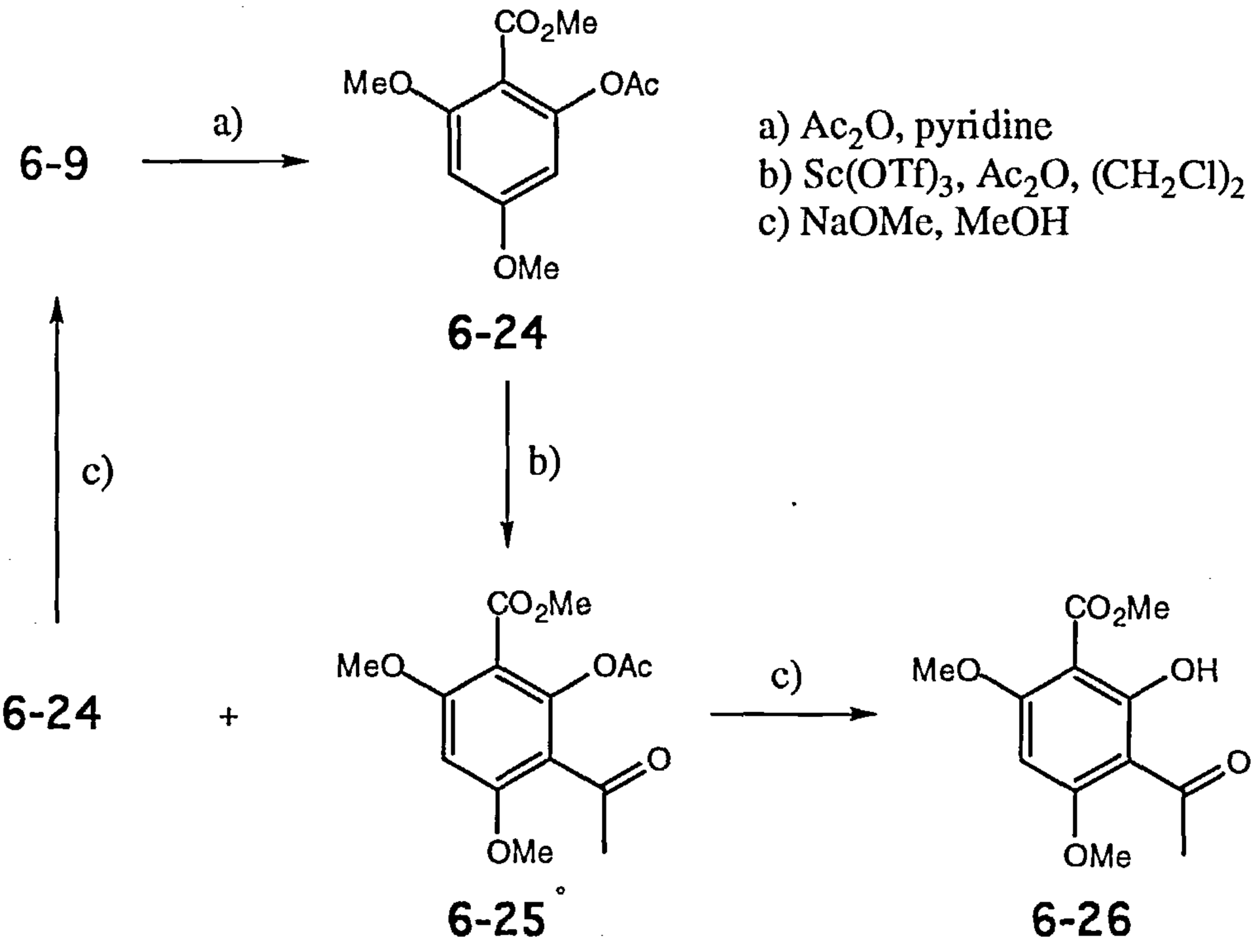
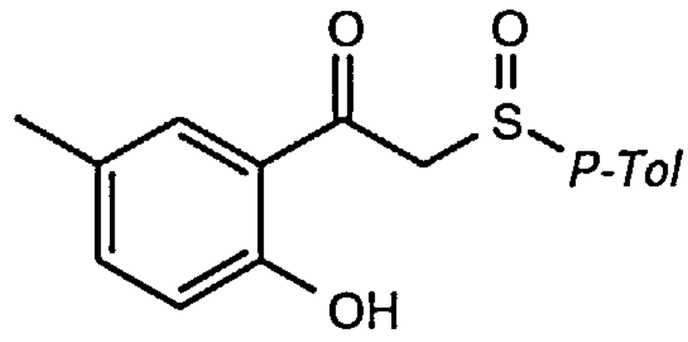


Figure 6.2.9

We reasoned that the mixture was in equilibrium between acetate and phenol, and that only the acetate **6-24** would react. Also that the equilibrium lay far over to the phenol side. Therefore we loaded the system with acetic anhydride in order to push this equilibrium over to the acetate side. This appeared to work quite well, giving a 17% yield. Since acetate was being formed in solution we felt no need to form the ester before the reaction began. This, and running the reaction in a strong (1:3) solution of acetic anhydride in 1,2-dichloroethane was sufficient to raise the yield to 36%. Most of the remainder, however, was acetate **6-24**, which could be recycled. Indeed even the catalyst could be recovered and reused by adsorption onto silica. The product **6-25** is the O,C-diacetate. This can be cleaved to the phenol **6-26** by using a solution of freshly prepared sodium methoxide in methanol, which prevents cleavage of the methyl ester. The cleavage runs in apparent 100% yield.



6-31a

Although the synthesis runs well to this point we did not continue. After repeated failure to react the Claisen product to gain **6-8** we reasoned that the methyl ester was simply too sterically crowded to allow a substitution in reasonable yield. We ran a test reaction on methyl 2-hydroxy-5-methylbenzoate in an attempt to produce the sulphoxide, **6-31a**, to check our methodology. This substitution went in 70% yield. Comforted by the knowledge that the problem did not lie exclusively in our bench skills, we turned to another synthesis.

6.2.2 Approaches to **6-8** *via* enolate chemistry

The advantages offered by the enolate approach to **6-8** seemed to be considerable. Given that our hypothesis was correct and the difficulty was due to steric hindrance the enolate route offered hope in that the reactive site was one carbon further out from the source of the steric hindrance. If the difficulty arose from the proximity of a phenoxide ion to the reactive site repelling nucleophiles the enolate route used the substrate as the nucleophile, not as an acceptor of nucleophiles. The problem that we had was that we could find few references to this phenolic form of enolate being used in the enantioselective displacement of menthol at a menthyl sulphinate (figure 6.2.10).

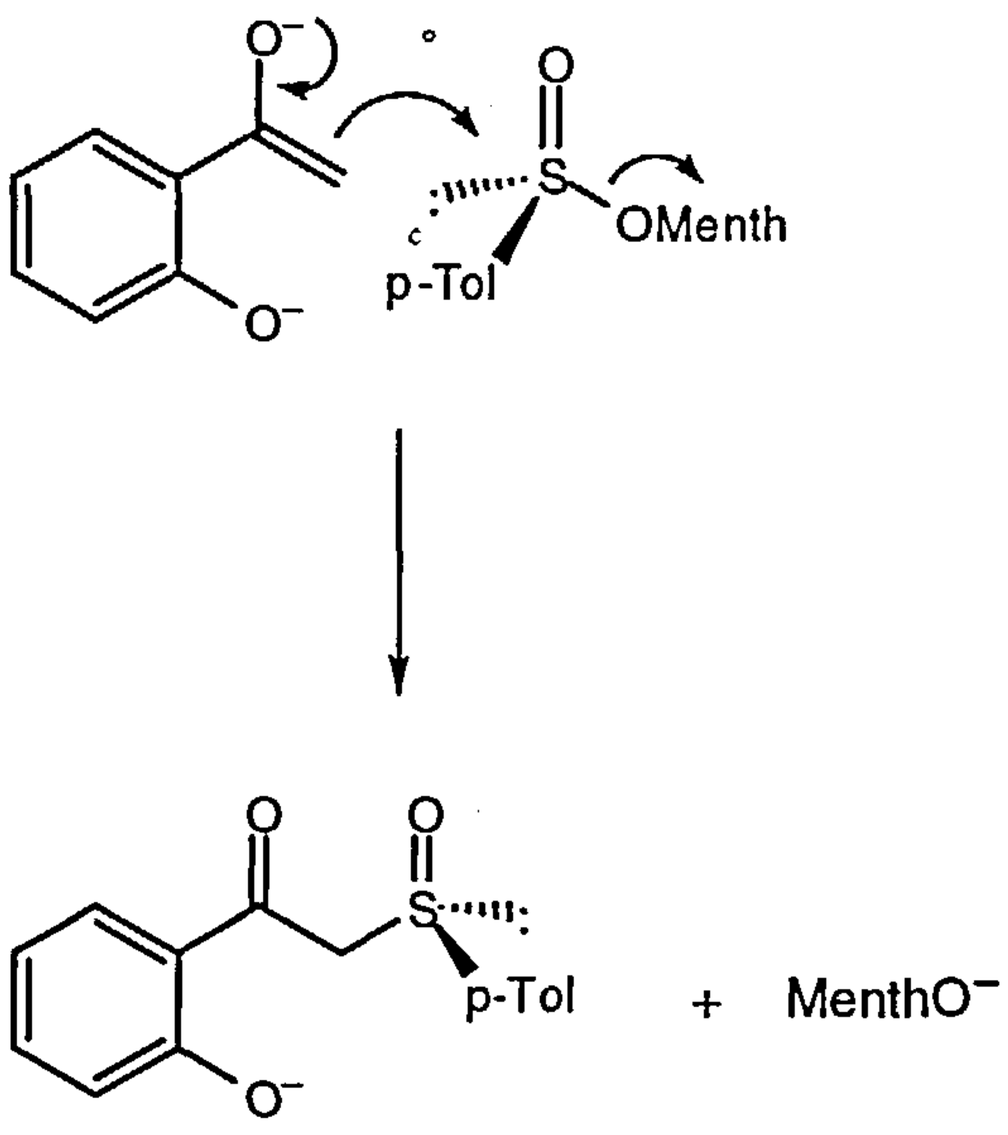
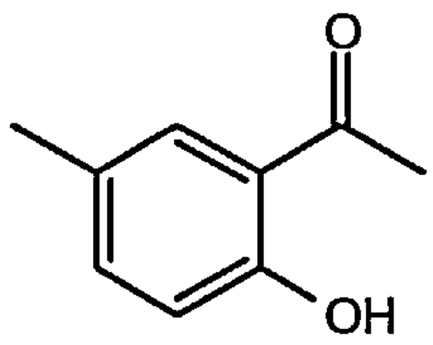


Figure 6.2.10

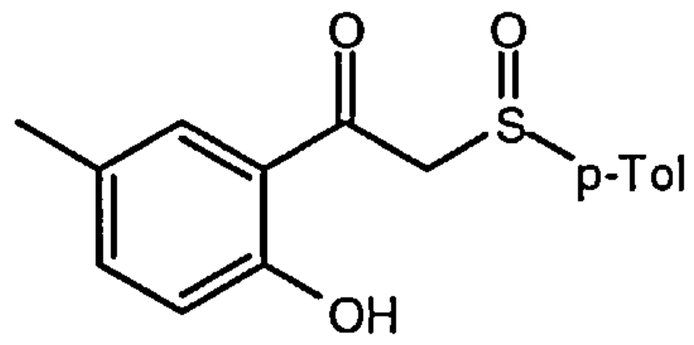
The substrate for this transformation was prepared in essentially the same way as the Claisen route earlier. 2,4,6-Trimethoxyacetophenone **6-27** could be demethylated using magnesium iodide etherate or boron trichloride. Alternatively 2-hydroxy-4,6-dimethoxyacetophenone **6-28** could be prepared using only two equivalents of dimethyl sulphate and 2,4,6-trihydroxyacetophenone in 45% yield. This could then be allylated with allyl bromide in 56% yield to give **6-29** and rearranged to **6-30** at 210°C in 92% yield. The structure of **6-30** was inferred by its close spectral similarity to our preceeding Claisen product **6-7a**, and was apparently confirmed by bromination

data given in the next section. This gave us our substrate for displacement. The scheme is summarised below (figure 6.2.11).

We decided to run trial displacements using two model compounds, 2-hydroxy-5-methylacetophenone **6-31** and 2,4,6-trimethoxyacetophenone **6-27**, to assess the viability of the reaction. The attempts to displace menthol with **6-31** to create **6-31a** produced some very interesting results.



6-31



6-31a

Using LDA on a small scale resulted in a transformation in only 12% yield. Having noted that displacements at sulphinate centres using alkyl carbanions were best performed with copper counterions we added cuprous iodide to the LDA deprotonated mixture. This gave us a yield of 42% of **6-31a** over 2 hours, with an $[\alpha]_D$ of +93. A 2-day reaction time gave an $[\alpha]_D$ of +74. Using potassium hydride as a base in 1,2-dimethoxyethane over 2 hours gave a yield of 30% with an $[\alpha]_D$ of -32, and over 2 days an $[\alpha]_D$ of -26. These results are unusual to say the least and will be discussed in full shortly. The low yield given by these reactions may partly be explained by the difficulty experienced in separating the reaction mixtures. None of the reactions went to completion so it was necessary to remove menthyl *p*-tolyl sulphinate, starting material, menthol and base residues. The sulphoxide **6-31a** stuck to silica very tightly indeed. Relatively pure product was only retrieved by washing with copious quantities of methanol, and even then some menthol contamination was detected. Florisil® and alumina failed to achieve a separation, as indeed did cellulose.

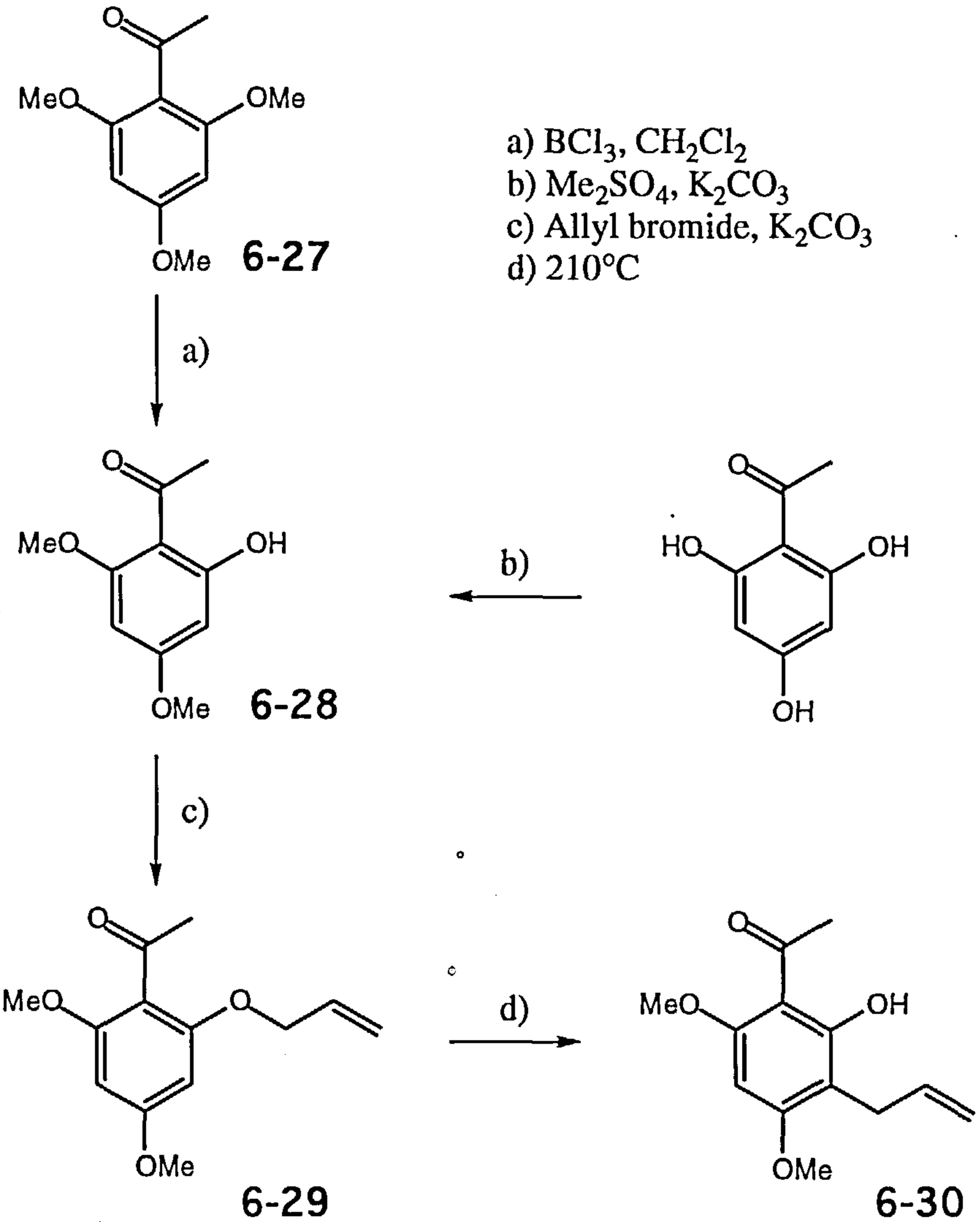


Figure 6.2.11

Our attempts to run a column using Celite met with very little success. Silica remains the best method, though losses are inevitable. For this reason we could not separate the enantiomers using chiral HPLC. Attempts to judge the e.e. by using a chiral shift reagent such as methoxyphenylacetic acid[184] met with limited success, as the peaks due to the shift reagent occurred in the same place as some of the peaks being assessed. We were left with the old fashioned method of assessing the e.e. by optical rotation. A pure sample of this material had been prepared by the conventional (ester) route[185] and found to have an $[\alpha]_D$ of +141±7. This was the expected isomer from the enolate reaction. Therefore, taking the short reaction times for both reactions in the first case we had an e.e. of 66%, in the second an e.e. of 23% in the opposite sense.

A thorough search of the literature revealed one other example of this. Hiroi[186] reacted the sodium and lithium enolates of cyclohexanone with chiral menthyl *p*-tolyl sulphinate to achieve $[\alpha]_D$ values of +17.5 and -12.5 but refrained from comment. This reversal of selectivity in the reaction could have a variety of causes. It is clear that some process due to the counterion is at work. It is also clear that to achieve a net retention of configuration at sulphur at least two separate inversions must take place at the sulphur centre. One other piece of evidence is that the invertive process is more efficient than the retentive, but that over time both have the tendency to produce less selection. We can suggest several processes that might be occurring and can tentatively put forward an explanation, though the reactions have not been sufficiently well explored to be certain of the mechanisms involved.

Let us suppose that all the *o*-hydroxyacetophenone in the pot is deprotonated in both cases. With copper present the possibility exists that the dianion exists as a cyclic complex with copper, that is acts as a bidentate ligand, bound through oxygen at each site, as in **6-32**. This form has the possibility of acting as a nucleophile through the enolate carbon more easily than through the phenolic oxygen (figure 6.2.12).

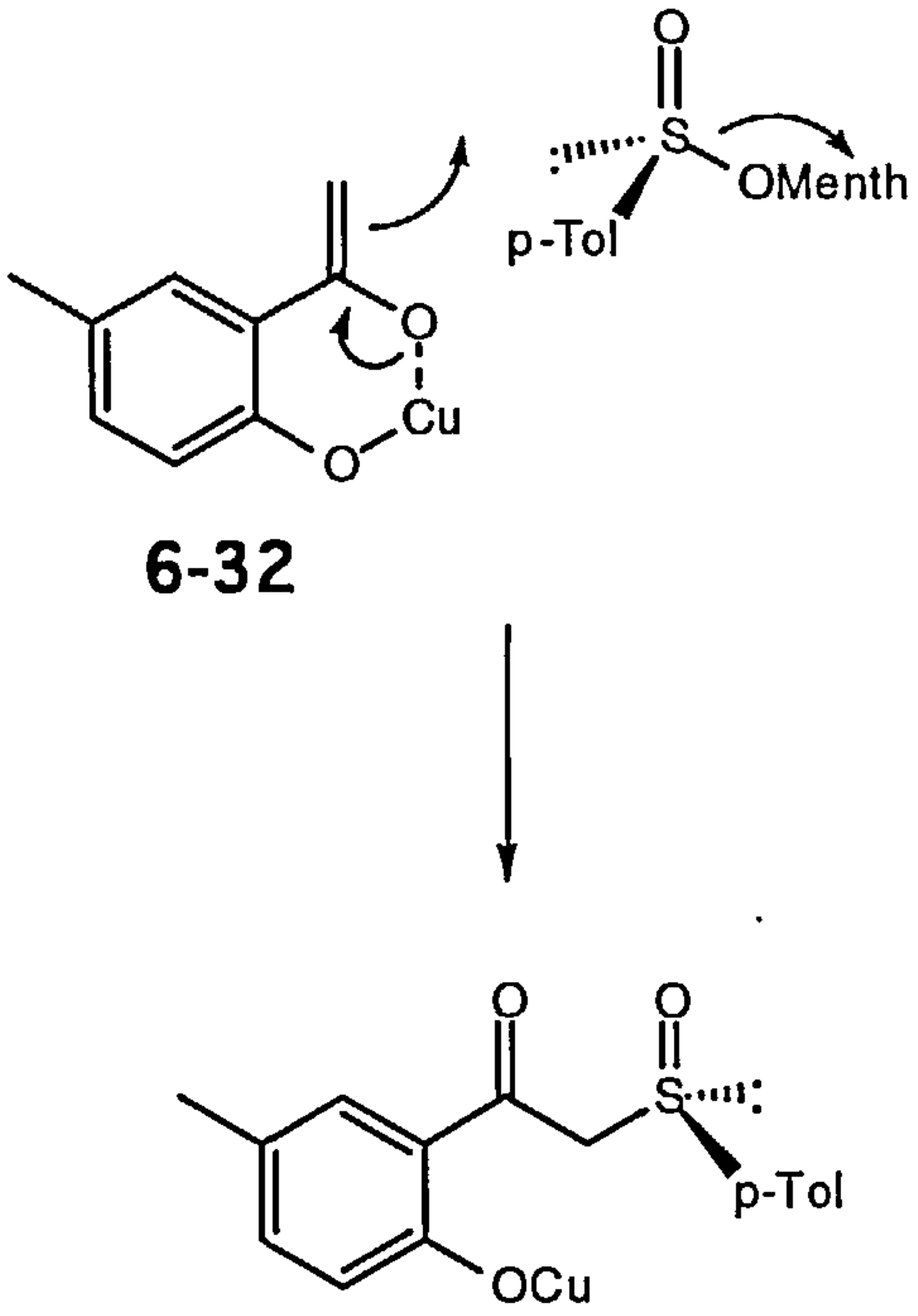


Figure 6.2.12

If we consider the same dianion in the potassium hydride solution we can see that both sites are open to become nucleophiles, particularly in a strongly chelating solvent like 1,2-dimethoxyethane. As in **6-33** we would, however, normally expect the enolate carbon to be far more nucleophilic than the phenolic oxygen.

If we take as a working hypothesis that the phenolic oxygen in the potassium hydride experiment attacks the sulphinate first, to give a clean inversion, we could then expect the enolate to attack, possibly intramolecularly, to give the second necessary inversion to achieve the observed net retention. The attack could, of course, be intermolecular, but the effective concentration of the enolate would be higher intramolecularly than intermolecularly. This amounts to a thia-Baker-Venkataraman rearrangement (figure 6.2.13). It is possible, however that the phenoxide anion has more solubility in 1,2-dimethoxyethane than the dianion. Thus the sequence would run:

1) Deprotonate phenol
2) Attack sulphinate
3) Deprotonate ketone to form enolate

4) Rearrange

A small scale experiment showed that one equivalent of base would also produce sulphoxide. This suggests that the above sequence can operate. It requires the ketone to be deprotonated by menthoxide (the pKa of a secondary alcohol is *ca.* 16.5; for a ketone 19-20), but this could be an equilibrium process rather than a quantitative one, as the end product is stable.

These mechanisms would of course be complicated by the fact that there is always a reserve of unreacted acetophenone in the mixture. It may be the case that a large number of intermolecular inversions take place. Attempts to react suitable O-protected analogues failed. This suggests that the enolate itself is quite unreactive. This mechanism is merely a proposal, and much work must be done to come to a full understanding of the process. The attempt to perform the same reactions with either **6-27** or **6-30** both produced only starting material. This is probably due to either steric crowding or a solubility effect, though several solvent systems were attempted. We therefore sought to produce **6-8** in a different way.

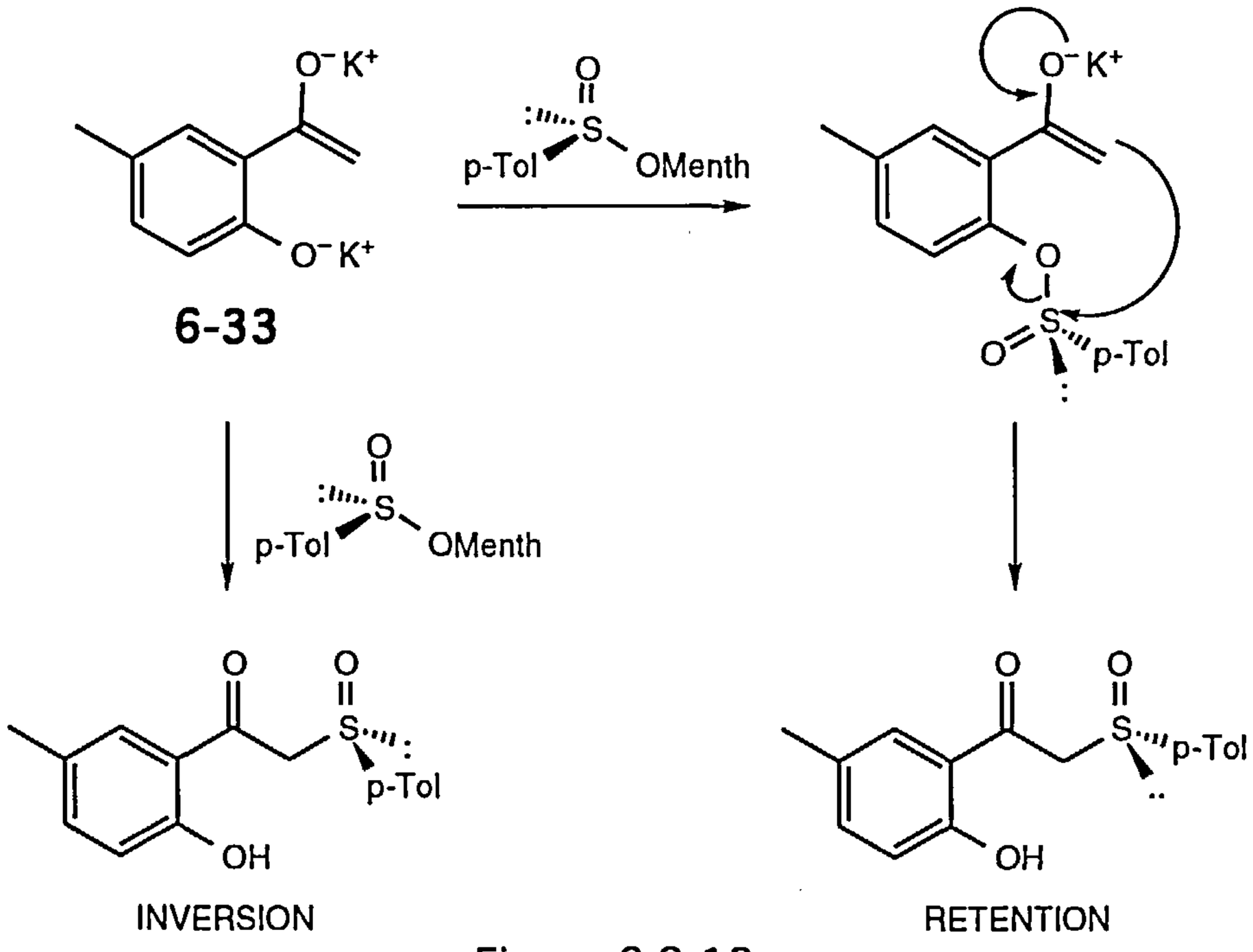
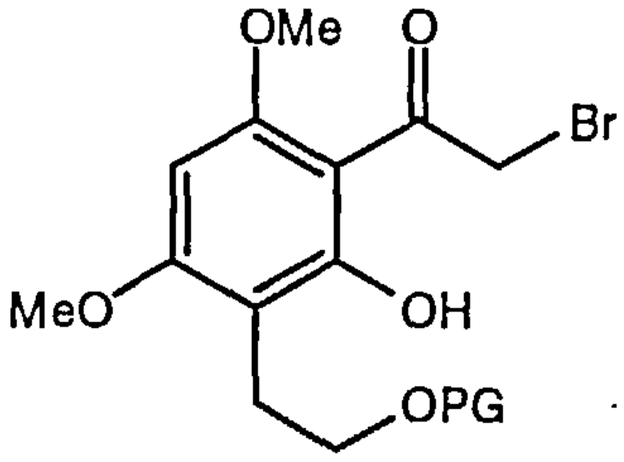


Figure 6.2.13

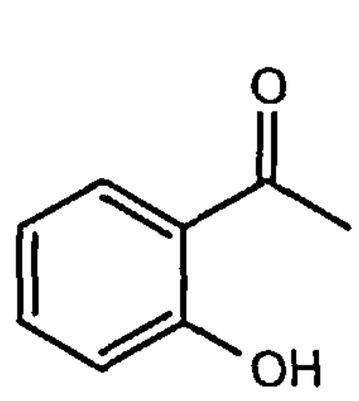
6.2.3 Approach to **6-8** *via* asymmetric oxidation

As stated in the introduction, many methods of oxidation of thioethers to asymmetric sulphoxides have met with success. The easiest to perform, and amongst the most successful, is the method of Kagan. Originally based on a Sharpless asymmetric epoxidation mixture doped with water, in recent years Kagan has modified his system to include doping with isopropanol. This is the system which he himself now recommends as the most effective.[187] All of the ingredients should be freshly prepared. We combined this system with the detailed preparative instructions alluded to earlier to attempt the asymmetric oxidation of a suitable thioether substrate for production of **6-8**. Thioethers α to a carbonyl are generally best prepared *via* a thia-Williamson method. A halide, often bromide, is displaced by the sodium salt of the required thiol. In our case the thiol would be 4-methylphenylthiol.

Our task therefore lay in the production of the requisite α-bromoketone **6-34**. At the same time we desired to test the oxidation. We had already experienced problems with peracid oxidation of our ring substrate and feared for its safety if exposed to the co-oxidant hydroperoxide in the Kagan mixture. We therefore decided to investigate the possibility of cyclising the thioketone to the corresponding 3-(4-methylphenylthio)chromone. We selected the simplest possible test bed for this strategy, 2-hydroxyacetophenone **6-35**.



6-34



6-35

The method selected for cyclisation was the mild 'formylimidazole' one described by Solladié.[188] A previous worker[189] supplied a stock of the *p*-tolylthiol derived from **6-35**. This was cyclised using the conditions described by Solladié to give 3-(4-methylphenylthio)chromone **6-36** in 30% yield over 2 steps. Two bromoketone

precursors were sought, one with the allyl group intact, the other with it cleaved under Lemieux/Johnson conditions to the aldehyde **6-37** then selectively reduced down to the alcohol **6-38** (figure 6.2.14), which proceeded in 40% and 74% yield respectively.

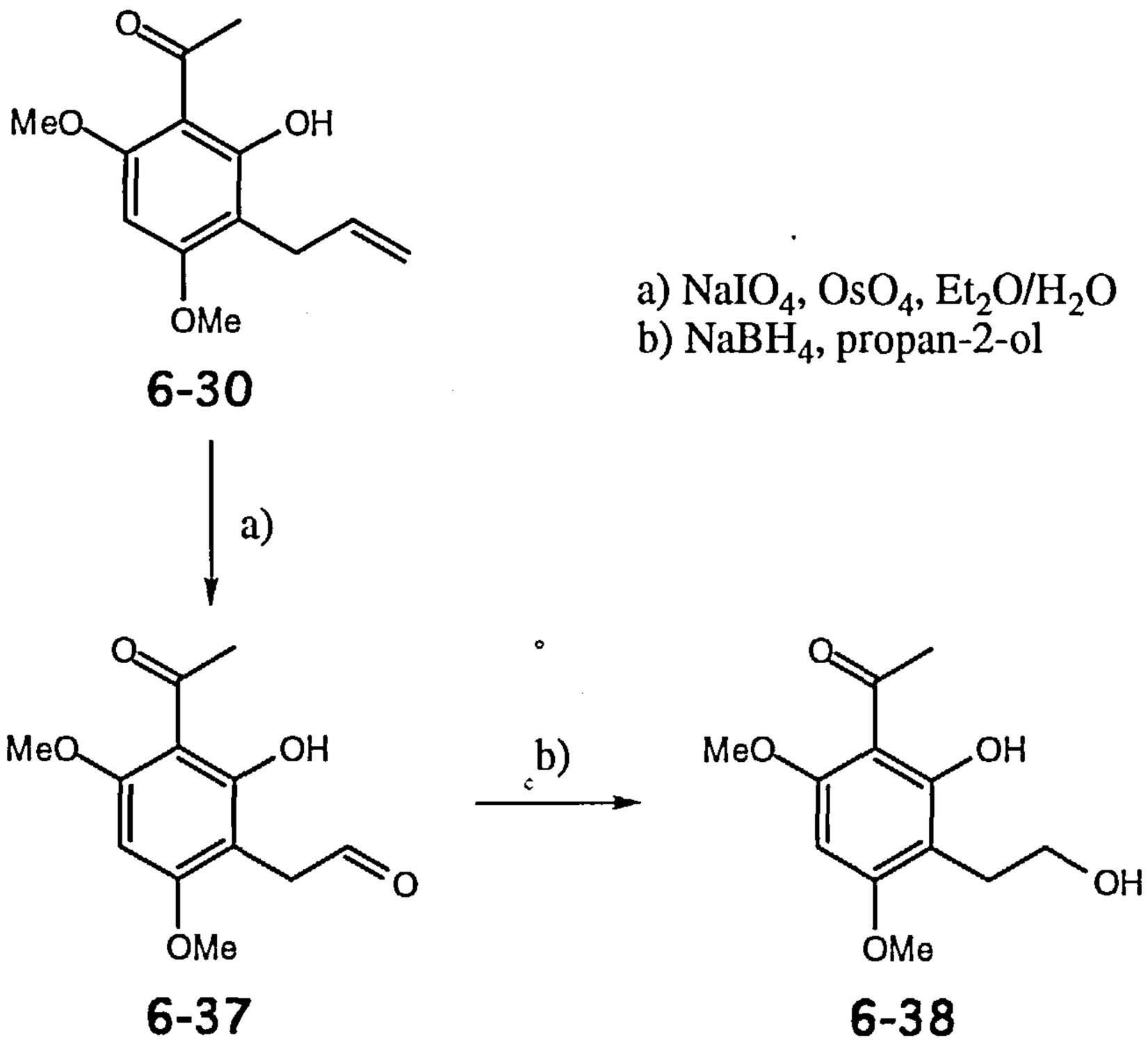
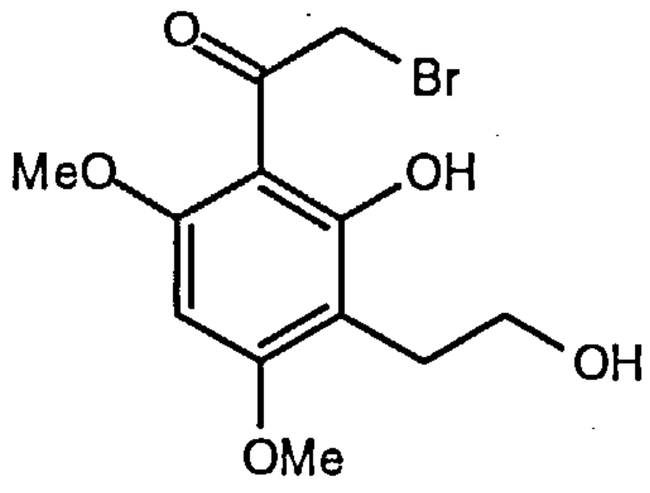
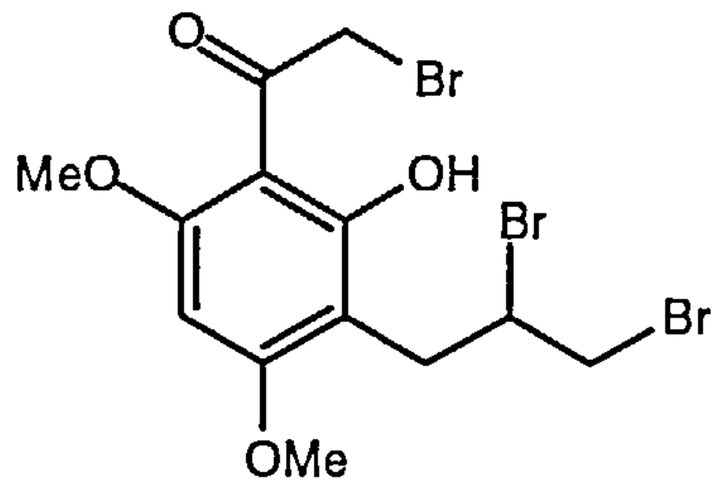


Figure 6.2.14

The subsequent bromination of the ketone **6-38** was undertaken using cupric bromide in 1:1 ethyl acetate - chloroform. The reaction took 10 h and yielded **6-39** (41%). Progress of the reaction could be followed in two ways; by aliquot NMR observing the appearance of a peak at δ 4.59 ppm or by observing the colour change of the copper compound (present as a fine dispersion) from dark green [copper (II)] to light green [copper (I)]. The bromination of the allyl compound **6-30** was undertaken with a similar system, though ethyl acetate - chloroform was exchanged for 1,4-dioxane after an unsuccessful attempt which led to the decomposition of the solvent mix in preference to the substrate. The reaction mixture (which was being monitored by aliquot NMR) quickly became complicated, with four separate aromatic peaks being present. After prolonged reflux we isolated one compound which was given the tribromide structure **6-40**. We sought some clarification of the mechanism.

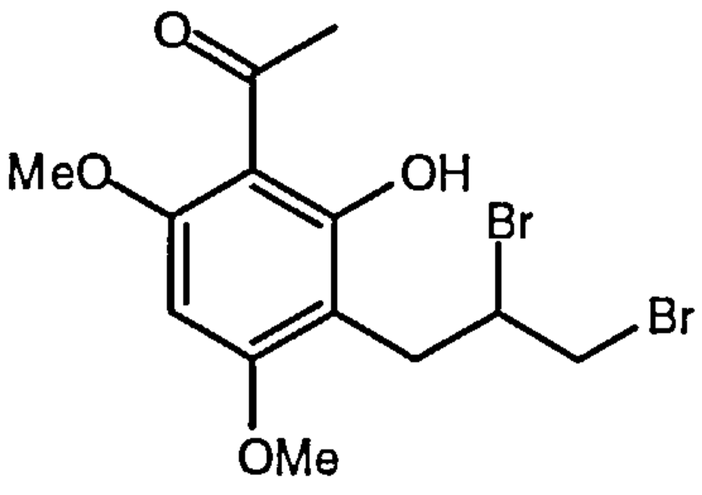


6-39

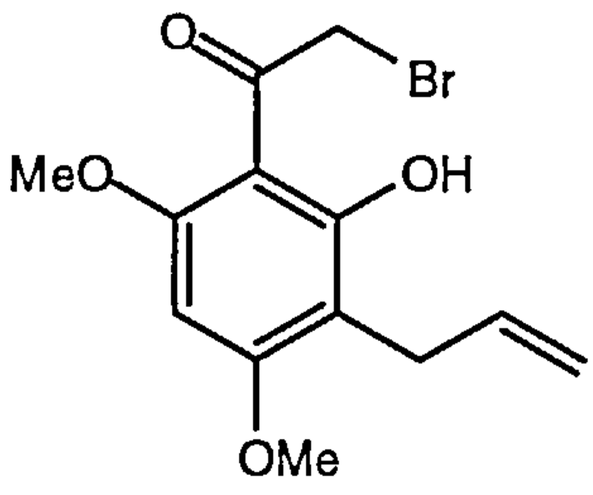


6-40

It crossed our minds to wonder whether in dioxane the mechanism of the reaction altered in some way. A possibility that sprang to mind was a decomposition of copper(II) bromide to copper(I) bromide and dioxane dibromide. This would be a far less selective brominating agent. We also knew that the reaction was not clean, and wondered if the final resolution to the tribromide was through bromination of the allyl group followed by the ketone or vice versa. With this in mind we prepared a sample of the dibromo compound **6-41**, by using dioxane dibromide. This was then treated with cupric bromide to transform to **6-40**. This reaction was slow, but resulted in a very complex mixture. This procedure did allow us to identify some of the peaks seen on the aliquot NMR, a breakdown of which is shown in figure 6.2.15. The reaction is best followed by looking at the hydroxyl peaks, δH 12-15 ppm.



6-41



6-42

The starting material is rapidly transformed into a mixture of compounds, including **6-40**, possibly **6-42**, and a majority of **6-41**. All other compounds transform fairly rapidly into **6-40** but **6-41** transforms very slowly. This accords with our experiment.

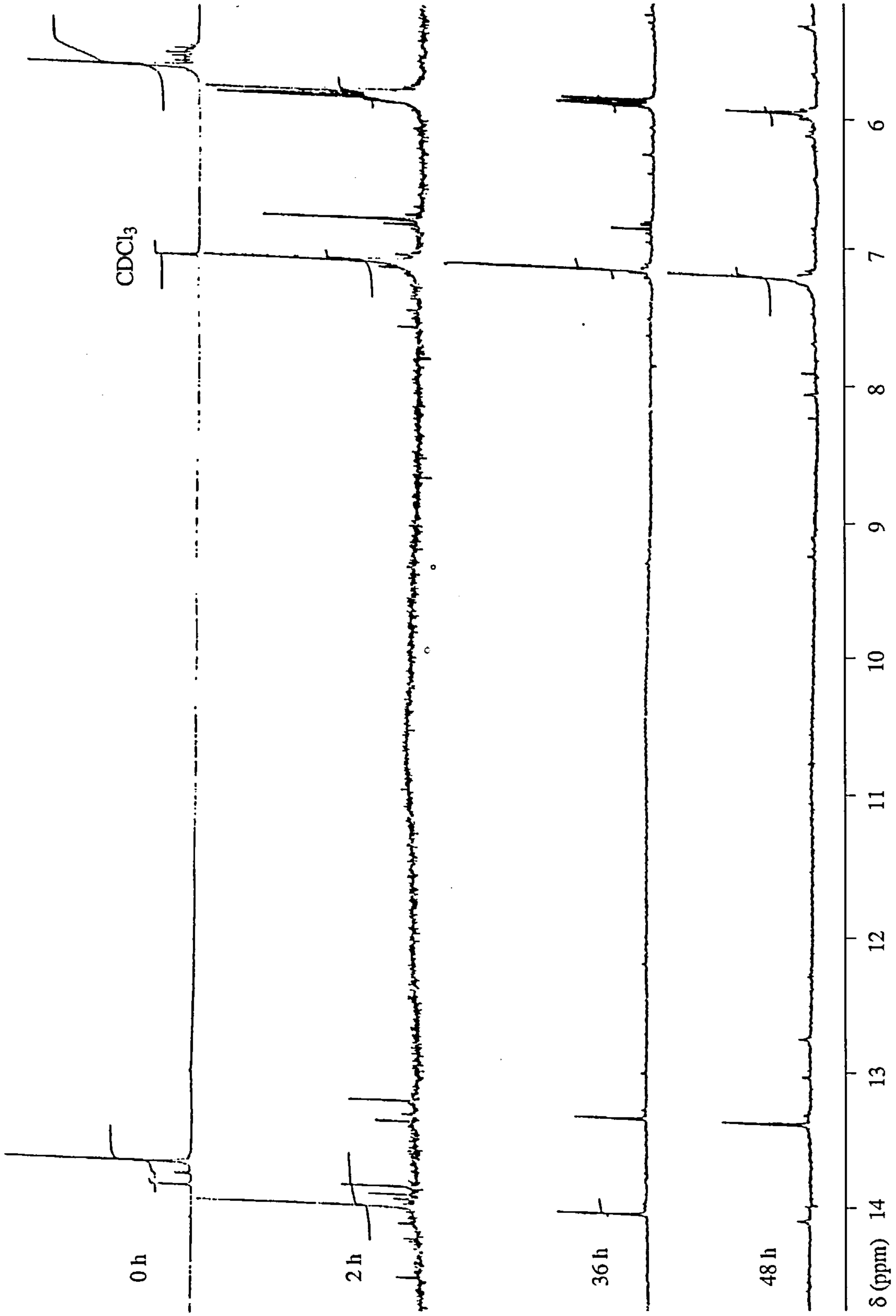
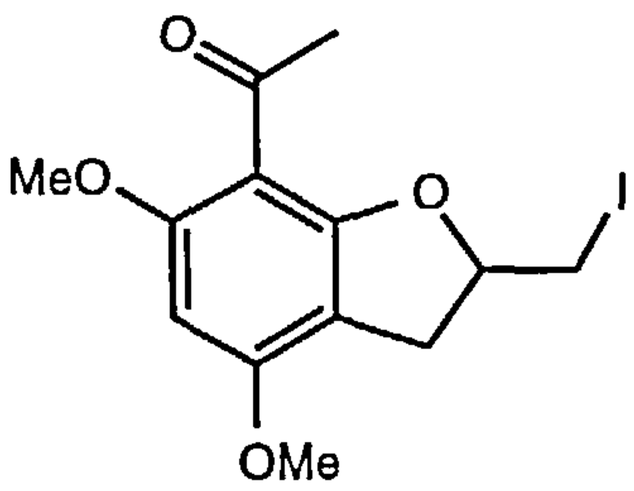
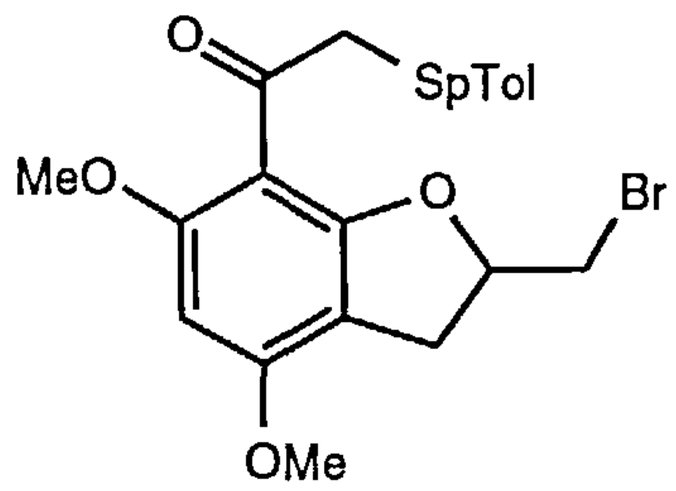


Figure 6.2.15

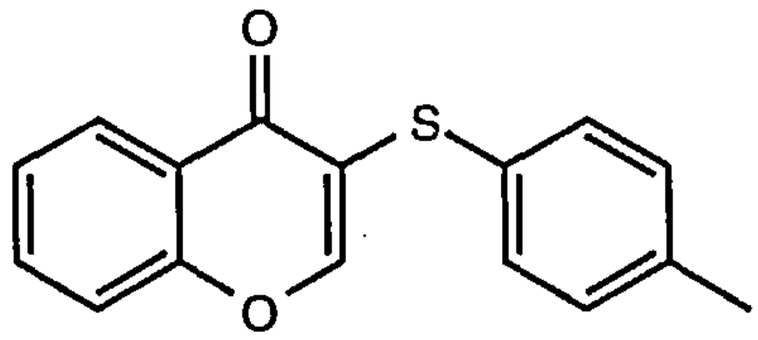
We did not feel that **6-40** was a real setback, as bromine could be removed in a number of ways to either regenerate the allyl group or to generate the desired skeleton. In fact our experience with **6-21** earlier suggested that if a structure such as **6-43** could be generated we could decompose it photochemically back to the allyl system. Conceivably this could be done by refluxing **6-44** with potassium iodide over a tungsten lamp. The bromo compound **6-44** should itself be a major product of the sodium thiocresolate displacement of bromine on **6-40**. In practice, however, the displacement reaction with **6-39** gave an intractable mixture, and that with **6-40** gave only a trace of a compound which could tentatively be assigned as **6-44**.



6-43



6-44

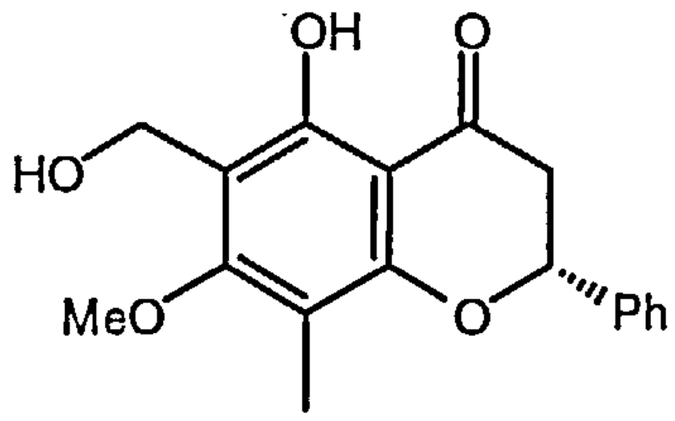


6-45

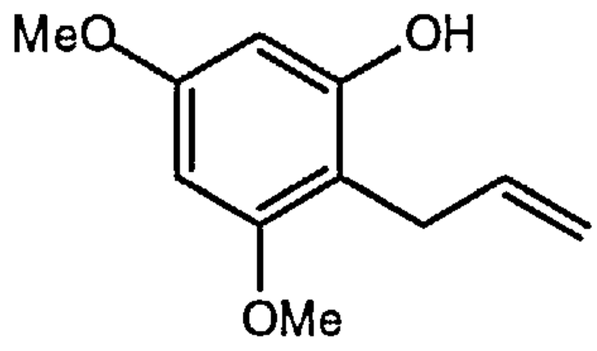
At the same time efforts to perform a Kagan type oxidation on our model compound **6-45** failed to achieve any oxidation. This combined with the failure of another oxidative synthesis mentioned earlier drove us to abandon this line of work and attempt to make **6-8** in another way.

6.2.4 Approaches to **6-8** *via* benzaldehydes

In his synthesis of (+)-(R)-5-hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone **6-46**, Solladié developed the chemistry of attack by the lithium anion of methyl *p*-tolyl sulphoxide on sterically hindered benzaldehydes.

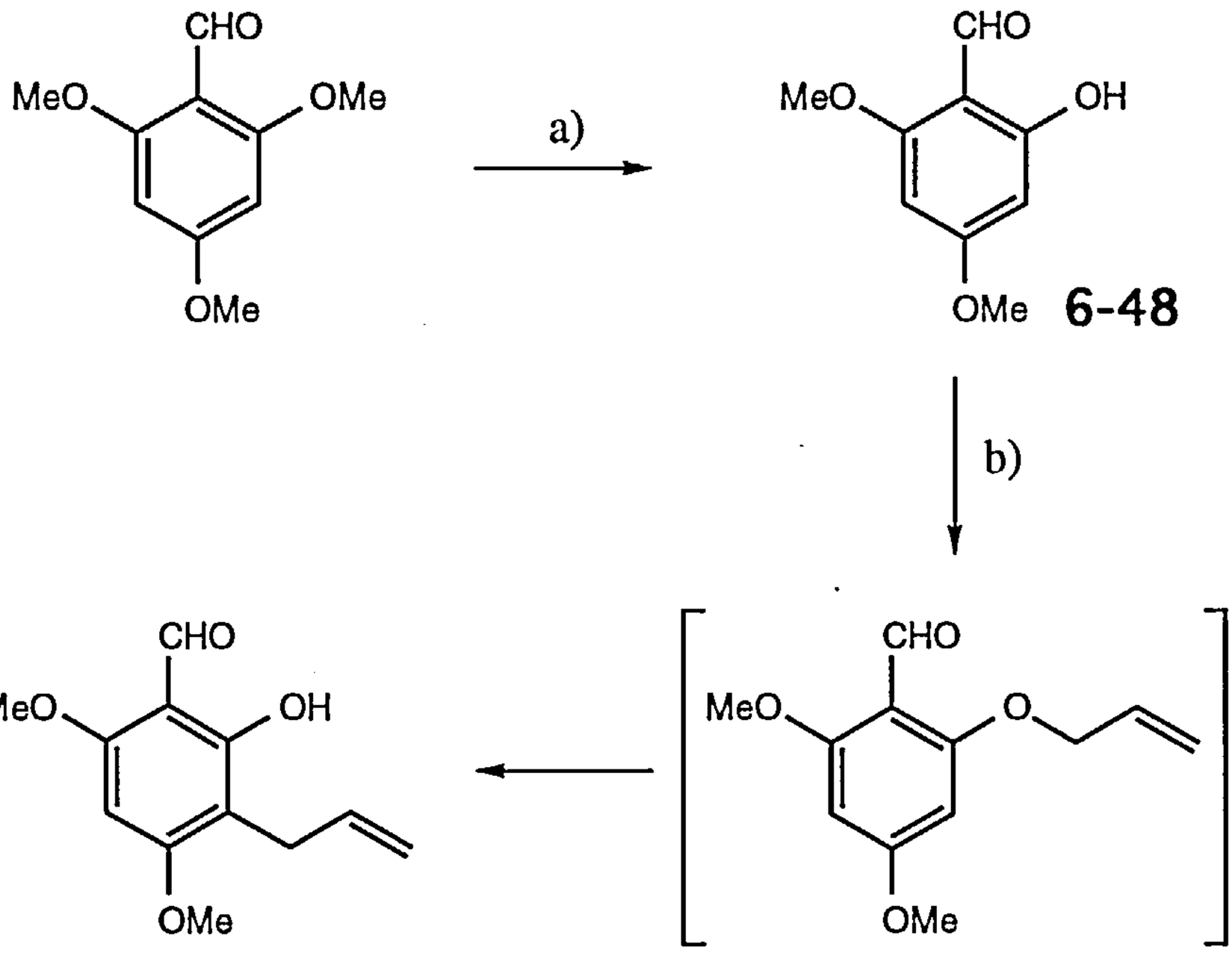


6-46



6-47

We decided to adopt this approach in a final effort to secure the elusive **6-8**. In order to procure this rarity we needed to synthesise **6-17**. We attempted to use essentially the same synthetic route that had previously been used in the ketone and ester syntheses, *viz.* selective demethylation, allylation and rearrangement (figure 6.2.16). We experienced very low yields in the demethylation step, 34% being the optimum. The difficulty here was the tendency of the substrate to undergo a deformylation. This reaction is known to be catalysed by Lewis acids such as scandium triflate[190] and has also been noted in the basic mix required for Kolbë-Schmidt reactions.[191] We found that varying the solvent affected the amount of deformylation. Cyclohexane biased the reaction toward total deformylation and benzene gave our best result for the demethylation.



a) $MgI_2.Et_2O$, C_6H_6 (34%); b) allyl bromide, K_2CO_3, then Δ (12% over two steps)

Figure 6.2.16

The allylation/rearrangement reactions were undertaken in one step, with low yield. To our dismay two separate C-allyl compounds could be discerned on the aliquot NMR. Separation and analysis showed one to be **6-17** and the other to be **6-47**, the result of an apparently thermal deformylation (figure 6.2.17). This meant that our synthesis was remarkably inefficient, having two low yield steps together. We decided to bypass this difficulty by a route involving Vilsmeier formylation of **6-47** which we would prepare by another means. We prepared **6-47** *via* the Claisen rearrangement of the known 1-allyloxy-3,5-dimethoxybenzene **6-48** in quantitative yield, and the 1-allyloxy-3,5-dimethoxybenzene itself was prepared from 3,5-dimethoxyphenol in 81% yield. The Vilsmeier formylation was accomplished in acetonitrile giving a 42% yield.

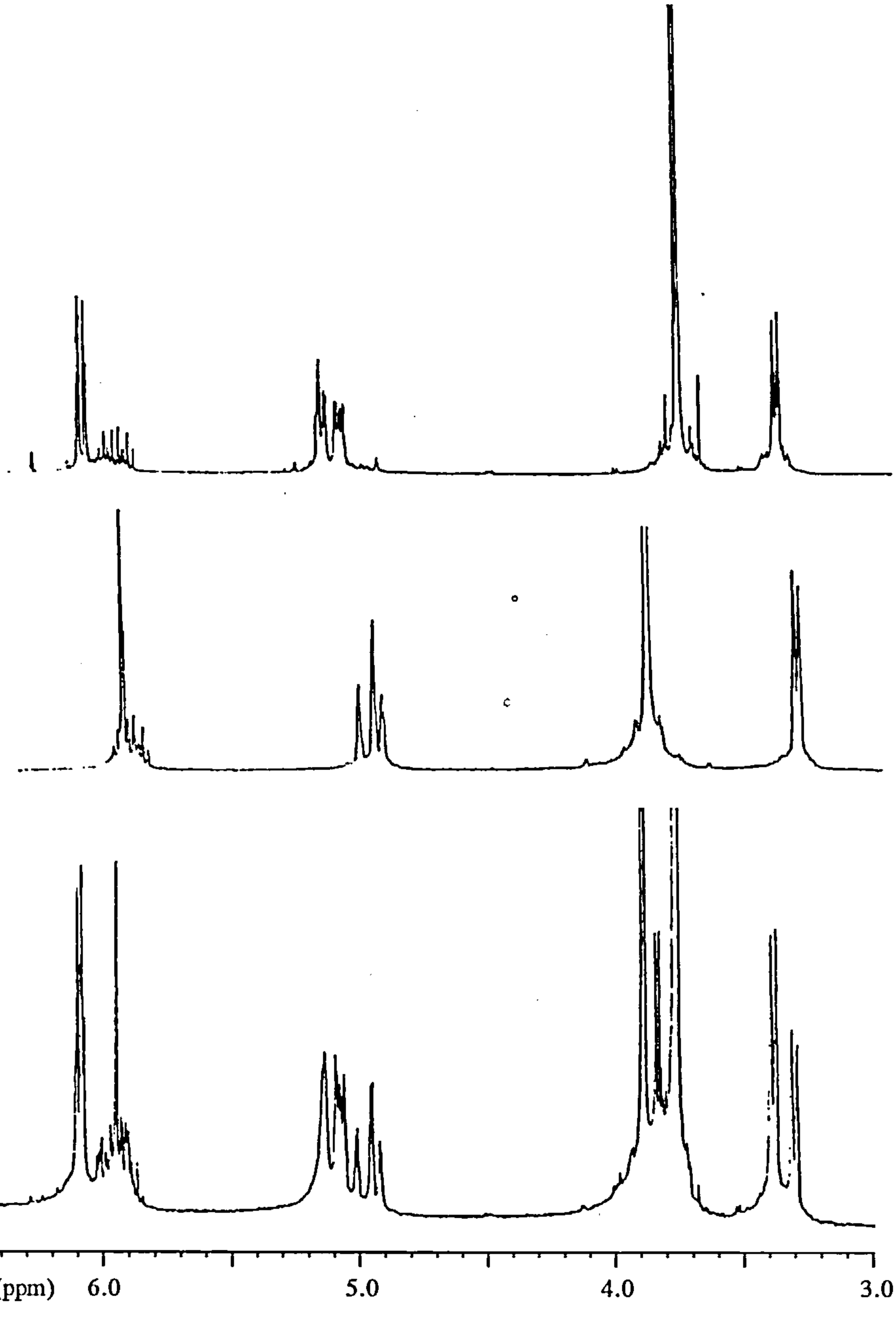
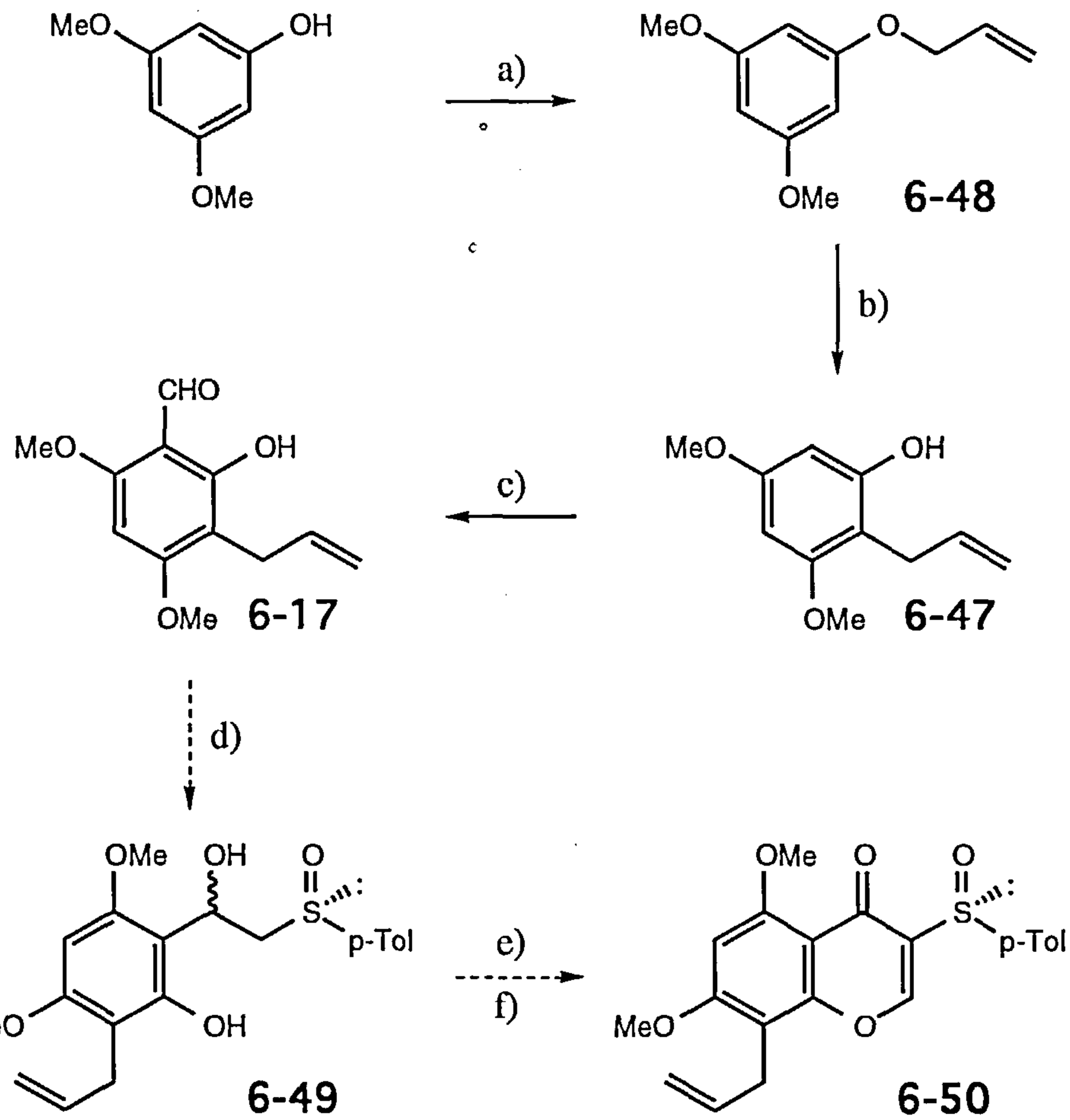


Figure 6.2.17

The upper line shows the deformylated product. The central line shows the normal claisen product, and the lower line shows the unseparated reaction mixture

With **6-17** in hand we attempted the Solladié sulphoxidation. The transformation from aldehyde to sulphoxide was run by Solladié without isolating any intermediates. In our hands the reaction ran to 12% yield, giving **6-8**, and we were able to isolate a small quantity of one of the β-hydroxysulphoxides **6-49** for an NMR spectrum. From this we needed to synthesise the chromone **6-50** with which to establish cuprate addition methodology (figure 6.2.18). Unfortunately not enough time was available to complete this approach to LL-D253α in chiral non-racemic form, though the work so far has revealed the complexities of the chemistry of 2,6-dioxygenated aryl carbonyl compounds.



a) K_2CO_3, allyl bromide; b) Δ; c) $POCl_3$, DMF, MeCN; d) p-TolS(O)Me, LDA; e) MnO_2; f) formylimidazole, H_2SO_4

Figure 6.2.18

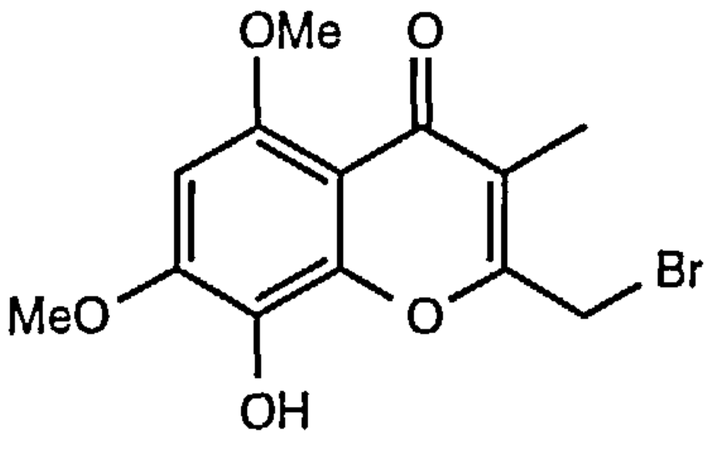
Chapter 7

Suggested further work

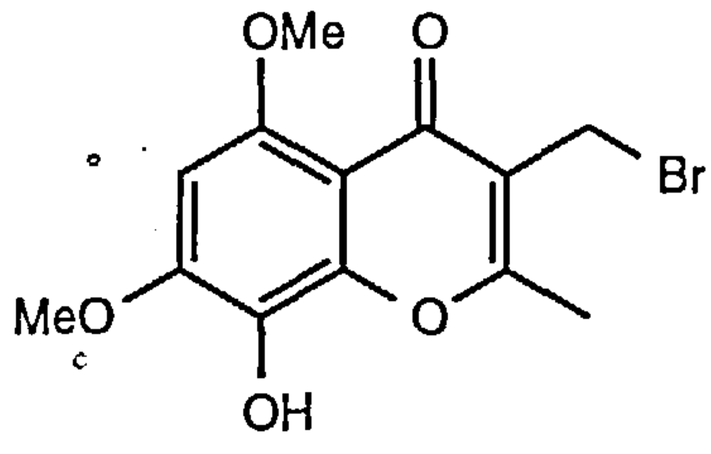
7.1 Matters arising from the stigmatellin fragment A syntheses

7.1.1 Coupling of fragments

As has already been noted this synthesis was geared towards the final coupling of our fragment with fragment B, which was to be produced elsewhere. This could be accomplished by the acid/base chemistry mentioned in chapter 3. An example of this kind of coupling is given in Alonso and Brossi's synthesis of hormothamnione.[192] It might be extended, however if **7-1** and **7-2** could be synthesised. These would allow a coupling of this fragment with many other molecules in the opposite sense in terms of charge.

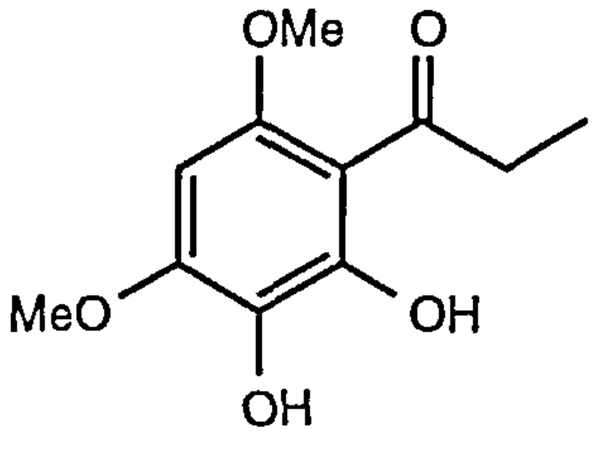


7-1

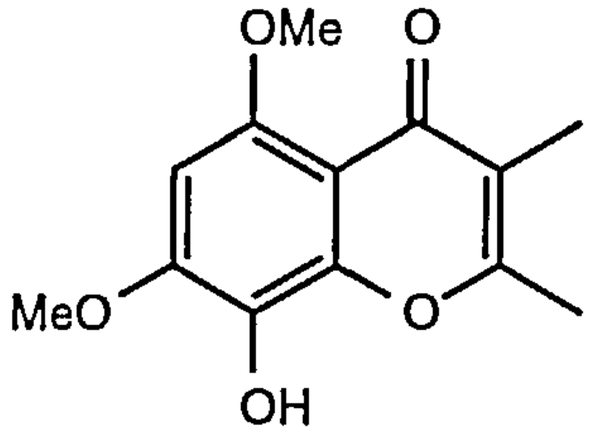


7-2

The synthesis of **7-1** could be approached through a standard sodium acetate induced cyclisation of **4-3** with bromoacetic anhydride. The direct bromination of stigmatellin fragment A **3-2** ought, perhaps to be avoided as the tendency to dibrominate under standard conditions has been noted.[193]



4-3

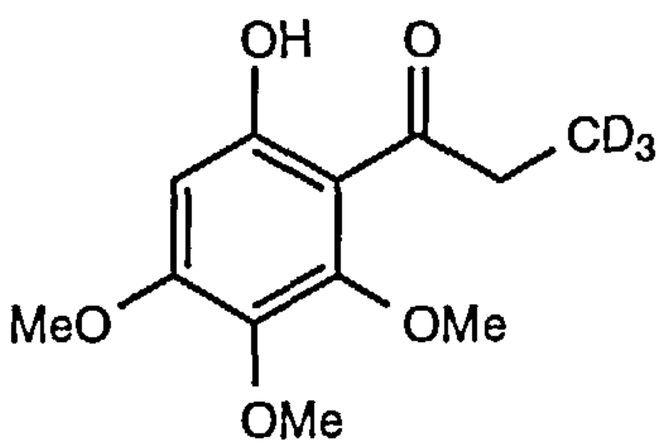


3-2

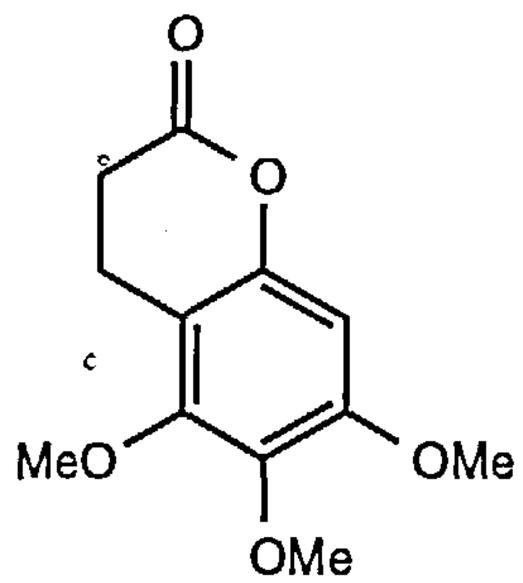
The chromone **7-2** on the other hand could be synthesised from **3-2** by the radical bromination techniques using NBS mentioned in chapter 4. Possession of both these molecules would allow the extension of the stigmatellin and iso-stigmatellin manifolds.

7.1.2 Rare earth triflate catalysed Fries chemistry

The nature of the Fries/Friedel-Crafts chemistry of the rare earth triflate catalysed reaction should be investigated. The inability to get the reactions to go to completion raised the possibility of a retro Friedel-Crafts process, and the need for excess acylating agent coupled with the ability of the rare earth triflates to deacylate aryl esters renders a Fries rearrangement somewhat less likely than would otherwise be the case. The first possibility could be dealt with by introducing a labeled compound, **7-3** into the reaction conditions already described. Any loss of labelling in the product would indicate deacylation.



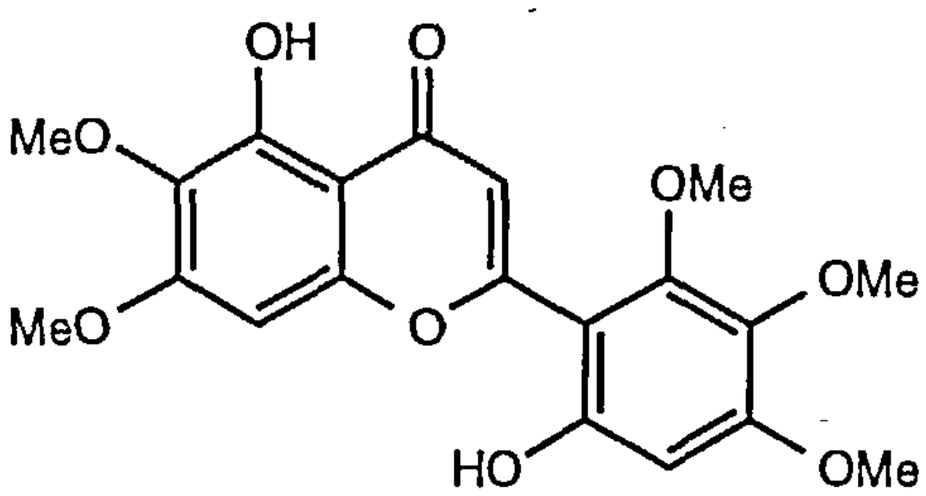
7-3



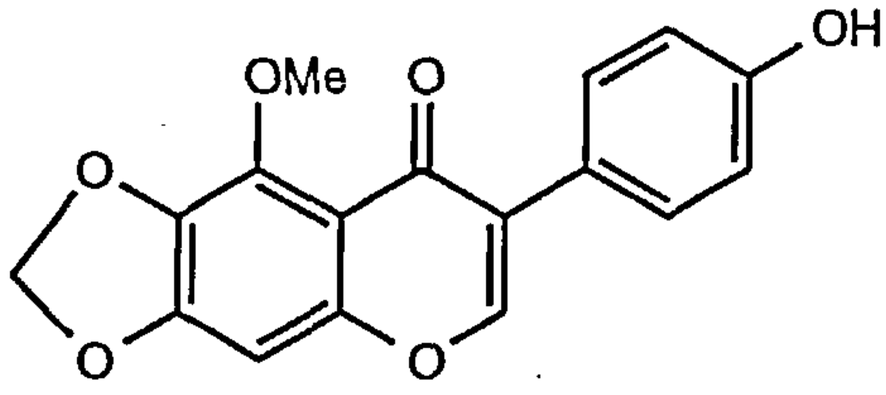
7-4

The exact mechanism of the reaction would be difficult to assess, but some light might be shown by using a molecule such as **7-4** in reaction conditions containing a large excess of propionic anhydride. In such conditions ester cleavage is unlikely to occur to a large extent as the cyclisation reaction is more likely than the transesterification. If **7-4** could be propionylated at the available 6-position it would at least demonstrate that the Friedel-Crafts mechanism was possible.

Another area of research would be extending the range of acyl groups introduced, to explore the limits of the reaction. For example using phenylacetic acid could give access to a range of isoflavones. Other targets that could be accessed *via* this methodology include brickellin **7-5** and irisolone **7-6**.



7-5

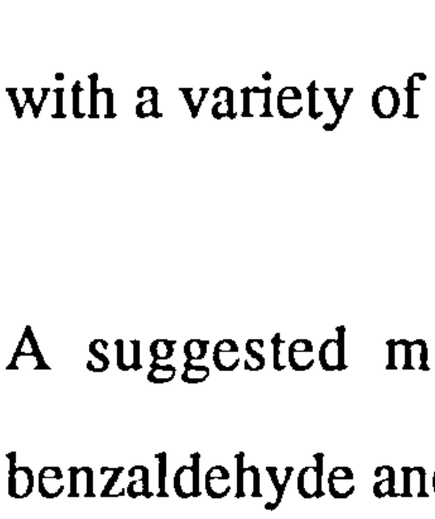


7-6

7.1.3 Dithioacetal formation

The fact that scandium triflate can catalyse the formation of dithioacetals in relatively mild conditions is of interest for the protection of sensitive systems, where the more traditional Lewis acids could cause problems. A series of reactions should be run with a variety of aldehydes, ketones and thiols to investigate the extent of the reaction.

A suggested minimum of substrates would be cyclohexanone, acetophenone, benzaldehyde and 2-methoxy-6-acetylbenzaldehyde **7-7**. This would determine if the reaction was capable of transforming alkyl ketones, aryl ketones and unactivated benzaldehydes. The reaction with **7-7** would determine if the reaction would selectively protect one kind of carbonyl group over another.



7-7

7.2 Matters arising from the synthesis of baicalein precursors

7.2.1 Oxidation of 3-thioarylchromones

In chapter 5 we proved that the chromone unit of 3-(4-phenylmethylthio)-5,6,7-trimethoxychromone **5-10** was stable to Kagan oxidation conditions. Unfortunately the sulphide itself remained unoxidised. We feel that this route to chiral non-racemic chromone-3-sulphoxides could still be viable given the correct oxidant. Many systems are available, as was mentioned in chapter 6. The search for a good system may take some time, but could have advantages, particularly for chromone systems where the precursive benzaldehydes are difficult to synthesise so that the latest Solladié procedure could not be utilised with ease. Among the systems which should be attempted are: Davis type chiral N-sulphonyloxaziridines,[194] systems with achiral oxidants in the presence of chiral auxiliaries, such as Bovine Serum Albumin[195] or biological oxidations. Of these last *Saccharomyces cerevisiae* is perhaps the ideal trial, as bakers yeast is easy to obtain, easy to grow and requires little in the way of biohazard protection. It has been applied in the oxidation of methyl thiostearate.[196] The development of this technique would provide a complement to the growing range of chiral sulphoxide syntheses.

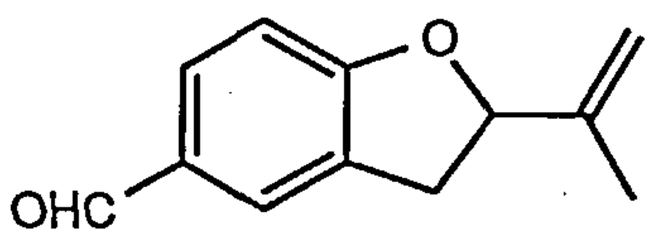
7.2.2 The auto-elimination of 2-phenyl-3-arylsulphinylchroman-4-ones

As we mentioned at the end of chapter 5 this phenomenon has been noticed by Solladié, who managed to use low temperatures to inhibit it prior to a successful desulphurisation.[197] The range of products that will undergo this reaction is not known, all of the observed cases of which we are aware being polyoxygenated chromones. Conducting trials with a variety of methoxylated and otherwise substituted chromone sulphoxide Michael acceptors would extend our knowledge of this reaction considerably.

7.3 Matters arising from the synthesis of LL-D253α synthetic intermediates

7.3.1 Lead(IV) induced dihydrobenzofuran formation

The reaction between an *ortho*-allylphenol and lead(IV) acetate to form a 2-acetoxymethyldihydrobenzofuran could be exploited in order to make a number of compounds, for example fommanoxin, **7-8**.[198] The scope of this reaction is unknown and investigation of its synthetic utility is indicated.



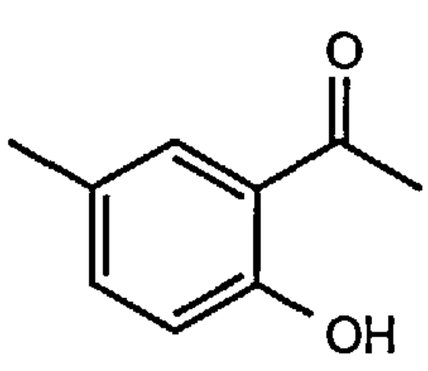
7-8

7.3.2 Synthesis of LL-D253α in chiral non-racemic form

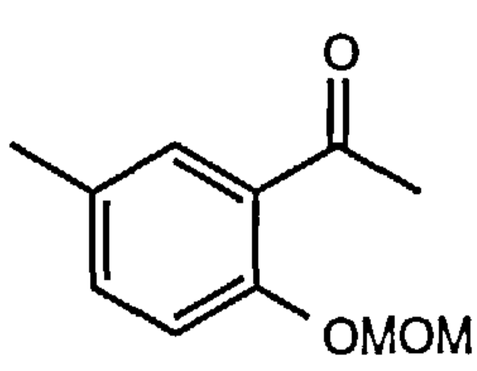
The synthesis of LL-D253α remains unfinished, and should be attempted. Our synthetic approach to the McGahren methyl ether, which would offer structural proof of the natural isomer, is also unfinished. This should be attempted also.

7.3.3 Investigation of mechanisms involved in the enolate displacement at sulphur of chiral sulphinates

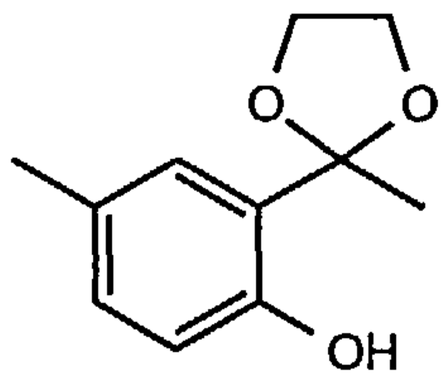
As has been mentioned in chapter six the displacement of menthyl *p*-tolylsulphinate with the dianion derived from **6-31** resulted in both inversion and retention at sulphur. The mechanism is obscure, but may involve a thia-Baker-Venkataraman rearrangement. To investigate this possibility displacements with the anions derived from **7-9** and **7-10** should be attempted.



6-31



7-9



7-10

If the displacement with **7-9** proceeds with inversion it suggests that a dual displacement must be responsible for the retention in the dianion case. If **7-10** proceeds at all to produce a sulphinate the possibilities of a rearrangement can be investigated. Other methods of producing a sulphinate suitable for rearrangement should be investigated, such as the displacement of sulphinamines with phenols.[199]

Chapter 8

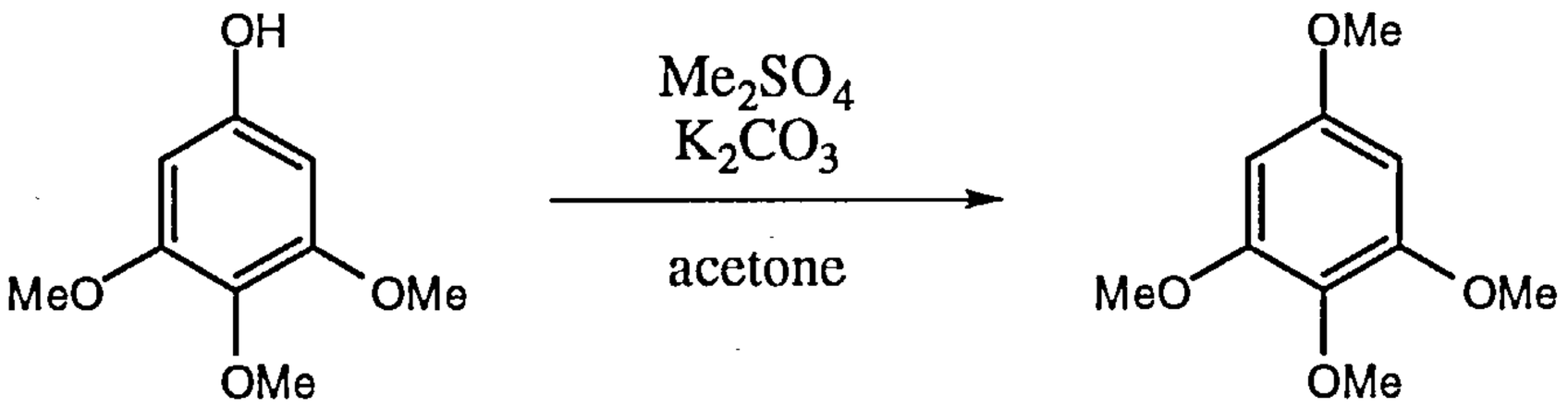
Experimental Section

EXPERIMENTAL

All compounds are racemic unless their names are preceded by stereochemical descriptors. Melting points were determined using an Electrothermal apparatus and are uncorrected. Unless otherwise stated, i.r. spectra were of thin films on NaCl plates, recorded on a Perkin-Elmer 1710FT spectrometer. NMR spectra were measured on a Bruker AC300 instrument at 300 MHz (^{1}H) and 75 MHz (^{13}C) for solutions in deuteriochloroform with tetramethylsilane as the internal standard, unless otherwise indicated. Mass spectra were measured on a Finnegan 4500 (low resolution) or Kratos Concept S1 (high resolution) instruments using the ammonia CI method unless stated. Data for most of the peaks of intensity <20% of that of the base peak are omitted. Optical rotations were measured at 589 nm using an AA-10 polarimeter (Optical Activity Ltd.).

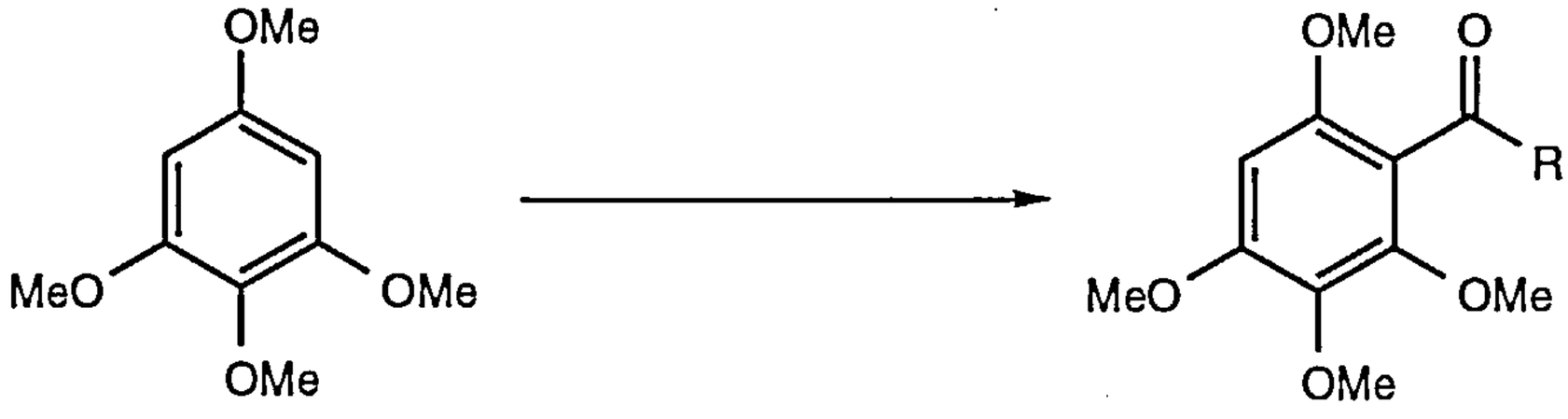
Starting materials and solvents were routinely purified by conventional techniques[200] and most reactions were carried out under nitrogen or argon. Organic solutions were dried using anhydrous magnesium sulphate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Camlab Polygram SIL G/UV_{254} plates. The chromatograms were visualised by the use of u.v. light or the following developing agents; methanolic phosphomolybdic acid (PMA) or ethanolic vanillin. Unless otherwise indicated, preparative (column) chromatography was carried out on 60H silica gel (Merck 9385) or Florisil® (60–100 mesh) using the flash technique.[201] Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to a light petroleum fraction, b.p. 40–60 ° C, unless otherwise stated. 'Ether' refers to diethyl ether.

1,2,3,5-Tetramethoxybenzene (3-7a)



To a suspension of 3,4,5-trimethoxyphenol (**3-7b**) (1.86g, 10 mmol) and potassium carbonate (3.0g) in dry acetone (20ml), held at the point of reflux, dimethyl sulphate (1.0ml) was added. The reflux was continued under argon. After 5 hours aqueous ammonia (1M, 20ml) was added, the heat removed and stirring continued for a further thirty minutes. The acetone was removed on the rotary evaporator, the residue extracted with dichloromethane (3x20ml) and the combined organics washed with water (2x20ml). The organic extracts were dried over magnesium sulphate, filtered and evaporated to dryness to give the product () as a yellow oil (1.3g) which could be purified by Kugelrohr distillation to NMR purity (1.07g, 5.4mmol, 54%), b.p. 160° C at 13mmHg). This compound undergoes rapid decomposition on exposure to air, rendering spectral analysis difficult; δ_H 3.85 (12 H, s, OMe), 5.70 (2 H, s, ArH) can be tentatively assigned. The compound was used directly after distillation.

Attempted acylations of 1,2,3,5-tetramethoxybenzene (3-7a)



R=Et, Me.

i) <u>Using iodine catalysis</u>[202]

To a stirred solution of freshly distilled 1,2,3,5-tetramethoxybenzene(**3-7a**) (0.4g, 2mmol) in acetic anhydride (5ml, excess), iodine (catalytic, 1 crystal) was added. The mixture was brought to reflux and maintained there for 12 hours. The mixture was poured into water (10ml), extracted with ether (3x10ml) and the organic extracts washed with dilute sodium carbonate (10ml), dilute sodium bisulphite (10ml) and water (10ml). The organic extracts were dried with anhydrous magnesium sulphate, filtered and evaporated to dryness at reduced pressure. The resulting brown liquid was distilled on the Kugelrohr (100° C, 13mmHg) to give a clear liquid (0.16g) which had an NMR spectrum containing no aromatic protons and a strong singlet δ_H 4.6

ppm, MH^+ 284. This suggested the diacylated product. The NMR spectrum of a second fraction (150-160° C, 13mmHg) showed a mixture of compounds, none relating to the desired product.

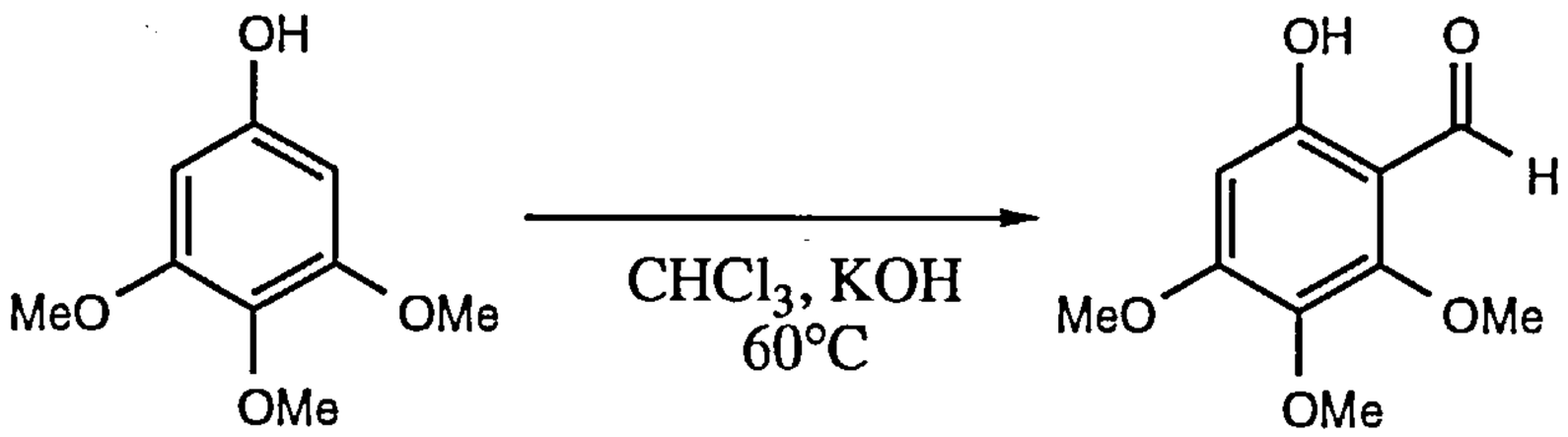
ii) Using polyphosphoric acid[203]

A solution of 1,2,3,5-tetramethoxybenzene, **3-7a** (0.99g, 5mmol), propionic anhydride (4.2g, excess) and polyphosphoric acid (7.5g) were stirred at 70° C under argon for 3h, then raised to reflux for 2 days. The mixture was poured into ice/water (30ml) and extracted with ether (3x30ml). The combined ethereal extracts were washed with sodium hydrogen carbonate (30ml), and water (30ml). The ethereal extract was dried with magnesium sulphate and evaporated to give starting material.

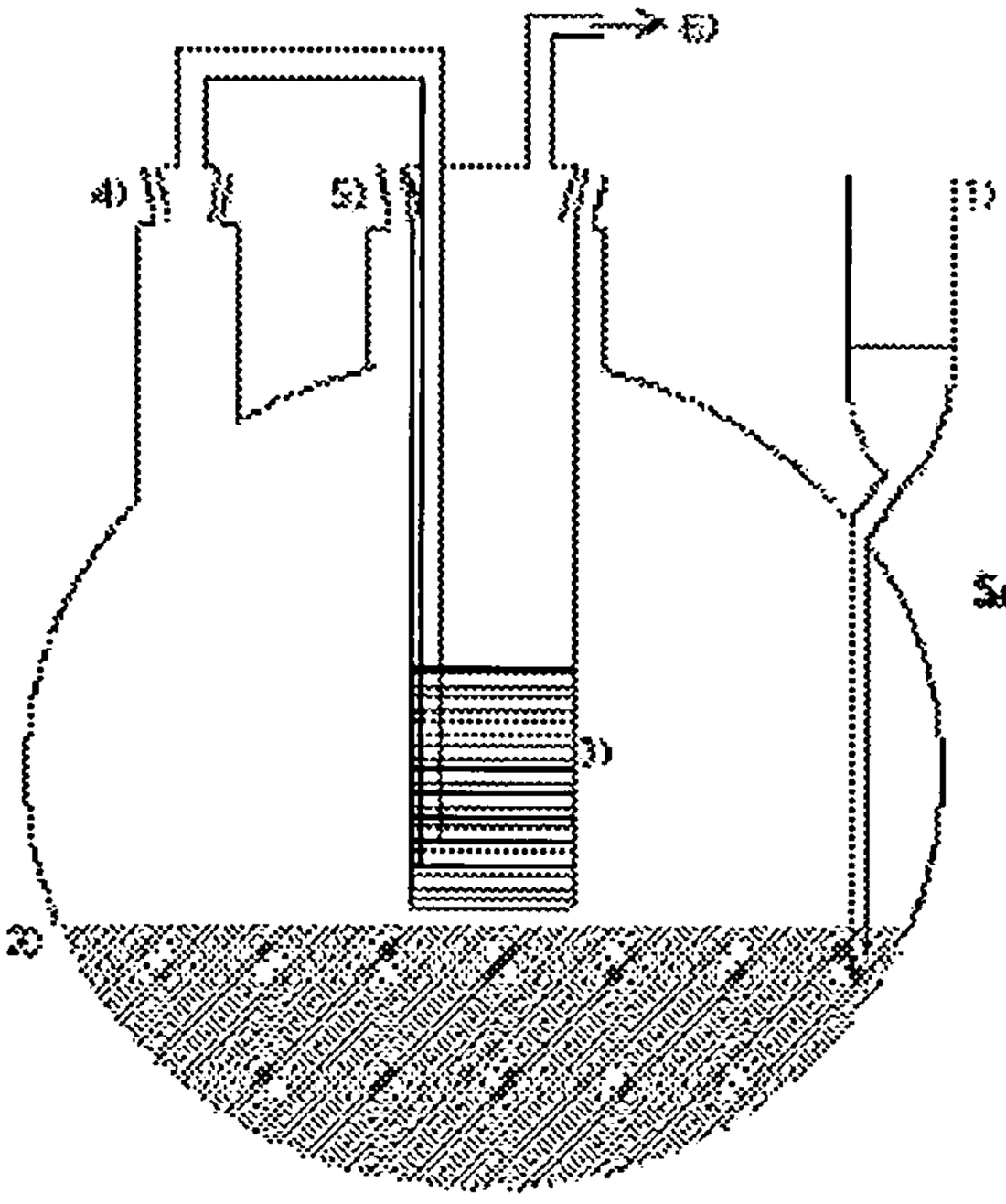
iii) Using zinc chloride

To a stirred solution of **3-7a**(0.4g, 2mmol) in propionic anhydride (5ml, excess), anhydrous zinc chloride (Aldrich, 2g, excess) was added. The mixture was brought to reflux and maintained there for 12 h. The mixture was poured into water (10ml), extracted with ether (3x10ml) and the organic extracts washed with dilute sodium carbonate (10ml) and water (2x10ml). The organic extracts were dried with anhydrous magnesium sulphate, filtered and evaporated to dryness at reduced pressure. The resulting brown liquid gave spectra showing it to be a mixture of the starting material and its decomposition products.

2,3,4-Trimethoxy-6-hydroxybenzaldehyde (3-12)[204]



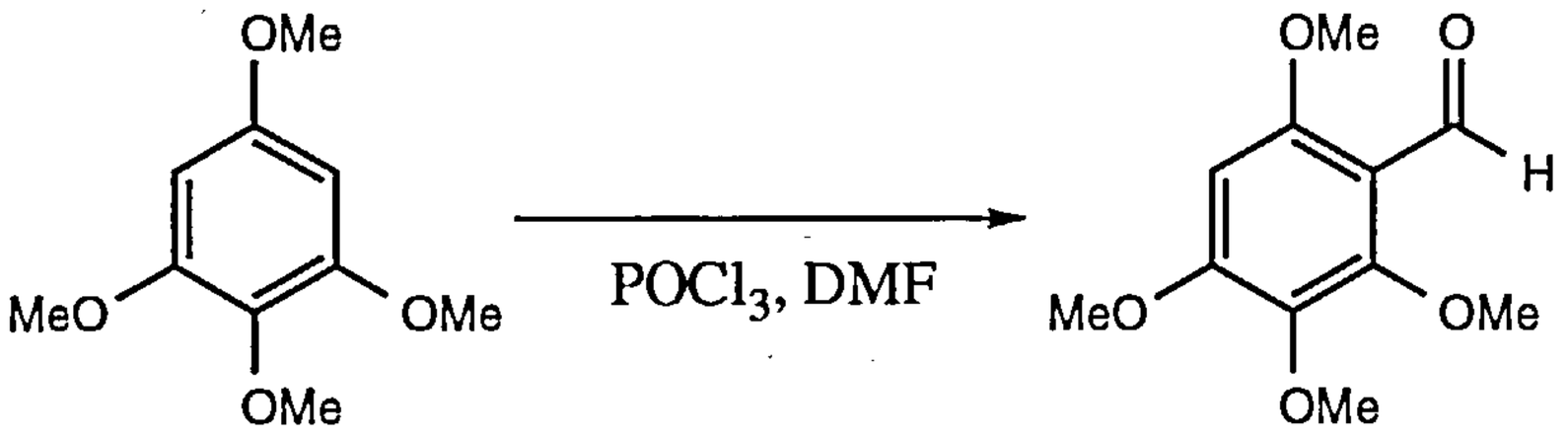
3,4,5-Trimethoxyphenol **3-7b**(0.2g, 1mmol) in KOH (50% aqueous, 50ml) was stirred under argon at room temperature under a reflux condenser. Chloroform (7.5ml) was added and the mixture heated to 60° C. Two further identical portions of chloroform were added at half-hour intervals. Heat and stirring were maintained for 3h, then the mixture allowed to cool. The flask was equipped for steam distillation (see diagram below) and the excess chloroform distilled off. The aqueous phase was cautiously acidified with HCl (13.5 M) to pH 4 as judged by Universal Indicator paper. The mixture was extracted with dichloromethane (3x50ml), washed with water (2x50ml) and sodium bicarbonate solution (saturated, 1x50ml). The solution was dried, evaporated under vacuum, and repeated attempts were made to extract a product. Crude NMR showed an exceedingly complex mixture.



Self-lacketing steam distillation apparatus

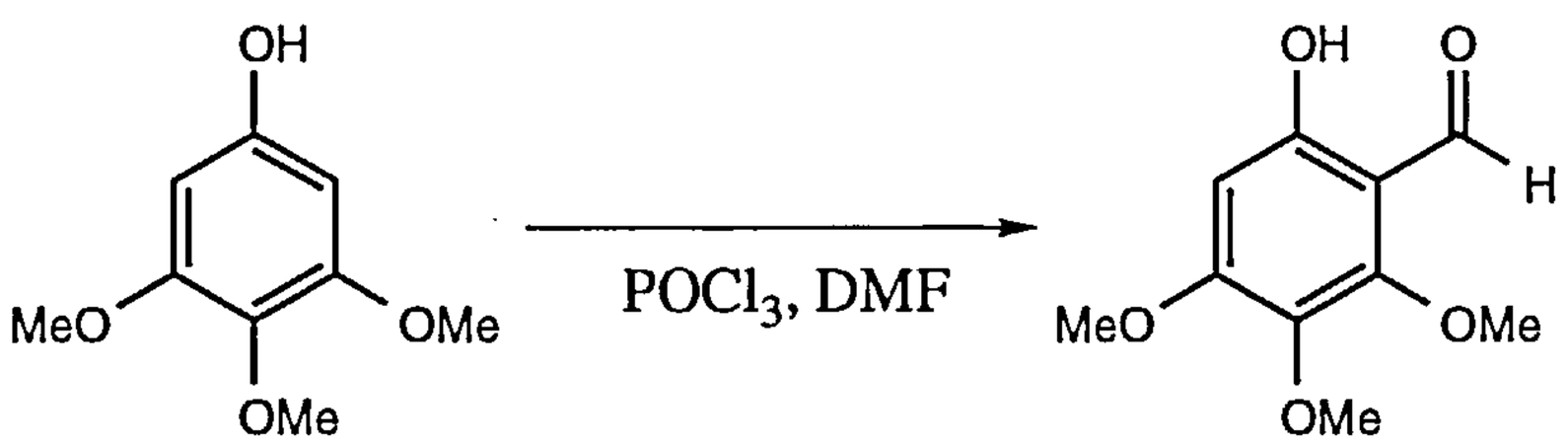
1) Pressure head/safety valve
2) Operating height of water
3) Distillation vessel
4) B14 joint
5) Nested B34/B29 joints
6) To condenser

2,3,4,5-Tetramethoxybenzaldehyde (3-11)[205]



A solution of freshly distilled tetramethoxybenzene , **3-7a** (0.5g, 2.5mmol) in dichloromethane (25ml) and N,N-dimethylformamide (0.9ml, 11 mmol) was brought to reflux in a two-necked flask equipped with dropping funnel and reflux condenser/drying tube. Phosphorus oxychloride (0.9ml, 10mmol) was added and the reflux continued for 4 h. The mixture was poured into water (20ml) containing sodium acetate (10g), then cooled to 0° C. The aqueous phase was extracted with dichloromethane (3x20ml) then the combined organics were washed with water (2x20ml), dried with anhydrous magnesium sulphate, filtered and evaporated to dryness under reduced pressure. The resulting solid was recrystallised from hexane to give the product (**3-11**) as a pale yellow solid (0.22g, 1mmol, 40%). The product could also be purified by steam distillation. M.p. 81-82° C; ν_{max} 2934, 2848, 1674 (C=O), 1594, 1490, 1252, 1217 (O–C), 1115 cm^{-1}; δ_H 3.75 (3 H, s, OMe, C3), 3.84 (3 H, s, OMe, C4), 3.89 (6 H, s, OMe, C2,C6), 6.21 (1 H, s, ArH), 10.24 (1 H, s, CHO) ppm; δ_C 56.0 (OMe), 56.12 (OMe), 61.06 (OMe), 61.97 (OMe), 91.61 (C5), 112.53 (C1), 135.87 (C3), 156.56 (C2), 158.80, 159.00 (C4 and C6), 187.83 (CHO); m/z 227 (MH^+), no other significant peaks; HRMS $C_{11}H_{14}O_5$ requires MH^+ 227.0919, found 227.0916, error on the order of 1.5 ppm. R_f (4:1 hexane - ethyl acetate) 0.43.

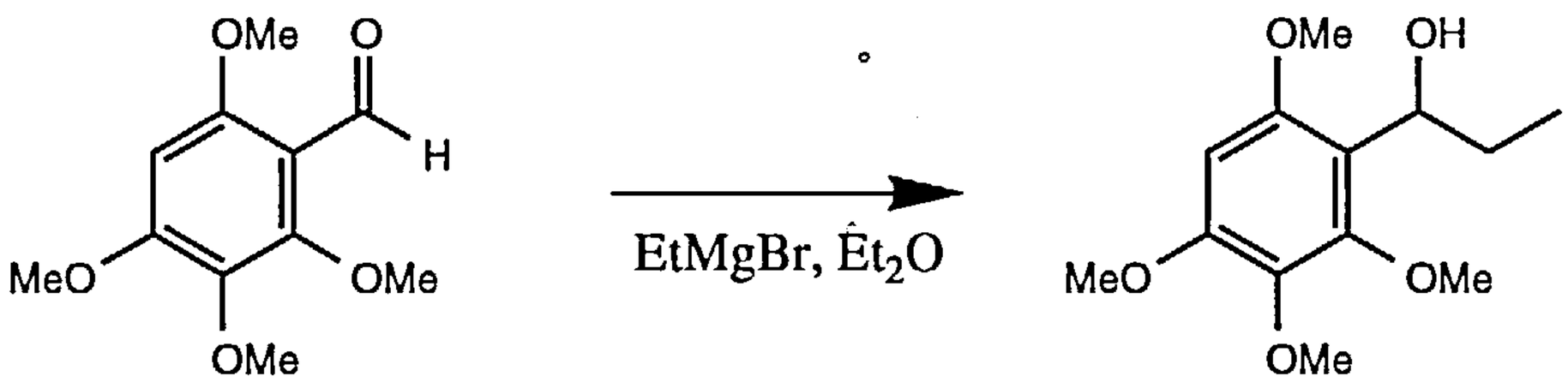
2,3,4-Trimethoxy-6-hydroxybenzaldehyde (3-12)



3,4,5-Trimethoxyphenol, **3-7b** (0.2g, 1mmol) in N,N-dimethylformamide (5ml) was stirred under argon at room temperature. Phosphoryl chloride (0.16g, 1mmol,0.094ml) was added and the mixture heated to 60° C. Heat and stirring were maintained for 3 H, then the mixture allowed to cool. Water (5ml) was added, and the mixture stirred for a further 30 min. The mixture was diluted with water (10ml), then extracted with ether (3x10ml). The ethereal extracts were combined, washed with

water (3x10ml) and saturated sodium hydrogen carbonate (2x10ml), then dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the resultant oil extracted with hexane (30ml). The hexane was evaporated and the product recrystallised from ether to give (**3-12**) as yellow crystals (0.11g, 52%); m.p. 92° C; ν_{max} 2943, 1637 (C=O), 1490, 1367, 1297, 1247, 1204, 1104 cm^{-1}; δ_H 3.76 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.01 (3 H, s, OMe), 6.16 (1 H, s, ArH), 10.02 (1 H, s, CHO), 12.08 (1 H, s, OH) ppm; δ_C 56.2, 61.2, 62.0 (3xOMe), 95.2 (C1), 108.4 (C5), 133.8 (C6), 155.1, 160.7, 162.0 (other aromatics), 192.7 (CHO) ppm; m/z 213 (MH^+), no other peaks above 5%.

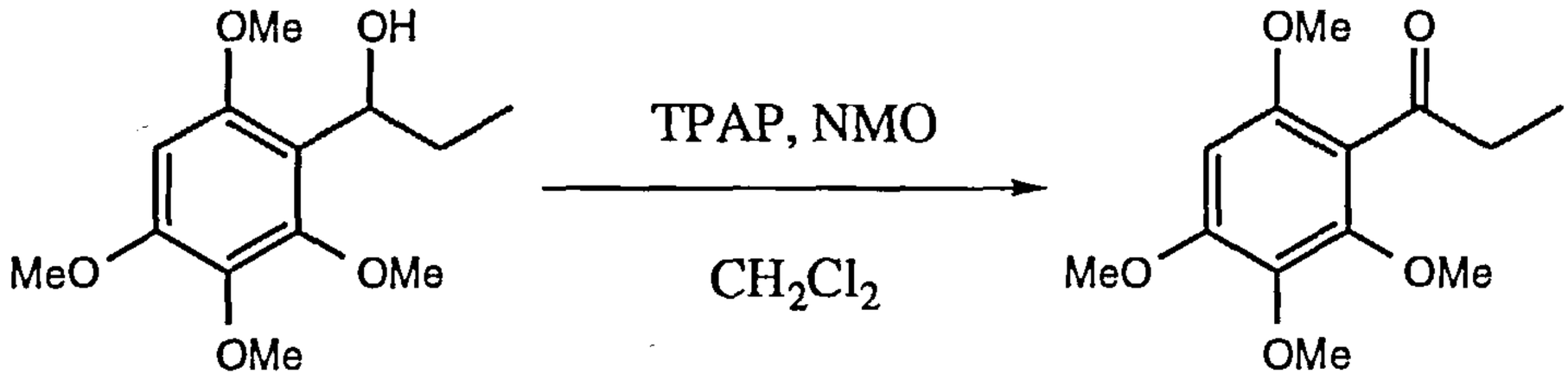
1-(2',3',4',6'-Tetramethoxyphenyl)propan-1-ol (3-10)



To a stirred solution of (**3-11**) (0.1g, 0.44mmol) in ether (anhydrous, 20 ml) at -10° C was added ethylmagnesium bromide (1.32ml, 1M in THF). Stirring was continued for 30 minutes, after which the mixture was poured onto ice (10g), allowed to reach room temperature and extracted with ether (2x10ml). The combined organics were washed with water, dried and evaporated to dryness under reduced pressure. The product was crystallised from methanol (3ml) to give a cream solid (0.08g, 0.31mmol, 71%); m.p. 56° C (dec.); δ_H 0.92 (3 H, t, J=7Hz, CH_2CH_3), 1.69 (1 H, m, CH_2), 3.69 (approx. 1 H, m, CHOH, overlaps OMe signal), 3.77 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.84 (1 H, br. s, OH), 6.26 (1 H, s, ArH) ppm.

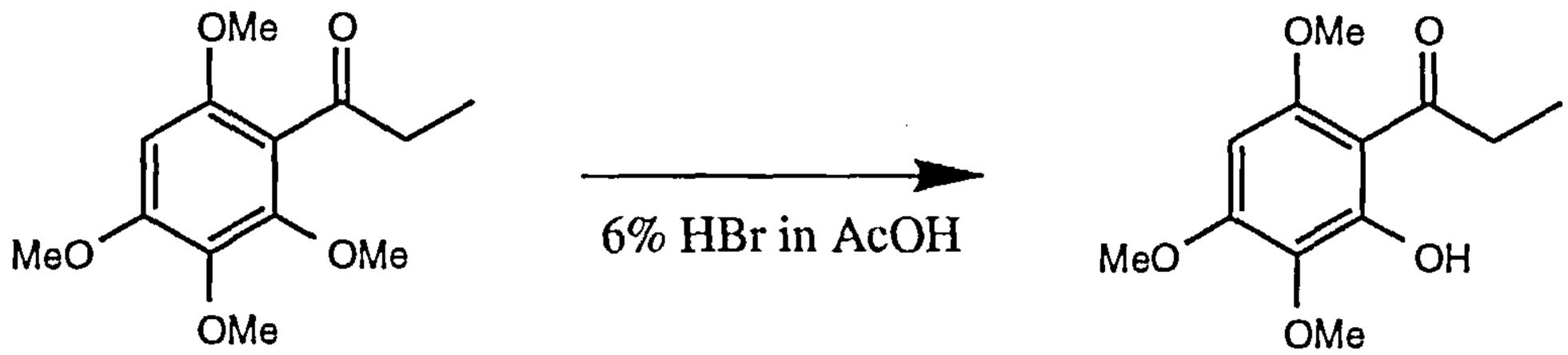
The spectrum indicated a mixture with demethylated starting material. The product proved unstable in solution at room temperature or as solid at elevated temperature.

2,3,4,6-Tetramethoxypropiophenone (3-6)



The alcohol (**3-10**) (0.3g, 1.17mmol) in dichloromethane (10ml) with N-methylmorpholine N-oxide (0.14g, 1.75mmol, 1.5 molar equiv.) was stirred under argon with active 4Å molecular sieves. Solid tetrapropylammonium perruthenate[206] (0.02g,0.5 mol%) was added and stirring was continued for 3 h. The mixture was run through a silica plug and chased with dichloromethane (10ml). The organic phase was washed with water, and dried. The solvent was removed under reduced pressure. The product was recrystallised from methanol to give (**3-6**) (0.16g, 2.2mmol, 54%), m.p. 56° C; ν_{max} 1700 (C=O), 1599, 1458, 1403, 1250, 1203 (C–O) cm^{-1}: δ_H (300 MHz) 1.118 (3 H, t, J=7.3 Hz, $CH_2\mathbf{CH_3}$), 2.73 (2 H, q, J 7.3 Hz, $\mathbf{CH_2}CH_3$), 3.75 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.86 (3 H, s, OMe), 6.23 (1 H, s, ArH) ppm; δ_C 7.9 ($CH_2\mathbf{CH_3}$), 38.2 ($\mathbf{CH_2}CH_3$), 56.0, 56.1, 61.0, 61.9 (methoxys), 92.3 (C1), 118.4, 136.0, 150.9, 152.3, 154.5 (aromatics), 204.7 (C=O); m/z (peaks >25%) 255 (MH^+), 239 (30), 210 (100), 151 (50), 133 (55). $C_{13}H_{18}O_5$ requires 255.1232, found 255.1229, an error on the close order of 1.5ppm; R_f (4:1 hexane - ethyl acetate) 0.25.

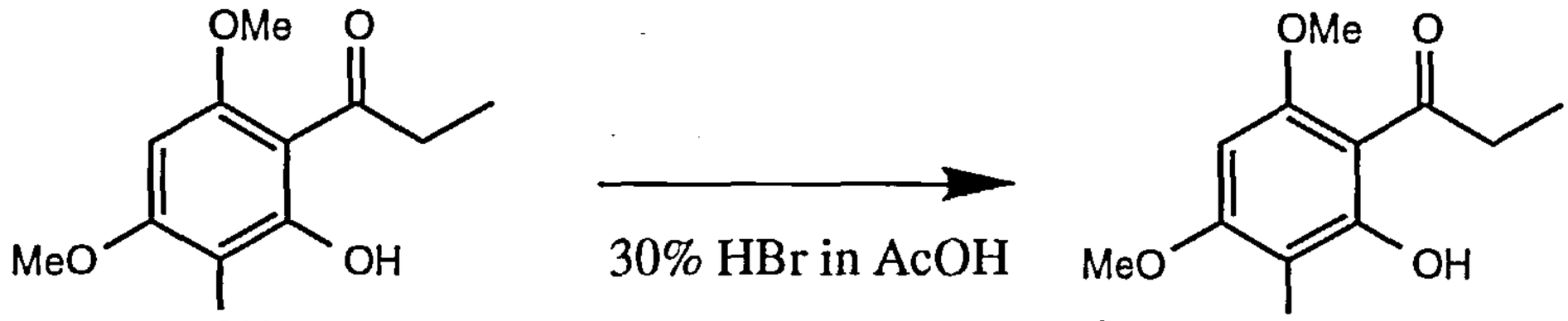
2,4,5-Trimethoxy-6-hydroxypropiophenone (4-2)[207]



To a stirred solution of (**3-6**) (0.1g, 0.4mmol) in glacial acetic acid (5ml) under argon was added a solution of HBr in dry acetic acid (*ca.* 36%, 1ml). Stirring was continued at room temperature for one week. The mixture was poured into ice water (25ml) and the aqueous phase extracted with dichloromethane (3x30ml), and the combined organics washed with sodium bicarbonate (saturated, 3x30ml) and water (1x30ml). The organic phase was dried and evaporated. The product was recrystallised from methanol to give yellow crystals (0.065g, 0.27mmol, 69%), m.p. 130° C; ν_{max} 2980, 2942, 1627 (C=O), 1592, 1250, 1211, 1129 cm^{-1}; δ_H 1.14 (3 H, t, J=7Hz, $CH_2\mathbf{CH_3}$), 3.01 (2 H, q, J=7Hz, $\mathbf{CH_2}CH_3$), 3.79 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.92 (3 H, s,

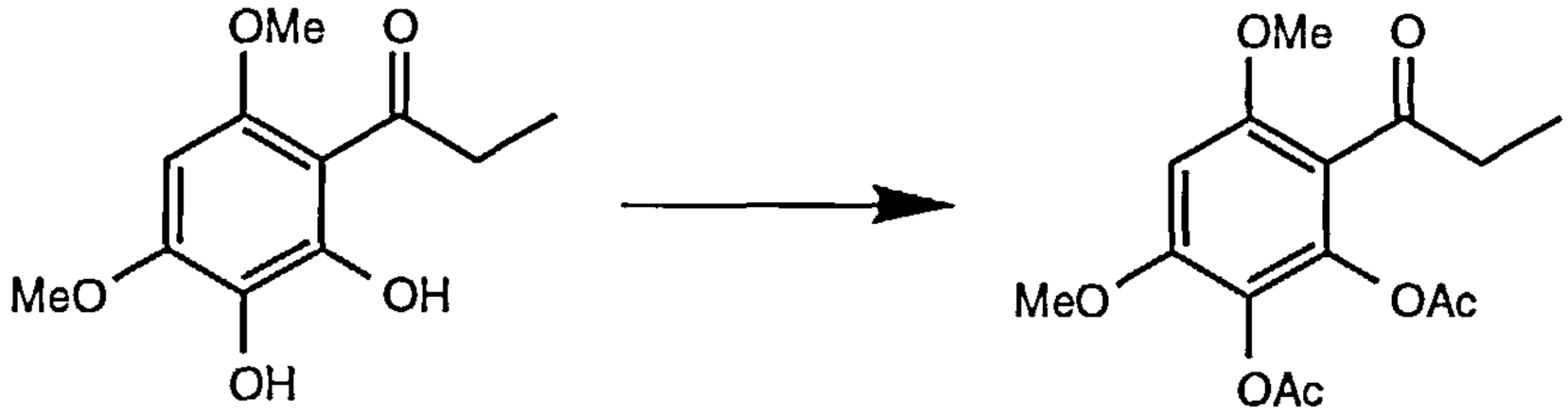
OMe), 5.95 (1 H, s, ArH), 13.88 (1 H, s, OH) ppm; δ_C 8.5 (C3'), 37.6 (C2'), 55.5 (OMe), 55.9 (OMe), 60.6 (OMe), 86.5 (C3), 106.0 (C6), 130.6 (C1), 158.7, 158.8 (C2 and C4), 206.9 (C1'); m/z 241 (MH^+), no other significant peaks; $C_{12}H_{16}O_5$ requires MH^+ 241.1076, found 241.1069, an error on the close order of 3ppm.

2,3-Dihydroxy-4,6-dimethoxypropiophenone (4-3)



To a solution of HBr in anhydrous acetic acid (36%, 5ml) under argon was added a solution of *o*-hydroxypropiophenone **4-2** (0.1g, 0.42mmol) in acetic acid (glacial, 1ml). The resulting mixture was stirred for 1 day, then tipped into ice water (20 ml). The solution was brought to pH 6 with KOH (10% aqueous, pH assessed by Universal Indicator paper). The aqueous phase was extracted with dichloromethane (3x30ml) and the combined organics washed with water (3x30ml). The organic phase was dried and evaporated and the resultant oil extracted repeatedly with cyclohexane (4x40ml). Evaporation and recrystallisation from methanol gave the product as a pale yellow solid (0.06g, 0.27mmol, 64%), m.p. 170° C (dec.); ν_{max} 2980, 2943, 1627 (C=O), 1424, 1250, 1211, 1128 cm^{-1}; δ_H 1.13 (3 H, t, J=7Hz, CH_2CH_3), 3.01 (2 H, q, J=7Hz, CH_2CH_3), 3.85 (3 H, s, OMe-4), 3.94 (3 H, s, OMe-6), 4.79 (1 H, br. s, 3-OH), 5.98 (1 H, s, ArH), 13.92 (1 H, s, 2-OH) ppm; δ_C 8.4 (C3'), 37.5 (C2'), 55.6 (OMe), 56.0 (OMe), 86.8 (C5), 105.1 (C1), 127.4 (C3), 151.6 (C4), 151.9 (C6), 207.1 (C1') ppm; m/z 244 (MNH_4^+), 227 (MH^+), 197, 168 no other significant peaks; HRMS MH^+ required 227.0919, found 227.0916, an error on the close order of 1.5 ppm. The spectra agreed with those in the literature.[208]

2,3-Diacetoxy-4,6-dimethoxypropiophenone (4-6)



i) <u>Using acetic anhydride/pyridine</u>

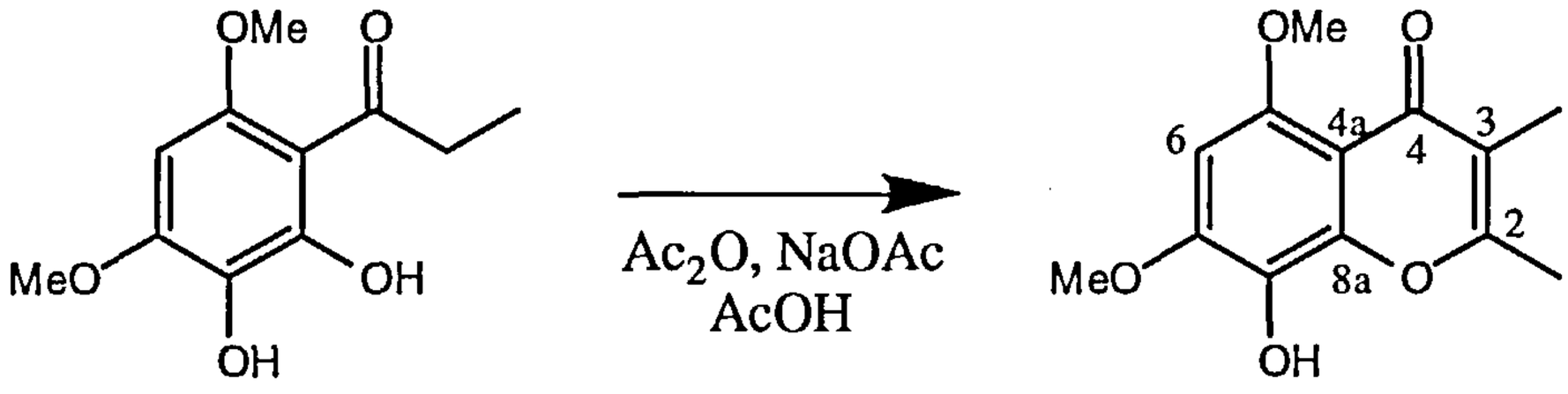
2,3-Dihydroxy-4,6-dimethoxypropiophenone (**4-3**) (0.1g, 0.44mmol) in EtOAc (3ml) with pyridine (1ml) was stirred under argon. Acetic anhydride (0.5ml) was added. The mixture was stirred for 2h then heated to 60° C for a further 2h. The reaction mixture was allowed to cool, then quenched with HCl (10ml, 2M). The aqueous

phase was extracted with ethyl acetate (3x10ml), washed with water (1x10ml) then brine (1x10ml), dried and evaporated under reduced pressure. Azeotropic drying with methanol (5ml) and ether (5ml) gave the product (0.12g, 88%) as a pure white powder.

ii) Using acetic anhydride/NaOAc

A solution of the dihydroxypropiophenone (0.1g, 0.44mmol) in acetic anhydride (10ml) with NaOAc (0.5g, freshly fused) was heated under reflux for 8h. The product was evaporated to dryness, then dissolved in water (5ml). The mixture was extracted with dichloromethane (3x10ml) and the combined organics washed with water (3x10ml), dried and evaporated. Azeotropic drying with methanol (3x5ml) and ether (2x5ml) yielded the product (**4-6**) (0.06g, 44%) as a cream powder, m.p. 64° C; ν_{max} 2922, 2850, 1774 (C=O ester), 1691 (C=O ketone), 1616, 1500, 1461, 1439, 1370, 1347, 1205, 1185 (C-O stretch ether) 1146, 1103 cm^{-1}; δ_H 2.21 (3 H, s, MeCO), 2.25 (3 H, s, MeCO), 3.84 (3 H, s, OMe), 3.85 (3 H, s, OMe), 6.41 (1 H, s, ArH) ppm; δ_C 20.0, 20.1 (CH_3CO), 56.0, 56.1 (both OMe), 93.9 (Ar C5), 112.5 (Ar C1), 116.6 (Ar C3), 153.5 (Ar C4), 155.6 (Ar C6), 167.8 (Ar C2), 201.8 ($CH_3CH_2C=O$), 208.9 (low intensity, MeC=O?), 211.5 (low intensity, MeC=O?) ppm; m/z 328 (MNH_4^+), 311 (MH^+), 269, 251 (100), 197; $C_{15}H_{18}O_7$ requires MH^+ 311.1131, found 311.1131, a zero error.

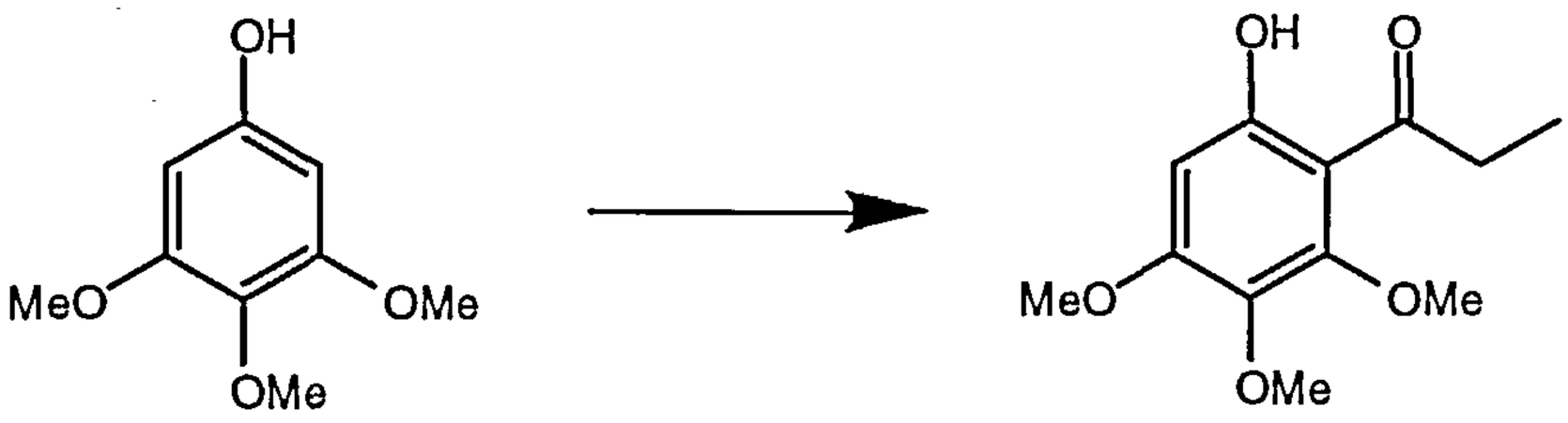
2,3-Dimethyl-5,7-dimethoxy-8-hydroxychromone (4-5) (stigmatellin fragment A)[209]



A solution of the dihydroxypropiophenone (**4-3**) (32mg, 0.14mmol) in acetic anhydride (3ml, 27mmol) with AcOH (glacial, 0.1ml, 1.7mmol) and NaOAc (freshly fused, 80mg, 0.98mmol) was heated under reflux for 8h. The product was evaporated to dryness, then dissolved in methanol (5ml) and HCl (1M, 5ml) added. The mixture was heated under reflux for 2h. The mixture was again evaporated to dryness, and the solid taken up in Laufmittel C (as defined in reference, dichloromethane (90ml), methanol (2ml), acetone (8ml), of which 0.5ml used). Chromatography on silica using the same solvent yielded the product (14mg, 40%), m.p. 269° C (lit. 274° C) ν_{max} 3392 (OH), 2921, 1765 (C=O), 1613, 1441, 1206, 1106 cm^{-1}; δ_H 1.97 (3 H, s, CH_3), 2.37 (3 H, s, CH_3), 3.91 (3 H, s, OMe), 3.98 (3 H, s, OMe), 5.21 (1 H, br. s,

OH), 6.41 (1 H, s, ArH) ppm; δ_C (d_6-DMSO) 9.7 (2-CH_3 ?), 17.7 (3-CH_3 ?), 56.1, 56.4 (both OMe), 93.9 (C6), 108.0 (C4a), 115.7 (C3), 127.4 (C8), 146.2 (C2), 150.7 (C8a), 151.7 (C7), 158.8 (C5), 175.7 (C4) ppm; m/z 251 (MH^+), 78, 61; $C_{13}H_{14}O_5$ requires MH^+ 251.0919, found 251.0919, a zero error; R_f (Laufmittel C) product 0.24, 8-O-acetyl product 0.25, di-o-acetyl starting material 0.97, starting material 0.99.

2-Hydroxy-4,5,6-trimethoxypropiophenone (3-8)[210]



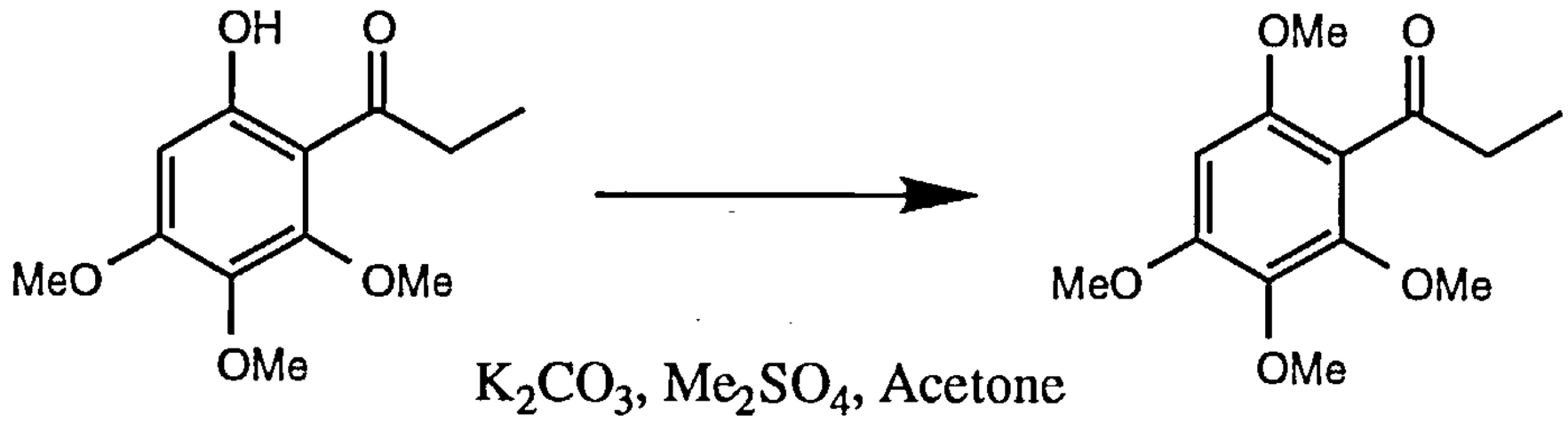
1) $Sc(OTf)_3$ (cat.), propionyl chloride, 1,2-dichloroethane

2) KOH, H_2O

3,4,5-Trimethoxyphenol monohydrate (1.08g, 5.34mmol), scandium triflate (0.2g, 0.41mmol, 7.5mol%) and propionyl chloride (20ml) in 1,2-dichloroethane (20ml) were stirred under argon at 80° C for 24h. The solvents were removed under reduced pressure and the residual anhydride removed with a toluene azeotrope (50ml). The resultant dark brown liquid was passed through a short silica plug and chased with copious dichloromethane. The straw coloured liquid thus obtained (0.7g) was diluted with KOH (10% aqueous) and stirred at 50° C for 3h. The mixture was allowed to cool, acidified to pH 5 (Universal indicator paper) with HCl (14M) and extracted with dichloromethane (3x50ml). The organics were washed with water (2x30ml), brine (1x30ml), dried and evaporated. The residual liquid was treated with ether (50ml) and left for 10min. The precipitate was filtered off and the filtrate evaporated to dryness. The etheric treatment was repeated twice. The final evaporation of the filtrate gave the title compound (0.3g, 1.25mmol, 23%). The solid proved to be pure 3,4,5-trimethoxyphenol which could be reused. The silica plug contained triflate residue which could be used to catalyse further reactions. The title compound had b.p. 155°C/7mBar; ν_{max} 3341(OH), 2980, 2941, 2841, 1757(C=O), 1603, 1489, 1456, 1434, 1351, 1196, 1142, 1113, 1001, 756 cm^{-1}; δ_H 1.14 (3 H, t, J=7Hz, CH_3CH_2), 3.03 (2 H, q, J=7Hz, CH_3CH_2), 3.74 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.95 (3 H, s, OMe), 6.20 (1 H, s, ArH), 13.46 (1 H, s, OH) ppm; δ_C 8.4 (CH_3CH_2), 36.3 (CH_3CH_2), 55.8 (OMe, ring C5), 60.7, 60.8 (both OMe), 96.0 (ring C3), 108.0 (ring C1), 134.6 (ring C5), 155.0 (ring C6), 159.6 (ring C4), 161.5 (ring C2), 206.4 (C=O)

ppm; m/z 241 (MH^+), 223, 202, 185, 169, 78, 61; $C_{12}H_{16}O_5$ requires MH^+ 241.1076, found 241.1080, an error on the close order of 2ppm.

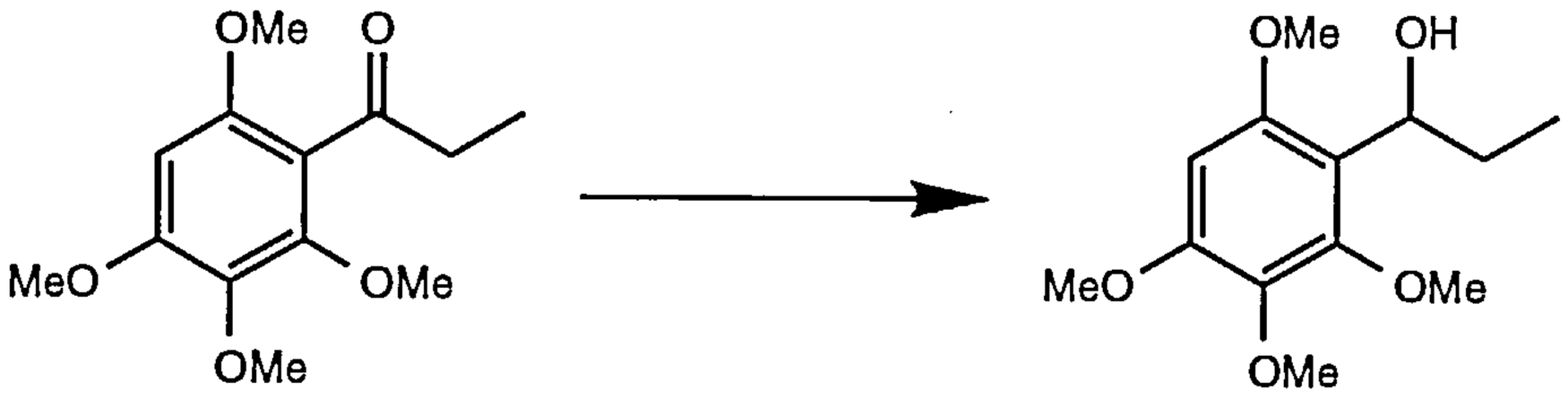
2,3,4,6-Tetramethoxypropiophenone (3-6)



K_2CO_3, Me_2SO_4, Acetone

2,3,4-Trimethoxy-6-hydroxypropiophenone **3-8** (0.3g, 1.25mmol), Me_2SO_4 (1ml, 10mmol), K_2CO_3 (anhydrous, 2g, 14mmol) in Analar® acetone (15ml) were heated under reflux for 2h. The mixture was allowed to cool, and the potassium carbonate filtered off. The mixture was tipped into NH_4OH (50ml, 1M) and stirred for 1h. The mixture was extracted with dichloromethane (3x30ml) and the combined organics washed with water (3x30ml) and brine (1x30ml). The organics were evaporated to give the title compound, which could be purified by recrystalisation from methanol (0.28g, 88%).

Attempted syntheses of 1-(2',3',4',6'-tetramethoxyphenyl)propan-1-ol (3-10)



i) <u>Using sodium borohydride</u>

To a solution of the propiophenone **3-6** (0.1g, 0.39mmol) in methanol (10ml) was added sodium borohydride (0.5g, 13mmol). The mixture was stirred under argon for 12h. The mixture was diluted with water (5ml) and stirred until effervescence ceased. The mixture was extracted with dichloromethane (3x5ml) and the combined organics washed with water (3x5ml). The solution was dried and evaporated under reduced pressure, to yield starting material.

ii) <u>Using lithium aluminium hydride</u>

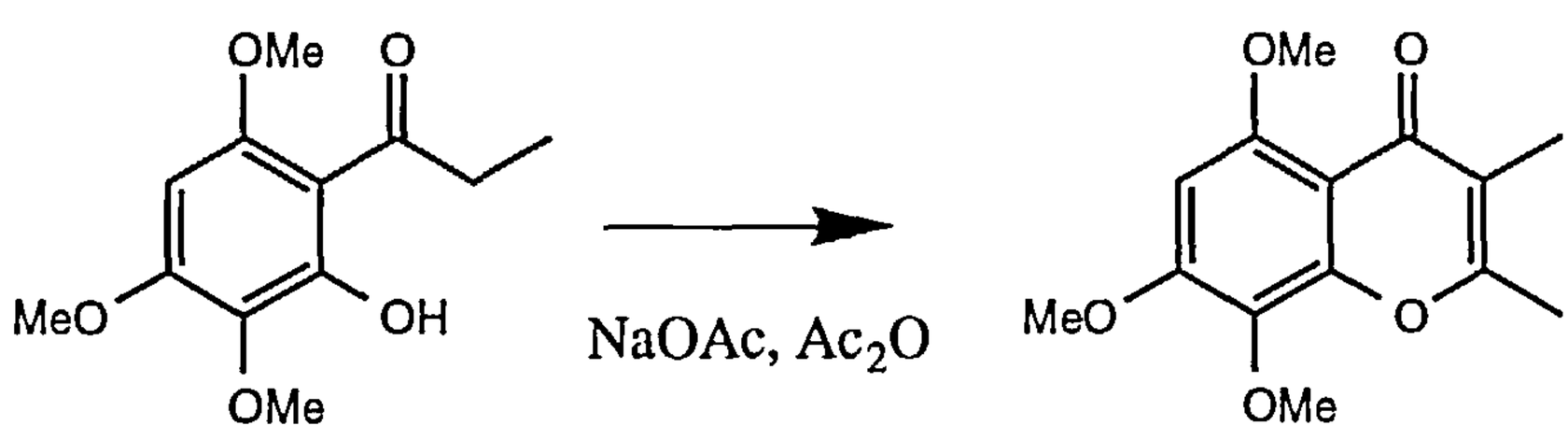
To a suspension of lithium aluminium hydride (0.2g, 5.3mmol) in THF (10ml) a solution of the propiophenone, **3-6** (0.1g, 0.39mmol) in THF (5ml) was slowly added. The solution was stirred under argon, then heated under reflux for 7 days, aliquots for NMR analysis being removed every 6h or so. Each aliqout (0.5ml) was treated with

isopropanol (1ml), then split between chloroform (2ml) and water (2ml). The chloroform layer was abstracted after vigorous mixing, and evaporated under vacuum. The resultant solid was prepared for NMR in the usual way. The NMR spectra showed no transformation. The lithium aluminium hydride was tested for reactivity and found to be potent.

iii) Using sodium/ethanol

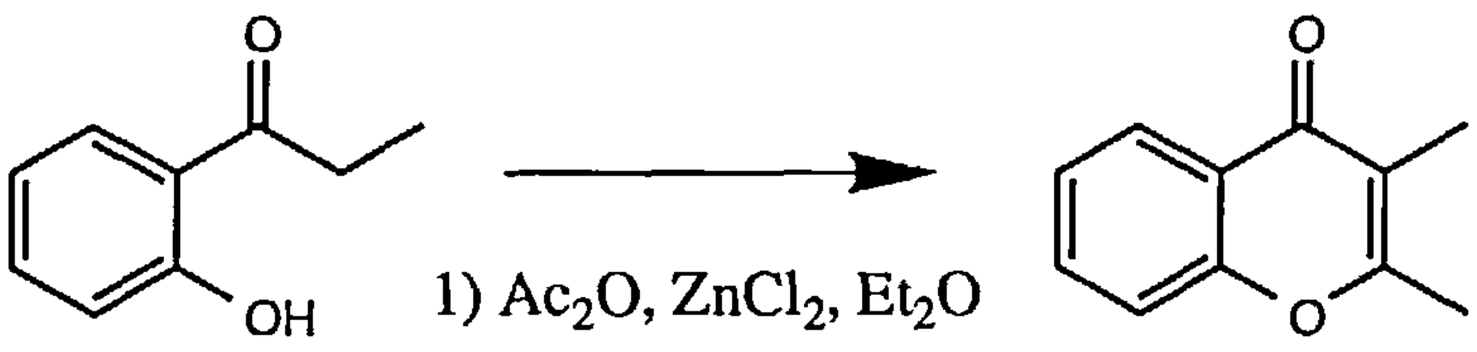
To a solution of the propiophenone, **3-6** (0.1g, 0.39mmol) in superdry ethanol (20ml) was added sodium (0.5g) in the form of small chips. The mixture was stirred under argon, with aliqouts being abstracted every 10 min for NMR analysis. Each aliquot (0.5ml) was treated with aq. oxalic acid (1ml, sat.) and mixed with chloroform (2ml). The chloroform layer was taken off and evaporated under vacuum. The sample was prepared for NMR in the usual way. NMR analysis showed no transformation.

2,3-Dimethyl-5,7,8-trimethoxychromone (4-4)



2-Hydroxy-3,4,6-trimethoxypropiophenone, **4-2** (0.1g, 0.42mmol) in Ac_2O (10ml) and NaOAc (freshly fused, 1g, 12mmol) was heated under reflux for 2 days. The mixture was allowed to cool, then evaporated to dryness. The residue was recrystallised from methanol to give a material giving peaks consistent with the title compound (0.03g, 27%), m.p. 110° C; δ_H 1.96 (3 H, s, 3-Me), 2.37 (3 H, s, 2-Me), 3.85 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.95 (3 H, s, OMe), 6.36 (1 H, s, ArH) ppm.

2,3-Dimethylchromone (4-7)



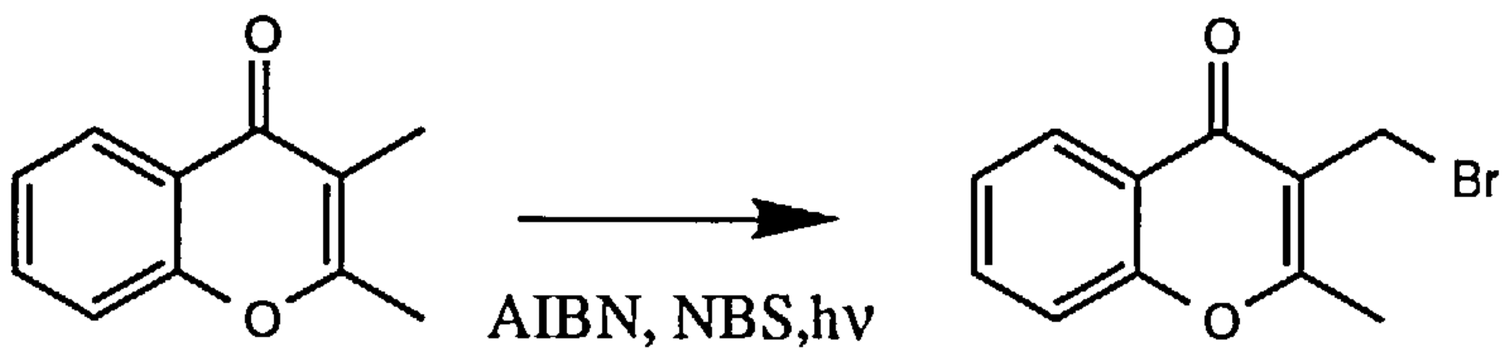
2-Hydroxypropiophenone (1.7g, 11mmol), Ac_2O (1g, 10mmol) and $ZnCl_2$ (proprietary anhydrous, 0.5g, 3.7mmol) were stirred under argon for 18h. The mixture was diluted with dichloromethane (20ml) then washed with water (3x20ml). The organic layer was dried, then evaporated. The crude mixture thus obtained could then be treated in one of two ways:

1) The mixture was dissolved in ether (30ml) and slowly passed into a thermostatted flash vacuum pyrolysis tube packed with glass beads, the tube being held at 325° C/15mmHg. After 2h the vacuum was released and the tube was allowed to cool, with a flow of argon passing through at atmospheric pressure. The product was collected, both from the cold trap at the tube exit and by washing the tube interior with ethyl acetate (300ml). After evaporation, crystallisation from minimal ether gave the product (0.5g, 25%).

2)[211] The product (3.5g in this case) was azeotroped with toluene (20ml), then diluted in DMSO (dry, 5ml). This mixture was syringed slowly into a suspension of sodium hydride (0.47g) in DMSO (10ml). The mixture was stirred until a strong yellow colouration occurred. The mixture was neutralized with sat. aq. oxalic acid (20ml). The mixture was extracted with ethyl acetate (3x20ml) and washed with water (3x20ml). The organic phase was dried and evaporated, then dissolved in acetic acid (glacial, 10ml) which was doped with sulphuric acid (10 drops). This mixture was heated under argon to 110° C, this being maintained for 3h. The mixture was diluted with ethyl acetate (10ml), washed with water (1x20ml) and saturated sodium bicarbonate solution (2x20ml) then dried, evaporated and recrystallised from ether. This gave the product (0.6g, 20%).

Both procedures give material with δ_H 2.02 (3 H, s, 3-Me), 2.36 (3 H, s, 2-Me), 7.1-7.8 (3 H, m, ArH), 8.0-8.3 (1 H, m, 5-H), identical with literature values.

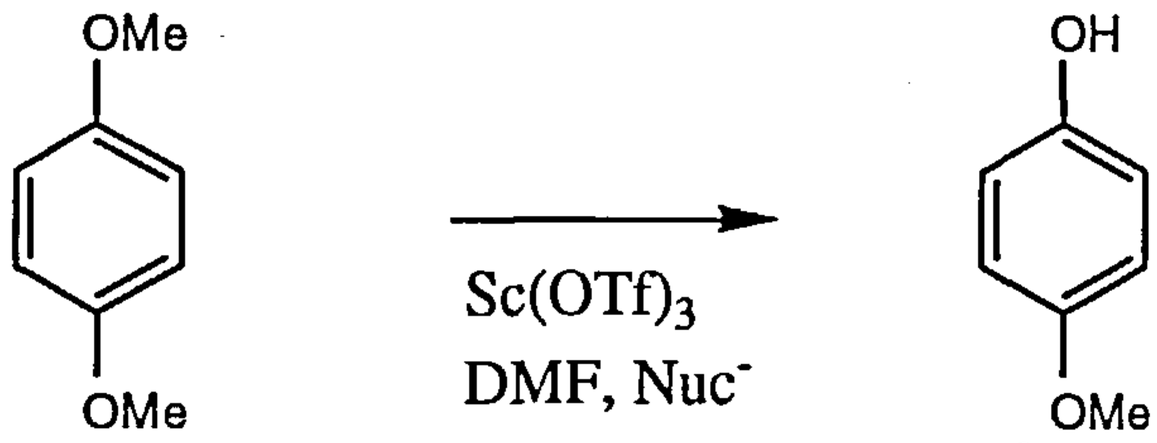
3-Bromomethyl-2-methylchromone (4-8)[212]



2,3-Dimethylchromone (0.17g, 1mmol), N-bromosuccinimide (0.18g, 1mmol) and AIBN (cat.) in dichloromethane (30ml) were heated under reflux over a 100W tungsten lamp for 0.5h. The solvent was then evaporated off, and the product

dissolved in minimal ethyl acetate and poured onto a short silica column. The by-products were run off with dichloromethane, then the product eluted with ethyl acetate to give the title compound (0.04g). Spectra accorded with literature[213]; δ_H 2.54 (3 H, s, Me), 4.53 (2 H, s, CH_2Br), 7.35-7.50 (2 H, m, ArH), 7.50-7.7 (1 H, m, ArH), 8.22 (1 H, m, 5-H) ppm.

Attemted demethylation of 1,4-dimethoxyphenol (4-9)



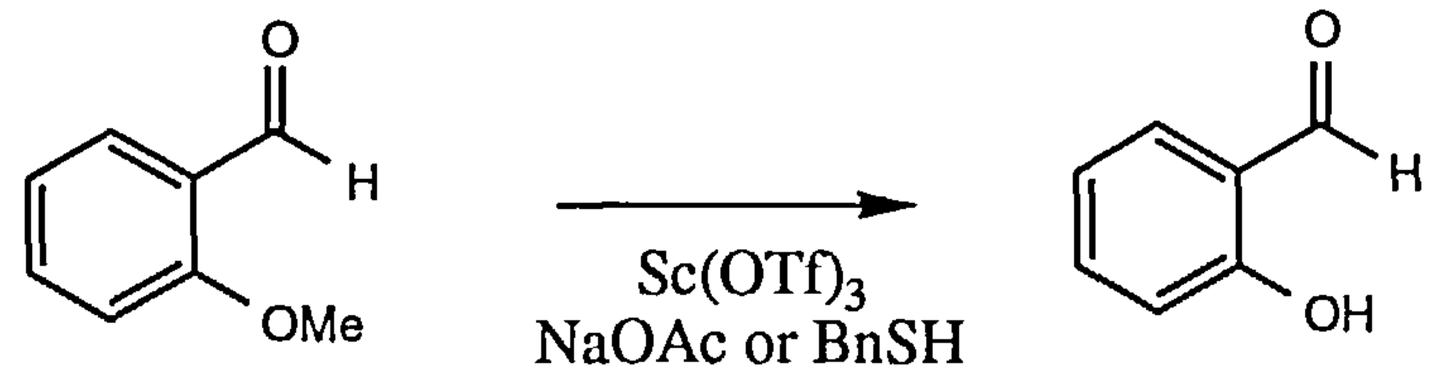
i) Using sodium iodide

To a solution of 1,4-dimethoxybenzene (0.2g, 1.4mmol) in DMF (5ml) were added scandium triflate (0.07g, 0.16mmol) and sodium iodide (0.22g, 1.5mmol). The mixture was stirred at 100°C under Ar. The mixture was diluted with dichloromethane (10ml), washed with HCl (1M, 2x20ml) and water (20ml), then dried and evaporated to give starting material.

ii) Using sodium acetate

The above procedure was repeated with all quantities the same except for the substitution of sodium acetate (fused, 1g, 12mmol) for sodium iodide. The result was the same.

Salicylaldehyde



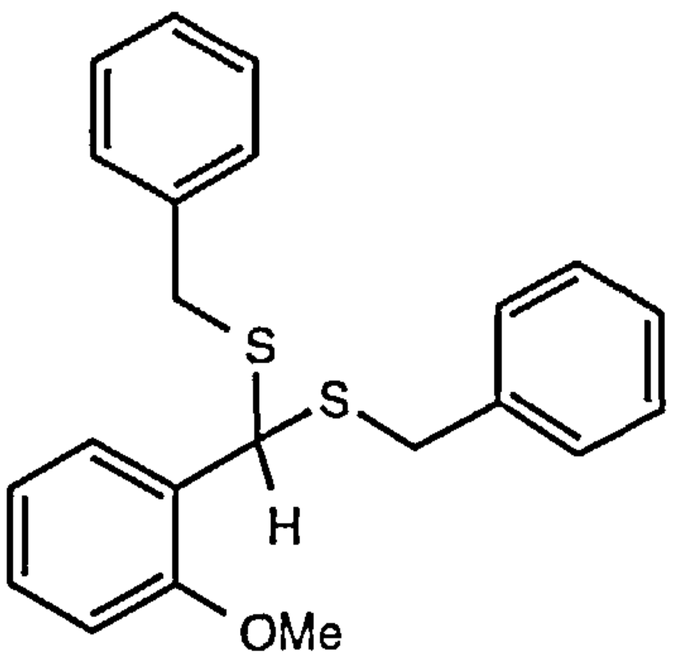
i) Sodium acetate

To a solution of *o*-anisaldehyde (0.2g, 1.6mmol) in DMF (3ml) was added scandium triflate (0.11g, 0.25mmol) and sodium acetate (1g, 12mmol). The mixture was stirred under Ar at 110°C for 3h. The mixture was then diluted with dichloromethane

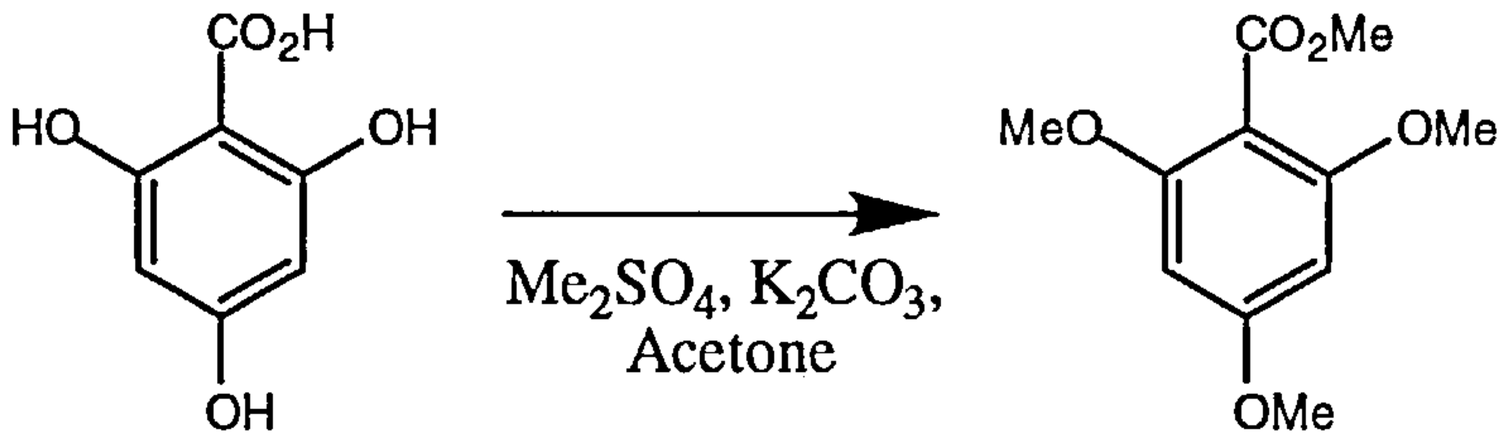
(10ml), washed with HCl (1M, 2x20ml), dried and evaporated, which gave starting material.

ii) With benzyl mercaptan

To a solution of *o*-anisaldehyde (0.3g, 2.5mmol) in benzyl mercaptan (3ml, 25.6mmol) was added scandium triflate (0.07g, 0.16mmol). The mixture was stirred under Ar for 14h, giving a yellow oily suspension. The mixture was tipped onto a short silica column and eluted with petroleum to remove the excess thiol. When the eluted solvent ceased to smell of thiol the column was eluted with ethyl acetate and then methanol. These were combined and evaporated to give a yellow liquid (0.53g) which gave spectra consistent with the structure below, of which it represented a 66% yield; δ_H 3.54 (2 H, d, J=13Hz, PhC**H**$_2$), 3.59 (3 H, s, OMe), 3.72 (2 H, d, J=13Hz, PhC**H**$_2$), 5.08 (1 H, s, SCHS), 6.77 (1 H, d, J=9Hz, salicyl H-6?), 6.94 (1 H, t, J= 8Hz, salicyl H-4), 7.09-7.31 (11 H, m, phenyl ArH + salicyl H-5), 7.65 (1 H, dd, J=7Hz, 1.5Hz, salicyl H-3); m/z 384 (MNH_4^+), 306, 243 (loss of SCH_2Ph), 165, 108, 91.

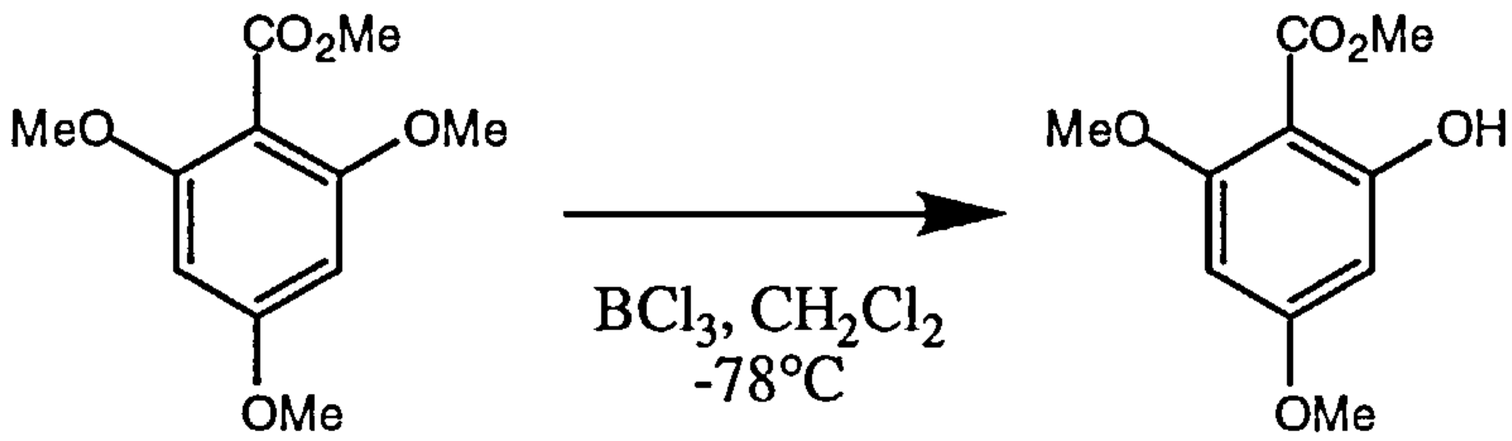


Methyl 2,4,6-trimethoxybenzoate (6-10a)[214]



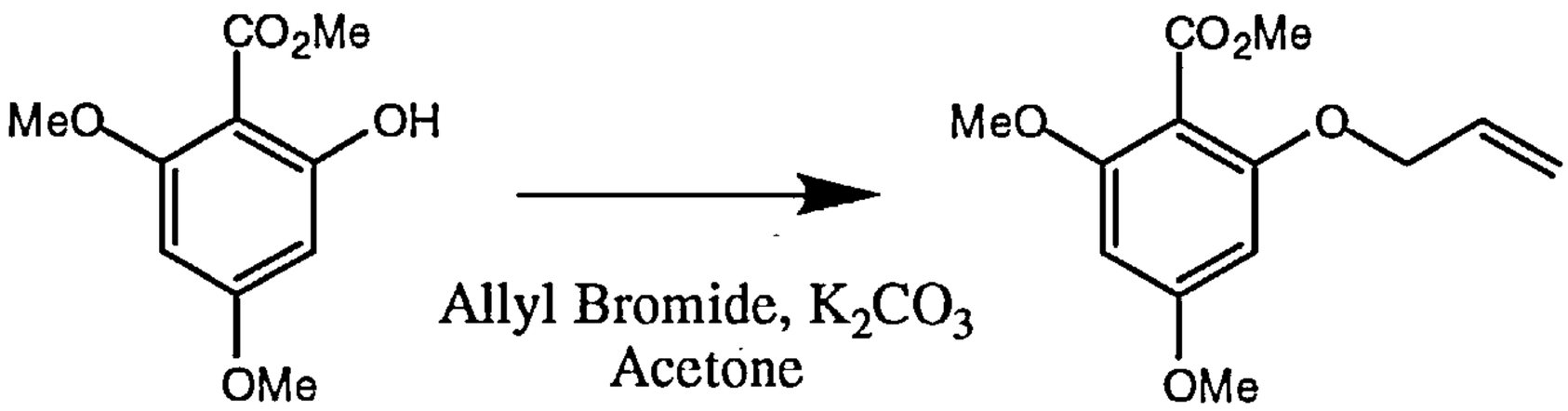
To a stirred suspension of 2,4,6-trihydroxybenzoic acid (4.99g, 29mmol) and potassium carbonate (anhydrous, 21.13g, 0.15mmol) in Analar® acetone (250ml) was added dimethyl sulphate (13.5ml, 18g, 0.14mol). The mixture was stirred for 27h. The excess potassium carbonate was filtered off and the mixture diluted with ammonia (aqueous, 2M, 200ml) and stirred for a further hour. The acetone was evaporated off and the residual liquid was extracted with ethyl acetate (3x100ml). The combined organics were washed with water (3x100ml), dried and evaporated. Recrystallisation of the product from methanol gave the title compound (3.8g, 16.7mmol, 57%), m.p. 67–68° C; δ_H 3.78 (6 H, s, 2,6-OMe), 3.81 (3 H, s, 4-OMe), 3.86 (3 H, s, CO_2Me), 6.08 (2 H, s, ArH) ppm. Data agree with literature values.

Methyl 2-hydroxy-4,6-dimethoxybenzoate (6-9)[215]



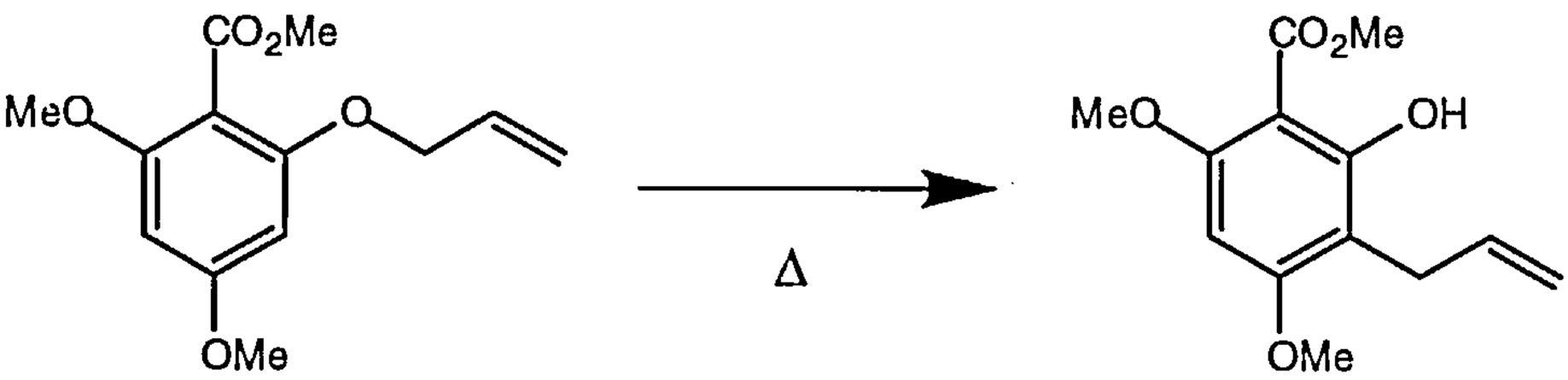
Methyl 2,4,6-trimethoxybenzoate, **6-10a** (0.7g, 3.1mmol) in dichloromethane (14ml) was cooled to -78° C with stirring and BCl_3 (1M in dichloromethane, 3.3ml, 3.3mmol) was added. The mixture was allowed to return to room temperature then quenched with HCl (25ml, 1M). The mixture was extracted with dichloromethane (3x20ml) and the combined organics were washed with water (1x100ml) then brine (1x100ml). The organic phase was dried and evaporated, then the residue recrystallised from methanol to give the title compound (0.4g, 2.2mmol, 62%), m.p. 105-106° C; δ_H 3.79 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.90 (3 H, s, CO_2Me), 5.95 (1 H, d, J=2Hz), 6.09 (1 H, d, J=2Hz), 14.16 (1H, s, OH) ppm. Figures agree with values and spectral information contained in the literature.

Methyl 2-allyloxy-4,6-dimethoxybenzoate (6-51)



To a stirred suspension of methyl 2-hydroxy-4,6,-dimethoxybenzoate, **6-9** (0.99g, 4.7mmol) and potassium carbonate (12g, anhydrous) in acetone (dry 100ml) in an Erlenmeyer flask fitted with a powerful stirrer and a drying tube was added allyl bromide (0.4ml, 0.564g, 4.7mmol). The mixture was stirred for a further 24h. The mixture was filtered then quenched with NH_4OH (1M, 100ml) and extracted with dichloromethane (3x100ml). The combined organics were dried and evaporated to give the crude product as a syrupy liquid (0.9g, 3.6mmol, 76%). The product was difficult to purify as it underwent rearrangement when distilled and proved difficult to separate by chromatography; ν_{max} 2949,1729 (C=O), 1608, 1422, 1266, 1226, 1209 (OMe), 1161 (OMe), 1124, 1054, 819$_c$cm^{-1}; δ_H 3.76 (6 H, s, OMe), 3.84 (3 H, s, CO_2Me), 4.49-4.51 (2 H, m, ArCH_2), 5.19-5.58 (2 H, m, CH=C**H$_2$**), 5.9-6.07 (2 H, m, C=C**H**– and ArH) ppm; m/z 253 (MH^+), 224, no other significant peaks; $C_{13}H_{16}O_5$ requires MH^+ 253.1076, found 253.1080, an error on the close order of 2ppm.

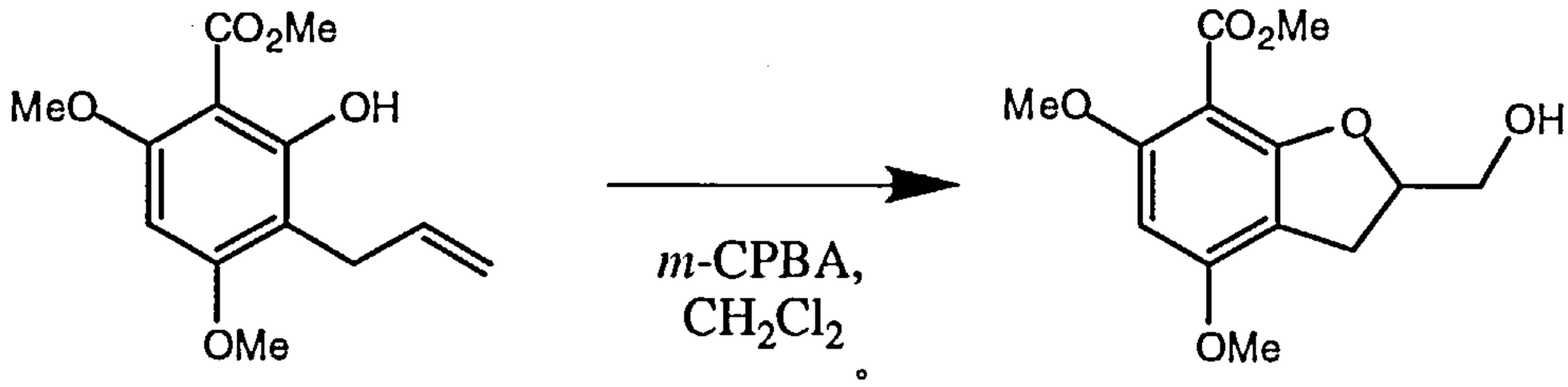
Methyl 2-hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxybenzoate (6-7a)



Methyl 2-allyloxy-4,6-dimethoxybenzoate, **6-51** (0.9g, 3.6mmol) was degassed by exposure to a good vacuum (0.01mmHg, 0.5h). The flask was then flushed with argon. The flask was fitted for reflux with a short, narrow air condenser and then heated on a Woods metal bath to 215° C. This temperature was maintained for 12h. The product was allowed to cool. The crude product could be recrystallised from methanol to give white crystals (0.9g, 100%). When a large pear shaped flask was used it was found that extremely pure product sublimed onto the inner surface of the flask, obviating recrystallisation. The product had m.p. 89° C, ν_{max} 3410 (OH), 3081, 2973, 1730 (C=O), 1639, 1613, 1469, 1408, 1278, 1205 (OMe), 1161 (OMe), 1120, 814 cm^{-1}; δ_H 3.31-3.47 (2 H, m, ArCH_2), 3.85, 3.86 (both 3 H, s, OMe), 3.90 (3 H, s,

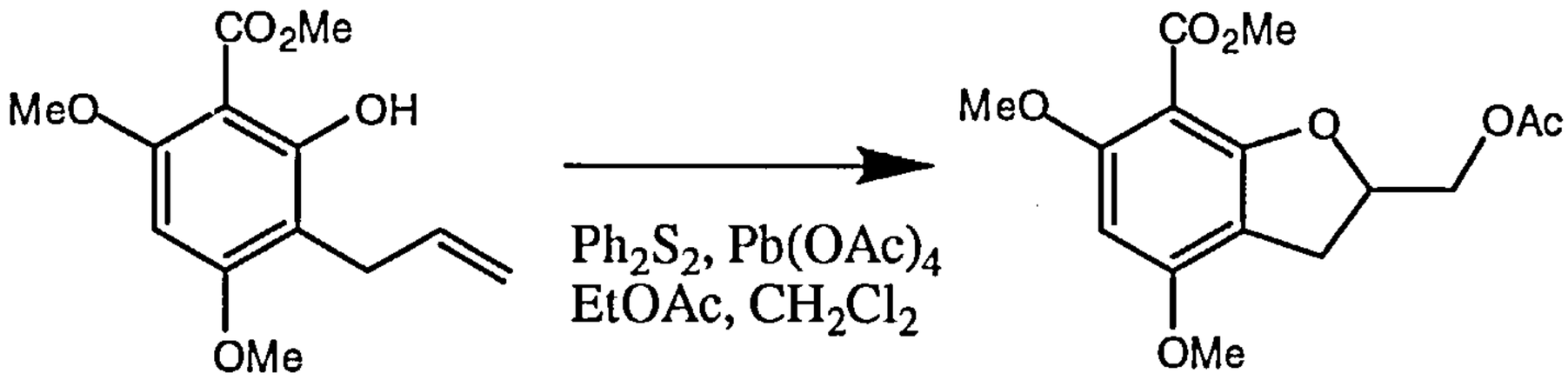
CO_2Me), 4.90-4.99 (2 H, m, CH_2=CH), 5.88-5.99 (2 H, m, C–CH=C and ArH), 11.31 (1 H, s, OH) ppm; δ_C 26.6 ($ArCH_2$), 52.1 (CO_2Me), 55.5, 56.1 (both OMe), 87.2 (ArH), 96.7 (C3), 107.9 (C1), 113.9 (CH=CH_2), 136.6 (C–CH=C), 161.0 (C2), 162.1, 162.7 (C4, C6), 171.9 (C=O) ppm; m/z 270 (MNH_4^+), 253 (MH^+), 227, 213, 195 (Found: C, 62.10; H, 6.31; $C_{13}H_{16}O_5$ requires C, 61.90; H, 6.39%).

Methyl 2-hydroxymethyl-4,6-dimethoxy-2,3-dihydrobenzofuran-7-carboxylate (6-52)



The ester (**6-7a**) (0.2g, 0.79mmol), 3-chloroperoxybenzoic acid (0.18g, 1mmol) and dichloromethane (10ml, dry) were stirred together in the dark under argon. The dichloromethane was washed with sodium hydrogencarbonate (3x30ml), then evaporated down. Crude NMR of the mixture showed partial transformation of starting material, but the product had no aromatic proton.

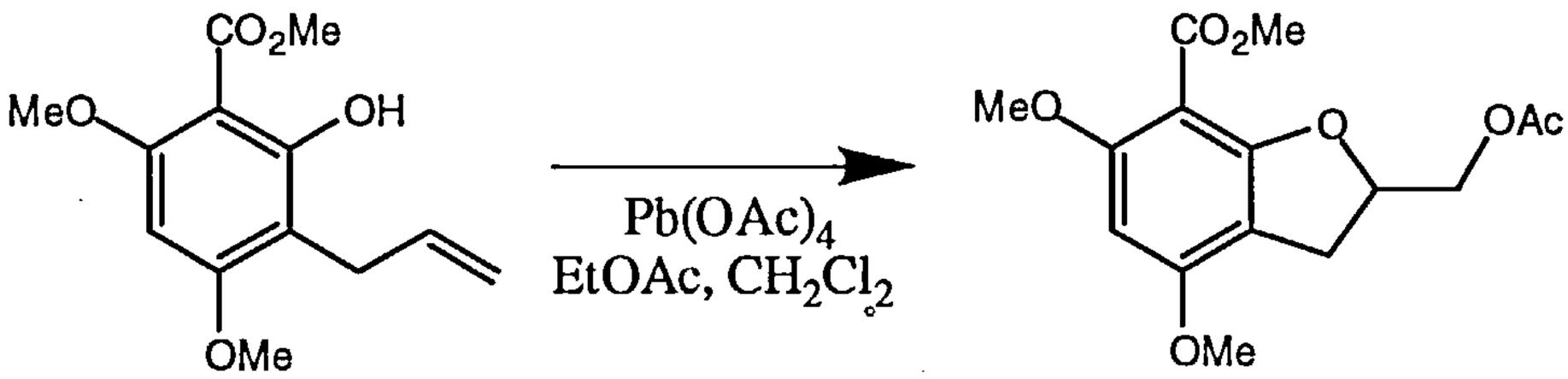
Methyl 2-(acetoxymethyl)-4,6-dimethoxy-2,3-dihydrobenzofuran-7-carboxylate (6-18)[216]



The ester (**6-7a**) (0.1g, 0.4mmol), $Pb(OAc)_4$ (0.2g, 0.45mmol), and diphenyl disulphide (0.1g, 0.46mmol) were stirred in a mixture of ethyl acetate and dichloromethane (1:1, 25ml) for 18h. The mixture was washed through a silica plug using the same solvent, then evaporated. The solid was extracted with copious ether - petroleum mixture (1:4), then recrystallised from ether to give a white solid (0.05g, 0.16mmol, 41%), m.p. 61° C, ν_{max} 2951, 2847, 1734 (br, C=O), 1618, 1504, 1466, 1434, 1373, 1274, 1238, 1215 (OMe), 1158 (OMe), 1105, 1034 cm^{-1}; δ_H 2.02 (3 H, s, Ac), 3.71-4.01 [12 H, m, $ArCH_2$, OCH–CH_2OAc, 3xOMe (3.83, 3.84, 3.85)], 4.41-4.68 (2 H, m, $AcOCH_2$?), 5.97 (1 H, s, ArH) ppm; δ_C 20.8 (MeC=O), 39.5 ($ArCH_2$), 51.8 (CO_2Me), 55.4 (OMe), 56.5 (OMe), 64.6 (CH_2OAc), 76.1 (ArOCH), 77.4 (Ar

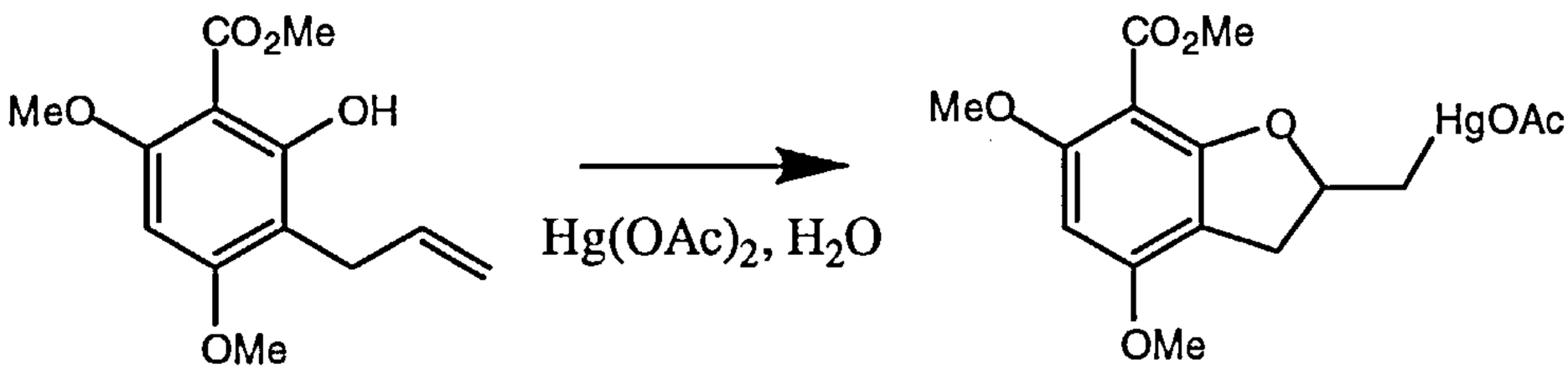
C3), 88.3 (Ar C5), 106.2 (Ar C1), 159.0 (Ar C2), 162.5, 163.5 (Ar C4, C6), 168.5 (MeC=O), 171.7 (CO_2Me) ppm; m/z 328 (MNH_4^+), 311 (MH^+), 279, 237, 193, 161 (Found: C, 58.05; H, 5.76; $C_{15}H_{18}O_7$ requires C, 58.06; H, 5.85%). Acid methanolysis of this mixture gives a complex, inseparable mixture, none of the spectral peaks of which resemble the previous product.

Methyl 2-(acetoxymethyl)-4,6-dimethoxy-2,3-dihydrobenzofuran-7-carboxylate (6-18)



The ester () (0.1g, 0.4mmol) and $Pb(OAc)_4$ (0.2g, 0.45mmol) were stirred in a mixture of ethyl acetate and dichloromethane (1:1, 25ml) for 12h. The mixture was washed through a silica plug using the same solvent, then evaporated. The solid was extracted with copious petroleum - ether mixture (4:1), then recrystallised from ether to give a white solid (0.06g, 0.2mmol, 49%).

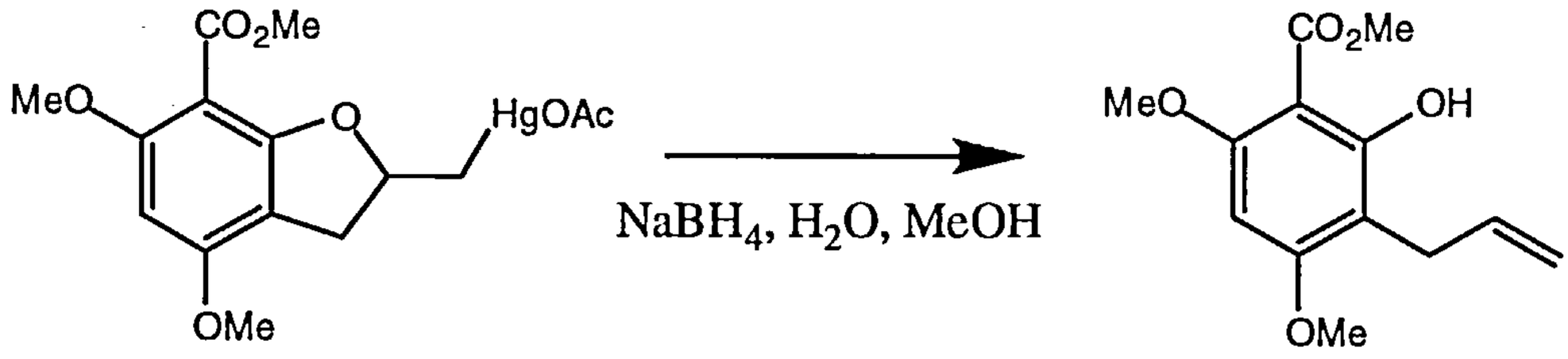
Methyl 2-(acetoxymercurimethyl)-4,6-dimethoxy-2,3-dihydrobenzofuran-7-carboxylate (6-20)[217]



The ester (**6-7a**) (0.2g, 0.8mmol) in water (deionised, 10ml) was stirred and $Hg(OAc)_2$ (0.38g, 1.2mmol) added. The mixture was stirred for a further 3h. The suspension was filtered on a frit (porosity 4), washed with water (2x5ml) and air dried. After desiccation, crystallisation from methanol gave the product (0.15g, 46%), m.p. 72° C (dec.); ν_{max} 3436, 1645 (C=O, 1614, 1572, 1434, 1410, 1281, 1208 (OMe), 1165 (OMe), 1112, 1013, 811 cm^{-1}; δ_H (d_6-DMSO) 1.73 (1 H, d, J=5Hz, CH_2Hg?), 1.85 (1 H, s, Ac), 2.52 (dd, 1 H, J=7Hz, 13Hz), 2.71 (dd, 1 H, J=8Hz, 13Hz) (both $ArCH_2$), 3.78, 3.80, 3.83 (all 3 H, s, OMe), 4.09 (1 H, m, $OCHCH_2Hg$), 6.22 (1 H, s, ArH) ppm; δ_C 20.8 ($HgCH_2$), 39.5 (MeC=O), 51.8 (CO_2Me), 55.4, 56.5

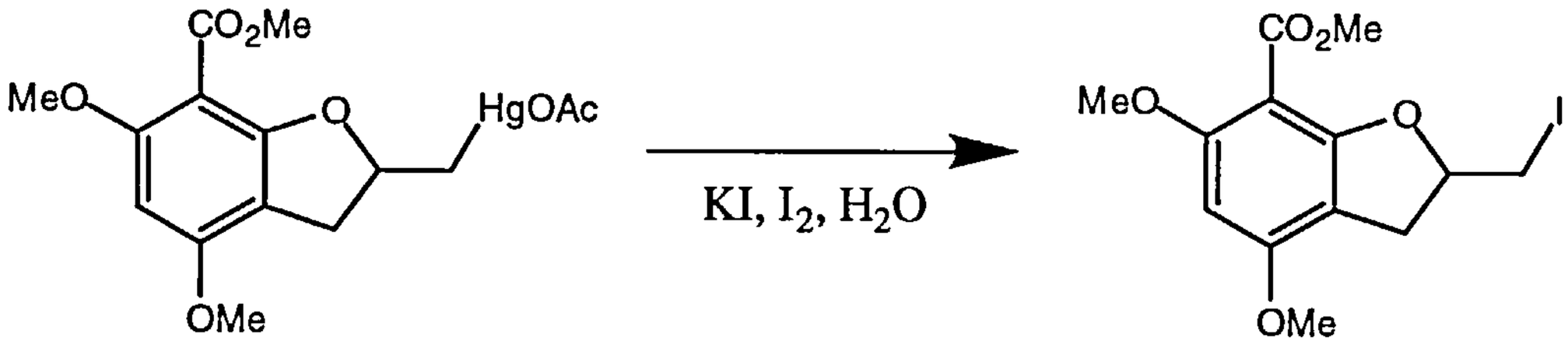
(both OMe), 64.6 ($ArCH_2$), 76.0 ($OCHCH_2Hg$), 88.3 (Ar C5), 105.9 [Ar C1 (under ester function)], 112.4 (Ar C3), 158.1 (Ar C2), 161.4, 161.7 (Ar C4, C6), 164.8 (MeC=O), 170.9 (MeC=O) ppm; m/z 253, no other significant peaks. Indicates demercuration.

Methyl 2-hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxybenzoate (6-7a)



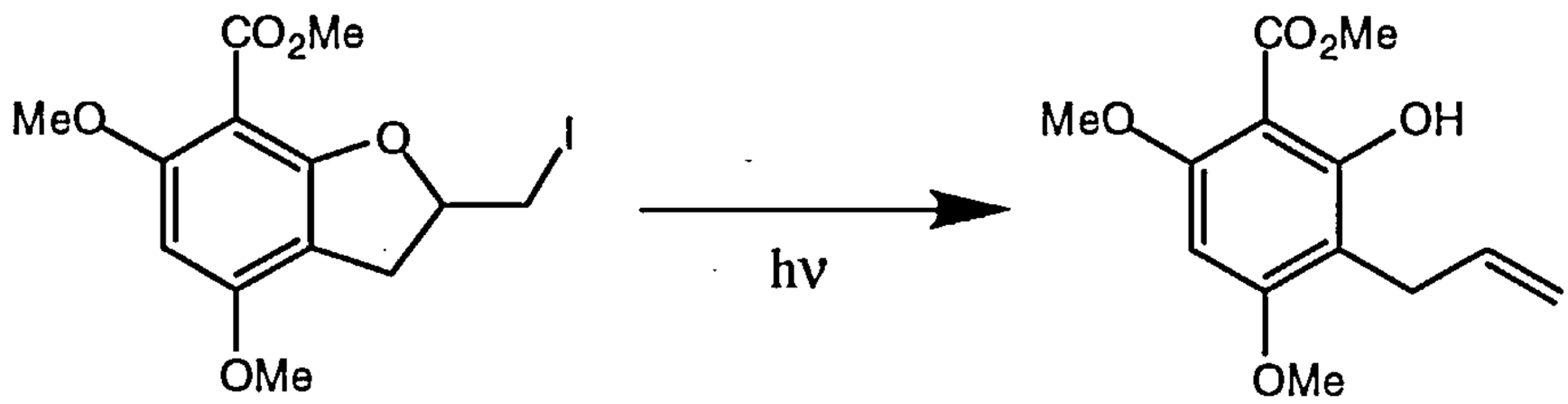
The mercury salt, **6-20** (0.05g, 0.1mmol) was stirred in methanol/water (1:2, 5ml) with $NaBH_4$ and the reaction followed by TLC in ether. On completion the mixture was extracted with dichloromethane (3x2ml) then the combined organics washed with water (1x2ml). The organic fraction was dried then evaporated to furnish the title compound (0.01g, 0.03mmol, 25%).

Methyl 2-(iodomethyl)-4,6-dimethoxy-2,3-dihydrobenzofuran-7-carboxylate (6-21)



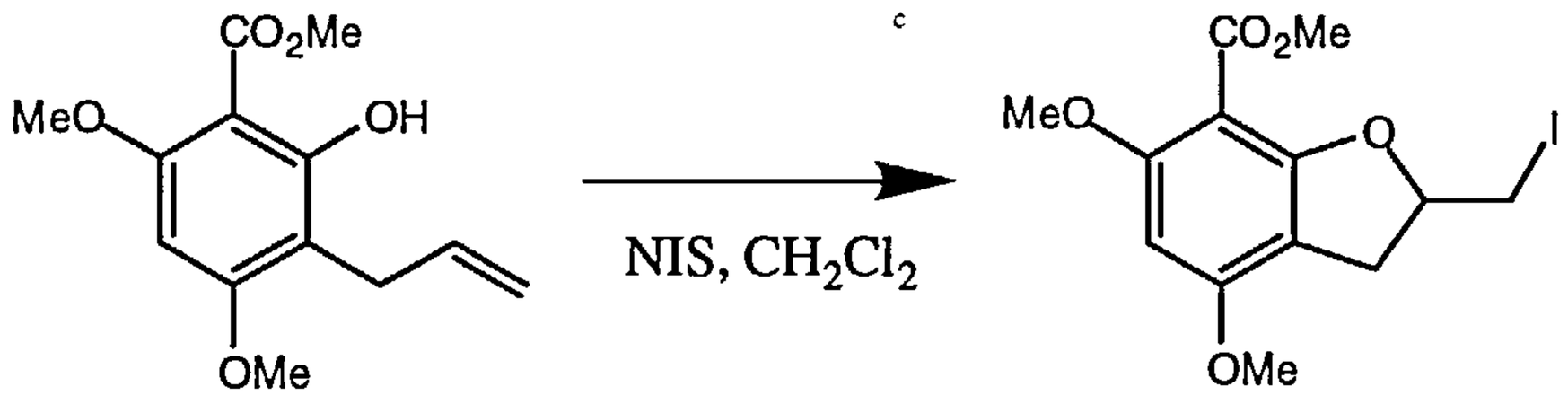
The mercury salt, **6-20** (0.1g, 0.2mmol) was treated with KI (1g, 6mmol) in water (15ml), then iodine (0.06g, 0.24mmol) added. The mixture was brought to the boil and maintained for 10min. On cooling the mixture was extracted with dichloromethane (3x20ml), washed with water, dried then evaporated at room temperature under vacuum, giving crude product (0.04g, 0.104mmol, 52%), m.p. 96° C (dec.); ν_{max} 2934, 1646 (C=O), 1615, 1575, 1434, 1408, 1281, 1208 (OMe), 1148 (OMe), 1111, 1010, 809 cm^{-1}; δ_H 3.19 (dd, 1 H, J=10Hz, 14Hz, $ArCH_2$), 3.30 (dd, 1 H, J=5Hz, 14Hz $ArCH_2$), 3.74 (t, 1 H, J=19Hz CH_2I), 3.85-3.98 [10 H, m, includes CH_2I and 3xOMe (all singlets, 3.87, 3.88, 3.90)], 4.72 (1 H, apparent septet, J=5Hz, $OCHCH_2I$), 5.97 (1 H, s, ArH) ppm; m/z 270, 253 (both show deiodination).

Methyl 2-hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxybenzoate (6-7a)



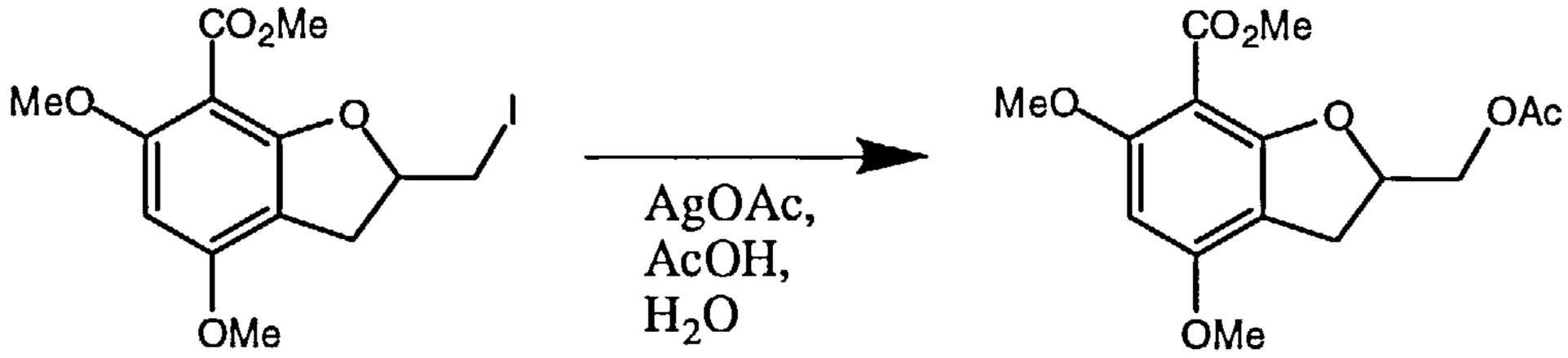
Methyl 2-(iodomethyl)-4,6-dimethoxy-2,3-dihydrobenzofuran-7-carboxylate (**6-21**) (0.1g, 0.26mmol) in deuteriochloroform (3ml) was exposed to light from a tungsten lamp (100W) for 2 min. The resultant red solution was subjected to NMR analysis which showed a quantitative transformation into the title compound.

Methyl 2-(iodomethyl)-4,6-dimethoxy-2,3-dihydrobenzofuran-7-carboxylate (6-21)



Methyl 2-hydroxy-3-(prop-2-en-1-yl)-4,6,-dimethoxybenzoate (**6-7a**) (0.1g, 0.39mmol) and N-iodosuccinimide (0.18g, 0.8mmol) were stirred in dichloromethane (15ml). After 24h the mixture was passed through a short silica plug and analysed by NMR, showing peaks consistent with the title and starting compounds, in a ratio of approximately 1:2. TLC analysis in ether also showed a mixture of the above compounds with R_f of 0.41 and 0.56 respectively.

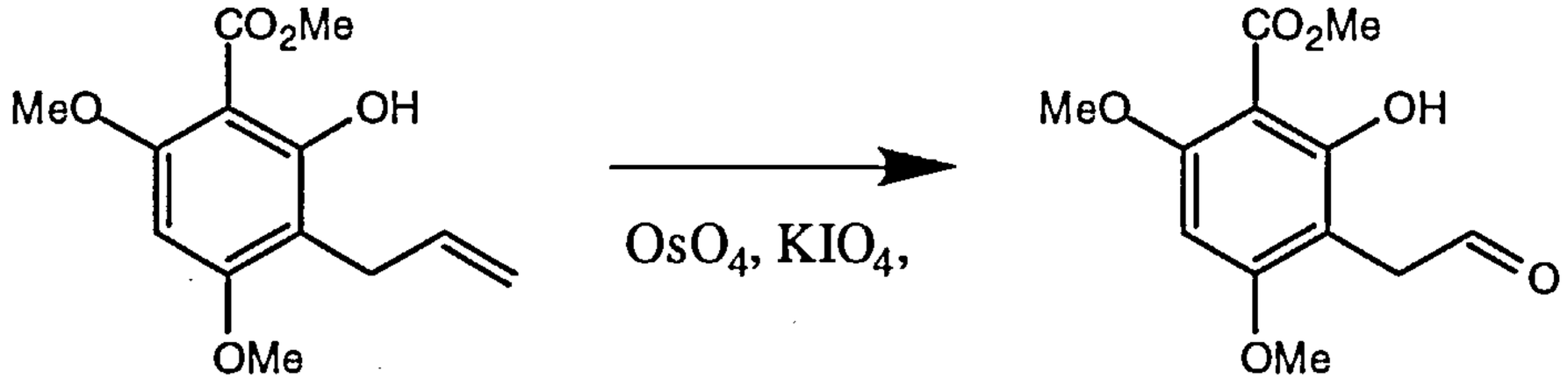
Methyl 2-(acetoxymethyl)-4,6-dimethoxy-2,3-dihydrobenzofuran-7-carboxylate (6-18)



The ester (**6-21**) (0.02g, 0.05mmol) and silver acetate (0.02g, 0.12mmol) in acetic acid (glacial, 2ml) and water (1ml) were stirred for 2h. Water was added, and the

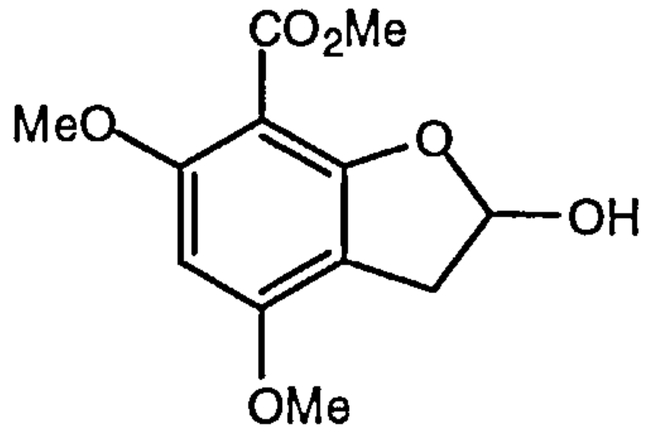
solution extracted with ether (3x10ml). The etheric extract was washed with sodium hydrogen carbonate (1x5ml, saturated), dried and evaporated. The resultant solid (0.005g, 32%) gave spectra in accordance with the title compound as prepared above.

Methyl 2-hydroxy-3-(2-oxoethyl)-4,6-dimethoxybenzoate (6-22)[218]



i) Using dioxane/water

To a solution of the allylphenol, **6-7a** (0.2g, 0.8mmol) in 1,4-dioxane (6ml) and water (2ml) was added osmium tetroxide (cat., as a 2.5% solution in *t*-butanol, 2 drops). The mixture was stirred until a dark colour appeared. Sodium periodate (0.4g, 1.9mmol) was then added and the mixture stirred for a further 3h. The mixture was diluted with water (5ml), extracted with ether (3x10ml), washed with water (1x10ml), dried with sodium sulphate, then evaporated under reduce pressure to give the title compound as a mixture with starting material. Careful recrystallisation from methanol gave the product in a somewhat purer form (0.06g, 30%). The NMR spectrum shows that the compound exists in equilibrium with its lactol form (shown below), this equilibrium rendering the analysis of carbon NMR spectra very difficult.

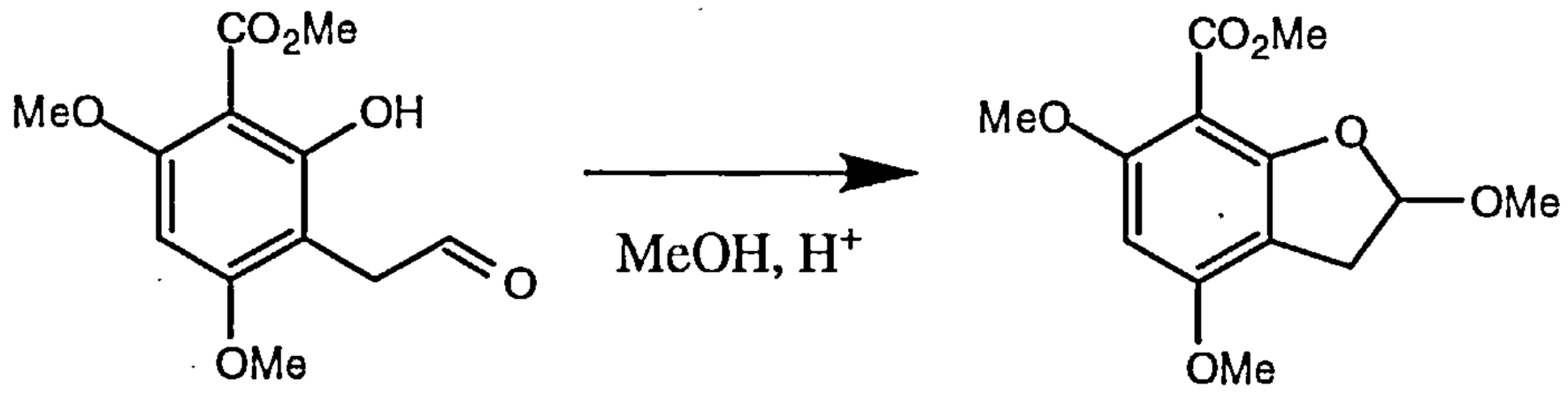


The product had m.p. 136° C; ν_{max} 3409 (OH), 2952, 1717 (C=O), 1651, 1619, 1578, 1456, 1435, 1416, 1290, 1227, 1208 (OMe), 1166 (OMe), 1124 (OMe), 1007, 803 cm^{-1}; δ_H 3.64 (2 H, d, J=2Hz, $ArCH_2$), 3.84 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.91 (3 H, s, OMe), 6.01 (1 H, s, ArH), 9.60 (1 H, t, J=2Hz, CHO), 12.16 (1 H, s, OH) ppm; lactol form δ_H 3.05 (1 H, t, J=4Hz, OCHOH), 3.84, 3.88, 3.91 (all 3 H, s, OMe), 4.25 (2 H, d, J=4Hz, CH_2Ar), 5.99 (1 H, s, ArH), 12.15 (1 H, s, OH) ppm; m/z 272 (MNH_4^+), 255 (MH^+), 223, 193; R_f (ether) 0.4. The ratio of aldehyde to lactol in $CDCl_3$ at 20° C was approx. 2:1.

ii) With THF/water

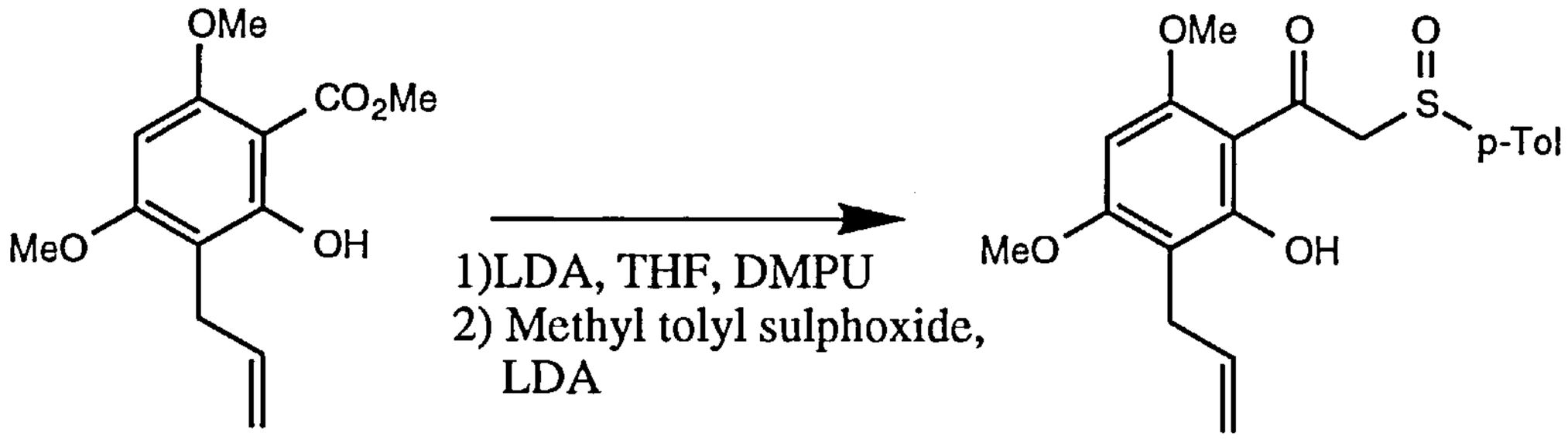
The above procedure was repeated using THF/H_2O (1:1) as a solvent. The product was obtained in 48% yield.

Methyl 2,3-dihydro-2,4,6-dimethoxybenzofuran-7-carboxylate (6-23)



To a sample of the aldehyde mixture produced above (0.05g, 0.2mmol) was added methanol (0.5ml) and two beads of freshly acid-washed Amberlyst® 15 ion exchange resin. The mixture was stirred under argon, then the catalyst removed with tweezers and the solvent evaporated off at room temperature/0.001mmHg. The resultant solid was dissolved in $CDCl_3$ (1ml) and subjected to NMR analysis. It was found that the compound was unstable in solution, decaying back to aldehyde in the space of some 1.5 h; ν_{max} 3479, 1715 ArC=O, 1644, 1435, 1289, 1111, 1055, 806 cm^{-1}; δ_H 2.88 (1 H, dd, J=3Hz, 15Hz) 3.14 (1 H, dd, J=7Hz, 15Hz) (both $ArCH_2$), 3.45, 3.48, 3.82, 3.87 (all 3 H, s, OMe), 5.69 (1 H, dd, J=3Hz, 7Hz, OC**H**OMe), 6.00 (1 H, s, ArH).

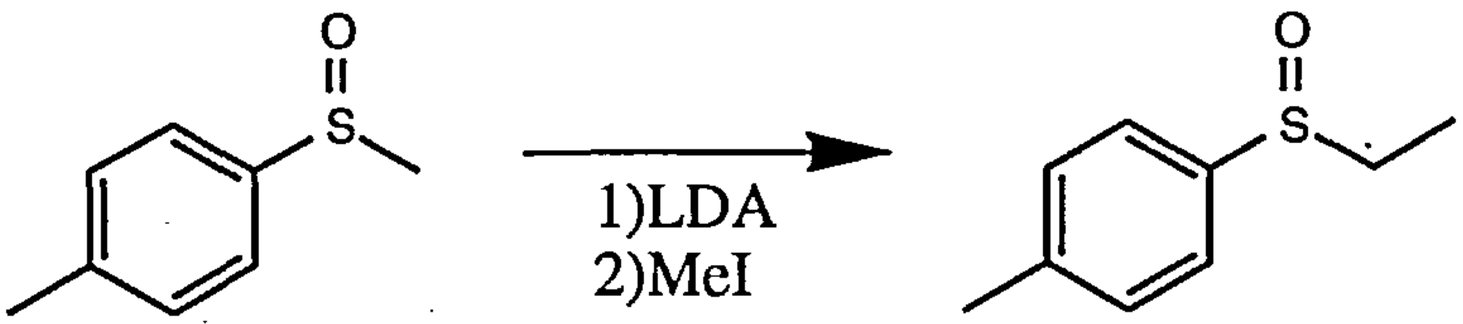
Attempted synthesis of 1-(2-hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxyphenyl)-2-(p-tolylsulphinyl)ethanone (6-8)



Method:[219] In flask A: To a solution of allylphenol, **6-7a** (0.242g, 1mmol) in THF (3ml) and DMPU (1.5ml), chilled to -78° C, was added LDA (1.5M in THF, 1ml, 1.5mmol). In flask B: To a solution of methyl *p*-tolyl sulphoxide (0.2g, 1.3mmol) in THF (dry, 3ml) and DMPU (1.5ml), chilled to -78° C was added LDA (1.5M in THF, 2ml, 3mmol). The contents of flask A were added to flask B at -78° C and the mixture stirred for 0.5h, then allowed to rise to room temperature and stirred overnight. The mixture was quenched with HCl (2M, 3ml), diluted with water (10ml) and extracted with ethyl acetate (3x20ml). The combined organics were washed with water (3x30ml), dried and evaporated under reduced pressure. The mixture could be

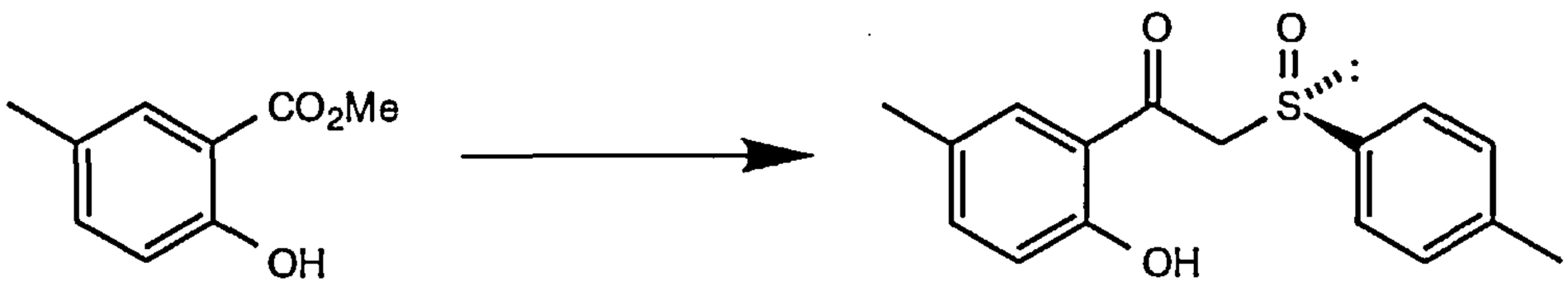
freed of excess DMPU by dissolving the solid in methanol - water 1:1 (10ml) and extracting with hexane (3x10ml). After drying and evaporation this yielded a solid (0.01g) which NMR analysis showed to contain a trace of product (signified by two doublets at 4.2 and 4.9) and mainly starting material.

Ethyl p-tolyl sulphoxide



To a solution of methyl tolyl sulphoxide (0.5M in THF, 2ml, 1mmol) at 0° C was added LDA (0.25M in THF, 4ml, 1mmol). The mixture was allowed to mature for 25 min and then quenched with MeI (1ml, 16mmol). The mixture was washed with NH_4OH (2M, 2ml), then dried and evaporated. The residue was taken up in $CDCl_3$ and submitted to NMR analysis; δ_H 1.16 (3 H, t, J=7Hz, $\mathbf{CH_3}CH_2$), 2.39 (3 H, s, MeAr), 2.76 (1 H, dq, J=7Hz, 2Hz), 2.83 (1 H, dq, J=7Hz, 2Hz) (both RCH_2SO), 7.29 (2 H, d, J=8Hz, tolyl), 7.47 (2 H, d, J=8Hz, tolyl) ppm.[220]

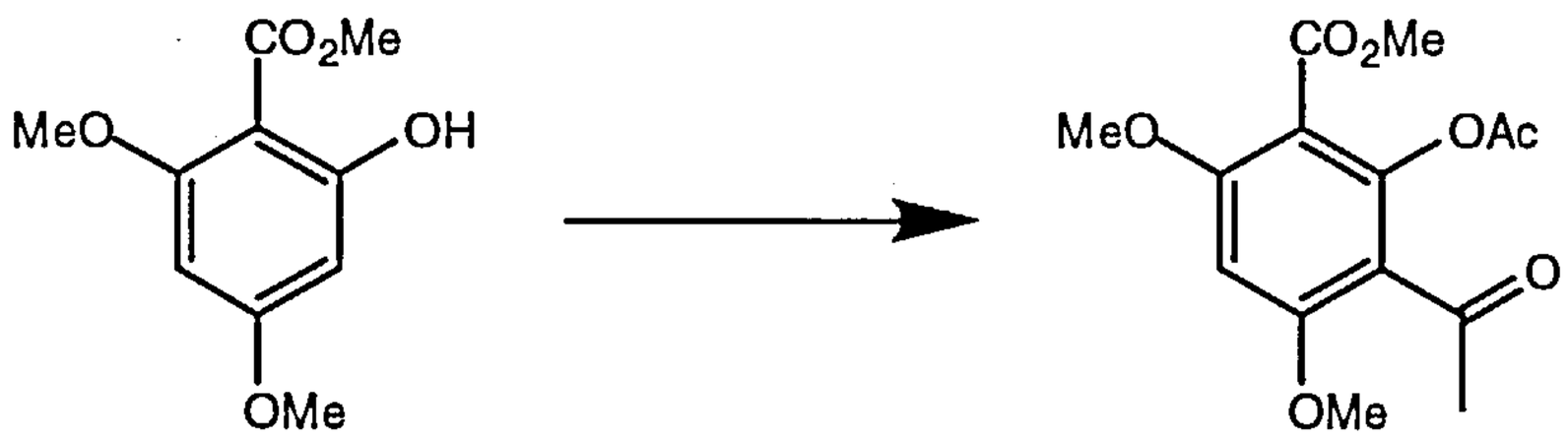
(R)-1-(2-Hydroxy-5-methylphenyl)-2-(p-tolylsulphinyl)ethanone (6-31a)[221]



In flask A: To a stirred solution of methyl 2-hydroxy-5-methylbenzoate (0.2g, 1.3mmol) in THF (2ml) under argon at -78° C was added LDA (1.5M in THF, 1ml, 1.5mmol), then the mixture stirred for 10 min. In flask B: To a stirred solution of R-(+)-methyl *p*-tolyl sulphoxide (0.2g, 1.3mmol) in THF (2ml) at -78° C under argon was added LDA (1.5M in THF, 2ml, 3mmol). The mixture was stirred for 10 min. The contents of flask A were added to flask B and the mixture stirred at -78° C for 0.5h, then allowed to rise to room temperature over the course of a further 0.5 h. The mixture was quenched with HCl (2M, 3ml), extracted with ethyl acetate (3x10ml), and the combined organics washed with brine (1x30ml), dried and evaporated under reduced pressure. This gave the product as a pale yellow solid (0.224g, 70%), m.p. 128° C (EtOH); $[\alpha]_D^{22}$ +141± 7 (*c* 1.0, $CHCl_3$); δ_H 2.25, 2.38 (both 3 H, s, ArMe),

4.21 (1 H, d, J=14Hz, CHSO), 4.50 (1 H, d, J=14Hz, CHSO), 6.85 (1 H, d, J=8Hz, ArH phenol ring, C6'), 7.25-7.35 (4 H, m, ArH), 7.53 (2 H, d, J=8Hz, ArH, tolyl ring), 11.56 (1 H, s, OH) ppm; m/z 306(trace), 289 (MH^+), 152, 151. (spectral data identical to those of an authentic sample provided by K.J. Hodgetts).

Methyl 2-acetoxy-3-acetyl-4,6-dimethoxybenzoate (6-25)[222]



i) Classical Fries approach

To a solution of methyl 2-hydroxy-4,6-dimethoxybenzoate (**6-9**) (1.01g, 4.76mmol) in acetic anhydride (25ml) was added freshly fused sodium acetate (3.10g, 37mmol). The mixture was heated under reflux for 3h, then filtered and distilled under reduced pressure, to drive off the acetic anhydride (21° C, 8.1mbar). The residue in the distillation flask was recrystallised from methanol to give methyl 2-acetoxy-4,6-dimethoxybenzoate (0.65g, 2.19mmol, 46%) [δ_H 2.24 (3 H, s, MeCO), 3.78, 3.80, 3.82 (all 3 H, s, OMe), 6.28 (1 H, d, J=2Hz), 6.32 (1 H, d, J=2Hz) (both ArH) ppm], a portion of which (0.276g, 0.93mmol) was dissolved in 1,2-dichloroethane (30ml). To this solution were added acetic anhydride (0.3ml) and scandium triflate (0.034g, 0.08mmol). The mixture was heated under reflux for 18h. The mixture was diluted with dichloromethane (50ml), washed with water (3x50ml) and brine (1x50ml), dried, evaporated under reduced pressure and separated by silica chromatography, the second eluted spot being collected, to give the title compound (0.10g, 0.39mmol, 42%; overall 19% over two steps).

ii) One pot procedure[223]

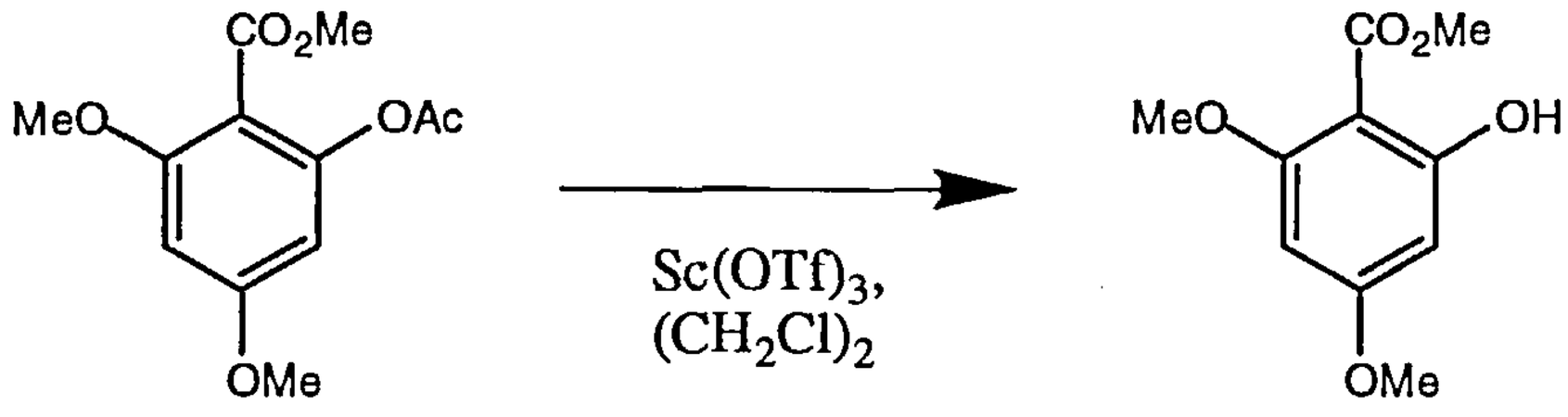
To a solution of methyl 2-hydroxy-4,6-dimethoxybenzoate (0.5g, 2.4mmol) in 1,2-dichloroethane (30ml) and acetic anhydride (10ml) was added scandium triflate (0.03g). The mixture was heated under reflux for 4 d. After this time the mixture was allowed to cool, filtered and the solvents distilled off. The resultant solid was passed through a silica column using ether as eluting solvent, the second spot being collected. This could be recrystallised from methanol to give the title compound (0.152g, 0.51 mmol, 22%).

iii) One pot procedure (yttrium triflate)

To a solution of methyl 2-hydroxy-4,6-dimethoxybenzoate (0.5g, 2.4mmol) in 1,2-dichloroethane (30ml) and acetic anhydride (10ml) was added yttrium triflate (0.03g). The mixture was heated under reflux for 4 d. After this time the mixture was allowed to cool, filtered, and the solvents distilled off. The resultant solid was passed through a silica column using ether as eluting solvent, the second spot being collected. This could be recrystallised from methanol to give the title compound (0.18g, 0.61mmol, 26%), m.p. 135° C; ν_{max} 2359, 1771 (ArOC=O), 1732 (MeOC=O), 1678 (ArC=O), 1613, 1433, 1373, 1275, 1223, 1195, 1094, 876, 821 cm^{-1}; δ_H 2.18 (3 H, s, MeCOAr), 2.44 (3 H, s, ArOCOMe), 3.82, 3.87, 3.89 (all 3 H, s, OMe), 6.34 (1 H, s, ArH) ppm; 20.5 ($ArCOCH_3$), 31.7 ($ArOCOCH_3$), 52.2 ($ArCO_2Me$), 56.0, 56.2 (both OMe), 93.0 (Ar C5), 110.3 (Ar C1), 117.5 (Ar C3), 147.5 (Ar C6), 160.2 (Ar C4), 164.5 (Ar C2), 168.6 (C=O), 171.9 (C=O), 198.6 ($ArCO_2$) ppm; m/z 314 (MNH_4^+), 297 (MH^+), 255 (retro Fries), 223; $C_{14}H_{16}O_7$ requires MH^+ 297.0974, found 297.0976, an error on the close order of 1ppm.

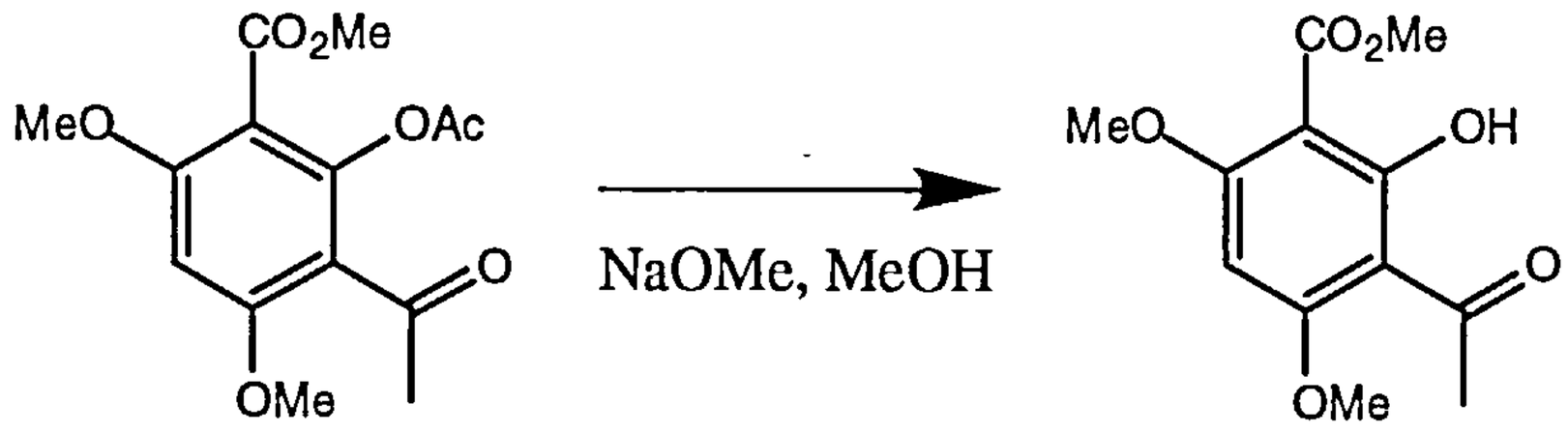
In all the above cases untransformed starting material can be recovered and recycled. Methyl 2-acetoxy-4,6-dimethoxybenzoate may also be recovered and recycled *via* methanolysis or used directly. The discoloured silica from the top of the columns may be retained and used to catalyse further transformations.

Methyl 2-hydroxy-4,6-dimethoxybenzoate (6-9)



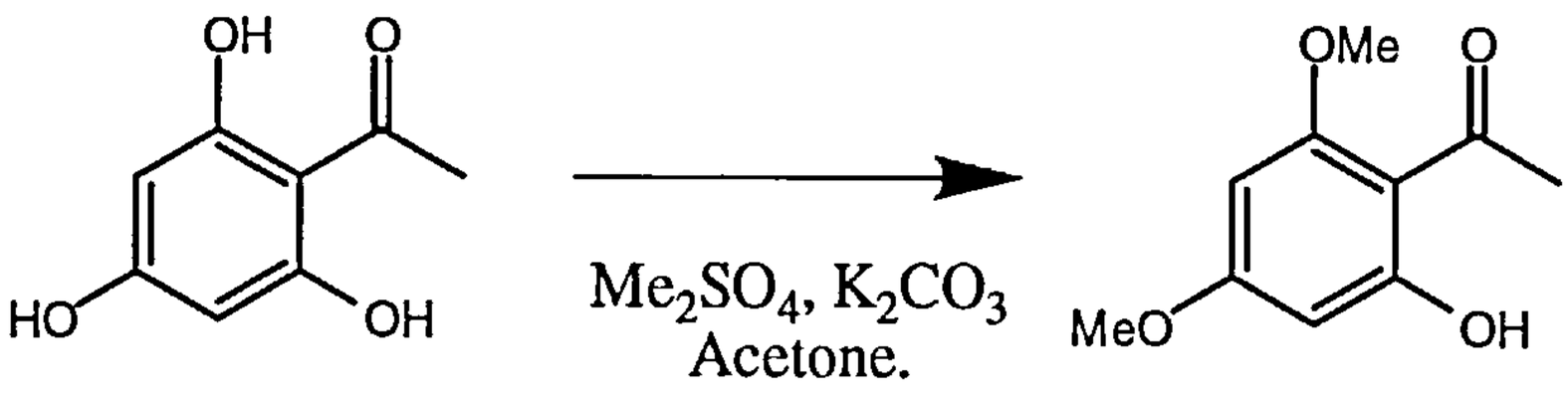
To a solution of methyl 2-acetoxy-4,6-dimethoxybenzoate, **6-24** (0.1g, 0.39mmol) in 1,2-dichloroethane (10ml) was added scandium triflate (0.02g, 0.04mmol). The mixture was heated under reflux for 5h. The mixture was allowed to cool, then water (20ml) added and the mixture extracted with dichloromethane (3x30ml) and washed with water (3x50ml) and brine (1x50ml) then dried and evaporated under reduced pressure. The remaining solid was recrystallised from methanol to give the title compound (0.12g, 0.28mmol, 72.5%).

Attempted synthesis of methyl 2-hydroxy-3-acetyl-4,6-dimethoxybenzoate (6-26)



To a stirred flask containing methanol (5ml) was added sodium (0.05g, 2.2mmol). Once the metal had dissolved a solution of methyl 2-acetoxy-3-acetyl-4,6-dimethoxybenzoate (**6-25**) (0.15g, 0.5mmol) was added and the mixture heated under reflux. After 0.5h the mixture was allowed to cool and the solvent removed under vacuum. The residue was diluted with HCl (1M, 10ml) and extracted with dichloromethane (3x15ml). The combined organics were dried and evaporated under reduced pressure, to yield the product (0.13g crude, 0.5mmol, 100%), which gave crystals, m.p. 96-97 °C, from methanol.; ν_{max} 3200-2800br, 1640-1590br (C=O), 1435, 1423, 1305, 1278, 1250, 1217, 1192, 1179, 1165, 1134, 1107, 1090, 954, 874, 798 cm^{-1}; δH 2.58 (3H, s, Ac), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 3.91 (3H, s, OMe), 5.92 (1H, s, ArH), 12.03 (1H, s, OH) ppm.; m/z 256, 255, 240, 213, 58 $C_{12}H_{14}O_6$ requires MH^+ 255.0869, found 255.0872 an error on the close order of 1ppm.

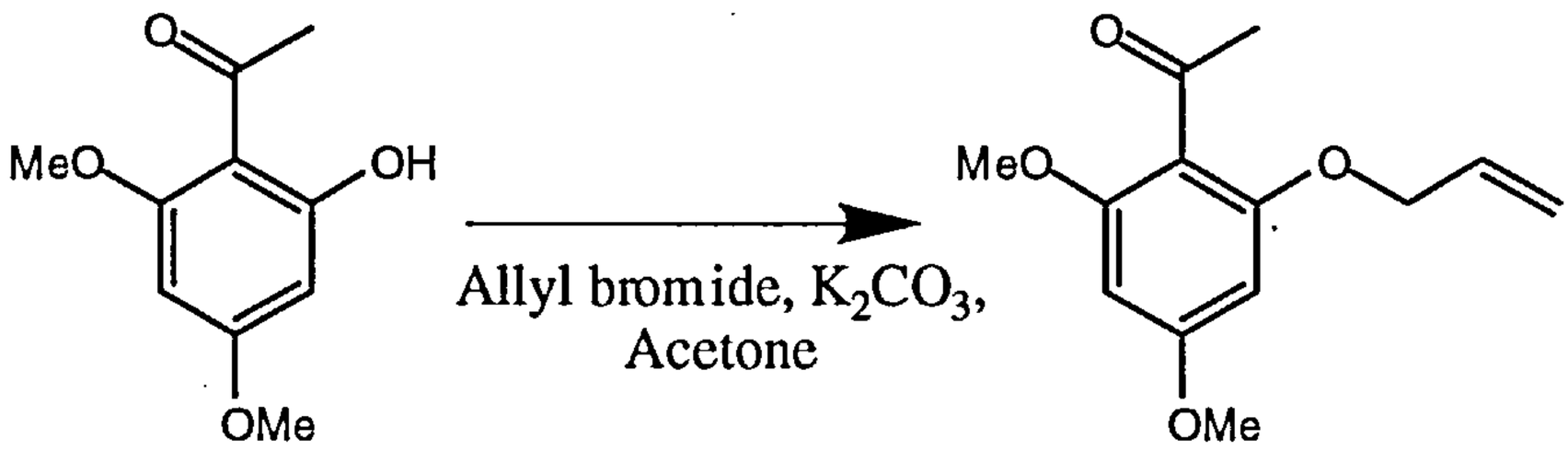
2-Hydroxy-4,6-dimethoxyacetophenone (6-28)



To a solution of phloracetophenone (1.7g, 10mmol) in Analar® acetone (50ml) was added potassium carbonate (4g). Dimethyl sulphate (1ml) in acetone (1ml) was added slowly and the mixture was stirred under argon for 1h, then heated to reflux for 12h. The solution was filtered, evaporated under reduced pressure and diluted with dichloromethane (50ml). The solution was washed with ammonia (0.1M, 50ml), water (3x50ml) and brine (1x50ml) then dried and evaporated under reduced pressure. The product (0.915g, 4.7mmol,) could be recrystallised from methanol. The spectra of the compound agreed with those of a sample from Lancaster synthesis; ν_{max} 2918, 1621, 1424, 1368, 1273, 1206 (OMe), 1112 (OMe), 1082 cm^{-1}; δ_{II} 2.59 (3 H, s,

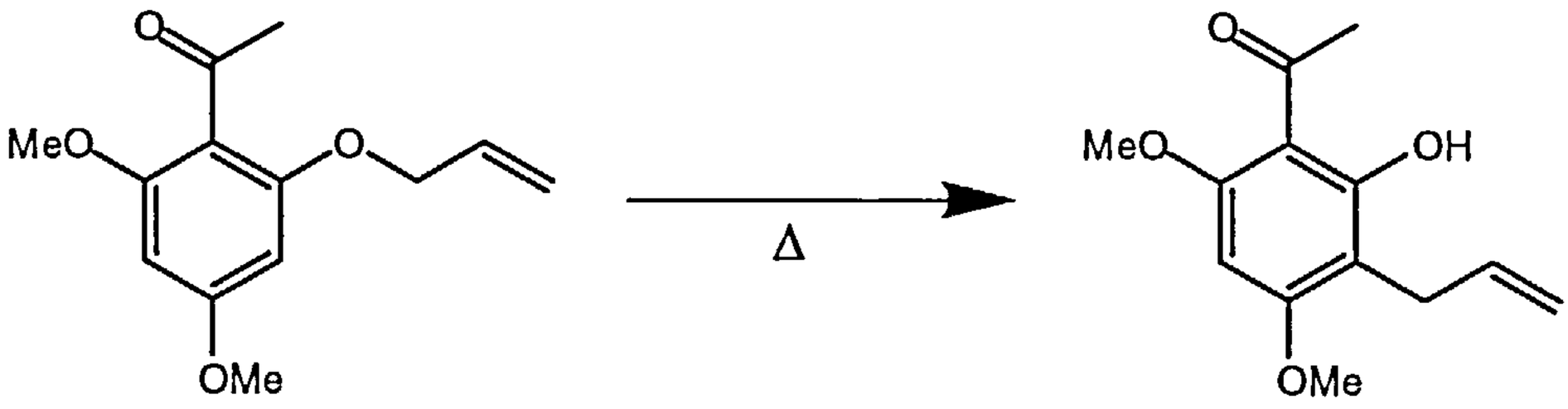
MeCO), 3.79, 3.83 (both 3 H, s, OMe), 5.9 (1 H, d, J=2Hz, ArH), 6.04 (1 H, d, J=2Hz, ArH), 14.03 (1 H, s, OH) ppm; m/z 197 (MH^+), no other significant peaks.

2-Allyloxy-4,6-dimethoxyacetophenone (6-29)



To a stirred suspension of potassium carbonate (anhydrous, 3g, 22mmol) in acetone (20ml) was added 2-hydroxy-4,6-dimethoxyacetophenone (**6-28**) (1g, 5mmol). Allyl bromide (1ml, 12mmol) was added and the mixture was heated under reflux for 18h. The mixture was allowed to cool, then quenched with ammonium hydroxide (2M, 10ml). The mixture was extracted with ether (3x30ml) then the combined organics washed with water (3x30ml), dried and evaporated under reduced pressure to give a product (0.68g, 2.88mmol, 56%) which appeared pure by NMR; b.p. not measureable due to rearrangement; ν_{max} 3082, 2924, 2844, 1696 (C=O), 1604, 1456, 1417, 1351, 1248, 1224, 1202 (OMe), 1121 (OMe), 1045, 1001, 968 cm^{-1}; δ_H 2.45 (3 H, s, MeCO), 3.76, 3.78 (both 3 H, s, OMe), 4.50 (2 H, d, J=5Hz, CH_2O), 5.23 -5.40 (m, 2 H, C=CH_2), 5.91-6.04 (1 H, m, CH allyl), 6.07 (1 H, s, ArH), 6.08 (1 H, s, ArH) ppm; δ_C 32.4 (CH_3CO), 55.3, 55.8 (both OMe), 69.4 (OCH_2), 90.9 (C5 ring), 91.8 (C3 ring), 117.5 (C=CH_2 + C4), 132.6 (CH=C), 157.2 (C2 ring?) 158.2, 169.1 (C4 + C6), 201.4 (C=O) ppm; m/z 237 (MH^+), 197 (– allyl), 175, 114, 78; $C_{13}H_{16}O_4$ requires MH^+ 237.1127, found 237.1132, an error on the close order of 2ppm.

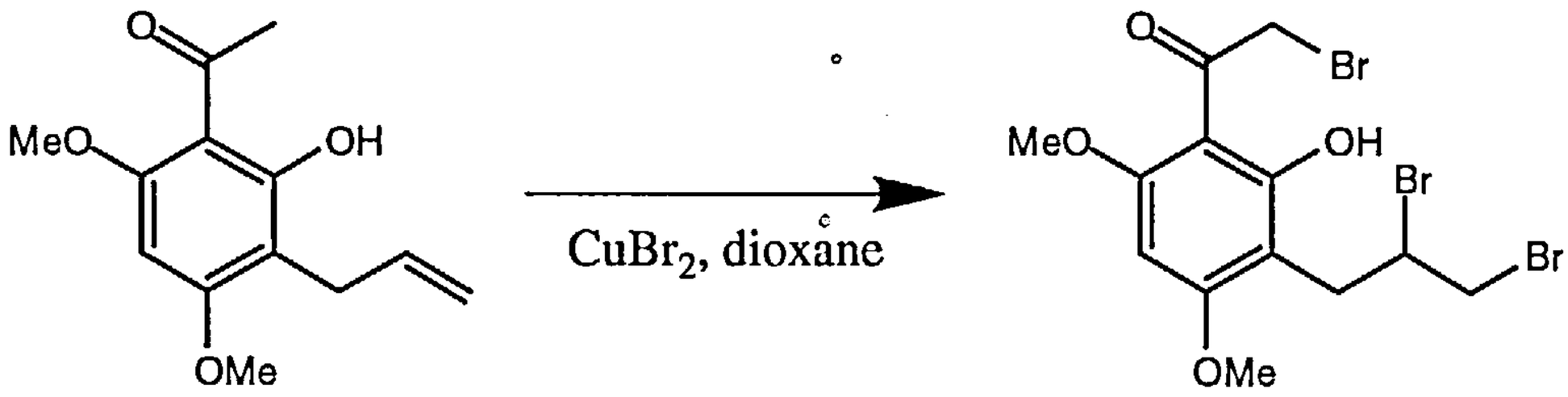
2-Hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxyacetophenone (6-30)



2-Allyloxy-4,6-dimethoxyacetophenone (0.5g, 2.1mmol) was degassed under high vacuum (0.01mmHg). The flask was flushed with argon and then equipped for reflux with a narrow air condenser. The flask was heated to 210° C on a Wood's metal bath, this temperature being maintained for 18h. The flask was allowed to cool then the

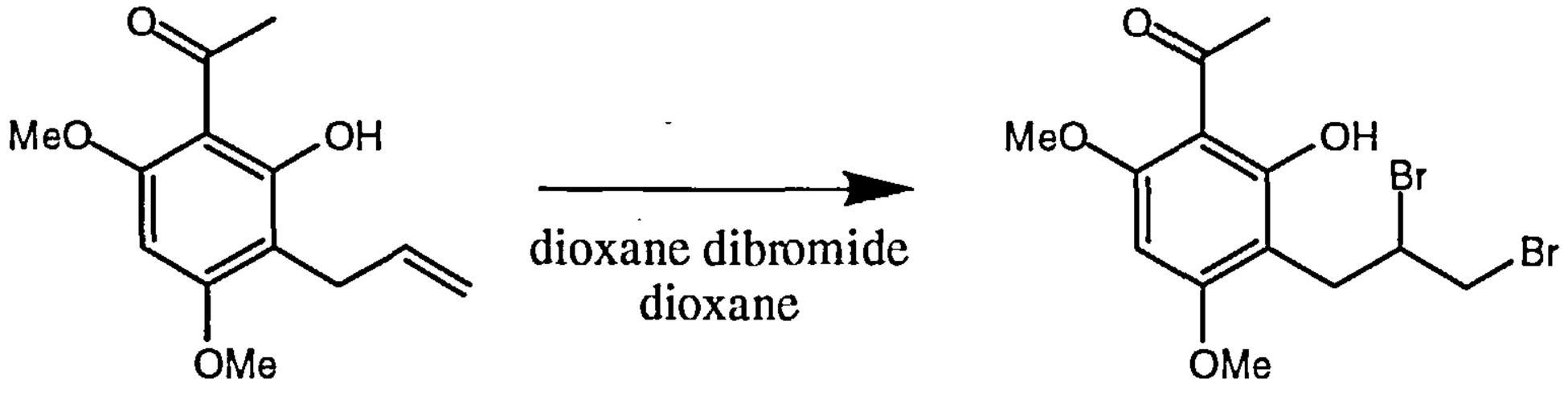
contents recrystallised from methanol, which gave the title compound (0.46g, 1.95mmol, 92%), m.p. 76° C; ν_{max} 2969, 2942, 1738, 1636 (C=O), 1593, 1470, 1458, 1422, 1283, 1270, 1234, 1138 (OMe), 1082 (OMe), 1001, 918, 897 cm^{-1}; δ_H 2.59 (3 H, s, MeCO), 3.30-3.34 (2 H, m, $ArCH_2$), 3.86, 3.89 (both 3 H, s, OMe), 4.89-4.99 (2 H, m, CH=C**H$_2$**), 5.85-6.04 [2 H, m, **CH**=C + ArH (5.94, s)], 13.97 (1 H, s, OH) ppm; δ_C 26.3 (**C**H_3CO), 33.1 (CH_2Ar), 55.4, 55.5 (both OMe), 85.9 (ring C5), 105.9 (ring C1?), 107.9 (ring C3?), 113.9 (C=CH_2), 136.5 (**C**H=CH_2), 162.0, 163.4, 163.6 (ring C2, C4, C6), 203.3 (C=O) ppm; m/z 237 (MH^+), no other significant peaks; $C_{13}H_{16}O_4$ requires MH^+ 237.1127, found 237.1124, an error on the close order of 1ppm.

2-Hydroxy-3-(2,3-dibromopropyl)-4,6-dimethoxy-2'-bromoacetophenone (6-40)[224]



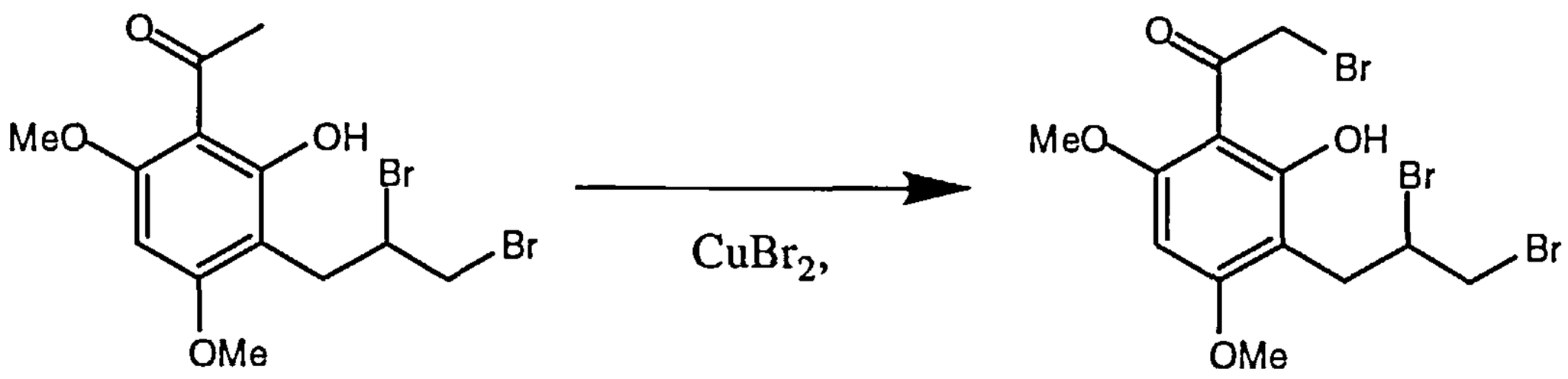
To a solution of 2-hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxyacetophenone (**6-30**) (0.3g, 1.27mmol) in 1,4-dioxane (20ml) was added cupric bromide (3g, 13.4mmol). The mixture was refluxed for 2 days, then filtered, evaporated under reduced pressure and extracted with petroleum (hot, 3x50ml). The product recrystallised from methanol to give the title compound (0.22g, 0.46mmol, 36%), m.p. 122-124° C; ν_{max} 2917, 1620 (C=O), 1600, 1466, 1453, 1415, 1293, 1223 (OMe), 1196 (OMe), 1164, 1139, 1114 cm^{-1}; δ_H 3.20-3.49 (2 H, m, $ArCH_2$), 3.65-3.68 (2 H, m, CH_2Br), 3.90 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.40-4.54 (1 H, m, CHBr), 4.59 (2 H, s, CO**CH$_2$**Br), 5.97 (1 H, s, ArH), 13.42 (1 H, s, OH) ppm; δ_C 25.6 ($ArCH_2$), 33.9 (CH_2Br), 39.0 (CHBr), 49.2 (COCH_2Br), 55.7, 55.8 (both OMe), 86.1 (C5), 103.9 (C1), 107.5 (C3), 161.3 (C2), 164.8, 165.0 (C4 + C6), 194.9 (C=O) ppm; m/z 472 (MH^+), 397, 317, 237; $C_{13}H_{15}O_4Br_3$ requires MH^+ 472.8600, found 472.8611, an error on the close order of 2ppm.

2-Hydroxy-3-(2,3-dibromopropyl)-4,6-dimethoxyacetophenone (6-41)[225]



'Dioxane dibromide' was prepared by adding bromine (0.31g, 0.10ml, 2mmol) to stirred 1,4-dioxane (10ml) under argon. After 5min the allylphenol (**6-30**) (0.15g, 0.63mmol) was added. The reaction was stirred for 1 day then the mixture evaporated under vacuum. The residue was triturated with ether (20ml), and the white precipitate filtered off. The precipitate could be recrystallised from methanol to obtain the product (0.07g, 0.18mmol, 28%), m.p. 80° C; ν_{max} 3454 (OH), 2916, 2848, 1619 (C=O), 1469, 1417, 1381, 1359, 1274, 1218 (OMe), 1153 (OMe), 1116, 1026 cm^{-1}; δ_H 2.60 (3 H, s, MeCO), 3.20 (1 H, dd, J=8Hz, 14Hz, $ArCH_2$), 3.31 (1 H, dd, J=6Hz, 14Hz, $ArCH_2$), 3.66-3.86 (2 H, m, CH_2Br), 3.88, 3.90 (both 3 H, s, OMe), 4.62 (1 H, m, CHBr), 5.94 (1 H, s, ArH), 14.11 (1 H, s, OH) ppm; δ_C 30.7 (CH_3CO), 33.1 (CH_2Ar), 37.7 (CH_2Br), 52.4 (CHBr), 55.4, 55.6 (both OMe), 85.8 (C5), 106.00, 106.01 (very close C1 + C3), 162.7 (C2), 163.7, 164.2 (C4 + C6), 203.5 (C=O) ppm; m/z 395 (MH^+), 316 (–Br) 237 (–2Br), 78, 61; $C_{13}H_{16}O_4Br_2$ requires MH^+ 394.9495, found 394.9497, an error of less than 1ppm.

Attempted synthesis of 2-hydroxy-3-(2,3-dibromopropyl)-4,6-dimethoxy-2'-bromoacetophenone (6-40)[226]



i) <u>In chloroform - ethyl acetate</u>

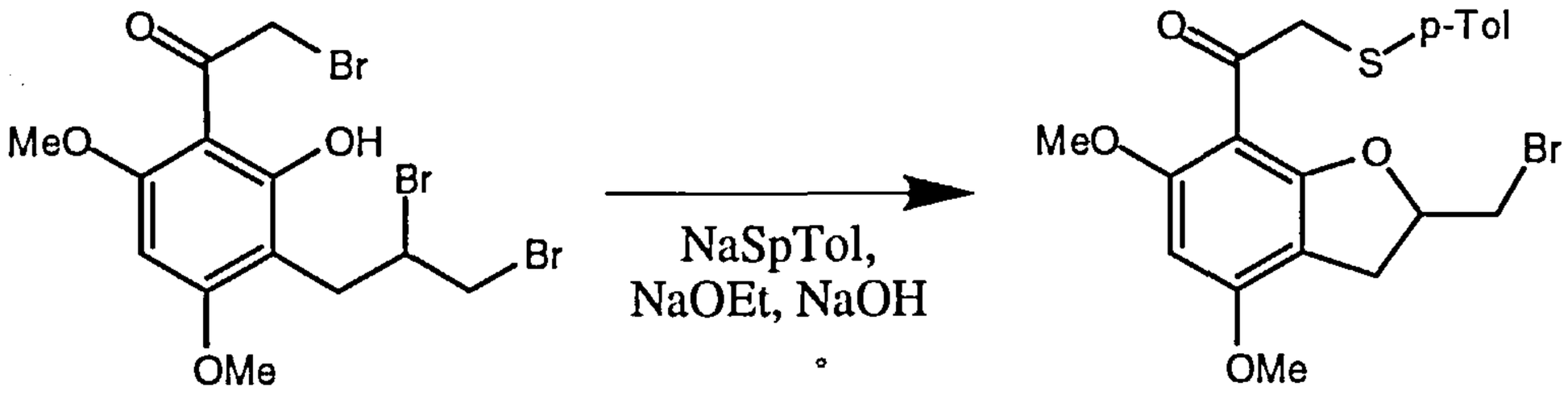
To a solution of 2-hydroxy-3-(2,3-dibromopropyl)-4,6-dimethoxyacetophenone (**6-41**) (0.04g, 0.1mmol) in chloroform - ethyl acetate (1:1, 10ml) was added $CuBr_2$ (0.12g, 0.54mmol). The mixture was heated under reflux for 3 days. The mixture was allowed to cool, filtered, evaporated under vacuum and the residue extracted with

petroleum (hot, 3x40ml). This solution was then evaporated to give a very complex mixture.

ii) In dioxane

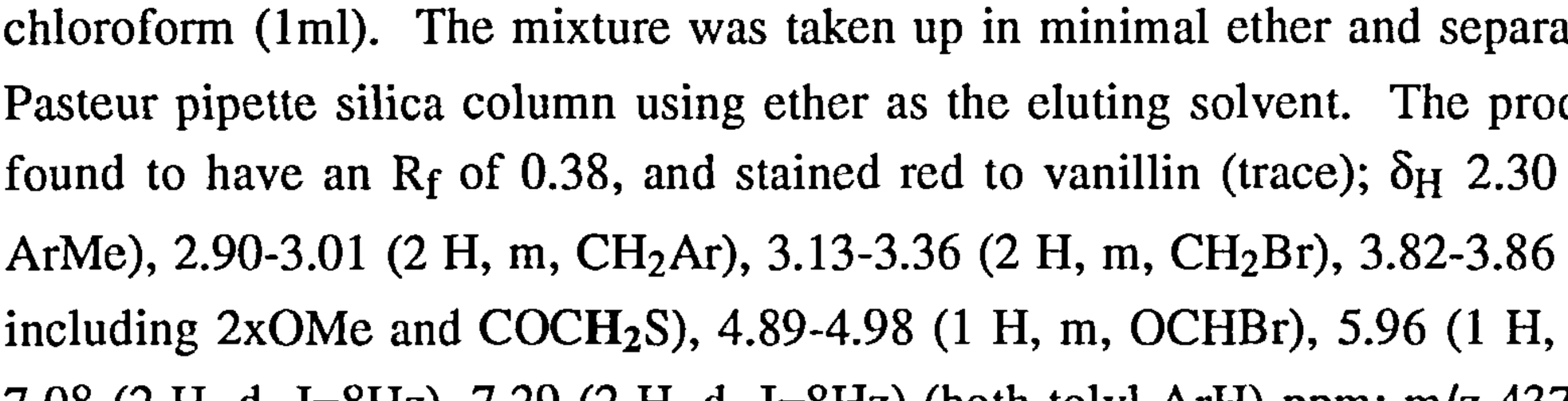
The above procedure was repeated using 1,4-dioxane (10ml) as the solvent. The result was in all respects similar..

Tentative synthesis of 2-bromomethyl-2,3-dihydro-4,6-dimethoxy-7-(2-(p-tolylthio)acetyl)-2,3-dihydrobenzofuran (6-44)



A solution of 2-hydroxy-3-(2,3-dibromopropyl)-4,6-dimethoxy-2'-bromoacetophenone (**6-40**) (10mg, 0.021mmol) in EtOH (1ml) was stirred whilst a solution of sodium thiocresolate and sodium ethoxide (each 1M in EtOH, 24µl, 0.024mmol). The solution was stirred for 1h then HCl (1M, 24µl, 0.024mmol) was added. The solution was evaporated under vacuum then azeotropically dried with chloroform (1ml). The mixture was taken up in minimal ether and separated on a Pasteur pipette silica column using ether as the eluting solvent. The product was found to have an R_f of 0.38, and stained red to vanillin (trace); δ_H 2.30 (3 H, s, ArMe), 2.90-3.01 (2 H, m, CH_2Ar), 3.13-3.36 (2 H, m, CH_2Br), 3.82-3.86 (8 H, m, including 2xOMe and $COCH_2S$), 4.89-4.98 (1 H, m, OCHBr), 5.96 (1 H, s, ArH), 7.08 (2 H, d, J=8Hz), 7.29 (2 H, d, J=8Hz) (both tolyl ArH) ppm; m/z 437 (MH^+), 417, 397, 359 (–Br), 235.

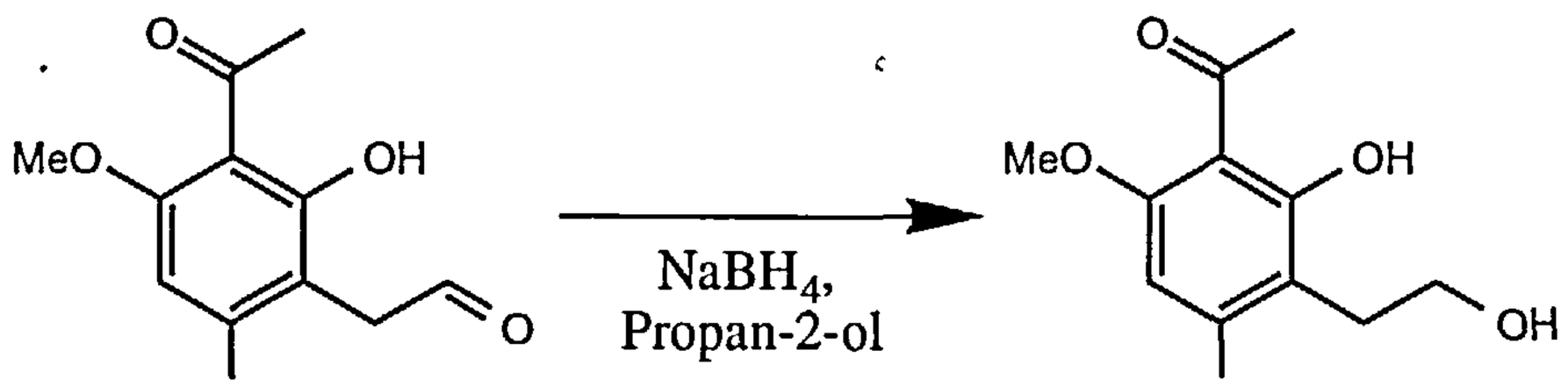
2-(2'-Hydroxy-3'-acetyl-4',6'-dimethoxyphenyl)ethananal (6-37)[227]



To a stirred solution of the allylphenol (**6-30**) (0.1g, 0.42mmol) in THF (20ml) and water (20ml) was added a small crystal of osmium tetroxide. Once the solution had darkened to a colour similar to tea, sodium metaperiodate (0.5g, 2.3mmol) was added.

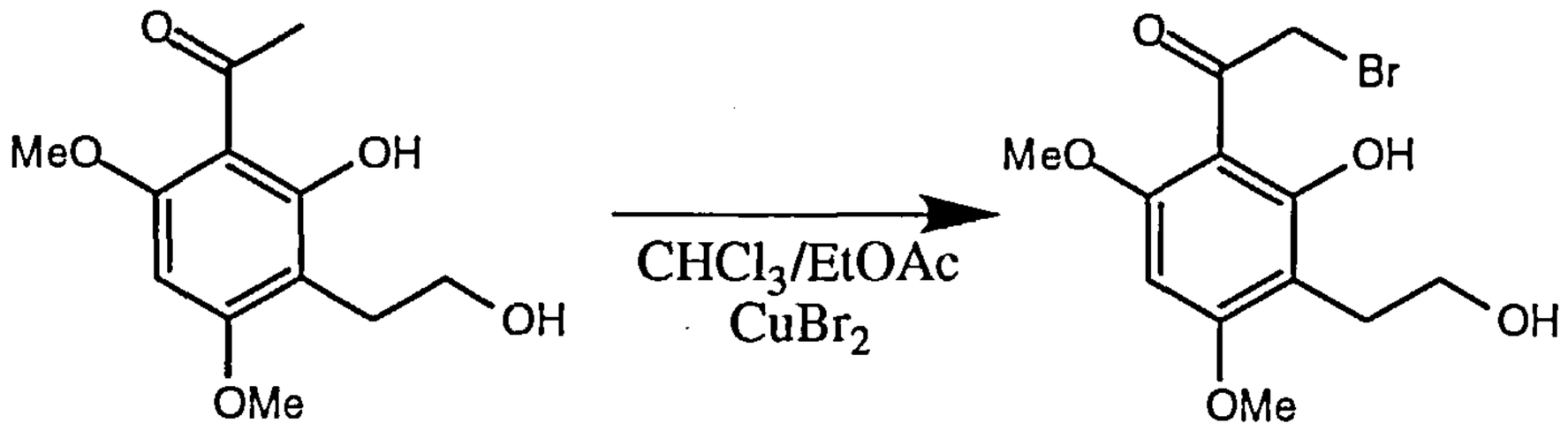
After 2h TLC monitoring showed completion (ether elution, starting material R_f 0.35, product R_f 0.16). The mixture was extracted into ether (3x20ml), washed with water (2x30ml), dried and evaporated under reduced pressure. The solid could be recrystallised from methanol with care (0.04g, 0.17mmol, 40%), m.p. 92-93° C; ν_{max} 3435 (OH), 2932, 1723, 1625 (C=O), 1592, 1470, 1421, 1358, 1276, 1225, 1128 (OMe), 1063 cm^{-1}; δ_H 2.59 (3 H, s, MeCO), 3.60 (2 H, d, J=2Hz, $ArCH_2$), 3.84, 3.89 (both 3 H, s, OMe), 5.96 (1 H, s, ArH), 9.58 (1 H, t, J=2Hz, CHO), 14.07 (1 H, s, OH) ppm; δ_C 33.0 (CH_3CO), 37.3 ($ArCH_2$), 55.5, 55.6 (both OMe), 85.8 (C5 aryl), 101.2 (C3 aryl), 105.9 (C1 aryl), 163.0, 163.8, 164.1 (C2, C4, C6 aryl), 200.4 (CHO), 203.4 (C=O) ppm; m/z 239 (MH^+), no other significant peaks; m/z (EI) 239 (65), 211, 210 (100, -CHO), 209 (56), 195, 191, 49; $C_{12}H_{14}O_5$ requires MH^+ 239.0919, found 239.0925, an error on the close order of 3ppm.

2-(2'-Hydroxy-3'-acetyl-4',6'-dimethoxyphenyl)ethanol (6-38)



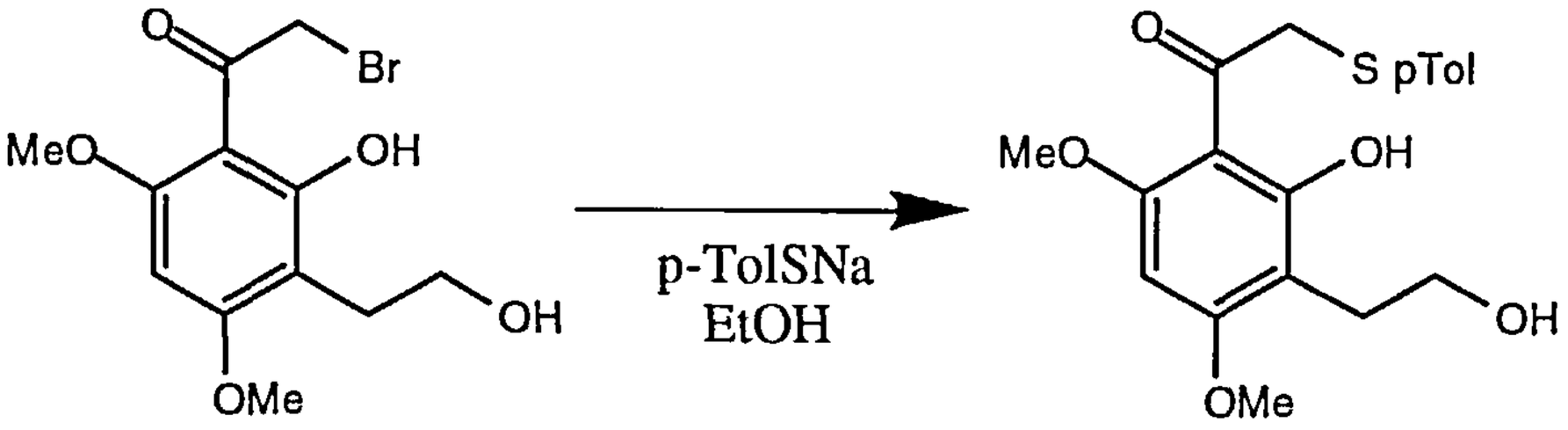
To a solution of 2-(2'-hydroxy-3'-acetyl-4',6'-dimethoxyphenyl)ethananal (**6-37**) (0.2g, 0.84mmol) in propan-2-ol (25ml) was stirred, and chilled to -9° C (ice/acetone). Sodium borohydride (0.032g, 0.84mmol) was added, then stirring continued for 10 min. The reaction was terminated by the addition of sat. aq. oxalic acid (5ml). The mixture was extracted into ether (3x20ml), washed with water (3x20ml), then brine (1x30ml), dried and evaporated under reduced pressure. The mixture was azeotropically dried with chloroform (10ml), to give the product (0.15g, 0.62mmol, 74%), m.p. 76° C; ν_{max} 3400, 2929, 1619 (C=O), 1599, 1416, 1275, 1220, 1123 (OMe), 1153, 1133, 796 cm^{-1}; δ_H 2.58 (3 H, s, MeCO), 2.84-2.88 (2 H, m, $ArCH_2$), 3.70-3.84 (2 H, m, CH_2OH), 3.86, 3.88 (both 3 H, s, OMe), 5.95 (1 H, s, ArH), 14.11 (1 H, s, OH) ppm; δ_C 25.5 (CH_3CO), 33.0 (CH_2Ar), 55.4, 55.5 (both OMe), 62.6 (CH_2OH), 85.9 (C5'), 87.4 (C3'), 105.9 (C1'), 162.2, 163.7, 164.1 (C2', C4', C6'), 203.5 (C=O) ppm; m/z 241 (MH^+), 209, no other significant peaks; $C_{12}H_{16}O_5$ requires MH^+ 241.1076, found 241.1075, an error of less than 1ppm.

2-(2'-Hydroxy-3'-(bromoacetyl)-4',6'-dimethoxyphenyl)ethanol (6-39)



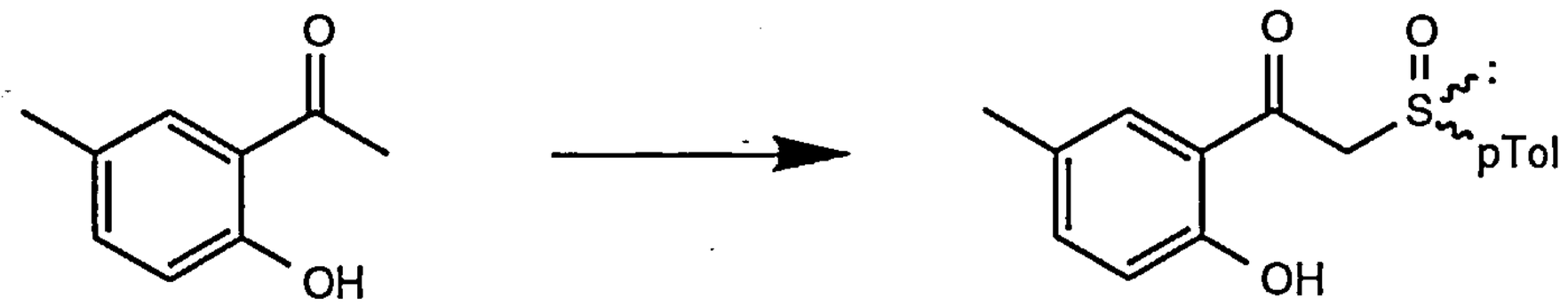
To a solution of 2-(2'-hydroxy-3'-acetyl-4',6'-dimethoxyphenyl)ethanol (**6-38**) (0.24g, 1.0mmol) in ethyl acetate (25ml) was added a mixture of cupric bromide (3g, 13mmol) and chloroform (25ml). The mixture was heated under reflux for 10h. The mixture was allowed to cool, filtered and evaporated to dryness. The mixture was extracted with hot cyclohexane (3x20ml) then the extract evaporated to dryness to give the product (0.13g, 0.41mmol, 41%), m.p. 100-102° C; ν_{max} 3410 (OH), 2977, 1735 (C=O), 1599, 1466, 1411, 1292, 1222, 1195 (OMe), 1153 (OMe), 1133, 798, 702 cm^{-1}; δ_H 3.13 (2 H, t, J=8Hz, CH_2Ar), 3.44 (2 H, t, J=8Hz, CH_2OH), 3.89, 3.93 (both 3 H, s, OMe), 4.59 (2 H, s, CH_2Br), 5.96 (1 H, s, ArH), 13.34 (1 H, s, OH) ppm; δ_C 26.2 ($ArCH_2$), 31.0 (CH_2OH), 38.0 (CH_2Br), 55.7, 55.8 (both OMe), 86.1 (C5'), 103.5 (C3'), 107.6 (C1'), 162.0, 164.4, 164.5 (C2', C4', C6'), 195.1(C=O) ppm; m/z 303, 252, 207, no MH^+ peak; HRMS not feasible.

Attempted synthesis of 1-(2-hydroxy-3-(2-hydroxymethyl)-4,6-dimethoxyphenyl)-2-(p-tolylthio)ethanone



To a solution of the bromoketone, **6-39** (0.007g, 0.022mmol) in ethanol (1ml), under argon, was added an ethanolic solution of sodium thiocresolate (1M, 66µl, 0.066mmol). The mixture was stirred for 2 days, then quenched with HCl (1M, 66µL, 0.066mmol), and evaporated under vacuum. Crude NMR showed no sign of the title compound, but revealed that the reactants had degenerated into a complex mixture.

Attempted syntheses of (R)-1-(2-hydroxy-5-methylphenyl)-2-[(p-tolyl)sulphinyl]ethanone (6-31a)[228]



i) Trial run with LDA

To a stirred solution of 5-methyl-2-hydroxyacetophenone (0.05g, 0.33mmol) in dry THF (3ml) at -9° C (ice/acetone) under argon was added a solution of LDA (0.25M, 4.0ml, 1.0mmol). The mix was stirred for 2h and then allowed to rise to room temperature over the course of a further 0.5h. The mixture was chilled to -78°C. A solution of (1R, 2S, 5R)-(–)-menthyl-(S)-*p*-toluenesulphinate (0.1g, 0.34mmol) in THF (3ml) was slowly added, the mixture raised to room temperature and stirring continued. The reaction was stirred for a further 24h. The progress of the reaction could be monitored on TLC (ether elution), progress being gauged by the intensity of the spots due to menthol and product (see below for retention factors.). The product was separated on a long silica plug, using an ether eluting solvent, then submitted to NMR analysis (0.011g, 0.038mmol, 11.5%). NMR showed relatively pure sample, with some menthol contamination; R_f values, sulphinate 0.68, menthol 0.49 (both blue to vanillin), product 0.5, (orange to vanillin, fading to yellow as it cools).

ii) Catalysed with cuprous iodide

To a stirred solution of the hydroxyacetophenone (0.05g, 0.33mmol) and CuI (0.063g, 0.33mmol) in THF (3ml), held at -78° C was added a solution of LDA in THF (0.25M, 4ml, 4mmol). The mixture was allowed to warm to room temperature over the course of 0.5 h, then cooled again to -78° C. A solution of (1R, 2S, 5R)-(–)-menthyl-(S)-*p*-toluenesulphinate (0.1g, 0.34mmol) in THF (3ml) was slowly added, the mixture raised to room temperature and stirring continued for 2h. The mixture was quenched with sat. aq. ammonium chloride (15ml) and extracted with ethyl acetate (3x15ml). The combined organics were washed with water (2x10ml) and HCl (0.5M, 10ml) then dried and evaporated under reduced pressure. The products were separated on a short silica column, eluting with ether. Evaporation of the eluate gave the product (0.040g, 0.14mmol, 42%).

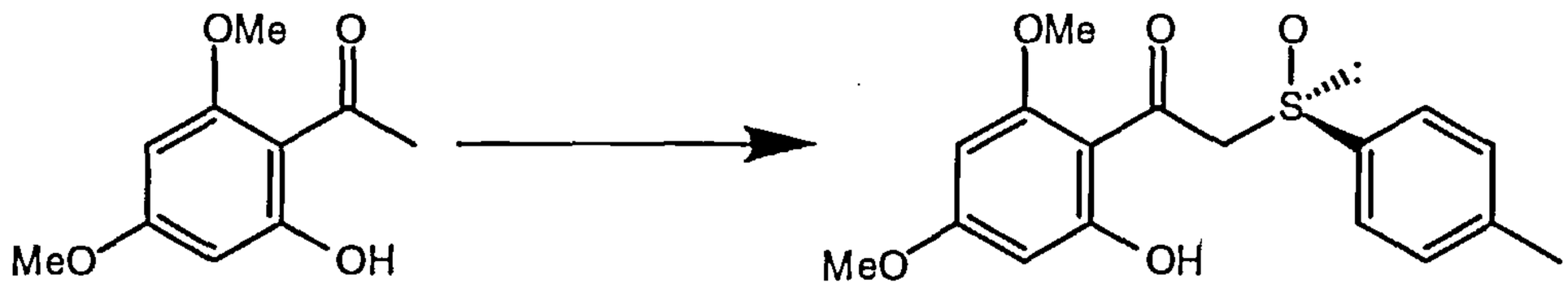
Reaction Time	**Measured $[\alpha]_D$**
2 hours	+93 (*c* 0.06, $CDCl_3$)
2 days	+74 (*c* 1.54, $CDCl_3$)

iii KH method

To a stirred suspension of KH (35% disp. in mineral oil, 0.161g, 1.4mmol) in THF (2.5ml) under argon at -78° C was added a solution of the hydroxyacetophenone (0.051g, 0.34mmol) in THF (2.5ml). The mixture was stirred for 3h until the second colour change (yellow to yellow-green) was complete. A solution of (1R, 2S, 5R)-(–)-menthyl-(S)-*p*-toluenesulphinate (0.1g, 0.34mmol) in THF (3ml) was added and stirring continued until TLC analysis showed at least a majority transformation (at least 3h). The mixture was quenched with sat. aq. ammonium chloride (15ml) then extracted into ethyl acetate (3x30ml). The combined organics were washed with water (3x30ml) then dried and evaporated under reduced pressure. The products were separated on a short silica plug, eluting with ether. Evaporation of the eluate gave the product (0.03g, 0.1mmol, 31%).

Reaction Time	**Measured $[\alpha]_D$**
3 hours	–32 (*c* 0.5, $CDCl_3$)
overnight (–18°C)	–26 (*c* 0.5, $CDCl_3$)

Attempted synthesis of (R)-1-(2-hydroxy-4,6-dimethoxyphenyl)-2-[(p-tolyl)sulphinyl]ethanone



i) Using LDA/CuI

Procedure as for the sulphoxide (**6-31a**) above (method ii), using 2-hydroxy-4,6-dimethoxyacetophenone (0.062g, 0.32mmol) with all other quantities similar. There was no isolable product.

ii) Using KH

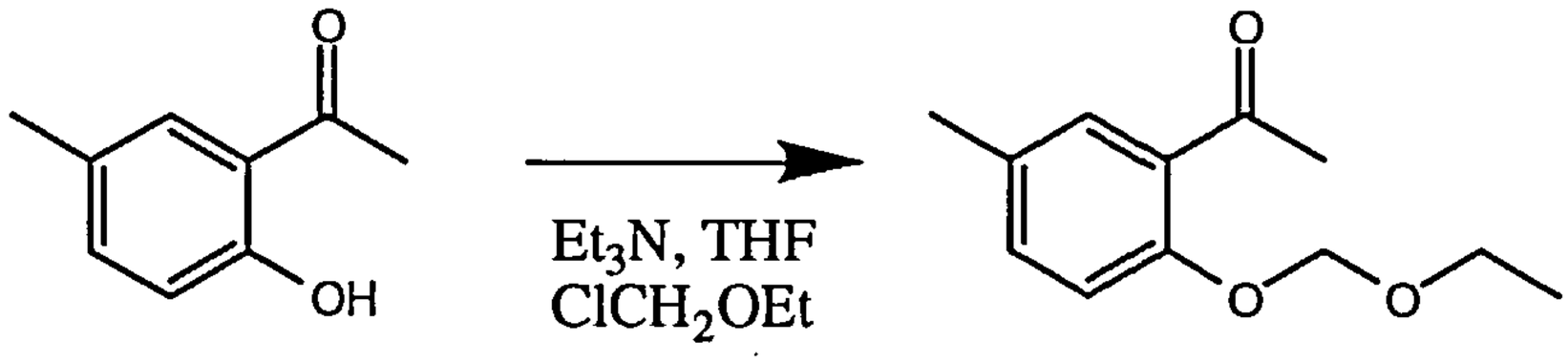
Procedure as for the sulphoxide (**6-31a**) above (method iii), using 2-hydroxy-4,6-dimethoxyacetophenone (0.062g, 0.32mmol) with all other quantities similar. There was no isolable product.

iii) Using potassium hexamethyldisilazide (KHMDS)

To a stirred suspension of KHMDS (0.214g, 1.1mmol) in THF (5ml) under argon was added a solution of hydroxyacetophenone (0.065g, 0.33mmol). A solution of menthyl

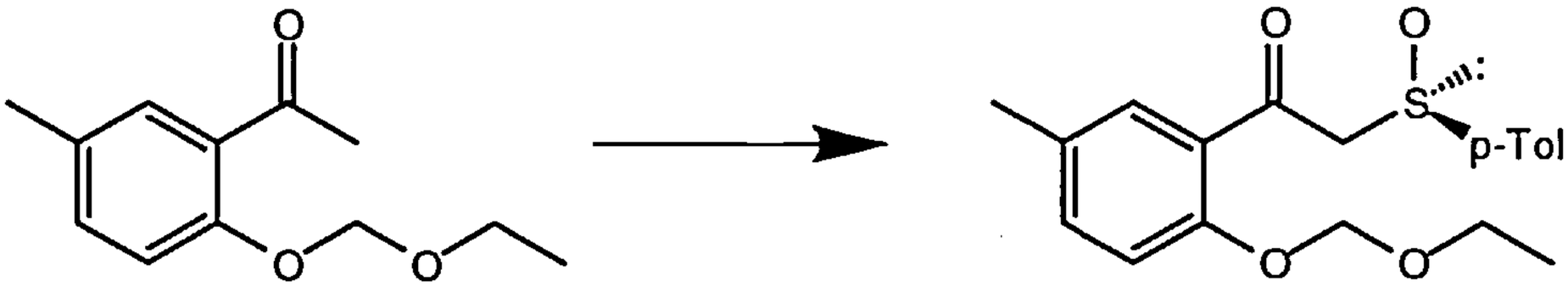
sulphinate (0.3g, 1.02mmol) in THF (4ml) was added. The solution was stirred for 3 days, then worked up as above, showing no transformation.

2-(Ethoxymethoxy)-5-methylacetophenone (6-53)



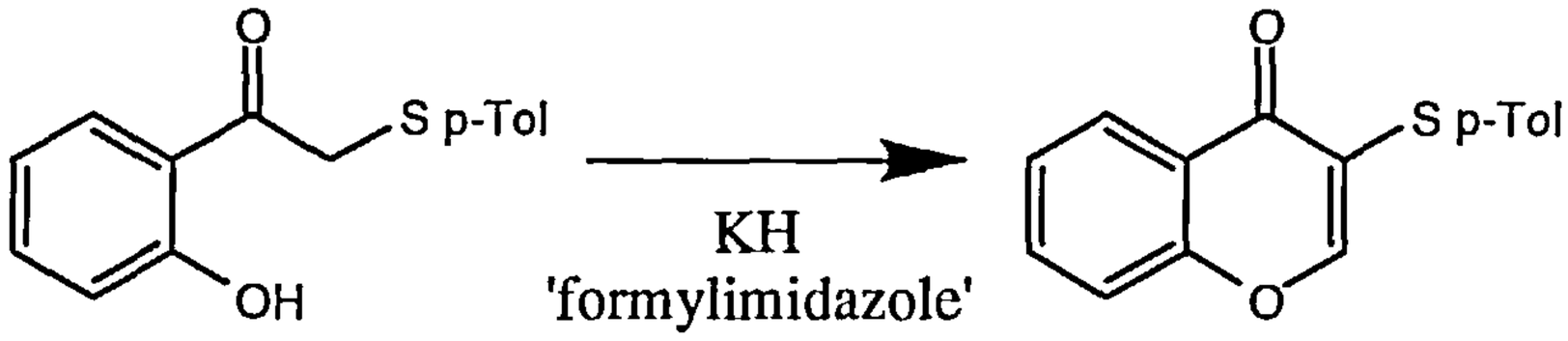
To a stirred solution of 5-methyl-2-hydroxyacetophenone (0.5g, 3.3mmol) in THF (10ml) under argon was added freshly distilled triethylamine (0.5ml, 5mmol) and chloromethyl ethyl ether (5ml,). The mixture was stirred for 5h then evaporated to dryness, the product being distilled to purity using a Kugelrohr bulb-to-bulb distillation apparatus (yield 0.6g, 2.9mmol, 86%); b.p. 110° C/0.05mmHg; ν_{max} 2978, 2926, 1676 (C=O), 1644, 1609, 1586, 1494, 1402, 1356, 1286, 1226 (OR), 1196 (OR), 1144, 1109, 1085, 987 cm^{-1}; δ_H 1.21 (3 H, t, J=7Hz, CH_2CH_3), 2.27 (3 H, s, ArMe), 2.59 (3 H, s, MeCO), 3.72 (2 H, q, J=7Hz, CH_2CH_3), 5.26 (2 H, s, OCH_2O), 7.06-7.49 (3 H, m, ArH) ppm; δ_C 15.0 (CH_3CH_2), 20.25 ($ArCH_3$), 31.7 ($COCH_3$), 64.6 (OCH_2CH_3), 93.27 (OCH_2O), 114.9 (C3 ring), 128.7 (C1 ring), 130.2 (C4 ring), 131.0 (C5 ring), 134.0 (C6 ring), 154.5 (C2 ring), 200.1 (C=O) ppm; m/z 209 (MH^+), 193 (loss of Me), 163, 138, 121, 59 ($^+CH_2OEt$); $C_{12}H_{16}O_3$ requires MH^+ 209.1178, found 209.1170, an error on the close order of 4ppm.

Attempted synthesis of (R)-1-(2-(ethoxymethoxy)-4,6-dimethoxyphenyl)-2-[(p-tolyl)sulphinyl]ethanone ()



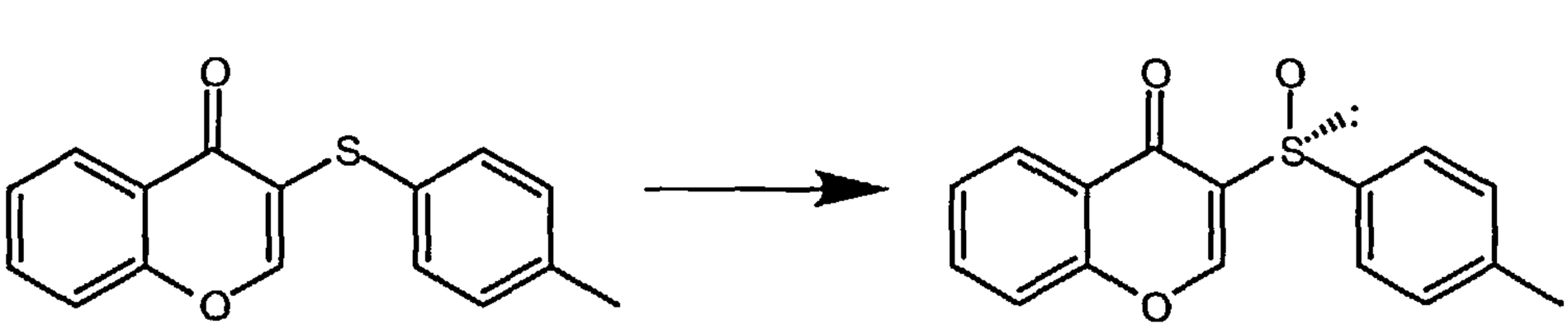
To a stirred suspension of KH (35% dispersion, 0.2g, 1.75mmol) in THF (2ml) under argon was added a solution of 2-(ethoxymethoxy)-5-methylacetophenone (0.05g, 0.24mmol). After 10min the solution was treated with menthyl sulphinate (0.1g, 0.34mmol) then the reaction stirred for a further 3h. The reaction was worked up as for (**6-31a**) previously. The crude product was subjected to NMR analysis which showed no trace of sulphoxide.

3-(4-methylphenylthio)chromone (6-45)



Method:[229] Flask A: To a stirred suspension of KH (35% disp in mineral oil, 0.133g, 1.2mmol) in 1,2-dimethoxyethane (5ml) at -9° C under argon was added a solution of 1-(2-hydroxyphenyl)-2-(p-tolylthio)ethanone (0.1g, 0.39mmol). The flask was stirred for 10 min at -9° C (ice/acetone). Flask B: To a stirred solution of N,N'-carbonyldiimidazole (0.12g, 0.74mmol) in 1,2-dimethoxyethane (5ml) was added formic acid (90%, 0.03ml, 0.72mmol). The flask was stirred for 5 min. Flask A was chilled to -78° C (cardice/acetone) then the contents of flask B were added to flask A, and the mixture was stirred overnight. The reaction was quenched with sulphuric acid (1M, 10ml), diluted water (10ml), then extracted with dichloromethane (3x15ml). The combined organics were washed with water (2x10ml), dried and evaporated under reduced pressure, giving the title compound as a white solid (0.031g, 0.12mmol, 30%), m.p. 124-126° C; ν_{max} 2918, 1646 (C=O), 1609, 1596, 1557, 1490, 1464, 1358, 1208 (OMe), 1112, 1082, 1020 cm^{-1}; δ_H 2.29 (3 H, s, $ArCH_3$), 7.07-7.45 (6 H, m, p-tolyl + chromone H5,6), 7.63-7.69 (1 H, m, chromone H7), 8.03 (1 H, s, chromone H2), 8.22 (1 H, dd, J=2Hz, 7Hz, chromone H5) ppm; δ_C 21.0 ($ArCH_3$), 118.05 (C8 chromone), 119.6 (C6 chromone), 121.1 (C4a chromone), 123.5 (tolyl C4), 125.6 (C5 chromone), 126.3 (C7 chromone), 128.5 (C1 tolyl), 129.7 (C8a chromone), 130.0 (Tolyl C2,6), 131.0 (tolyl C3,5), 133.8 (chromone C3), 137.6 (chromone C2), 156.2 (C=O) ppm; m/z 269 (MH^+), 212, 195, 108, 78, 61; $C_{16}H_{12}O_2S$ requires MH^+ 269.0636, found 269.0649, an error on the close order of 4ppm.

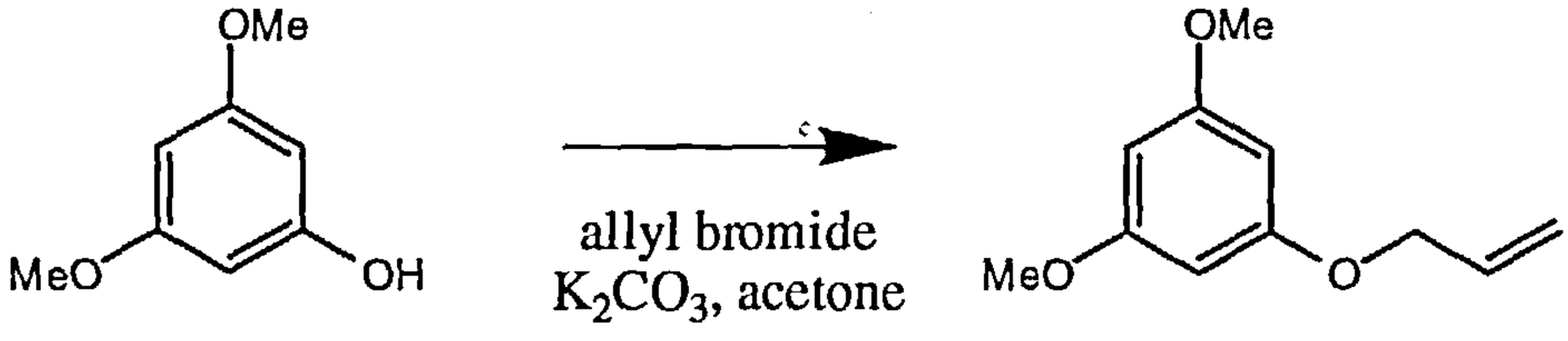
Attempted synthesis of 3-(p-tolylsulphinyl)chromone



Method:[230] To L-(+)-diethyl tartrate (0.12ml, 0.7mmol, 4 equivalents) in dry dichloromethane (2.5ml), stirred under argon, was added titanium tetraisopropoxide (0.055ml, 0.186mmol, 1 equivalent), as rapidly as possible. After 2.5 min

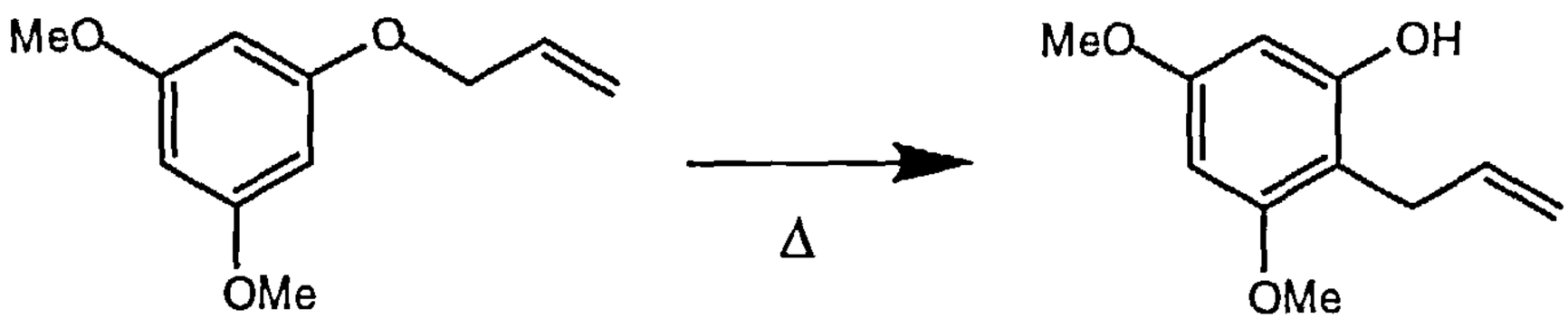
isopropanol (0.055ml, 0.7mmol, 4 equivalents) was added dropwise, waiting 15 s between drops. The mixture was stirred for 20 min and then placed in a freezer (-28° C) without stirring for a further 20 minutes. The chromone sulphide (**6-45**) (0.05g, 0.186mmol, 1 equivalent) and pre-cooled cumene hydroperoxide (0.052ml, 0.37mmol, 2 equivalents) were added rapidly and the flask left in the freezer overnight. The mixture was then poured into a solution of ferrous sulphate heptahydrate (0.3g), citric acid (0.1g), 1,4-dioxane (1.5ml) and ether (2.5ml) in water (3ml), then stirred for 15 min. The aqueous mixture was extracted with ether (3x10ml), the combined organics washed with brine (10ml), dried and evaporated under reduced pressure. TLC analysis and crude NMR analysis of the evaporated mixture showed no transformation.

1-Allyloxy-3,5-dimethoxybenzene (6-48)



To a solution of 3,5-dimethoxyphenol (4.80g, 31mmol) in Analar® acetone (100ml) were added K_2CO_3 (17g, 123mmol) and allyl bromide (7.5ml, 58mmol). The resultant suspension was refluxed under acetone for 12 h. The suspension was allowed to cool, then the potassium carbonate was filtered off. The solution was evaporated on the rotary evaporator and then the high vacuum system giving a yellow oil (4.89g, 25mmol, 81%), which could be used without further purification; ν_{max} 3081, 3006, 2939, 2839, 1605, 1476, 1423, 1384, 1205, 1152, 1065, 1033 cm^{-1}; δ_H 3.75 (6 H, s, OMe), 4.46-4.48 (2 H, m, OCH_2), 5.21-5.42 (2 H, m, OCH_2CHCH_2), 5.93-6.15 (2 H, m, CH_2CHCH_2) ppm; R_f (5:1, petroleum - ethyl acetate) product 0.63, starting material 0.27.

1-(2'-Hydroxy-4',6'-dimethoxyphenyl)prop-2-ene (6-47)[231]



1-Allyloxy-3,5-dimethoxybenzene (**6-48**) (4.89g, 25mmol) was placed in a flask fitted with an air condenser arranged for reflux, and thoroughly purged with argon. The

flask was lowered into a Woods metal bath heated to 190° C, and maintained at that temperature for 4h. The mixture was raised from the bath and allowed to cool, then dissolved in dichloromethane and passed through a short silica plug then chased with dichloromethane. The resultant oil (4.8g, 98%) was pure to NMR, and could be used without further purification. The product had ν_{max} 3424 (OH), 3076, 3002, 2939, 2839, 1618, 1510, 1206, 1149, 996 cm^{-1}; δ_H 3.31-3.39 (2 H, m, $ArCH_2CHCH_2$), 3.73 (3 H, s, OMe), 3.75 (3 H, s, OMe), 5.03-5.14 (2 H, m, $ArCH_2CH=CH_2$), 5.88-6.08 (2 H, m, ArH + $ArCH_2CHCH_2$) ppm.

2-Hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxybenzaldehyde (6-17)

i) <u>In 1,2-dichloroethane</u>

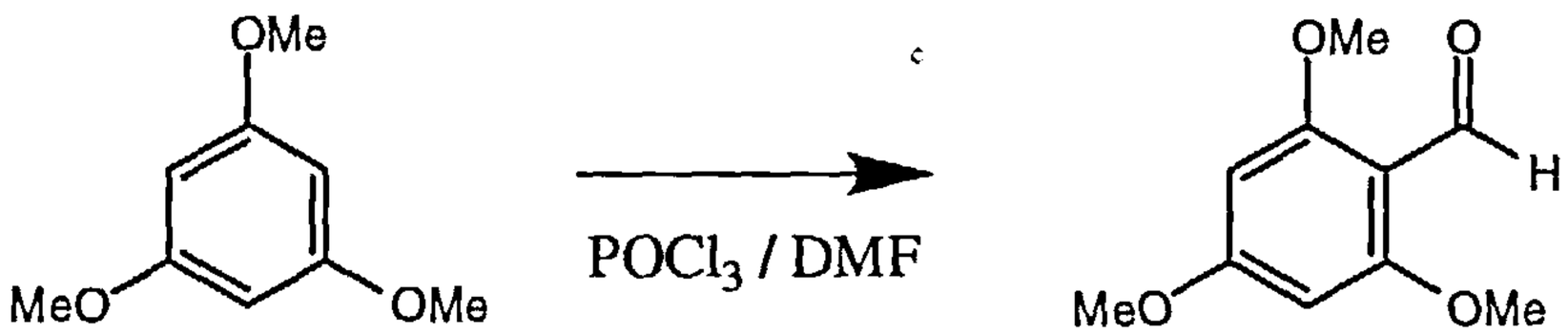
The phenol (**6-47**) (3g, 15mmol) in 1,2-dichloroethane (20ml) with N,N-dimethylformamide (4ml, 51mmol) was stirred under argon. Phosphoryl chloride (3ml, 32mmol) was added, and the temperature controlled by addition rate to below 100° C. After addition the mixture was stirred for 20 min. The mixture was tipped into ice water (20ml) and diluted with dichloromethane (20ml). The layers were separated, and the aqueous layer extracted with dichloromethane (2x20ml). The combined organics were washed with water (2x20ml), brine (1x20ml), dried over magnesium sulphate and evaporated. The resultant solid was dissolved in dichloromethane and washed through a silica plug with copious solvent. After evaporation the resultant oil was triturated with petrol to give the product (0.79g, 3.6mmol, 23%) (for data see below).

<u>ii) Acetonitrile solution</u>

A stirred solution of DMF (5ml, 65mmol) in acetonitrile (20ml) at room temperature was treated dropwise with phosphoryl chloride (5ml, 54mmol). After 1 h the solution was cooled to 0 ° C and treated dropwise with a solution of the phenol (**6-47**) (4.85g, 25 mmol) in acetonitrile (20ml). After the addition the mixture was left for 1 h at 0 ° C and the ice-bath then removed. The mixture was stirred for 7 h and then added slowly to ice (*ca.* 200 g). The mixture was stirred for 30 min and then left to stand overnight. The medium contained a mass of beige needles and some dark resinous material. The product was collected on a Buchner funnel and washed well with water.

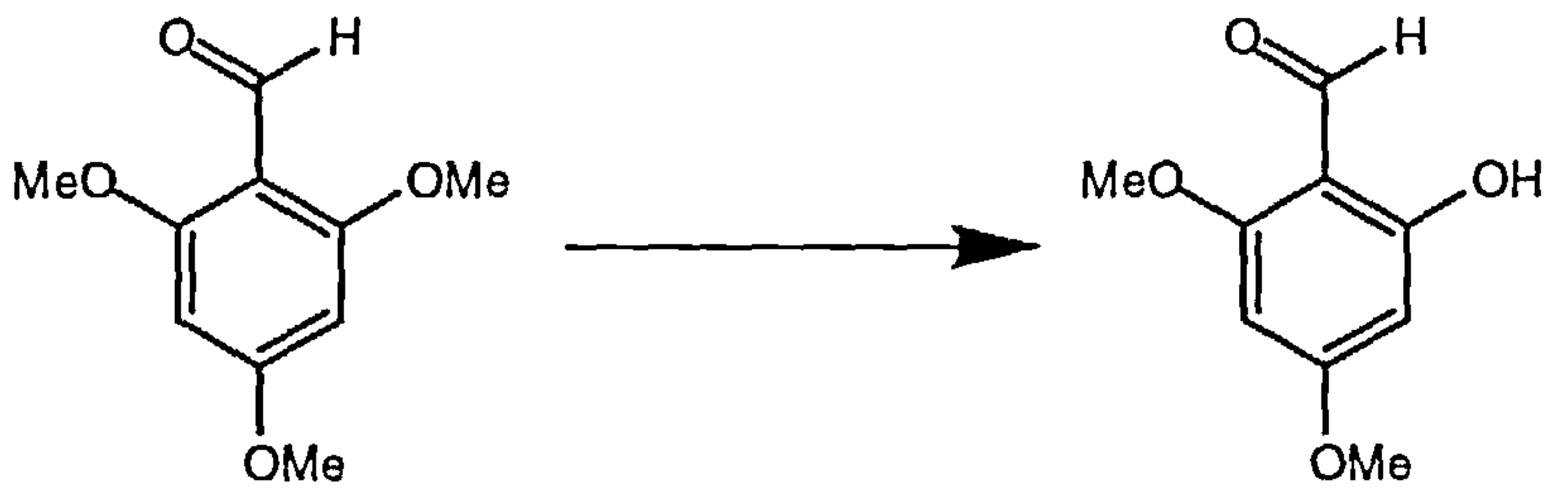
The organic material was dissolved in dichloromethane (total 75 ml), and the solution dried, filtered and evaporated. The concentrate in dichloromethane was filtered through a short plug of silica, eluting with more dichloromethane. The eluate was evaporated to a golden yellow oil (4.60g, 83%) which solidified. Crystallisation from ethanol gave the title compound (2.82 g, 51% in 2 crops) as pale yellow needles, m.p. 85–86 ° C; ν_{max} 1621, 1496, 1455, 1433, 1293, 1249, 1219, 1204, 1118, 796 cm^{-1}; δ_H 3.28 (2 H, d, J=6 Hz, ArC**H**$_2$CHCH$_2$), 3.87 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.90–5.02 (2 H, m, CH=C**H**$_2$), 5.8–6.0 (1 H, m, C**H**=CH$_2$), 5.93 (1 H, s, 5-H), 10.11 (1 H, s, CHO), 10.93 (1 H, s, OH); δ_C 25.9 (ArCH$_2$), 55.7, 55.8 (OMe), 71.4 (CH=**C**H$_2$), 85.8 (ArH), 87.3 (ArCHO), 114.2 (**C**H=CH$_2$), 162.5, 162.9, 165.5 (C2, C4, C6), 191.9 (CHO); m/z 240 (MNH_4^+), 223 (MH^+), 211 (MNH_4^+ – CHO), 69 (100); $C_{12}H_{14}O_4$ requires MH^+ 223.0970, found 223.0969, an error on the close order of 1ppm; R_f 0.29 (5:1 petroleum - ethyl acetate).

2,4,6-Trimethoxybenzaldehyde



To a solution of phloroglucinol trimethyl ether (10g, 59mmol) in N,N-dimethylformamide (100ml) was added phosphoryl chloride (20ml, 215mmol), slowly with vigorous stirring. The mixture was stirred overnight, then tipped onto an intimate mixture of ice (200ml) and sodium acetate (5g). The mixture was stirred until it reached room temperature, then brought to pH 3 using NaOH (solid). The precipitate thus formed was collected, and recrystallised from methanol to give the product (3.2g, 16mmol, 27%), m.p. 119-121° C; ν_{max} 2922, 1667 (C=O), 1600, 1454, 1409, 1333, 1213 (OMe), 1126 (OMe), 808 cm^{-1}; δ_H 3.84 (3 H, s, 4-OMe), 3.85 (6 H, s, 2-OMe, 6-OMe), 6.05 (2 H, s, ArH), 10.32 (1 H, s, CHO) ppm. These data match those of a sample supplied by Aldrich. (cat. no.13,871-1)

2-Hydroxy-4,6-dimethoxybenzaldehyde (6-48)[232]



i) <u>Benzene solution</u>

Clean, dry magnesium (0.41g, 17mmol) and iodine (4.34g, 17mmol) were added to a mixture of ether (25ml) and benzene (150ml). The mixture was stirred for 20 min until the solids had dissolved. 2,4,6-Trimethoxybenzaldehyde (3.35g, 17mmol) was added as a solution in benzene (75ml). The mixture was refluxed for 5h, then evaporated under reduced pressure and the residue extracted with hot petroleum (4x20ml). The resulting solution was allowed to cool and the crystals collected. These could be recrystallised from methanol to give the title compound (1.06g, 5.8mmol, 34%); ν_{max} 2919, 2359, 1620 (C=O), 1424, 1374, 1334, 1300, 1219 (OMe), 1157, 1112, 791, 727 cm^{-1}; δ_H 3.81 (3 H, s, OMe), 3.82 (3 H, s, OMe), 5.88 (1 H, d, J=2Hz, 3-H), 5.99 (1 H, d, J=2Hz, 5-H), 10.07 (1 H, s, CHO), 12.51 (1 H, s, OH) ppm.

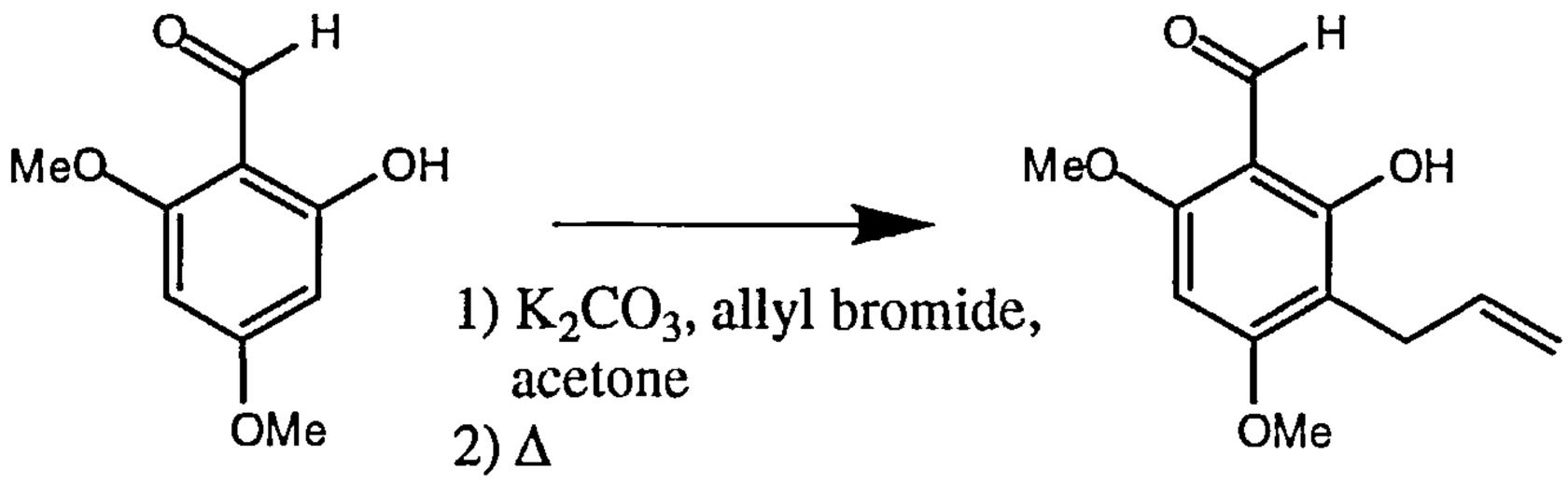
ii) Cyclohexane solution

The above procedure was repeated with the substitution of cyclohexane for benzene. This gave phloroglucinol trimethyl ether as the only isolable product.

iii) THF solution

The above procedure was repeated with the substitution of THF for cyclohexane. This resulted in a complex mixture.

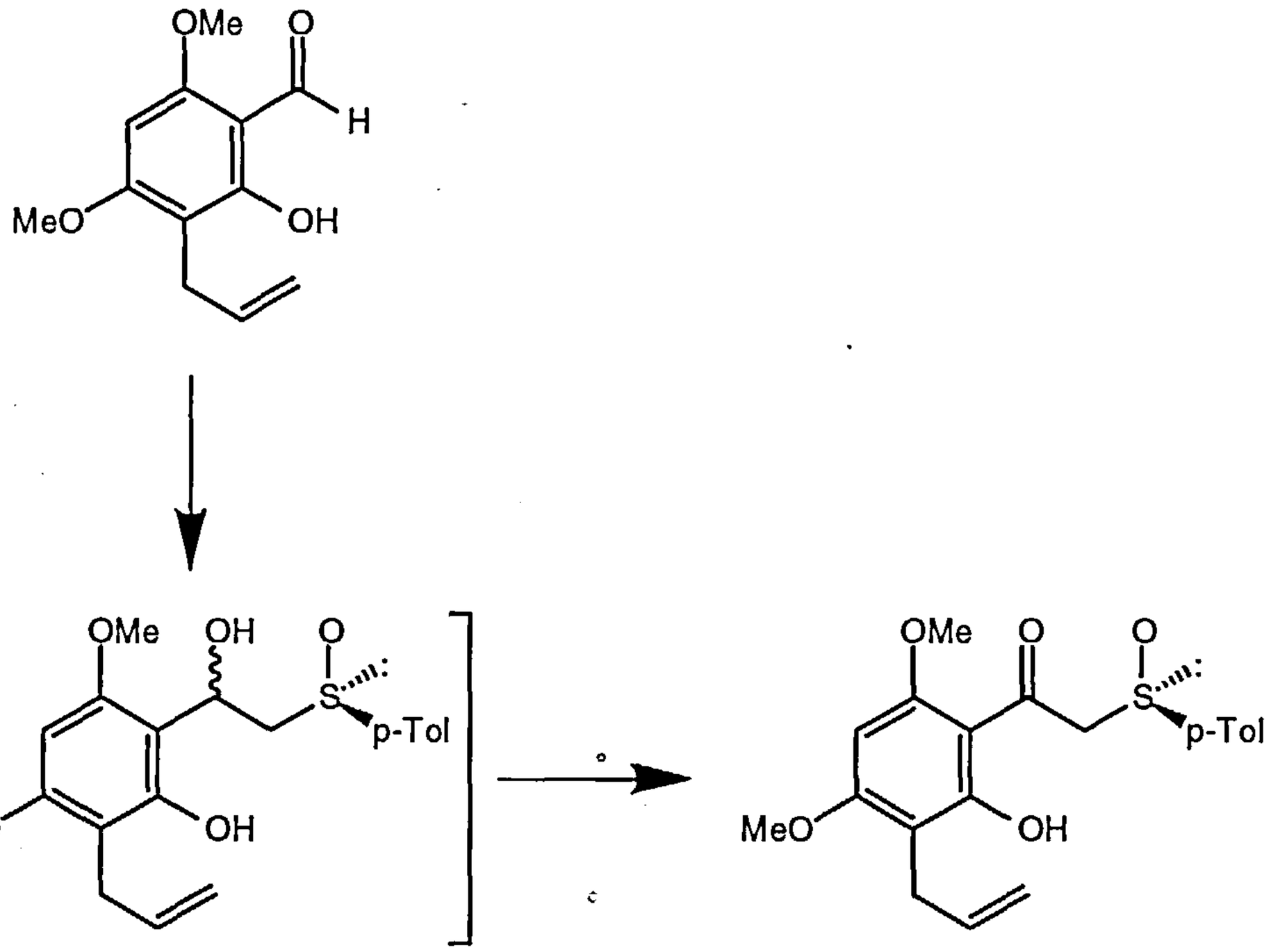
2-Hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxybenzaldehyde (6-17)[233]



To a solution of 2-hydroxy-4,6-dimethoxybenzaldehyde (**6-48**) (1.06g, 5.8mmol) in Analar® acetone (100ml) was added potassium carbonate (12g, 87mmol) and allyl bromide (0.52ml, 6mmol). The mixture was stirred for 18h then filtered, evaporated under reduced pressure and taken up into cold ether (30ml). The mixture was cooled in the freezer for 20 min. then filtered again. The mixture was concentrated down to 20ml, then cooled and filtered once more. This relatively pure solution of the allyloxy derivative was evaporated to dryness under vacuum, well purged with argon, fitted with a narrow air condenser in the reflux position and heated to 180° C. This temperature was maintained for 4h, then the mixture allowed to cool, and the resultant solid recrystallised from methanol. The product was found to be a mixture of the title

compound (0.15g, 0.7mmol, 12%) and 1-(2'-hydroxy-4',6'-dimethoxyphenyl)prop-2-ene () (0.60g, 3.1mmol, 53%).

(R)-1-(2-Hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxyphenyl)-2-(p-tolylsulphinyl)ethanone (6-8)

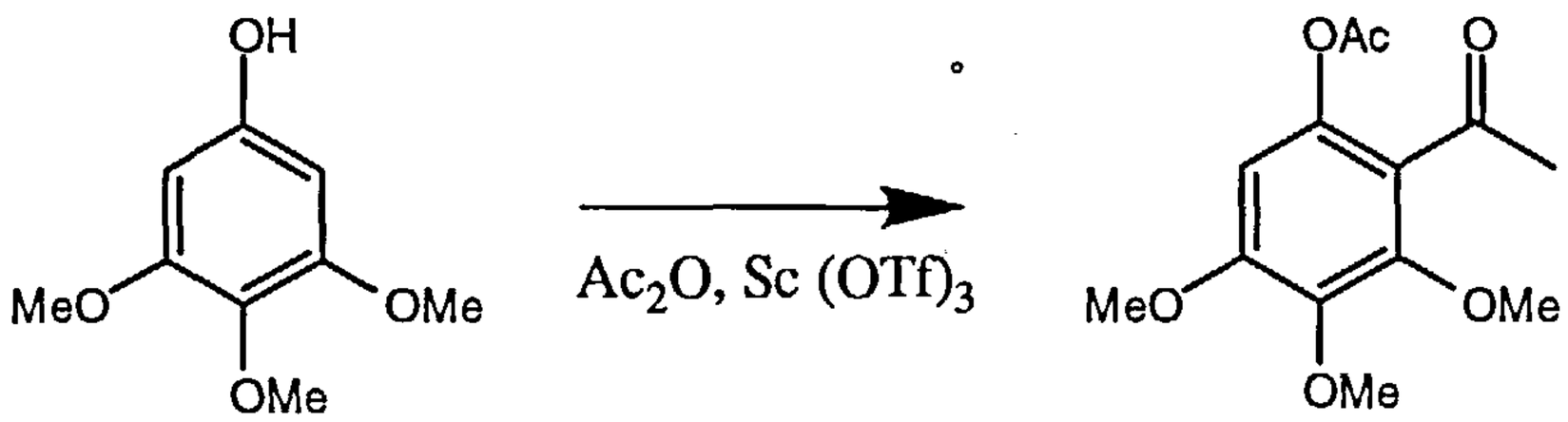


Method:[234] Flask A: To a stirred solution of the aldehyde (**6-17**) (0.05g, 0.2mmol) in dry THF (5ml) at -78° C under Ar was added LDA (0.1M in THF, 3ml, 0.3mmol), and the resultant solution was maintained at -78° C. Flask B: To a stirred solution of S-(–) methyl p-tolyl sulphoxide (0.035g, 0.23mmol) in dry THF (5ml) at -78° C under Ar was added LDA (0.1M in THF, 3ml, 0.3mmol). The mixture was allowed to warm to -20° C and maintained there for 20 min before being cooled to -78° C. The contents of flask B were added to flask A with alacrity, then the resultant mixture was allowed to reach room temperature. The reaction could be monitored by TLC (5:1 petroleum - ethyl acetate, R_f methyl sulphoxide 0.9, aldehyde 0.22, diastereoisomer 1 0.1, residue baseline). The reaction was quenched with HCl (1M, 10ml), then extracted with dichloromethane (3x10ml). The combined organics were washed with water (3x10ml), dried and evaporated. The mixture was separated on a silica column, eluting with petroleum - ethyl acetate (5:1); the baseline was eluted with methanol. Diastereoisomer 1* and the baseline were evaporated, then redissolved in dichloromethane (dry 10ml) and stirred with MnO_2 (active proprietary, 0.5g). The mixture was stirred overnight. The mixture was filtered through a short Celite® pad, and washed with dichloromethane (5ml). On evaporation the mixture was dissolved in minimal ethanol and triturated with minimal cold water, to give pure product (0.01g, 0.027mmol, 11.9% over 2 steps); δ_H 2.38 (3 H, s, ArMe), 3.27-3.29 (2 H, m, $ArCH_2$), 3.88 (3 H, s, OMe), 3.91 (3 H, s, OMe), 4.31 (1 H, d, J=14Hz, CH_2SO), 4.74 (1 H, d, J=14Hz, CH_2SO), 4.89-4.97 (2 H, m, $CHCH_2$), 5.8-5.92 (2 H, m, ArH + $CHCH_2$), 7.26-7.56 (4 H, m, tolyl ArH), 13.14 (1 H, s, OH) ppm; δ_C 21.5 (ArMe),

26.2 ($ArCH_2$), 55.7 (OMe), 72.0($CHCH_2$), 86.1 (ArH), 108.3 (ArC1), 114.2 (CH_2SO), 124.4, 129.2 (tolyl C2, C3), 136.2 ($CH=CH_2$), 141.1 (tolyl C4), 142.3 (tolyl C1), 161.7, 163.5, 164.5 (Ar C2, C4, C6), 194.2 (C=O) ppm; ν_{max} 3392 (OH), 2922, 1620, 1586, 1469, 1412, 1291, 1216, 1140, 1047, 809 cm^{-1}; m/z 392 (MNH_4^+), 375 (MH^+), 237, no other significant peaks; $C_{20}H_{22}O_3S$ requires m/z 375.1266, found 375.1271, an error on the close order of 1.5 ppm.

*δ_H 2.46 (3 H, s, ArMe), 3.27-3.89 [10 H, m, SCH_2, $ArCH_2$ and 2xOMe (3.52, 3.73)], 4.64 (1 H, s, CHOH), 4.84-4.96 (2 H, m, $CHCH_2$), 5.65-6.15 (2 H, m, CH_2CH, ArH), 7.37-7.83 (4 H, m, tolyl ArH), 8.87 (1 H, s, ArOH) ppm.

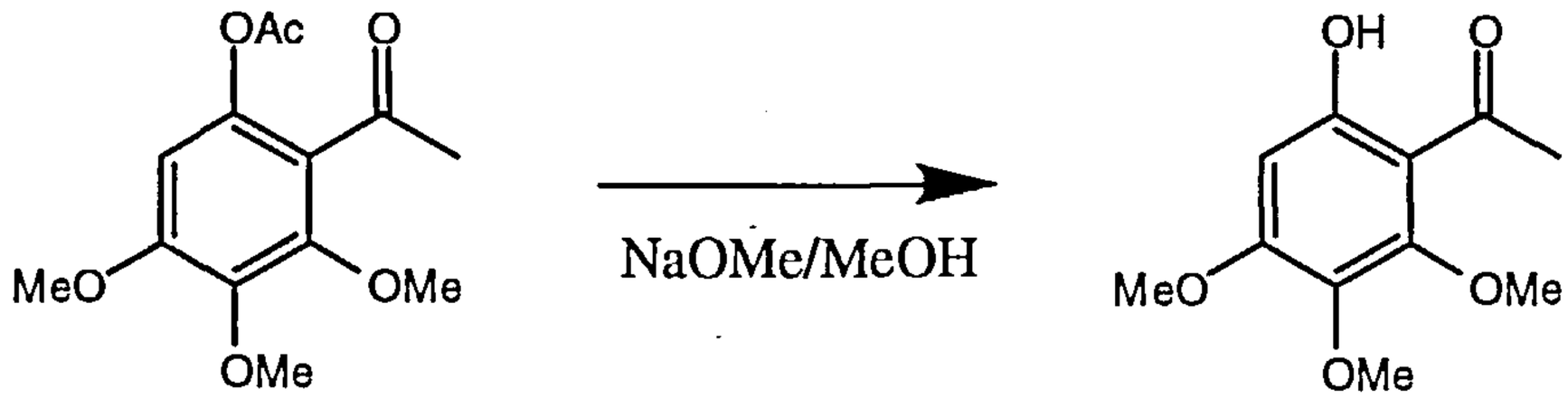
2-Acetyl-3,4,5-trimethoxyphenyl acetate (5-7)



To a solution of 3,4,5-trimethoxyphenol (**3-7b**) (3g, 16mmol) in 1,2-dichloroethane (60ml) was added acetic anhydride (10ml) and scandium triflate (0.01g, 0.02mmol). The mixture was heated to 70° C and maintained there with stirring for 24h. After this time the mixture was evaporated under reduced pressure and the residue taken up in dichloromethane (30ml). The mixture was passed through a short silica plug and chased with copious dichloromethane (the silica from the top third of the plug was retained to recycle the catalyst). The solution was evaporated to dryness and recrystallised from methanol to afford product (1.58g, 5.9mmol, 36%). The methanolic liquor was retained to provide 3,4,5-trimethoxyphenylacetate which could be cycled through the reaction again. The product had m.p. 56° C; ν_{max} 2942, 2841, 1766 (C=O ester), 1694 (C=O ketone), 1604, 1491, 1456, 1400, 1368, 1332, 1269, 1203 (OMe), 1154 (OMe), 1129 (OMe), 1106, 1069, 896, 822 cm^{-1}; δ_H 2.20 (3 H, s, $MeCO_2Ar$), 2.44 (3 H, s, MeCOAr), 3.81 (6 H, s, OMe), 3.89 (3 H, s, OMe), 6.37 (1 H, s, ArH) ppm; δ_C* 20.8 (ester Me), 31.7 (ketone Me), 56.1 (2xMeO), 60.9 (MeO), 99.1 (ring C2), 102.5 (ring C6), 143.4 (ring C1), 151.9, 153.4, 155.2 (C3, C4, C5 ring), 169.4 (C=O ester), 200.0 (C=O ketone) ppm; m/z 286 (MNH_4^+), 269 (MH^+), 244, 227 (loss of acetyl), 211; $C_{13}H_{16}O_6$ requires MH^+ 269.1025, found 269.1025, a zero error.

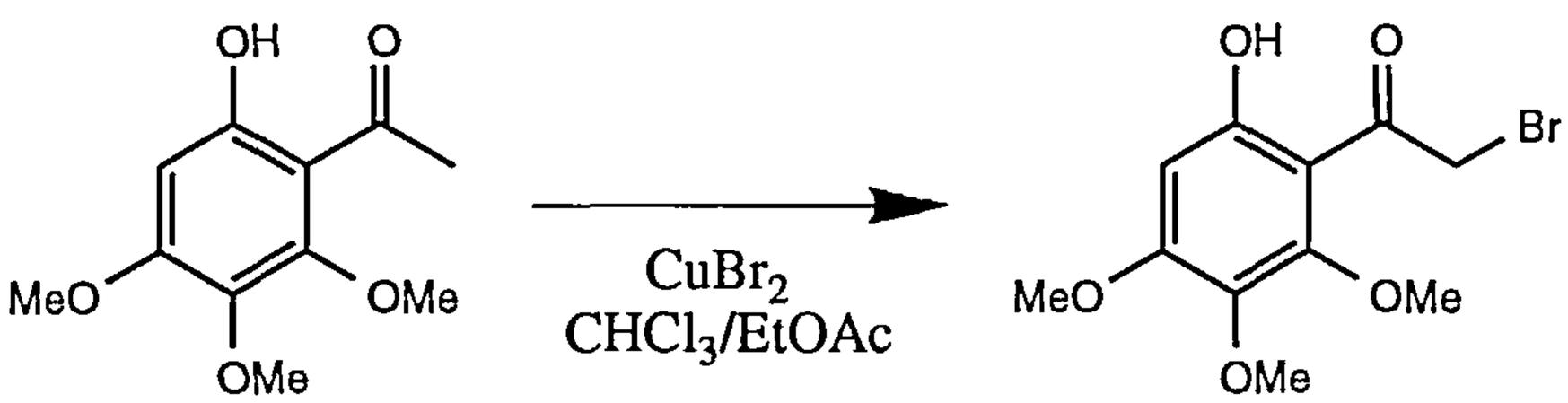
*unavoidable contamination with co-crystalline 3,4,5-trimethoxyphenyl acetate renders some carbon assignments tentative, though probable.

2,3,4-Trimethoxy-6-hydroxyacetophenone (5-6)



To a solution of sodium methoxide in methanol [from sodium (0.7g, 30mmol) and methanol (120ml)] was added 2-acetyl-3,4,5-trimethoxyphenyl acetate (**5-7**) (6.2g as an impure co-crystal with 3,4,5-trimethoxyphenyl acetate, nominally 23mmol). The mixture was heated under reflux for 0.5h and the methanol then evaporated off. The mixture was diluted with HCl (0.5M, 100ml) then extracted with ethyl acetate (3x100ml). The combined organics were washed with water (3x100ml) and brine (100ml) then dried and evaporated. The mixture was diluted with cyclohexane (100ml) then left to precipitate. The precipitate was filtered off (3,4,5-trimethoxyphenol, 0.5g) then the liquor concentrated to give product (2.5g, 11mmol) as an oil), b.p. 180° C/0.05mmHg (some decomposition); ν_{max} 3409 (OH), 2942, 1620 (C=O), 1492, 1447, 1401, 1364, 1315, 1280, 1256, 1206 (OMe), 1108 (OMe), 1082, 997, 882 cm^{-1}; δ_H 2.60 (3 H, s, MeCO), 3.76 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.97 (3 H, s, OMe), 6.22 (1 H, s, ArH), 13.41 (1 H, s, OH) ppm; δ_C 31.8 (CH_3CO); 55.9 (2xOMe), 60.9 (OMe), 96.0 (ring C5), 108.3 (ring C1), 134.6 (ring C3), 155.1 (C6), 160.0, 161.8 (C4, C2), 203.2 (C=O) ppm; m/z 227 (MH^+), 211, no other significant peaks; $C_{11}H_{14}O_5$ requires MH^+ 227.0919, found 227.0916, an error on the close order of 1.5 ppm.

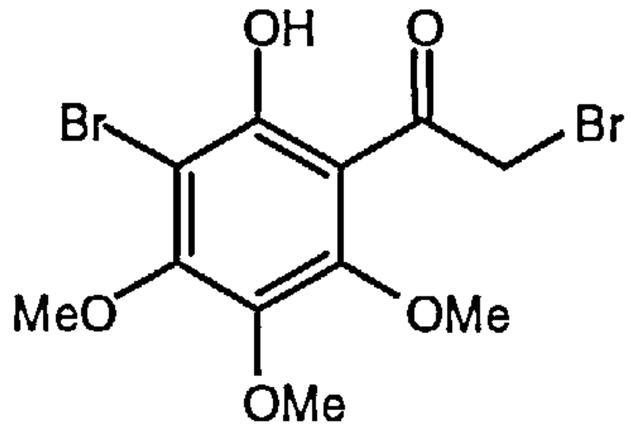
1-(2',3',4'-Trimethoxy-6-hydroxyphenyl)-2-bromoethanone (5-5)



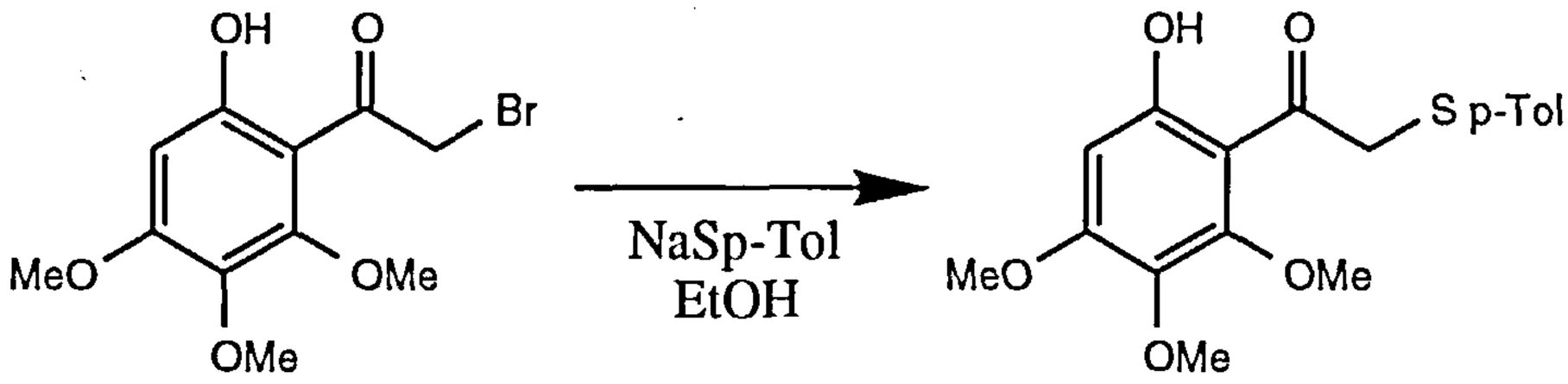
To a solution of the acetophenone (**5-6**) (0.45g, 2mmol) in ethyl acetate (20ml), chloroform (20ml) and 1,4-dioxane (5ml) was added cupric bromide (3g, 13mmol), and the mixture refluxed under argon for 18h. The mixture was evaporated to dryness, diluted with chloroform (20ml), filtered, evaporated to dryness and separated on a silica column using hexane (350ml) doped with methanol (5ml). The separation was poor, necessitating a long column, but no better was found (R_f 0.05). This gave the title compound (0.3g, 1mmol, 49%), m.p. 110° C/0.1mmHg (dec.); ν_{max} 2917,

2848, 1630 (C=O), 1600, 1490, 1496, 1315, 1287, 1148 (OMe), 1109 cm^{-1}; δ_H 3.74, 3.87, 4.06 (all 3 H, s, OMe), 4.64 (2 H, s, CH_2Br), 6.23 (1 H, s, ArH), 12.85 (1 H, s, OH) ppm; δ_C 37.1 (CH_2Br), 56.2 (2xOMe), 60.9 (OMe), 96.2 (C5'), 106.0 (C1'), 134.1 (C3), 154.4, 158.0 (C2, C4), 161.1 (C6), 195 (C=O) ppm; m/z 305 (MH^+), 289, 253, 225 (loss of Br), 211; $C_{11}H_{13}O_5Br$ requires MH^+ 305.0025, found 305.0023, an error on the close order of 1ppm.

Chief impurity: ν_{max} 2926, 1713, 1598, 1477, 1417, 1393, 1358, 1257, 1202, 1080, 1017, 805 cm^{-1}; δ_H 3.80 (3 H, s, OMe), 4.02 (3 H, s, OMe), 4.15 (2 H, s, ?), 4.66 (2 H, s, $COCH_2Br$?) ppm; m/z faint 384, strong 304, 289, 259, 211. No aromatic protons might suggest that the ring has been brominated. This would require 384 to be taken as the molecular ion rather than an impurity. Requires a misreading of the integration for peak 4.15ppm. A possible structure is shown below.

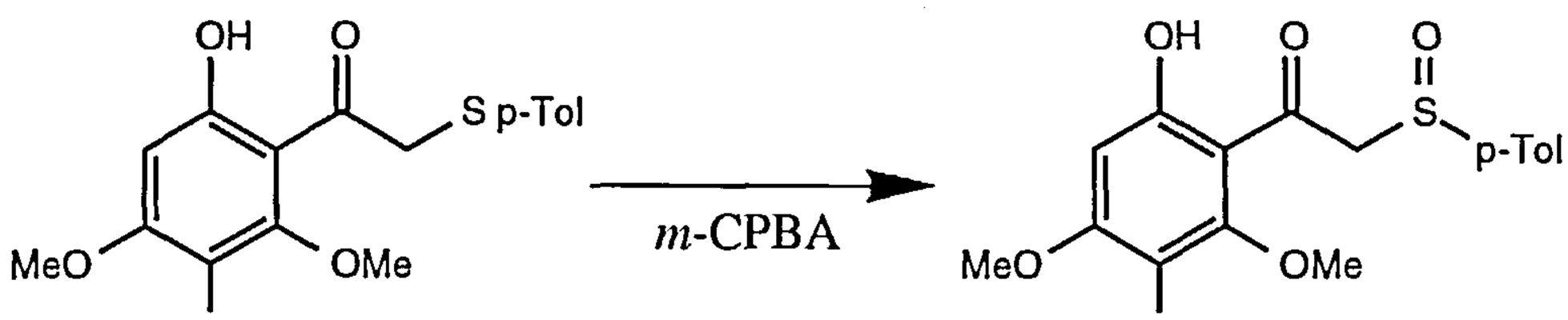


1-(2',3',4'-Trimethoxy-6'-hydroxyphenyl)-2-(p-tolylthio)ethanone (5-3)



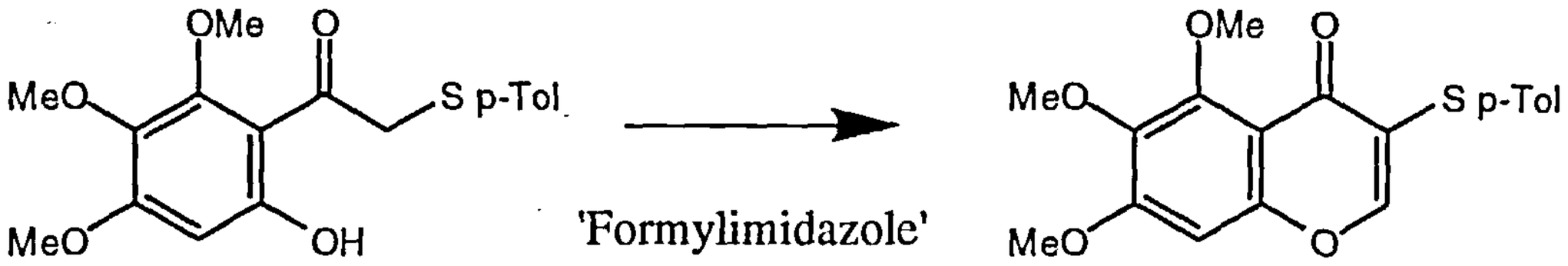
To a stirred solution of the bromoketone (**5-5**) (0.3g, 1mmol) in dry ethanol (15ml) under Ar was added ethanolic sodium thiocresolate (1M, 2ml, 2mmol). Stirring was continued overnight. The mixture was evaporated to dryness and taken up in dichloromethane (30ml). The solution was washed with water (2x20ml) and brine (1x20ml) then separated on a silica column using 9:1 petroleum - ethyl acetate (R_f 0.05), which gave the product (0.1g, 29%), m.p. 65° C; ν_{max} 2943, 1620(C=O), 1492, 1446, 1397, 1286, 1257, 1233, 1205 (ΘMe), 1136 (OMe), 1104, 1009, 809 cm^{-1}; δ_H 2.29 (3 H, s, ArMe), 3.76 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.25 (2 H, s, CH_2S), 6.22 (1 H, s, ArH), 7.09 (2 H, d, J=8Hz, tolyl H3, H5), 7.28 (2 H, d, J=8Hz, tolyl H2, H6), 12.97 (1 H, s, OH) ppm; δ_C 21.0 (ArMe), 46.4 (CH_2), 56.0, 60.9, 61.5 (all OMe), 96.1 (C5'), 106.8 (C1'), 124.1 (tolyl C4), 129.7 (tolyl C3, C5), 131.2 (tolyl C2, C4), 134.4 (C3'), 137.1 (tolyl C1), 154.6, 160.5 (C2', C4') 162.4 (C6'), 199.1 (C=O) ppm; m/z 349 (MH^+), 211, 137; $C_{18}H_{20}O_5S$ requires MH^+ 349.1110, found 349.1107, an error on the close order of 1ppm.

Attempted synthesis of 1-(6-hydroxy-2',3',4'-trimethoxyphenyl)-2-(p-tolylsulphinyl)ethanone (5-4)



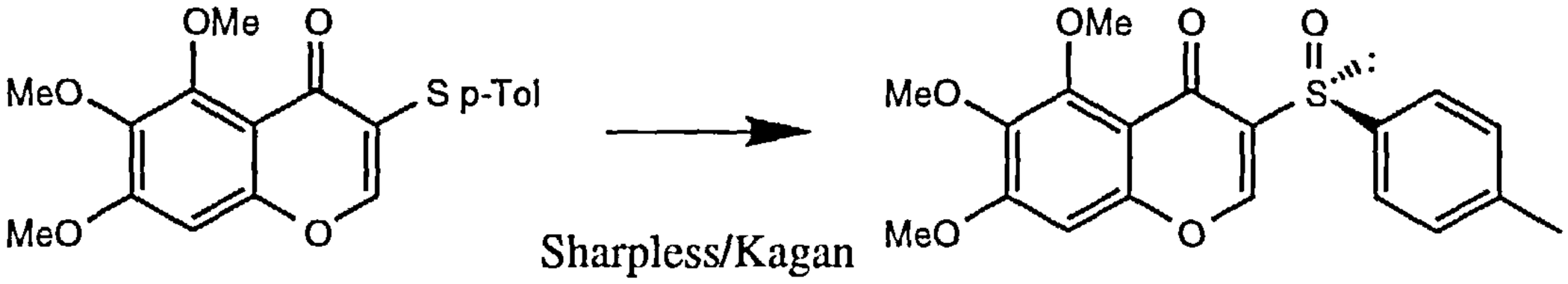
To a stirred suspension of 3-chloroperoxybenzoic acid (0.5mmol, 0.09g) in dichloromethane (10ml) under argon at 0° C was added a solution of the mercaptoketone (**5-3**) (0.5mmol, 0.174g) in dichloromethane (10ml). The solution was stirred for 18h and then poured into water (10ml). The solution was washed with water (2x20ml), dried and evaporated at room temperature under reduced pressure. The procedure gave only one product, which had no hydroxyl or aromatic hydrogen peaks in its spectrum, and which was assumed to be the product of ring oxidation.

3-(p-Tolylthio)-5,6,7-trimethoxychromone (5-10)



Flask A: To a stirred suspension of KH (35% dispersion in mineral oil, 0.09g, 0.7mmol) in 1,2-dimethoxyethane (3ml) at -9° C under Ar was added a solution of 1-(2,3,4-trimethoxy-6-hydroxyphenyl)-2-(p-tolylthio)ethanone (**5-3**) (0.1g, 0.3mmol). The flask was stirred for 10 min at -9° C (ice/acetone). Flask B: To a stirred solution of N,N'-carbonyldiimidazole (0.1g, 0.6mmol) in 1,2-dimethoxyethane (2ml) was added formic acid (90%, 0.025ml, 0.5mmol). The flask was stirred for 5 min. Flask A was chilled to -78° C (cardice/acetone) then the contents of flask B were added to flask A, then the mixture was stirred overnight. The reaction was quenched with sulphuric acid (1M, 10ml), diluted with water (10ml) and extracted with dichloromethane (3x15ml). The combined organics were washed with water (2x10ml), dried and evaporated under reduced pressure, giving the title compound as a white powder (0.08g, 78%), m.p. 132-134° C; ν_{max} 2926, 1712 (C=O), 1613, 1489, 1446, 1321, 1287, 1256, 1204 (OMe), 1101, 1002, 806, 756 cm^{-1}; δ_H 2.28 (3 H, s, ArMe), 3.87 (3 H, s, OMe), 3.92 (6 H, s, OMe), 6.63 (1 H, s H8), 7.08 (2 H, d, J=8Hz, tolyl H3, H5), 7.31 (2 H, d, J=8Hz, tolyl H2, H6), 7.79 (1 H, s, H2) ppm; δ_C 20.9 (ArMe), 56.2, 61.4, 62.1 (all OMe), 112.5 (chromone C4a), 121.8 (tolyl C4), 129.9 (tolyl C3,C5), 131.0 (tolyl C2, C6), 137.4 (tolyl C1), 140.1 (chromone C3), 152.7 (chromone C6), 153.9 (chromone C8a + C2), 154.6 (chromone C5), 157.9 (chromone C7), 173.2 (chromone C4) ppm; m/z 359 (MH^+), 253, 212, 157, 123, 78; $C_{19}H_{18}O_5S$ requires MH^+ 359.0953, found 359.0960, an error on the close order of 1.5ppm.

Attempted synthesis of 3-(p-tolylsulphinyl)-5,6,7-trimethoxychromone (5-2)



To L-(+)-diethyl tartrate (0.11ml, 0.8mmol, 4 equiv.) in dry dichloromethane (2.5ml), stirred under Ar, was added titanium tetraisopropoxide (0.054ml, 0.2mmol, 1 equiv.), as rapidly as possible. After 2.5 min isopropanol (0.055ml, 0.8mmol, 4 equiv.) was

added dropwise, waiting 15 s between drops. The mixture was stirred for 20 min then placed in a freezer (-28° C) without stirring for a further 20 minutes. The chromone sulphide (**5-10**) (0.065g, 0.2mmol, 1 equiv.) and pre-cooled cumene hydroperoxide (0.054ml, 2 equiv.) were added rapidly and the flask left in the freezer overnight. The mixture was poured into a solution of ferrous sulphate heptahydrate (0.3g), citric acid (0.1g), 1,4-dioxane (1.5ml) and ether (2.5ml) in water (3ml), then stirred for 15 min. The aqueous mix was extracted with ether (3x10ml), the combined organics washed with brine (10ml), dried and evaporated under reduced pressure. TLC analysis and crude NMR analysis of the evaporated mixture showed no transformation.

Chapter 9

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