A STUDY OF THE REACTIONS OF FLAVANOIDS WITH NUCLEOPHILES

A Thesis submitted to the
Board of the Faculty of Physical Sciences
in partial fulfilment of the requirements for the
Degree of Doctor of Philosophy

by

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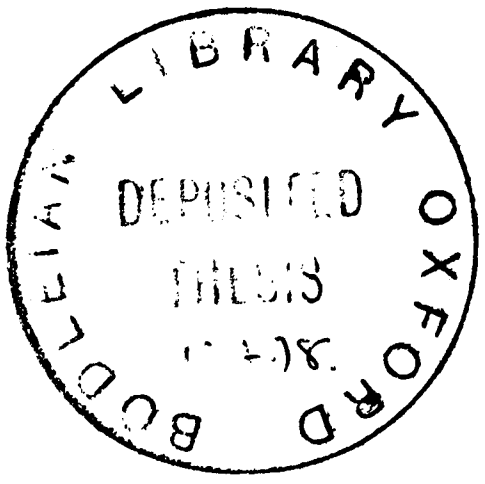

Dyson Perrins Laboratory
Oxford
December, 1977

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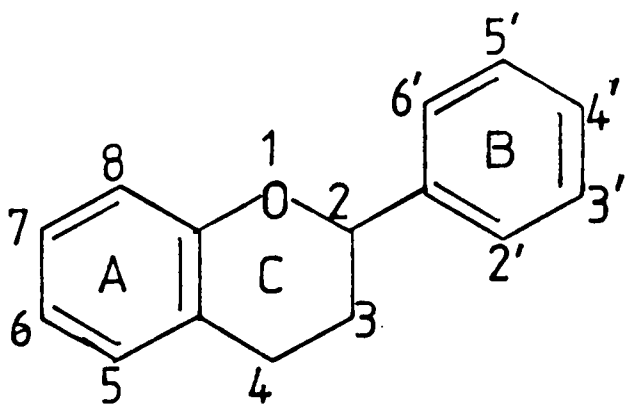
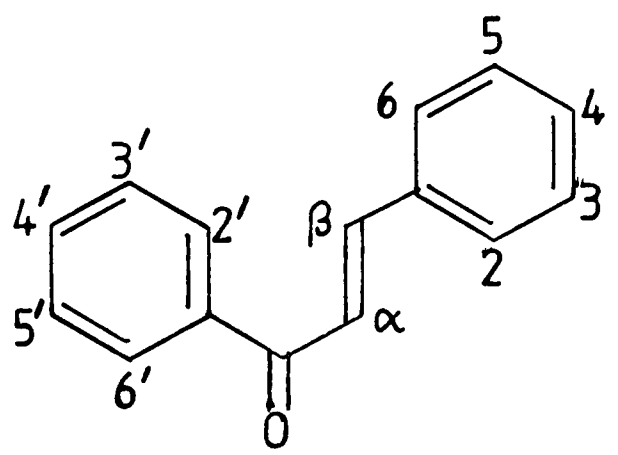
M.R.A.

A note on nomenclature and stereochemistry

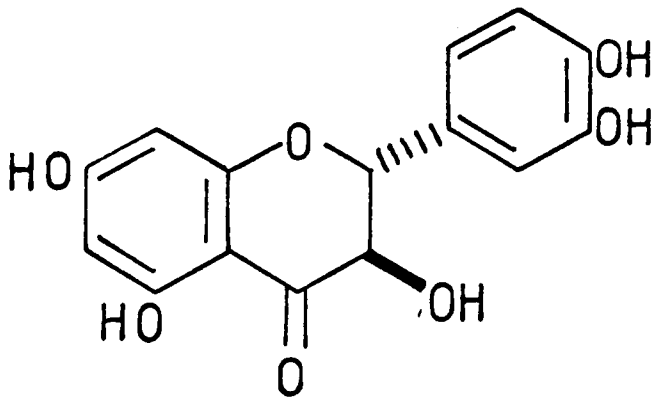
The flavan ring system is numbered:



The chalcone ring system is numbered:

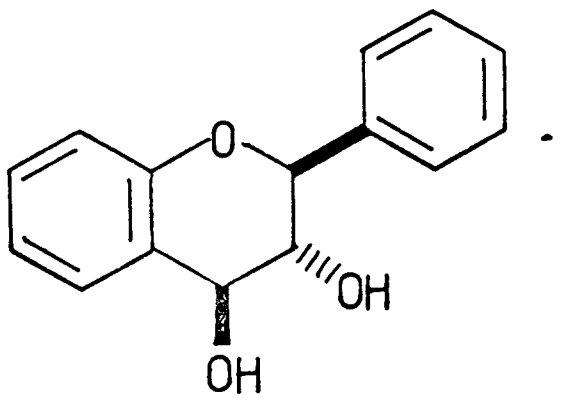


When it is significant, stereochemistry is indicated in structural formulae by the use of heavy and broken lines. Optically active compounds (derived from natural sources) are represented by formulae of the correct absolute configuration. Thus:



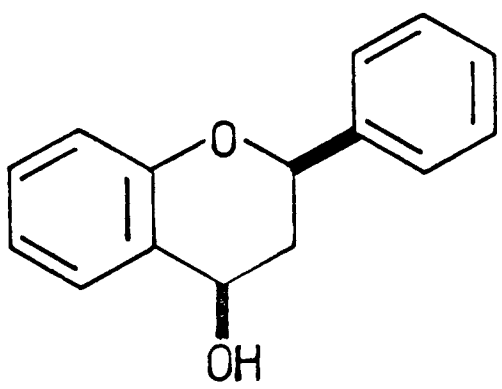
(+)-dihydroquercetin

Most naturally occurring optically active flavanoids have the corresponding (R) configuration at the 2-position. Therefore racemic compounds, in order to distinguish them, are represented by the formula of the unnatural (2S) enantiomer. In the text, compounds described without mention of optical rotation are always racemic. Thus:



2,3-*trans*-3,4-*trans*-flavan-3,4-diol

The stereochemical prefixes α and β are reserved for 4-substituted flavans having 2,4-*trans*- and 2,4-*cis*- stereochemistry respectively. Thus:



flavan-4β-ol

There is some disagreement over the use of the generic terms 'flavanoid' and 'flavonoid'. Since compounds in this thesis are named chiefly as derivatives of flavan and the term 'flavonoid' is sometimes restricted to compounds possessing the 2-phenylbenzopyrone structure the author prefers the usage flavanoid for all species containing the basic flavan skeleton.

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A study of the reactions of flavanoids with nucleophiles.
M.R. Attwood, B.A., Oriel College.
A thesis submitted for the degree of Doctor of Philosophy, Hilary term, 1978.

ABSTRACT

The reactions with nucleophiles of 4-substituted flavans variously methoxylated are studied. The partial epimerisation of 4β-acetoxyflavans in acetic acid/acetic anhydride mixtures and of flavan-4β-ols in aqueous acid, providing preparatively useful routes to 4α-acetoxyflavans and flavan-4α-ols, occur by an S_N1 mechanism. Reaction is greatly facilitated by methoxyl groups at the 5- and, especially, the 7-position. No effect of B-ring substitution on reaction rates was detected. Equilibrium mixtures of epimers studied contained 5-10% of the 4α-isomer.

2,3-Trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (1) is considerably less reactive than 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (2). An equilibrium mixture of (1) with its 4-epimer contains ca. 16% of (1). Some puzzling reactions reported in the literature are explained by the results of this study or shown to be wrong.

The 4-carbocation generated by decomposition of (2) also reacts with phenols, providing the first satisfactory route to 4α-aryloxy-5,7,3',4'-tetramethoxyflavans. The phenols (and yields of aryloxyflavan) are: phenol (60%), m-methoxyphenol (46%), m-benzoyloxyphenol (51%) and 3,5-dimethoxyphenol (9%). Generation of the necessary carbocation for synthetic purposes from flavanoids possessing a 3-oxygen substituent or lacking a 5-methoxyl substituent requires a better leaving group. Benzoate and p-nitrophenoxy are convenient for ease of preparation and reaction. Thus, 4α-phenoxy-7,3',4'-trimethoxy-

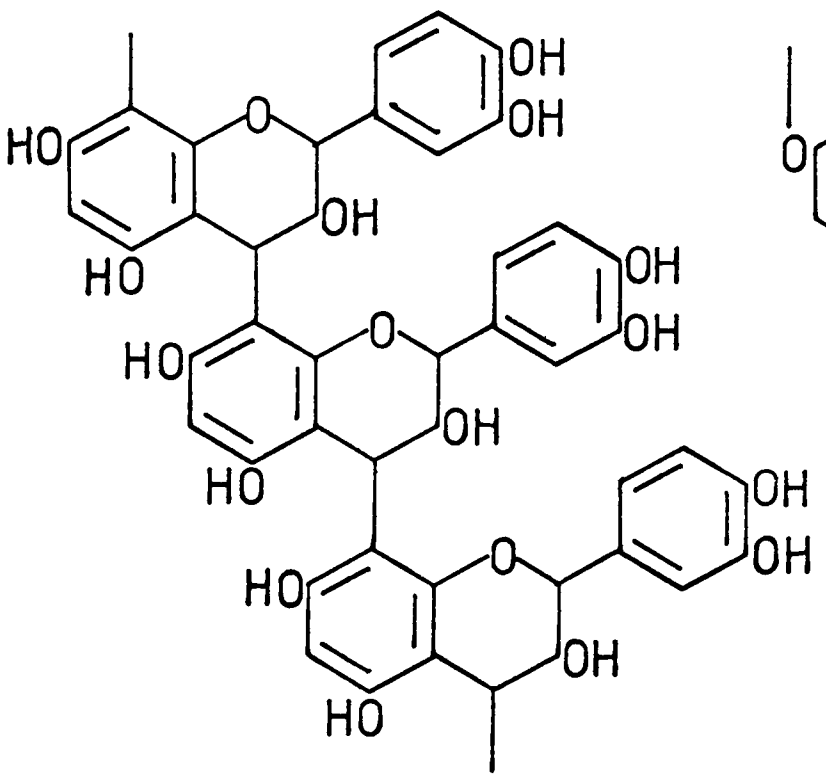
flavan (39%) and 2,3-*trans*-3,4-*cis*-4-phenoxy-5,7,3',4'-tetramethoxyflavan-3-ol (15%) and its 4-epimer (1%) are prepared.

7-Hydroxyflavanoids, intended to act as nucleophiles in syntheses of ether-linked flavanoid dimers (modelling postulated naturally occurring polymers) are synthesised with the aid of protection of the 7-hydroxyl group. Those which possess a 4-acyloxy group or 3,4-double bond are too labile, particularly in the presence of base, to be isolated. 7-Hydroxy-3',4'-dimethoxyflavanone (3), 2,3-*trans*-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol (4) and also 2,3-*trans*-3',4'-dimethoxyflavan-3,7-diol and 2,3-*trans*-3,4-*cis*-3',4'-dimethoxyflavan-3,4,7-triol were isolated. The reagent osmium tetroxide/*N*-methylmorpholine-*N*-oxide was used to accomplish stereoselective bis-hydroxylation of flav-3-enes in high yield.

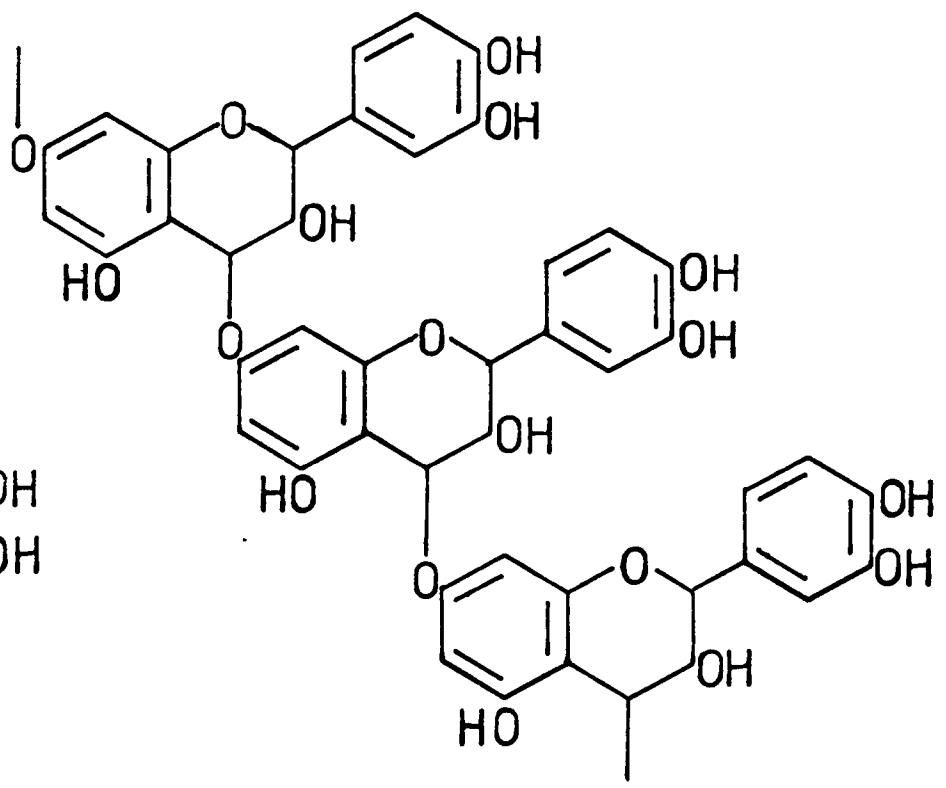
(3) And (4) react with 4β-(*p*-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan. 7-(5,7,3',4'-tetramethoxyflavan-4α-yloxy)-3',4'-dimethoxyflavan-4β-ol (formed by sodium borohydride reduction) and its acetate, and 7-(5,7,3',4'-tetramethoxyflavan-4α-yloxy)-2,3-*trans*-3-benzoyloxy-3',4'-dimethoxyflavan were isolated. Their structures are confirmed by n.m.r. and mass spectroscopy.

FULLER ABSTRACT

Flavanoids are known to be the constituents of the so-called "condensed tannins" from which they may be isolated as monomers by degradation with sulphur nucleophiles in the presence of acid.[1,2] Such naturally occurring flavanoids are polyphenols and have been found to bind protein in soil when released from decaying vegetation.[3] It is not known, however, whether the tannins responsible for this action are formed in live vegetation or only after death, and it has been suggested[4] that the durable carbon-carbon linked tannins (such as 1) extracted from plants represent the products of breakdown and repolymerisation of ether-linked species (such as 2).



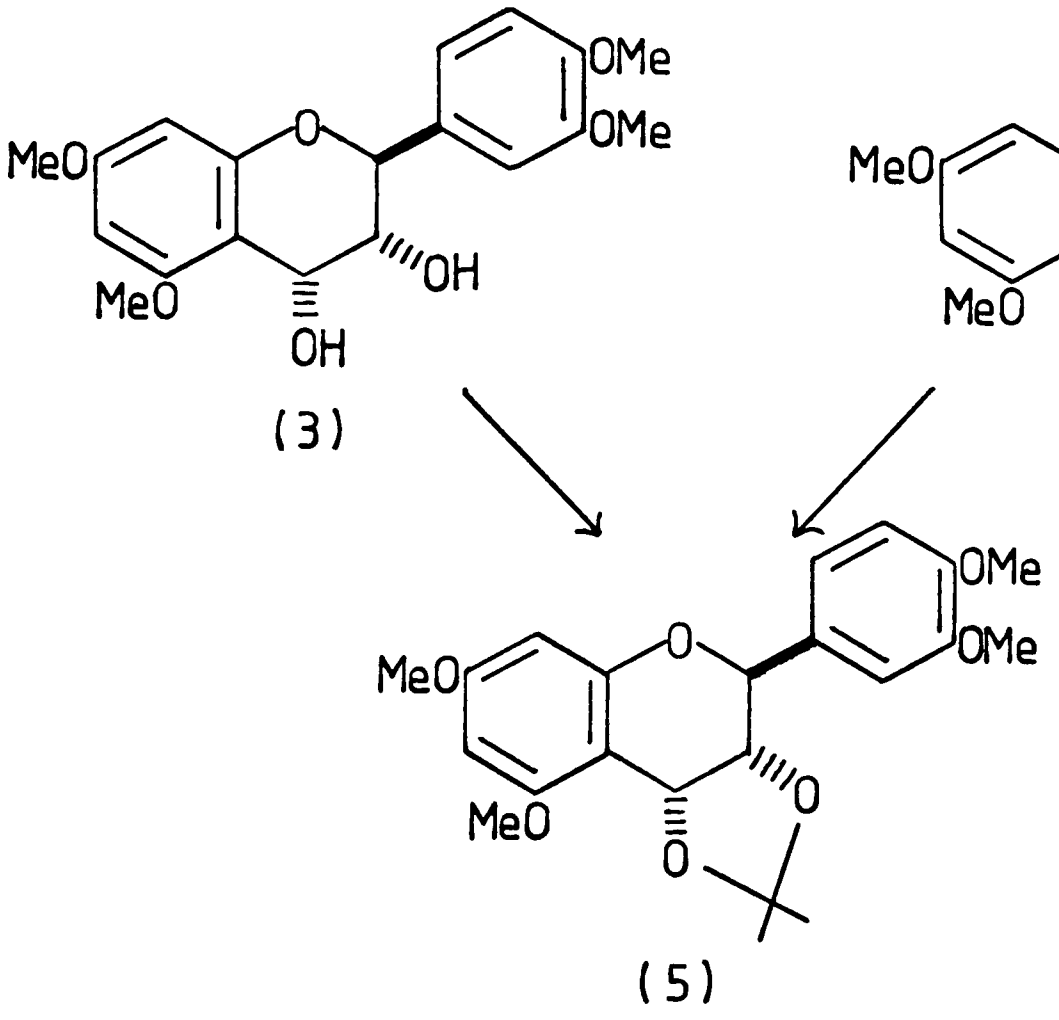
(1)



(2)

The investigation of this hypothesis has hitherto involved the synthesis of 4-aryloxyflavans, intended to serve as model compounds for the polymer (2). Syntheses of 4-aryloxyflavans which lack aromatic substituents have been found to fail when

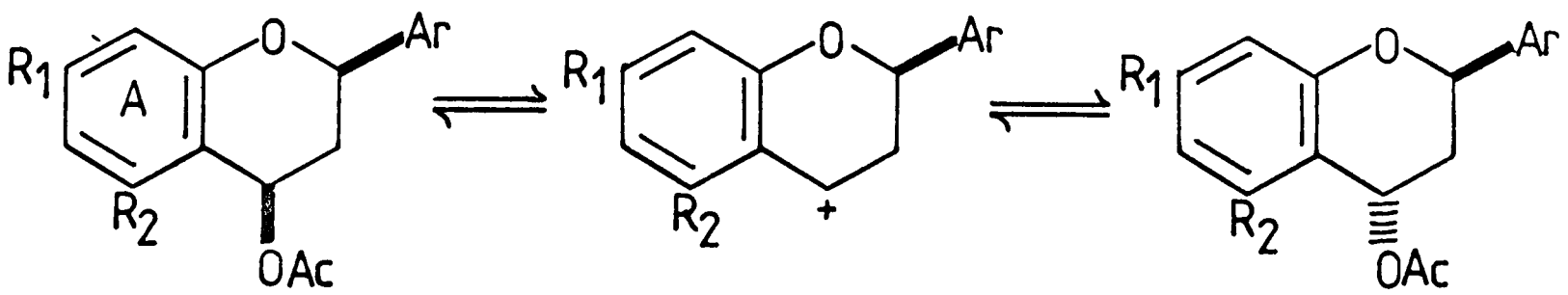
applied to flavanoids with methoxyl substituents.[4-6] The syntheses attempted all employed reaction of a 4-substituted flavanoid with a nucleophile, but reactions of highly substituted flavanoids with nucleophiles have hitherto been poorly understood and unpredictable. For instance, Fujise et al.[7] found that the two diols (3) and (4) treated with acetone and anhydrous copper sulphate both readily formed the same isopropylidene derivative (5). The lack of study given to reactions of highly substituted flavanoids led therefore to vagueness as to why the syntheses of 4-aryloxyflavanoids which worked for flavanoids without aromatic substituents could not be extended to those possessing aromatic methoxyl groups.



It was the purpose of the present investigation to understand and be able to predict the reactions of highly-substituted flavanoids with nucleophiles and to use this knowledge to synthesise highly-methoxylated 4-aryloxyflavanoids

and ether-linked flavanoid dimers which would serve as closer models than those already available for ether-linked polymers such as (2).

It was found that 4β-acetoxyflavans of the type (6) when treated with acetic acid were substantially epimerised to the corresponding 4α-acetoxyflavans (8). The epimerisation was catalysed by acid but the strength of acid or temperature necessary for reaction to occur depended on the substitution pattern of the flavanoid A-ring, the mildest conditions being employed for epimerisation of 5,7-dimethoxy-4β-acetoxyflavans (6, R_1=R_2=OMe). The observed dependence of the reaction conditions on A-ring substitution pattern but not B-ring substitution pattern reflects the differing stabilities of the 4-carbocations (7), stability being greatest with methoxyl groups at the 5- and 7-positions (7, R_1=R_2=OMe). It had previously been suggested that the 4α-stereochemistry of the products of solvolysis of flavan-4β-ols resulted from sterically favoured attack on the α-face of an intermediate 4-carbocation by a nucleophile.[8] The present work shows that 4α-stereochemistry is thermodynamically as well as kinetically determined, the ratio at equilibrium between corresponding 4α- and 4β-acetates, in the cases for which it was measured, being 10-20:1.

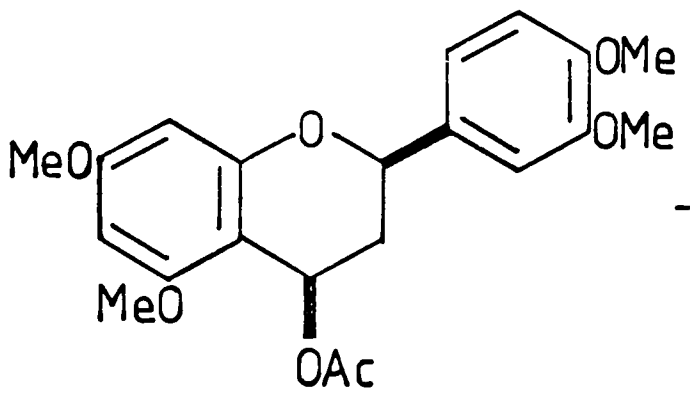


(6) (7) (8)

Conversion of flavan-4β-ols to flavan-4α-ols could be brought about similarly by treating the former substances with aqueous acid. Flavan-4α-ols have previously not been easily accessible and no general method of preparation of them, comparable in utility to the sodium borohydride reduction of flavanones for the preparation of flavan-4β-ols,[9] has been reported. Epimerisation of flavan-4β-ols with aqueous acid not only proved convenient, but it also showed that a previously claimed general route[10] to flavan-4α-ols was limited by the poorly understood reactivity of highly-substituted flavans mentioned above. Thus, re-investigation of the reaction of 4-bromo-5,3',4'-trimethoxyflavan with ethanolic alkali which was claimed[10] to give 5,3',4'-trimethoxyflavan-4α-ol by an S_N2 reaction was shown by the present author to give 4α-ethoxy-5,3',4'-trimethoxyflavan by an S_N1 reaction.

The ease of epimerisation of 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (9) suggested the first satisfactory synthesis of highly-substituted 4-aryloxyflavans, which was achieved by warming the acetate (9) with excess of a phenol in pyridine. By this means 46-60% yields of the 4α-aryloxyflavans (10)-(12) were obtained and a 9% yield of (13).

O'Neill[4] had obtained a maximum of 7% of the phenoxyflavan (10) by heating the corresponding flavan-4β-ol with phenol. It seemed that the important feature of the new method was the replacement of a good leaving group (acetoxy) by a poorer leaving group (phenoxy) so that under the reaction conditions, the desired product does not decompose repeatedly to the intermediate 4-carbocation until the latter is irreversibly lost by elimination, polymerisation or electrophilic attack on the aromatic ring of a phenol.



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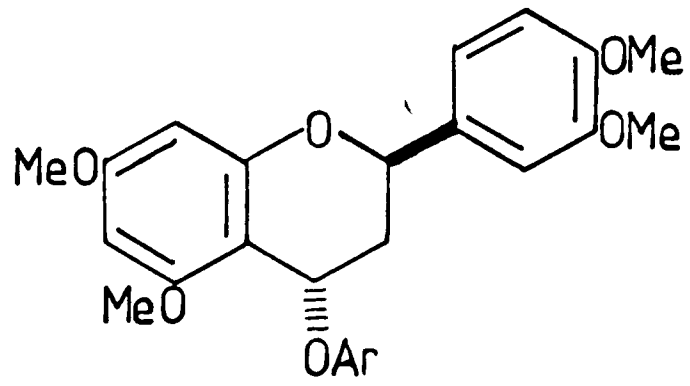
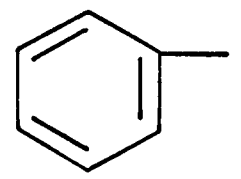
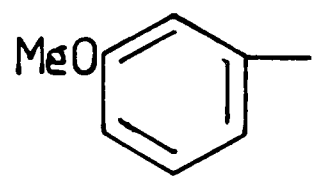
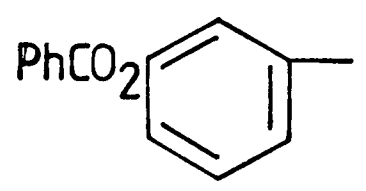
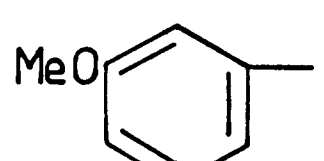


Ar =  (10)

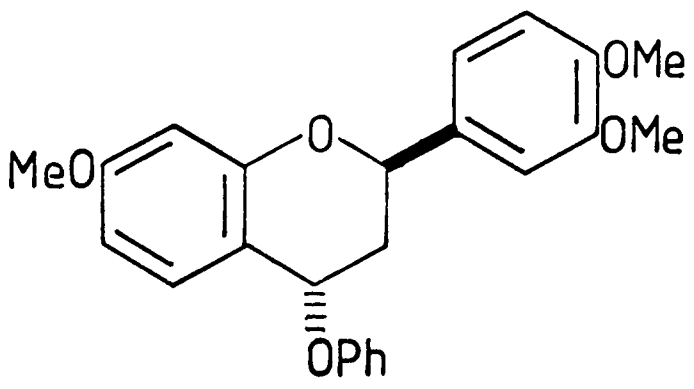
Ar =  (11)

Ar =  (12)

Ar =  (13)

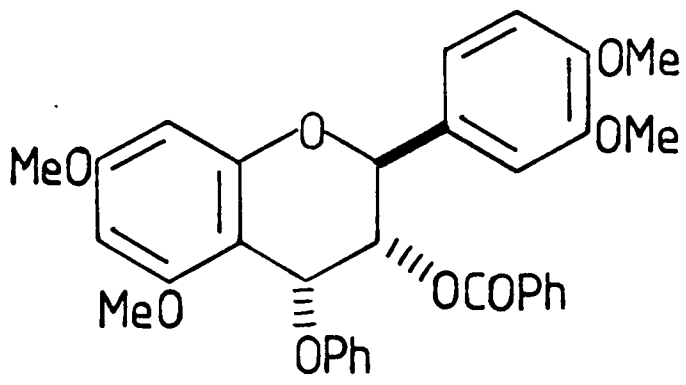
MeO

p-Nitrophenoxy was found to be an even better leaving group than acetoxy, and 4-p-nitrophenoxyflavans were readily prepared by treatment of the sodium salts of flavan-4-ols with p-fluoronitrobenzene in dimethylsulphoxide. (The use of non-acidic conditions for preparation of flavanoids substituted with a good leaving group at the 4-position is essential because of the high sensitivity to acid of such flavanoids). This leaving group proved convenient for preparing a less highly-substituted 4-aryloxyflavan, 4α-phenoxy-7,3',4'-trimethoxyflavan (14), as did the benzoate leaving group.



(14)

The diacetate of the tetramethoxyflavan-3,4-diol (3) was found to be less reactive than 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (9), the difference being attributed to the inductive effect of the 3-substituent. Use of the benzoate leaving group for conversions of the diol (3) allowed the synthesis of 2,3-trans-3,4-cis-3-benzoyloxy-4-phenoxy-5,7,3',4'-tetramethoxyflavan (15), although in only 15% yield. Substantial amounts of 3-benzoyloxy-4-(hydroxyaryl)-flavanoids were formed concomitantly and it was shown that the 4-aryloxy-flavanoid (15) was unstable under the conditions of its preparation, and thus that the synthesis did not satisfy the criterion mentioned above (p. iv). The reactions of the 4-carbocation (16) were stereochemically much more complex than those of (7). Both 3,4-cis and 3,4-trans isomers of 4-phenoxy- and 4-(hydroxyphenyl)-flavans were formed by the combination of (16) with phenol, and it was noted that attempted epimerisation of the diacetate of (4) proceeded less far towards the stabler diacetate of (3) than did that of (9) towards its stabler 4α-epimer. It is tentatively suggested that predominantly the 3,4-cis-configuration results from thermodynamic control of product stereochemistry, while kinetic control (such as was observed for electrophilic attack of the 4-carbocation (16) on the phenol nucleus) gives chiefly 3,4-trans-stereochemistry.



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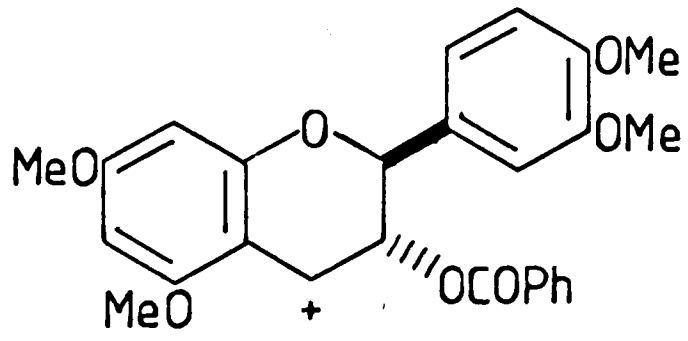
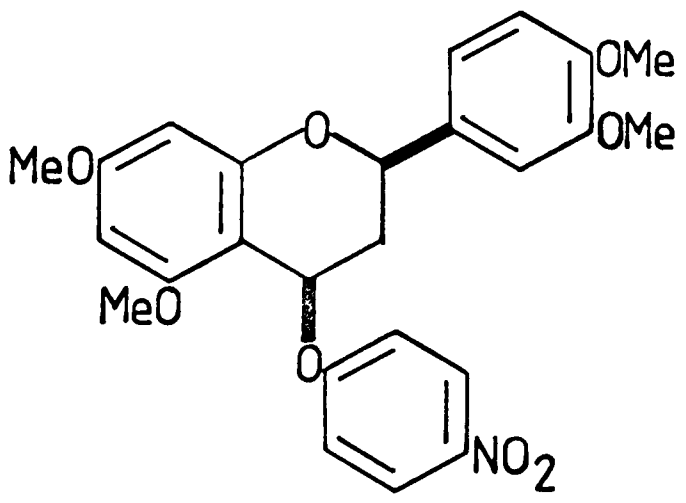


(16)

It was decided to attempt the synthesis of ether-linked flavanoid dimers by causing 4-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (17), which had been found to be more reactive than 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (9), to react with flavanoids bearing a phenolic hydroxyl group at the 7-position to yield products of the type (18) (R"=flavan-4-yl).



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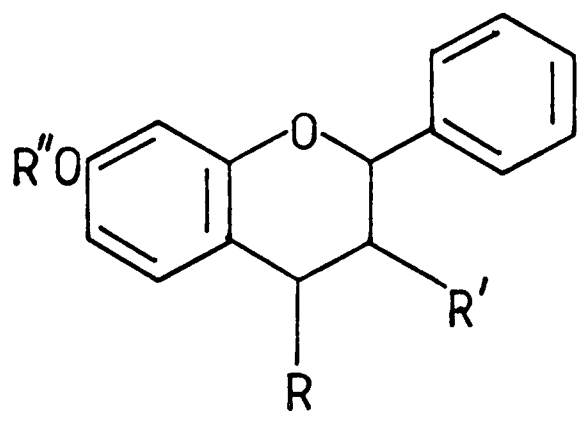


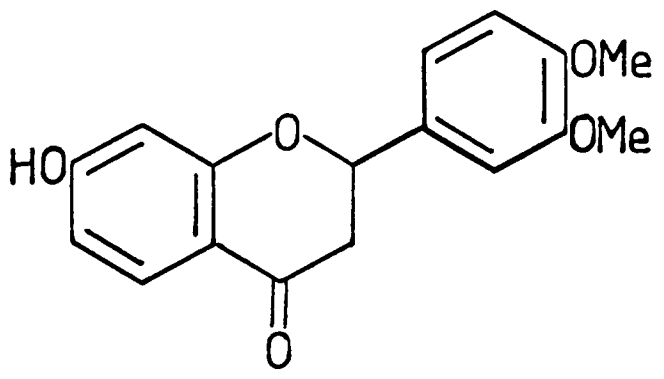
(18)

Only a very limited range of 7-hydroxyflavans had previously been synthesised ((18): R=R'=R''=H or R=keto,R'=R''=H). It seemed that the 7-hydroxyl group itself rendered difficult or impossible what were otherwise standard syntheses, for example condensation of a benzaldehyde and a 2,4-dihydroxy-acetophenone to give a 7-hydroxyflavanone,[11] or sodium borohydride reduction of a 2',4'-dihydroxychalcone to give a

7-hydroxyflav-3-ene.[12]

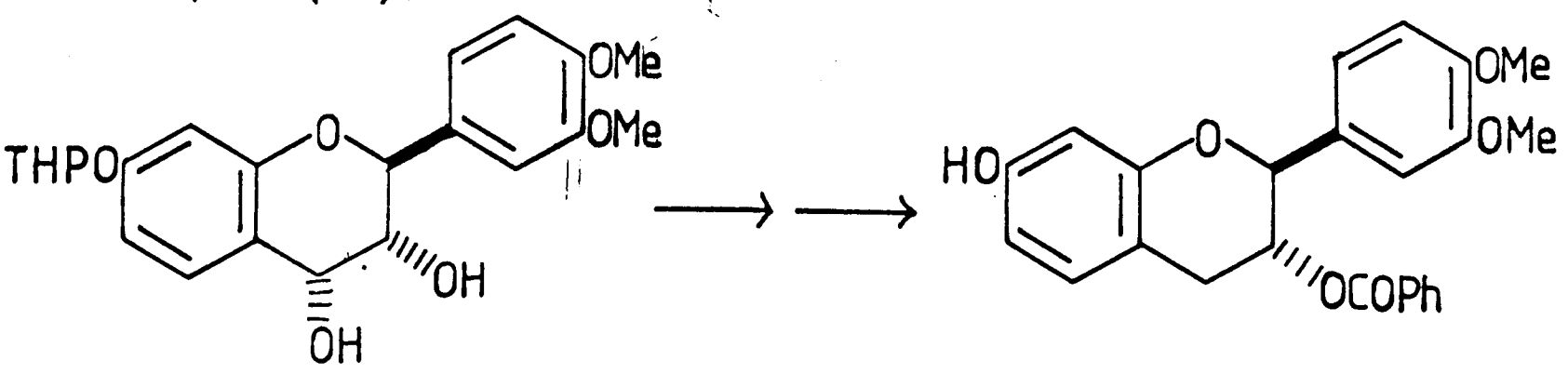
For the present work it was therefore decided to protect the 7-hydroxyl group during the synthetic transformations and three types of protecting group were investigated.

The methoxymethyl group, which could be removed by toluene-p-sulphonic acid in acetic acid, allowed the synthesis of 7-hydroxy-3',4'-dimethoxyflavanone (19).



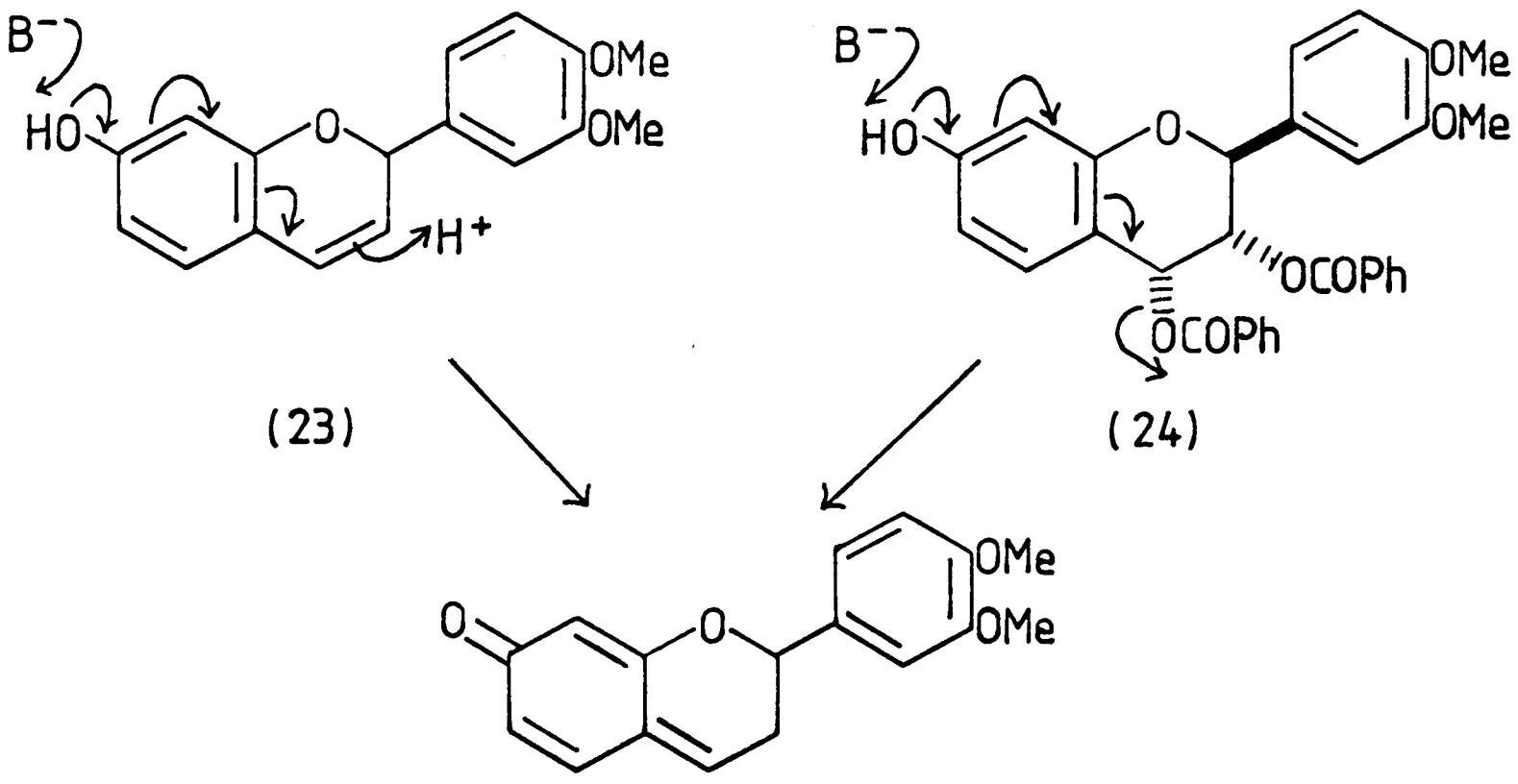
(19)

It had already been found in the present work that N-methylmorpholine-N-oxide in the presence of osmium tetroxide[13] was an excellent reagent for the conversion of 5,7,3',4'-tetramethoxyflav-3-ene into 2,3-trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (3). Use of this reagent in conjunction with the tetrahydropyranyl protecting group permitted the synthesis of the protected phenolic diol (20). The 4-hydroxyl group of this compound was hydrogenolysed, the 3-hydroxyl benzoylated and the protecting group removed by mild acid treatment to furnish 2,3-trans-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol (21).



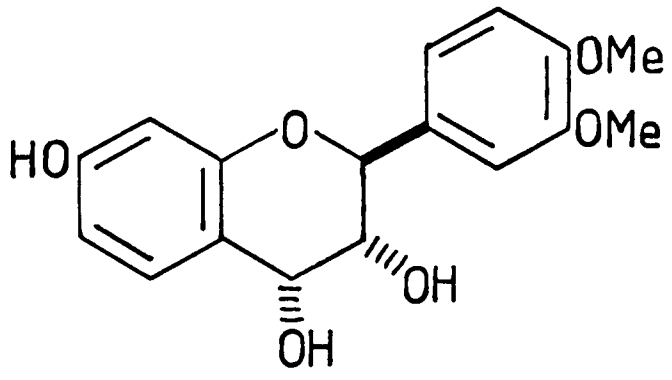
(20) (21)

Attempts to prepare the phenolic flav-3-ene (23) and dibenzoate (24) with the aid of the tetrahydropyranyl protecting group were unsuccessful. Samples having nuclear magnetic resonance spectra consistent with these structures were obtained, but they could not be obtained pure. The exceptional reactivity of these compounds is enhanced by base and is thought to result from loss of a proton from the 7-hydroxyl group and formation of a quinone-methide:



It was similarly found impossible to prepare the dibenzoate (24) or the corresponding 3,4-diacetoxyflavan by means of the photo-sensitive o-nitrobenzyl protecting group,[14] although this protecting group could be used to prepare 2,3-trans-3,4-cis-3',4'-dimethoxyflavan-3,4,7-triol (25).

The two stable phenolic flavanoids (19) and (21) were caused to react with 4β-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (17) and the dimeric flavanoids (26), (27) and (28) were isolated.



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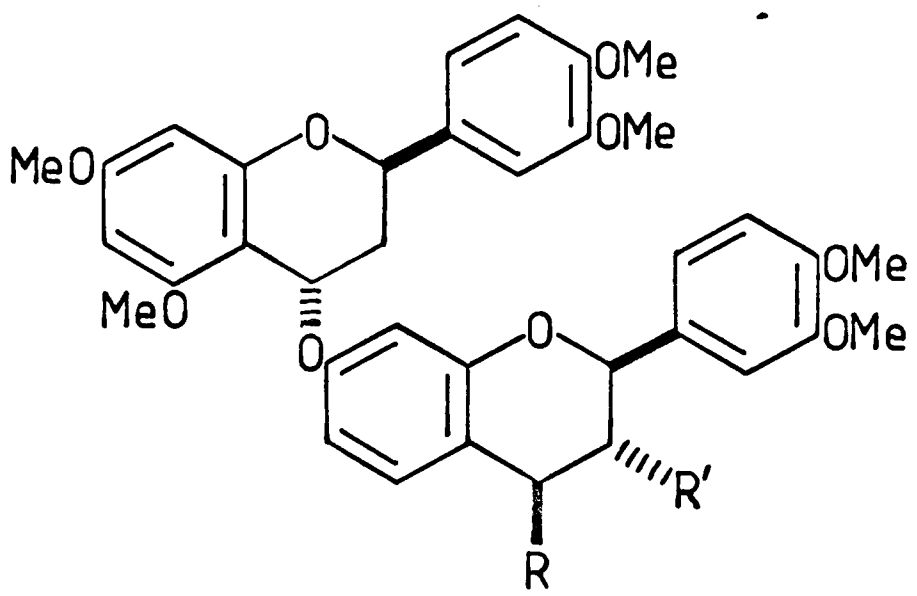

(26) R = OH ; R' = H

(27) R = OAc; R' = H

(28) R = H ; R' = OCOPh

Because the monomeric flavanoid starting materials were racemic, the dimers were obtained as non-crystalline mixtures of diastereoisomers. The two flavan skeleta in each were plainly observed in the mass spectra of the dimers and in the nuclear magnetic resonance spectra, which also indicated the 2,4-trans stereochemistry of the "upper" flavan nuclei and the 4β-configuration of (26) and (27).

These reactions represent the first syntheses of ether-linked flavanoid dimers having methoxyl substituents in the

A-ring of either flavan nucleus and are particularly relevant to the question of naturally occurring ether-linked tannins because the "upper" flavan nuclei possess the very common cyanidin aromatic substitution pattern.

The principles applied in the present work to the synthesis of phenolic flavanoids and their conversion into flavanoid dimers by reaction with another flavanoid species having an appropriately chosen leaving group at the 4-position could be extended to the preparation of dimers more nearly resembling the postulated naturally occurring polymers. Further work on such syntheses of ether-linked flavanoid dimers bearing free hydroxyl groups is required.

References to fuller abstract

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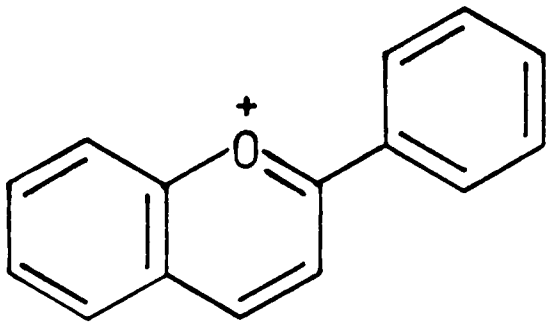

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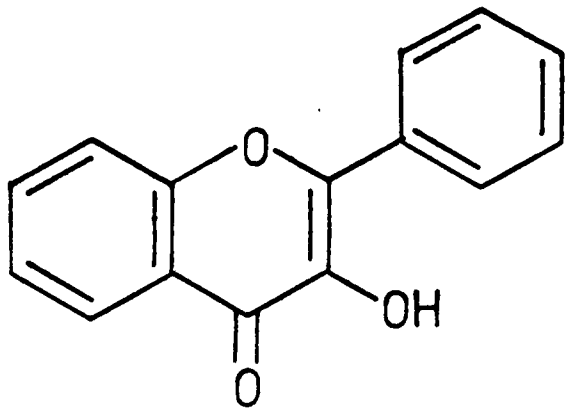

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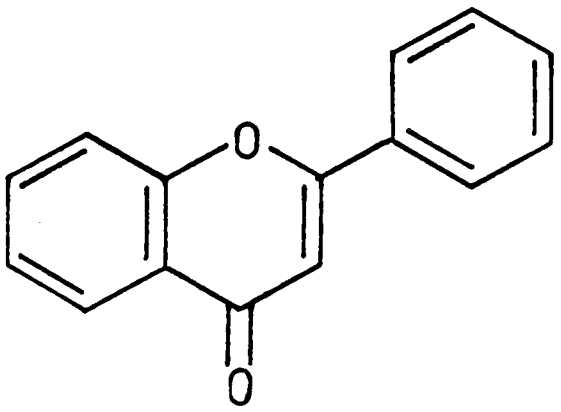

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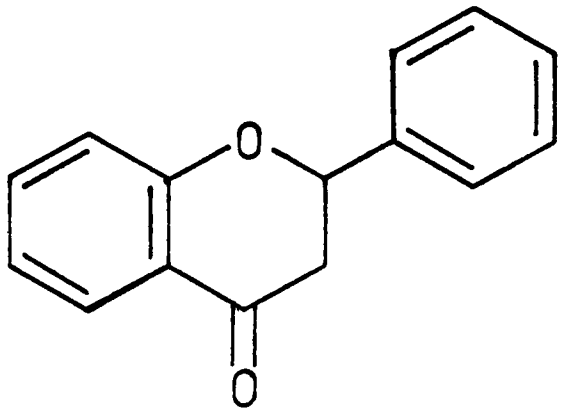

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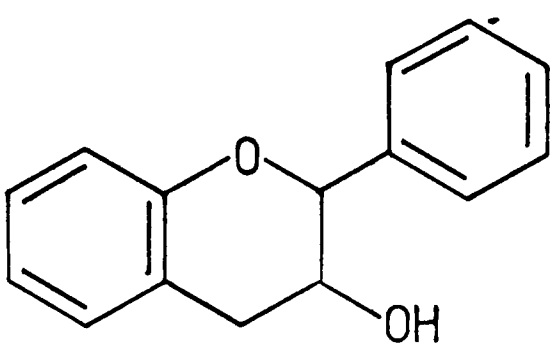

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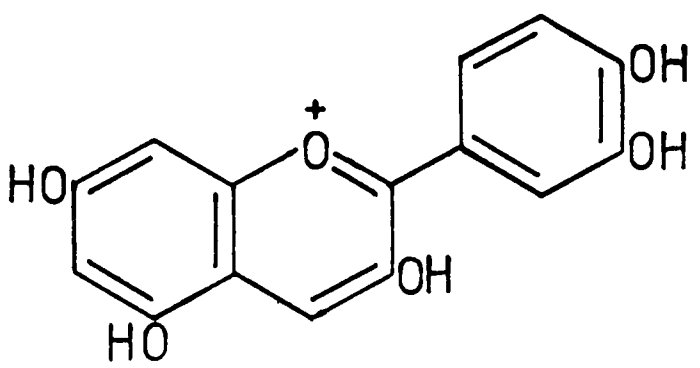


VI

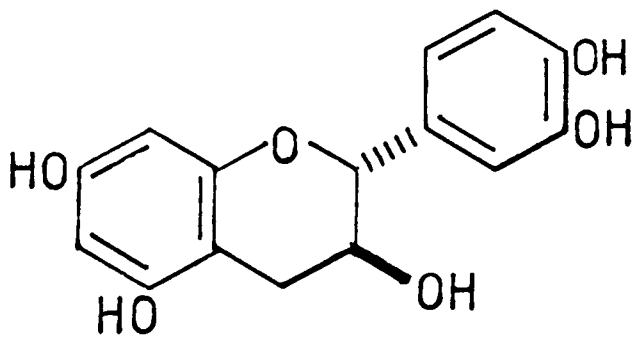
INTRODUCTION

Flavanoid compounds occur widely in the plant kingdom, being found in the flowers, leaves, fruits and woody parts of a great many species. Anthocyanidins (flavylium salts) (I) and flavonols (II), both as glycosides, contribute to the colours of flowers, fruits and leaves,[1] although the botanical significance of flavones (III), flavanones (IV) and flavan-3-ols (V) is less obvious.[2]

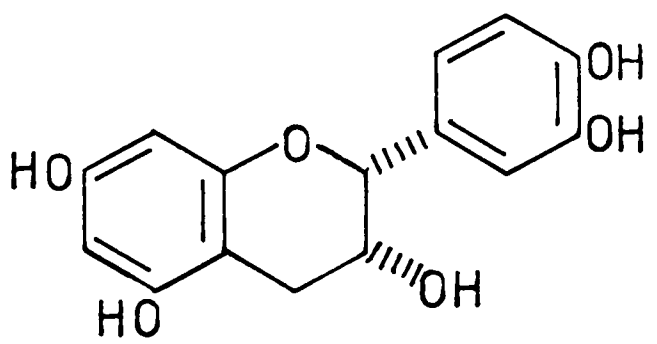
The naturally occurring flavanoids possess several phenolic hydroxyl or methoxyl substituents (with only rare exceptions, such as flavone itself[3]), the most common substitution pattern being that of cyanidin (VI). The presence of hydroxyl substituents renders the flavanoids soluble in water, much more chemically reactive and capable of hydrogen-bonding to protein. The latter effect is of ecological and technological importance: ecological, in that protein-polyphenol complexes from decaying vegetation can regulate the supply of utilisable nitrogen in the soil;[4] and technological, in that polyphenols are responsible for the tanning effect of traditional vegetable tannins on animal hides.[5] In the tanning process, protein fibres are cross-linked by hydrogen bonding to the tannin molecules. Too small a molecule will not provide adequate linking, while too large a molecule will not penetrate between the fibres. The molecular weight range appropriate for tannin molecules is 500–3000[6] and two distinct types of polymer with this property are available from natural sources.

The so-called 'hydrolysable tannins' are esters of carbohydrates and polyphenolic carboxylic acids, deriving

their name from their ready hydrolysis with aqueous acid.[7] These tannins are not composed of any flavanoid materials and will not be further considered in the present work; but the 'condensed tannins' appear to be made up exclusively of flavanoid polymers. Attempts to hydrolyse the latter type of tannin cause further polymerisation to yield insoluble phlobaphenes,[8] but treatment with hot alcoholic hydrochloric acid gives rise, in limited yield, to anthocyanidins[9] (whence the name 'proanthocyanidins' for substances with this property). Degradation with acid in the presence of sulphur nucleophiles such as mercaptoacetic acid,[10] thiophenol[11] and toluene-α-thiol[12] has permitted the isolation of flavanoid monomers. The separation of various oligomeric components of condensed tannins has also been achieved. Some of these components have been unambiguously identified as carbon-carbon linked dimers of (+)-catechin (VII), (-)-epicatechin (VIII) and, less commonly, other polyhydroxyflavan-3-ols.[13,14,15]

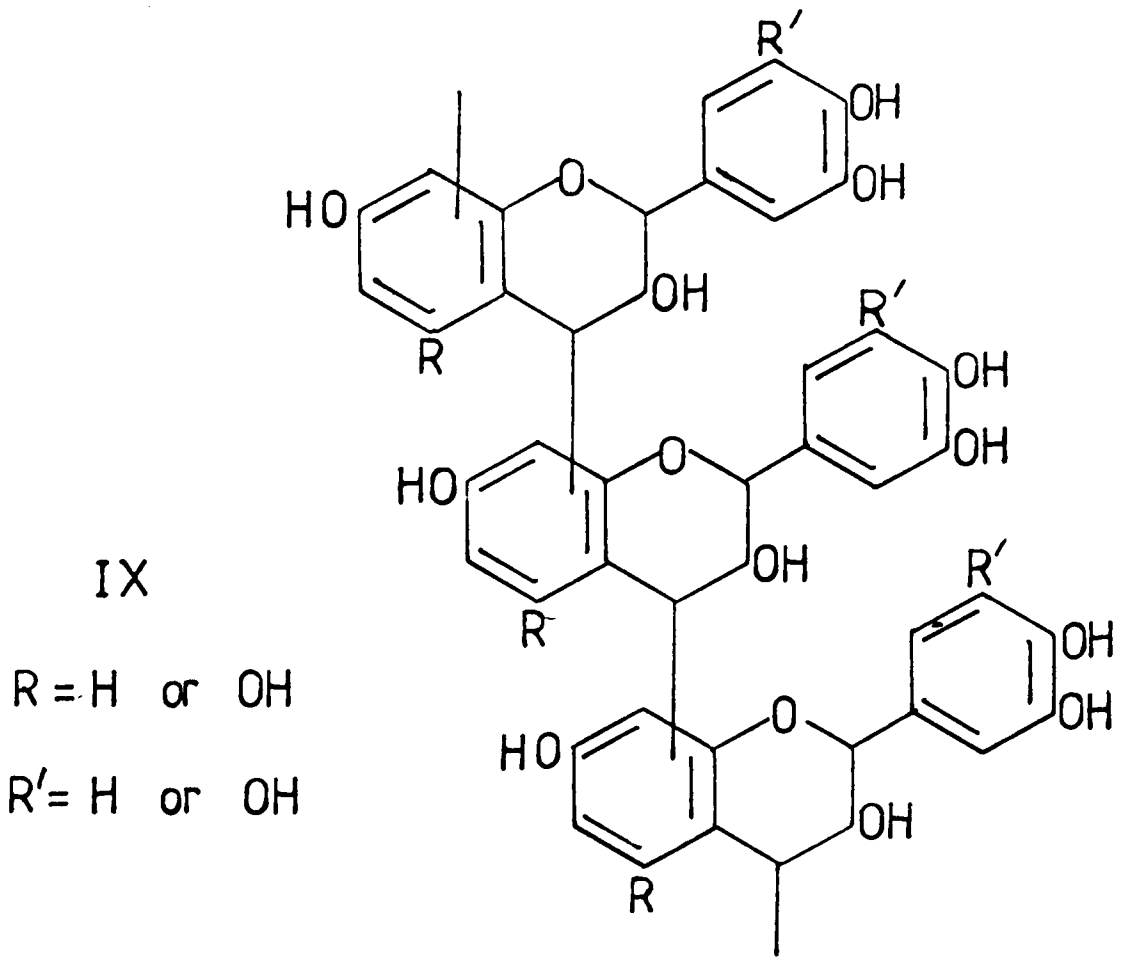


VII



VIII

This success has led to the view expressed by a recent reviewer[16] that condensed tannins are made up of carbon-carbon linked flavanoid polymers of the general form (IX).



IX

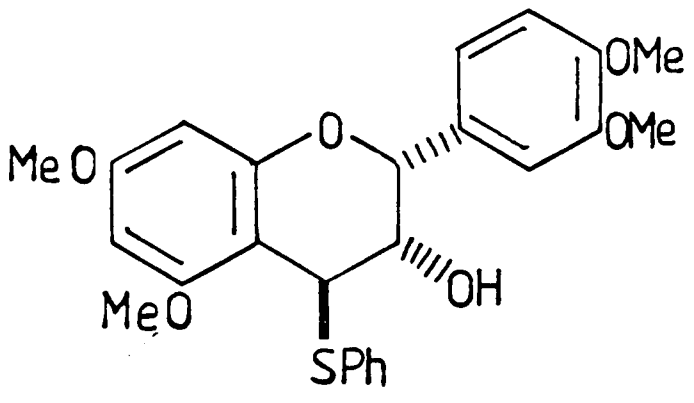
R = H or OH

R′ = H or OH

Earlier investigators had attempted to assay free phenolic and alcoholic hydroxyl groups in tannins by methylation, acetylation and spectroscopic techniques and inferred that ether links must be present in the polymers.[17-20] Some of these results have been reversed by further work[13,14,21] and most now seem so inconclusive that they are ignored (for example, by Haslam in his review[16]).

However, there is more weighty evidence for the presence of ether links in one tannin in particular, that from common heather (Calluna vulgaris). Degradation of the tannin on heating in the presence of thiophenol occurred in the absence of acid, whereas other tannins were degraded only when acid was added to the mixture.[11] This ready cleavage, to give after methylation the thioether (X), was interpreted as implying highly labile ether rather than carbon-carbon linkages in the polymer. In addition, ozonolysis of this tannin and

permethylation yield dimethyl trimethoxyglutarate (XI),[10] suggesting the presence of oxygen substituents on C-2, C-3 and C-4 of the original flavanoid nuclei.



X

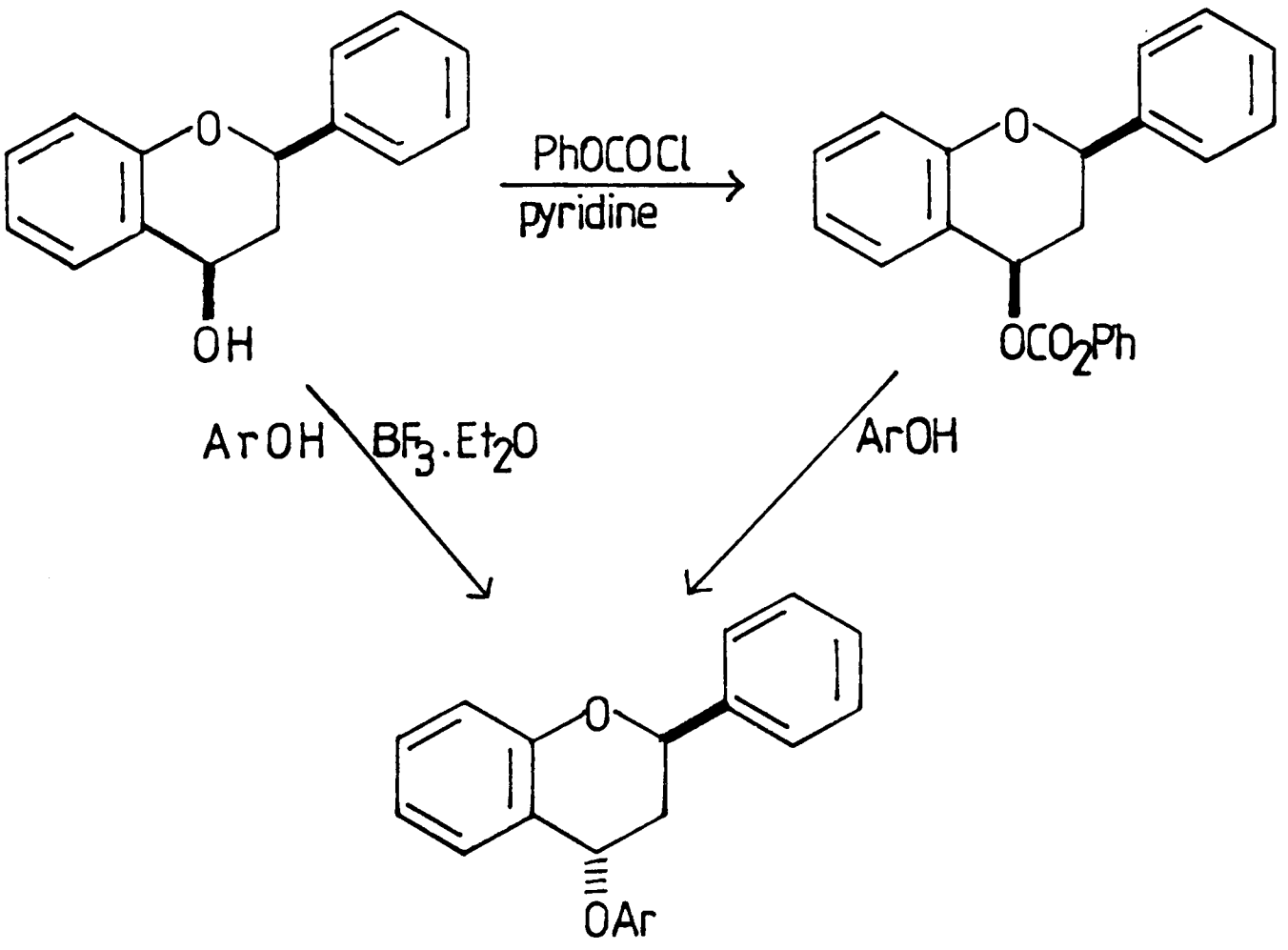
XI

O'Neill[22] further showed that the degradability of Calluna tannin depended on how it had been extracted, concluded that the chemical constitution of the tannin could be altered during the extraction process and suggested that carbon-carbon linked polymers might be merely artefacts, tannins existing in vivo in an ether-linked form.

If this suggestion is to be seriously entertained for those condensed proanthocyanidins isolated from natural sources which have been identified with certainty as carbon-carbon linked, then it is necessary to show that their assumed ether linked precursors have sufficient stability to exist in plants but sufficient reactivity to isomerise during extraction (e.g. maceration at room temperature with aqueous acetone). To this end studies on the synthesis of 4-aryloxyflavans, intended to serve as model compounds for ether linked polymers, have been made.[22-26] Substitution at the 4-position in particular is relevant because this position in highly substituted

flavanoids is the most susceptible to nucleophilic substitution,[11] the isolated carbon-carbon linked oligomers are known to be polymerised through this position and the Calluna degradation product (X) has a phenyl sulphide substituent at this position, marking it as the site of linkage in Calluna tannin.

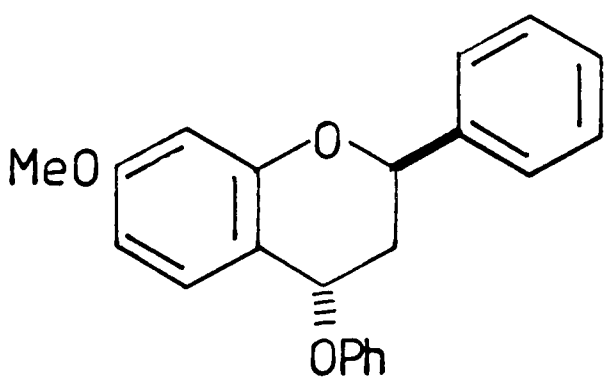
Bateman[23] synthesised 4α-aryloxyflavans by coupling flavan-4β-ol with phenols either under catalysis with boron trifluoride etherate or via flavan-4β-yl phenyl carbonate (scheme 1).



Scheme 1

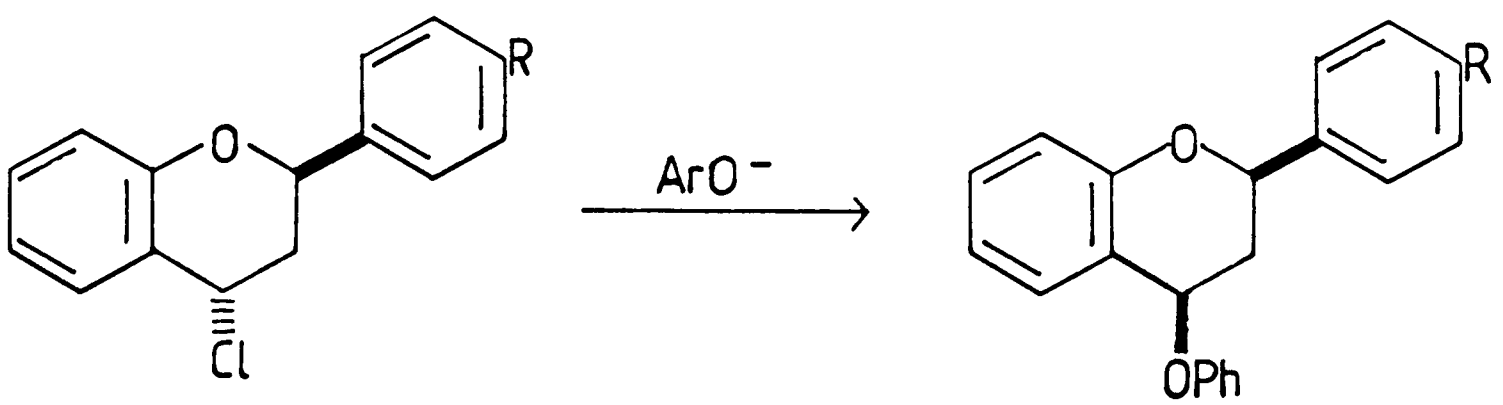
Bateman prepared aryloxyflavans from a variety of phenols but was unable to extend his methods to convert 7-methoxyflavan-4β-ol into aryloxy derivatives. Further studies by Johnson[24] confirmed that the carbonate route was unsatisfactory for

7-methoxy substituted 4-aryloxyflavans: 7-methoxyflavan-4β-yl phenyl carbonate could not be isolated. An attempt to prepare this carbonate and allow the crude material to react with phenol gave only 4% of 4α-phenoxy-7-methoxyflavan (XII).



XII

Smart[25] prepared 4α-chloroflavan and 4α-chloro-4'-methoxyflavan and showed that they reacted with phenate anions to give 4β-aryloxyflavans (scheme 2). 4α-Chloro-7-methoxyflavan could not be isolated, but the crude compound treated with potassium phenate afforded after chromatography a mixture of 4α- and 4β-phenoxy-7-methoxyflavans, identified by its nuclear magnetic resonance spectrum.

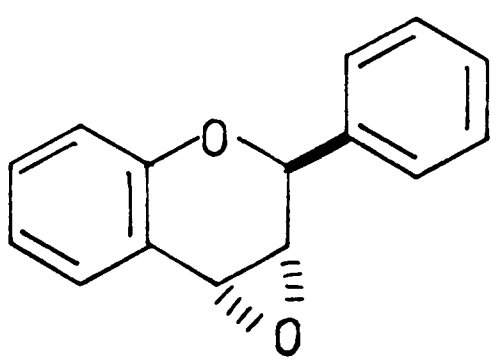


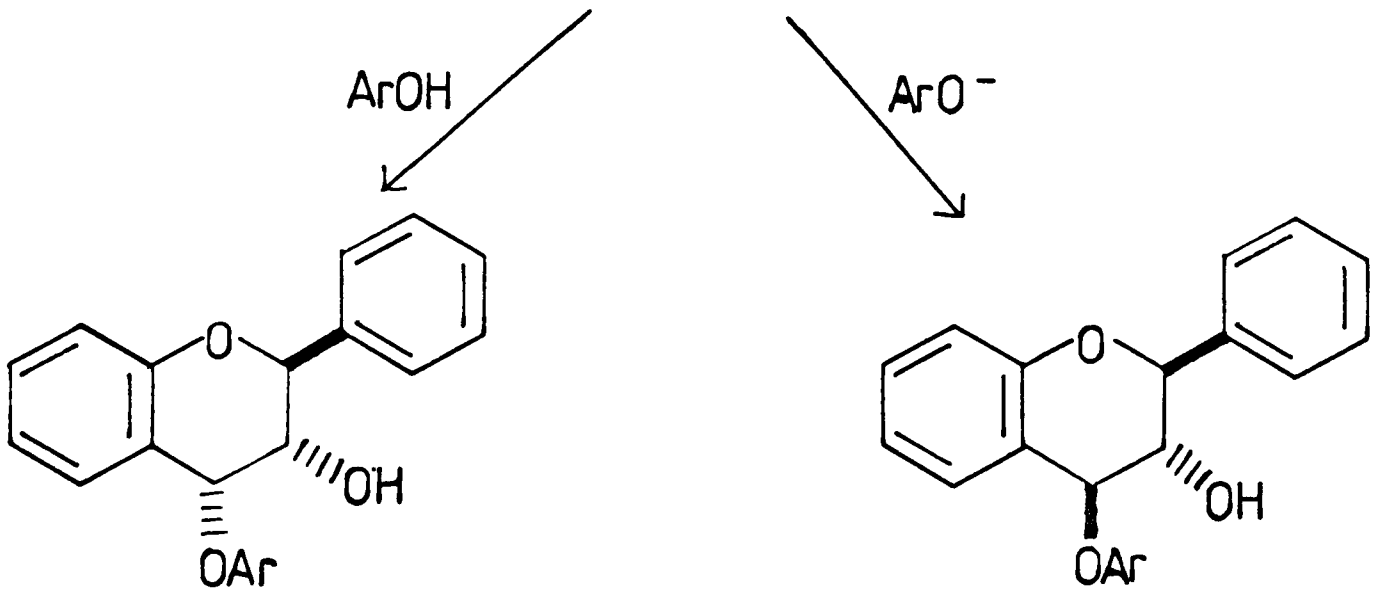
Scheme 2

Smart's synthesis gave low yields (20-30%). Higher yields were obtained by Kahn[26] using phase transfer catalysis.

Quaternary ammonium ions were added to a two-phase reaction mixture to convey phenate anion from aqueous solution into dichloromethane containing dissolved chloroflavan.

Shaw[27] caused 2,3-trans-3,4-epoxyflavan to react with phenols giving 3,4-cis-4-aryloxyflavan-3-ols, and with phenate anions giving 3,4-trans-4-aryloxyflavan-3-ols (scheme 3). O'Neill[22] was unable to extend this method to synthesise 7-methoxy-4-aryloxyflavan-3-ols because the necessary epoxide could not be isolated, but by generating the 2,3-cis-epoxide in the presence of sodium phenate he obtained the aryloxy compound (XIII).

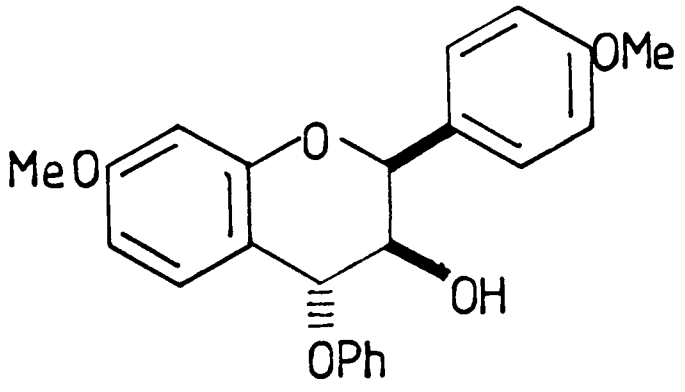




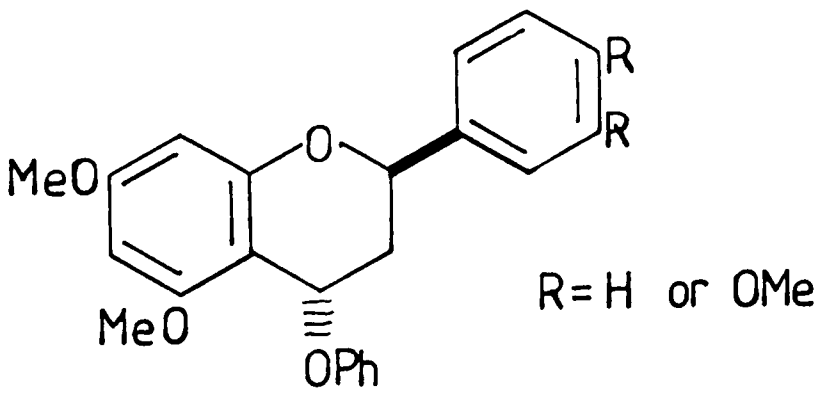
Scheme 3

O'Neill[22] attempted to prepare more highly substituted aryloxyflavans by direct reaction of flavan-4β-ols and flavan-3,4-diols with phenol in an inert solvent. He reported

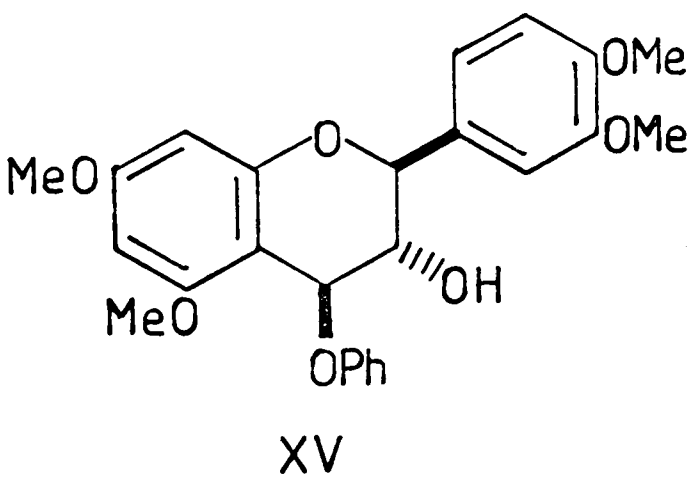
the syntheses in very low yields of the aryloxyflavans (XIV), (XV) and (XVI).



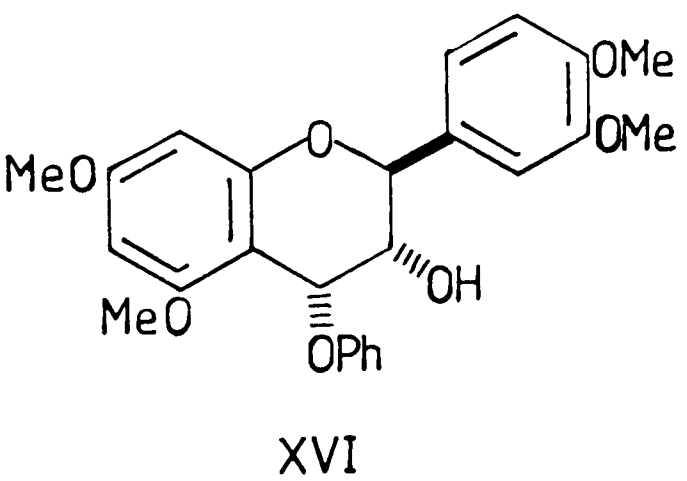
XIII



XIV



XV



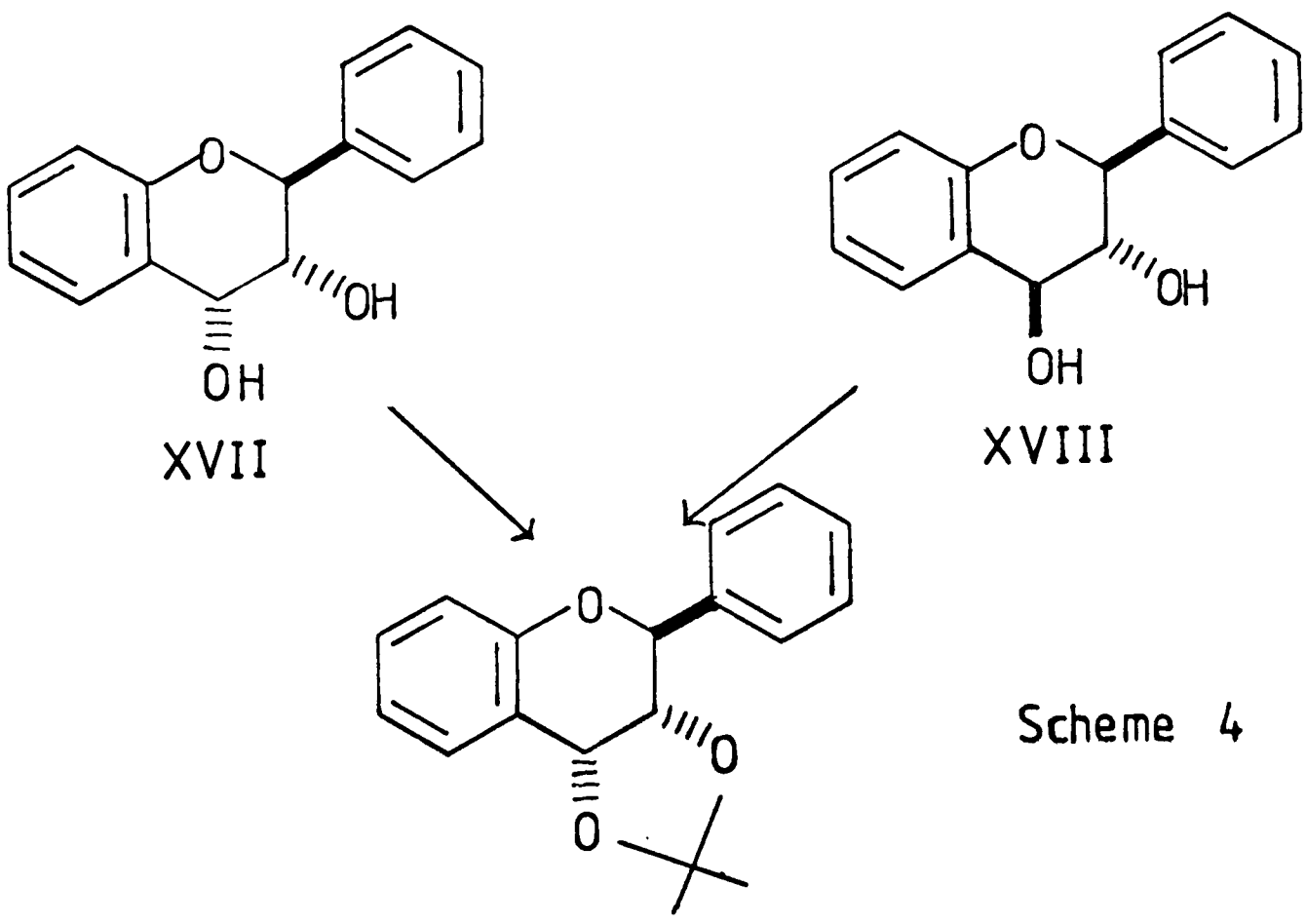
XVI

These attempts to prepare aryloxyflavans demonstrate that the presence of electron-donating substituents in the A-ring of flavans greatly affects the course of nucleophilic substitutions. The chemical literature contains many other examples of reactions of simple 4-substituted flavans which, when they were applied to more highly substituted flavans gave results which surprised, disappointed or misled investigators. Some of these examples are worth describing as illustrations of the need for more careful study of the reactivities towards nucleophiles of highly substituted flavans.

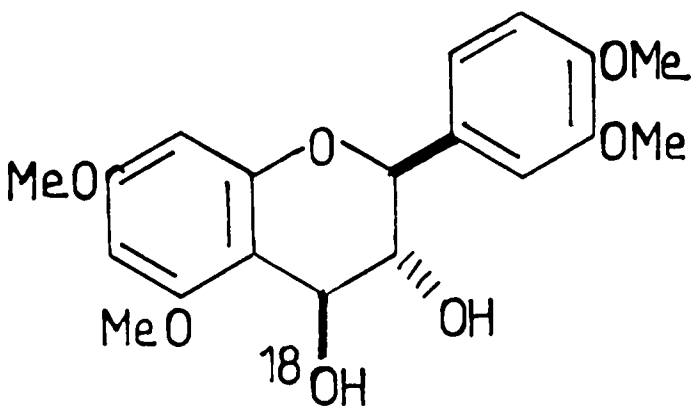
Some unexpected reactions of 4-substituted flavanoids with nucleophiles.

The stereochemistry of flavan-3,4-diols has been a source of much confusion. Assignments of cis or trans stereochemistry to the two hydroxyl groups have been based on the ease of formation of cyclic derivatives and on n.m.r. spectra of other derivatives and of the diols themselves. When interpretations of the proton magnetic resonance spectra of the diols have been made, stereochemistry has been correctly assigned on the basis of coupling constants.[28] But during the preparation of derivatives inversion of configuration at the 4-position may occur, leading to derivatives whose stereochemistry is different from that of their diol precursors.

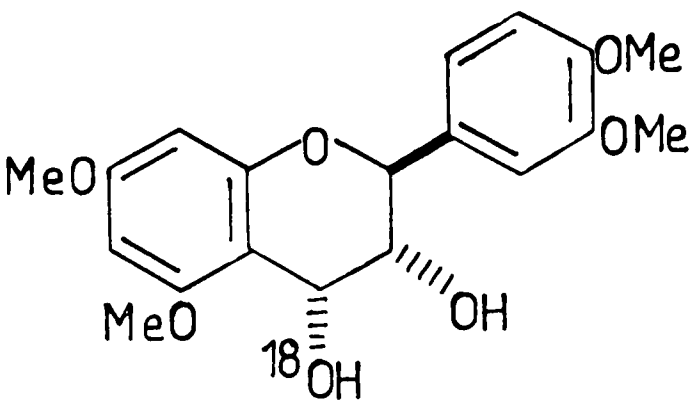
Bokadia[29] et al. showed that 2,3-trans-3,4-cis-flavan-3,4-diol (XVII) formed an isopropylidene derivative readily and in high yield. 2,3-Trans-3,4-trans-flavan-3,4-diol (XVIII), however, formed the same derivative (by inversion of configuration at the 4-position) but in low yield (scheme 4).



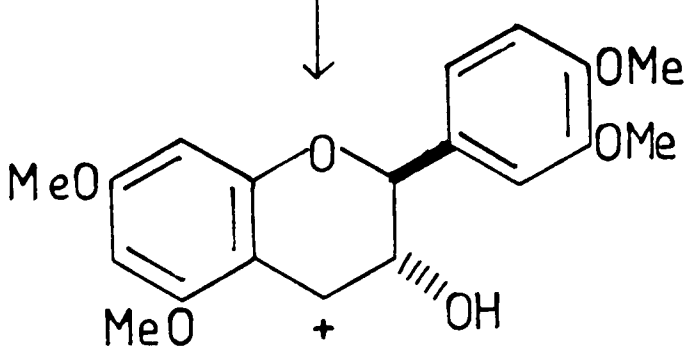
Scheme 4

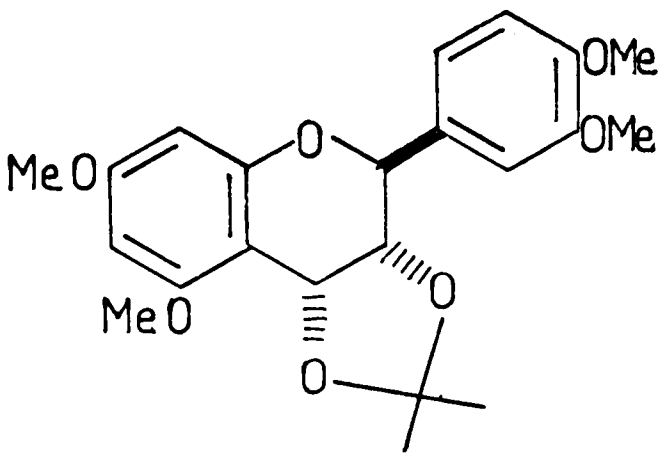


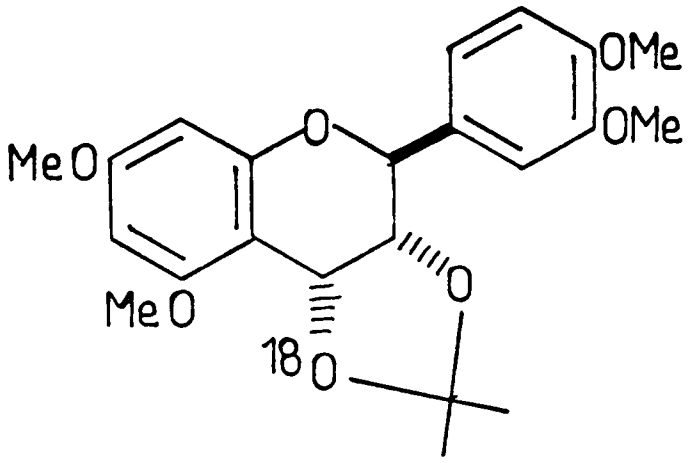
XX



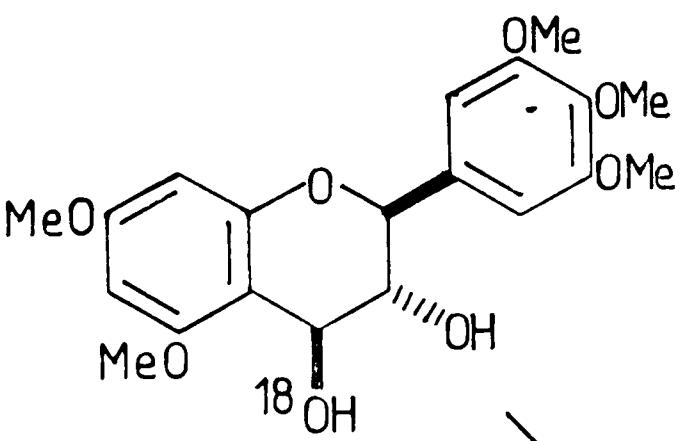
XIX

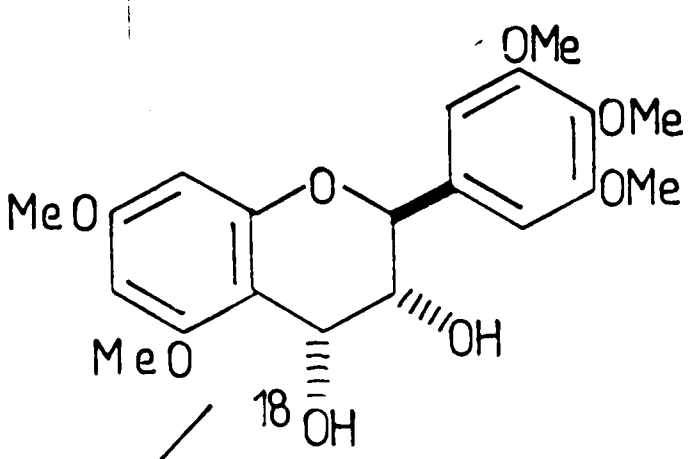


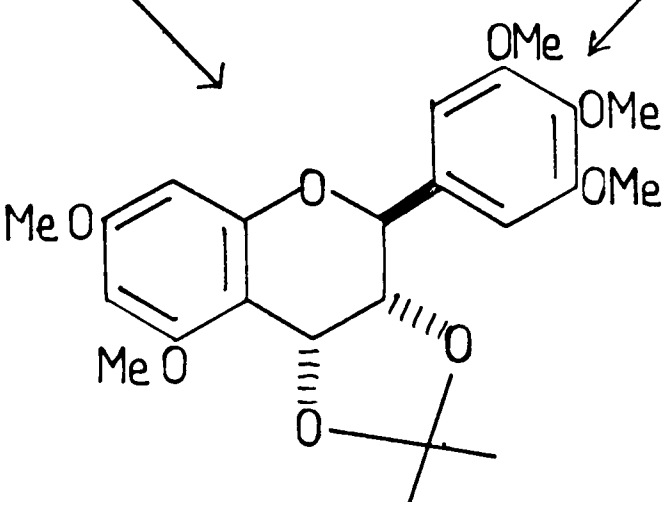




Scheme 5







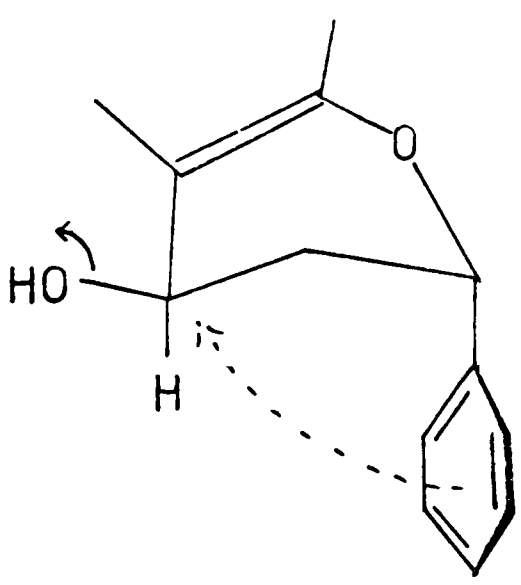
Scheme 6

Fujise *et al.*[30] investigated the formation of isopropylidene derivatives by 2,3-*trans*-3,4-*cis*-5,7,3',4'-tetramethoxyflavan-3,4-diol (XIX) and its 4-epimer (XX). They found that the two diols readily formed the same isopropylidene derivative in high yield. By isotopic labelling, Hishida and co-workers[31] showed that the 3,4-*trans*-diol (XX) lost its original 4-oxygen atom substituent on conversion to an isopropylidene derivative, while the 3,4-*cis*-diol (XIX) retained its 4-oxygen substituent. The epimerisation of the 3,4-*trans*-diol (XX) was thought to occur *via* a 4-carbocation stabilised by electron release from the 5- and 7-methoxyl substituents (scheme 5). On the other hand, investigation of the analogous conversions of the 5,7,3',4',5'-pentamethoxyflavan-3,4-diols showed that with this substitution pattern, even the 3,4-*cis*-diol lost its 4-oxygen substituent during formation of an isopropylidene derivative (scheme 6).

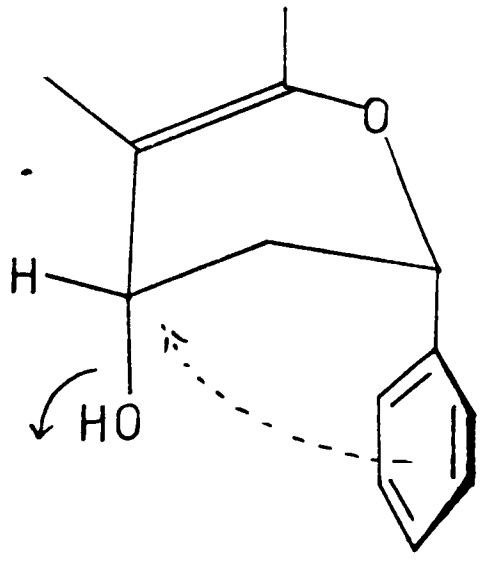
Hishida *et al.*[31] offered no explanation of this labilising effect on a 4-substituent of further methoxyl substitution in the B-ring. However Betts[32] suggested that the π-electrons in a flavan B-ring might stabilise a 4-carbocation, and Shaw[27] extended this hypothesis by proposing that the B-ring could render anchimeric assistance during departure of the 4-substituent to form a 4-carbocation (scheme 7). According to this mechanism, increased methoxyl substitution in the B-ring should increase its electron density and aid departure of the leaving group.

Smith's study[33] of the effect of B-ring substitution on lability of the 4-substituent undoubtedly confirms this effect

for the 2,4-trans-4-aryloxyflavans he investigated, though Shaw's[27] mechanism is unconvincing for 2,4-cis-compounds since it amounts to S_Ni attack with retention of configuration (scheme 7).



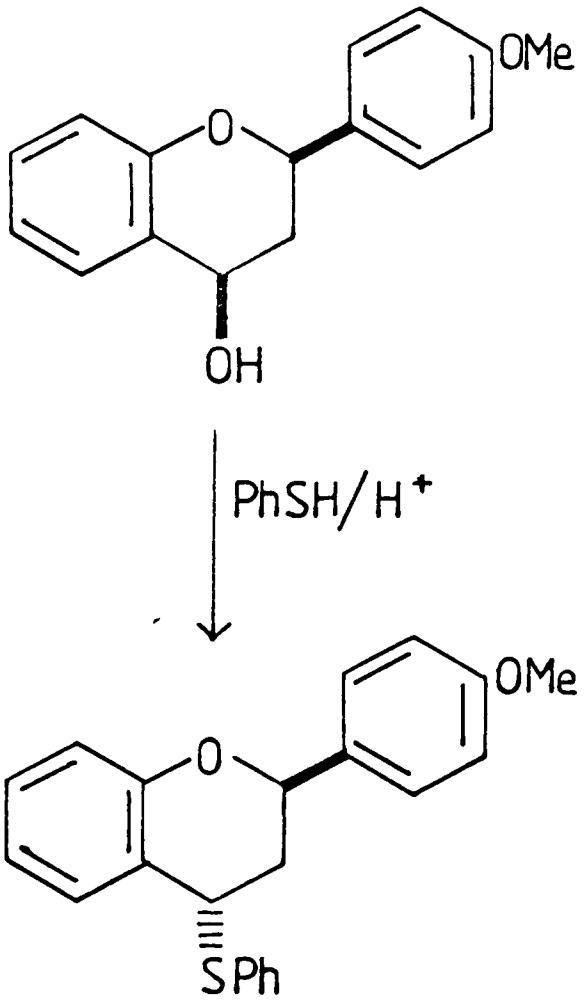
2,4-trans: Acceptable

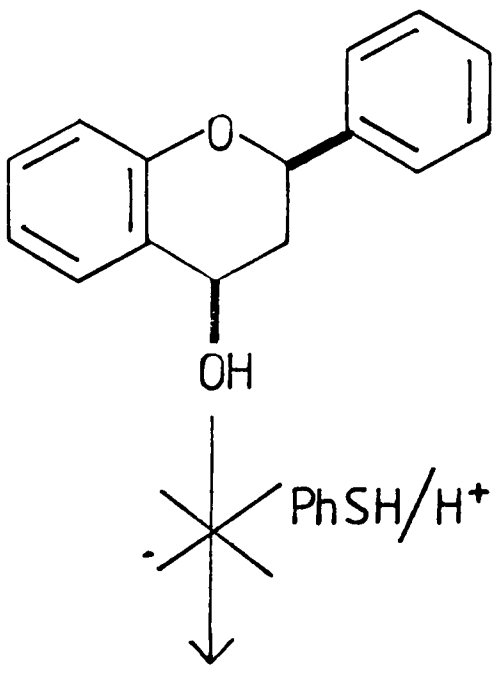


2,4-cis: Unacceptable

Scheme 7

Indeed, Campbell[34] discovered that 2,4-cis-4-phenoxyflavan solvolysed in aqueous acidic ethanol at only half the rate of 2,4-trans-4-phenoxyflavan and commented that for 2,4-cis-stereochemistry anchimeric assistance by the B-ring would be hindered. Nevertheless, Brown and Shaw[11] report an example of a striking difference in reactivity between flavan-4β-ol and 4'-methoxyflavan-4β-ol, which they attribute to just this effect. Under conditions in which 4'-methoxyflavan-4β-ol reacts with thiophenol to give 68% of 4α-thiophenoxy-4'-methoxyflavan, flavan-4β-ol is said to undergo negligible reaction (scheme 8).

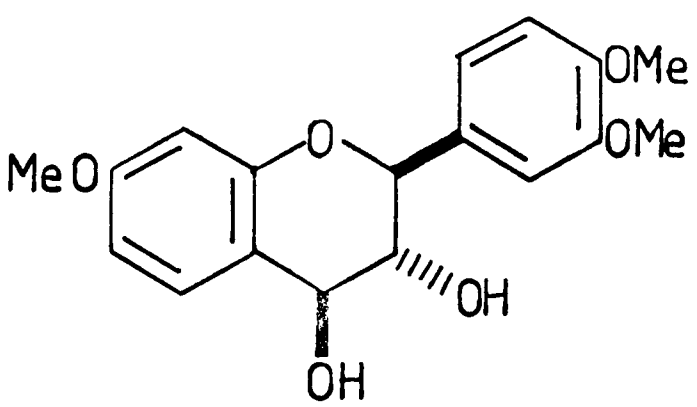




Scheme 8

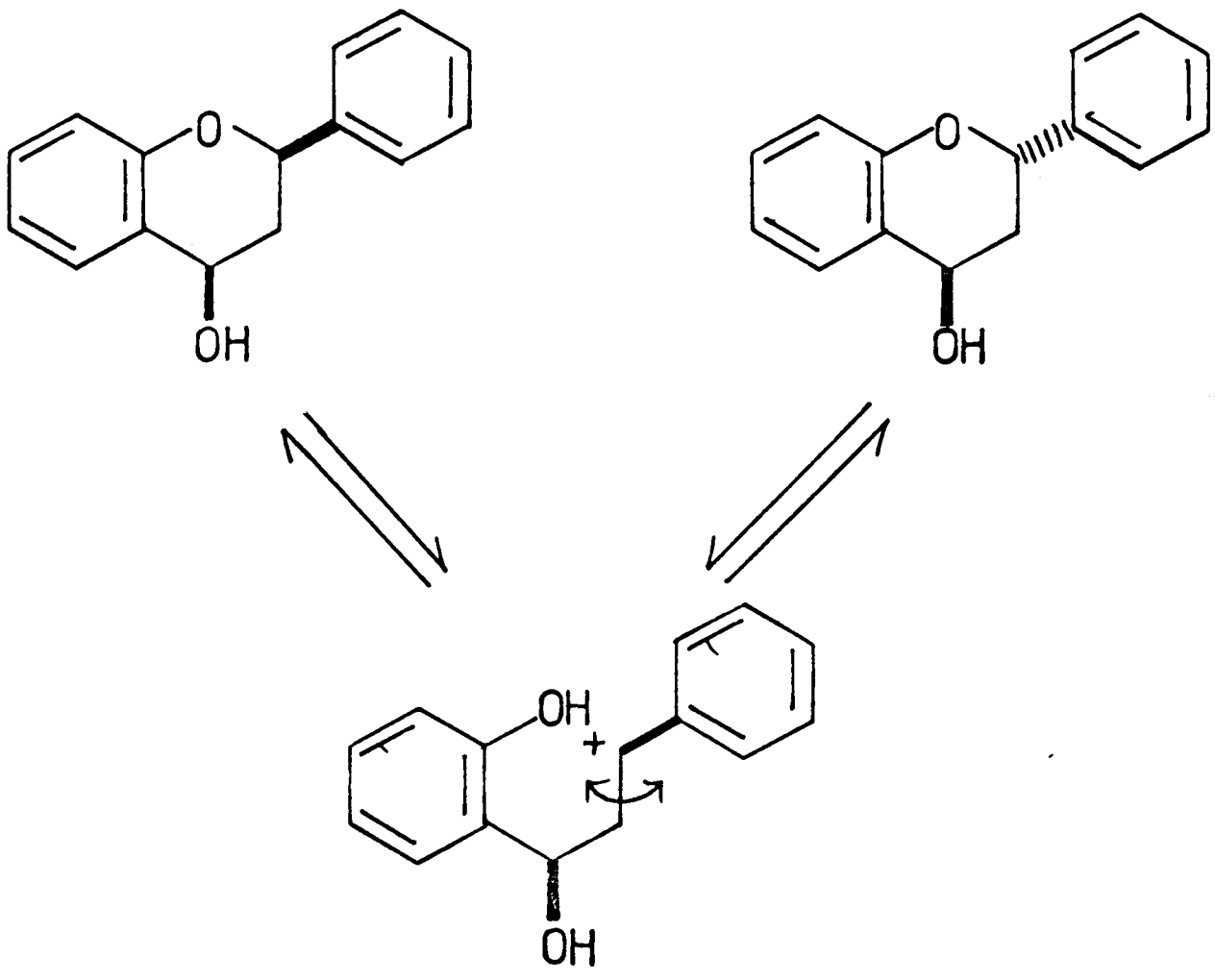
A different type of mechanism for nucleophilic substitutions was postulated by Clark-Lewis and Williams.[35] They report that diols such as 2,3-trans-3,4-trans-7,3',4'-trimethoxyflavan-3,4-diol (XXI) when treated with ethanol containing 2% of hydrochloric acid undergo epimerisation at the 4-position before reacting with the ethanol.

XXI



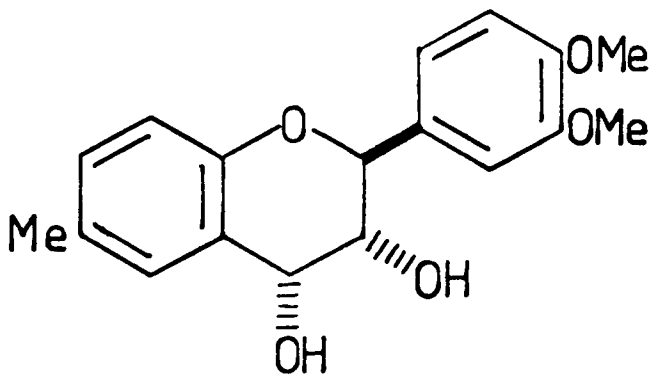
Epimerisation was suggested as taking place *via* a tight ion-pair to form the thermodynamically more stable 2,3-*trans*-3,4-*cis*-diol. However, these authors followed the reactions by thin-layer chromatography and the possibility of hydrolysis on a moist chromatographic plate cannot be ruled out.

Bateman[23] invoked the tight ion-pair mechanism to explain the conversion of flavan-4β-ol to flavan-4α-ol by dry ethanolic hydrogen chloride. The alternative mechanism for the latter conversion, involving epimerisation at the 2-position, is less plausible because it proceeds by cleavage of the heterocyclic ring and formation of a carbocation less stable than the 4-carbocation (scheme 9). Experimental evidence against it is lacking, though.

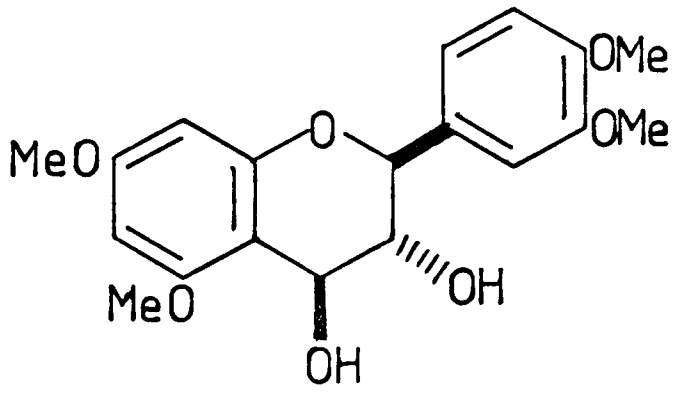


Scheme 9

Acetates have proved convenient derivatives of flavan-3,4-diols for nuclear magnetic resonance studies,[28] but two examples of acetylation by acetic anhydride in the presence of acetic acid and sodium or potassium acetate indicate the need for caution in assuming the same stereochemistry for the diol and the diacetate prepared from it. Clark-Lewis and Williams[36] took 2,3-trans-3,4-cis-6-methyl-3',4'-dimethoxyflavan-3,4-diol (XXII) and by acetylation with the reagents mentioned above obtained 2,3-trans-3,4-trans-diacetoxy-6-methyl-3',4'-dimethoxyflavan (XXIII). Yet Fujise and co-workers,[37] starting from 2,3-trans-3,4-trans-5,7,3',4'-tetramethoxyflavan-3,4-diol (XXIV) obtained under these conditions the corresponding 2,3-trans-3,4-cis-diacetate (XXV).



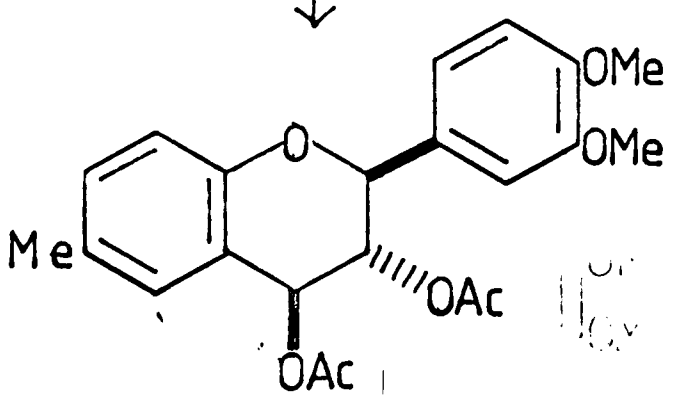
XXII



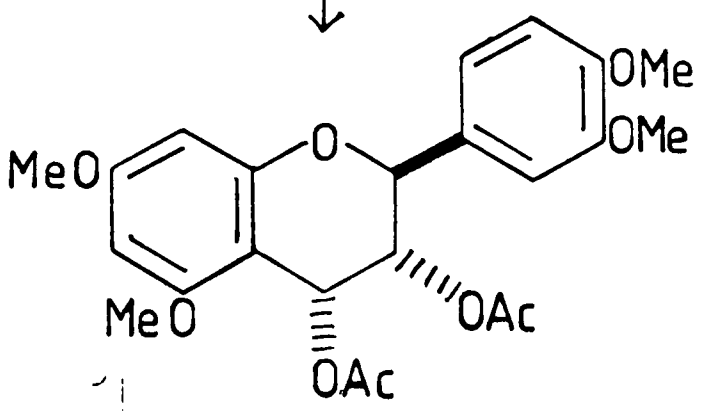
XXIV

$Ac_2O/AcOH$
KOAc

$Ac_2O/AcOH$
NaOAc

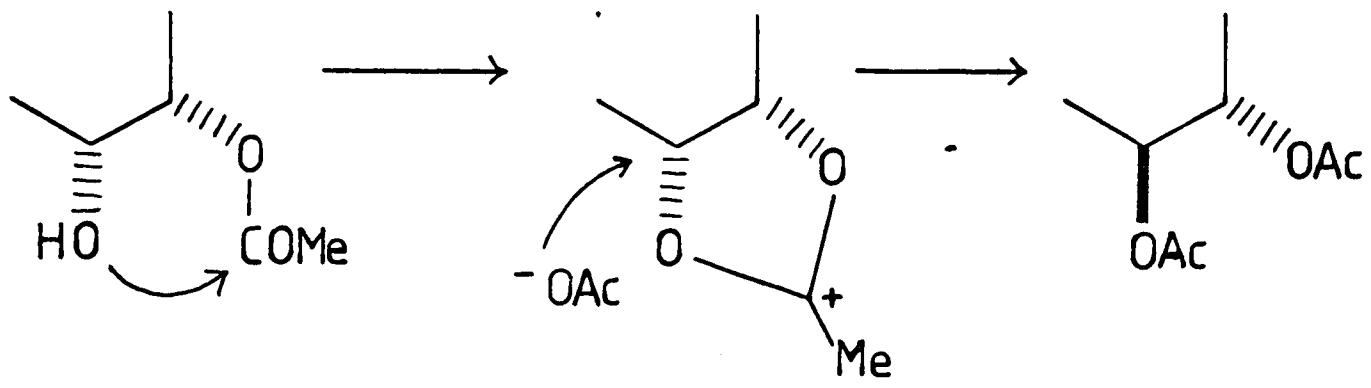


XXIII



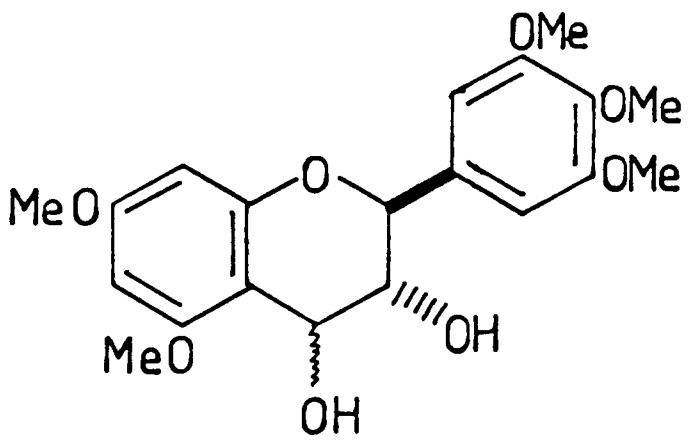
XXV

The latter transformation was rationalised as occurring *via* the familiar 4-carbocation with the eventual formation of the thermodynamically more stable 3,4-*cis* isomer of the diacetate. The other transformation was explained by the sequence (scheme 10):



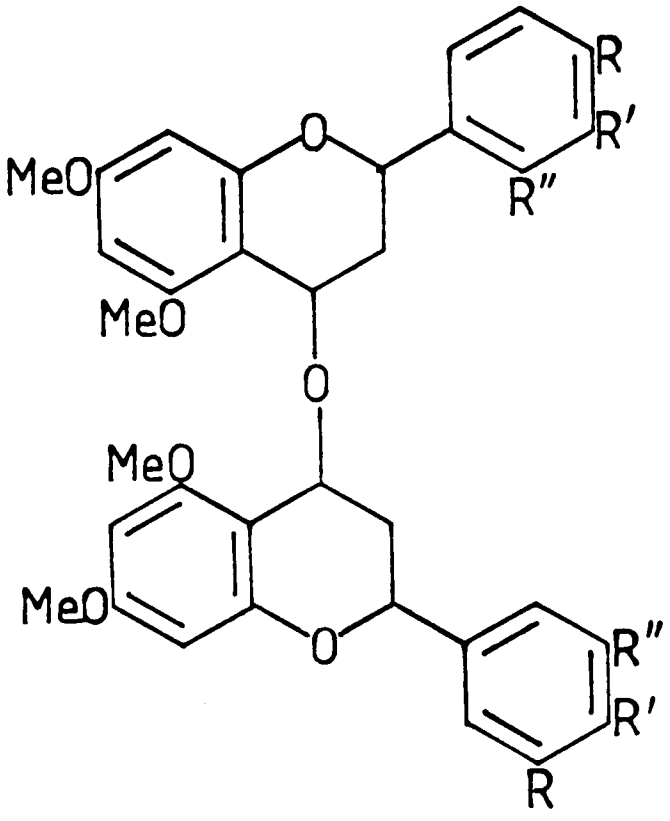
Scheme 10

Acetylation of either of the above diols (XXII) or (XXIV) with acetic anhydride/pyridine yields the expected diacetate of unchanged stereochemistry,[36,37] but once again an extra methoxyl substituent in the B-ring alters the course of reaction and the 3,4-*cis* and 3,4-*trans* isomers of 2,3-*trans*-5,7,3',4',5'-pentamethoxyflavan-3,4-diol (XXVI) afford a single diacetate with acetic anhydride/pyridine.[37]



XXVI

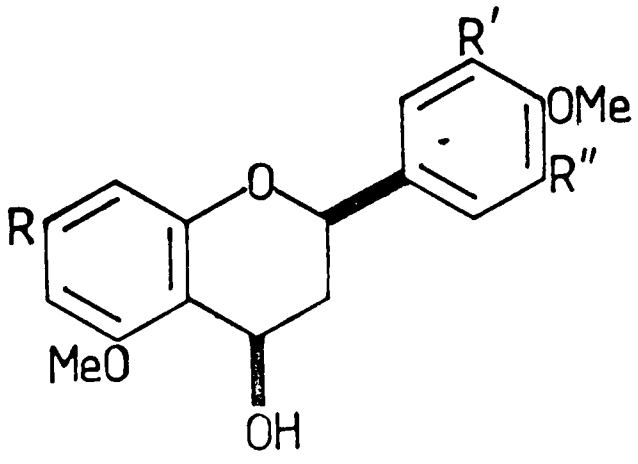
Krishnamurthy *et al.*[38] were taken aback to find that 5,7,3',4'-tetramethoxy- and 5,7,4'-trimethoxyflavan-4β-ols



XXIX R = R'' = H ; R' = OMe

or R = H ; R = R'' = OMe

or R = R' = R'' = OMe



XXX R = R' = R'' = H

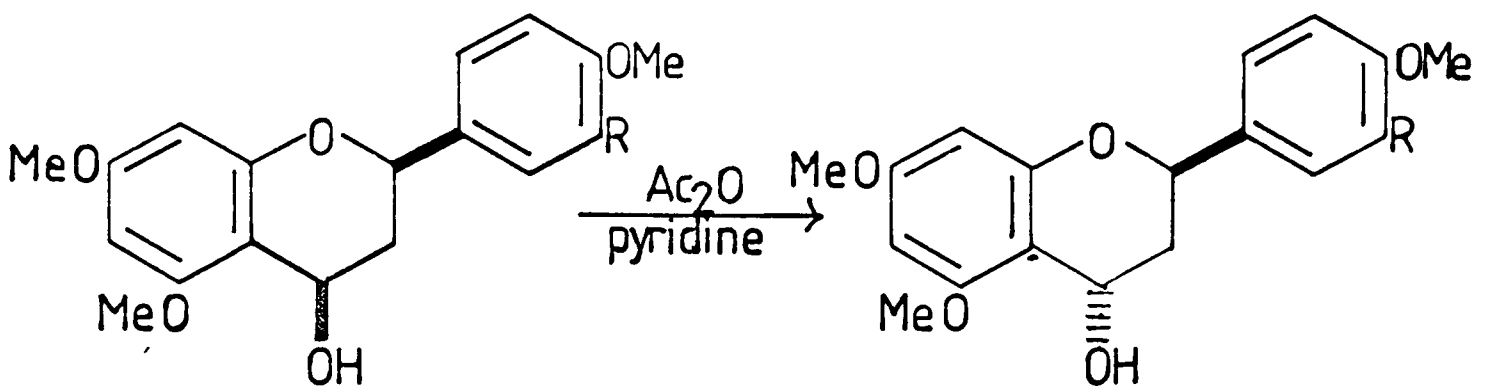
or R = R' = H ; R'' = OMe

or R = OMe ; R' = R'' = H

or R = R'' = OMe ; R' = H

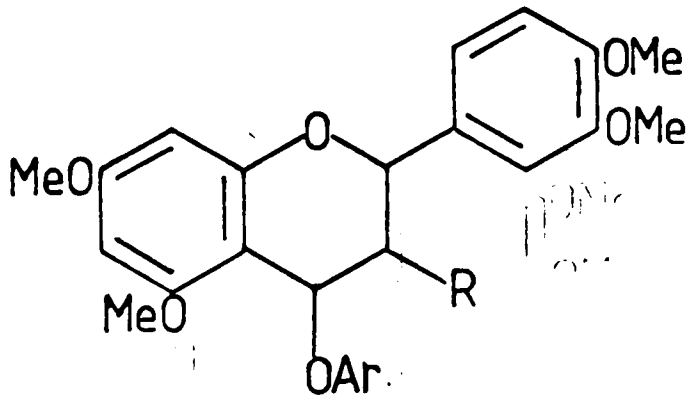
or R = R' = R'' = OMe

(XXVII, R=OMe and R=H, respectively) gave no acetate at all with acetic anhydride/pyridine, affording instead the corresponding flavan-4α-ols (XXVIII, R=OMe and R=H).

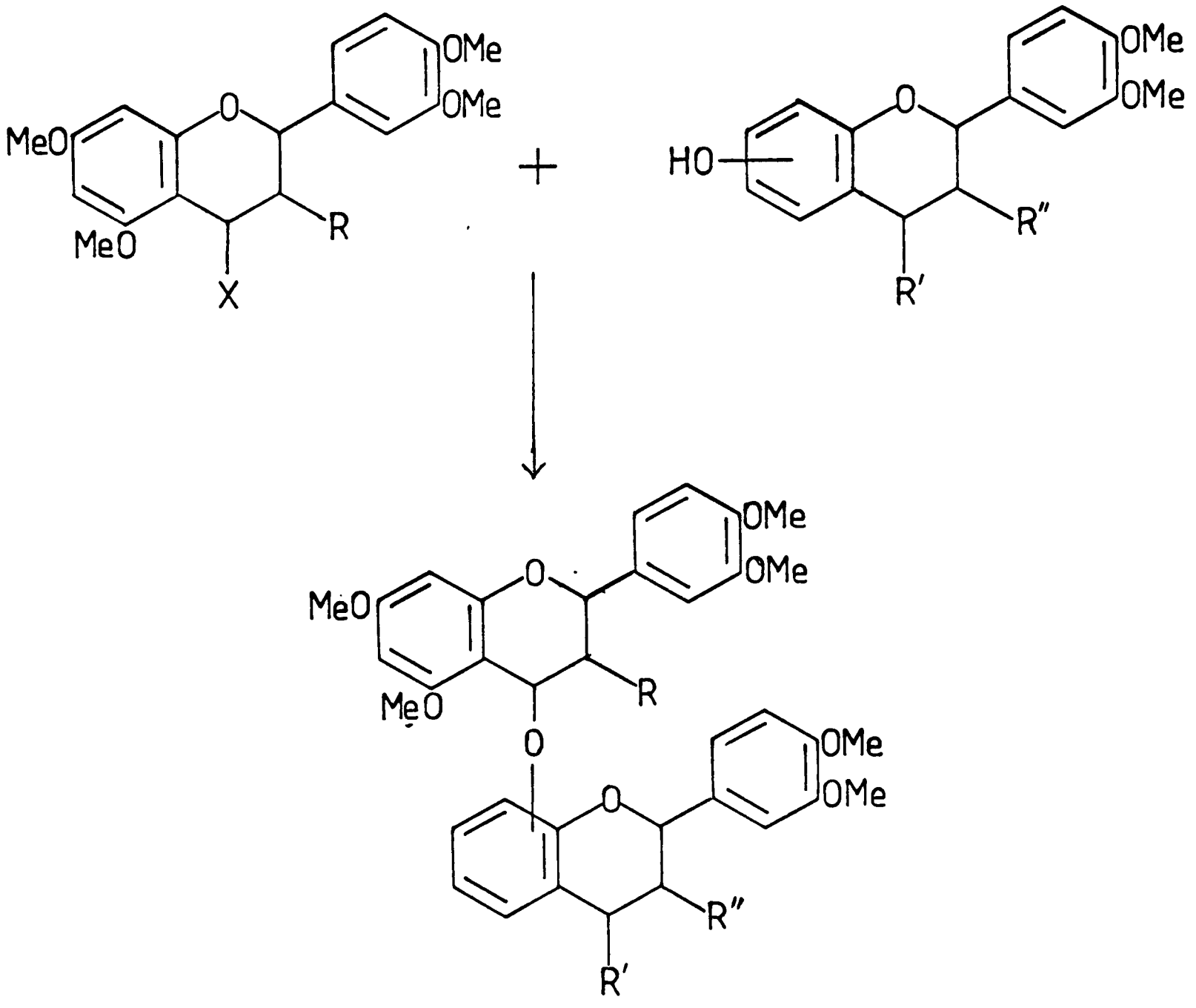


XXVII XXVIII

These authors argued that steric hindrance had prevented the formation of the acetate and proposed a mechanism for the epimerisation resembling the tight ion-pair scheme. They did not comment on the role of the acetic anhydride or pyridine. Kamat et al.[39] with the same reagent obtained the bis-flavanyl ethers (XXIX). These workers found that phosphorus tribromide also effected formation of the bis-flavanyl ethers (XXIX), but in another paper[40] they reported the use of phosphorus tribromide to convert the flavan-4β-ols (XXX) into flavan-4α-ols by hydrolysis of the assumed intermediate bromides with ethanolic potassium hydroxide. The whole process was explained[40] as the formation of a 4β-bromide followed by S_N2 hydrolysis. However, halides formed under the conditions of Kamat et al.[40] have been shown to possess 4α-stereochemistry,[25] so that the hydrolysis must occur with retention of configuration hence, presumably, by an S_N1 mechanism. The fact that the flavan-4α-ols were obtained in good yield without any



XXXI



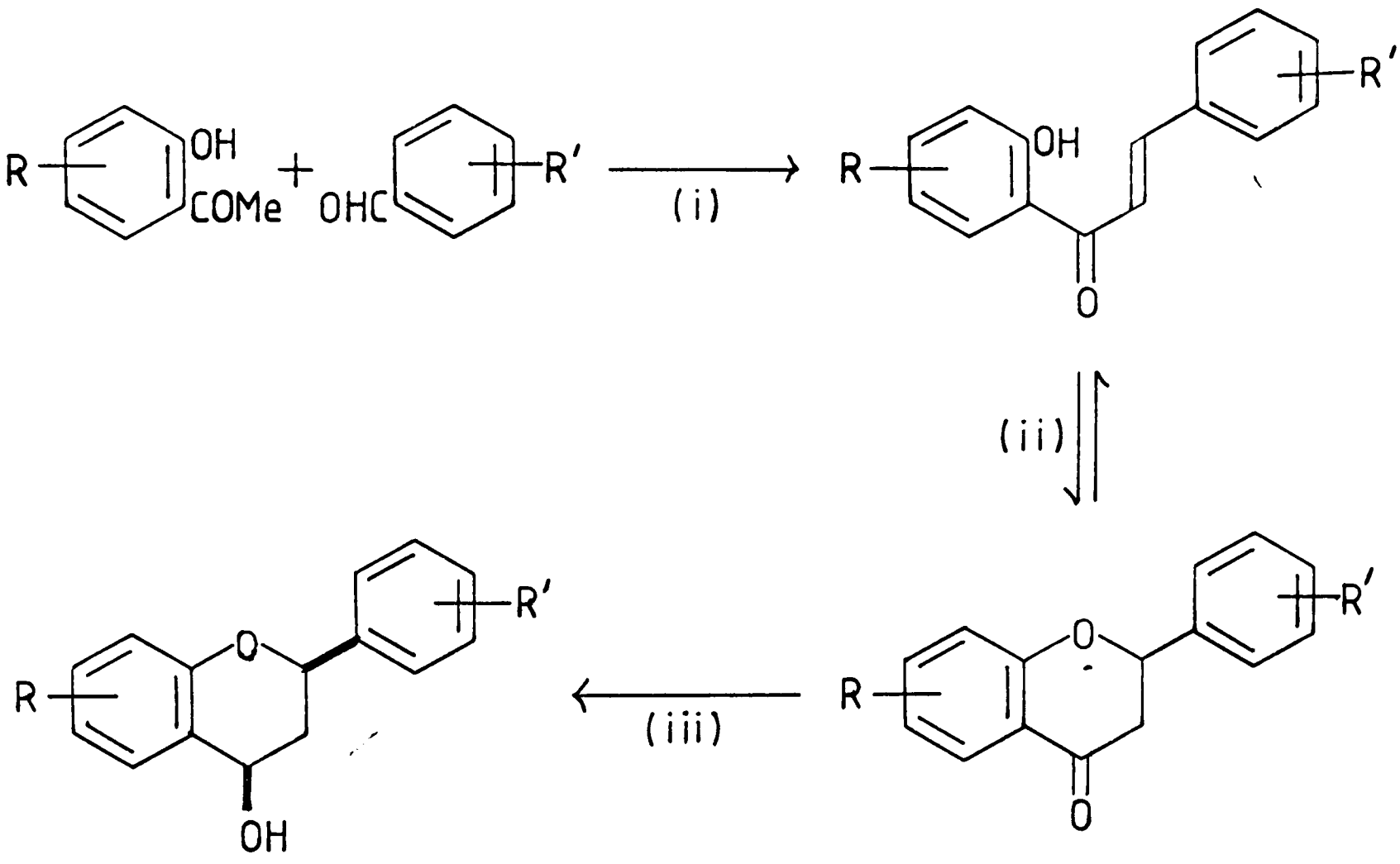
Scheme 11

4-ethoxyflavans being observed implies exceptional selectivity of the intermediate 4-carbocation towards hydroxide ion in the presence of a large excess of ethanol.

The aims of the present work

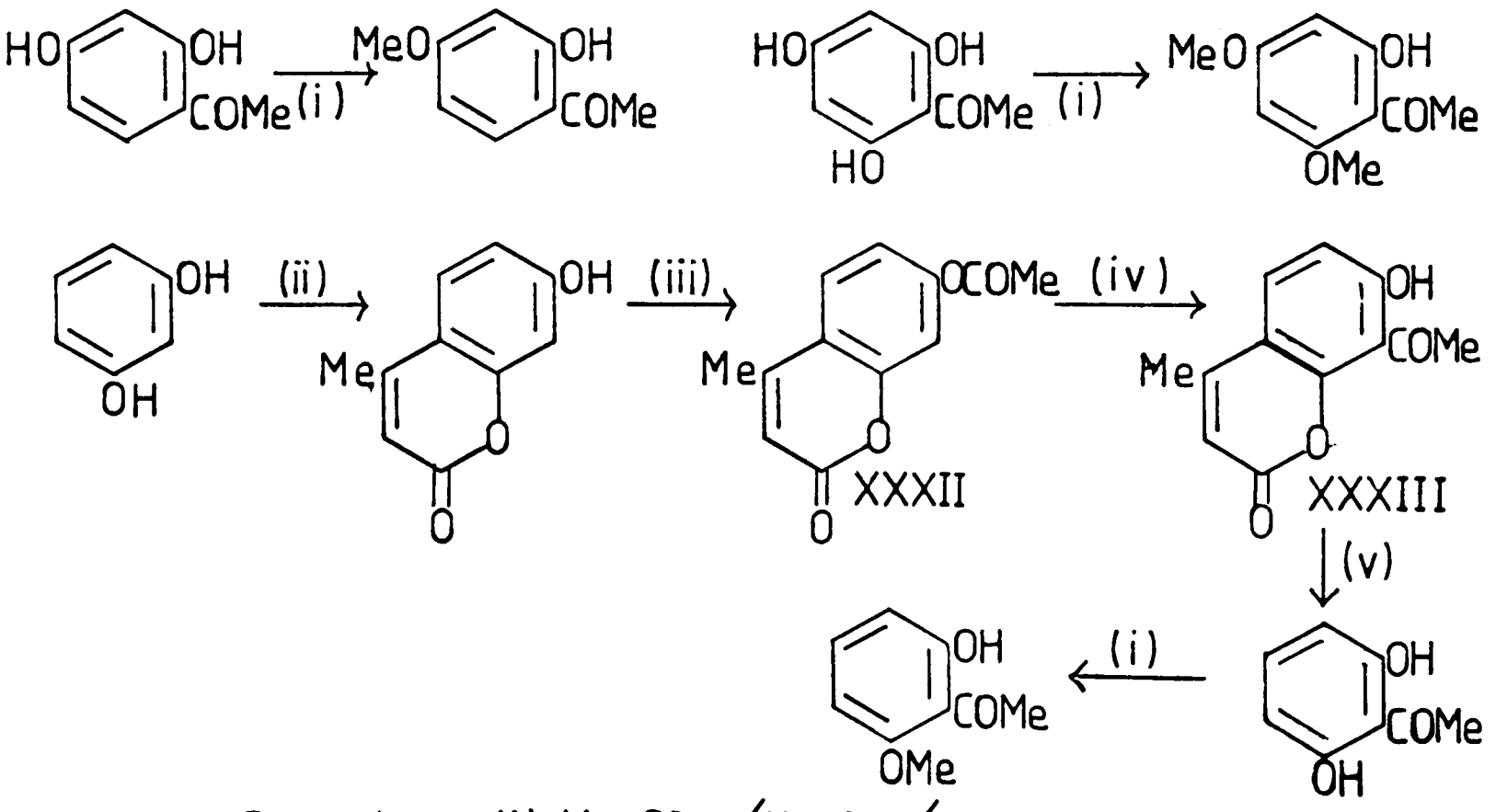
It was the intention of the present author to study the reactivity at the 4-position towards nucleophiles of flavanoids of various substitution patterns. It was hoped that this study would enable the reactions of highly substituted flavanoids to be understood and predicted, and that synthetically useful transformations would be developed. It was then desired to use this knowledge to synthesise 4-aryloxyflavans of the type (XXXI), because of the common natural occurrence of the cyanidin aromatic substitution pattern.

The final target of the research was to be the synthesis of ether-linked flavanoid dimers resembling those suggested as occurring in nature. The strategy envisaged was the reaction of a highly-methoxylated 4-substituted flavan with a suitable monophenolic flavanoid (scheme 11). Previous syntheses of phenolic flavanoids had been very limited in scope. For the present work it would therefore be necessary to devise versatile synthetic routes to flavanoids having a single phenolic hydroxyl group.



Reagents: (i) KOH/EtOH/H_2O
(ii) HCl/EtOH/H_2O or NaOH/H_2O
(iii) $NaBH_4$

Scheme 12



Reagents: (i) Me_2SO_4/K_2CO_3/Me_2CO
(ii) $MeCOCH_2CO_2Et$/H_2SO_4
(iii) Ac_2O (iv) $AlCl_3$
(v) NaOH/H_2O

Scheme 13

CHAPTER 1

Investigations of the reactivity of 4-substituted flavans

Synthesis and reactivity of 4-acetoxyflavans

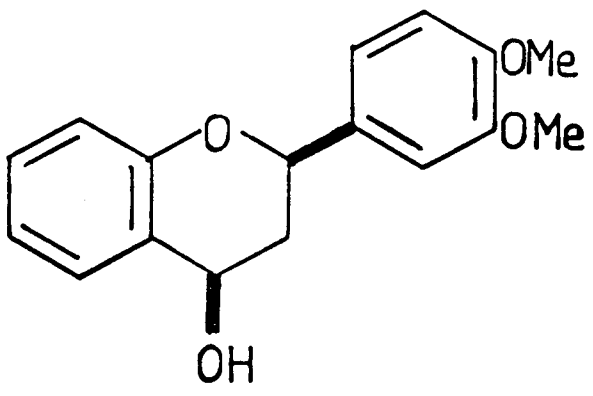
In the introduction some surprising reactions involving highly-substituted 4-acetoxyflavans were discussed. In order to make a systematic study of the effect of substitution pattern on reactivity at the 4-position, which was the first aim of the present work, it was decided to synthesise 4-acetoxyflavans with a range of aromatic substitution patterns. It was hoped that this study would also make it clear why 5,7-dimethoxy substituted flavan-4β-ols gave the anomalous products on attempted acetylation which have already been described.

The desired 4β-acetoxyflavans were to be obtained by acetylation of flavan-4β-ols, prepared by the standard method from appropriately substituted benzaldehydes and o-hydroxy-acetophenones (scheme 12). The preparation of the necessary acetophenones (scheme 13), using reported methods, merits two comments. Firstly, treatment of polyhydroxyacetophenones with dimethyl sulphate in the presence of potassium carbonate methylates all phenolic hydroxyl groups except a single one which is firmly hydrogen bonded to the ortho-carbonyl group. Secondly, the rather inaccessible 2,6-dihydroxyacetophenone was prepared from resorcinol via 7-acetoxy-4-methylcoumarin (XXXII) which undergoes Fries rearrangement to 7-hydroxy-8-acetyl-4-methylcoumarin (XXXIII).

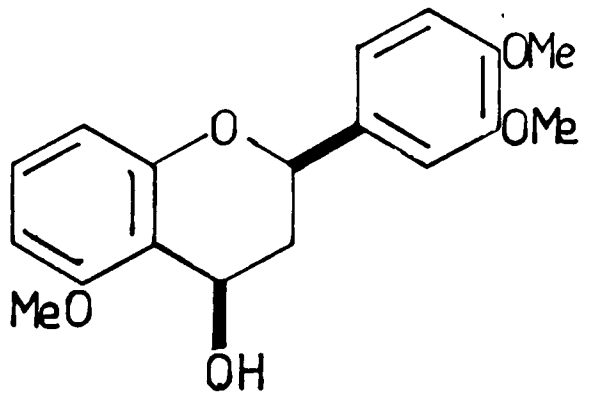
Condensation of the o-hydroxyacetophenone and benz-aldehyde is accomplished in cold alkali. Cyclisation of the resultant 2'-hydroxychalcone occurs on heating with dilute

acid or alkali. The flavanone produced is separated by crystallisation from an equilibrium mixture with the chalcone and reduced stereoselectively with sodium borohydride to give the required flavan-4β-ol. This stereoselectivity in the reduction of flavanones with sodium borohydride is well-attested.[27,41-43] Betts[32] has attributed it to steric hindrance to attack on one face of the carbonyl group by the B-ring of the flavanone.

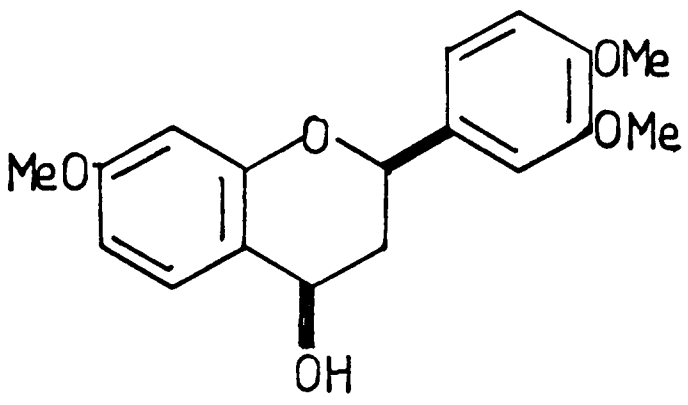
For the present work, the flavan-4β-ols (XXXIV) to (XXXVIII) were prepared.



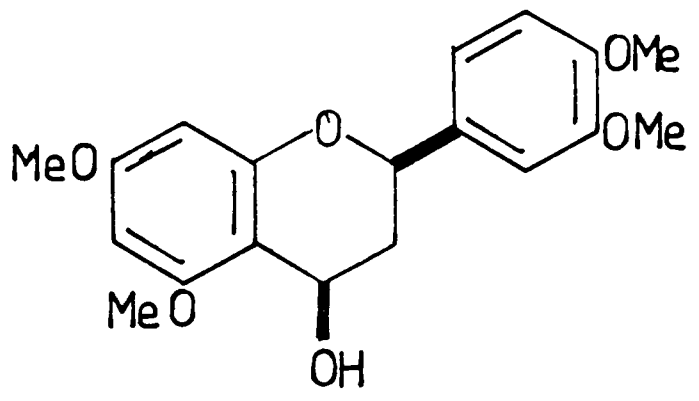
XXXIV



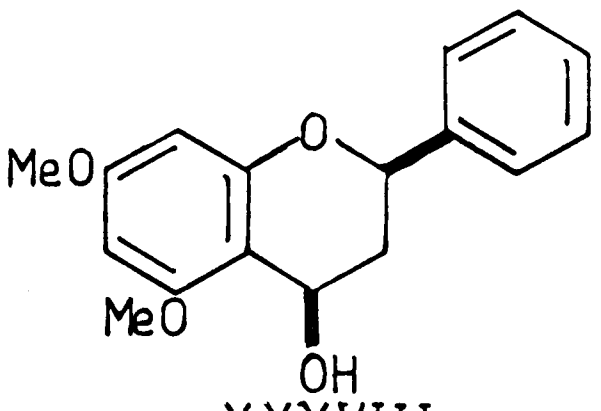
XXXV



XXXVI

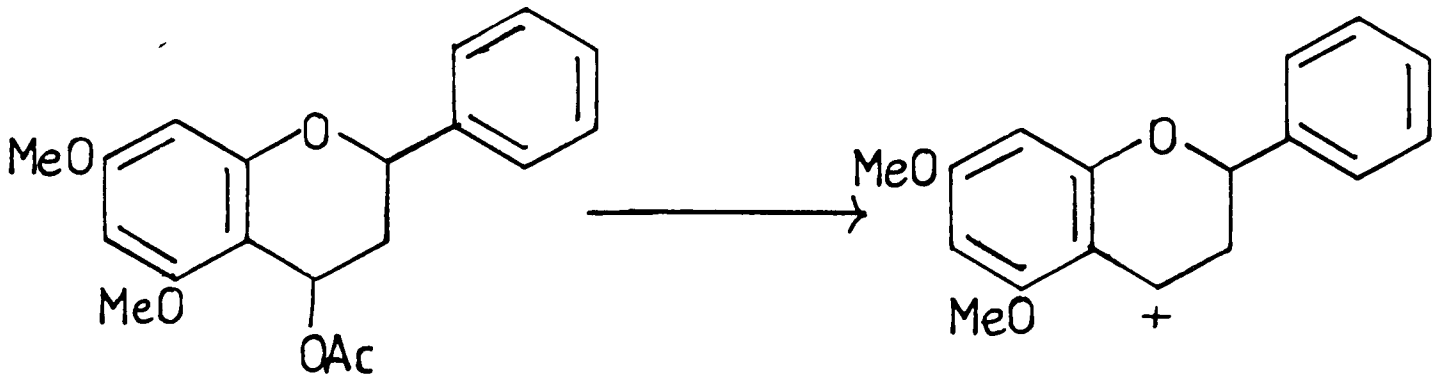


XXXVII

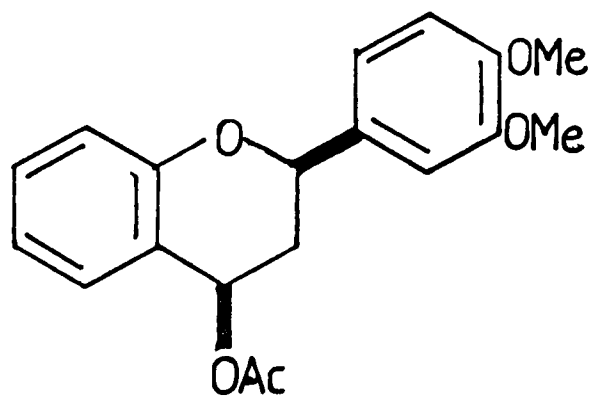


XXXVIII

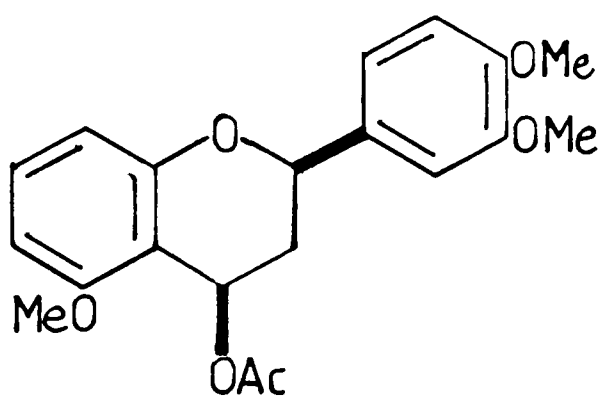
Acetylation of the flavan-4β-ols was then attempted with pyridine/acetic anhydride at room temperature. Water was avoided during the work-up procedure because it was feared that its high dielectric constant might promote formation of the 4-carbocation from highly substituted flavanyl acetates, (cf. ref. 37), e.g.:



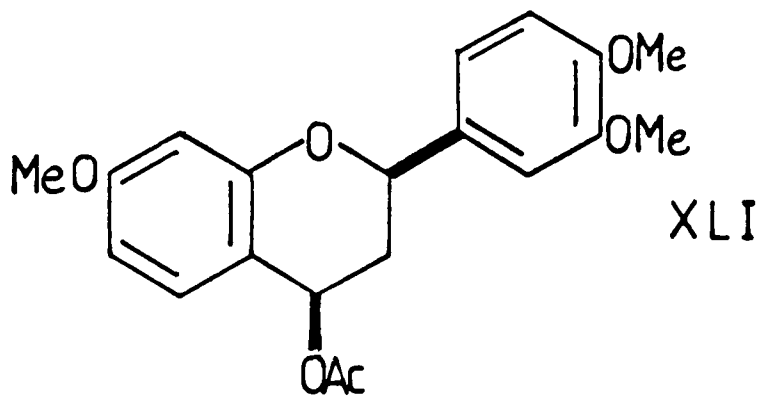
Excess of acetylating agent and the acetic acid formed during the reaction were instead removed by evaporation at low pressure (ca. 0.2 torr) and a temperature of 30° to 40°. By crystallising the residue from a non-polar solvent, the 4β-acetoxyflavans (XXXIX) to (XLI) were isolated.



XXXIX

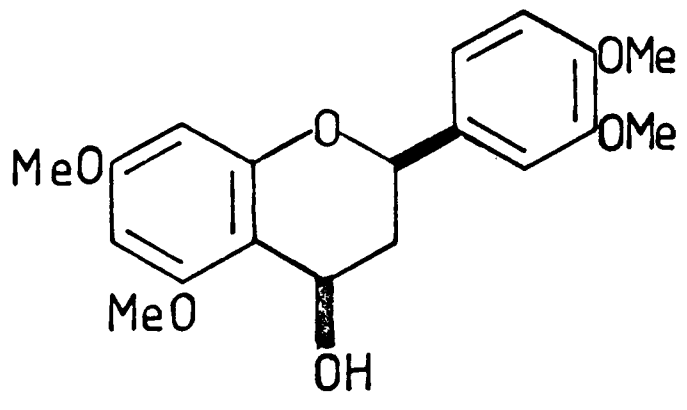


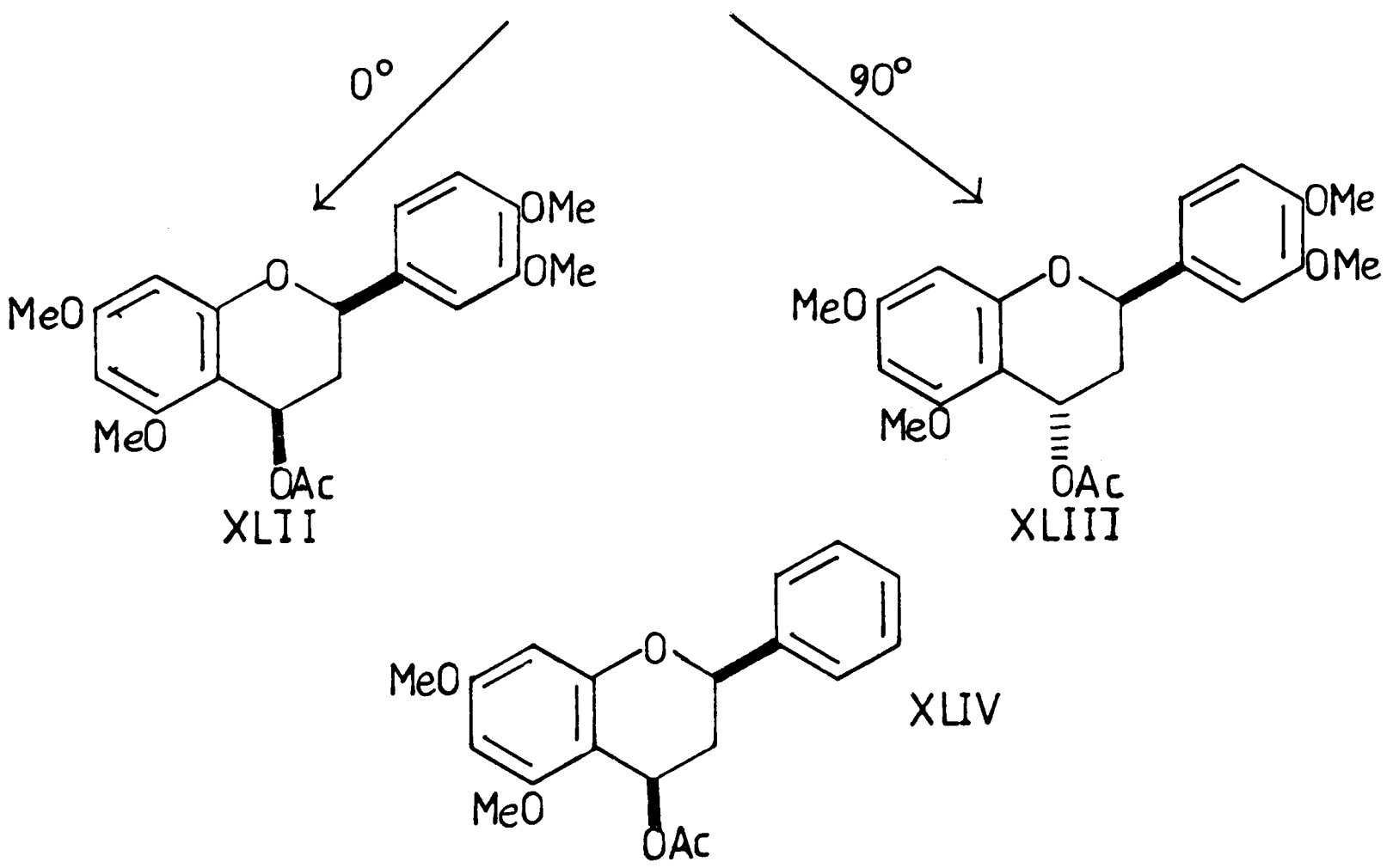
XL



XLI

4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (XLII) (one of the acetates Krishnamurthy *et al.*[38a] had been unable to prepare) was similarly obtained in 77% yield by acetylation of the corresponding flavan-4β-ol (XXXVII) at 0°. However, when the reaction mixture was heated to 90°, the product was the epimeric 4α-acetoxy-5,7,3',4'-tetramethoxyflavan (XLIII) in 64% yield. 4β-Acetoxy-5,7-dimethoxyflavan (XLIV) was also obtained as a crystalline solid by acetylation at 0° of 5,7-dimethoxyflavan-4β-ol (XXXVIII).



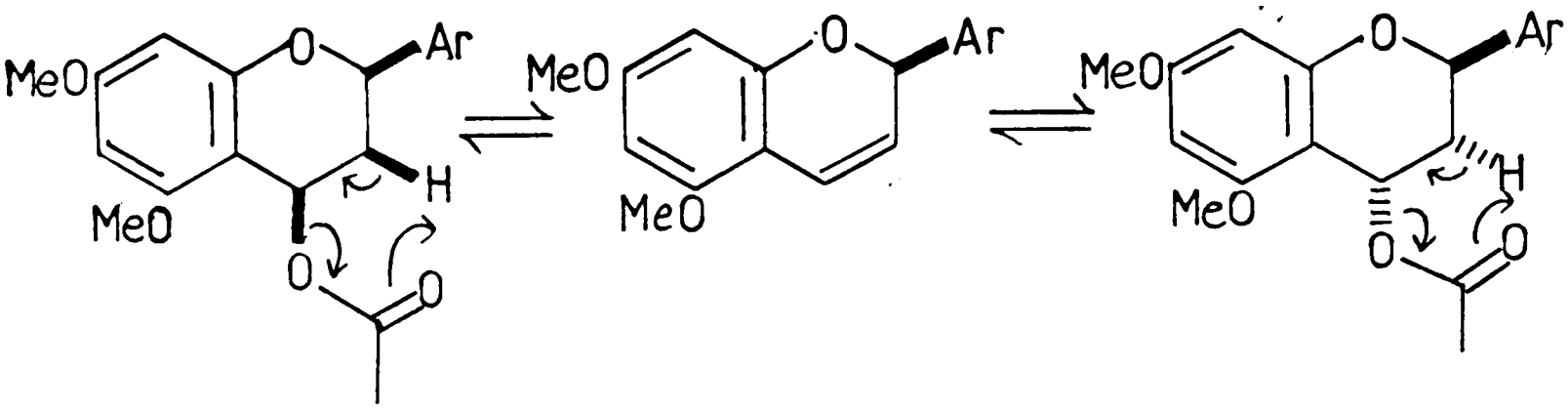


Satisfactory elemental analyses were obtained for all these compounds and the proton magnetic resonance peaks at

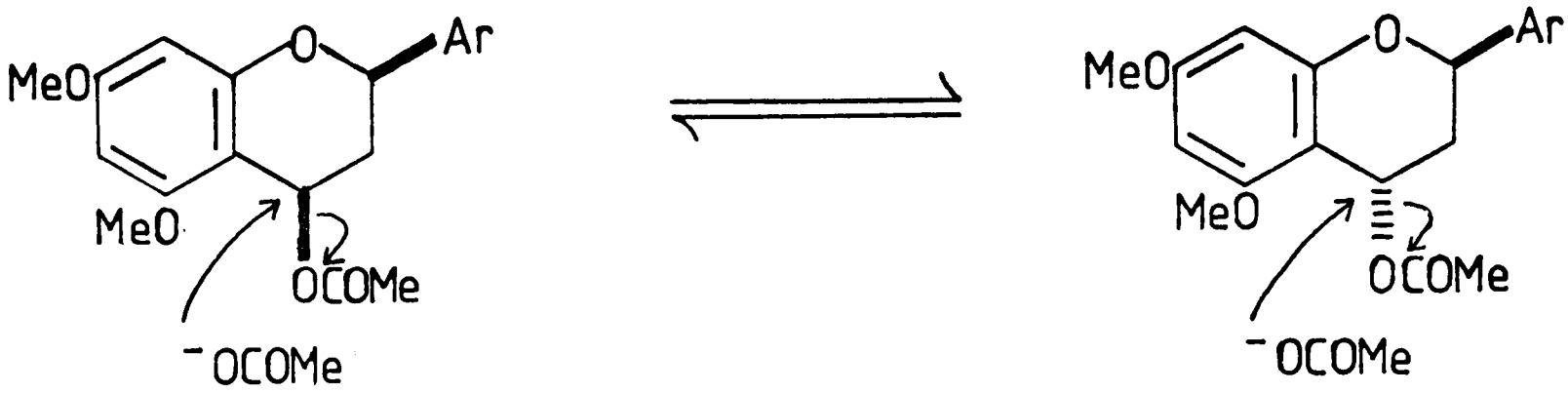
ca. 8τ confirm that in each case acetylation had occurred, contrary to the findings of Krishnamurthy et al.[38] Justification of the stereochemical assignments made will be deferred until the end of this chapter when all the compounds described can conveniently be dealt with together.

Returning now to the formation of two epimeric acetates from 5,7,3',4'-tetramethoxyflavan-4β-ol (XXXVII), the observations suggest that the 4β-derivative (XLII), formed at low temperature, results from kinetic control and the 4α-derivative (XLIII), formed at high temperature, from thermodynamic control. To test this hypothesis, samples of the pure 4β- and 4α-acetates were heated to 90° for 2h in acetic anhydride/pyridine with a trace of acetic acid. After removal of the volatile matter the products were examined by proton magnetic resonance spectroscopy. The spectra of the two samples were identical and indicated the presence of a mixture of the 4β- and 4α- isomers, (XLII) and (XLIII). By comparison of the intensities of the acetyl resonances due to each isomer, the mixtures were found to contain 5-10% of the 4β-isomer. This proportion, having been obtained starting from either pure isomer, must represent the equilibrium between the two and provides the first straightforward proof of the greater thermodynamic stability of a 4α-substituted flavan than its 4β-epimer.

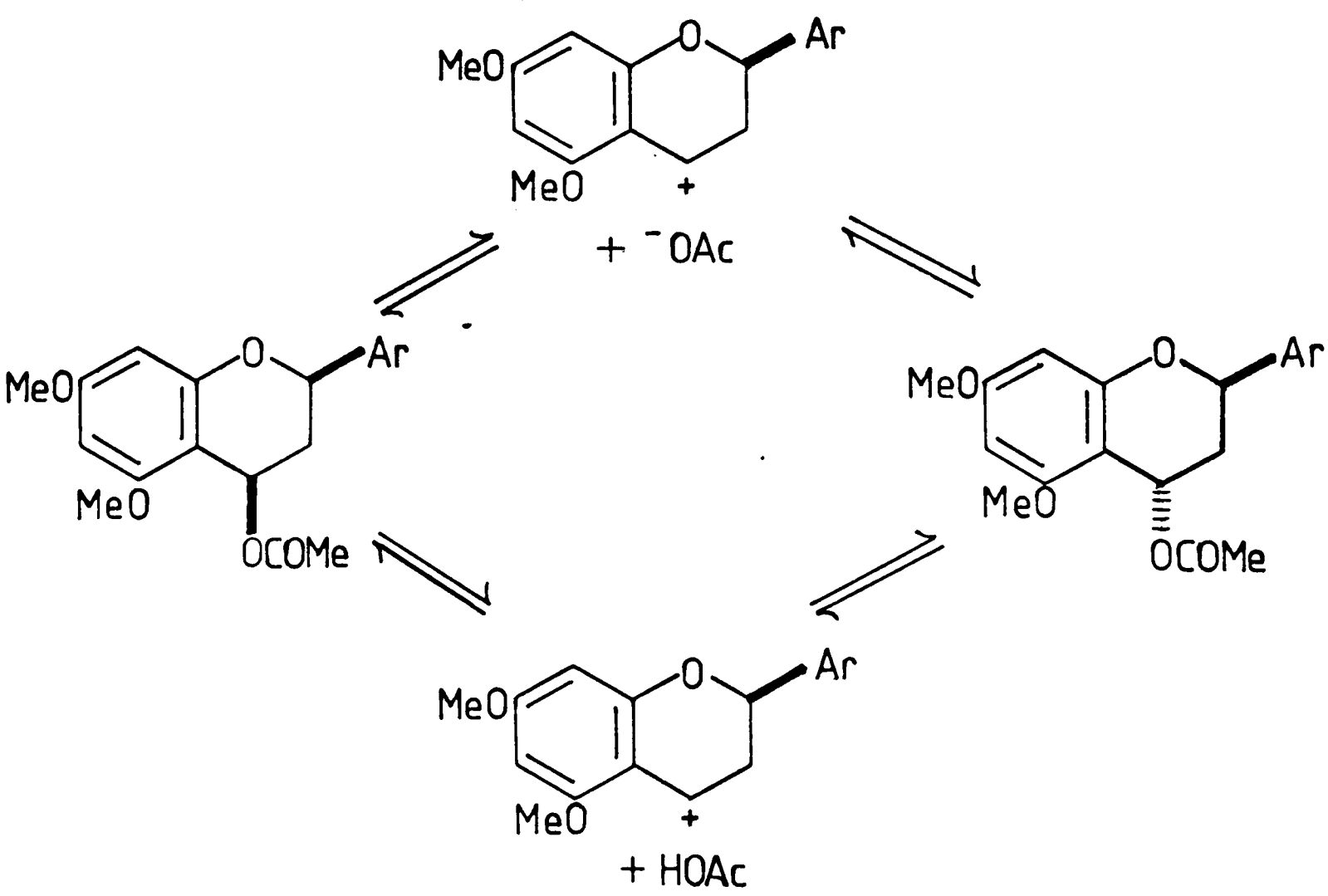
Three mechanisms might be suggested for the conversion of 4β- to 4α-acetoxy-5,7,3',4'-tetramethoxyflavan. Of these, the first (scheme 14) is elimination of acetic acid to give a flav-3-ene, followed by re-addition of acetic acid to the other face of the flav-3-ene molecule to give the 4α-acetate. This



Scheme 14



Scheme 15



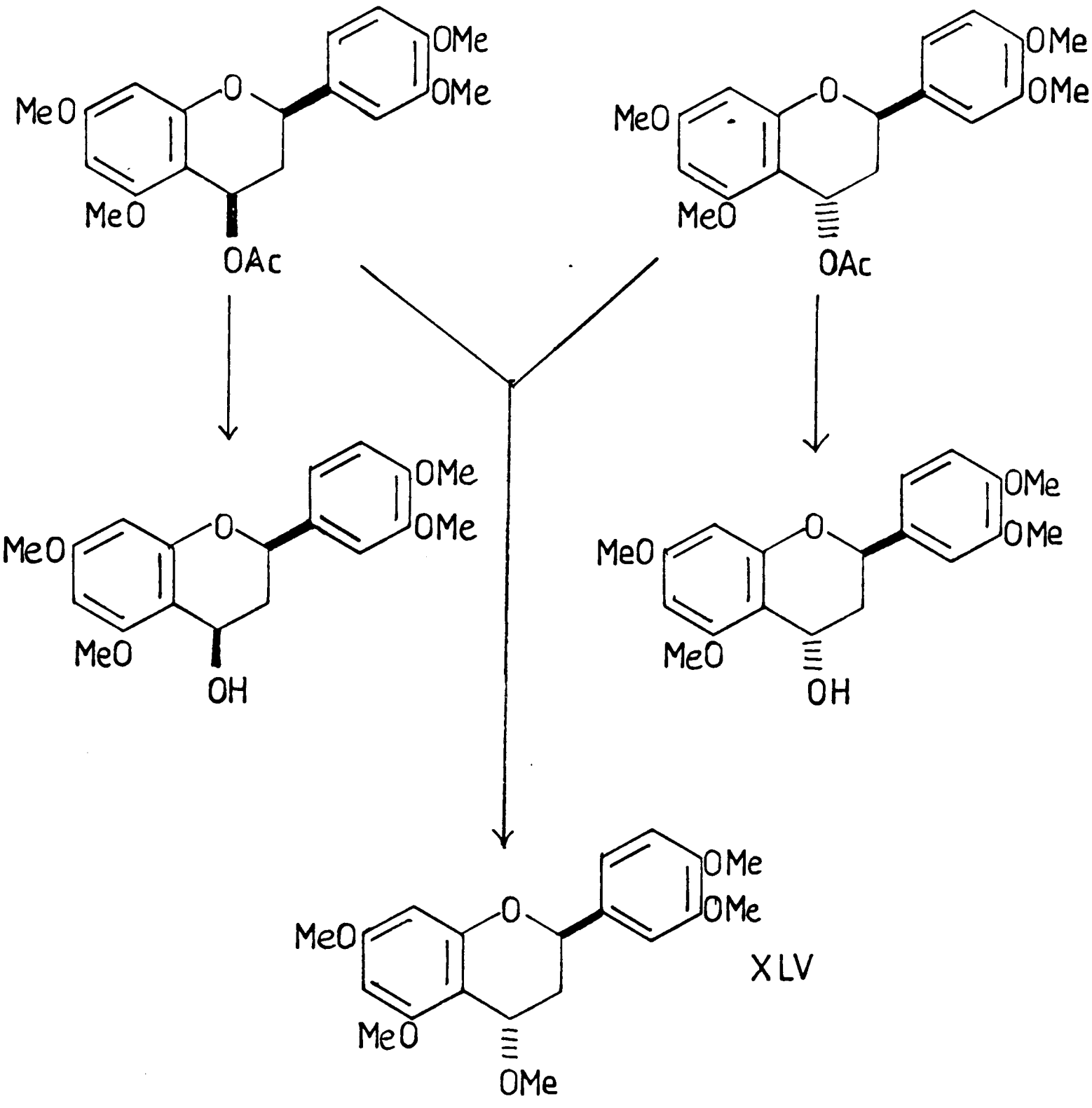
Scheme 17

possibility was ruled out by the observation that the postulated intermediate flav-3-ene is inert under the reaction conditions.

The second mechanism (scheme 15) is S_N2 attack by acetic acid or acetate ion. There is strong circumstantial evidence against this proposal. Other reactions in pyridine of both 4β- and 4α-acetoxy-5,7,3',4'-tetramethoxyflavan, (XLII) and (XLIII), with nucleophiles will be described later in this thesis in which the products all have 4α-stereochemistry: this is not consistent with simple S_N2 attack which would lead to inversion of configuration at the 4-position. There is direct evidence against an S_N2 mechanism only in a different solvent, methanol. Thus, treatment of each acetate with boiling methanolic potassium hydroxide resulted partly in cleavage of the ester by the normal acyl-oxygen fission (giving the alcohol of unchanged stereochemistry) and partly in cleavage by alkyl-oxygen fission (giving in either case 4α-methoxy-5,7,3',4'-tetramethoxyflavan, (XLV)) (scheme 16). 4β-Methoxy-5,7,3',4'-tetramethoxyflavan was shown to be inert to methanolic potassium hydroxide (see Chapter 2), and so would have been detected had it been formed as a result of S_N2 attack on the 4α-acetate (XLIII).

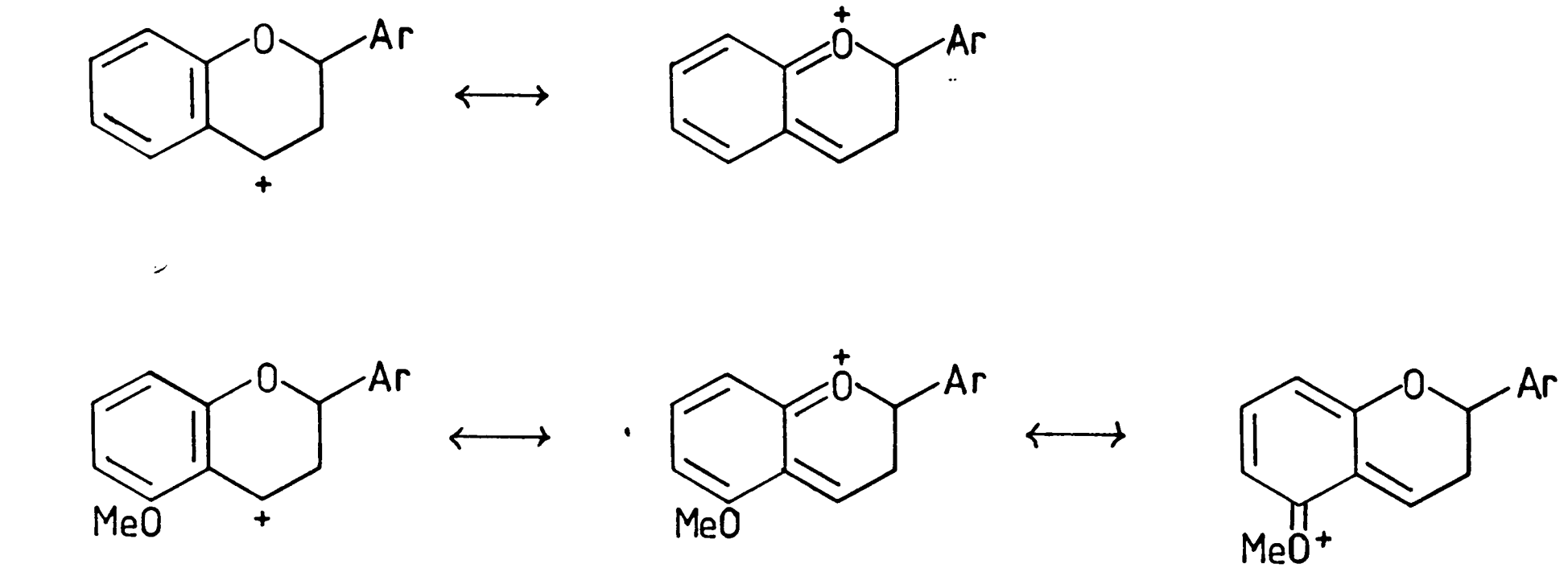
The most likely route for equilibration of the 4-acetoxy-5,7,3',4'-tetramethoxyflavans (XLII) and (XLIII) is therefore the third mechanism (scheme 17): an S_N1 reaction in which cleavage of the acetate gives a 4-carbocation (which process might occur by acid catalysis), followed by recombination with acetate ion (or acetic acid). The ester cleavage in methanolic potassium hydroxide can hardly be acid catalysed, but in the

less polar acetic anhydride/pyridine mixture protonation of the leaving group (by acetic acid which invariably contaminates acetic anhydride) seems to be necessary for reaction to occur. Thus 4β-acetoxy-5,7,3',4'-tetramethoxyflavan was recovered unchanged after being heated in pyridine alone to 80° for 2h.



Scheme 16

It was then of interest to see whether the other available 4β-acetoxyflavans would epimerise and, if so, under what conditions. Since the epimerisation was expected to be acid



Scheme 18

catalysed, the proportion of acetic acid in the acetic anhydride was made up to a standard 25 mole percent (monitored by proton magnetic resonance spectroscopy) and this "acetic anhydride mixture" was used for all investigations of reactivity.

4β-Acetoxy-5,7-dimethoxyflavan (XLIV) was found to be indistinguishable in reactivity from its tetramethoxy analogue (XLII), each affording the corresponding 4α-acetoxyflavan, (XLVI) and (XLIII) in 60% isolated yield on heating to 80° for 2h in pyridine/acetic anhydride mixture, and each undergoing ca. 50% epimerisation (estimated by nuclear magnetic resonance spectroscopy) with the same reagent at 65° for 1h. 4β-Acetoxy-7,3',4'-trimethoxyflavan (XLI) was inert to pyridine/acetic anhydride mixture but treatment with acetic anhydride mixture alone readily gave 4α-acetoxy-7,3',4'-trimethoxyflavan (XLVII). 4β-Acetoxy-5,3',4'-trimethoxyflavan (XL) required more vigorous heating with acetic anhydride mixture alone before conversion to 4α-acetoxy-5,3',4'-trimethoxyflavan (XLVIII) occurred, while 4β-acetoxy-3',4'-dimethoxyflavan (XXXIX) was unaffected even under these vigorous conditions (table 1).

Assuming that the transition state for formation of the 4-carbocation intermediate resembles that intermediate in structure and hence in energy, then the observed order of reactivity is just what would be expected for an S_N1 reaction mechanism (illustrated for the 4-acetoxy-5,7,3',4'-tetramethoxyflavans in scheme 17). This is because the stability of the 4-carbocation is increased by interaction with methoxyl substituents in the 5- and 7-positions (scheme 18). The greater

Table 1: The effect of various mixtures containing acetic acid on 4β-acetoxyflavans

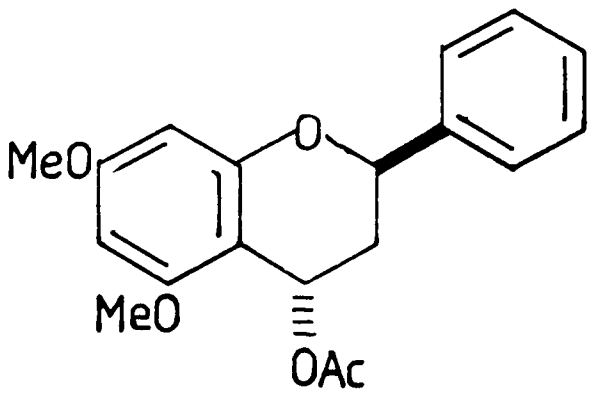
Compound	Methoxylation pattern	Effect of treatment with reagent (i)	(ii)	(iii)	(iv)
XLII	5,7,3',4'	✓✗	✓		
XLIV	5,7	✓✗	✓		
XLI	7,3',4'		×	✓	
XL	5,3',4'		×	×	✓
XXXIX	3',4'				×

× indicates starting material isolated

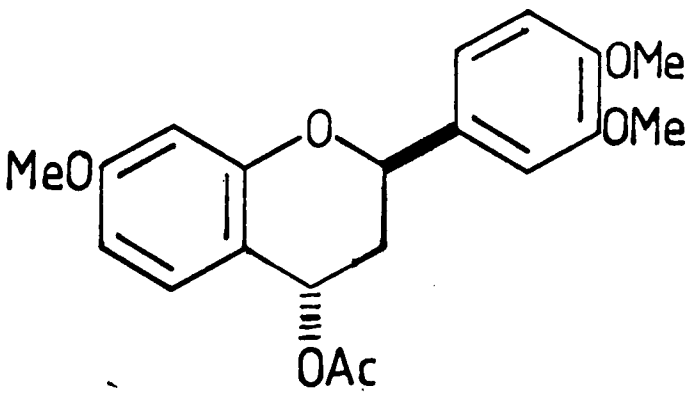
✓ indicates 4α-epimer isolated

✓✗ indicates ca. 50% epimerisation detected by n.m.r.

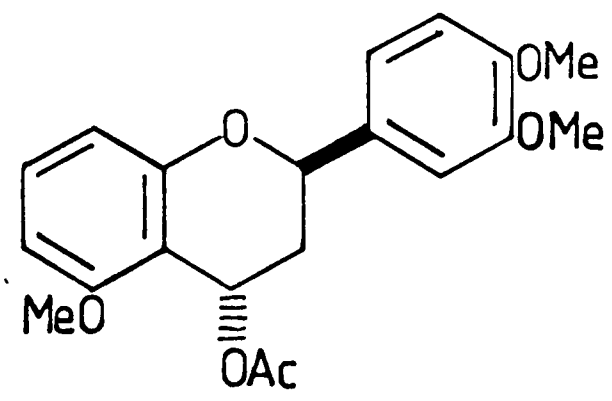
Reagents: (i) acetic anhydride mixture/pyridine, 65°
(ii) acetic anhydride mixture/pyridine, 80°
(iii) acetic anhydride mixture, 60°
(iv) acetic anhydride mixture, 90°



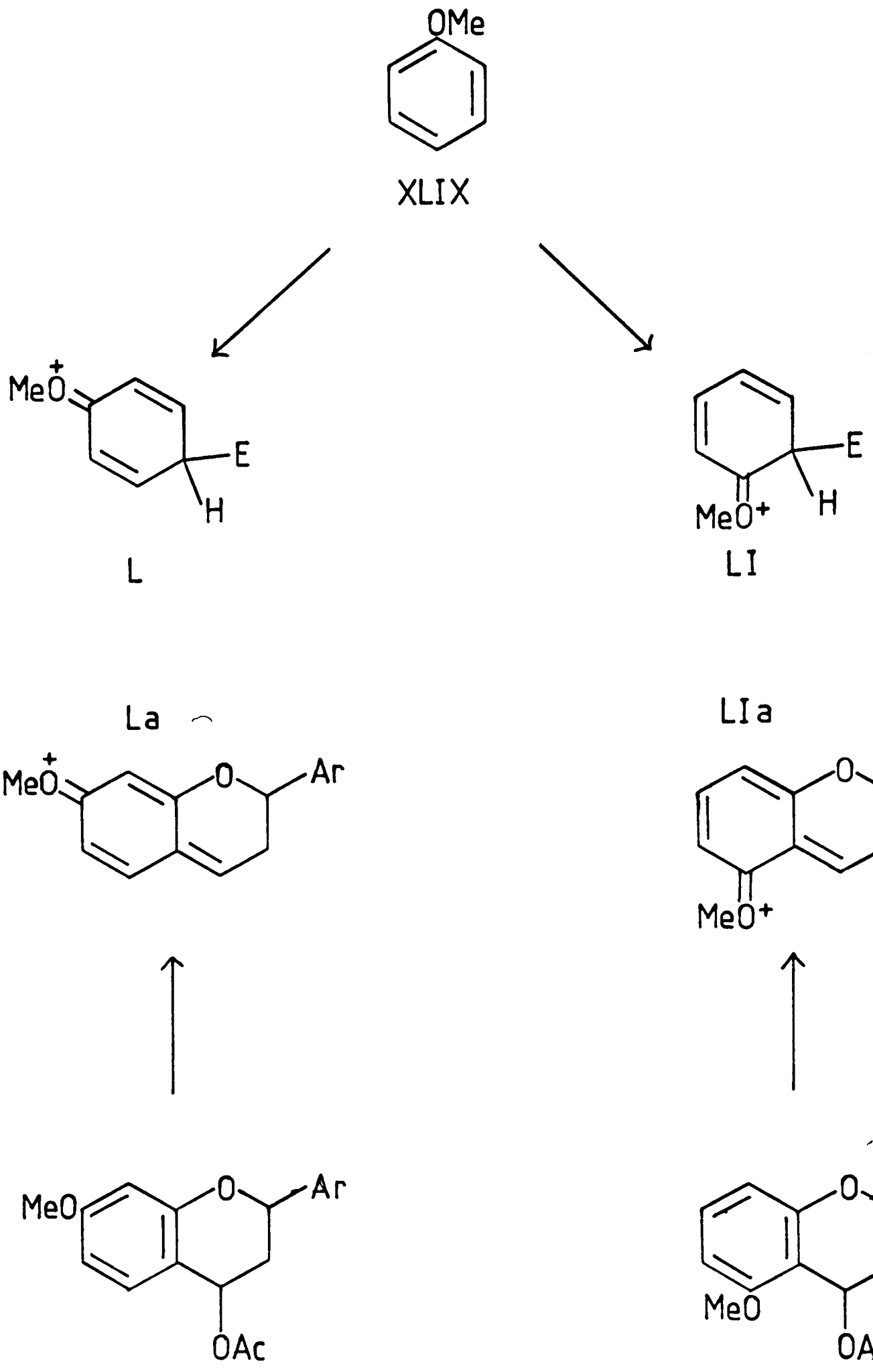
XLVI



XLVII



XLVIII


OMe
XLIX
MeO+
E
H
L
MeO+
E
H
LI
La
LIa
MeO+
O
Ar
MeO+
O
Ar
MeO
O
Ar
OAc
MeO
O
Ar
OAc

Scheme 19

reactivity of 7,3',4'- than 5,3',4'-trimethoxy-4β-acetoxyflavan is reminiscent of the greater reactivity of anisole (XLIX) towards electrophiles at the para- than the ortho-position (for instance, chlorination of anisole with one equivalent of chlorine in acetic acid gives ortho- and para-chloroanisole in the ratio 21:79[44]). Scheme 19 illustrates the intermediates derived from anisole and the flavanoid 4-carbocations with which they are to be compared.

The reasons advanced for the greater reactivity of anisole at the para- than the ortho-position (see, for example, Gould[45]) are:

i) steric hindrance to attack by an electrophile at the ortho-position;

ii) an unfavourable withdrawal of electrons by the inductive effect of the methoxyl group, this effect being strongest at the ortho-position;

iii) the intrinsically lower energy of the para-quinonoid canonical (L) than of the ortho-quinonoid canonical (LI).

A consideration of the same three factors as possible explanations of the greater reactivity of 7,3',4'- (XLI) than 5,3',4'-trimethoxy-4β-acetoxyflavan (XL) suggests:

i) reaction in this case proceeds by loss of acetic acid. Dreiding models give no hint that this process might be hindered by a 5-methoxyl group;

ii) the reaction centre in this case is one bond removed from that in electrophilic attack at the ortho-position of

anisole: the inductive effect would thereby be greatly diminished;

iii) the difference in energy between the ortho- and para-quinonoid canonicals remains.

The intrinsic difference in energy between the canonicals (La) and (LIa) must therefore be the explanation of the greater reactivity of 7,3',4'- than 5,3',4'-trimethoxy-4β-acetoxyflavan.

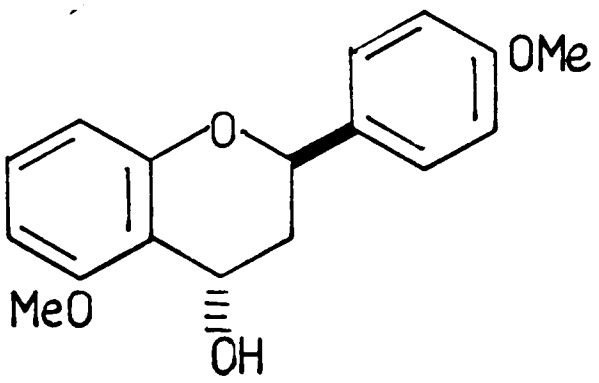
Epimerisation of flavan-4β-ols

Since, as has been shown, 4β-acetoxyflavans isomerise under acid catalysis to the thermodynamically more stable 4α-acetoxyflavans (the extent of isomerisation being great, but not 100%), it was of interest to determine whether flavan-4β-ols would similarly epimerise to give thermodynamically more stable flavan-4α-ols. There were three reasons why this possibility was particularly significant. Firstly, flavan-4α-ols have hitherto been much less accessible than their 4β- analogues. Epimerisation of the corresponding readily available flavan-4β-ol might provide the most convenient route to a flavan-4α-ol. Secondly, the identities of the 4α-acetoxyflavans already described could be confirmed by acetylation of the appropriate flavan-4α-ols. Thirdly, flavan-4α-ols figured in some of the unexpected reactions described in the introduction. An independent synthesis of these flavan-4α-ols was desirable.

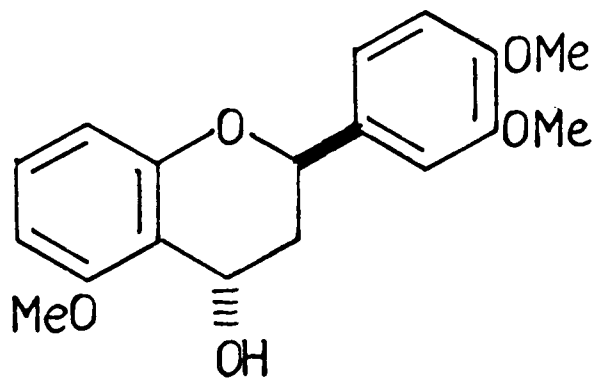
Previous routes to flavan-4α-ols

No satisfactory general route to flavan-4α-ols has been reported, but various flavan-4α-ols have been obtained through the use of methods of limited applicability.

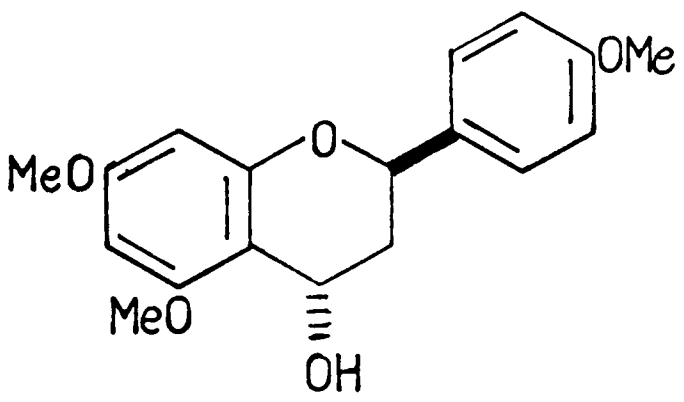
The method reported by Kamat et al.,[40] mentioned in the introduction, is the conversion of a flavan-4β-ol by phosphorus tribromide into a 4-bromoflavan which is then hydrolysed with ethanolic potassium hydroxide. Kamat et al.[40] claimed the synthesis of 5,4'-dimethoxy, 5,3',4'-trimethoxy-, 5,7,4'-trimethoxy-, 5,7,3',4'-tetramethoxy- and 5,7,3',4',5'-pentamethoxyflavan-4α-ol, (LII) to (LVI), by this route.



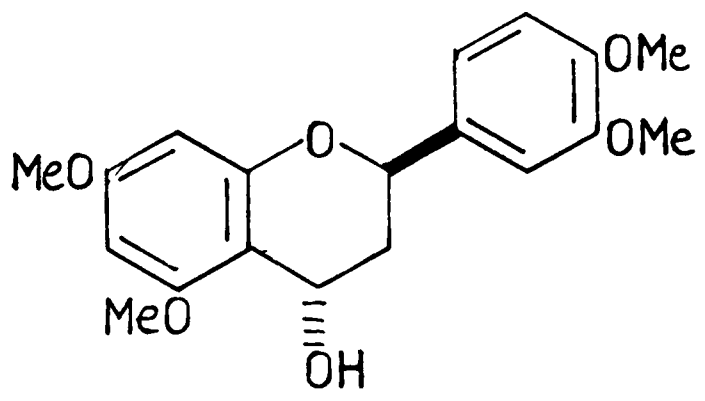
LII



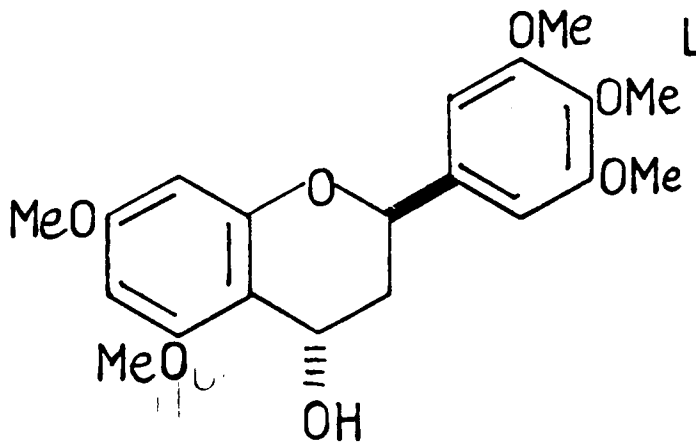
LIII



LIV



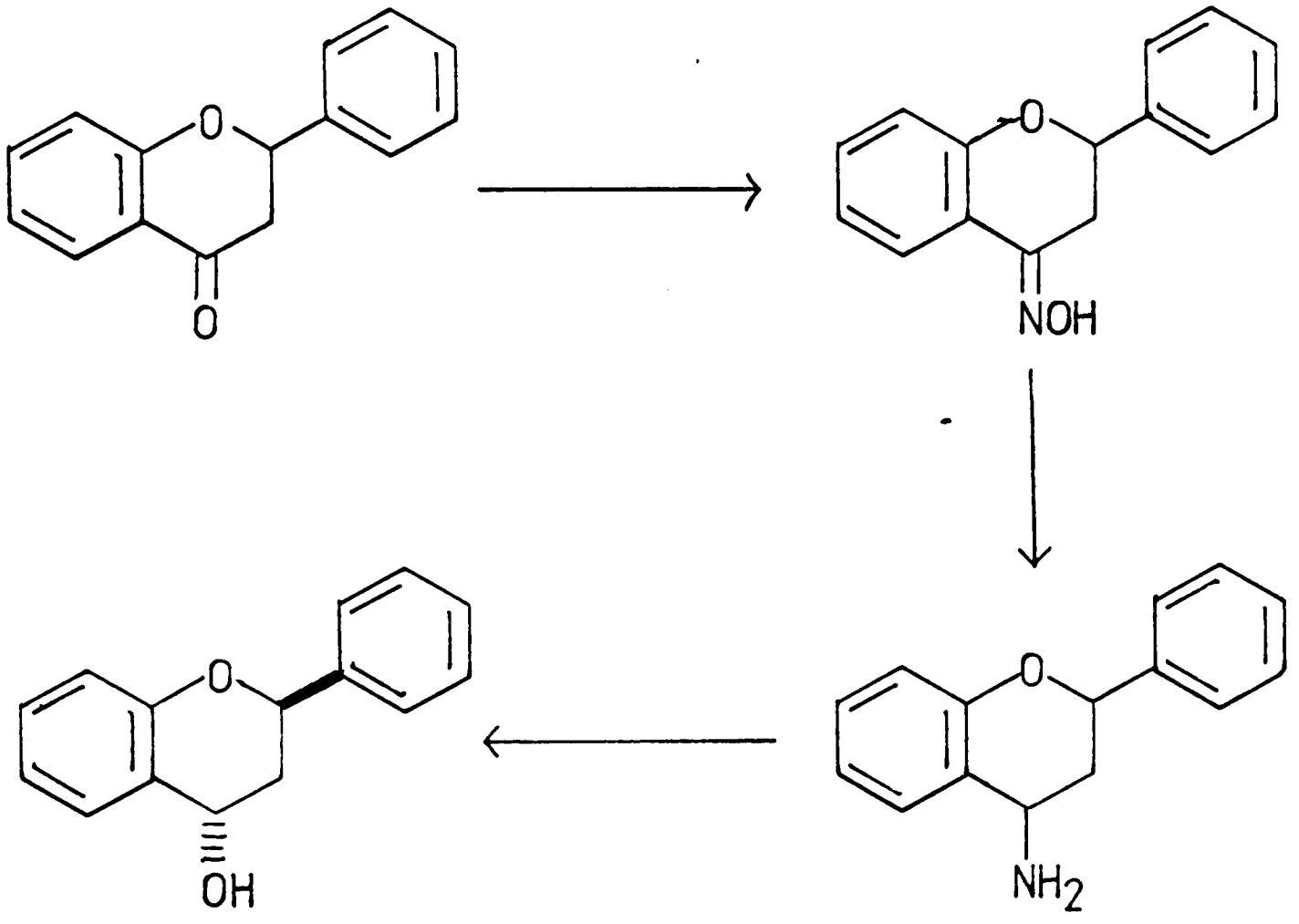
LV



LVI

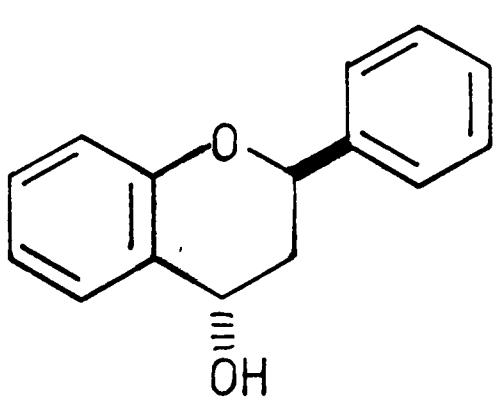
A second route, due to Bognar and co-workers,[46] is outlined in scheme 20. A flavanone is converted to its oxime, reduced to an amine and treated with nitrous acid. The overall

yield is 20-30%.[47]

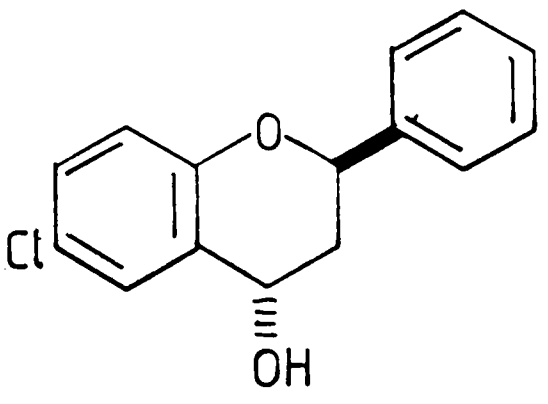


Scheme 20

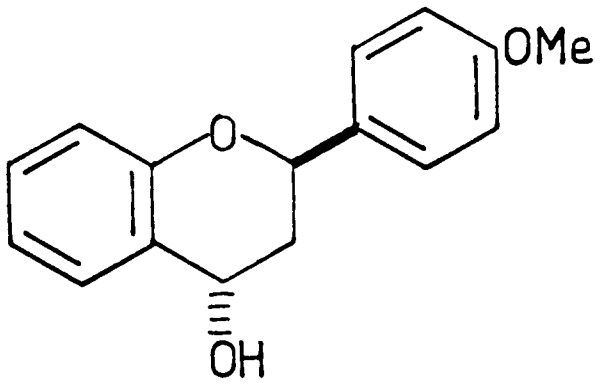
By this route, Bognar et al.[48] synthesised unsubstituted, 6-chloro- and 4'-methoxyflavan-4α-ol, (LVII), (LVIII) and (LIX); Munro[47] prepared 3',4'-dimethoxyflavan-4α-ol (LX), and Sharpe[49] prepared 6-methyl-4'-methoxyflavan-4α-ol (LXI).



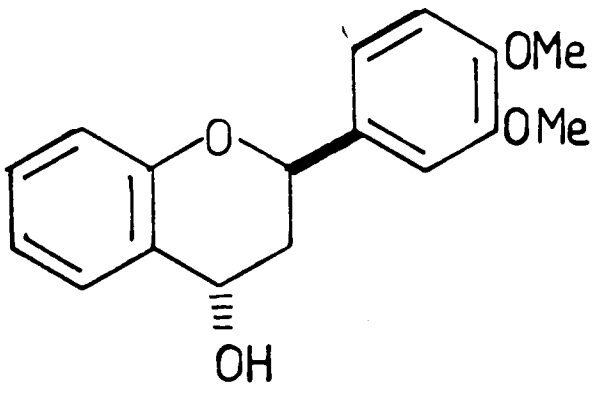
LVII



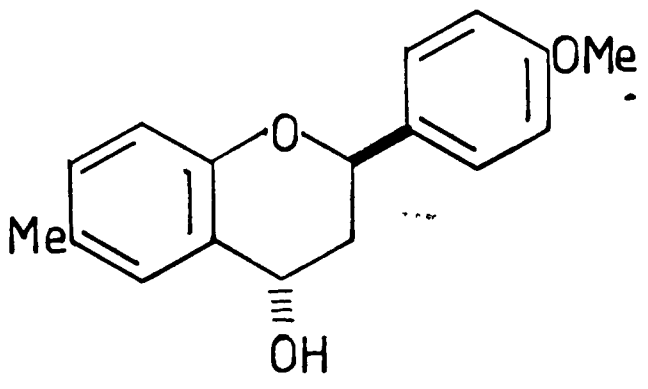
LVIII



LIX



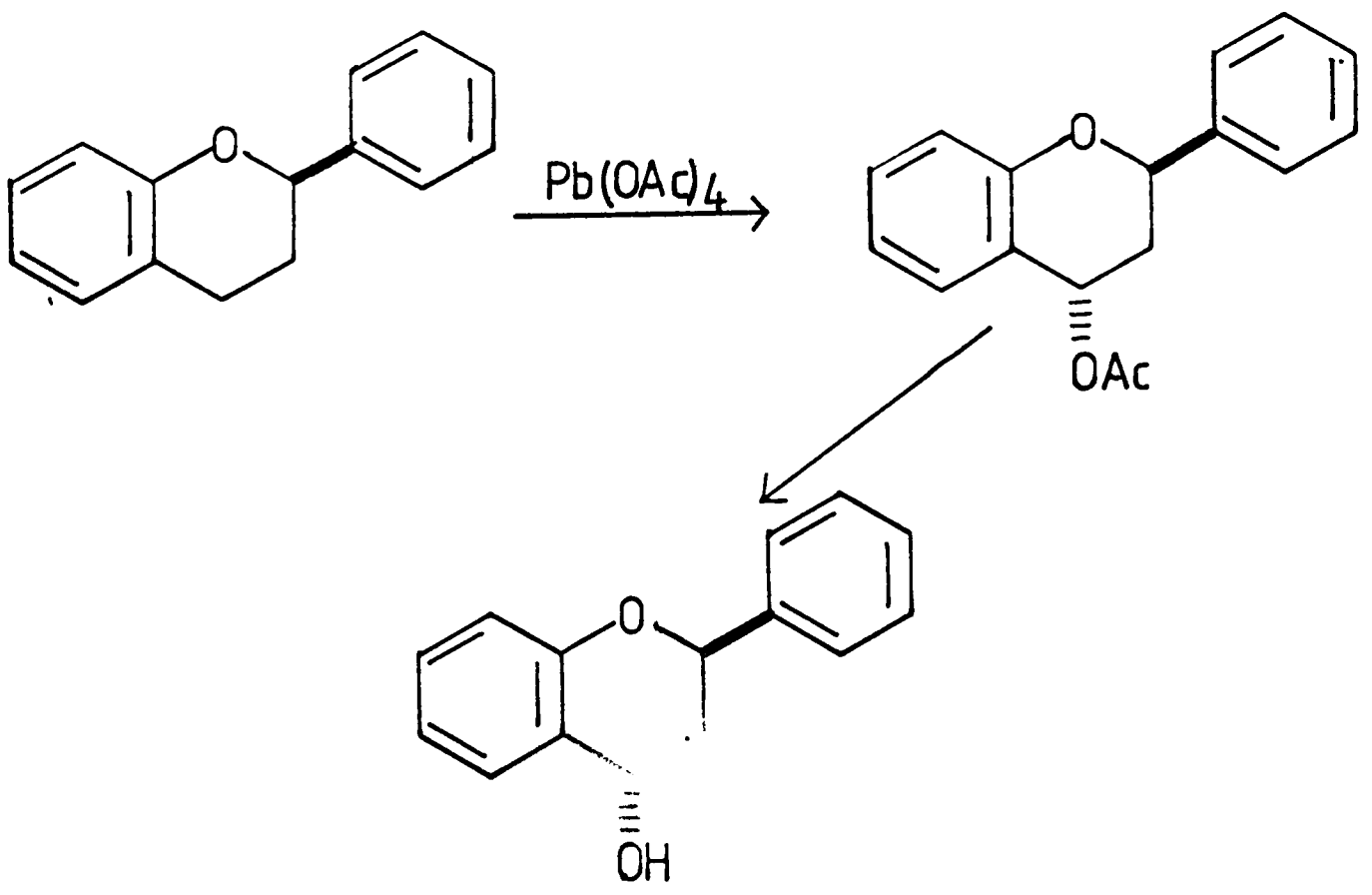
LX



LXI

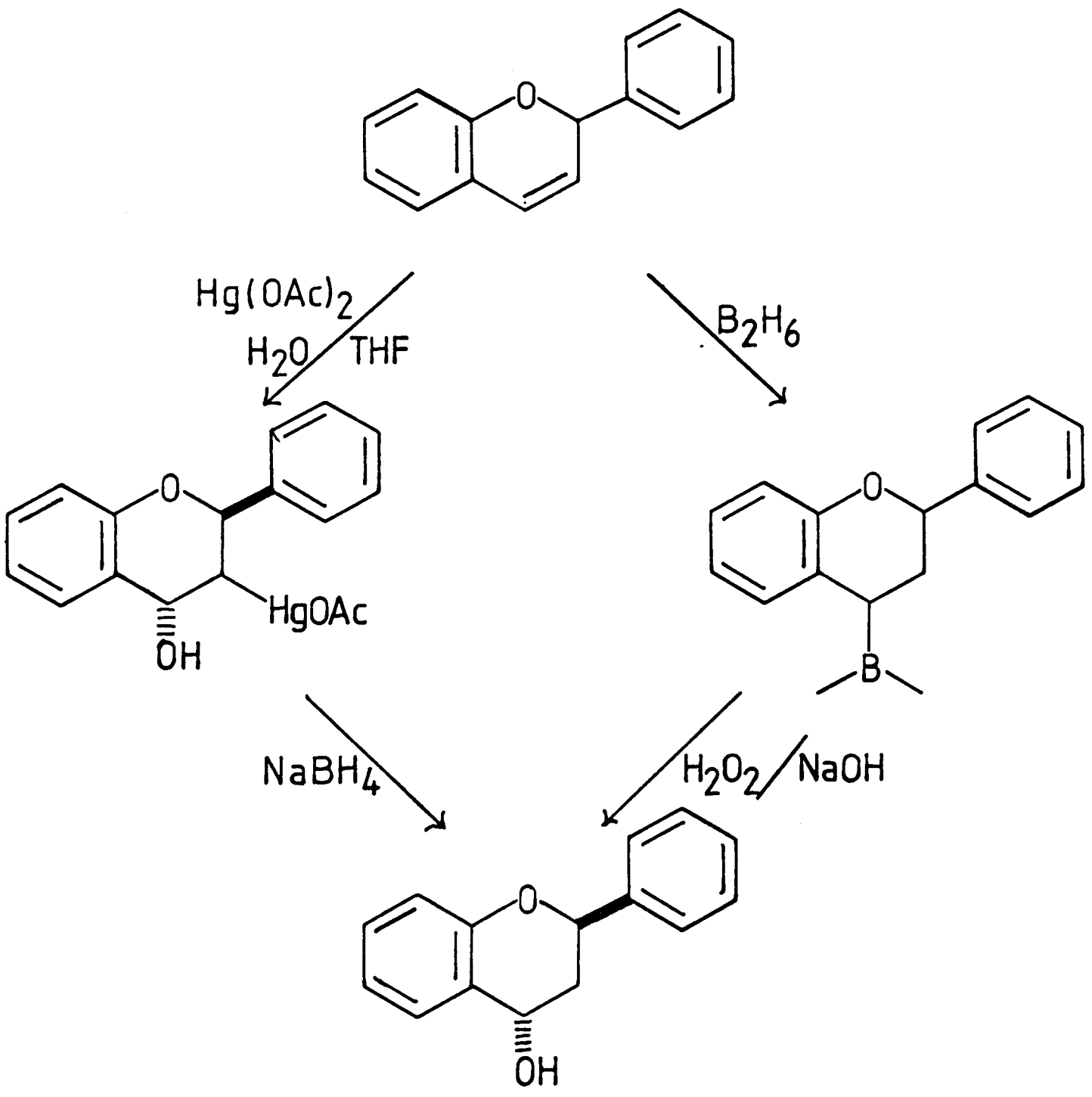
Flavan-4α-ols have also been obtained by reaction of flavans with lead tetra-acetate and hydrolysis of the resulting 4α-acetoxyflavans (scheme 21). This route enabled Bokadia et al.[41] to obtain flavan-4α-ol (LVII) and 4'-methoxyflavan-4α-ol (LIX), but it is unpromising as a preparative method

Scheme 21



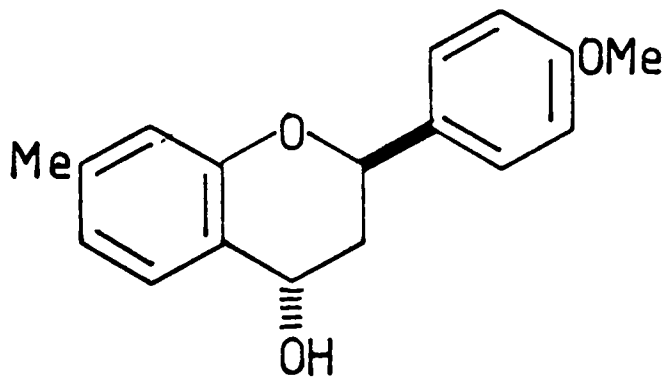
because the necessary flavans are not readily available,[50] yields are poor (40% for 4'-methoxyflavan-4α-ol[41]) and side reactions (attack on aromatic nuclei and on methoxyl groups) are expected to become more significant with more highly substituted flavans.[41]

More recently, Clark-Lewis and McGarry have investigated the conversion of flav-3-enes (to which an excellent synthetic route is now available[51,52]) to flavan-4α-ols <u>via</u> mercury[52] or boron[53] derivatives (scheme 22).

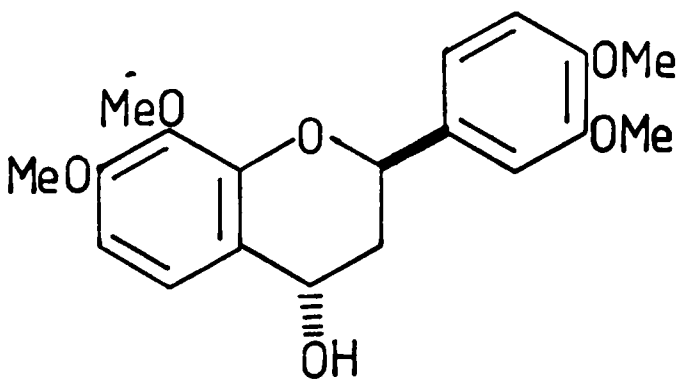


Scheme 22

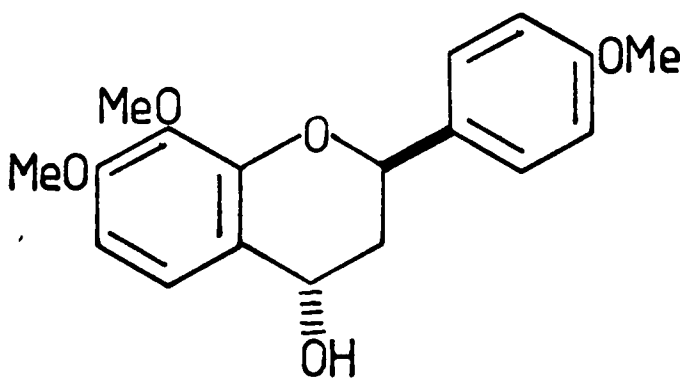
By the oxymercuration route Clark-Lewis and McGarry[52] obtained 4'-methoxy-, 4'-methoxy-7-methyl-, 7,8,3',4'-tetramethoxy-, 7,8,4'-trimethoxy- and 7,4'-dimethoxyflavan-4α-ol, (LIX) and (LXII) to (LXV). Yields were 21-48%,[52] being poorest for flavan-4α-ols with a methoxyl group in the 7-position.



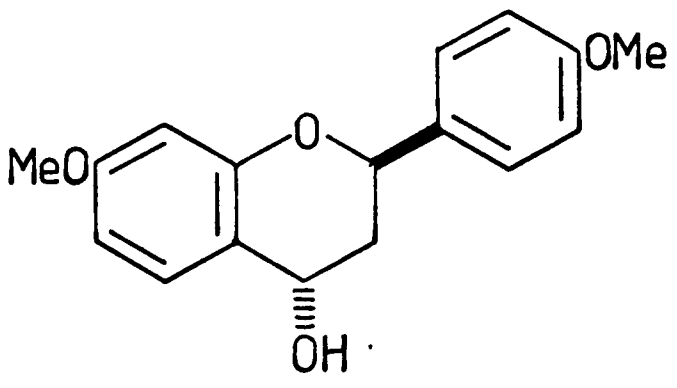
LXII



LXIII



LXIV



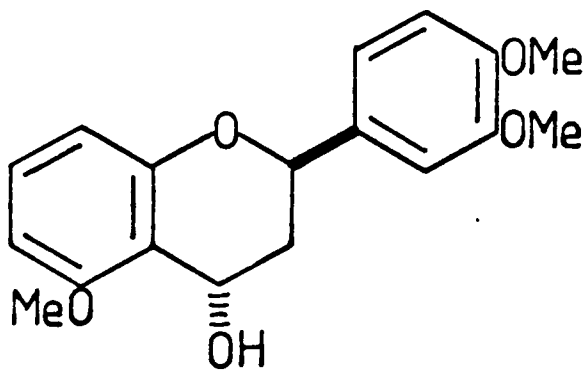
LXV

Hydroboration with oxidative work up of flav-3-enes gave the flavan-4α-ols (LIX), (LXI) and (LXII) (17-48% yield).[53] Flav-3-enes possessing methoxyl groups in the A-ring, however, gave only flavan-3-ols and products derived from fission of the heterocyclic ring.

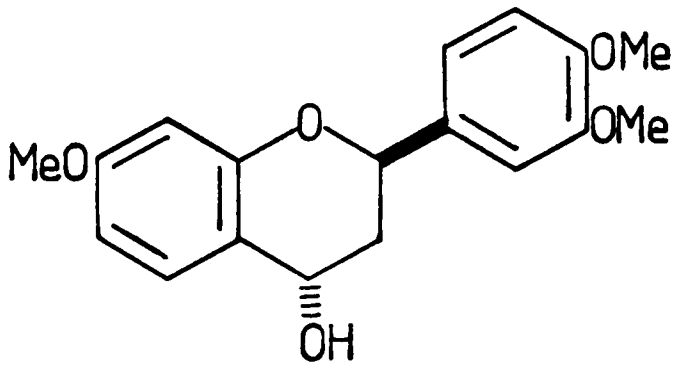
The effect of acid on flavan-4β-ols

Bateman[23] had already discovered that flavan-4β-ol yielded flavan-4α-ol on treatment with ethanolic hydrogen chloride, and Shaw[27] had used aqueous acid to effect the same transformation. Shaw, however, noted that flav-3-ene was also formed during the reaction with aqueous acid and he reached the (unnecessarily cautious) conclusion that thermodynamic control in the formation of the flavan-4α-ol was plausible but not proven.

The present author found that both 5,3',4'- and 7,3',4'-trimethoxyflavan-4β-ol, (XXXV) and (XXXVI), were converted to the corresponding flavan-4α-ols, (LIII) and (LXVI), on treatment with aqueous acidic acetonitrile at room temperature. This provides the first genuine syntheses of the flavan-4α-ols and unequivocal evidence that in each case the 4α-isomer is thermodynamically the more stable. The compound claimed by Kamat *et al.*[40] to be 5,3',4'-trimethoxyflavan-4α-ol (LIII) will be discussed presently.

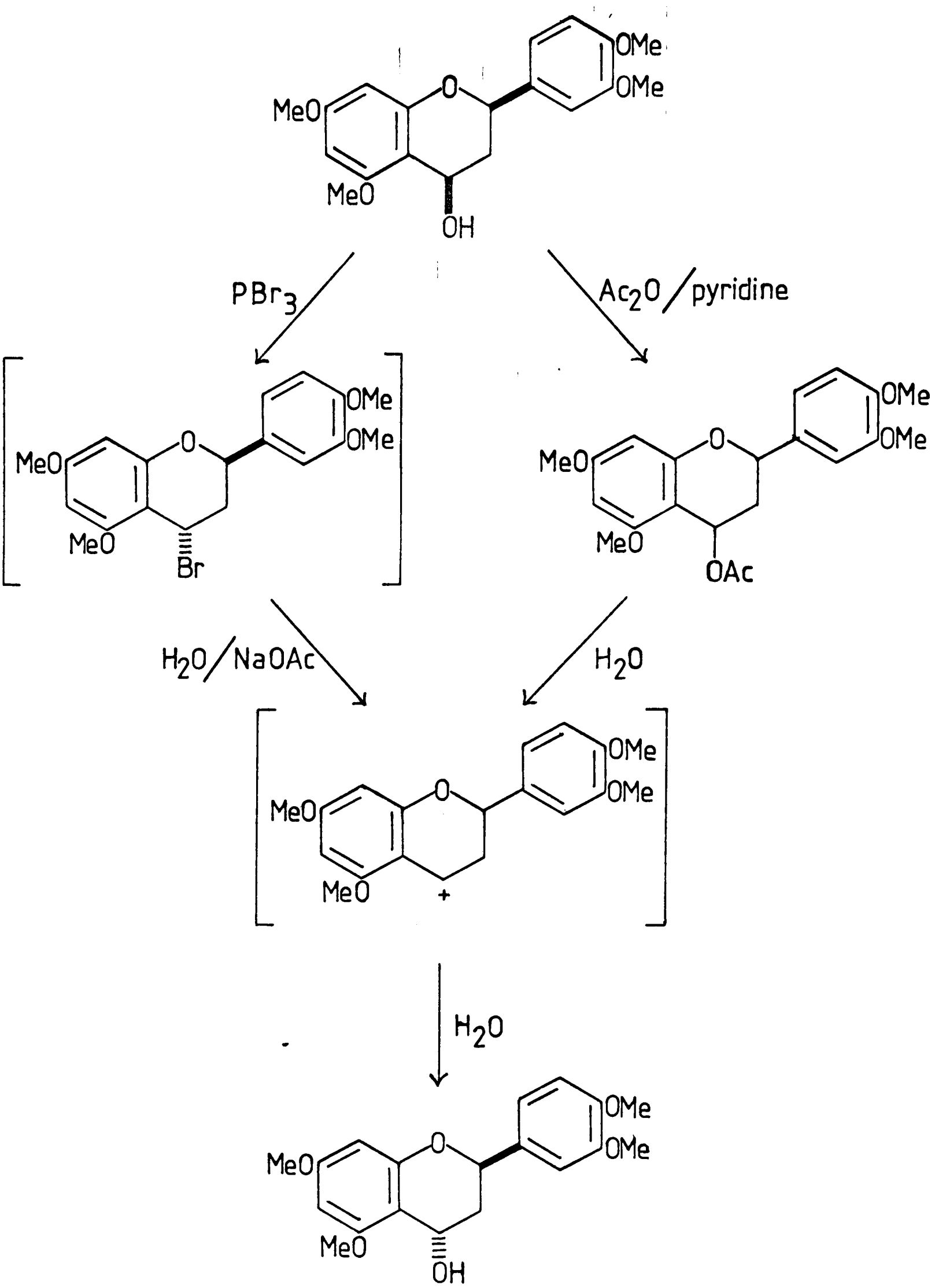


LIII



LXVI

Acetylation of each flavan-4α-ol, (LIII) and (LXVI), gave the 4α-acetate, identical to the samples obtained by epimerisation of the corresponding 4β-acetates.


OMe
OMe
MeO
O
MeO
OH
PBr3
Ac2O / pyridine
OMe
OMe
MeO
O
MeO
Br
OMe
OMe
MeO
O
MeO
OAc
H2O / NaOAc
H2O
OMe
OMe
MeO
O
MeO
+
H2O
OMe
OMe
MeO
O
MeO
OH

Scheme 23

5,7,3',4'-Tetramethoxyflavan-4α-ol (LV) could also be obtained from the corresponding flavan-4β-ol (XXXVII), although with a wide melting range (80-90°) which was not greatly altered by recrystallisation. A pure sample of the tetramethoxyflavan-4α-ol (LV) with identical nuclear magnetic resonance spectrum but melting point 126.5-128.5° was obtained by reduction of 4α-acetoxy-5,7,3',4'-tetramethoxyflavan (XLIII) with lithium aluminium hydride.

It is noteworthy that Krishnamurthy *et al.*[38] claim 89° for the melting point of the tetramethoxyflavan-4α-ol (LV), while Kamat *et al.*[40] quote 90°. In both these cases as well as that of direct epimerisation of the flavan-4β-ol (XXXVII), the low melting point may be the result of contamination with some polymeric flavanoid material which could not be removed by crystallisation. 5,7-Dimethoxy substituted flavanoids have been reported[22] to polymerise very readily by attack of a 4-carbocation on the electron-rich A-ring of another flavanoid molecule.

The formation of 5,7,3',4'-tetramethoxyflavan-4α-ol (LV) when Krishnamurthy *et al.*[38] tried to acetylate the flavan-4β-ol (XXXVII) is now easily explained. The presence of water during the work up provided a medium of high dielectric constant which favoured cleavage of the flavanyl acetate to give the 4-carbocation, and this, by reaction with water under kinetic or thermodynamic control, formed the flavan-4α-ol (LV) (scheme 23). Similarly, in the preparation reported by Kamat *et al.*,[40] involving formation and hydrolysis of a 4-bromoflavan, it seems likely that hydrolysis of the bromoflavan occurred during the washing of the ethereal solution with aqueous sodium acetate

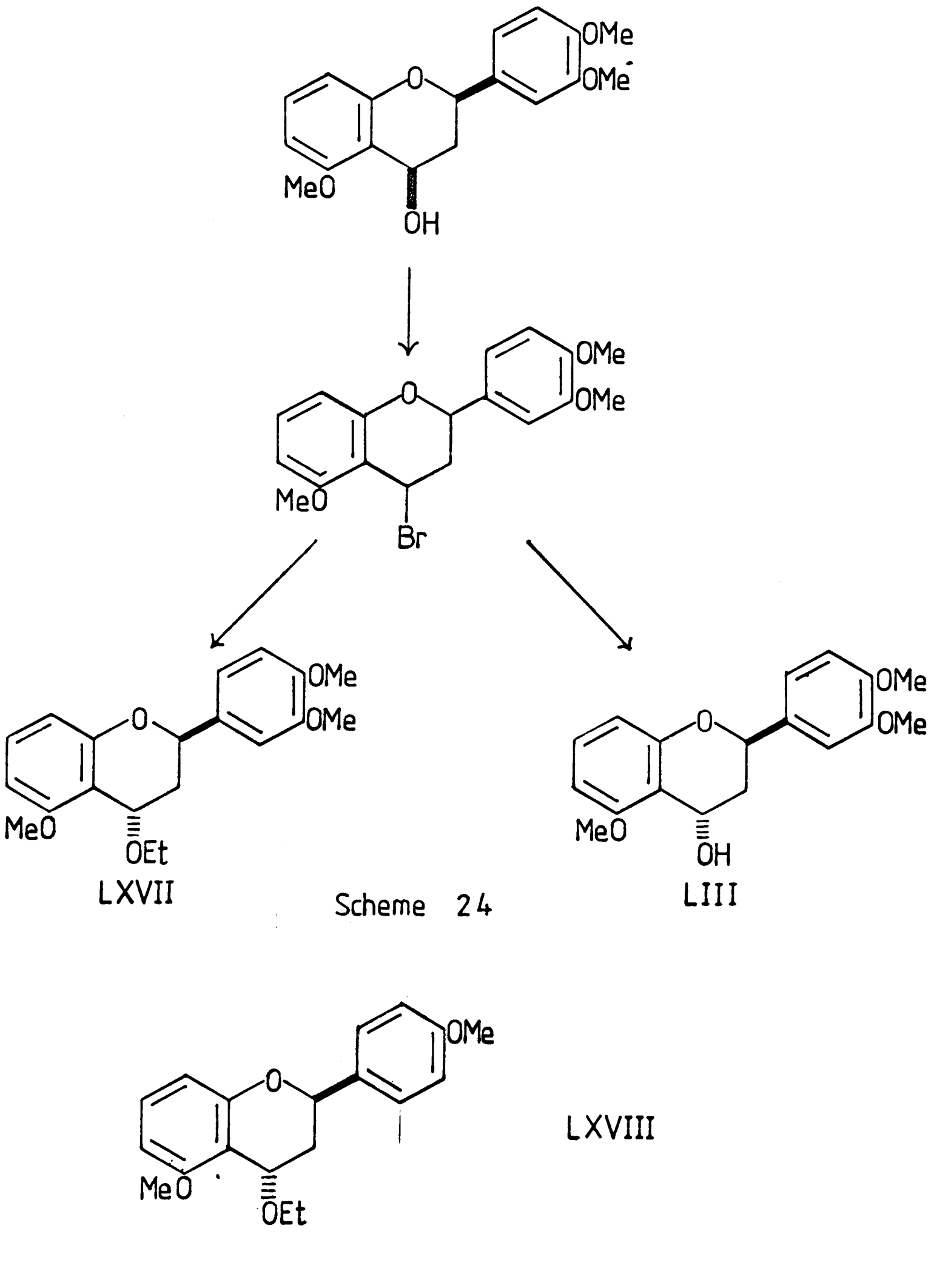
and not during the subsequent treatment with alcoholic potassium hydroxide (scheme 23).

This latter interpretation received confirmation when the present author attempted to repeat the preparation of 5,3',4'-trimethoxyflavan-4α-ol (LIII), described by Kamat *et al.*[40] With this substitution pattern, the 4-bromoflavan intermediate is stable enough to survive washing with aqueous sodium acetate and it was isolated as a pink solid, in agreement with the report of Kamat *et al.*[40] Treatment of this solid with ethanolic potassium hydroxide gave a product of m.p. 86-88° as had been found by Kamat *et al.*[40] The proton magnetic resonance spectrum and elemental analysis of this compound, however, left no doubt that it was not the flavan-4α-ol, as had been claimed,[40] but rather 4α-ethoxy-5,3',4'-trimethoxyflavan (LXVII). By contrast, genuine 5,3',4'-trimethoxyflavan-4α-ol (LIII) had m.p. 121-123° and was conclusively different in its proton magnetic resonance spectrum and elemental analysis. It could be obtained by a modification of the method of Kamat *et al.*[40] in which the ethanolic alkali was replaced by aqueous alkaline dioxan (scheme 24).

It may be confidently inferred from this investigation that Kamat *et al.*[40] had also mistaken 4α-ethoxy-5,4'-dimethoxyflavan (LXVIII) for the flavan-4α-ol (LII), since with this substitution pattern also they isolated the intermediate 4-bromoflavan.

Reaction of 4-bromoflavans with ethanolic potassium hydroxide therefore follows the pattern established for S_N1 reactions at the 4-position of flavanoids in giving products of

4α-stereochemistry; and kinetic control of product formation results from irreversible reaction of the intermediate 4-carbocation (irreversible because under alkaline conditions 4-ethoxyflavans cannot regenerate the 4-carbocation) with the most abundant nucleophile, in this case ethanol.

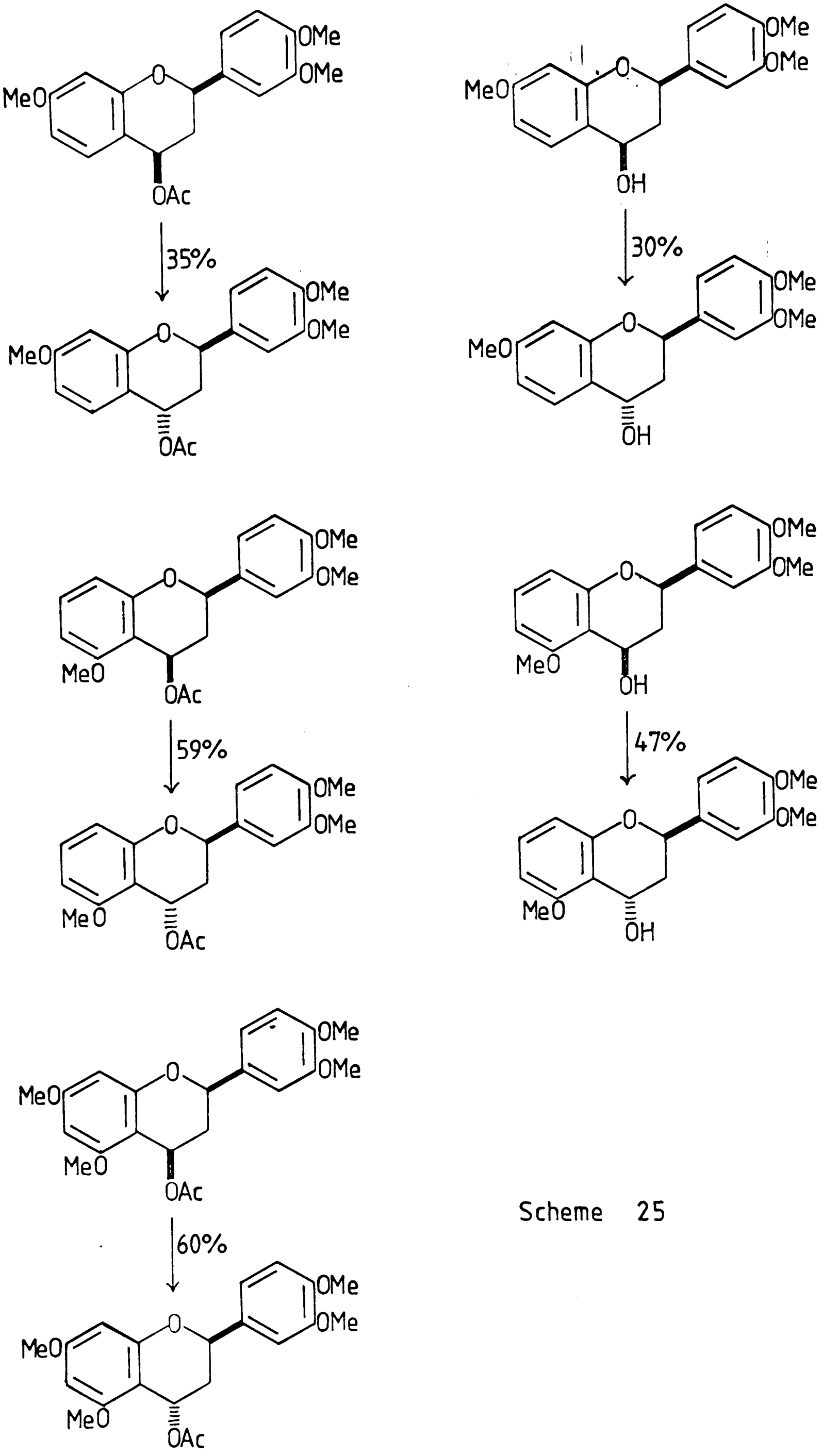


LXVII

Scheme 24

LIII

LXVIII


MeO
OMe
OMe
O
OAc
35%
OAc
MeO
OMe
OMe
O
59%
MeO
OMe
OMe
O
OAc
MeO
OMe
OMe
O
60%
MeO
OMe
OMe
O
OAc
MeO
OMe
OMe
O
OH
30%
MeO
OMe
OMe
O
OH
MeO
OMe
OMe
O
47%
MeO
OMe
OMe
O
OH

Scheme 25

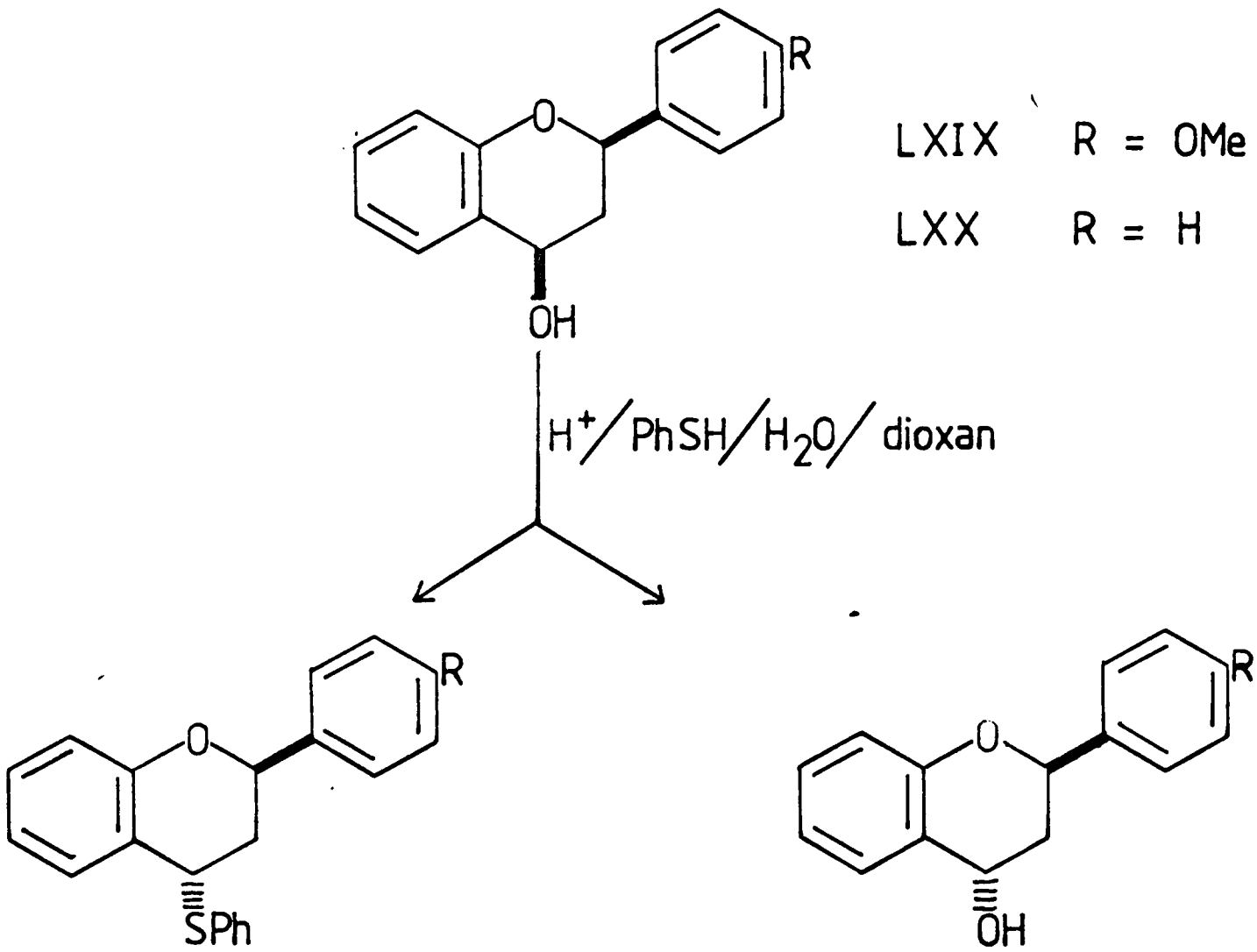
General conclusions on the reactivity of 4-substituted flavans

It has been shown that the flavan-4β-ols (XXXV) to (XXXVII) epimerise under acid conditions to give thermodynamically favoured flavan-4α-ols (LIII), (LXVI) and (LV). The 4β-acetoxyflavans (XL) to (XLII) and (XLIV) likewise are converted in the presence of acid into the 4α-acetoxyflavans (XLVIII), (XLVII), (XLIII) and (XLVI). The reaction of either isomer of 4-acetoxy-5,7,3',4'-tetramethoxyflavan, (XLII) or (XLIII) with methanolic potassium hydroxide to give 4α-methoxy-5,7,3',4'-tetramethoxyflavan (XLV) but not its 4β-epimer shows that kinetic control of stereochemistry also leads to a 4α-substituted product; a similar conclusion can be drawn from the hydrolysis of 4-bromo-5,3',4'-trimethoxyflavan in aqueous alkaline dioxan giving 5,3',4'-trimethoxyflavan-4α-ol (LIII). This result has been anticipated by other workers,[11,22,32] although the many examples of reactions yielding products of 4α-stereochemistry almost all take place under acidic conditions for which it is uncertain whether the stereochemical control results from kinetic or thermodynamic factors (or both).

It is noticeable that for flavanoids lacking a 5-methoxyl substituent, the isolated yields of 4α-substituted products resulting from equilibrium control are lower than the corresponding yields of 4α-substituted products from flavanoids possessing a 5-methoxyl substituent. This is illustrated in scheme 25 for the acid catalysed epimerisations of various 4-acetoxyflavans and flavan-4-ols. It is uncertain, however, whether this reflects a difference in ease of isolation of the 4α-substituted products, or less overwhelming preference for

4α-stereochemistry on the part of flavanoids lacking a 5-methoxyl substituent than those possessing a 5-methoxyl substituent.

The marked effect of A-ring substitution pattern on reactivity at the flavanoid 4-position has been discussed at some length. The difference of B-ring substitution pattern between 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (XLII) and 4β-acetoxy-5,7-dimethoxyflavan (XLIV), on the other hand, made no detectable difference either to reactivity or to the position of equilibrium between the 4α- and 4β-epimers (the equilibrium mixture of 4-acetoxy-5,7-dimethoxyflavans contained 6-7% of the 4β-epimer, compared with 5-10% of 4β-epimer in the equilibrium mixture of 4-acetoxy-5,7,3',4'-tetramethoxyflavans). This is in accord with the opinion of Campbell[34] that anchimeric assistance by the B-ring in reactions of 4β-substituted flavans is unlikely, but it called into question the report of Brown and Shaw[11] that 4'-methoxyflavan-4β-ol (LXIX) reacts with thiophenol to the extent of 68% (isolated yield of product) under conditions where flavan-4β-ol itself (LXX) undergoes negligible reaction. In the hands of the present author, however, the two reactions proceeded at the same rate as estimated by thin layer chromatography. The reaction mixtures were worked up when only a trace of 4'-methoxyflavan-4-ol was judged to remain and isolation of the products by crystallisation gave for each substitution pattern a comparable yield of the flavan-4α-yl phenyl sulphide, (LXXI) or (LXXII) (64% or 60%), and of the flavan-4α-ol, (LIX) or (LVII) (10% or 16%). The flavan-4α-ol resulted from reaction of the 4-carbocation intermediate with water in the reaction mixture.



LXIX R = OMe

LXX R = H

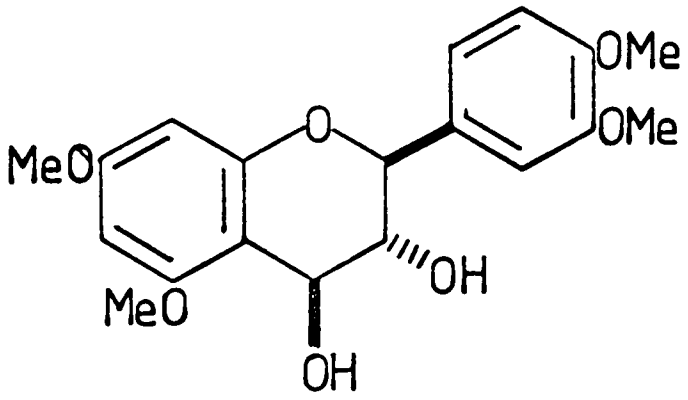
LXXI R = OMe

LXXII R = H

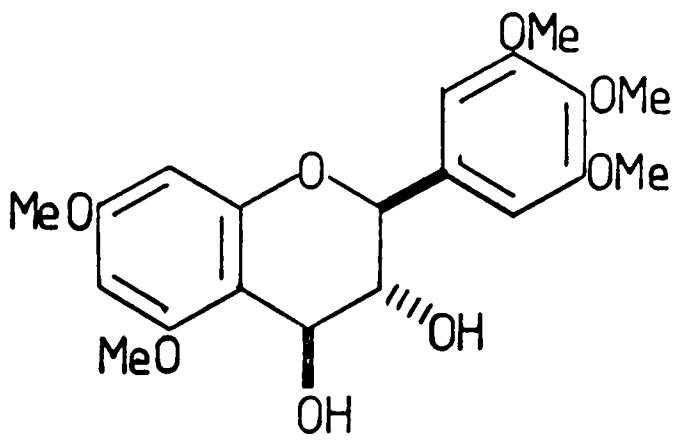
LIX R = OMe

LVII R = H

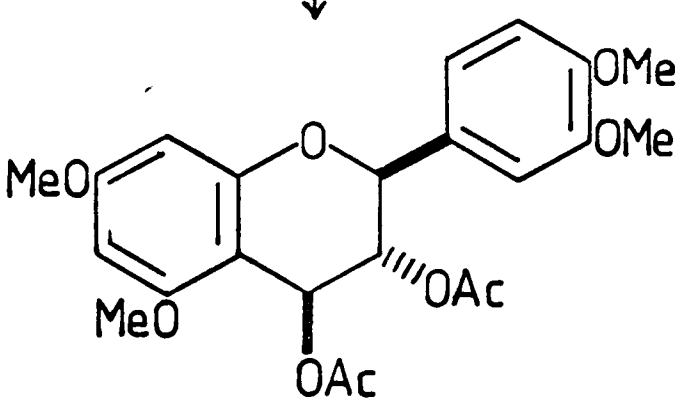
The only other evidence known to the author that B-ring substitution may affect the reactivity at the 4-position of 2,4-cis-substituted flavans is the report of Fujise et al.[37] that 2,3-trans-3,4-trans-5,7,3',4'-tetramethoxyflavan-3,4-diol (XX) with pyridine/acetic anhydride yields the diacetate (LXXIII) of unchanged stereochemistry, while 2,3-trans-3,4-trans-5,7,3',4',5'-pentamethoxyflavan-3,4-diol (LXXIV) with the same reagent gives a diacetate with 2,3-trans-3,4-cis-stereochemistry (LXXV) by epimerisation at the 4-position.



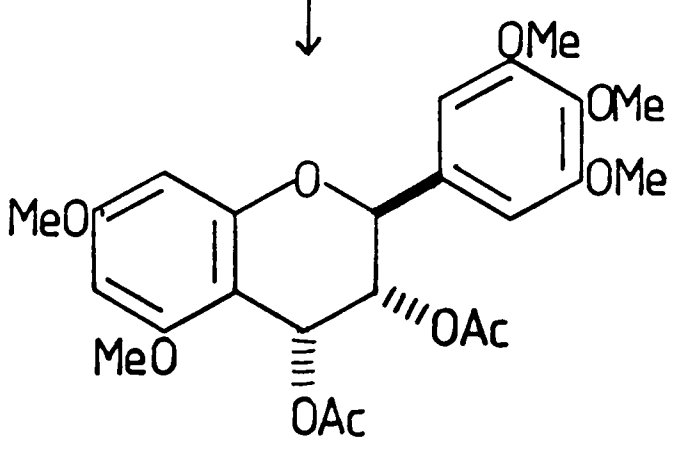
XX



LXXIV



LXXIII



LXXV

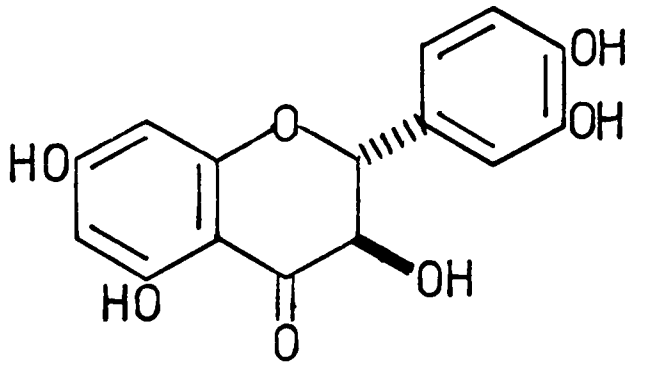
This claim has not been checked. In view of the traps for the unwary which the handling of 4-acetoxyflavans lays, it would be unwise to rely on this single report. The conclusion is therefore that any effect of B-ring substitution pattern on reactivity at the 4-position of 2,4-cis-substituted flavans has yet to be proved. On the other hand, there seems no reason to doubt that the work of Smith[33] and Campbell[34] has demonstrated a small (up to a factor of two) but definite effect of B-ring substitution on the rate of reaction of 2,4-trans-substituted flavans.

The isomeric 2,3-trans-5,7,3',4'-tetramethoxyflavan-3,4-diols and their acetates

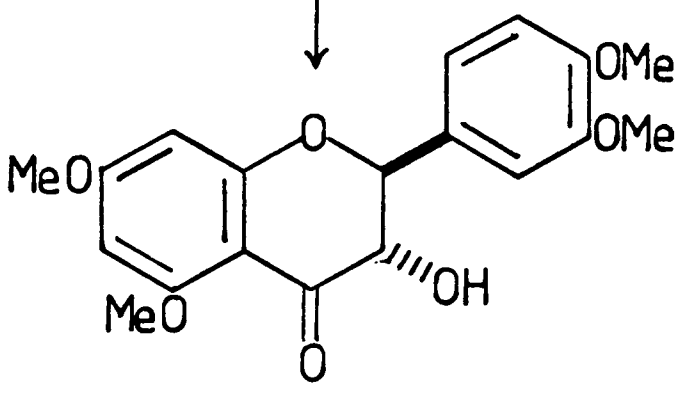
It has already been mentioned that the aromatic substitution pattern most commonly encountered among natural

flavanoids is that of cyanidin (VI). The monomeric flavanoid components of the condensed tannins usually conform to this pattern and, it seems, invariably also possess a hydroxyl group at the 3-position. By studying the reactivity of 4-acetoxyflavans having a 3-oxygen substituent it would be possible to place these compounds in the spectrum of reactivity already established for 4β-acetoxyflavans and thus assess the effect of the 3-hydroxyl group on the reactivity of natural tannins and of synthetic tannin models.

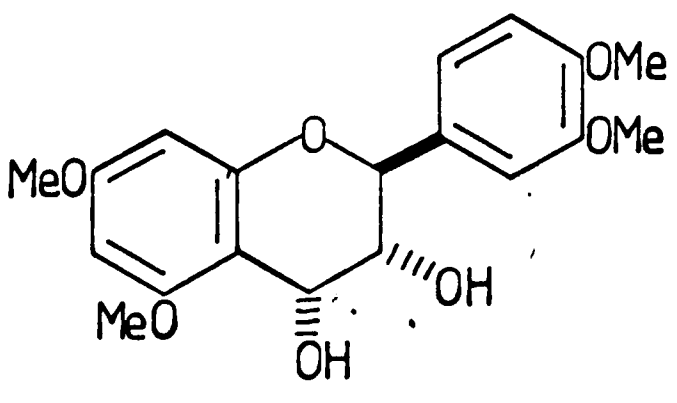
Accordingly, 2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-5,7,3',4'-tetramethoxyflavan-3,4-diol, (XX) and (LXXVIII), were prepared by reduction of 2,3-*trans*-3-hydroxy-5,7,3',4'-tetramethoxyflavanone (LXXVII) with sodium borohydride, the two diols



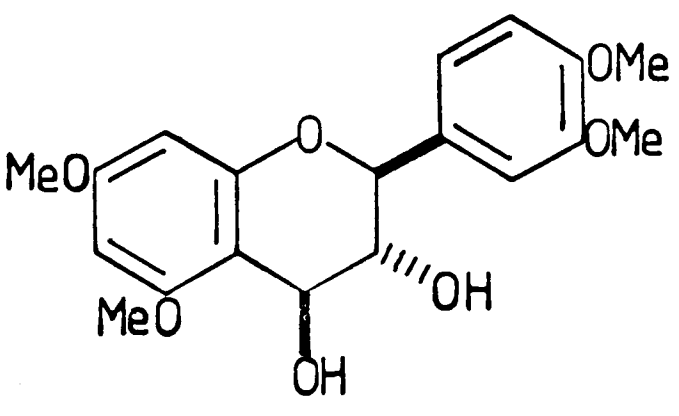
LXXVI



LXXVII



LXXVIII

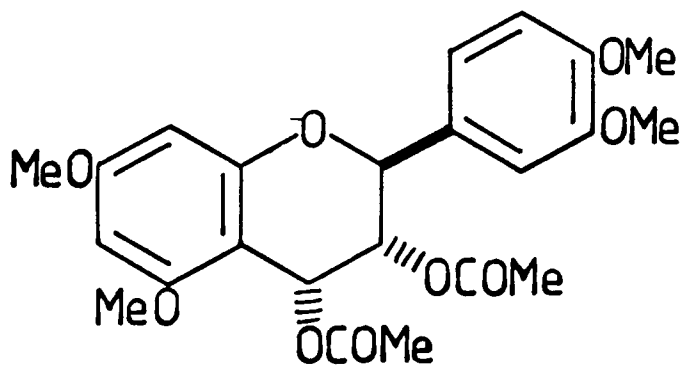


XX

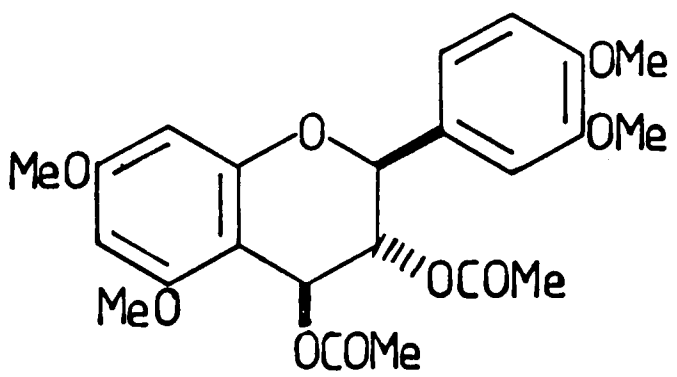
being separable by virtue of the different stabilities of their borate complexes. The 3-hydroxyflavanone (LXXVII) was prepared by methylation of the naturally occurring (+)-dihydroquercetin (LXXVI), during which process substantial racemisation occurs. The optical purity of the product was less than 25%, calculated from its optical rotation and the value given by Clark-Lewis and Korytnyk[54] for a sample of unknown optical purity.

The diols, (LXXVIII) and (XX), were completely racemic. The 2,3-trans-3,4-cis-diol, (LXXVIII), exhibited negligible optical rotation and the 2,3-trans-3,4-trans-diol (XX), although too insoluble for its optical rotation to be measured, gave racemic derivatives.

Acetylation of each diol with acetic anhydride/pyridine gave the known diacetates (XXV) and (LXXIII).



XXV

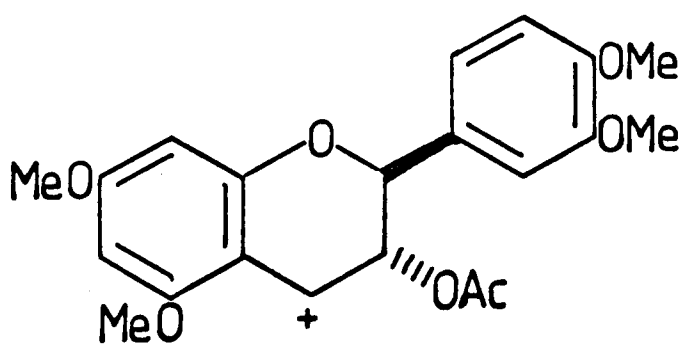


LXXIII

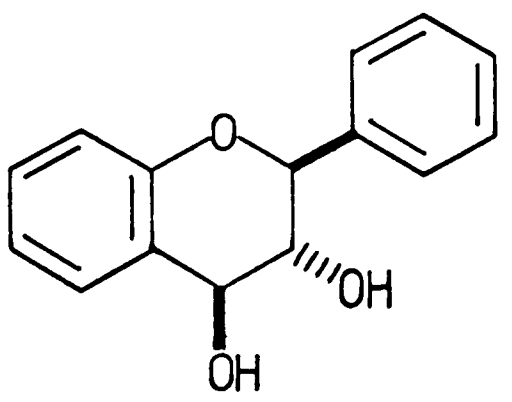
2,3-Trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (LXXIII) was unaffected by pyridine/acetic anhydride mixture at 80°, but acetic anhydride mixture at 60° converted it into the thermodynamically more stable 2,3-trans-3,4-cis-diacetoxy-5,7,3',4'-tetramethoxyflavan (XXV) in 70% isolated yield. Equilibration of the two diacetates in acetic anhydride

mixture gave 14-18% of the 2,3-trans-3,4-trans- and 82-86% of the 2,3-trans-3,4-cis-isomer.

In reactivity, then, the diacetate (LXXIII) resembles 4β-acetoxy-7,3',4'-trimethoxyflavan (XLI) (cf. table 1). The presence of the 3-acetoxy group thus decreases the reactivity at the 4-position. Presumably this is because the inductive effect of the acetoxy group destabilises the 4-carbocation (LXXIX). A hydroxyl group at the 3-position would have a similar (though weaker) inductive effect and is thus also expected to decrease reactivity at the 4-position. The reduced reactivity of 2,3-trans-3,4-trans-flavan-3,4-diol (LXXX) compared with flavan-4β-ol (LXX) has been noted by Brown and Shaw[11] who also pointed out that reactions of the diol (LXXX) give a less clear-cut stereochemical outcome than do those of flavan-4β-ol (LXX). This same reduction in stereochemical preference is shown by the equilibrium between the diacetates (XXV) and (LXXIII), (which contains about 16% of the less stable epimer) compared with that between 4α- and 4β-acetoxy-5,7,3',4'-tetramethoxyflavan, (XLIII) and (XLII), (which contains only about 7% of the less stable epimer).



LXXIX



LXXX

It will be seen in the next chapter that the lower reactivity of 3,4-disubstituted tetramethoxyflavans than of 4-monosubstituted tetramethoxyflavans is a disadvantage as regards synthetic transformations of the former. Furthermore, the less clear-cut thermodynamic control of stereochemistry of 3,4-disubstituted flavans is matched by an even less straightforward kinetic control of stereochemistry. Hence the determination of the stereochemistry of products of such reactions relies more heavily on interpretation of nuclear magnetic resonance spectra.

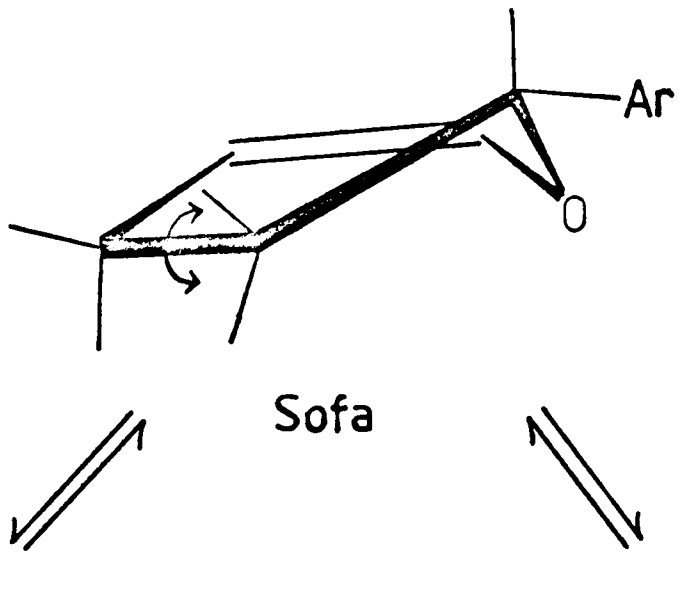
A discussion of the proton magnetic resonance spectra of 3,4-disubstituted- and 4-monosubstituted-flavans ends this chapter. Since the same principles apply to the interpretation of the spectra of both groups of flavanoids, the characteristics of both are described in this chapter. Reference back to this section will be made in subsequent chapters when the stereochemistry of 3,4-disubstituted flavans is discussed.

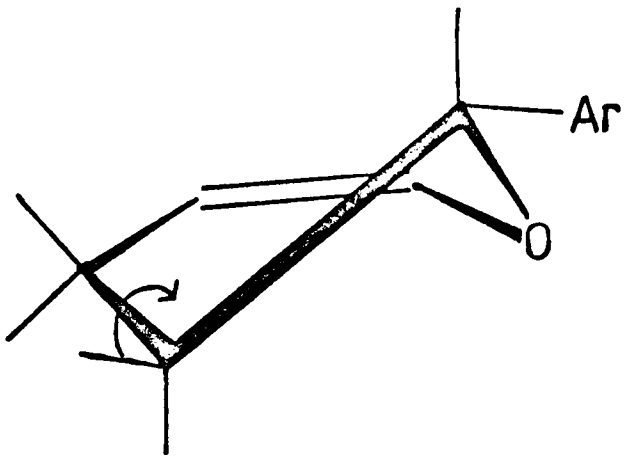
The preferred conformations and proton magnetic resonance spectra of flavans substituted at the 3- and/or 4-position

Whereas chemical methods of assigning relative stereochemistry to 4-substituted and 3,4-disubstituted flavans have proved questionable, nuclear magnetic resonance studies have provided reliable assignments for a large number of such species (see, for example, ref. 55). In many instances it has been possible to assign both configuration and preferred conformation from the values of the coupling constants between protons in the heterocyclic ring, since these constants may be related to dihedral angles by the Karplus equation and the calculated angles are often compatible with only a narrow range of con-

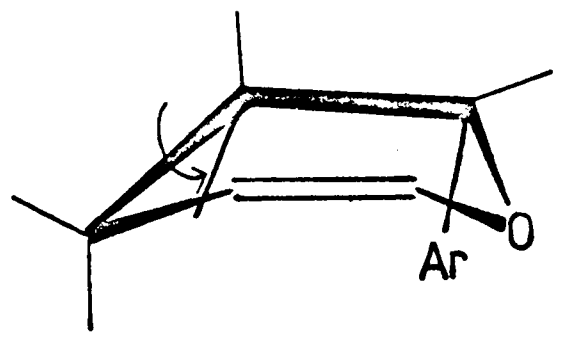
formations of a single configuration.[28,42]

Conformations may be conveniently explored on a Dreiding model of the flavan nucleus which when unstrained adopts the so-called 'sofa' conformation in which C-3 is slightly and C-2 greatly above the plane of the other four atoms of the B-ring. By twisting about the bond between C-3 and C-4 this conformation is distorted in one direction into the 'half-chair' and in the other into the 'half-boat' (scheme 26).





Half - chair



Half - boat

Scheme 26

It is found that these three conformations account for the coupling constants of the majority of flavans (though not for flavanoids having sp^2 hybridised carbons in the heterocyclic ring) with the B-ring occupying an equatorial position.[28,56] The 'half-boat' conformation is unusual[57-59] and since the 'half-chair' and 'sofa' conformations lead to similar coupling

constants for a given configuration,[88] the assignment of stereochemistry to a 3- or 4-substituted or 3,4-disubstituted flavan is reduced in principle to correlation of experimental coupling constants with the calculated values. Table 2 (after Clark-Lewis *et al.*[28]) gives calculated coupling constants and, as an indication of what is considered satisfactory agreement, experimental values for the four stereoisomers of 5,7,3',4'-tetramethoxyflavan-3,4-diol:[55]

Table 2: Calculated coupling constants (Hz) for flavanoid 'sofa' and 'half-chair' conformations, and the experimental values for the four isomeric 5,7,3',4'-tetramethoxyflavan-3,4-diols

	2,3-*trans*	2,3-*cis*	3eq4ax	3ax4eq	3eq4eq	3ax4ax
Half-chair	10.7	0.9	3.9	3.3	0.4	10.5
Sofa	10.9	1.5	6.4	7.0	0.3	8.6
5,7,3',4'-tetramethoxy-flavan-3,4-diols:						
2,3-*trans*-3,4-*trans*	10.1					7.3
2,3-*trans*-3,4-*cis*	10.1			4.1		
2,3-*cis*-3,4-*trans*		*ca.*0.9			2.5	
2,3-*cis*-3,4-*cis*		*ca.*1.0	4.8			

Obtaining the coupling constants of a 3,4-disubstituted flavan from its proton magnetic resonance spectrum is often a straightforward matter because the 2-,3- and 4-proton signals are generally well separated, forming an AMX spin system for which measured line splittings are equal to the desired coupling constants. The 3-H resonance is readily identifiable as a doublet of doublets or triplet, being split by coupling to both the 2-proton and 4-proton. The 2-H and 4-H resonances are both doublets as a result of coupling to the 3-proton. The 2-H

signal is relatively insensitive to the nature of substituents at the 3- and 4-positions and occurs at 4.5-5.5τ. Only if the 4-proton resonates in the same region is there any difficulty in assigning the spectrum. Even then a distinction may be possible because the 4-proton resonances are sometimes more broadened by weak coupling to the adjacent A-ring aromatic protons than are the 2-proton resonances by the B-ring protons.[59,6]

The stereochemistry of a 4-substituted flavan is less easily assigned from its nuclear magnetic resonance spectrum because the two protons at the 3-position have similar chemical shifts, the axial proton of the pair resonating at slightly higher field.[42] An ABMX spin system results, with $J_{m,x}=0$ because coupling between the 2-proton and 4-proton is negligible. When the 3-proton multiplets are sufficiently well resolved for line splittings to be measured from this part of the spectrum, then first-order analysis leads to little error. For example, if $J_{2,3eq}=2Hz$, $J_{2,3ax}=10Hz$ and $J_{3eq,3ax}=13Hz$, then the 3-H and 3*-H multiplets will not overlap provided that the chemical shift difference between the centres of the multiplets is at least 25Hz, the sum of the coupling constants. Applying the equations quoted by Wiberg and Nist,[61] the true coupling constants will then differ from the apparent first-order values by only 0.5Hz.

However, when the 3-H resonances overlap substantially, the apparent coupling constants may be wildly inaccurate, while insufficient lines are detectable in the 3-H region for a second-order analysis to be feasible. Fortunately, even under second-order conditions, the sums of coupling constants $(J_{2,3eq}+J_{2,3ax})$ and $(J_{3eq,4}+J_{3ax,4})$ remain equal to the sums of line splittings measured from the 2-H and 4-H regions alone,

and these sums suffice to provide a clear indication of stereochemistry.[42,60] The value of ($\underline{J}_{3eq,4}+\underline{J}_{3ax,4}$) is much greater for 2,4-cis (β) stereochemistry than for 2,4-trans (α) stereochemistry; the value of ($\underline{J}_{2,3eq}+\underline{J}_{2,3ax}$) is slightly larger for α than for β stereochemistry. Combining values quoted by Clark-Lewis,[60] Bolger et al.[42] and Bateman[23] for flavans with a variety of substituent at the 4-position gives the following ranges (table 3).

Table 3: Experimentally determined sums of coupling constants for 4α- and 4β-substituted flavans

	$\underline{J}_{2,3}+\underline{J}_{2,3*}$ (Hz)	$\underline{J}_{3,4}+\underline{J}_{3*,4}$ (Hz)
4α-	11.5-15.4	5.5-10.0
4β-	13.0-14.4	16.0-18.5

Table 4 collates data from the proton magnetic resonance spectra of compounds discussed in this Chapter. Stereochemistry may be directly inferred from the values of $\underline{J}_{3,4}+\underline{J}_{3*,4}$.

Table 4: N.m.r. data for 4-substituted flavans discussed in Chapter 1

Compound	Methoxyl substitution pattern	4-substituent	$J_{2,3}+J_{2,3*}$ (Hz)	$J_{3,4}+J_{3*,4}$ (Hz)	Vacetyl (τ)
		β:			
XXXVI	7,3',4'	OH	13.6	16.4	-
XXXVIII	5,7	OH	14.0	17.0	-
XL	5,3',4'	OAc	12.6	14.4	8.08
XLI	7,3',4'	OAc	13.4	16.6	7.88
XLII	5,7,3',4'	OAc	12.4	15.0	8.10
XLIV	5,7	OAc	12.4	13	8.24
		α:			
XLVIII	5,3',4'	OAc	14.2	6.0	7.90
XLVII	7,3',4'	OAc	14.4	6.0	7.90
XLIII	5,7,3',4'	OAc	14.2	<11	7.90
XLVI	5,7	OAc	15.0	<11	7.90
LIII	5,3',4'	OH	14	<10	-
LXVI	7,3',4'	OH	14.0	6.0	-
LV	5,7,3',4'	OH	13.4	4	-
LXVII	5,3',4'	OEt	14.4	5.6	-
XLV	5,7,3',4	OMe	14.4	5.2	-

CHAPTER 2

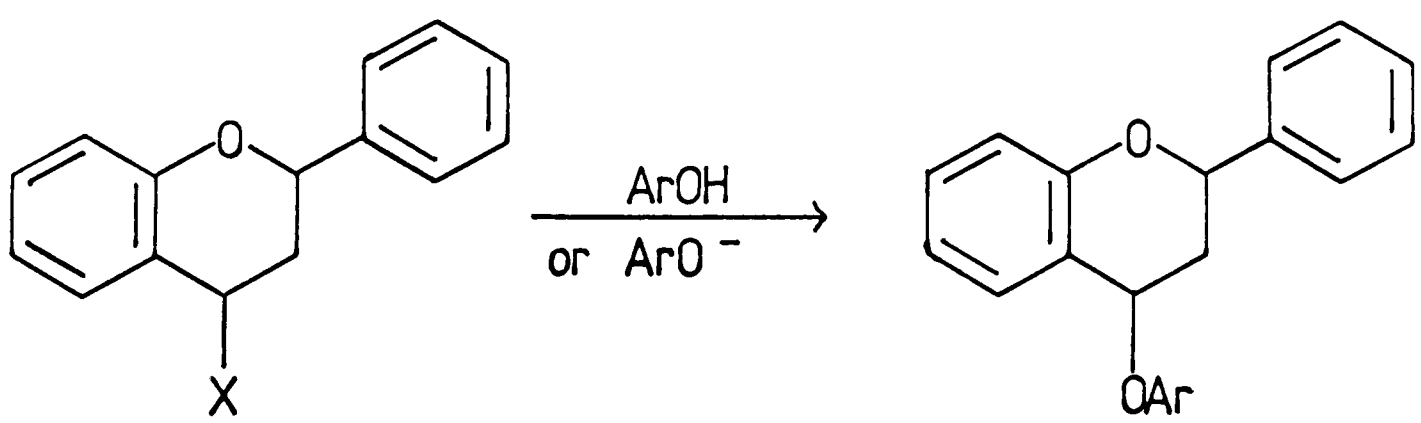
Synthetic transformations of 4-substituted flavans

The second aim of the present work, outlined in the introduction, was the study of the synthetic utility of 4-substituted flavanoids. Those flavanoids possessing 5,7-dimethoxy substitution in the A-ring were of special interest because of the importance of this substitution pattern in nature and the dearth of known synthetic transformations of such compounds. A synthetic route to highly substituted 4-aryloxyflavans in particular was required, and it was hoped that this route might be extended to the synthesis of ether-linked flavanoid dimers.

Previous work on the synthesis of 4-aryloxyflavans will first be discussed in the light of the understanding gained in Chapter 1 of the reactivity of 4-substituted flavanoids.

4-Aryloxyflavans: previous synthetic strategies

Previous syntheses of 4-aryloxyflavans have all been of the type illustrated in scheme 27. A flavan bearing a leaving group at the 4-position undergoes nucleophilic substitution by a phenol or phenate anion with formation of the desired 4-aryloxyflavan.

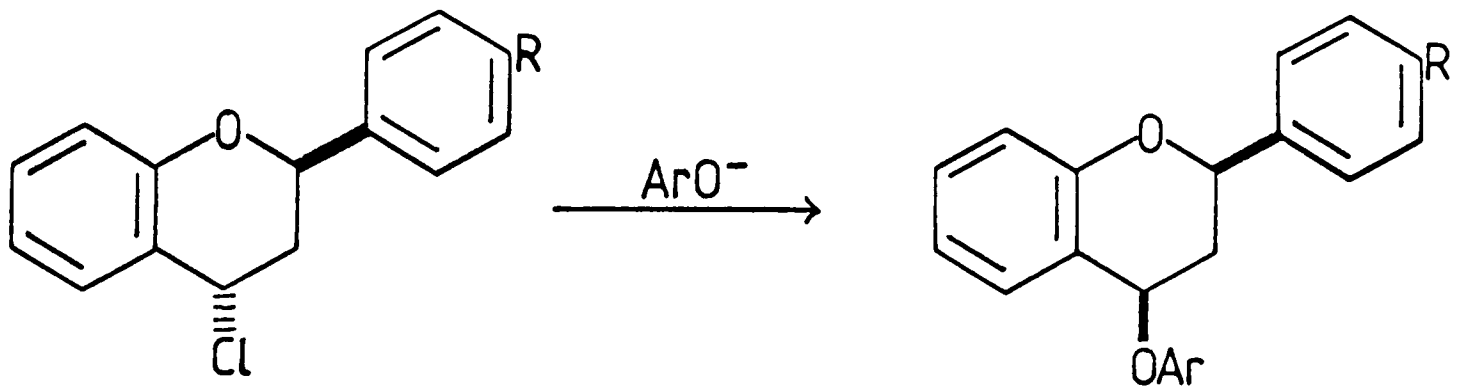


Scheme 27

These reactions may be divided on the basis of their mechanism into S_N1 and S_N2 classes. One synthesis, however, the reaction of a 3,4-epoxyflavan with a phenol, fits neither class because it proceeds with retention of configuration at the 4-position. It is discussed below.

S_N2 reactions are known only for flavanoids without a methoxyl substituent in the A-ring at the 5- or 7-position (with one possible exception, mentioned below). Increasing methoxyl substitution in the A-ring has been shown in Chapter 1 greatly to increase the rate of S_N1 substitution at the 4-position, but electron-donating substituents are expected to have a much smaller effect on the rate of S_N2 substitution, because the latter mechanism involves much less build up of positive charge at the 4-position. It is not surprising, therefore, that the S_N2 syntheses of 4-aryloxyflavans have not been successful with flavanoids possessing A-ring methoxyl substituents, because these flavans react instead by the S_N1 mechanism.

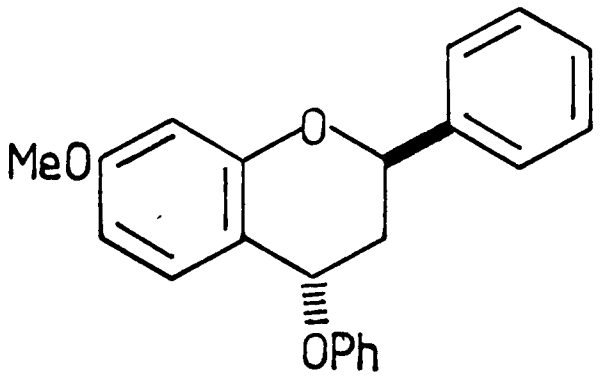
Two types of S_N2 synthesis of 4-aryloxyflavanoids are known. Smart[25] and Kahn[26] used the reaction of 4α-chloroflavan (LXXXI) and 4α-chloro-4'-methoxyflavan (LXXXII) with various phenate anions to synthesise 4β-aryloxyflavans (scheme 28).



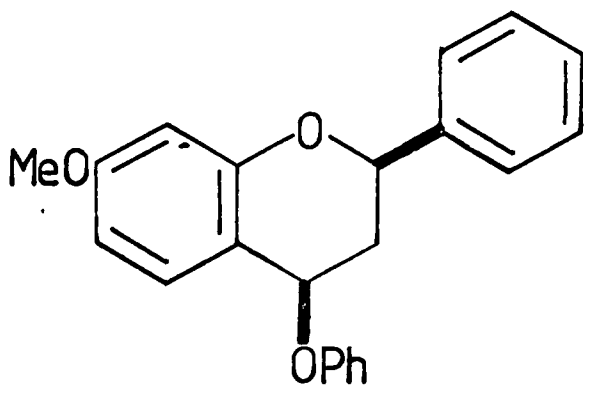
LXXXI R = H
LXXXII R = OMe

Scheme 28

Smart[25] found that 4α-chloro-7-methoxyflavan could not be isolated and that the crude material reacted with sodium phenate to give, after chromatography, a 29% yield of a mixture of 4α- and 4β-phenoxy-7-methoxyflavans, (XII) and (LXXXIII), by simultaneous S_N1 and S_N2 routes.

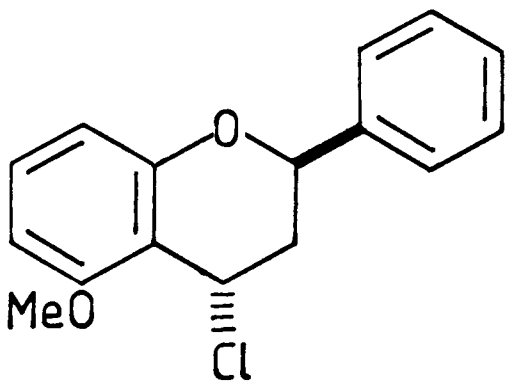


XII

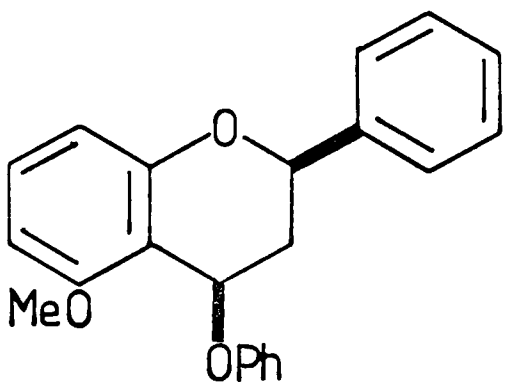


LXXXIII

The corresponding reaction of 4α-chloro-5-methoxyflavan (LXXXIV) has not been investigated, but the lower reactivity of 5-methoxy- than 7-methoxy-substituted flavans by the S_N1 mechanism (discussed in Chapter 1) suggests that an S_N2 synthesis of 4β-phenoxy-5-methoxyflavan (LXXXV) might be viable.



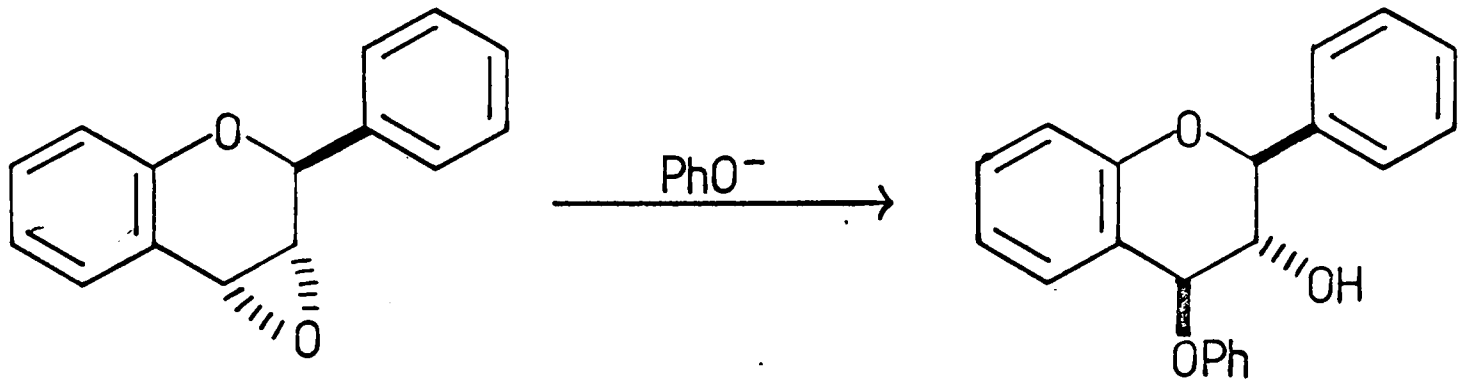
LXXXIV



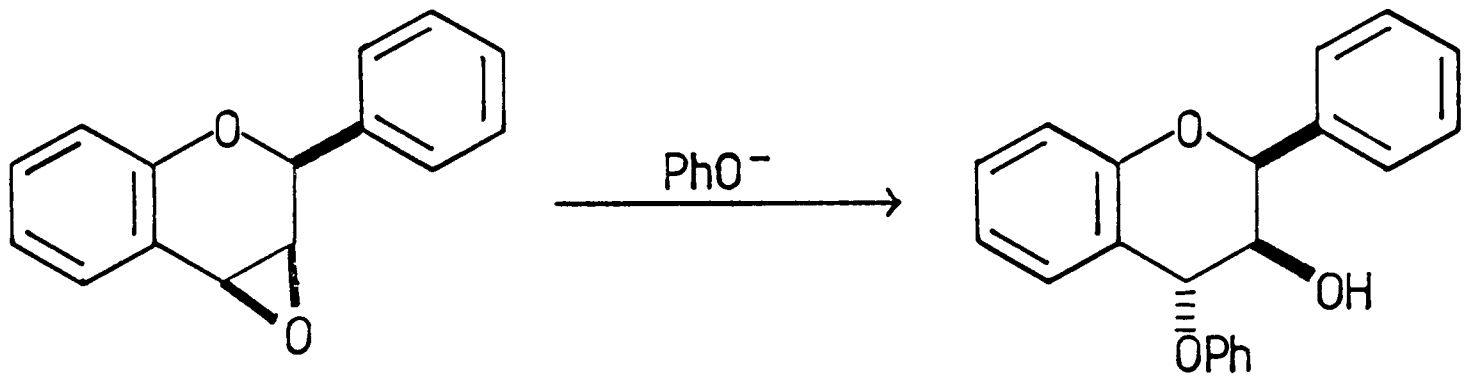
LXXXV

The second S_N2 synthesis of 4-aryloxyflavanoids is that due to Shaw[27] who showed that 2,3-<u>trans</u>-3,4-epoxyflavan

(LXXXVI) reacts with phenate ion with inversion of configuration at the 4-position to give 2,3-trans-3,4-trans-4-phenoxyflavan-3-ol (LXXXVII); and to O'Neill[22] who showed that 2,3-cis-3,4-epoxyflavan (LXXXVIII) similarly gives 2,3-cis-3,4-trans-4-phenoxyflavan-3-ol (LXXXIX).

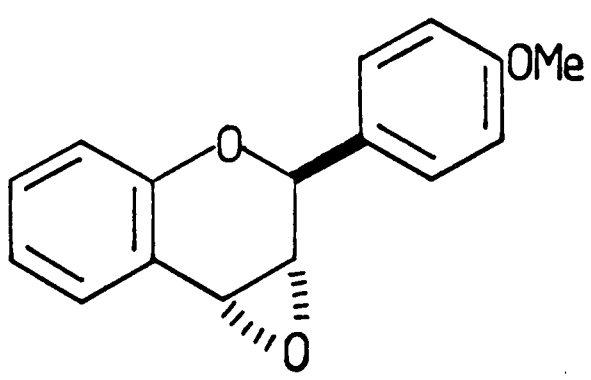


LXXXVI LXXXVII

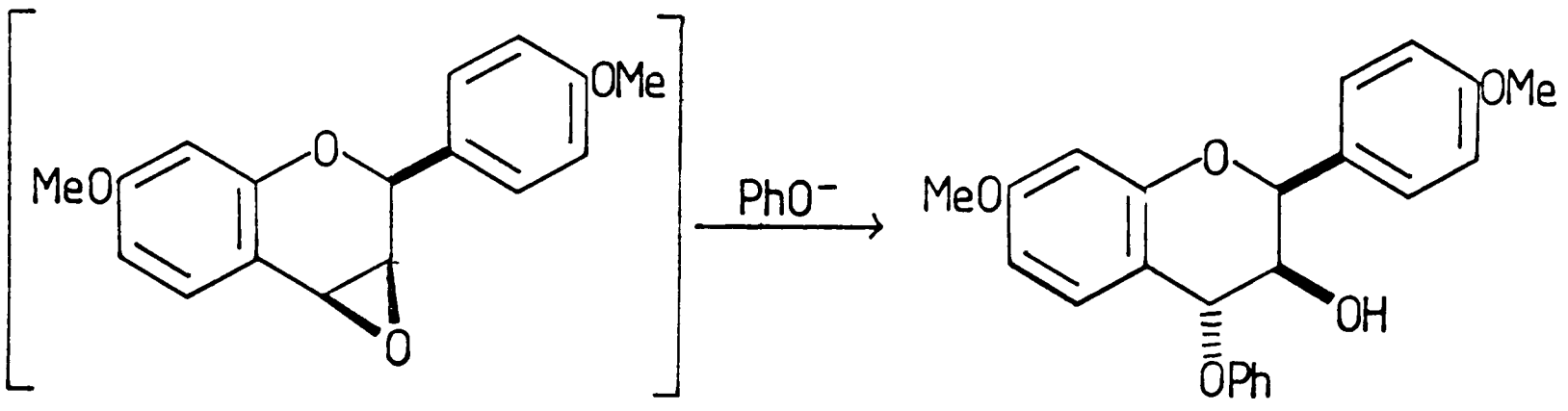


LXXXVIII LXXXIX

O'Neill[22] found that 2,3-trans-3,4-epoxy-4'-methoxyflavan (XC) reacted in the same way, but methoxyl substitution in the A-ring made 2,3-cis-7,4'-dimethoxy-3,4-epoxyflavan (XCI)



XC



XCI XIII

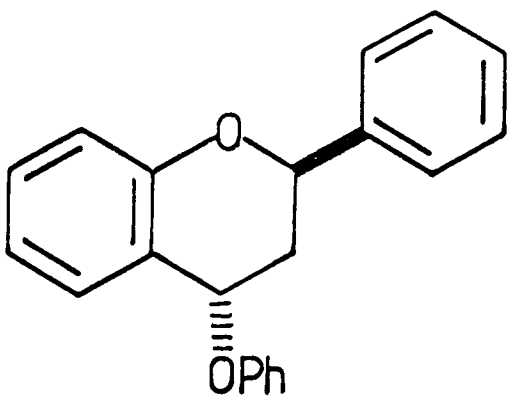
too reactive (presumably by an S_N1 process) to be isolated. When it was generated in the presence of sodium phenate, however, 2,3-cis-3,4-trans-4-phenoxy-7,4'-dimethoxyflavan-3-ol (XIII) could be isolated.[22]

This reaction is the possible exception to the generalisation that S_N2 syntheses are only known for flavanoids lacking A-ring methoxyl substituents. However, the stereochemistry of the product, (XIII), does not necessarily imply an S_N2 mechanism, since for 2,3-cis-substituted flavans, 3,4-trans stereochemistry has been found to be the outcome also of S_N1 solvolyses.[35,55] Thus the formation of the 2,3-cis-3,4-trans-substituted product (XIII) may well be the result of S_N1 opening of the epoxide (XCI).

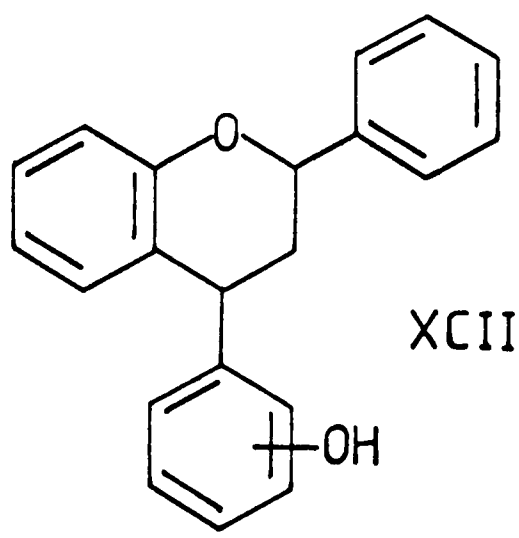
S_N1 syntheses of 4-aryloxyflavans may in principle be subdivided according to whether they proceed with kinetic control of product stereochemistry (when the 4-aryloxyflavan is formed by irreversible reaction of the intermediate carbocation with a nucleophile) or with thermodynamic control of stereochemistry (when conditions are sufficiently vigorous for the 4-aryloxyflavan to be cleaved and repeatedly regenerate the carbocation). In practice, this distinction is blurred,

but it has an important consequence. The intermediate 4-carbocation can react not only at the hydroxyl group of a phenol, but also by electrophilic substitution of the aromatic nucleus of the phenol (to give 4-(hydroxyaryl)-flavans) or of another flavanoid molecule (to give dimers and higher polymers). The carbon-carbon linked species which result are formed essentially irreversibly and divert the 4-carbocation from the desired reaction at the hydroxyl group of the phenol. Reversible formation of the carbocation from the 4-aryloxy-flavan (i.e. thermodynamic control of the stereochemistry of the latter) therefore involves the risk that thermodynamic control will go too far and the major product will be 4-(hydroxyaryl)-flavan or polymer.

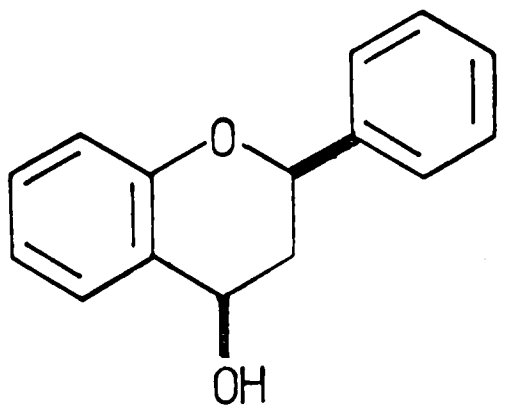
Thus Bateman[23] tried to obtain 4α-phenoxyflavan (XCII) by the condensation of phenol with flavan-4β-ol in the presence of toluene-p-sulphonic acid but found that the products were isomers of 4-(hydroxyphenyl)-flavan (XCIII). Bateman inferred, correctly, that the direct coupling of flavan-4β-ol with phenol to give 4α-phenoxyflavan (XCII) was thermodynamically feasible but that the catalyst he had chosen to promote the reaction allowed reversible formation of the 4-carbocation from the desired aryloxyflavan, which was thereby converted entirely into the thermodynamically more favourable 4-arylflavans (XCIII).



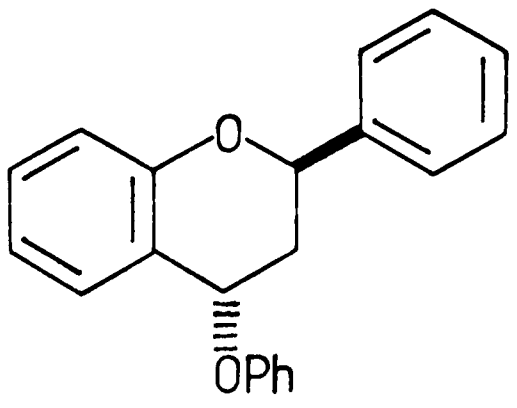
XCII



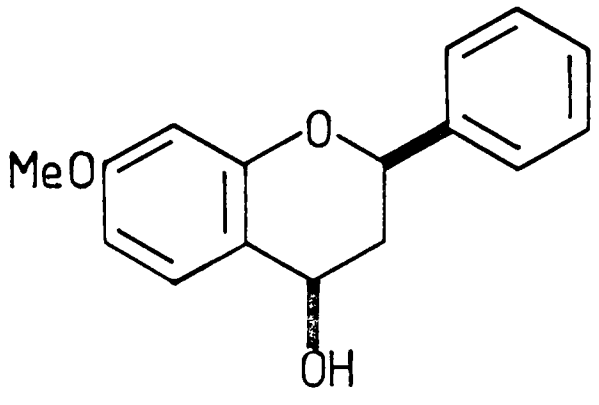
XCIII



LXX

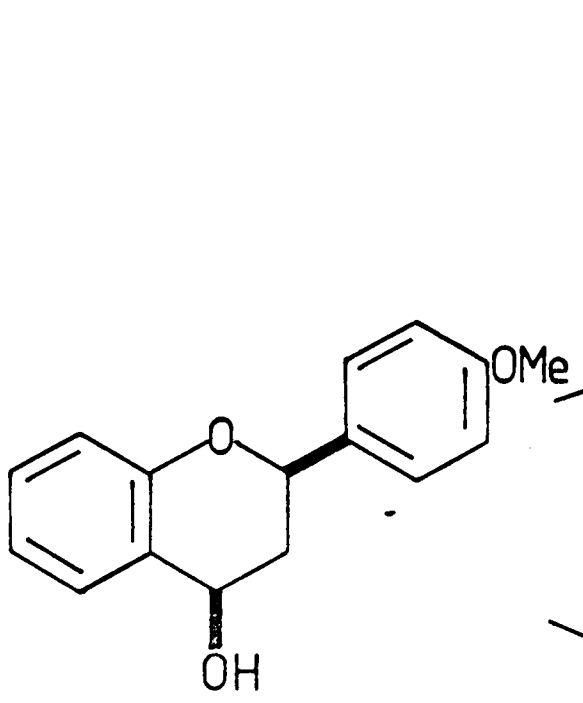


XCII

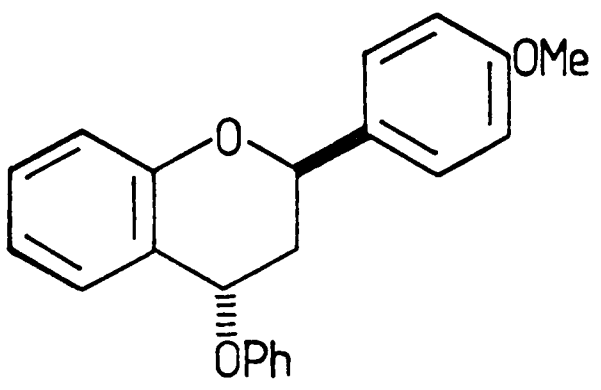


XCIV

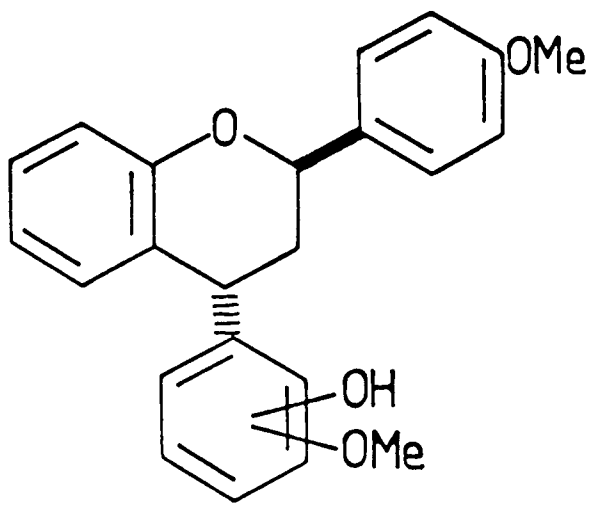
polymer



LXIX



XCV

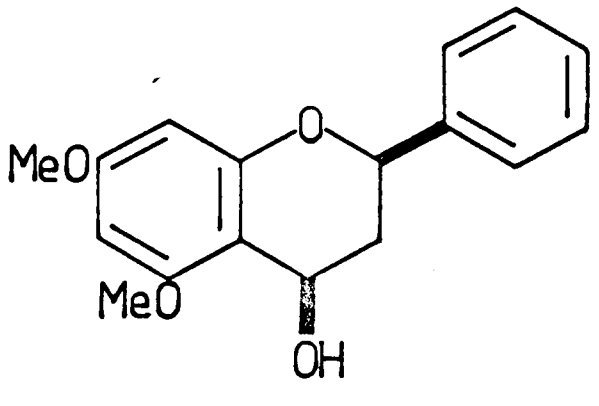


XCVI

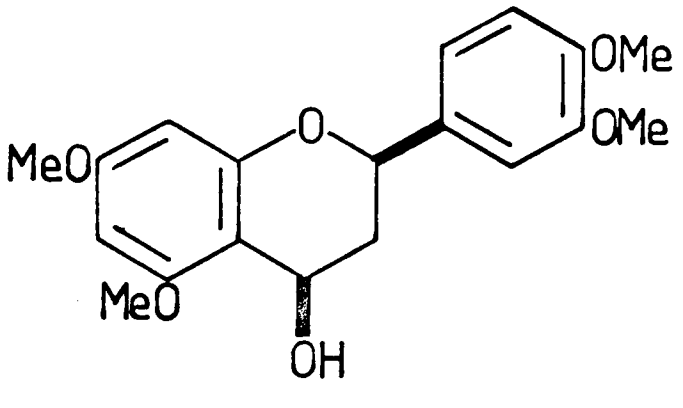
When Bateman[23] used boron trifluoride etherate instead as the catalyst, he was able to isolate 4α-aryloxyflavans in modest yield (up to 47%). He recommended that the reaction be worked up before all the starting material reacted, because even with boron trifluoride as catalyst, long reaction times led to poor yields of 4-aryloxyflavan as a result of reversion to the 4-carbocation and loss of the latter through electrophilic substitution on aromatic nuclei. Such loss of the 4-carbocation is expected to occur even more readily with phenols or flavanoids that are more susceptible to electrophilic attack. It is therefore not surprising that although Bateman caused flavan-4β-ol (LXX) to react with phenol to give 4α-phenoxyflavan (XCII), 7-methoxyflavan-4β-ol (XCIV) with the same reagents gave only polymeric material; nor is it surprising, as Troke[62] showed, that although 4'-methoxyflavan-4β-ol (LXIX) reacts with phenol under boron trifluoride catalysis to give 4α-phenoxy-4'-methoxyflavan (XCV), the same flavan-4β-ol (LXIX) with m-methoxyphenol gives only an isomer of the carbon-carbon linked species (XCVI).

O'Neill[22] showed that 5,7-dimethoxy- and 5,7,3',4'-tetramethoxyflavan-4β-ol, (XXXVIII) and (XXXVII), were sufficiently reactive to condense with phenol in the absence of an added catalyst, but the best yield of 4-aryloxyflavan obtained from the mixtures was 11% of 4α-phenoxy-5,7-dimethoxyflavan (XCVII): polymerisation and the formation of 4-(hydroxyaryl)-flavans once again limited the yield. Flav-3-enes were also detected amongst the reaction products. Their formation, by elimination of a proton from the intermediate 4-carbocation, indicates a third way in which the carbocation is lost.

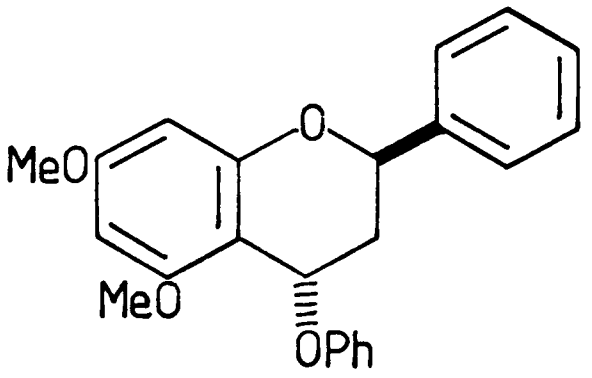
The reactions of 2,3-trans-3,4-trans- and 2,3-trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol, (LXXX) and (XCVIII), with phenol were also unsatisfactory. O'Neill[22] isolated only small amounts of monomers which he took to be 4-phenoxyflavan-3-ols, although the present study shows them to be 4-(hydroxyphenyl)-flavan-3-ols.



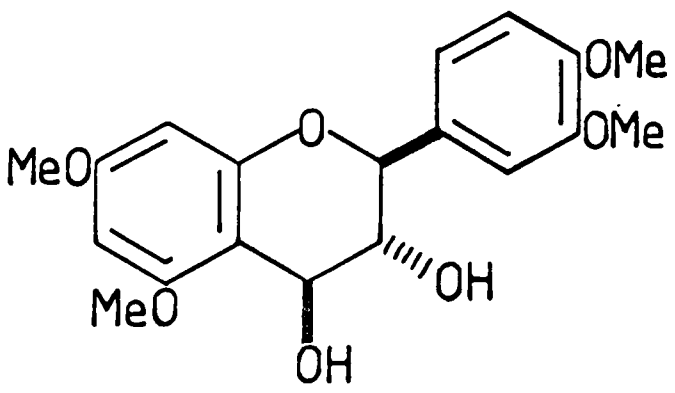
XXXVIII



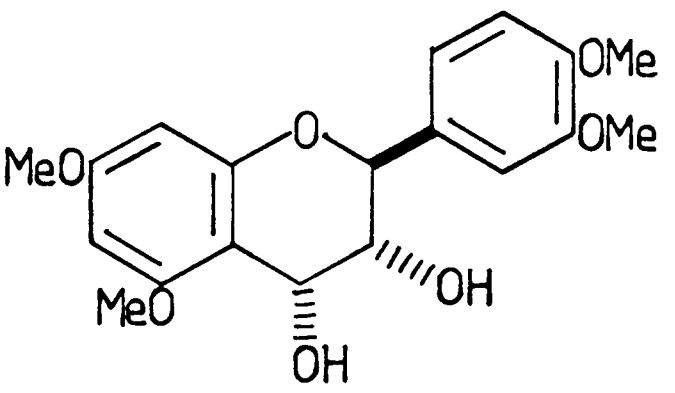
XXXVII



XCVII



LXXX

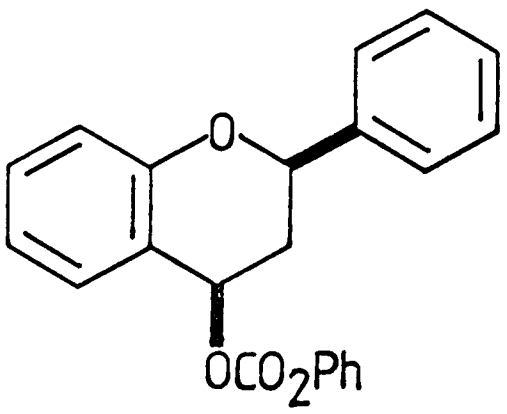


XCVIII

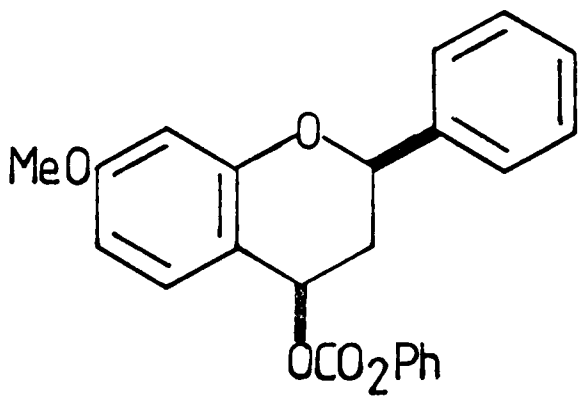
In order to provide better syntheses of 4-aryloxyflavans, Bateman[23] proposed that flavan-4β-ols should first be converted to derivatives possessing a better leaving group than

hydroxyl at the 4-position, so that conversion into a 4-aryloxyflavan would occur under conditions that more nearly approached kinetic control. He found that flavan-4β-yl phenyl carbonate (XCIX) reacted with phenol to give 4α-phenoxyflavan (XCII) in ca. 70% yield under conditions in which the product is inert. This method therefore proceeds by pure kinetic control, but Bateman[23] did not take advantage of the fact to attempt the preparation of aryloxyflavans from phenols with more reactive aromatic nuclei (such as m-methoxyphenol).

The phenyl carbonate route proved not to be applicable to 7-methoxy substituted flavanoids. Bateman[23] and Johnson[24] found that 7-methoxyflavan-4β-yl phenyl carbonate (C) could not be isolated, and the crude material gave only a 4% yield of 4-aryloxyflavan on reaction with phenol. The required 7-methoxyflavan-4β-yl phenyl carbonate (C) is probably so reactive by the S_N1 mechanism that during its preparation, formation of the 4-carbocation occurs and substantial polymerisation results.



XCIX

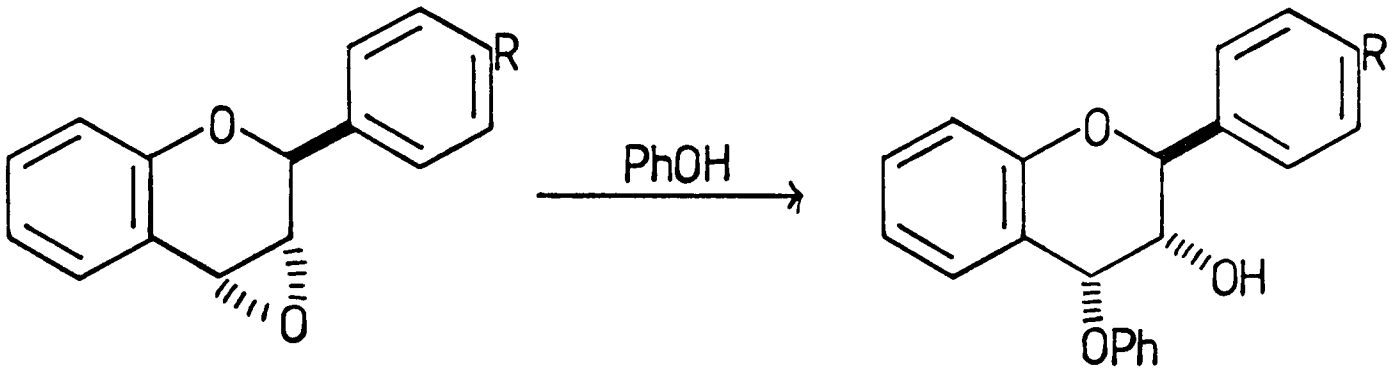


C

Kinetic control of product formation was also found by Shaw[27] for the reaction of 2,3-trans-3,4-epoxyflavan (LXXXVI) with phenol to give 2,3-trans-3,4-cis-4-phenoxyflavan-3-ol (CI).

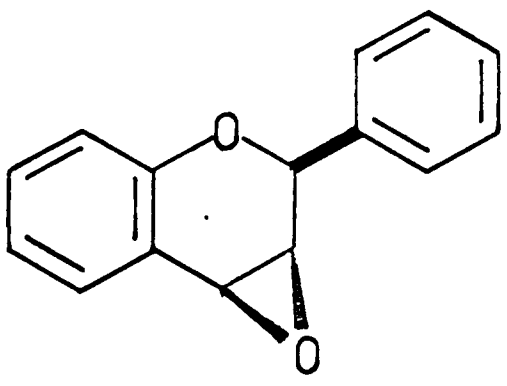
O'Neill[22] showed that 2,3-trans-3,4-epoxy-4'-methoxyflavan (XC) reacted in an exactly analogous manner to give 2,3-trans-3,4-cis-4-phenoxy-4'-methoxyflavan-3-ol (CII), but reaction with phenols more susceptible to aromatic electrophilic substitution has not been investigated for either epoxide, (LXXXVI) or (XC).

O'Neill[22] further showed that 2,3-cis-3,4-epoxyflavan (LXXXVIII) reacted with phenol to give 2,3-cis-3,4-cis-4-phenoxyflavan-3-ol (CIII), whereas simple S_N1 reaction would proceed via the carbocation (CIV) which is expected[62] to give products with 2,3-cis-3,4-trans-stereochemistry. The reaction of 3,4-epoxyflavans with phenols is therefore mechanistically

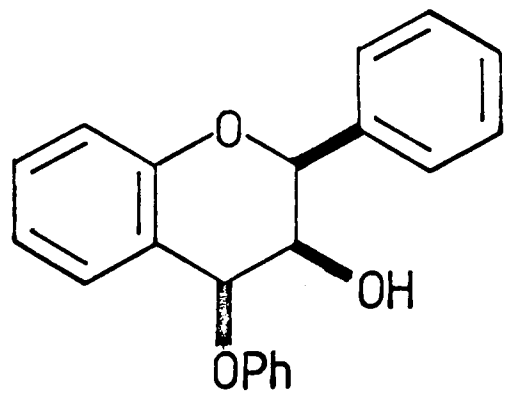


LXXXVI R = H
XC R = OMe

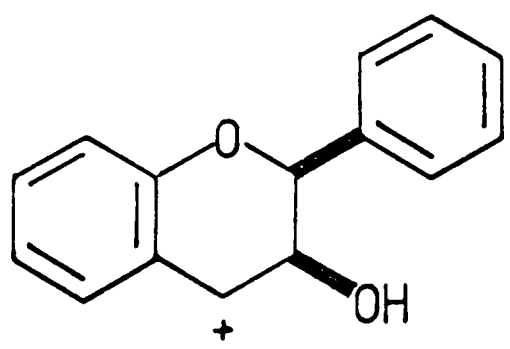
CI R = H
CII R = OMe



LXXXVIII



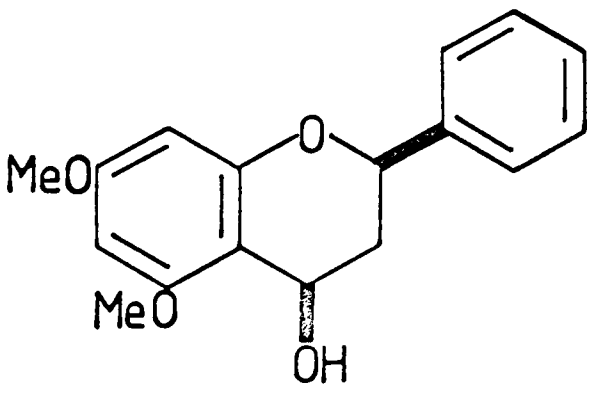
CIII



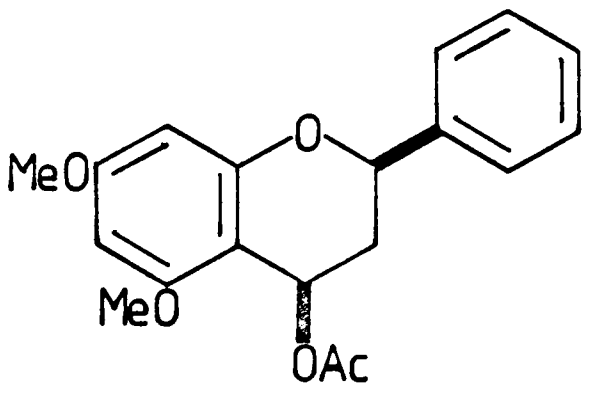
CIV

in a category of its own. The mechanism has been discussed by both O'Neill[22] and Shaw[27] and may be described as an S_Ni process, but for the purpose of classifying syntheses of aryloxyflavans, the important characteristics of this reaction are that it occurs with kinetic control of product formation, because the epoxide function provides a much better leaving group than hydroxyl at the 4-position, and that it is limited to flavanoids without methoxyl substituents in the A-ring, unless 5-methoxy substituted 3,4-epoxyflavans prove sufficiently stable to be isolated.

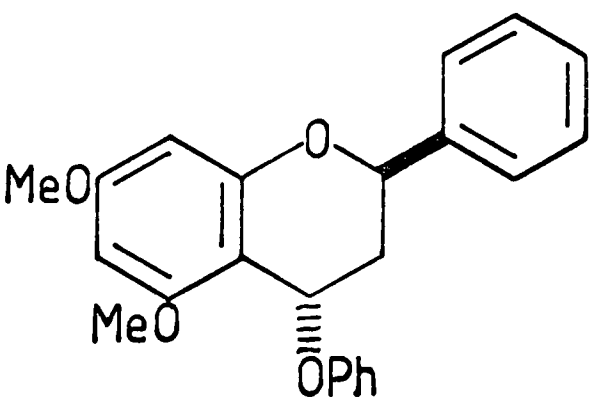
O'Neill[22] sought to replace the hydroxyl group of 5,7-dimethoxyflavan-4β-ol (XXXVIII) by a better leaving group by acetylating it. He did not appreciate the high reactivity of 4β-acetoxy-5,7-dimethoxyflavan (XLIV) and, as the acetyl peaks at 7.90 and 8.24τ in the nuclear magnetic resonance spectrum of his product indicate, he obtained a mixture of 4β- and 4α-acetoxy-5,7-dimethoxyflavan as a gum. Furthermore, in an



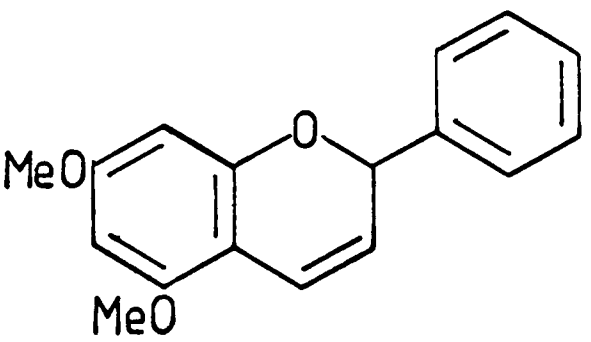
XXXVIII



XLIV



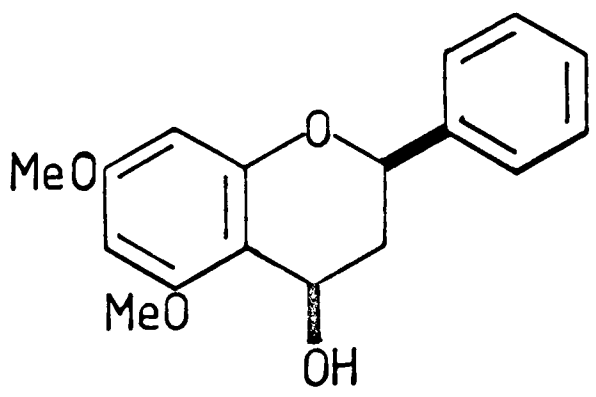
CV



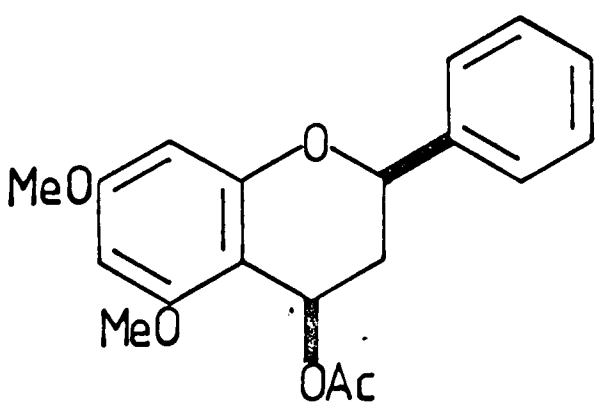
CVI

attempted synthesis of 4α-phenoxy-5,7-dimethoxyflavan (CV) by heating the mixture of acetates with phenol, he employed conditions (heating under reflux in chloroform) very similar to those which, in the reaction of 5,7-dimethoxyflavan-4β-ol (XXXVIII) with phenol, had given a low yield (11%) of 4α-phenoxy-5,7-dimethoxyflavan (CV). The reaction of 4-acetoxy-5,7-dimethoxyflavan with phenol, not surprisingly, gave none of the aryloxyflavan (CV), and the only isolated product was 5,7-dimethoxyflav-3-ene (CVI).

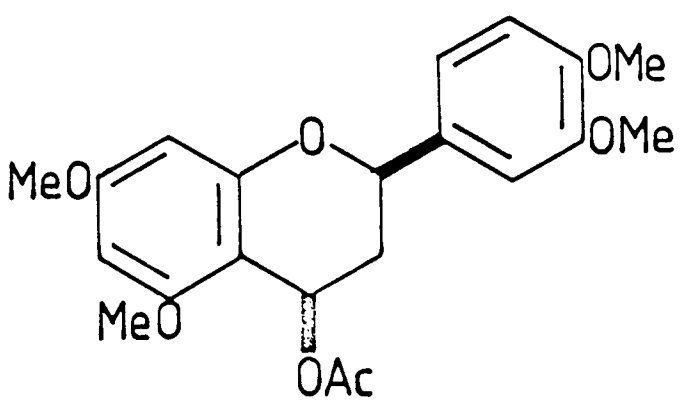
If the analysis of syntheses of 4-aryloxyflavans that has been presented is correct, then 4α-aryloxy-5,7-dimethoxy substituted flavans could only be synthesised in good yield under conditions much milder than those required to bring about reaction of 5,7-dimethoxyflavan-4β-ol (XXXVIII) with phenol. The discussion in Chapter 1 of the ease with which 4β-acetoxy-5,7-dimethoxyflavan (XLIV) and its tetramethoxy analogue (XLII) are converted by pyridine/acetic anhydride in the presence of acetic acid to mixtures of the 4α- and 4β- epimers, and the S_N1 mechanism proposed for this conversion, suggested that



XXXVIII



XLIV



XLII

reaction of the acetoxyflavans (XLII) and (XLIV) with phenol in pyridine might provide a kinetically controlled route to highly substituted 4α-phenoxyflavans and this route was investigated by the present author.

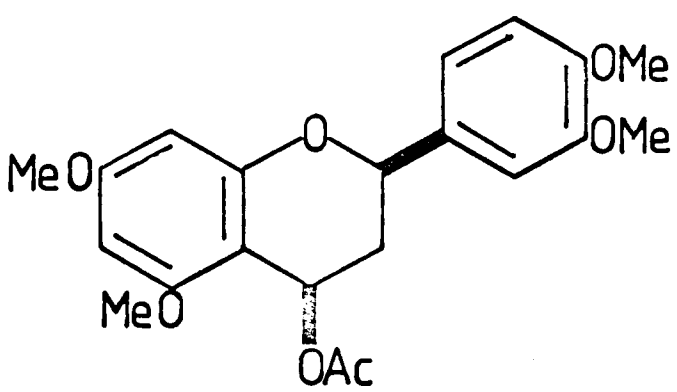
Syntheses of 4-aryloxyflavans from 4-acetoxyflavans: the present work

It was reported in Chapter 1 that 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (XLII) was unaffected on being heated in pyridine alone. The proposed reaction of this acetoxyflavan (XLII) with phenol in pyridine was expected to be catalysed by acid, but it was found that the acidity of the phenol itself was sufficient to bring about reaction. When 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (XLII) was heated to 40° for 5 days with a 12-fold excess of phenol, 4α-phenoxy-5,7,3',4'-tetramethoxyflavan (CVII) was isolated in 60% yield by crystallisation. The nuclear magnetic resonance spectrum of the compound was consistent with this structure and in accord with that reported by O'Neill[22] for a sample of the 4α-phenoxyflavan (CVII) with melting point 6° lower.

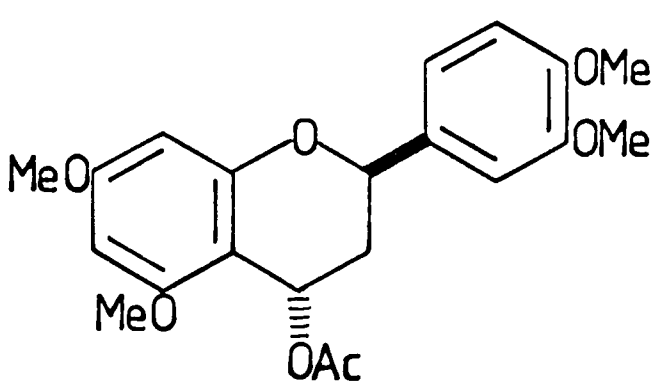
The same product was formed in the same yield from 4α-acetoxy-5,7,3',4'-tetramethoxyflavan (XLIII). The retention of configuration at the 4-position during this reaction confirms that it occurs by the expected S_N1 mechanism and not an S_N2 mechanism.

4α-Phenoxy-5,7-dimethoxyflavan (CV) was obtained crystalline in 48% yield by the analogous reaction of 4β-acetoxy-5,7-dimethoxyflavan with phenol in pyridine. Nuclear magnetic resonance spectroscopy confirmed the structure of this compound and its identity with the sample obtained as an oil by O'Neill.[22]

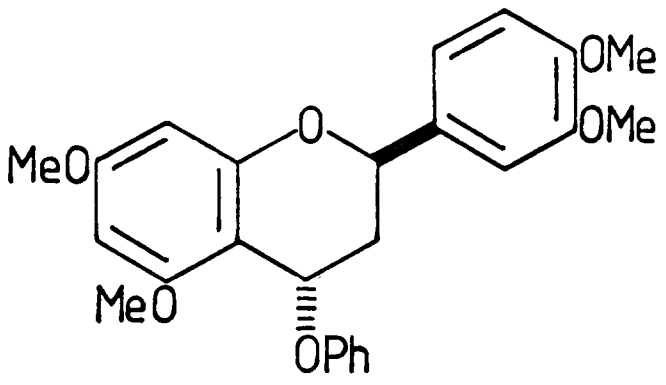
The reactions of 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (XLII) with phenols possessing electron-donating substituents (which activate them towards electrophilic aromatic substitution) were then investigated. m-Methoxyphenol (CVIII) and m-benzoyloxyphenol (CIX) were found to react with the acetate (XLII) to give 46% of 4α-(m-methoxyphenoxy)-5,7,3',4-tetramethoxyflavan (CX) and 51% of 4α-(m-benzoyloxyphenoxy)-5,7,3',-4'-tetramethoxyflavan (CXI), respectively:



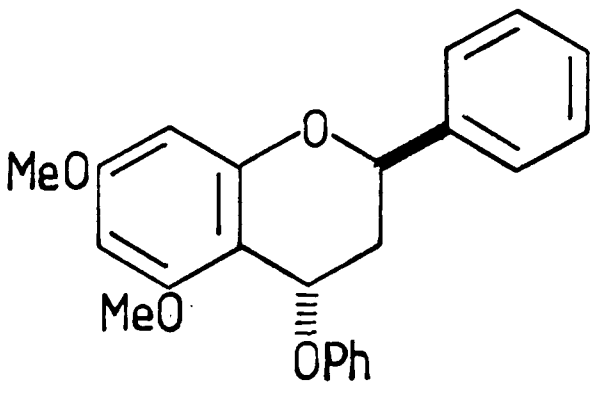
XLII



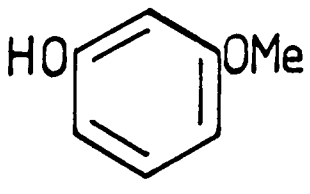
XLIII



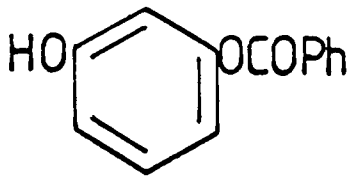
CVII



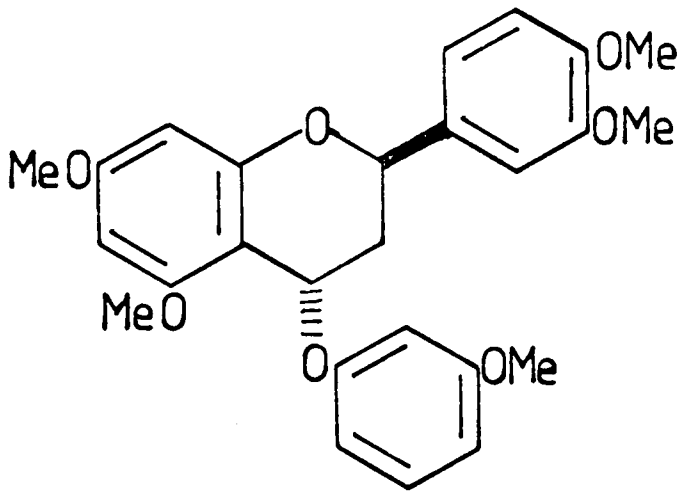
CV



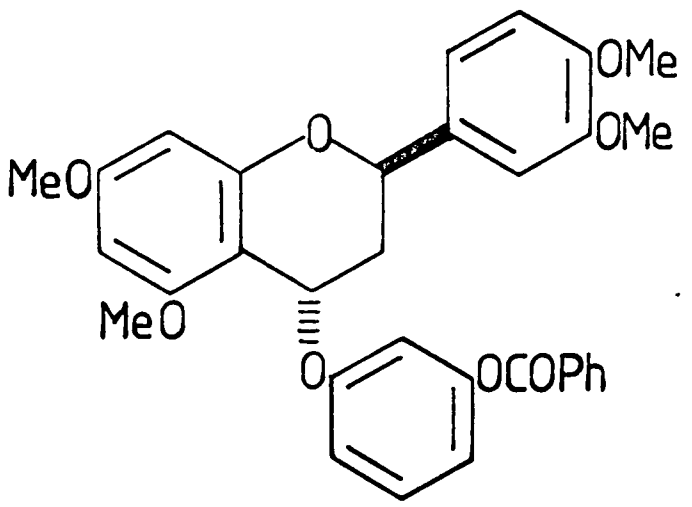
CVIII



CIX

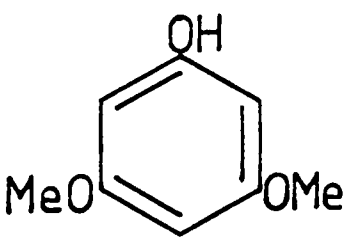


CX

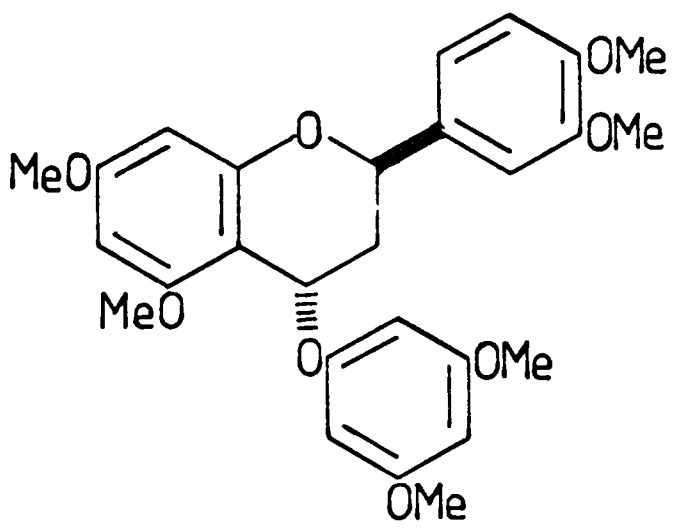


CXI

3,5-Dimethoxyphenol (CXII), which has a highly reactive phloroglucinol nucleus, yielded 4α-(3,5-dimethoxyphenoxy)-5,7,3',4'-tetramethoxyflavan (CXIII), though in only 9% isolated yield. This drop in yield probably reflects substantial attack by the intermediate 4-carbocation on the aromatic ring of the phenol rather than on the phenolic hydroxyl group, even under conditions approximating to kinetic control of reaction.

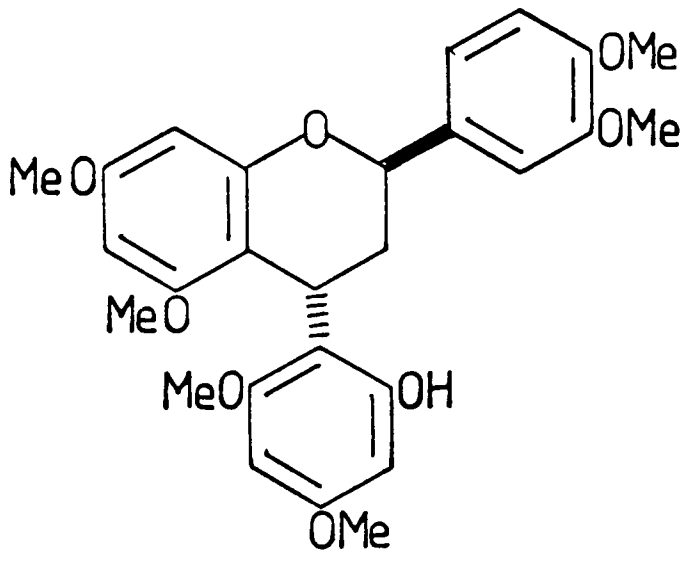


CXII



CXIII

It is, of course, important to prove that the compounds obtained by these reactions of 4-acetoxyflavans with phenols are indeed 4-aryloxyflavans and not the isomeric 4-(hydroxy-aryl)-flavans, such as (CXIV).



CXIV

The compound assigned structure (CXIII) is readily identified from its proton magnetic resonance spectrum by the doublet at 3.72τ due to two equivalent aromatic protons, split by coupling to a third proton. This implies that the 3,5-dimethoxyphenol has reacted on the hydroxyl group and not on the aromatic nucleus. In general for 4-aryloxyflavans, however, the aromatic proton resonances cannot be uniquely assigned and other methods of distinguishing between 4-hydroxyaryl- and 4-aryloxy-substituted flavans must be used.

O'Neill[22] has discussed six ways of making this distinction.

i) 4-(Hydroxyaryl)-flavans are phenolic and therefore soluble in alkali. O'Neill comments that extraction of such species into aqueous alkali is inefficient and does not constitute a reliable method of separating hydroxyaryl- from aryloxy-flavans.

ii) The phenolic hydroxyl groups of hydroxyarylflavans absorb in the infrared. O'Neill found that the bands are weak and difficult to detect.

iii) Hydroxyarylflavans are less mobile on chromatographic plates than isomeric aryloxyflavans. This distinction has not

been of much use to the present author, because in only a few instances have isomeric hydroxyaryl- and aryloxy-flavans both been available.

iv) 4-Aryloxyflavans readily fragment in a mass spectrometer and give only small molecular ion peaks. O'Neill supposed that 4-(hydroxyaryl)-flavans give strong molecular ion peaks, but it appears that this is not always so. The assumption led O'Neill to misidentify two 4-hydroxyphenyl-substituted flavanoids as 4-phenoxyflavanoids. These compounds are discussed presently. As a result, mass spectra have not been relied upon by the present author to distinguish between hydroxyaryl- and aryloxy-flavanoids. However, the low intensity molecular ion peaks observed for all aryloxyflavanoids prepared according to scheme 27 in the present work at least provide confirmatory evidence for their structure. A brief outline of the expected mass spectra of substituted flavans is relegated to the end of this Chapter.

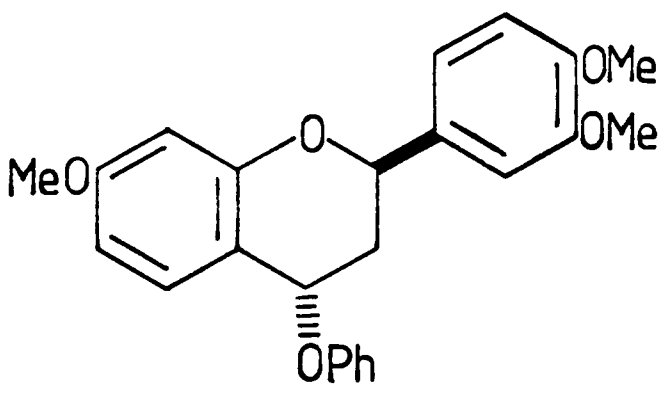
v) 4-Aryloxyflavans possess a better leaving group at the 4-position than do 4-(hydroxyaryl)-flavans and are therefore expected to react at this position with nucleophiles more readily. Unless samples of isomers of both types are available, it seems to the present author that such chemical studies would be inconclusive.

vi) In a proton magnetic resonance spectrum, the position of the signal from the flavanoid 4-proton depends on the nature of the 4-substituent. For 4-aryloxyflavans, the 4-proton resonance is said[22] to occur about 1p.p.m. downfield (i.e. to lower τ value) of the corresponding resonance in 4-arylflavans. The

present author has found the chemical shifts of flavanoid 4-proton resonances to be a reliable way of distinguishing 4-aryloxy- from 4-hydroxyaryl-substituted flavanoids.

Bateman[23] has pointed out that the sum of the coupling constants $J_{3,4}+J_{3^*,4}$ is higher for 4-arylflavans than for 4-aryloxyflavans, and attributed the difference to the greater electronegativity of a 4-aryloxy- than a 4-aryl-substituent.

The conjunction of these two characteristic differences provides convincing evidence for the structures of the 4α-aryloxyflavans already described. Table 5 combines data for these aryloxyflavans (and for 4α-phenoxy-7,3',4'-trimethoxy-flavan (CXVIII), described below, and 4α-phenoxyflavan itself) with data for comparable 4α-arylflavans taken from other sources. The difference in position of the 4-H resonance for the two types of compound is marked, and there is a significant difference in the value of $J_{3,4}+J_{3^*,4}$, though the values of $J_{3,4}+J_{3^*,4}$ are all appropriate to 4α-substituted flavans, as discussed in Chapter 1.

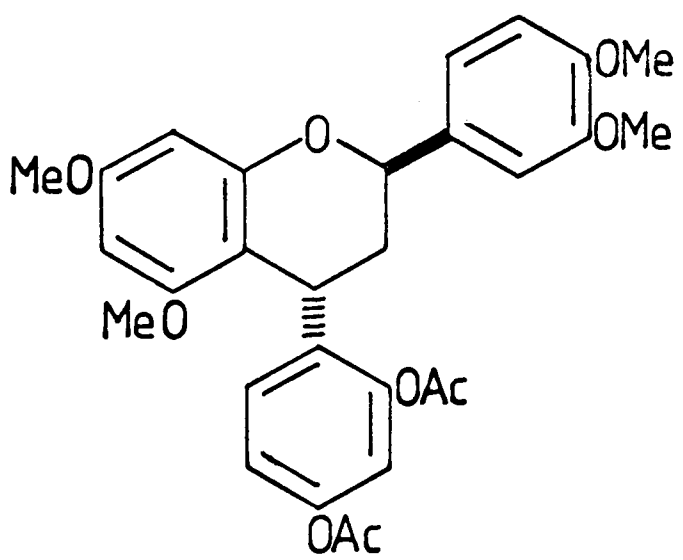


CXVIII

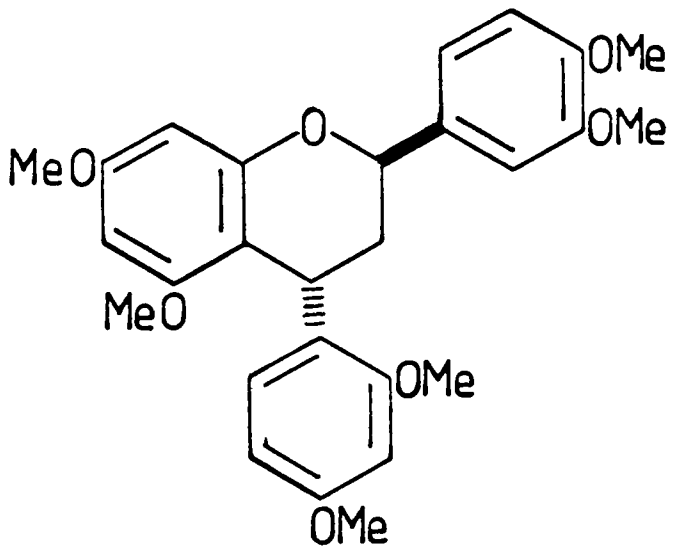
It was next decided to attempt the synthesis of 4α-phenoxy-7,3',4'-trimethoxyflavan (CXVIII). 4β-Acetoxy-7,3',4'-trimethoxyflavan (XLI) was known to be considerably less

Table 5: N.m.r. data for 4α-aryl- and 4α-aryloxyflavans

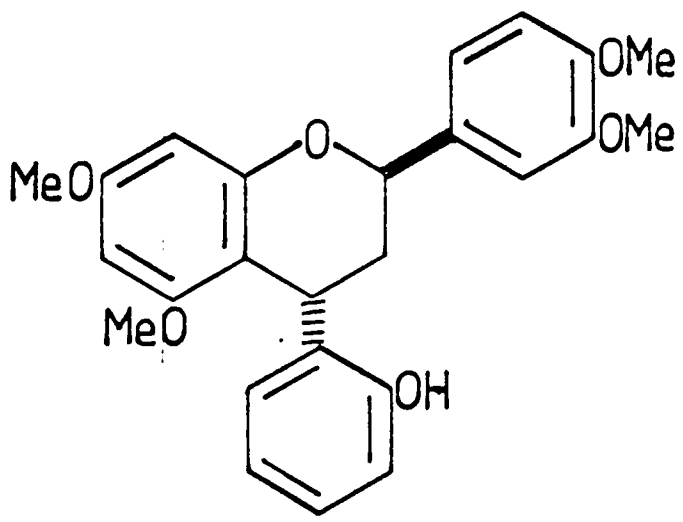
Compound	Methoxyl substitution pattern	4α-substituent	4-H (τ)	$\pm J_{3,4} + \pm J_{3^*,4}$ (Hz)
Aryloxy-flavans				
CVII	5,7,3',4'	phenoxy	4.42	5.2
CV	5,7	phenoxy	4.42	5.2
CX	5,7,3',4'	m-methoxyphenoxy	4.40	5.6
CXI	5,7,3',4'	m-benzoyloxyphenoxy	4.40	5.2
CXIII	5,7,3',4'	3,5-dimethoxyphenoxy	4.44	5.2
XCII[23]	-	phenoxy	4.64	6.0
CXVIII	7,3',4'	phenoxy	4.66	5.2
Aryl-flavans				
CXV[63]	5,7,3',4'	2,4-diacetoxyphenyl	5.55	-
CXVI[63]	5,7,3',4'	2,4-dimethoxyphenyl	5.41	8.0
CXVII[23]	-	o-hydroxyphenyl	5.53	9.0



CXV

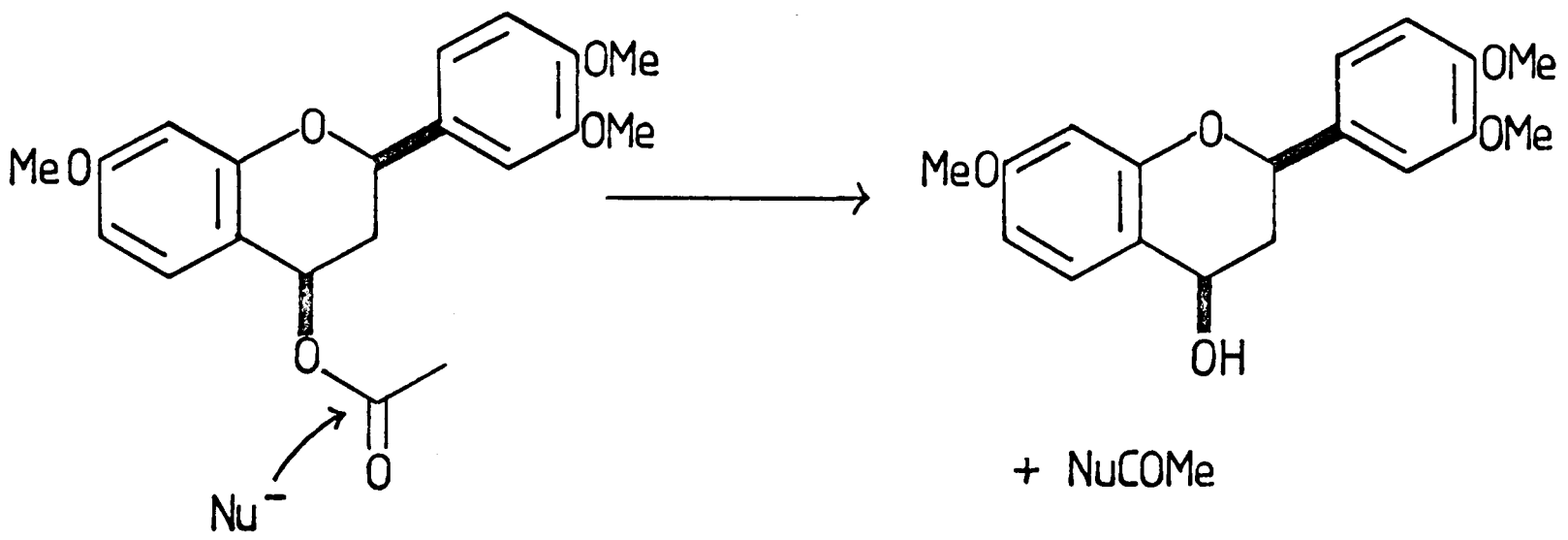


CXVI



CXVII

reactive than its tetramethoxy analogue (XLII) and there were two reasons why it seemed less satisfactory as a precursor for an aryloxyflavan. Firstly, if vigorous treatment was required in order to expel the leaving group, the reaction could not be extended to the reaction of flavans and phenols bearing other sensitive functional groups. Secondly, it was feared that under vigorous conditions nucleophilic attack might occur at the carbonyl group of the acetate function with formation of 7,3',4'-trimethoxyflavan-4β-ol (scheme 29).



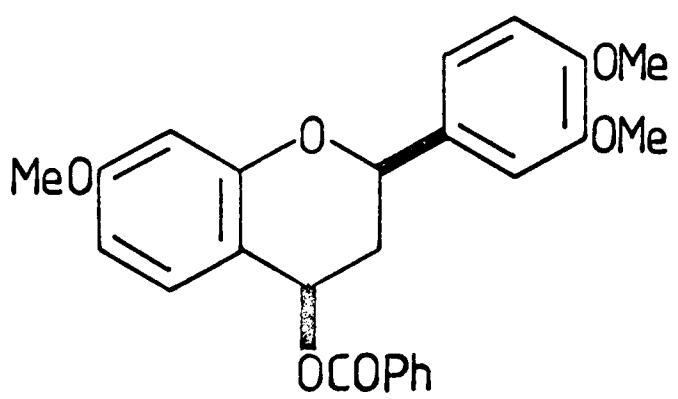
Scheme 29

A more promising 4-substituent on both counts was benzoate. Benzoic acid (pk_a=4.19)[64] is stronger than acetic acid (pk_a=4.75)[64] and would therefore be expected to be a better leaving group.[45] The benzoyl function is also less susceptible to nucleophilic attack than the acetyl function (contrast, for example, the reactivities of benzoyl chloride and acetyl chloride towards water or alcohols). 4β-Benzoyloxy-7,3',4'-trimethoxyflavan (CXIX) was therefore prepared by treatment of 7,3',4'-trimethoxyflavan-4β-ol with benzoyl chloride in pyridine. Dilution of the mixture with ethyl acetate, washing with aqueous sodium bicarbonate and removal

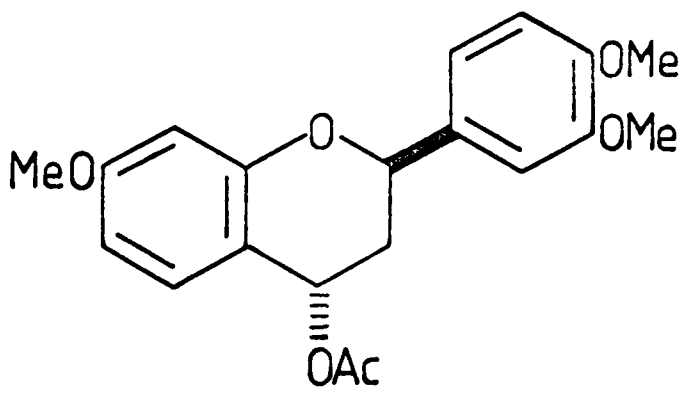
of the solvent gave the desired 4β-benzoyloxyflavan (CXIX), the 4β-stereochemistry of which is indicated by the value of $\underline{J}_{3,4}+\underline{J}_{3*,4}$ of 16Hz.

Preparation and synthetic transformations of 4-benzoyloxy-substituted flavanoids

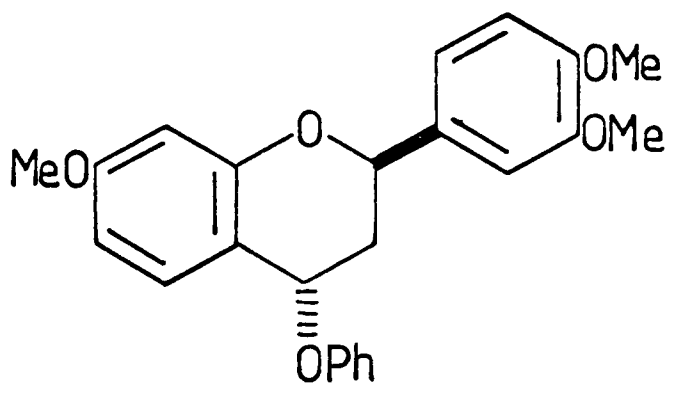
The benzoate (CXIX) did indeed prove more reactive than the corresponding acetate (XLI). It was converted by acetic anhydride mixture/pyridine at 90° into 4α-acetoxy-7,3',4'-trimethoxyflavan (XLVII), whereas 4β-acetoxy-7,3',4'-trimethoxyflavan (XLI) had proved inert to this reagent. As had



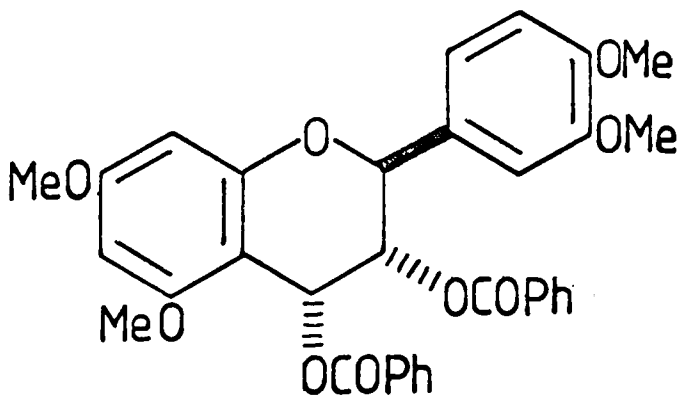
CXIX



XLVII



CXVIII



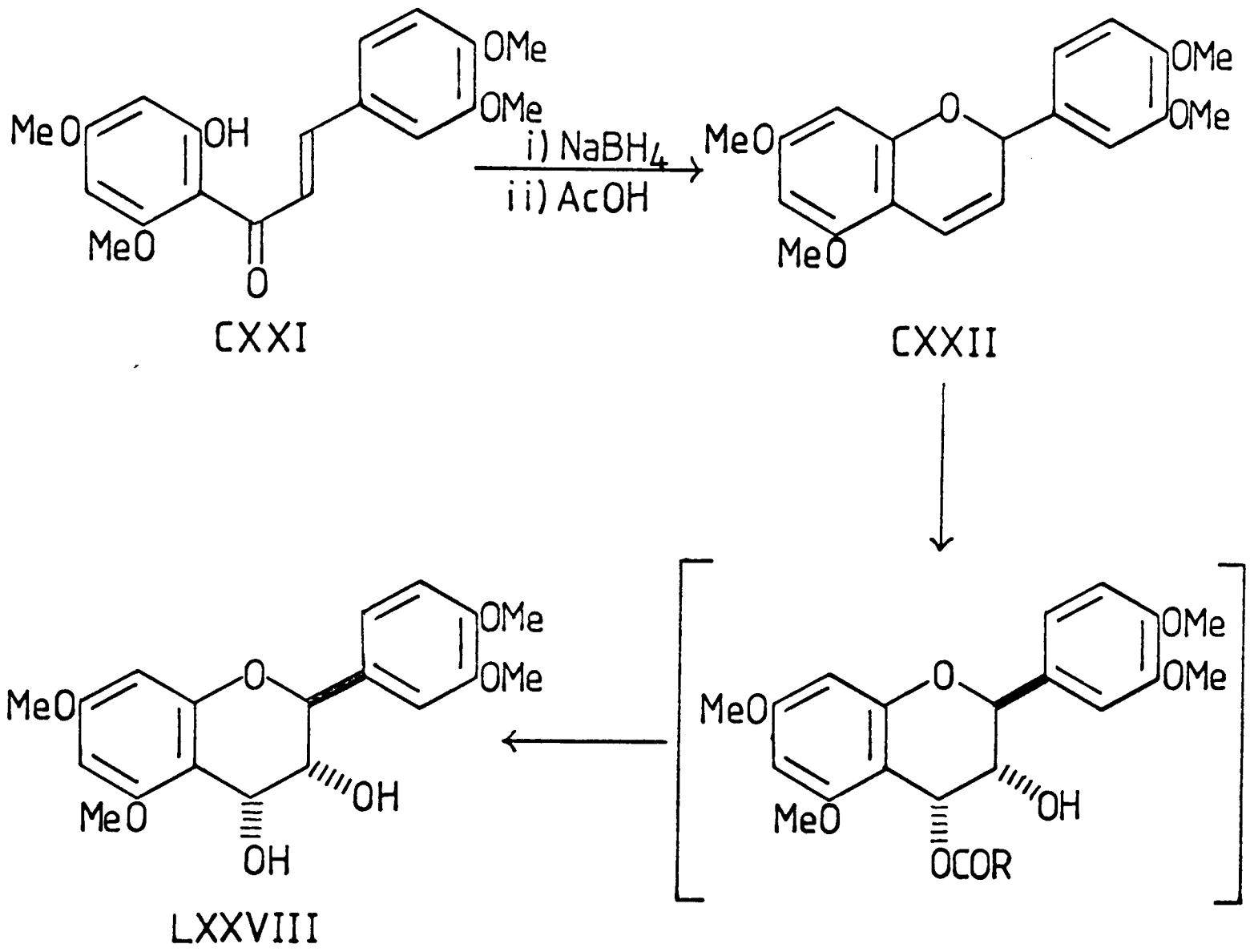
CXX

been hoped, reaction of 4β-benzoyloxy-7,3',4'-trimethoxyflavan (CXIX) with phenol in pyridine gave, after 9 days at 75°, 4α-phenoxy-7,3',4'-trimethoxyflavan (CXVIII), which was isolated by crystallisation in 39% yield. (N.m.r. data for this compound are included in table 5).

It was then decided to prepare 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (CXX), since the very similar reactivity of 4β-acetoxy-7,3',4'-trimethoxyflavan (XLI) and 2,3-trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (LXXIII), noted in Chapter 1, suggested that the monobenzoate (CXIX) and the dibenzoate (CXX) might also exhibit comparable reactivity. The previously described preparation of the necessary 2,3-trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (LXXVIII), however, was inconvenient and its precursor, the naturally occurring dihydroquercetin (LXXVI) was very expensive. It was therefore desirable to design a synthetic route to the diol (LXXVIII).

The simple synthesis of 5,7,3',4'-tetramethoxyflav-3-ene (CXXII) by reductive cyclisation of 2'-hydroxy-3,4,4',6'-tetramethoxychalcone (CXXI), due to Clark-Lewis and co-workers[51,52] made this flav-3-ene an attractive precursor of the diol (LXXVIII). Reaction of other flav-3-enes with peracids has been shown by Clark-Lewis et al.[65,66] to give 2,3-trans-3,4-cis-4-acyloxyflavan-3-ols, which may be hydrolysed to the corresponding flavan-3,4-diols. Clark-Lewis et al.[65,66] report only moderate yields of the desired products and the experience of the present author was similar: reaction of 5,7,3',4'-tetramethoxyflav-3-ene (CXXII) with peracetic or m-chloroperbenzoic acid under various

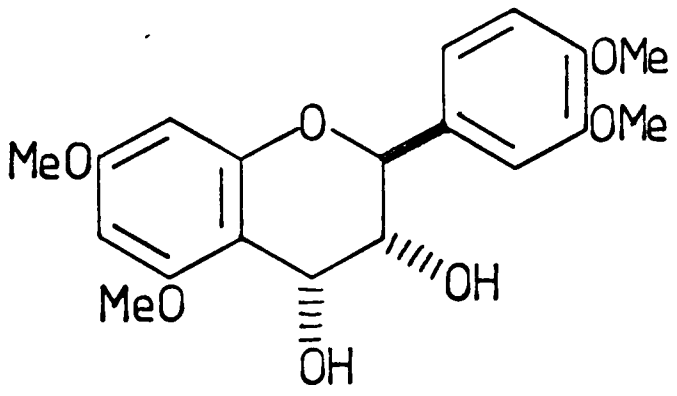
conditions gave a maximum yield of the diol (LXXVIII) of 34% (scheme 30).



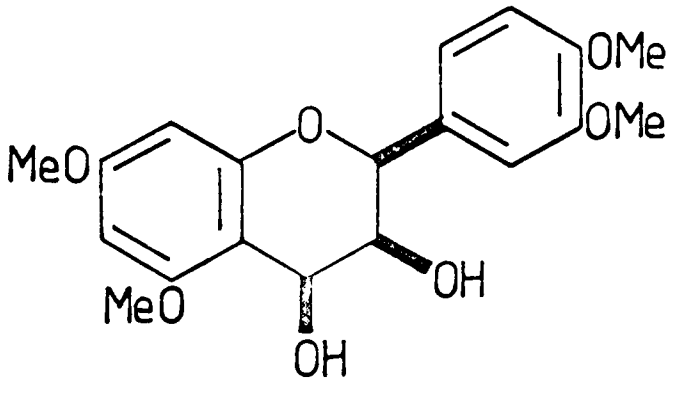
Scheme 30

Osmium tetroxide has also been used for converting flav-3-enes into 2,3-trans-3,4-cis-flavan-3,4-diols,[22,67] including the diol (LXXVIII).[68] Yields, however, have been poor (36% for the diol (LXXVIII)[68]) and the high price of the reagent makes it unsuitable for large scale preparations. A recent report,[69] describing the use of a catalytic quantity of osmium tetroxide in conjunction with a stoichiometric quantity of N-methyl-morpholine-N-oxide for the hydroxylation of olefins, sometimes in higher yield than was achieved by osmium tetroxide alone, overcame both objections. By this new method it was found by

the author that the flav-3-ene (CXXII) was converted directly into the diol (LXXVIII), which was isolated by crystallisation in 78% yield. Chromatography of the mother liquor afforded 4% of the isomeric 2,3-cis-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (CXXIII), the nuclear magnetic resonance spectrum of which agreed with that already reported,[55] although the melting point was 6° lower than the literature value.[55]



LXXVIII

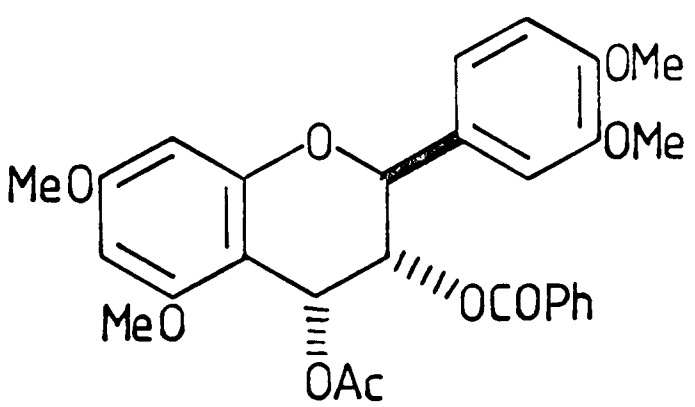


CXXIII

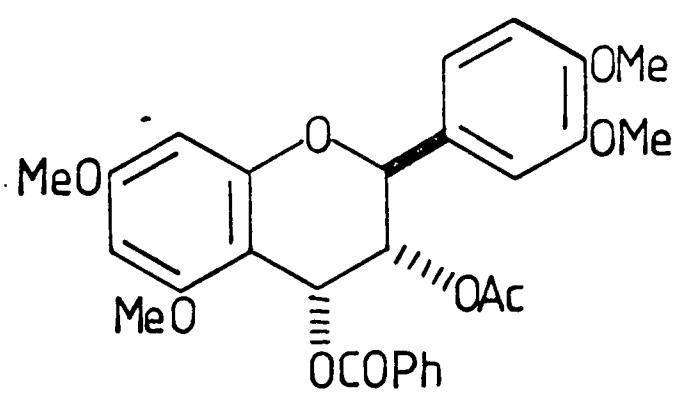
Benzoylation of the diol (LXXVIII) was readily accomplished with benzoyl chloride in pyridine and yielded 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (CXX). The proton magnetic resonance spectrum of this compound exhibited coupling constants $J_{2,3}$=10.8Hz and $J_{3,4}$=3.6Hz, which are characteristic of 2,3-trans-3,4-cis-stereochemistry (Chapter 1).

The dibenzoate (CXX) proved to be less reactive than 4β-benzoyloxy-7,3',4'-trimethoxyflavan (CXIX). Thus when it was heated to 90° for 4h in pyridine/acetic anhydride mixture, crystallisation of the reaction products furnished 34% of impure starting material, and chromatography of the mother liquor afforded a further 12% of the starting material and 28% of 2,3-trans-3,4-cis-3-benzoyloxy-4-acetoxy-5,7,3',4'-tetramethoxy-flavan (CXXIV). However, with acetic anhydride mixture alone

at 60°, the dibenzoate (CXX) readily yielded 2,3-trans-3,4-cis-3-benzoyloxy-4-acetoxy-5,7,3',4'-tetramethoxyflavan (CXXIV), isolated in 56% yield by crystallisation. The 2,3-trans-3,4-cis configuration of this compound follows from the coupling constants, $J_{2,3}$=11.0Hz, $J_{3,4}$=3.2Hz.

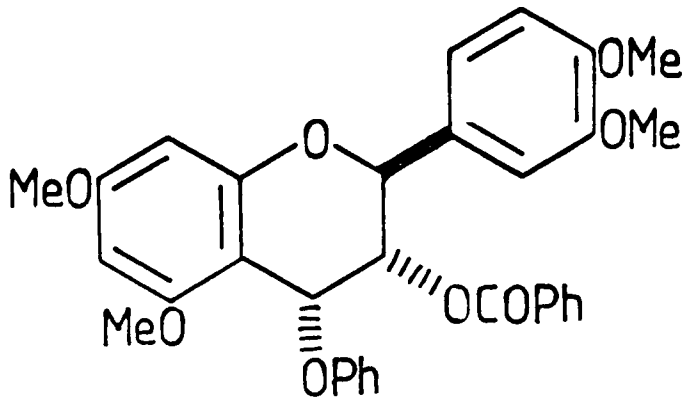


CXXIV

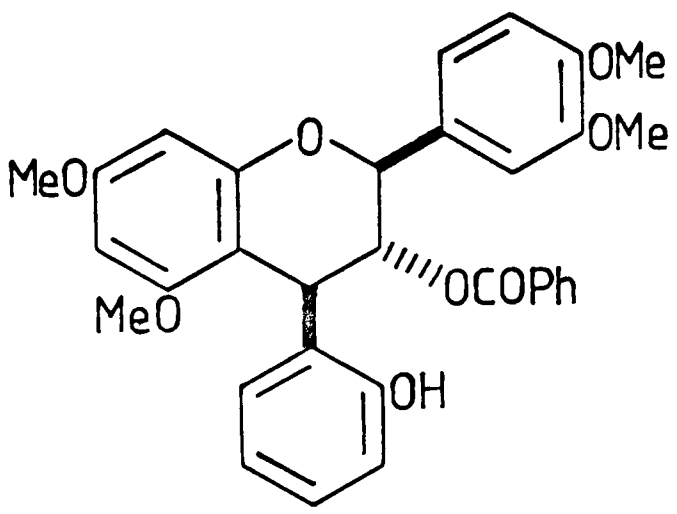


CXXV

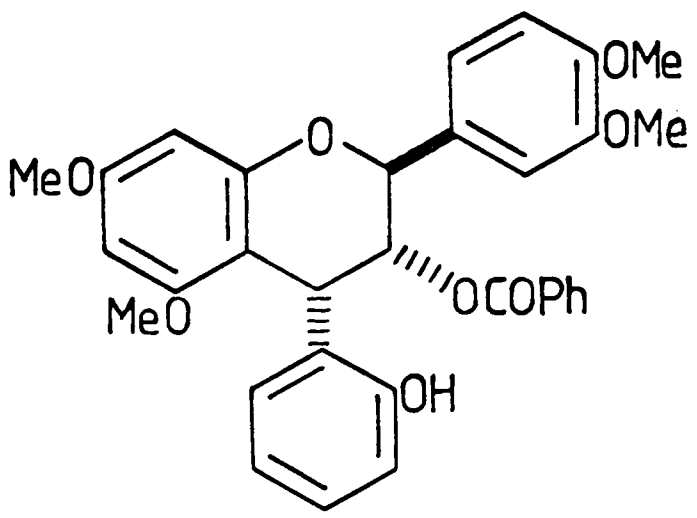
There is no conclusive evidence that the compound assigned structure (CXXIV) is not in fact 2,3-trans-3,4-cis-3-acetoxy-4-benzoyloxy-5,7,3',4'-tetramethoxyflavan (CXXV). However, the method of preparation of the compound strongly suggests that reaction has occurred at the 4-position (as may be unambiguously shown for reaction with nucleophiles other than acetic acid). The mass spectrum of the product of reaction of the dibenzoate (CXX) with acetic anhydride mixture provides some confirmation of this deduction. The molecular ion (M^+, 508) is observable as a small peak; so also are peaks due to loss of acetic acid or of acetate, (M-60) and (M-59), but not due to loss of benzoic acid or benzoate, (M-122) and (M-121). Loss of the 4-substituent (followed by further disintegration) is known to be a major fragmentation mode for flavans bearing a leaving group at the 4-position, therefore since a peak due to loss of acetate alone, but not loss of benzoate alone is observed, it is likely that



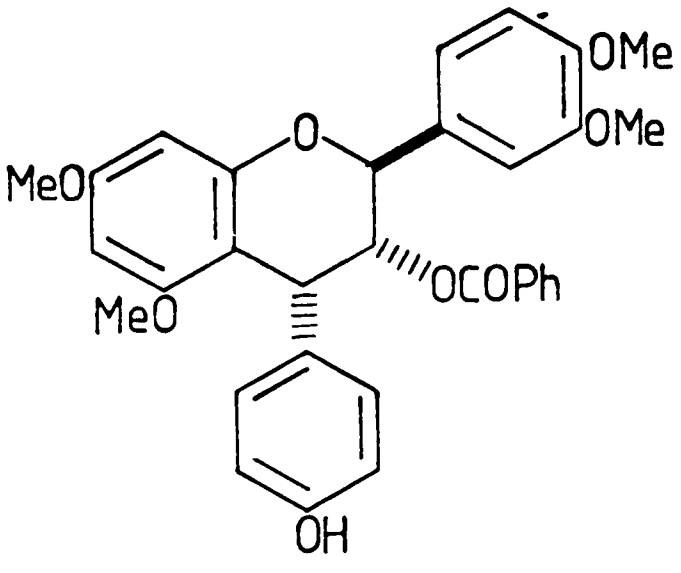
CXXVI



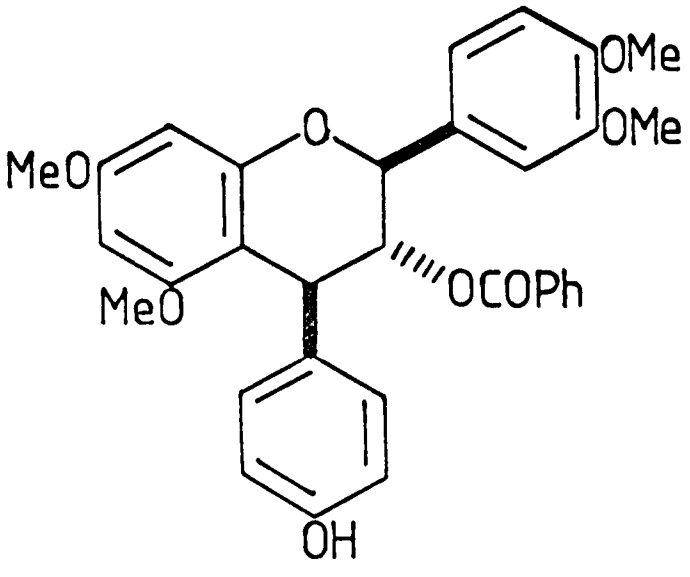
CXXVII



CXXVIII



CXXIX



CXXX

the acetate group is at the 4-position and benzoate at the 3-position.

The reaction of 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan with phenol was next investigated. The incomplete reaction of the dibenzoate (CXX) with acetic acid in pyridine suggested that the reaction with phenol in pyridine would be inconveniently slow, so toluene, a non-basic solvent, was tried first.

After reaction at 75° for 30h, 5 products were isolated by chromatography. One of the desired 3-benzoyloxy-4-aryloxy-flavans (CXXVI) was obtained in 15% yield. The other four products were the 3-benzoyloxy-4-(hydroxyphenyl)-flavans, (CXXVII) (5%), (CXXVIII) (3%), (CXXIX) (7%) and (CXXX) (22%). Each of these products possessed a benzoate group at the 3-position which could be hydrolysed by methanolic potassium hydroxide. This change was attended by a shift upfield of 1.5-2τ in the position of the 3-proton signal in the nuclear magnetic resonance spectrum, and much smaller shifts of the 2-proton and 4-proton signals, confirming the position of the benzoyloxy group. (According to Jackman,[133] a shift of 1.3τ downfield in the position of an α-H resonance is typical when a secondary alcohol is benzoylated).

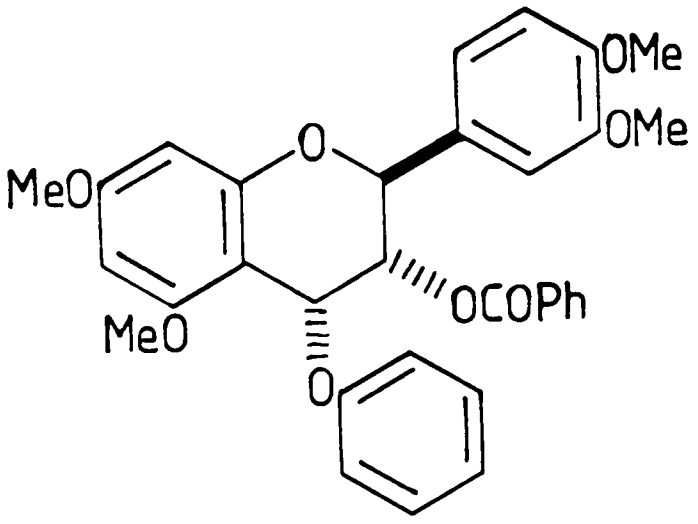
The resulting 4-substituted flavan-3-ols (including a sixth compound, whose benzoate precursor was not isolated), (CXXXI) to (CXXXVI) are derived from reaction of the 4-carbocation (CXL) with phenol at the hydroxyl group, or at the activated nuclear ortho- or para-positions, followed by hydrolysis of the 3-benzoyloxy group. Combining the three

Table 6: N.m.r. data for the isomeric 2,3-trans-4-phenoxy- and 2,3-trans-4-(hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan-3-ols, and for the 2,3-trans-3-acetoxy-4-(p-acetoxyphenyl)-5,7,3',4'-tetramethoxyflavans.

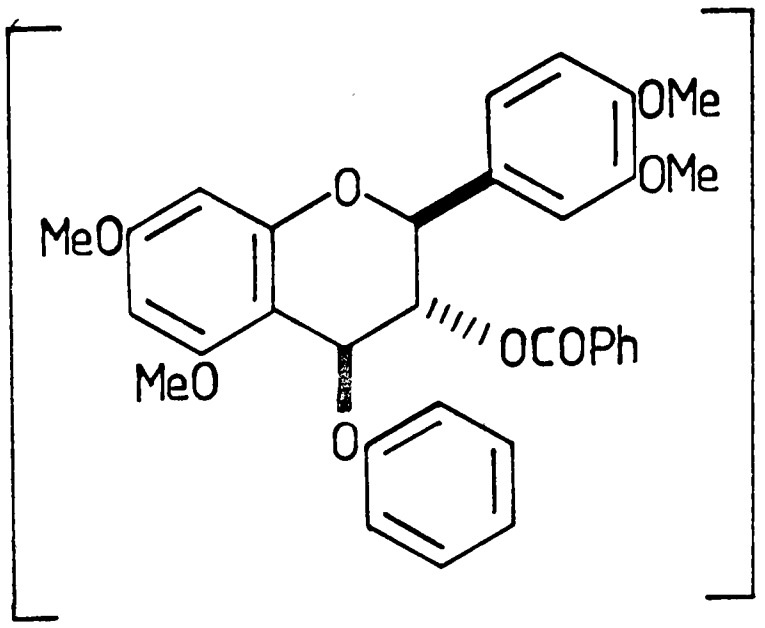
Compound	4-Substituent	τ			Hz		3,4-configuration
		2-H	3-H	4-H	$J_{2,3}$	$J_{3,4}$	
CXXXI	phenoxy	4.86	5.86	4.38	10.4	3.6	cis
CXXXII	phenoxy	4.98	5.58	4.46	7.4	5.4	trans
CXXXIII	o-hydroxyphenyl	5.36	5.98	5.54	9.0	7.8	trans
CXXXIV	o-hydroxyphenyl	5.34	5.70	5.06	10.0	5.4	cis
CXXXV	p-hydroxyphenyl	5.32	5.88	5.54	9.8	5.8	cis
CXXXVI	p-hydroxyphenyl	5.40	ca.6.2	ca.6.2	-	-	trans
CXXXVIII	p-acetoxyphenyl	5.08	4.60	5.34	10.4	5.8	cis
CXXXIX	p-acetoxyphenyl	5.02	4.48	5.82	7.4	6.6	trans

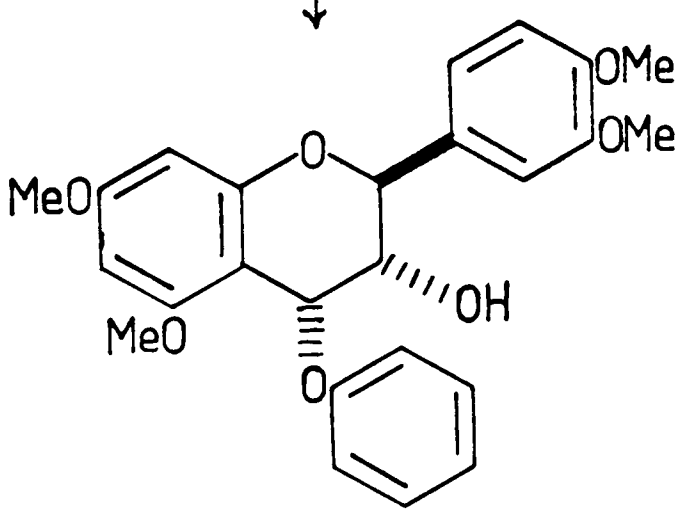
Table 7: N.m.r. data for the isomeric 2,3-trans-3-acyloxy-4-phenoxy- and 2,3-trans-3-benzoyloxy-4-(hydroxyphenyl)-5,7,3',4'-tetramethoxyflavans.

Compound	4-Substituent	τ			Hz		3,4-configuration
		2-H	3-H	4-H	$J_{2,3}$	$J_{3,4}$	
CXXVI	phenoxy	4.40	4.40	3.96	-	-	cis
CXXXVII	phenoxy	4.54	4.74	4.12	10.8	2.8	cis
CXXVII	o-hydroxyphenyl	4.50	4.16	5.42	4.4	3	trans
CXXVIII	o-hydroxyphenyl	4.86	4.28	4.80	10.0	5.8	cis
CXXIX	p-hydroxyphenyl	4.96	4.40	5.26	10.6	5.8	cis
CXXX	p-hydroxyphenyl	4.92	4.28	5.70	7.4	6.4	trans

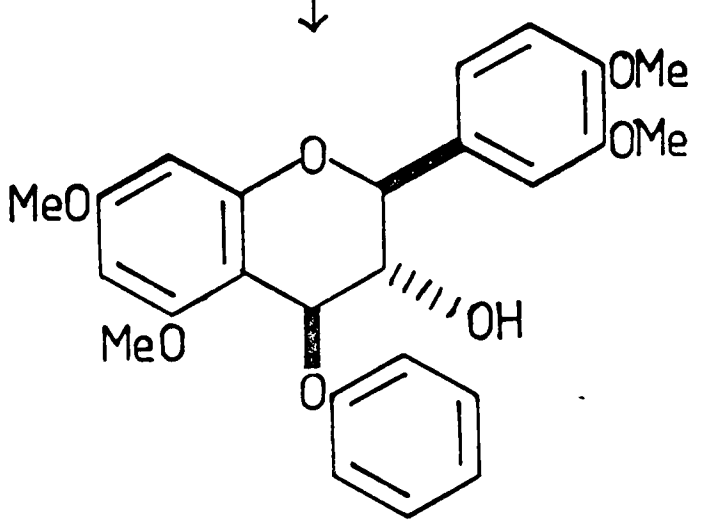


CXXVI

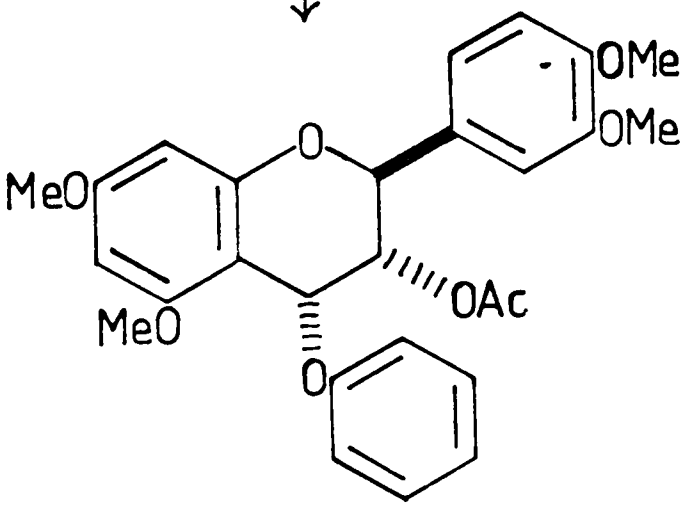




CXXXI



CXXXII



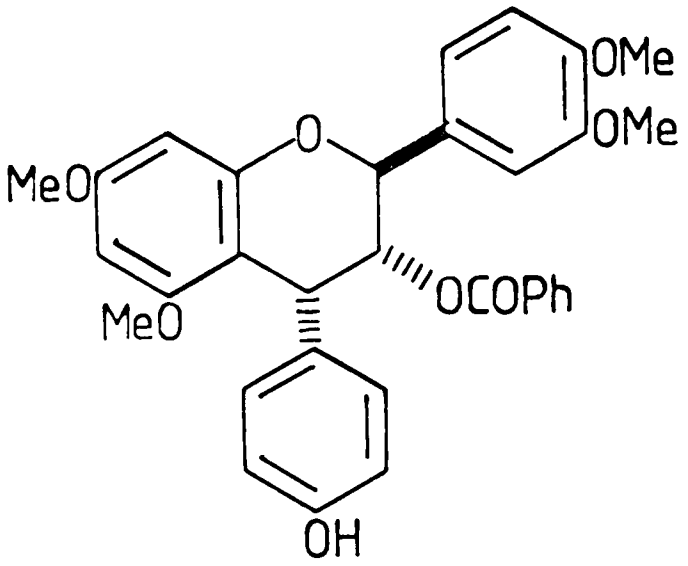
CXXXVII

Scheme 31

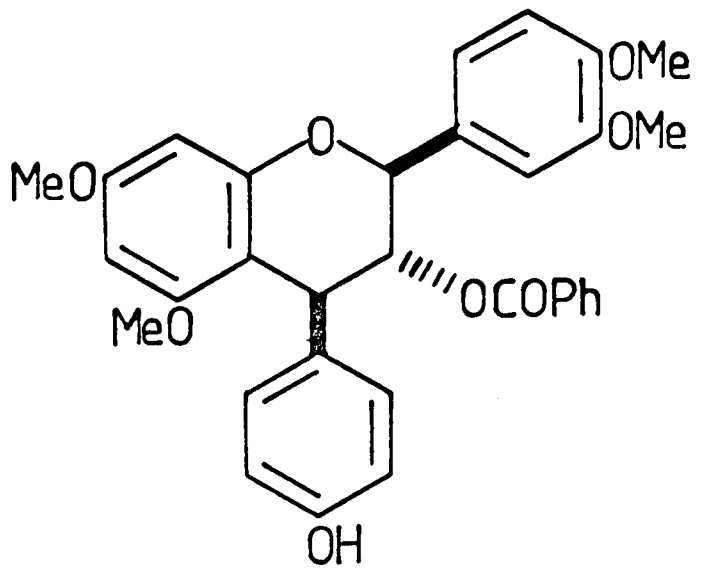
possible positions of reaction on phenol with two possible flavanoid stereochemistries (3,4-cis and 3,4-trans), gives six structures, but assigning these to the compounds obtained is by no means straightforward.

The two 4-phenoxyflavan-3-ols, (CXXXI) and (CXXXII), may first be picked out. They are readily distinguished from the other isomers by their relatively low field 4-proton resonances (table 6). Confirmation of this assignment was achieved by acetylation of (CXXXI) to give a mono-acetate (CXXXVII) (scheme 31). Lack of material prevented acetylation of (CXXXII), but further evidence for the presence of a 4-phenoxy substituent in both (CXXXI) and (CXXXII) is the near absence of a molecular ion in the mass spectra of these compounds. The coupling constants obtained from the proton magnetic resonance spectrum of (CXXXI) (table 6) are characteristic of 2,3-trans-3,4-cis-stereochemistry. The 4-phenoxyflavan-3-ol (CXXXII) must therefore possess 2,3-trans-3,4-trans-stereochemistry. Its coupling constants (table 6) do not agree well with those predicted for "sofa" or "half-chair" conformations, nor are they appropriate to the "anomalous conformations" which have been suggested[57-59] (see Chapter 1); but they are very close to the values found experimentally for 2,3-trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (LXXIII), $J_{2,3}$=7.4Hz, $J_{3,4}$=5.2Hz.[60]

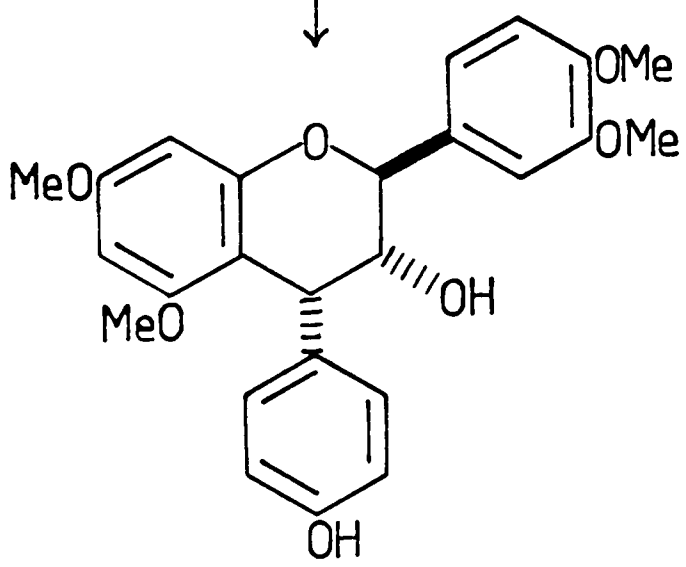
The second pair of epimeric 4-substituted flavan-3-ols which may be picked out is (CXXXV) and (CXXXVI). Each of these compounds in its proton magnetic resonance spectrum exhibits a pair of doublets in the aromatic region, integrating to 4



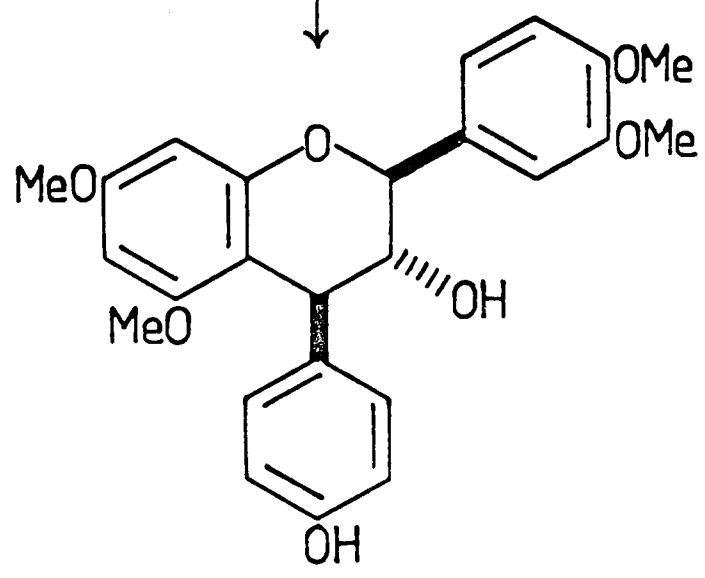
CXXIX



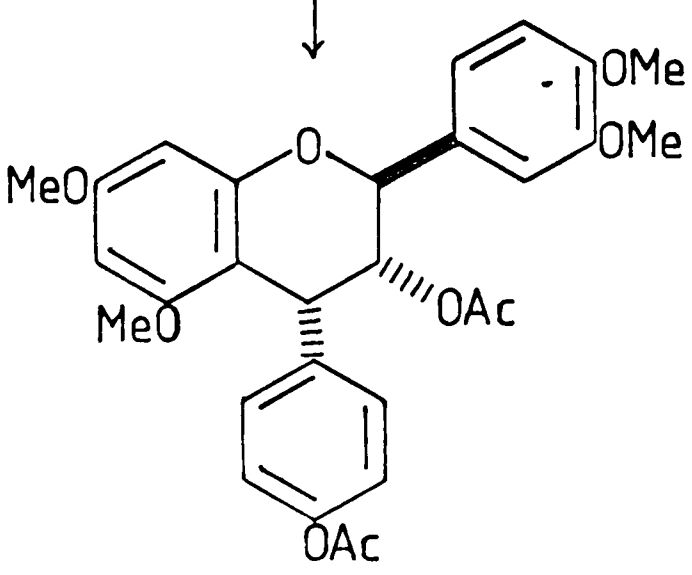
CXXX



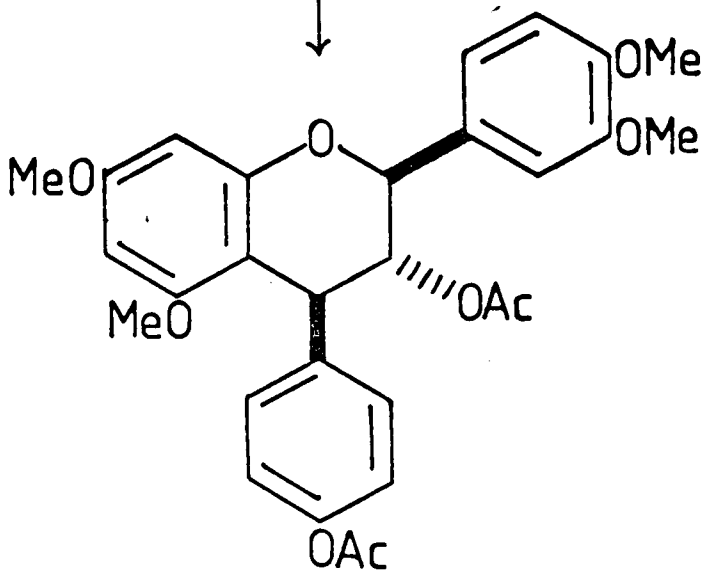
CXXXV



CXXXVI



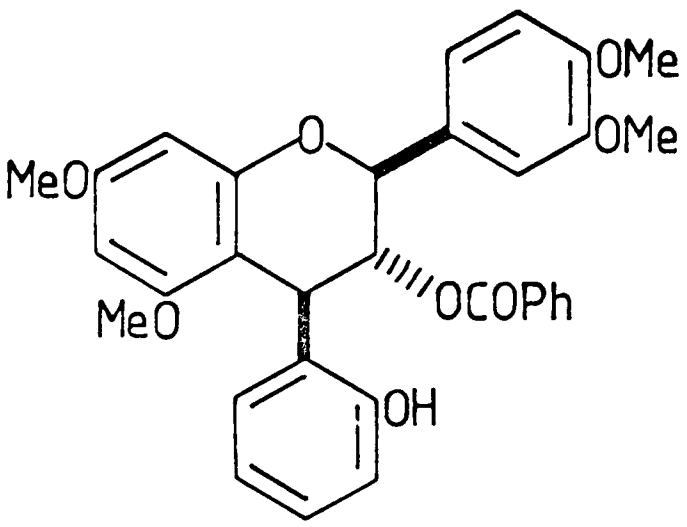
CXXXVIII



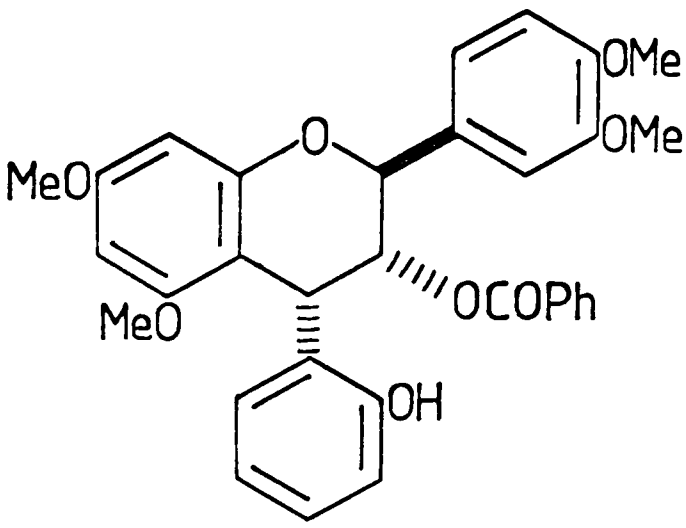
CXXXIX

Scheme 32a

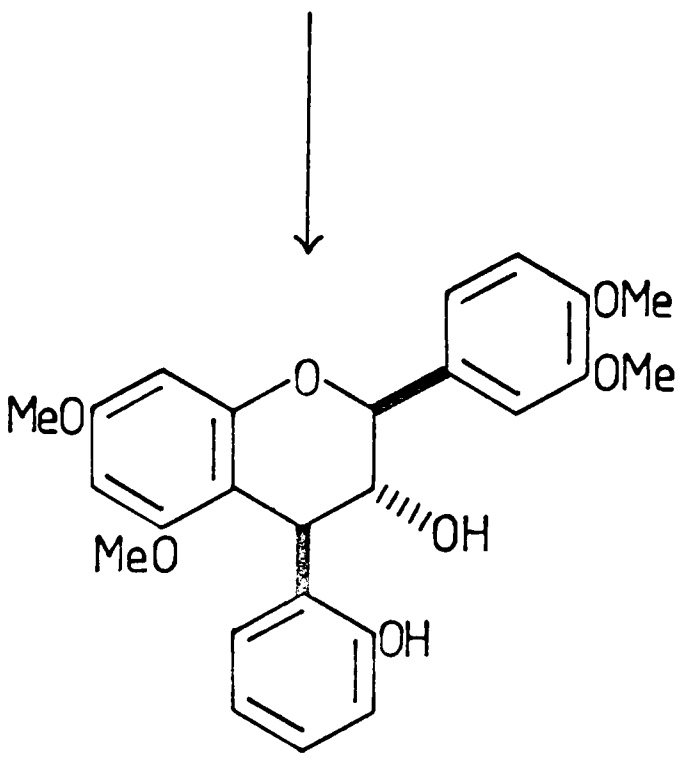
protons and having a coupling constant of 8 or 9Hz, appropriate to adjacent protons on a benzene ring. These doublets (which are absent from the spectra of (CXXXIII) and (CXXXIV)) indicate para-substitution in the D-ring which must therefore be a p-hydroxyphenyl group. (For comparison, p-cresol was found to exhibit doublets at 2.96 and 3.30τ, J=8Hz). The coupling constants, $J_{2,3}$=9.8, $J_{3,4}$=5.8Hz for (CXXXV) are appropriate to the "five-point coplanar" conformation (which lies between the "half-chair" and "half-boat" shapes) of the 2,3-trans-3,4-cis-configuration,[59] therefore this configuration is assigned to (CXXXV). However, the overlapping of the 3-H and 4-H signals of (CXXXVI) means that the coupling constants of the latter cannot be determined. Acetylation of (CXXXV) and (CXXXVI) gives, as expected, the diacetates (CXXXVIII) and (CXXXIX) (Scheme 32a). The nuclear magnetic resonance spectra are consistent with a p-acetoxyphenyl substituent at the 4-position: the spectrum of (CXXXIX) exhibits the characteristic pair of doublets (at 3.12 and 3.24τ, J=7Hz), while in the spectrum of (CXXXVIII) the resonances of the p-acetoxyphenyl group fortuitously coincide at 2.96τ. The configurations of these diacetates may also be assigned by nuclear magnetic resonance spectroscopy. Thus, the diacetate (CXXXIX) has $J_{2,3}$=7.4 and $J_{3,4}$=6.6Hz, which are close to the values already quoted for 2,3-trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan. It is therefore assigned 3,4-trans-stereochemistry and its epimer (CXXXVIII), with $J_{2,3}$=10.4Hz and $J_{3,4}$=5.8Hz, must possess 3,4-cis-stereochemistry. The 3-benzoyloxyflavans, (CXXX) and (CXXIX), which were the precursors of these diacetates, have coupling constants almost identical to those of the corresponding diacetates (table 7).



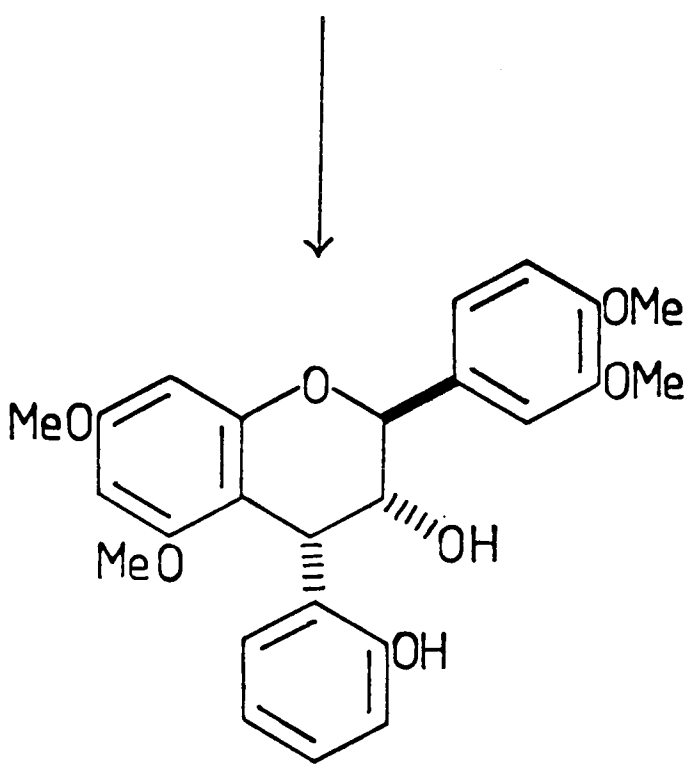
CXXVII



CXXVIII



CXXXIII



CXXXIV

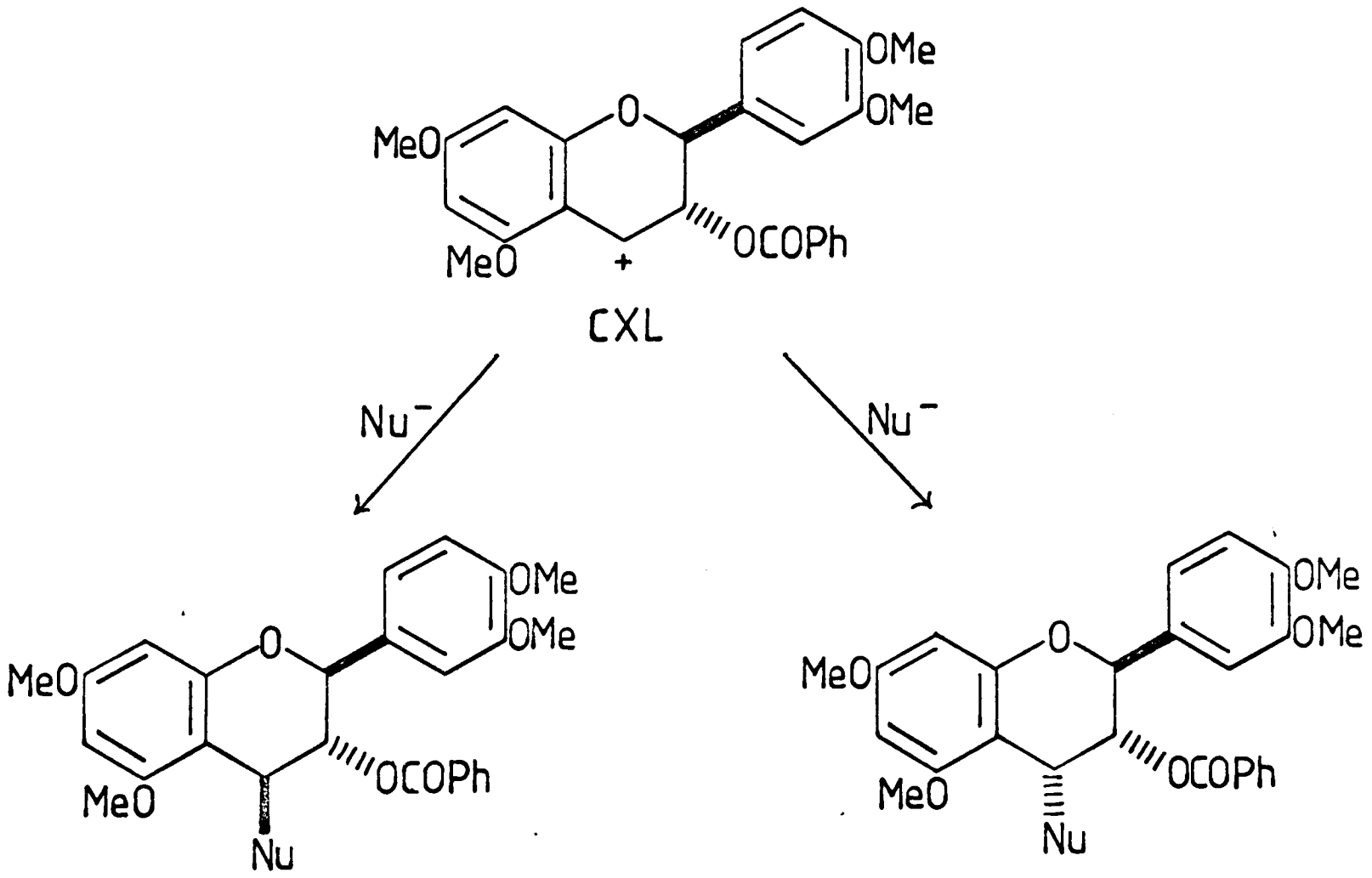
Scheme 32b

Turning now to the remaining epimeric pair of 4-(o-hydroxyphenyl)-flavan-3-ols, (CXXXIII) and (CXXXIV), (Scheme 32b) there seems little doubt that the coupling constants $J_{2,3}$=10.0, $J_{3,4}$=5.4Hz indicate 3,4-cis-stereochemistry for (CXXXIV), while $J_{2,3}$=9.0, $J_{3,4}$=7.8Hz indicate 3,4-trans-stereochemistry for (CXXXIII). This pair of epimers was obtained by O'Neill[22] (the proton magnetic resonance data reported by him agrees very closely with that obtained by the present author), though the epimer (CXXXIII) which he obtained crystalline had a melting point 20° lower than was found in the present work. O'Neill[22] assumed that these compounds, (CXXXIII) and (CXXXIV), (apparently the only products he isolated from the reaction of 2,3-trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol with phenol) were aryloxy derivatives. The positions of 4-H resonances given in table 6, however, clearly indicate that (CXXXI) and (CXXXII) are aryloxyflavanoids, while (CXXXIII) and (CXXXIV) are hydroxyarylflavanoids. Unfortunately, lack of material precluded the conversion of the latter epimeric pair into diacetates, which would have confirmed their structure.

It must be admitted that for several of the compounds (CXXVI) to (CXXXIX) it is not obvious from the proton magnetic resonance signals, which are those of the 2-proton and which, of the 4-proton. In order to interpret the less obvious spectra it has been assumed that the 2-H resonance is less sensitive to changes in the nature of the 4-substituent than is the 4-H resonance. The resulting assignments (tables 6 and 7) turn out to be quite consistent as regards coupling constants (compare, for example, compounds (CXXX) and (CXXXII)) which confirms the correctness of the assignments made. This

difficulty in distinguishing between 2-H and 4-H resonances has, surprisingly, not been mentioned by some previous workers[12,15,70] who have interpreted the spectra of flavanoid dimers. Deuteration studies would be valuable as a means of proving the assignments made in these and in the present investigation, placing on a sure footing the coupling constants obtained and the configurational and conformational inferences drawn.

The relative yields of the various products of the reaction of 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (CXX) with phenol provide a clue to the kinetically and thermodynamically controlled stereochemistries of the products of reaction of the carbocation (CXL) with nucleophiles shown in scheme 33.



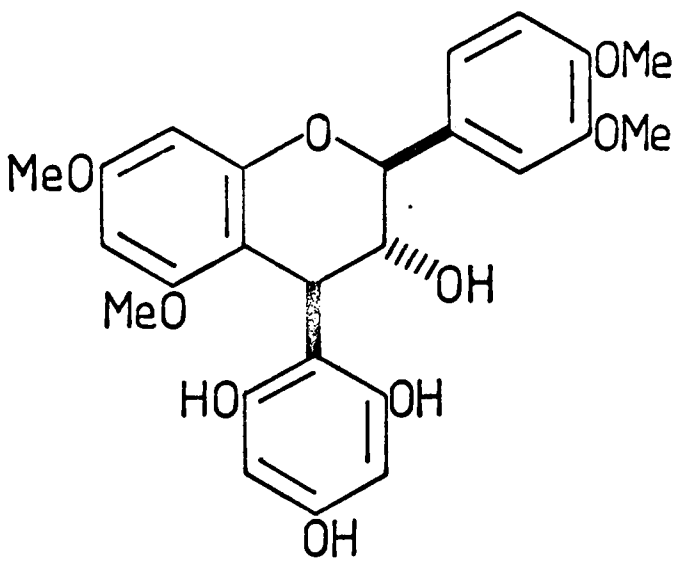
Scheme 33

The work up of the reaction mixture involved washing an ethereal solution with aqueous sodium hydroxide to remove unreacted phenol (present in large excess). This washing was conducted with the smallest amount of alkali that adequately removed the phenol, in the hope that the relative concentrations of 4-(hydroxyaryl)-flavanoids (which are also phenolic, but more difficult to extract into aqueous alkali[22]) would not be significantly affected. That this was indeed the case is suggested by the fact that more p-hydroxyphenyl-flavanoids (29%) were obtained than o-hydroxyphenylflavanoids (8%) (phenol being more reactive towards electrophiles at the para than the ortho position; nitrous acid at 40°, for instance, gives para- and ortho-nitrosophenols in the ratio 10:1[71]), and that within both of these classes, the 3,4-trans-isomer (22 or 5%) outweighed the 3,4-cis-isomer (7 or 3%). On the other hand, for the 3-benzoyloxy-4-phenoxyflavan products, the 3,4-cis-isomer (CXXVI) predominated (>15%) over the trans-isomer (<10%).

It was readily shown by thin layer chromatography that, under the reaction conditions, the pure 4-phenoxyflavanoid (CXXVI) was converted into a mixture containing predominantly 4-(hydroxyaryl)-flavanoids, but that the 4-arylflavanoid (CXXX) was unchanged. In other words, the aryloxyflavan (CXXVI) is reversibly formed while the hydroxyarylflavan (CXXX) is irreversibly formed. It is possible therefore that thermodynamic (i.e. reversible) control of stereochemistry gives chiefly 3,4-cis products, while kinetic (i.e. irreversible) control results chiefly in 3,4-trans products. It would be interesting to know the stereochemical outcome of reactions of

(CXL) and related 2,3-trans-4-carbocations with other nucleophiles under both conditions of stereochemical control, but unfortunately the available evidence is limited and inconclusive.

i) Jurd and Lundin[72] found that reaction of 2,3-trans-3,4-trans-5,7,3',4'-tetramethoxyflavan-3,4-diol (XX) with phloroglucinol occurred on brief treatment with boiling water and gave 87% of the 4-arylflavanoid (CXLI) which has 3,4-trans stereochemistry. Under such mildly acidic conditions it seems likely that stereochemistry is kinetically controlled.

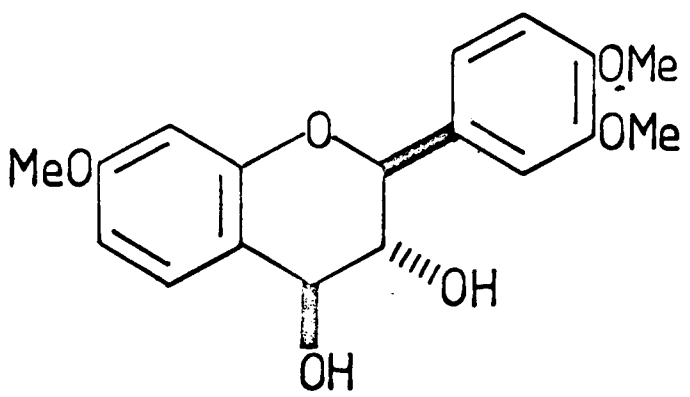


CXLI

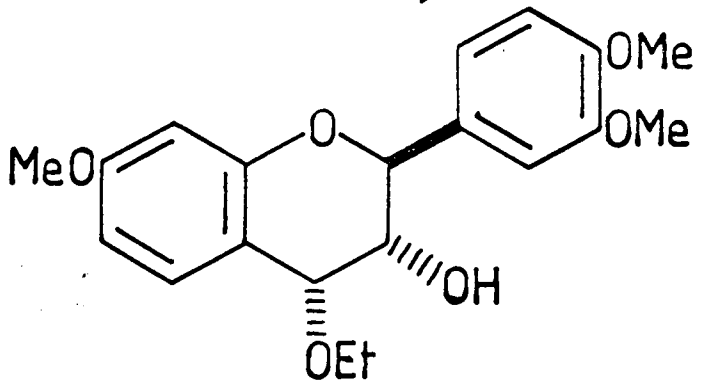
ii) 2,3-Trans-3,4-cis-diacetoxy-5,7,3',4'-tetramethoxyflavan (LXXV) has been shown in Chapter 1 to be thermodynamically more stable than 2,3-trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (LXXIII).

iii) Clark-Lewis and Williams[35] studied the reaction of 2,3-trans-3,4-trans-7,3',4'-trimethoxyflavan-3,4-diol (CXLII) with ethanolic acid by thin layer chromatography. They concluded, on the other hand, that kinetic control (i.e. short reaction times) gave 2,3-trans-3,4-cis-4-ethoxy-7,3',4'-trimethoxyflavan-3-ol (CXLIII), while thermodynamic control (longer reaction times) gave roughly equal proportions of (CXLIII)and

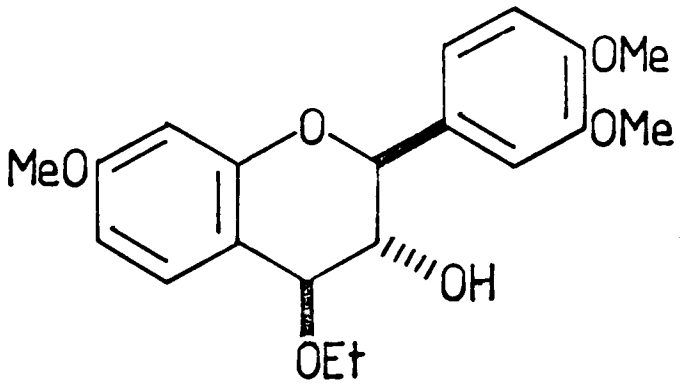
the epimeric 2,3-trans-3,4-trans-4-ethoxy-7,3',4'-trimethoxy-flavan-3-ol (CXLIV). The experience of the present author is that thin layer chromatography is a poor guide to the relative concentrations of components of a mixture; a quantitative study of this reaction is required if reliable conclusions as to stereochemical control are to be drawn.



CXLII



CXLIII



CXLIV

More work is clearly needed in order to elucidate the stereochemistry of reactions of 2,3-trans-3,4-disubstituted flavans. Although the reaction of 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (CXX) with phenol in toluene has not solved the stereochemical problem, it has provided the first route to a 4-aryloxyflavan with the cyanidin substitution pattern (including the hydroxyl group at the 3-position). The instability of the 4-aryloxyflavanoid (CXXVI) under the reaction conditions suggests that its yield

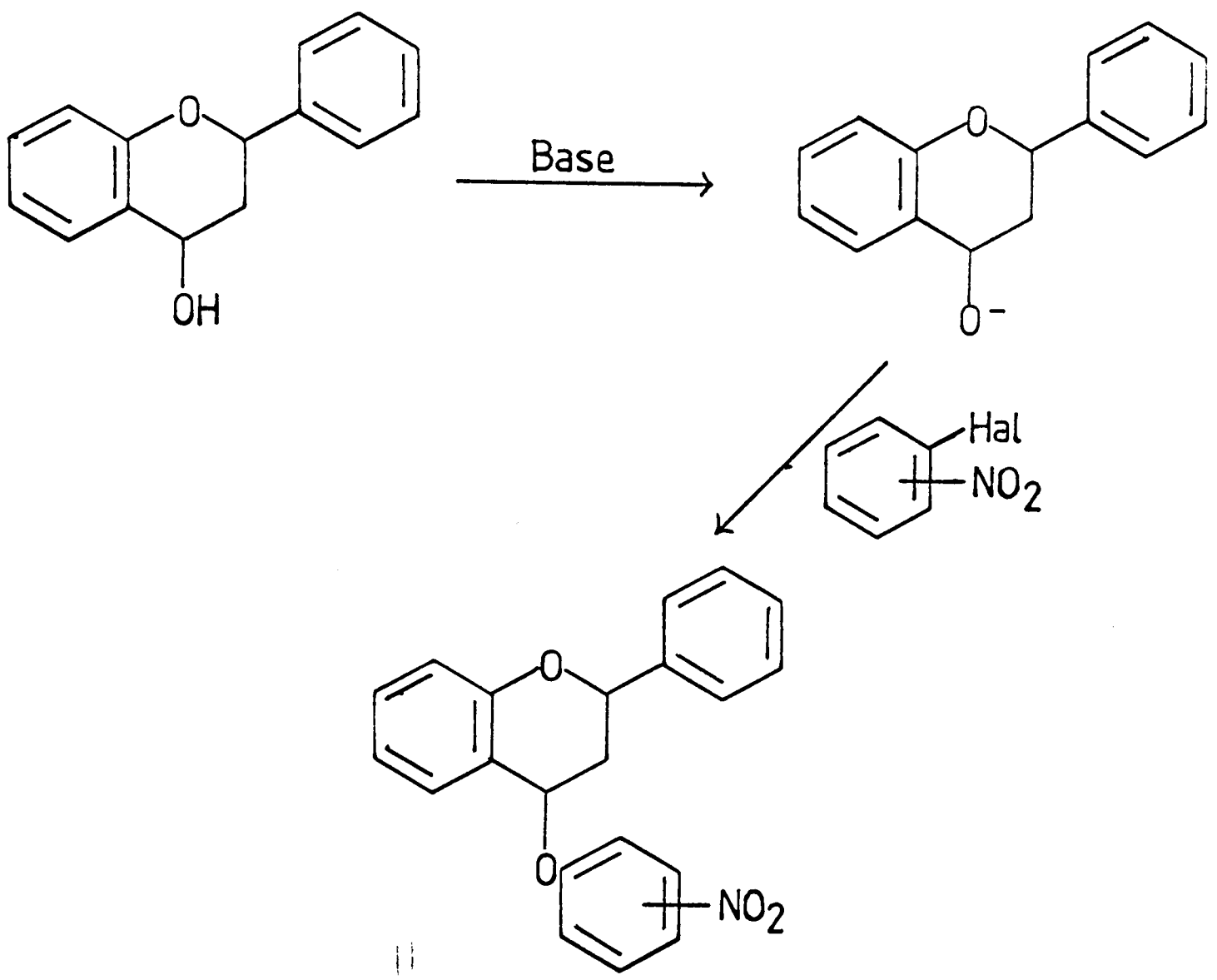
(15%) might be improved if the reaction is stopped before all the starting material has disappeared. Pyridine instead of toluene as solvent was found not to be beneficial. Reaction in pyridine gave, after hydrolysis of the 3-benzoyloxy group, only 8% of the 4-aryloxyflavan-3-ol (CXXXI).

The synthetic potential of 4-(p-nitrophenoxy)-flavans

Before proceeding to the synthesis of an ether-linked flavanoid dimer, it was decided to extend beyond acetate and benzoate the range of leaving groups investigated. Comparison of the properties of benzoate and acetate as leaving groups had shown that the better leaving group was derived from the stronger acid. It therefore seemed likely that p-nitrophenoxy- would prove a better leaving group than phenoxy-, because p-nitrophenol has pK_a 7.15 and phenol, pK_a 9.89.[64]

Troke[62] had tried to prepare 4β-(p-nitrophenoxy)-4'-methoxyflavan by reaction of 4'-methoxyflavan-4β-ol in tetrahydrofuran with sodium hydride and then p-chloronitrobenzene. He obtained less than 5% of an unidentified solid product. The present author aimed to utilise analogous reactions of flavan-4-ol anions with nitro-substituted aryl halides to produce nitro-substituted aryloxyflavans (scheme 34), which, although they would not resemble the postulated naturally occurring aryloxyflavans, might prove valuable synthetic intermediates.

Since the desired nitroaryloxyflavans were expected to be unstable compounds and Troke[62] had found that the proposed transformation was not easily accomplished, it was decided first to investigate the reactions of flavanol anions with

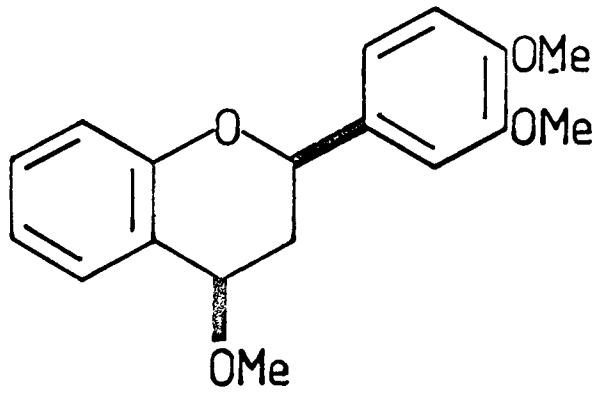


Scheme 34

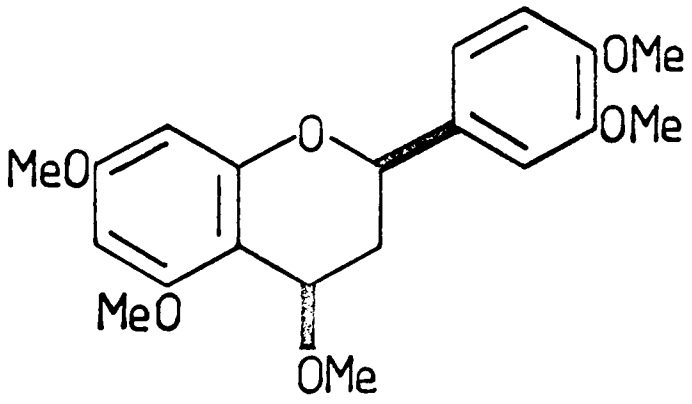
methyl iodide in the hope of obtaining stable 4β-methoxyflavans. For this purpose samples of various flavan-4β-ols in a suitable solvent were treated with a strong base and then methyl iodide.

3',4'-Dimethoxyflavan-4β-ol was converted into 4β,3',4'-trimethoxyflavan (CXLV) by using tetrahydrofuran as solvent and phenyllithium as base. Faster methylation took place in tetrahydrofuran if sodium hydride was the base employed (the conditions of Stoochnoff and Benoiton[73]). It was therefore concluded that the nature of the cation materially influenced the reactivity of the anion and that sodium as the cation was preferable to lithium. Dimethylformamide as solvent was also

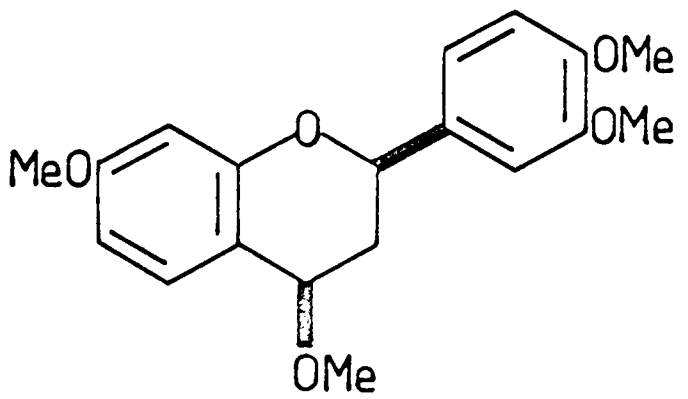
satisfactory in conjunction with sodium hydride as base, but did not seem to enhance the reactivity of the anions. 4β,5,7,3',4'-Pentamethoxyflavan (CXLVI) and 4β,7,3',4'-tetramethoxyflavan (CXLVII) were prepared in this solvent at roughly the same rate as was 4β,3',4'-trimethoxyflavan, (CXLV), in tetrahydrofuran.



CXLV



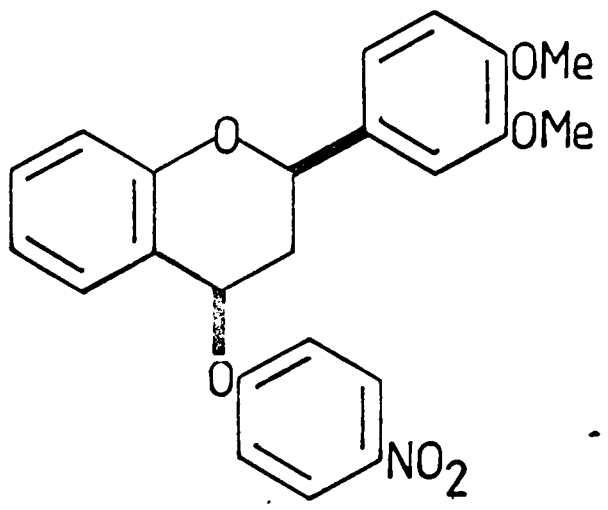
CXLVI



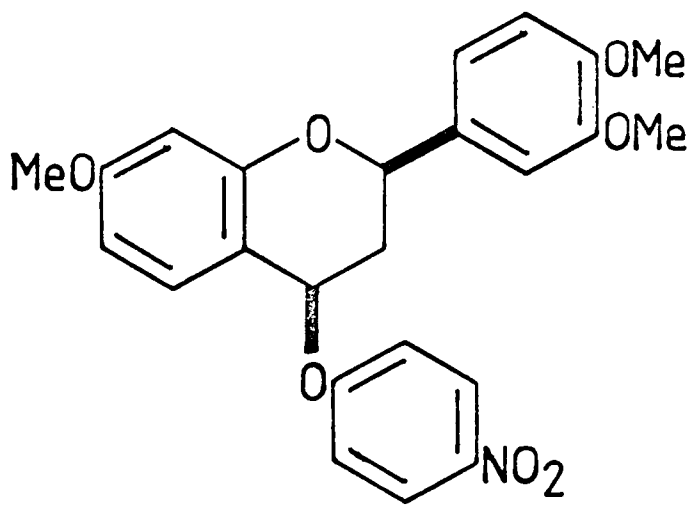
CXLVII

Sodium hydride possessed the disadvantage that it reacted only slowly with flavanols. Treatment of sodium hydride with dimethylsulphoxide, however, gives the strongly basic "dimsyl sodium".[74] This base, in dimethylsulphoxide as solvent, was found to react rapidly with flavanols. By treating the solutions so obtained with excess of p-fluoronitrobenzene (chosen because it is more reactive than p-chloronitrobenzene[75]) for 30min or less at room temperature, 4β-(p-nitrophenoxy)-3',4'-dimethoxyflavan (CXLVIII), 4β-(p-nitrophenoxy)-7,3';4'-trimethoxyflavan (CXLIX) and 4β-(p-nitro-

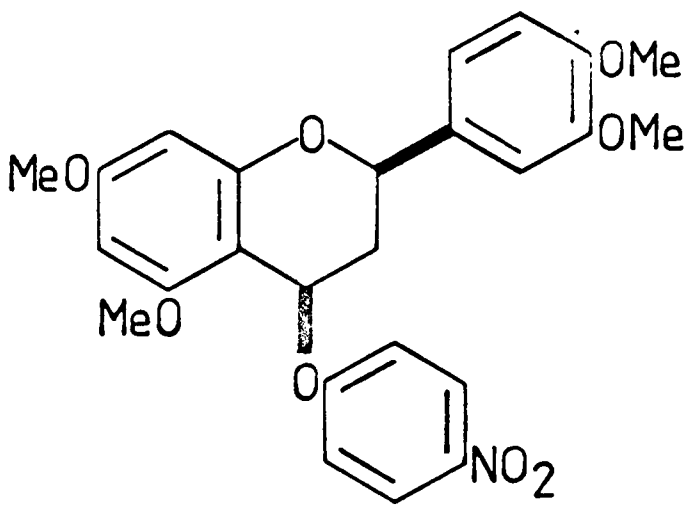
phenoxy)-5,7,3',4'-tetramethoxyflavan (CL) were prepared in 63-79% isolated yield.



CXLVIII



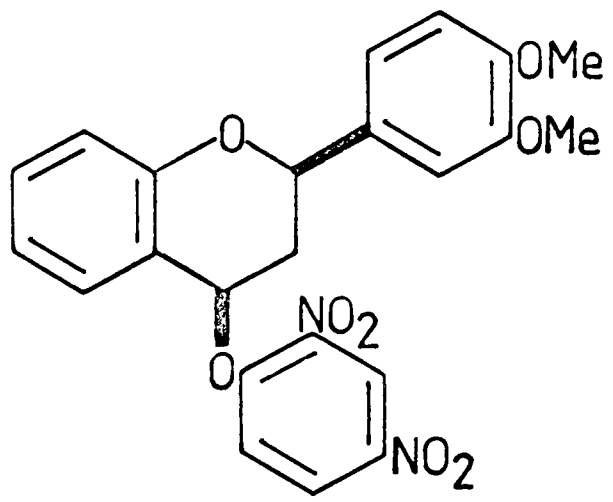
CXLIX



CL

Surprisingly, 4β-(2,4-dinitrophenoxy)-3',4'-dimethoxyflavan (CLI) could not be prepared in the same way from 3',4'-dimethoxyflavan-4β-ol and 2,4-dinitrofluorobenzene. When the flavanol anion was prepared as usual using "dimsyl sodium" in dimethylsulphoxide, treatment with 2,4-dinitrofluorobenzene for 4h at room temperature led to recovery of 42% of the starting material. 7,3',4'-Trimethoxyflavan-4β-ol was also recovered in 33% yield under these conditions.

On the other hand, 4β-(2,4-dinitrophenoxy)-3',4'-dimethoxyflavan (CLI) was readily prepared from 3',4'-dimethoxyflavan-4β-ol and 2,4-dinitrofluorobenzene when phenyllithium was used as the base in tetrahydrofuran.

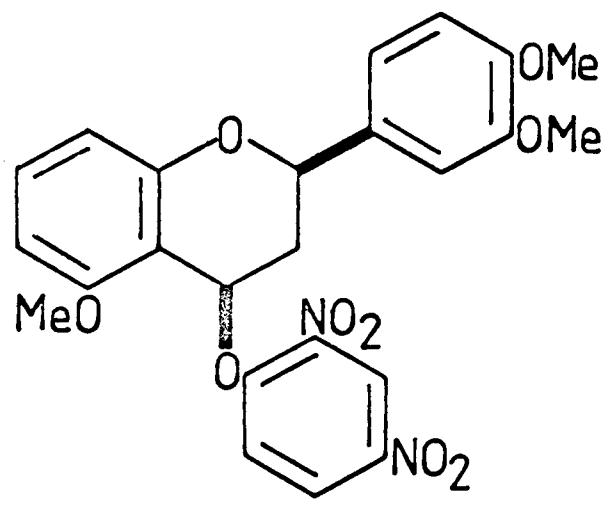


CLI

It is difficult to understand why 2,4-dinitrofluorobenzene should not react smoothly with the sodium salts of flavanols in dimethylsulphoxide. The fact that reaction does occur with the lithium salt of a flavanol in tetrahydrofuran shows that the explanation cannot be steric hindrance to nucleophilic attack by the ortho-nitro group of 2,4-dinitrofluorobenzene. That reaction to form the desired product followed by decomposition did not occur is indicated by the isolation of flavan-4β-ols: had decomposition via a 4-carbocation taken place, the products would have had 4α-stereochemistry. A third possibility which may be ruled out is reaction of the 2,4-dinitrofluorobenzene with dimethylsulphoxide. The reaction of piperidine with 2,4-dinitrofluorobenzene in benzene has been shown[76] to be accelerated by a factor of five by the addition of 0.2M dimethylsulphoxide. Further work is needed in order to clarify the effect of dimethylsulphoxide on the reaction of flavanol anions with 2,4-dinitrofluorobenzene.

An attempt was made to prepare 4β-(2,4-dinitrophenoxy)-5,3',4'-trimethoxyflavan (CLII) by reaction of the corresponding flavan-4β-ol with phenyllithium in tetrahydrofuran and then

2,4-dinitrofluorobenzene. The product obtained had a nuclear magnetic resonance spectrum appropriate to 4β-(2,4-dinitrophenoxy)-5,3',4'-trimethoxyflavan, but attempted recrystallisation from benzene/light petroleum led to decomposition (indicated by the appearance of extra peaks in the nuclear magnetic resonance spectrum) and the compound was not obtained pure. It was concluded that 2,4-dinitrophenoxy- is too good a leaving group to permit the purification of the aryloxyflavan (CLII). This conclusion was justified by the observation that the analogous reaction of 7,3',4'-trimethoxyflavan-4β-ol led to a mixture of products from which no solid could be isolated.

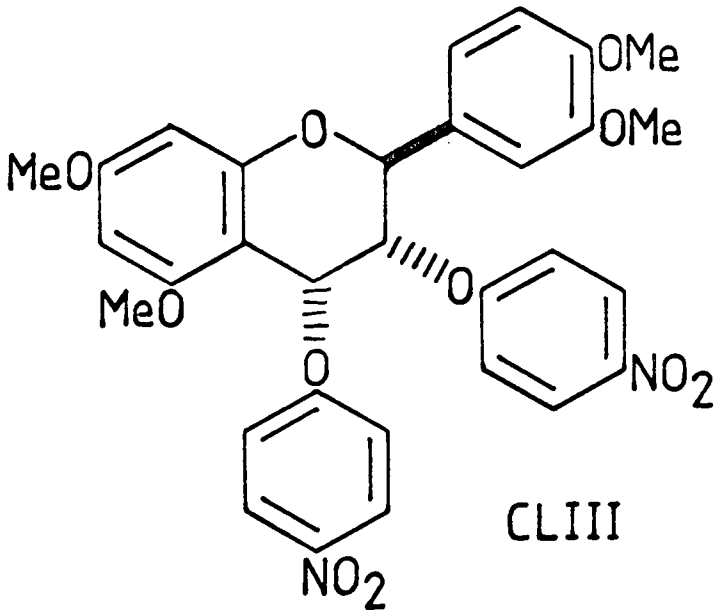


CLII

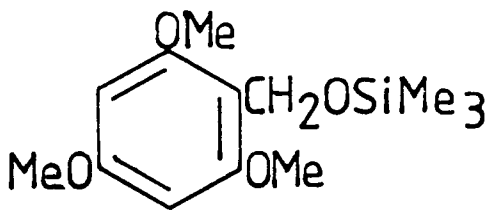
The expectation that p-nitrophenoxy- would prove a useful leaving group was borne out by the observation that each of the 4β-(p-nitrophenoxy)-flavans (CXLIX) and (CL) reacted with phenol in pyridine to give the corresponding 4α-phenoxyflavans (CXVIII) and (CVII), isolated by crystallisation in 43% and 50% yields, respectively, reaction occurring more rapidly than with 4β-benzoyloxy-7,3',4'-trimethoxyflavan (CXIX) or 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (XLII).

It was found that 2,3-trans-3,4-cis-di-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (CLIII) was readily prepared by

treatment of 2,3-*trans*-3,4-*cis*-5,7,3',4'-tetramethoxyflavan-3,4-diol (LXXVIII) with dimsyl sodium and then *p*-fluoronitrobenzene. This indicates the feasibility of preparing derivatives of the diol (LXXVIII) *via* the dianion, but the di-(*p*-nitrophenoxy) derivative (CLIII) is not synthetically useful because of the impossibility of removing the unwanted *p*-nitrophenyl function from the 3-hydroxyl group. That this would be so was confirmed when 4β-(*p*-nitrophenoxy)-7,3',4'-trimethoxyflavan (CXLIX) was boiled in ethanol containing sodium ethoxide or potassium hydroxide in methanol in an attempt to remove the *p*-nitrophenyl group by nucleophilic displacement. Thin layer chromatography indicated the presence of 4β-(*p*-nitrophenoxy)-7-3',4'-trimethoxyflavan but no 7,3',4'-trimethoxyflavan-4β-ol.



CLIII



CLIV

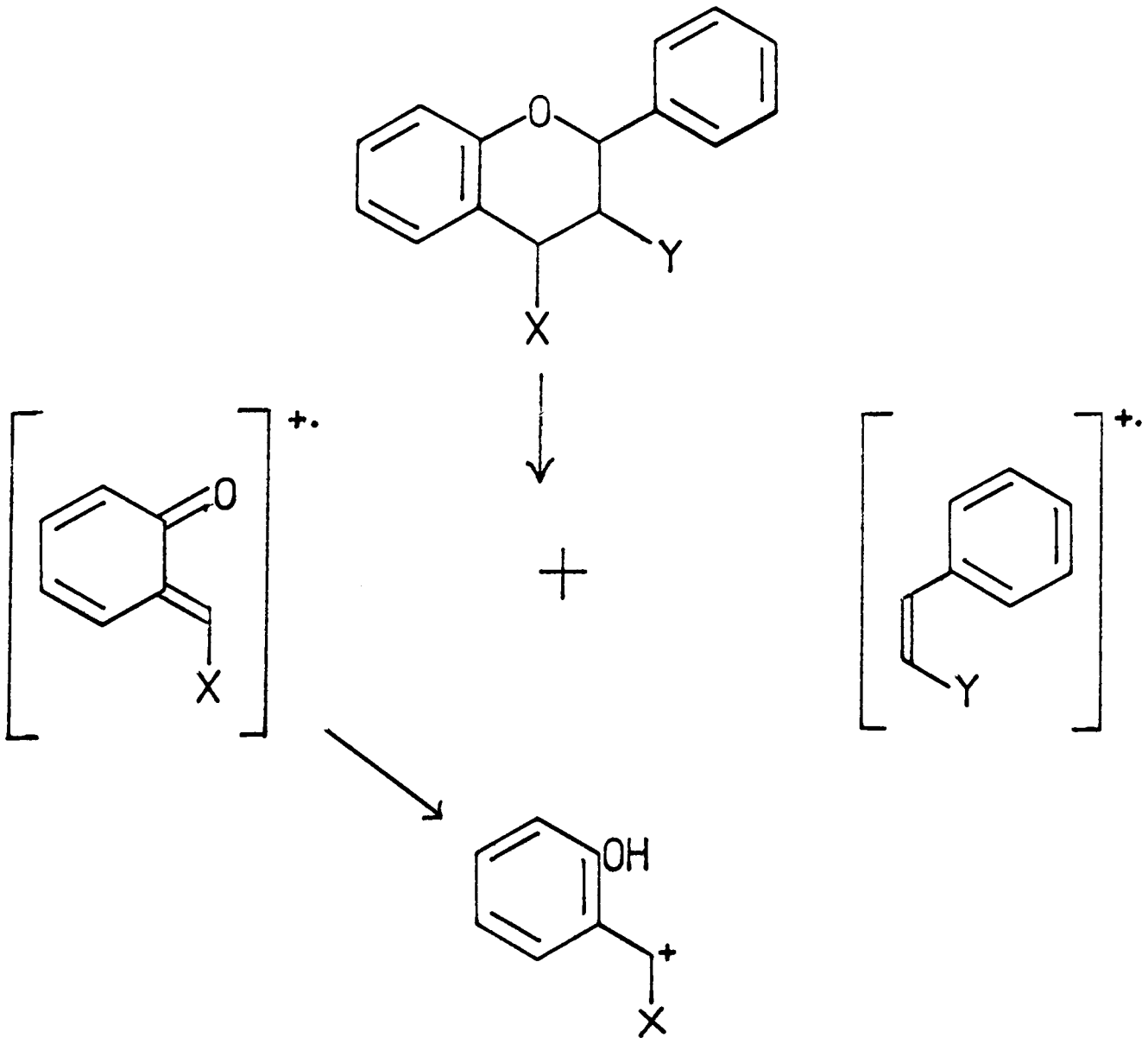
Time did not permit the study of other leaving groups which might avoid this problem. An attractive possibility as a leaving group is trialkylsilyloxy-, following the observation of Midgley *et al.*[77] that the trimethylsilyloxy group is readily lost by the 2,4,6-trimethoxybenzyl ether (CLIV) in reactions with nucleophiles. Silyl ethers may be cleaved under neutral conditions with fluoride ion[78] and

therefore the presence of a silyl group on the 3-hydroxyl would not be objectionable. Whether silyloxy leaving groups would lead to an improved synthesis of 2,3-trans-3,4-cis-4-aryloxy-5,7,3',4'-tetramethoxyflavan-3-ols remains to be seen, however.

This chapter is concluded with a brief outline of the principles of interpretation of the mass spectra of 4-substituted and 3,4-disubstituted flavans.

Mass spectra of 4-substituted and 3,4-disubstituted flavans

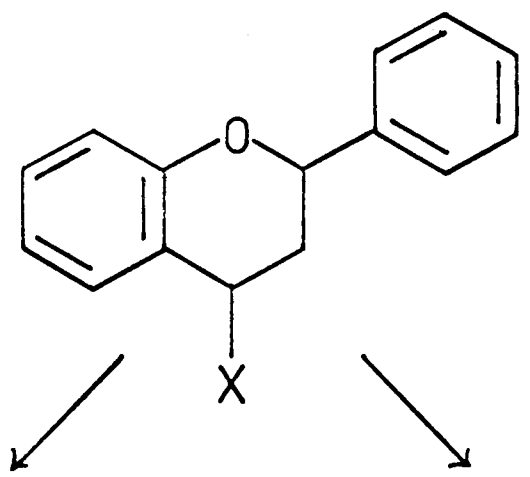
Mass spectrometry is not used extensively in this thesis for the elucidation of structures, but an outline is here given of the main modes of fragmentation of 4-substituted and 3,4-disubstituted flavans.[79,80,81]

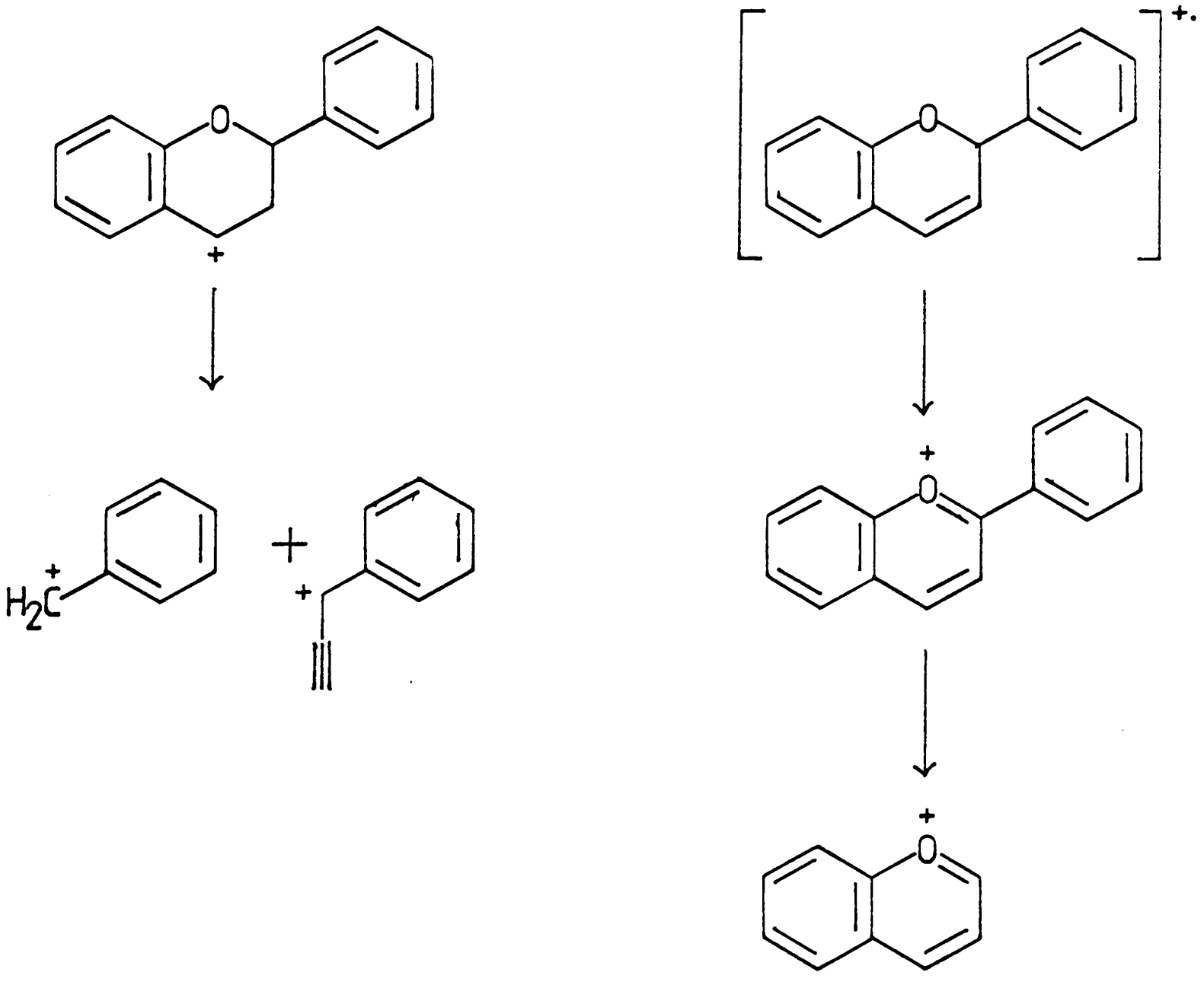


Scheme 35

Scheme 35 illustrates the "retro Diels-Alder" fragmentation.[79] This pathway is most important for flavans which lack a good leaving group.[22]

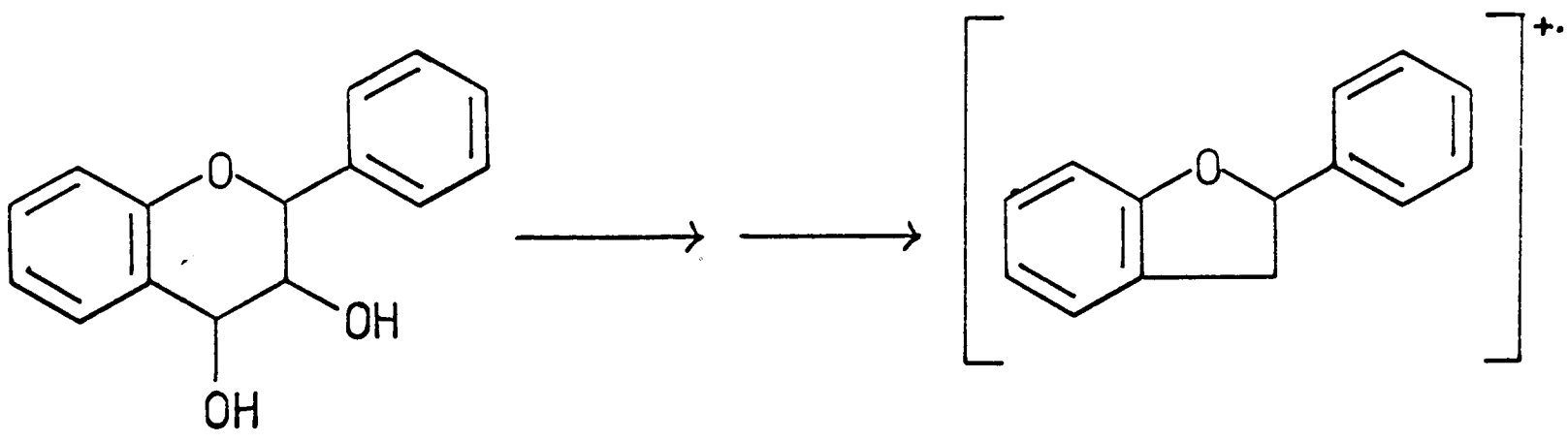
For flavans with a good leaving group at the 4-position (including aryloxy-), especially if methoxyl groups are present in the A-ring, a more important fragmentation mode may be that represented in scheme 36.[22,32]





Scheme 36

Drewes[80] and Clark-Lewis[81] have both noted another fragmentation of flavan-3,4-diols and their derivatives, in which the 3- and 4-substituents are both lost, as is one of the carbons of the heterocyclic ring. (Scheme 37).



Scheme 37

CHAPTER 3

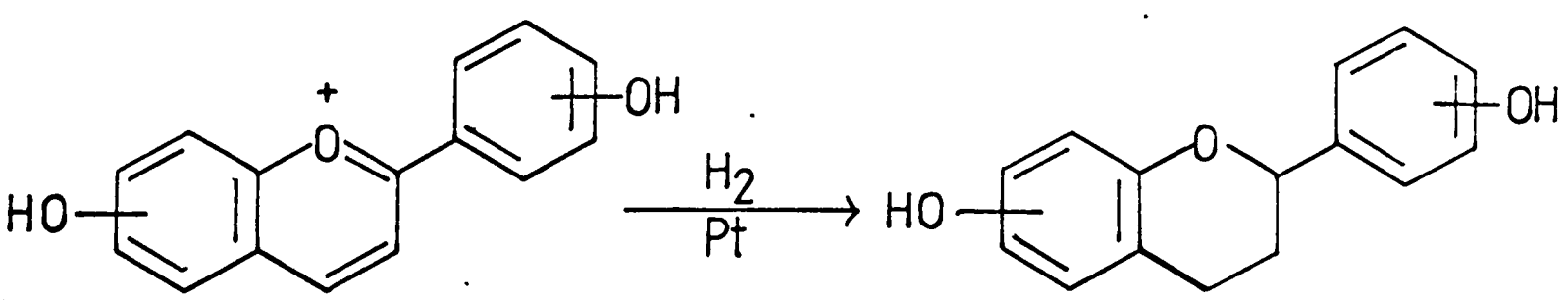
Synthesis of 7-hydroxyflavanoids

In the previous chapter it has been shown that suitably substituted flavanoids react with the hydroxyl group of phenols to yield 4-aryloxyflavans. If the phenol used in this reaction were itself a flavanoid species, then the product would be an ether-linked flavanoid dimer. It was hoped that such a reaction would satisfy the third aim of the present work, the discovery of a synthesis of ether-linked flavanoid dimers resembling those suggested as occurring in nature.

The mechanism of the proposed reaction, attack by the phenol as nucleophile on a flavanoid 4-carbocation, requires that the phenolic flavanoid possess no other nucleophilic groups which might react with the carbocation. Previous syntheses of phenolic flavanoids have been acceptable on this count, but only a narrow range of phenolic flavanoids has been synthesised. The two routes that have been employed are described first.

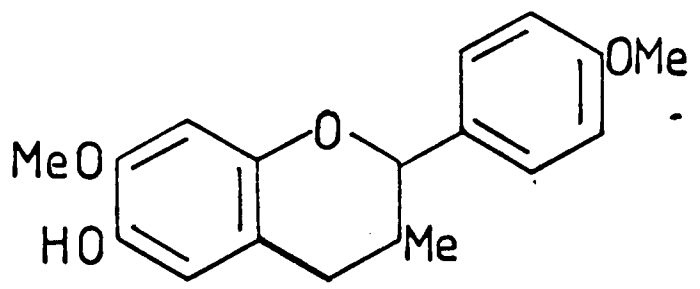
Previous syntheses of phenolic flavanoids

Freudenberg and co-workers[82,83] showed that hydrogenation of phenolic flavylium salts led to flavans with phenolic hydroxyl groups (scheme 38).



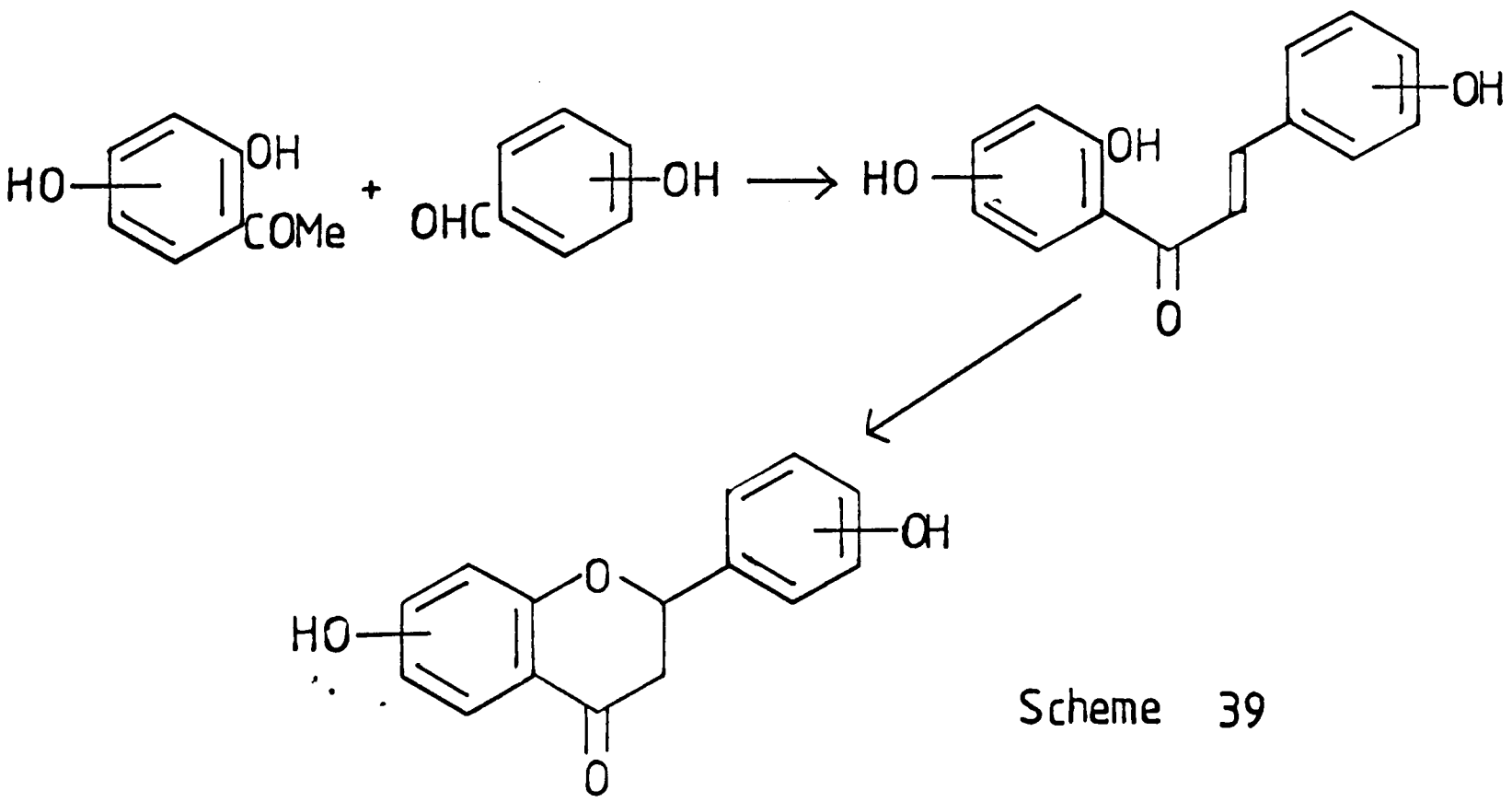
Scheme 38

This route has been used to synthesise monophenolic flavans such as 6-hydroxy-7,4'-dimethoxy-3-methylflavan (CLV),[84] but it could not be elaborated to lead to flavans with synthetically useful functional groups, such as acyloxy, in the heterocyclic ring because the necessary flavylium salts are not available.



CLV

The second type of phenolic flavanoids for which syntheses have been reported are flavanones. The preparation of these compounds by cyclisation of chalcones does not permit the introduction of an acyloxy group at the 3-position (although Clemmensen reduction provides another route to phenolic flavans lacking 3- or 4-substituents[85]). Further drawbacks are that syntheses of the intermediate chalcones (which need not necessarily be isolated) according to scheme 39 are sometimes



Scheme 39

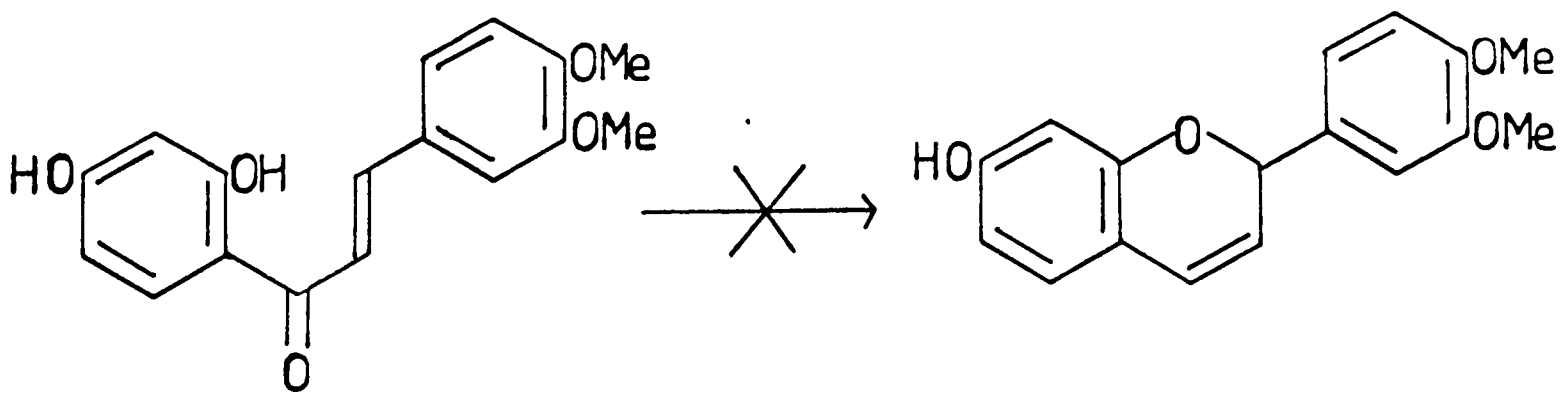
unsuccessful,[86,87] usually require lengthy purifications of the products[88,89] and lead eventually to low yields of the desired flavanone.[22,50,62]

Synthesis of phenolic flavanoids: the present work

It has been shown that published synthetic routes to phenolic flavanoids were inflexible or tedious, or both. Two ways in which phenolic flavanoids might be made more accessible were investigated in the present work.

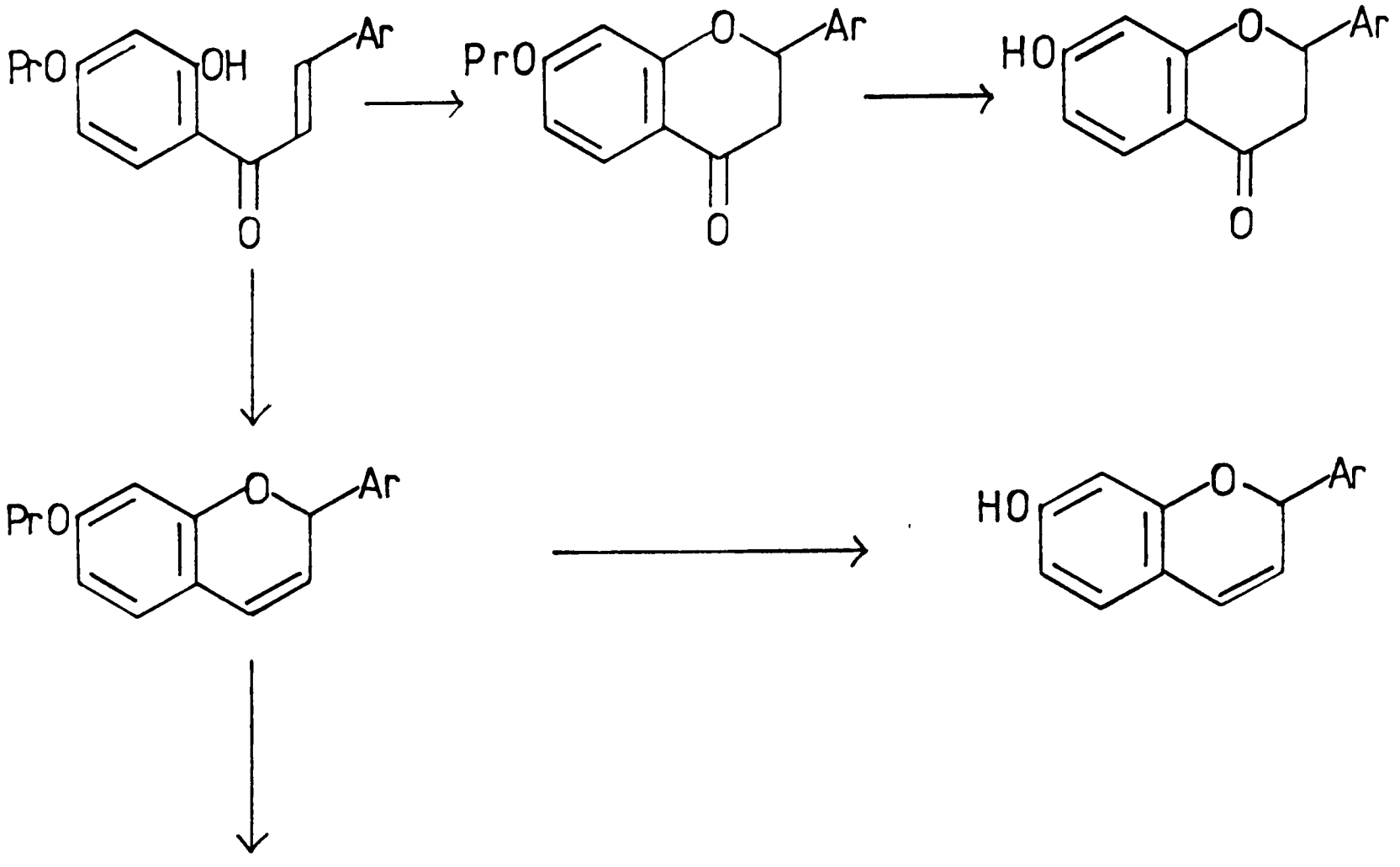
Firstly, it was noted that whereas phenolic flavanones were prepared only with difficulty, flavanones lacking a phenolic hydroxyl group are readily synthesised. Phenolic flavanones might therefore be best prepared if the hydroxyl function were protected and the protecting group removed only after cyclisation of the intermediate chalcone.

Secondly, it was shown in Chapter 2 that the combination of osmium tetroxide and N-methylmorpholine-N-oxide provides an excellent reagent for converting 5,7,3',4'-tetramethoxyflav-3-ene into 2,3-trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol. If a flav-3-ene with a protected phenolic hydroxyl group were so treated, the resulting flavan-3,4-diol could be transformed into other types of flavanoid before freeing the desired



CLVI CLVII

Scheme 40


PrO
OH
Ar
O
PrO
O
Ar
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HO
O
Ar
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PrO
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O
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hydroxyl. It was known[88] that 2',4'-dihydroxy-3,4-dimethoxychalcone (CLVI) could not be converted by sodium borohydride in ethanol into 7-hydroxy-3',4'-dimethoxyflav-3-ene (CLVII). It therefore seemed essential to protect the phenolic hydroxyl group throughout the synthetic scheme.

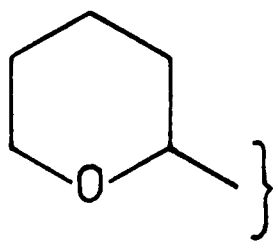
All the synthetic possibilities envisaged are outlined in scheme 40, in which the protecting group is represented as Pr- and the potential phenolic hydroxyl group is shown at the 7-position. The 7-position was chosen because it was expected to be less hindered than the 5-position and would therefore allow easier linkage to another flavanoid nucleus: both 5- and 7-positions have been suggested[10] as sites of linkage in the postulated naturally occurring ether-linked tannins.

In choosing a protecting group, two sorts of limitation were borne in mind. Firstly, the protecting group would have to withstand strong alkali in the preparation of the chalcone, sodium borohydride in hot ethanol followed by acetic acid in chloroform during cyclisation to a flav-3-ene and N-methylmorpholine-N-oxide during preparation of the flavan-3,4-diol. Secondly, the protecting group would have to be removable without the use of strong acid in order to avoid loss of the flavanoid 4-substituent (see Chapter 1) or cleavage of the heterocyclic ring.[50,90]

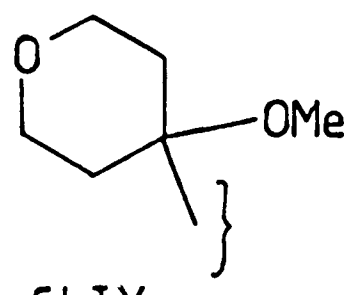
Haslam[91] has reviewed methods of protecting phenolic hydroxyl groups. The protecting groups which satisfied the first criterion (stability to the synthetic reaction conditions) were methyl, benzyl, t-butyl, methoxymethyl and possibly tetrahydropyranyl. The tetrahydropyranyl group may be cleaved with aqueous acetic acid.[91] It was therefore uncertain whether this

protecting group would survive the treatment with acetic acid in boiling chloroform necessary during the conversion of a chalcone to a flav-3-ene. If it did survive, its very acid lability would make it the most attractive of the five protecting groups mentioned according to criterion two: the necessity of removing the protecting group without using strong acid.

Nevertheless, tetrahydropyranyl possesses the disadvantage that it introduces an asymmetric centre into the flavanoid molecule protected. Flavanoids already possess an asymmetric centre at the 2-position and therefore in tetrahydropyranyl derivatives of flavanoids the likelihood arises of non-crystalline mixtures of diastereoisomers being formed. To avoid the difficulties resulting from the asymmetry of the tetrahydropyranyl group (CLVIII), Reese and co-workers[92] have recommended the use of 4-methoxytetrahydropyranyl (CLIX) as a symmetrical protecting group for the hydroxyl function which has roughly the same stability to acid as tetrahydropyranyl (CLVIII). This group had not previously been employed for protection of phenols, but it seemed a valuable alternative to tetrahydropyranyl for the present work.



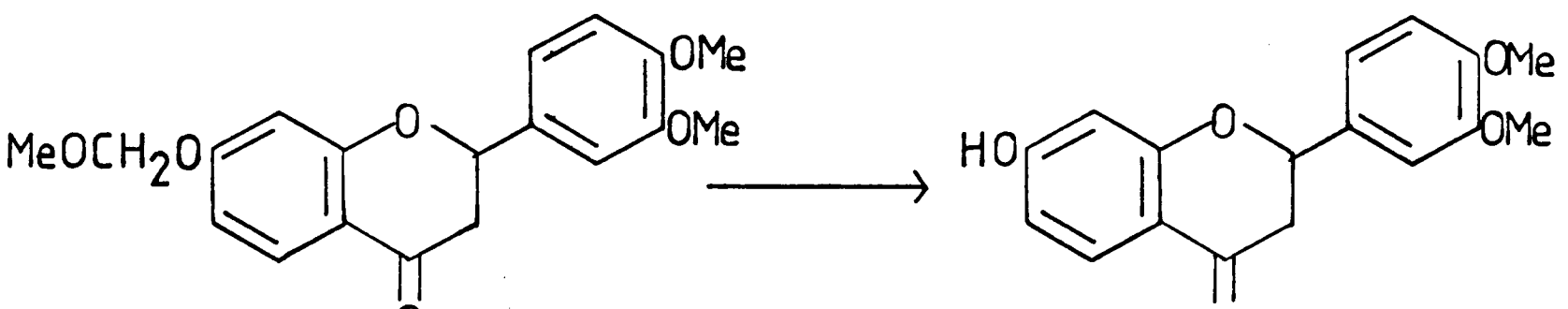
CLVIII



CLIX

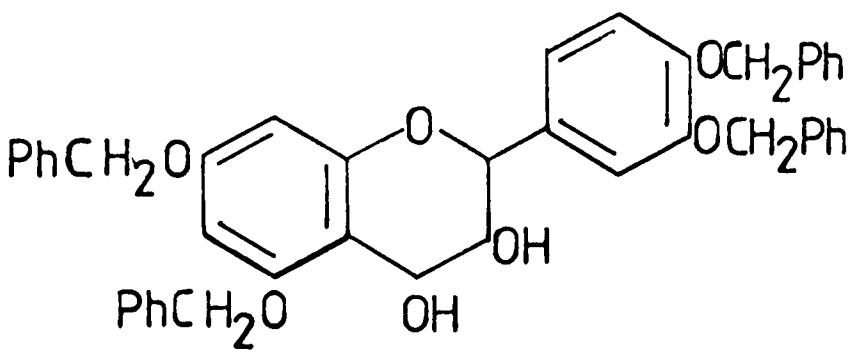
Bellini and Venturella[93] had successfully used the methoxymethyl group to protect the 4'-hydroxyl function in a

synthesis of 2',4'-dihydroxy-3,4-dimethoxychalcone (CLVI). To liberate the hydroxyl function, these workers had used acetic acid containing dilute sulphuric acid at 100°. Such vigorous conditions seemed certain to bring about unwanted reactions at the 4-position of 3,4-disubstituted flavans possessing a 7-oxygen substituent,[35] but were acceptable for removal of a protecting group from a flavanone. It was therefore decided to attempt the synthesis of 7-methoxymethoxy-3',4'-dimethoxy-flavanone (CLX) and hence 7-hydroxy-3',4'-dimethoxyflavanone (CLXI).



CLX CLXI

The benzyl group has been used for protecting phenols and removed by hydrogenolysis instead of treatment with acid (see, for example, ref. 91). It was thought unsuitable for the present work because of the difficulty in hydrogenolysing the protecting group without simultaneously cleaving a (benzylic) flavanoid 4-oxygen substituent. This difficulty has been overcome in a single instance by Freudenberg and Weinges[95] who successfully debenzylated the leucoanthocyanidin derivative (CLXII) without loss of the 4-hydroxyl substituent by using as the catalyst palladium on barium sulphate in dimethylformamide as solvent. It is unclear whether this method would be generally applicable.



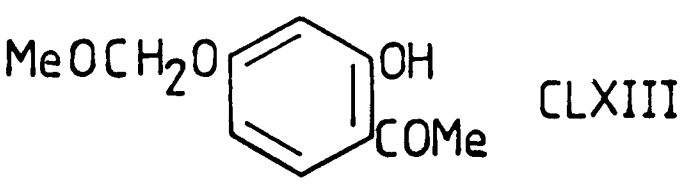
CLXII

Another protecting group which seemed attractive, because its removal did not require acid treatment, was o-nitrobenzyl. This group had not been used to protect phenols, but it had been employed for protection of alcohols and could be removed in high yield by photolysis with long wavelength (ca. 320nm) ultra-violet light.[96,97] The o-nitrobenzyl group was therefore added to the list of protecting groups to be investigated in the present work.

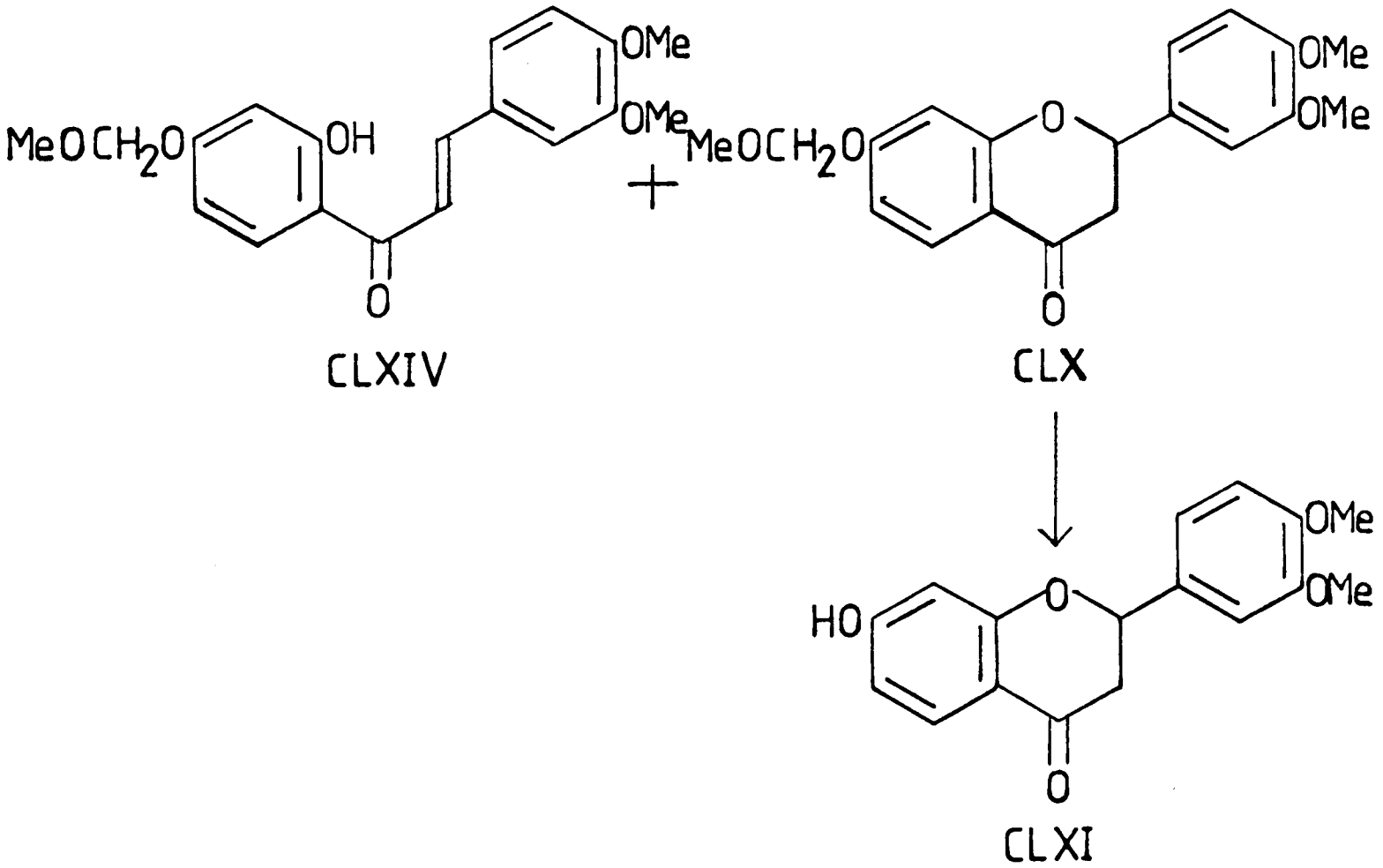
Use of the methoxymethyl protecting group

2-Hydroxy-4-methoxymethoxyacetophenone (CLXIII) was prepared by treatment of resacetophenone in acetone with potassium carbonate and one equivalent of methoxymethyl chloride. Distillation of the reaction mixture was found to yield the methoxymethyl ether (CLXIII) contaminated with unchanged resacetophenone. Bellini and Venturella[93] had apparently avoided this difficulty by using excess of methoxymethyl chloride, but they only obtained a 44% yield of the desired product. The present author found, however, that use of one equivalent of methoxymethyl chloride and steam distillation of the crude reaction product readily furnished chromatographically and spectroscopically pure 2-hydroxy-4-methoxymethoxyaceto-phenone (CLXIII) in 62% yield.

Condensation of the protected resacetophenone (CLXIII) with veratraldehyde gave both 2'-hydroxy-4'-methoxymethoxy-3,4-dimethoxychalcone (CLXIV) and 7-methoxymethoxy-3',4'-dimethoxyflavanone (CLX) which were separated by fractional crystallisation. Removal of the protecting group from the flavanone was readily achieved with toluene-p-sulphonic acid in acetic acid, furnishing the hitherto unknown 7-hydroxy-3',4'-dimethoxyflavanone (CLXI) in 73% yield.



CLXIII



CLXIV

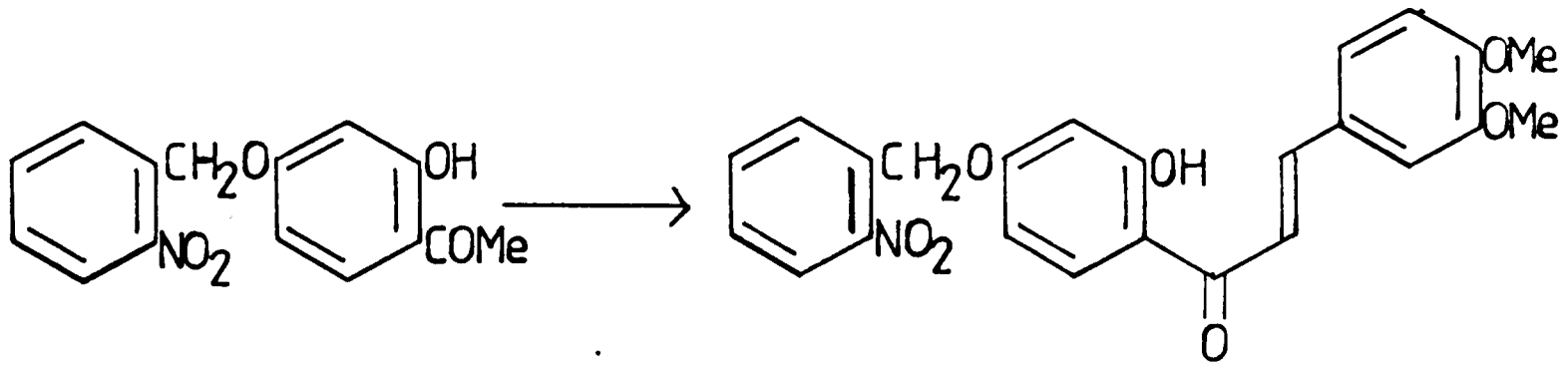
CLX

CLXI

Use of the o-nitrobenzyl protecting group

Although 2-hydroxy-4-(o-nitrobenzyloxy)-acetophenone (CLXV) was readily prepared in 80% yield from 2,4-dihydroxyacetophenone

and o-nitrobenzyl bromide, condensation of this protected resacetophenone with veratraldehyde furnished only a few crystals of 2'-hydroxy-4'-(o-nitrobenzyloxy)-3,4-dimethoxychalcone (CLXVI). It is likely that reaction was complicated by reduction of the nitro group by the ethanolic alkali[98] or by participation of the o-nitrobenzyl group in condensation with the veratraldehyde.[99]

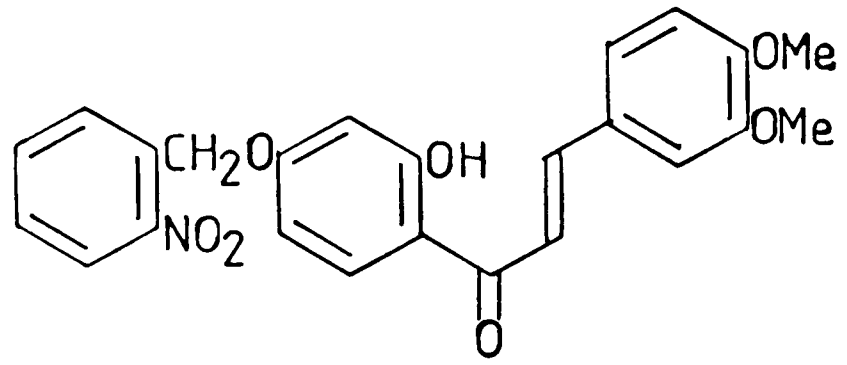


CLXV CLXVI

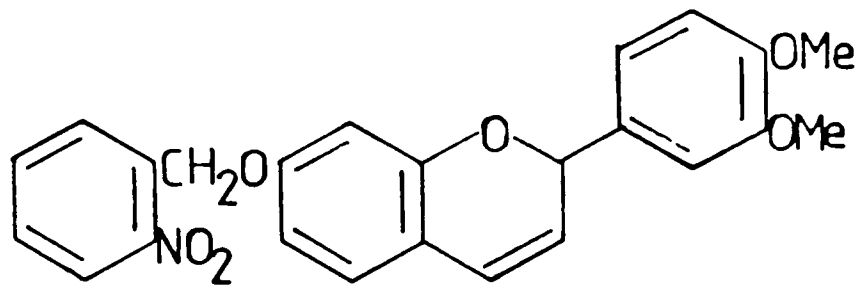
The desired o-nitrobenzyloxychalcone (CLXVI) could, however, be prepared in 64% yield by reaction of o-nitrobenzyl bromide with 2',4'-dihydroxy-3,4-dimethoxychalcone (CLVI) (a convenient preparation of which is described later). Reaction occurs at the 4'-hydroxyl group because the 2'-hydroxyl is rendered less reactive by hydrogen-bonding to the carbonyl group, the latter being indicated by its low field resonance (-3.5τ) in the nuclear magnetic resonance spectrum.

The protected chalcone (CLXVI) underwent the Clark-Lewis reductive cyclisation[51,52] to give 58% of 7-(o-nitrobenzyloxy)-3',4'-dimethoxyflav-3-ene (CLXVII) which it was found easier to purify by chromatography on a short column of alumina than by repeated crystallisation.

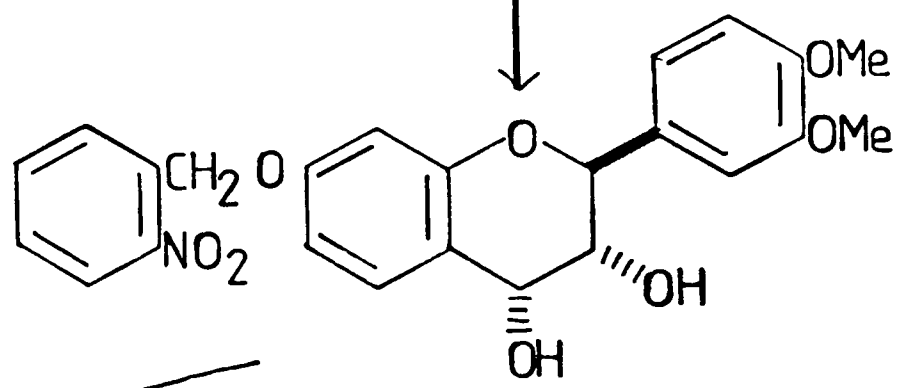
Oxidation of the flav-3-ene (CLXVII) with N-methyl-



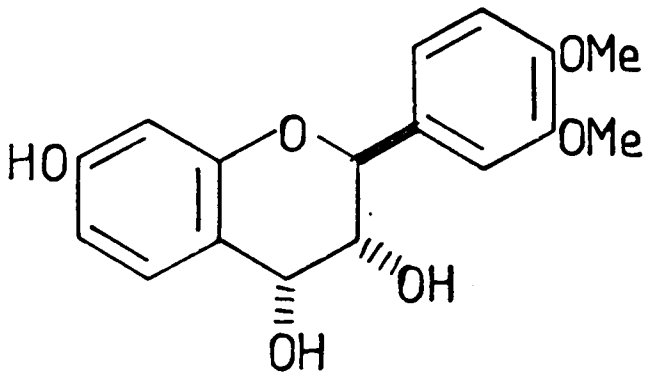
CLXVI



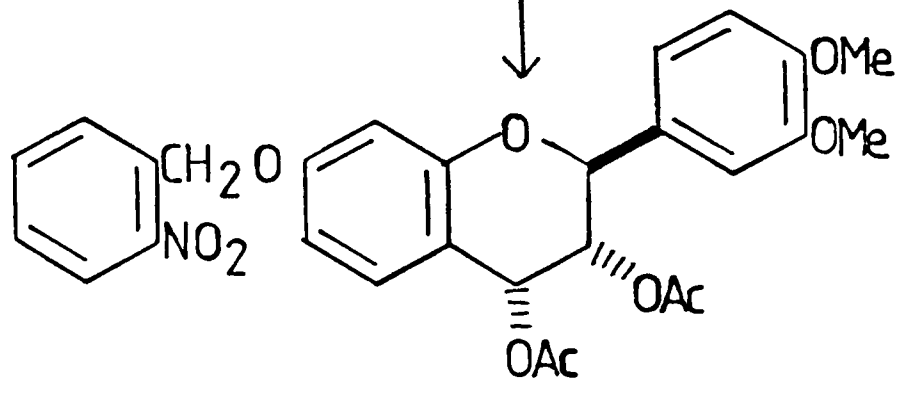
CLXVII



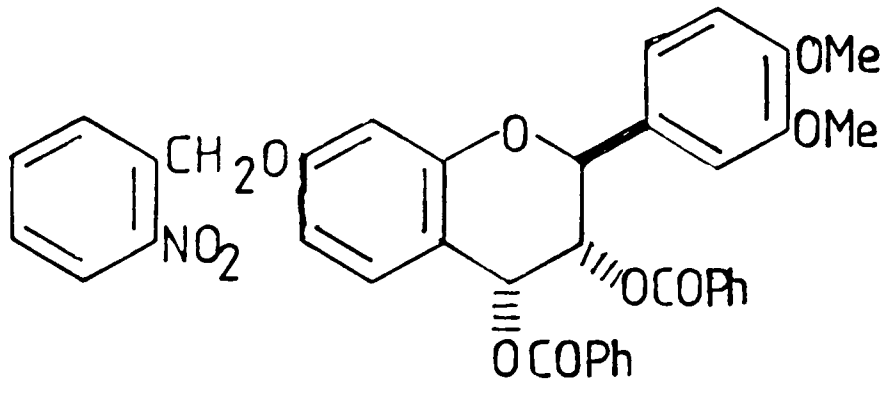
CLXVIII



CLXIX



CLXXI



CLXX

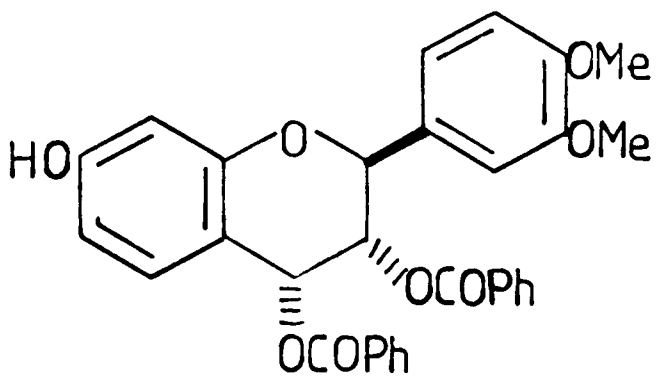
morpholine-N-oxide in the presence of a catalytic quantity of osmium tetroxide furnished 84% of 2,3-trans-3,4-cis-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan-3,4-diol (CLXVIII). The coupling constants, $J_{2,3}$=9.0Hz, $J_{3,4}$=3.4Hz are characteristic (see Chapter 1) of the expected 2,3-trans-3,4-cis stereochemistry (cf. Chapter 2).

It was then demonstrated that the protecting group could be removed by irradiating the diol (CLXVIII) at 300nm: 53% of the expected 2,3-trans-3,4-cis-3',4'-dimethoxyflavan-3,4,7-triol (CLXIX) was isolated by chromatography as a crystalline solid which gave a satisfactory elemental analysis and proton magnetic resonance spectrum ($J_{2,3}$=9.6Hz, $J_{3,4}$=3.6Hz).

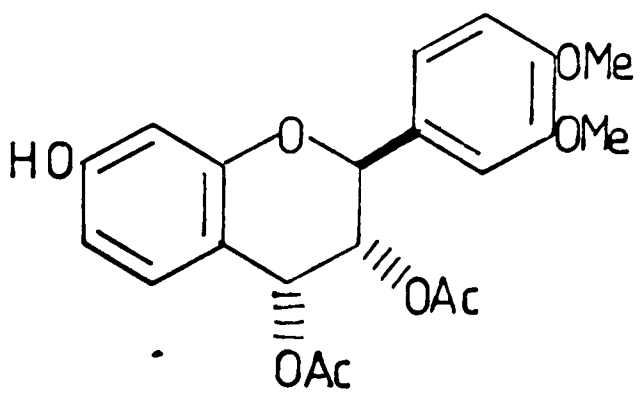
The o-nitrobenzyloxyflavan-3,4-diol (CLXVIII) could also be acylated to give 2,3-trans-3,4-cis-dibenzoyloxy-7-o-nitrobenzyloxy-3',4'-dimethoxyflavan (CLXX) and 2,3-trans-3,4-cis-diacetoxy-7-o-nitrobenzyloxy-3',4'-dimethoxyflavan (CLXXI). These compounds were irradiated at 300nm and the products were subjected to preparative thin layer chromatography. Removal of the major band from the photolysis of either diacyloxy derivative (CLXX) or (CLXXI) yielded mixtures of products, as indicated by thin layer chromatography. It seemed possible that the photolyses had given the desired phenolic flavanoids, (CLXXII) and (CLXXIII), but that these compounds had decomposed during chromatography. This hypothesis was confirmed when an attempt was made to synthesise the dibenzoate (CLXXII) using the tetrahydropyranyl protecting group (see below).

It might have proved possible by catalytic hydrogenolysis of the o-nitrobenzyl substituted dibenzoate (CLXX) to remove both the o-nitrobenzyl group and the (benzylic) 4-substituent

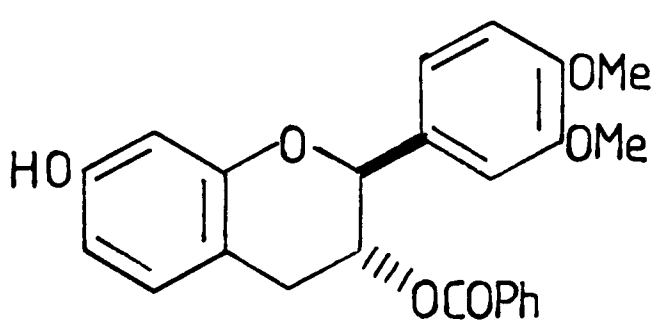
with formation of 2,3-trans-3-benzoyloxy-7-hydroxy-3',4'-dimethoxyflavan (CLXXIV).



CLXXII



CLXXIII



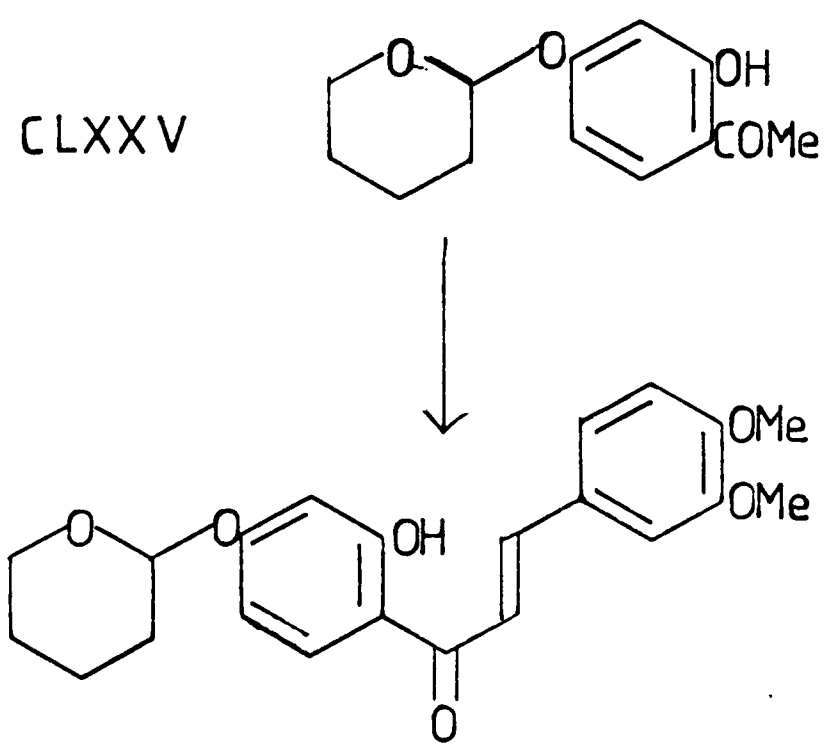
CLXXIV

However, in view of the possibility that hydrogenolysis might first yield the unstable 7-hydroxy-3,4-dibenzyloxyflavan (CLXXII), and the likelihood that reduction of the aromatic nitro group would yield a complex mixture of products, it was decided first to investigate the synthesis of the monobenzoate (CLXXIV) with the aid of the tetrahydropyranyloxy and 4-methoxytetrahydropyranyloxy protecting groups, and this route proved successful.

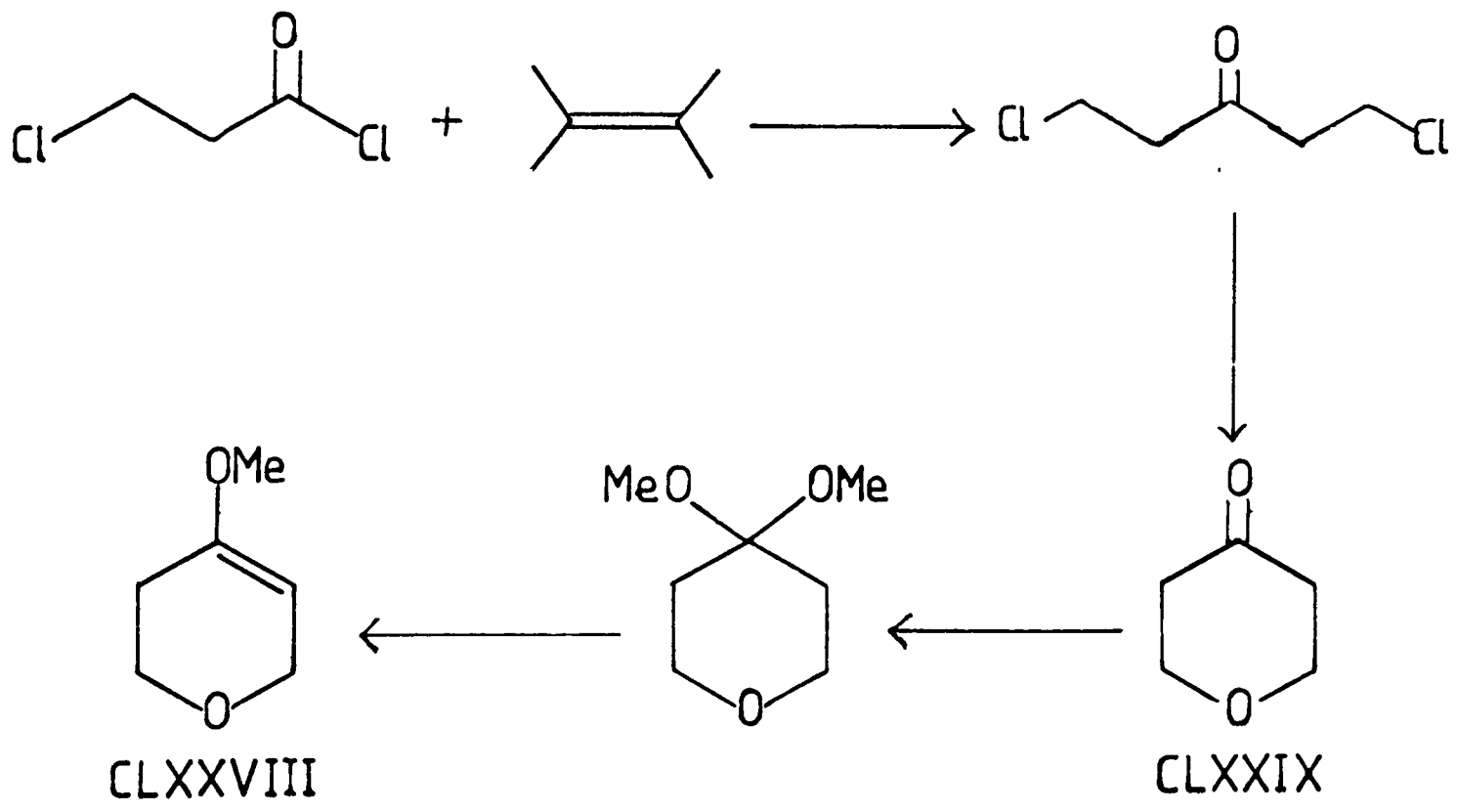
Use of the tetrahydropyranyl and 4-methoxytetrahydropyranyl protecting groups

The known 2-hydroxy-4-tetrahydropyranyloxyacetophenone (CLXXV) was prepared by reaction of resacetophenone with dihydropyran and readily condensed with veratraldehyde to give 2'-hydroxy-4'-tetrahydropyranyloxy-3,4-dimethoxychalcone

(CLXXVI). Removal of the protecting group from this chalcone with aqueous acetic acid containing toluene-p-sulphonic acid provided a convenient route to 2',4'-dihydroxy-3,4-dimethoxychalcone in 49% overall yield from resacetophenone. The chalcone (CLXXVI) could also be reductively cyclised to give 7-tetrahydropyranyloxy-3',4'-dimethoxyflav-3-ene (CLXXVII) which was obtained after chromatography on alumina as a chromatographically, spectroscopically and analytically pure sample, but which only partially solidified presumably because, as had been anticipated, it was a mixture of two diastereoisomers.



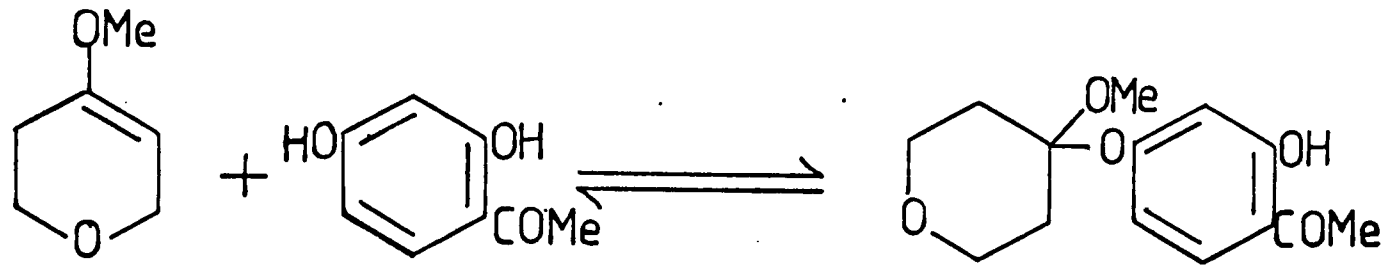
Since the tetrahydropyranyl group had survived the treatment with acetic acid in chloroform needed during reductive cyclisation of a chalcone to a flav-3-ene, it seemed worthwhile investigating the use of the 4-methoxy-tetrahydropyranyl protecting group advocated by Reese et al.[92] The reagent which reacts with the hydroxyl group to be protected is 5,6-dihydro-4-methoxy-2H-pyran (CLXXVIII), and this compound was prepared by a simplification of the method of Reese et al.[100] (scheme 41): it was found that the intermediate tetrahydro-γ-pyrone (CLXXIX) did not need vacuum distillation and that the trimethyl orthoformate recommended[100] during the final step of the synthesis was not only unnecessary but that, until it had almost all distilled from the mixture, it prevented the desired elimination of methanol from taking place.



Scheme 41

Reaction of the dihydropyran (CLXXVIII) with 2,4-dihydroxyacetophenone proved disappointing in that only a 29%

yield of 2-hydroxy-4-(4-methoxytetrahydropyranyloxy)-acetophenone (CLXXX) was obtained even when 2 equivalents of protecting reagent were used. Thin layer chromatography indicated that considerable resacetopheone remained and it was concluded that the equilibrium represented by scheme 42 lies to the left and does not favour the adduct (CLXXX).

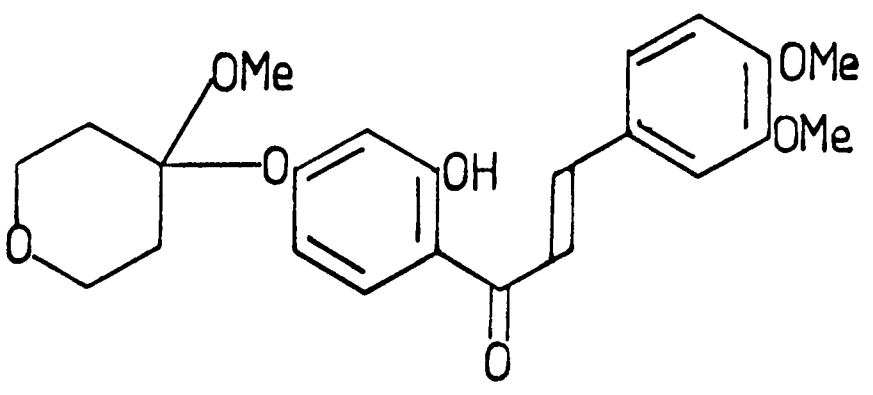


CLXXVIII CLXXX

Scheme 42

Reese et al.[92] do not draw attention to such a failing, but their experimental procedures[92,101] regularly involve the use of a four- to eight-fold excess of the reagent (CLXXVIII). Since this reagent proved awkward and time-consuming to prepare on a large scale, the necessity of using a large excess of it severely limits its potential as a protecting reagent.

This drawback, however, was overshadowed in the present work by the fact that the chalcone (CLXXXI) obtained by condensation of the protected dihydroxyacetophenone (CLXXX) with veratraldehyde could not be induced to crystallise even after chromatography had furnished a substantially pure specimen,

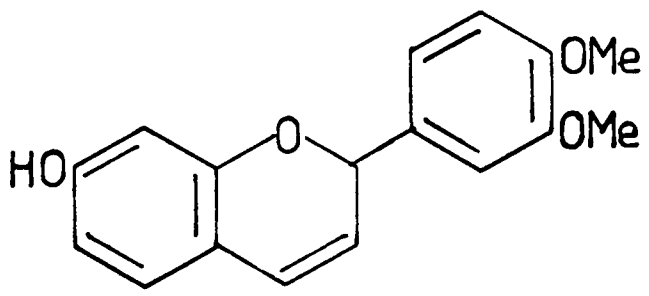


CLXXXI

as judged from its nuclear magnetic resonance spectrum (though not by thin layer chromatography, which indicated that some reaction or decomposition had occurred during the attempted purification).

This problem was considered to outweigh any advantages that the 4-methoxytetrahydropyranyl group might exhibit later on in the synthetic scheme 40, and it was decided to persevere instead with the traditional tetrahydropyranyl group (CLVIII).

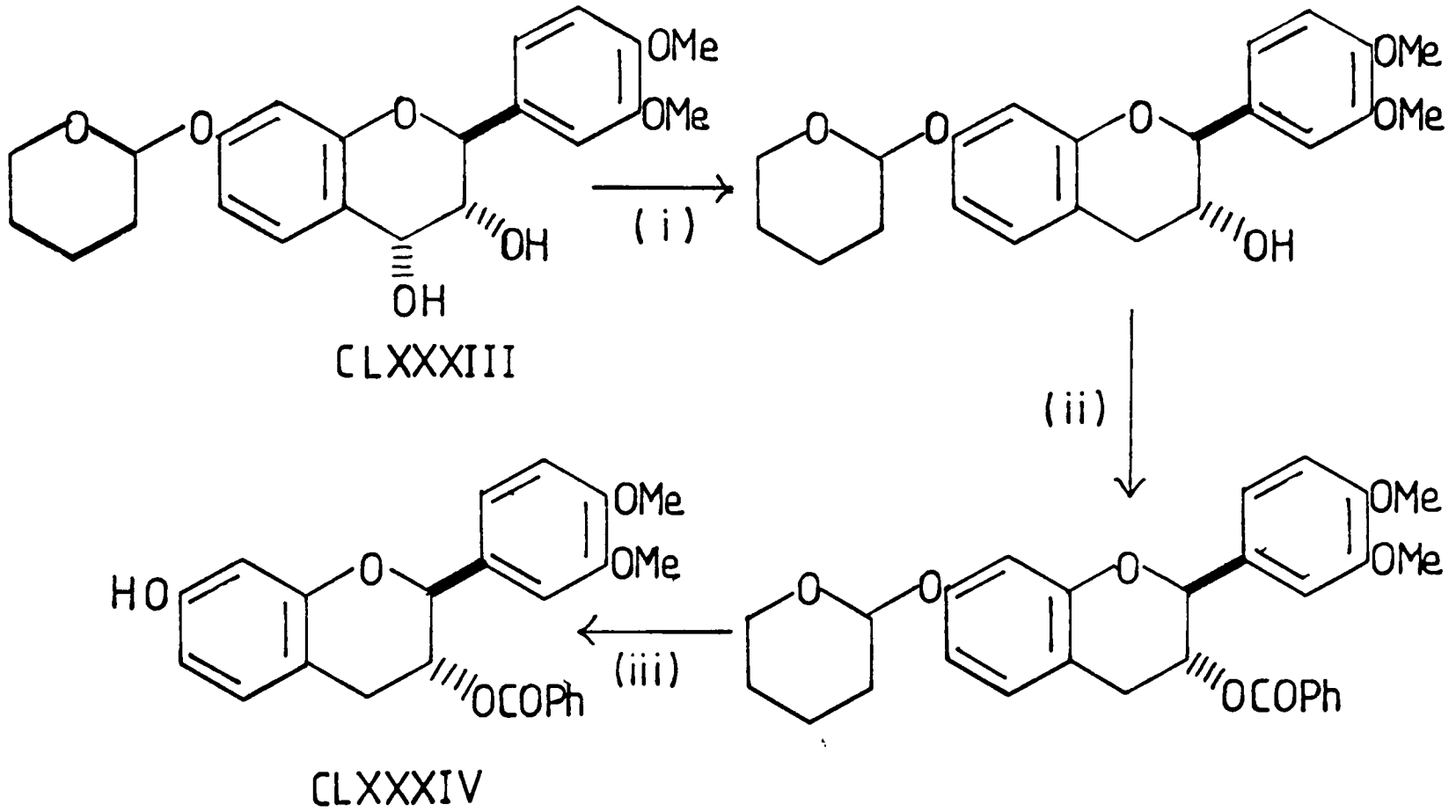
An attempt was made to remove the tetrahydropyranyl group from the flav-3-ene (CLXXVII) by treatment with methanolic acid. Thin layer chromatography indicated the formation of several products and although preparative chromatography yielded a sample of 7-hydroxy-3',4'-dimethoxyflav-3-ene (CLXXXII) sufficiently pure to be identified from its proton magnetic resonance spectrum, this compound (like the phenolic flavanoids (CLXXII) and (CLXXIII)) could not be obtained chromatographically pure.



CLXXXII

Reaction of the tetrahydropyranyloxyflav-3-ene (CLXXVII) with N-methylmorpholine-N-oxide in the presence of osmium tetroxide furnished solid 2,3-trans-3,4-cis-7-tetrahydropyranyloxy-3',4'-dimethoxyflavan-3,4-diol (CLXXXIII) in 68% yield, whose stereochemistry follows from the coupling

constants $J_{2,3}$=9.6Hz, $J_{3,4}$=3.6Hz. This diol underwent hydrogenolysis to give one major product, as indicated by thin layer chromatography. Benzoylation followed by treatment with methanolic acid to remove the tetrahydropyranyl group yielded 2,3-trans-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol (CLXXXIV) in 71% overall yield from the diol (CLXXXIII) as a gum which could not be induced to crystallise although it was chromatographically, spectroscopically and analytically pure. - Scheme 43 represents this transformation and the assumed intermediates.



CLXXXIII

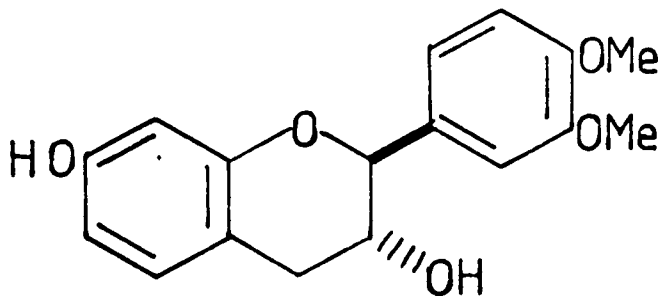
CLXXXIV

Reagents : (i) H_2 / Pd-C
(ii) PhCOCl / pyridine
(iii) MeOH / HCl

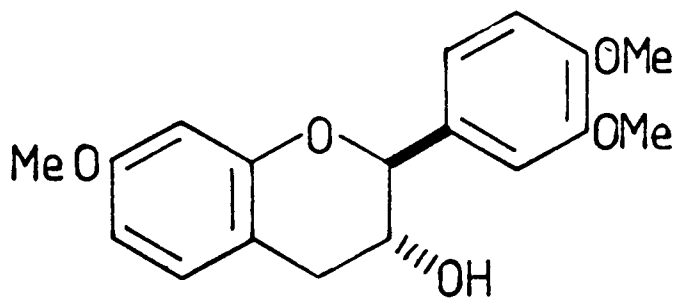
Scheme 43

The structure of the phenolic benzoate (CLXXXIV) may be deduced from its proton magnetic resonance spectrum. The 2-proton resonates as a doublet with J=6.6Hz. This indicates

that there is a substituent at the 3-position and that the molecule has 2,3-trans stereochemistry. The 4-proton signals at 7τ integrate to two protons, showing the absence of a 4-substituent. Saponification of the benzoate ester brought about a shift of the 3-proton resonance from 4.46τ to 6.0τ confirming that the benzoyloxy group had been at the 3-position, and yielded crystalline 2,3-trans-3',4'-dimethoxyflavan-3,7-diol (CLXXXV). This diol could be methylated to give 2,3-trans-7,3',4'-trimethoxyflavan-3-ol (CLXXXVI) as an oil identified by its proton magnetic resonance spectrum,[28] thereby confirming the structural assignments made.



CLXXXV

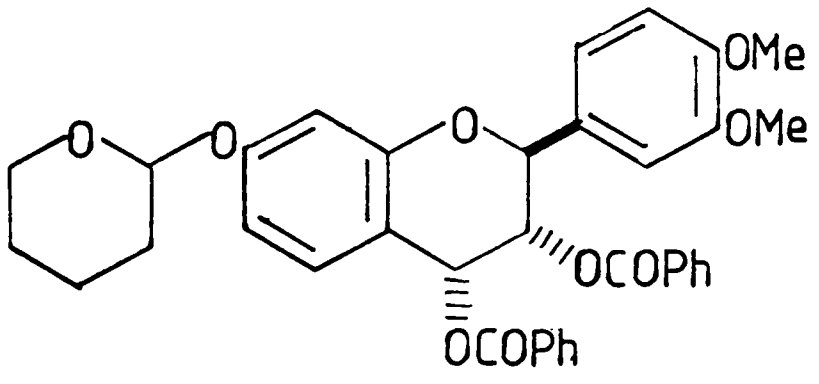


CLXXXVI

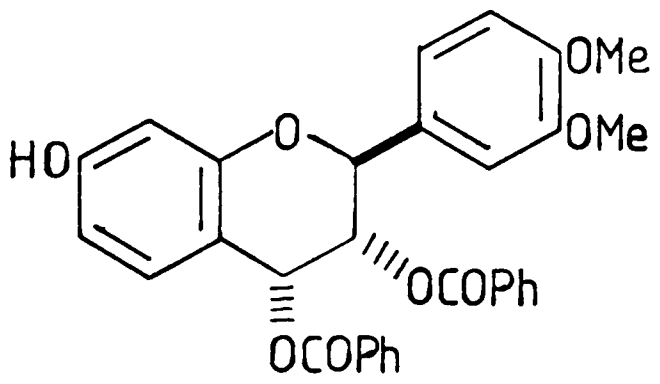
Reference to scheme 40, which displays the four types of phenolic flavanoid taken as synthetic goals, shows that representative compounds of two types (the flavanones and 3-acyloxyflavans) had been prepared, while that of a third (the flav-3-enes) had been found too reactive to isolate.

It was decided finally to attempt to prepare 2,3-trans-3,4-cis-dibenzoyloxy-3',4'-dimethoxyflavan-7-ol (CLXXII) (representing the fourth type of phenolic flavanoid in scheme 40) by benzoylation of the flavan-3,4-diol (CLXXXIII) and removal of the tetrahydropyranyl protecting group.

Benzoylation with excess of benzoyl chloride in pyridine proceeded smoothly to give a single product, as judged by thin layer chromatography. Unreacted benzoyl chloride was removed by neutral alumina and the product (assumed to be the tetrahydropyranyloxy dibenzoate, (CLXXXVII)) on treatment with methanolic acid gave a single major product and only traces of the starting material and other products, as estimated by thin layer chromatography.



CLXXXVII

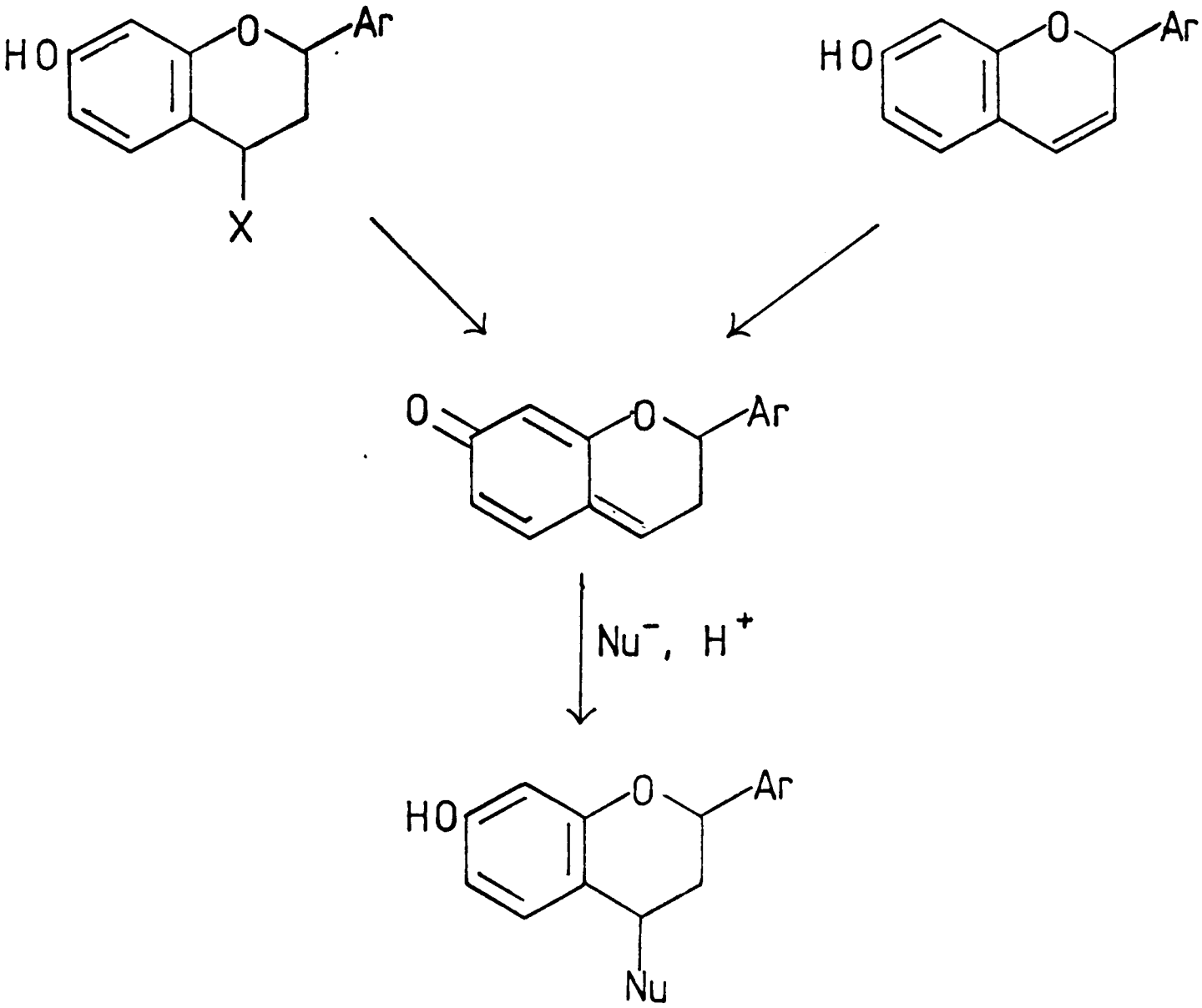


CLXXII

The crude product could not be induced to crystallise but was found by nuclear magnetic resonance spectroscopy to be chiefly the desired 2,3-trans-3,4-cis-dibenzoyloxy-3',4'-dimethoxyflavan-7-ol (CLXXII). Preparative thin layer chromatography, although accomplished as rapidly as possible, proved not to bring about further purification. It was concluded that the dibenzoate (CLXXII) reacted or decomposed on the silica plate, thus confirming the hypothesis made earlier that removal of the o-nitrobenzyl protecting group from the dibenzoate (CLXX) had led to the phenolic dibenzoate (CLXXII) but that the latter was too reactive to be isolated.

It was mentioned in Chapter 2 that 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (CXX) survived

chromatography on a silica plate. The great reactivity of the phenolic dibenzoate (CLXXII) is therefore, at first sight, surprising, as is the intractability of the phenolic flav-3-ene (CLXXXII) compared with 5,7,3',4'-tetramethoxyflav-3-ene (CXXII). The reactivity of the 5,7,3',4'-tetramethoxy substituted flavans, however, results from their tendency to form a 4-carbocation by loss of the 4-substituent. In the case of 7-hydroxy substituted flavanoids, the loss of the 4-substituent might be expedited by simultaneous loss of a proton from the 7-hydroxyl group to give a quinone methide; the same intermediate would result from protonation of a 7-hydroxyflav-3-ene at the 3-position and simultaneous loss of a proton from the 7-hydroxyl (scheme 44).

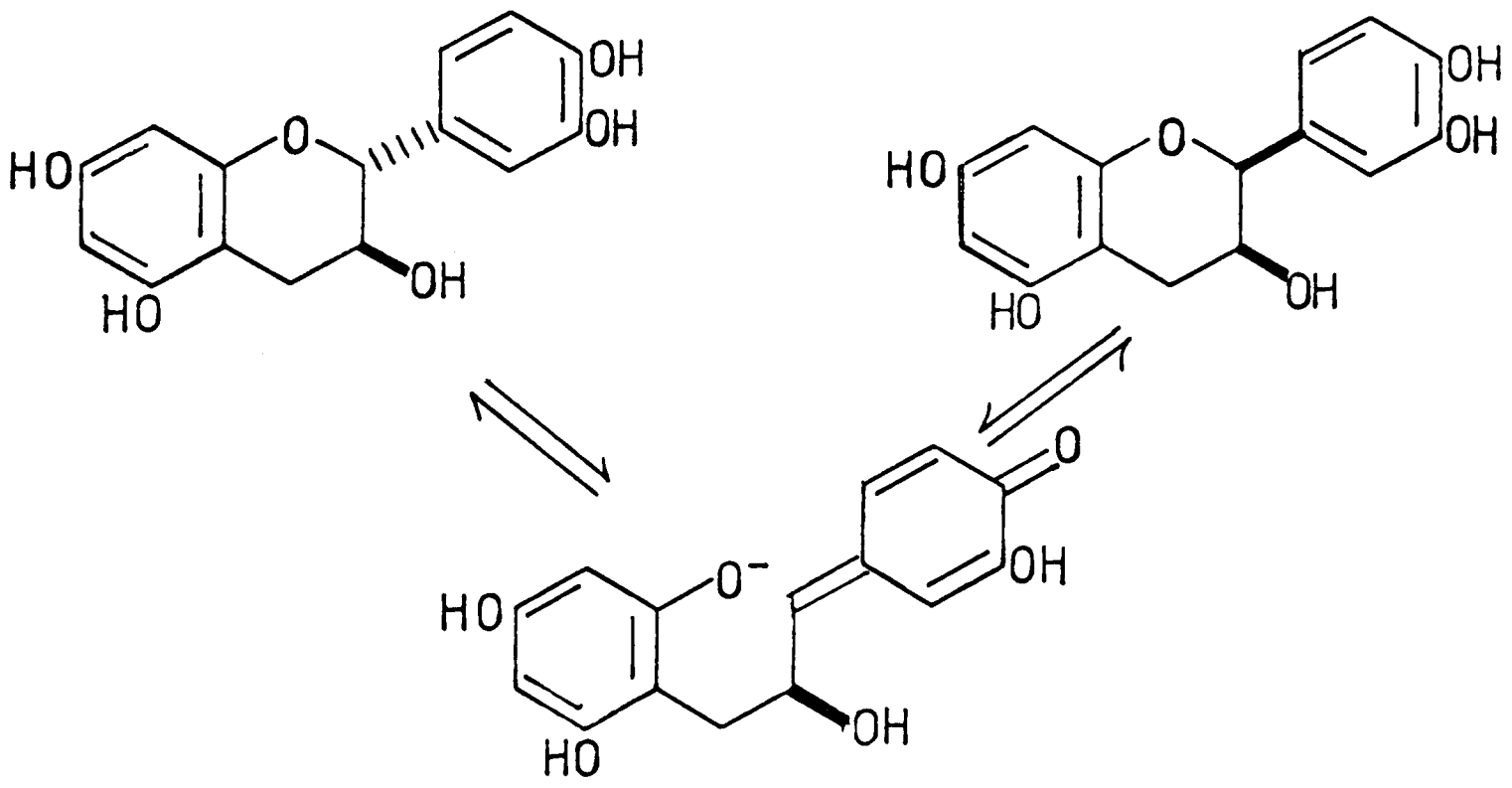


Scheme 44

Reaction of the quinone methide with a nucleophile and a proton regenerates the aromatic A-ring and accounts for the formation of several products during the attempted syntheses of the phenolic flav-3-ene (CLXXXII) and 3,4-dibenzoate (CLXXII).

A very similar mechanism has been proposed[102] for the ready epimerisation of (+)-catechin to (+)-epicatechin[103] (scheme 45). This reaction is catalysed by bases[103] and it was similarly found by the present author that the reactivity of the phenolic dibenzoate (CLXXII) was dramatically increased by the addition of a base.

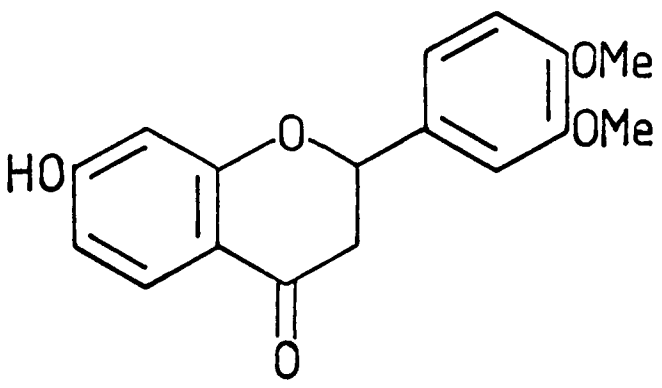
When the dibenzoate (CLXXII) had been prepared by treatment of its tetrahydropyranyl protected precursor (CLXXXVII) with toluene-p-sulphonic acid in methanol, the addition of a drop of triethylamine to a sample of the reaction mixture caused the immediate appearance of a yellow colour which faded rapidly. The reaction mixture which had previously contained only one major flavanoid component was now found by thin layer chromatography to contain comparable quantities of several.



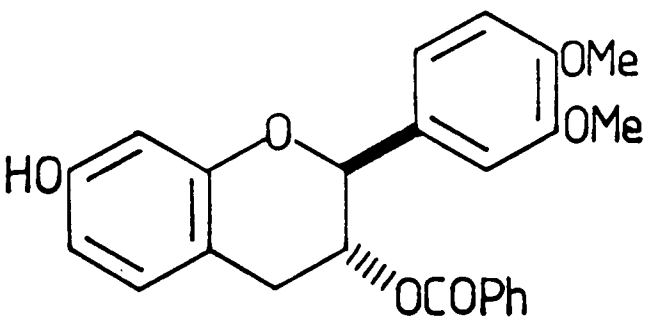
Scheme 45

The present investigations have therefore indicated that when flavanoids with a leaving group at the 4-position or a 3,4-double bond also possess a 7-hydroxyl group, they are exceptionally reactive. This has significant consequences for the hypothesis that natural carbon-carbon linked tannins result from the breakdown and repolymerisation of ether-linked precursors,[22] since although the fully methylated aryloxyflavans described in this thesis have proved tolerably stable to chromatography or recrystallisation from non-acidic solvents, the corresponding phenolic aryloxyflavans would be expected to be considerably more reactive.

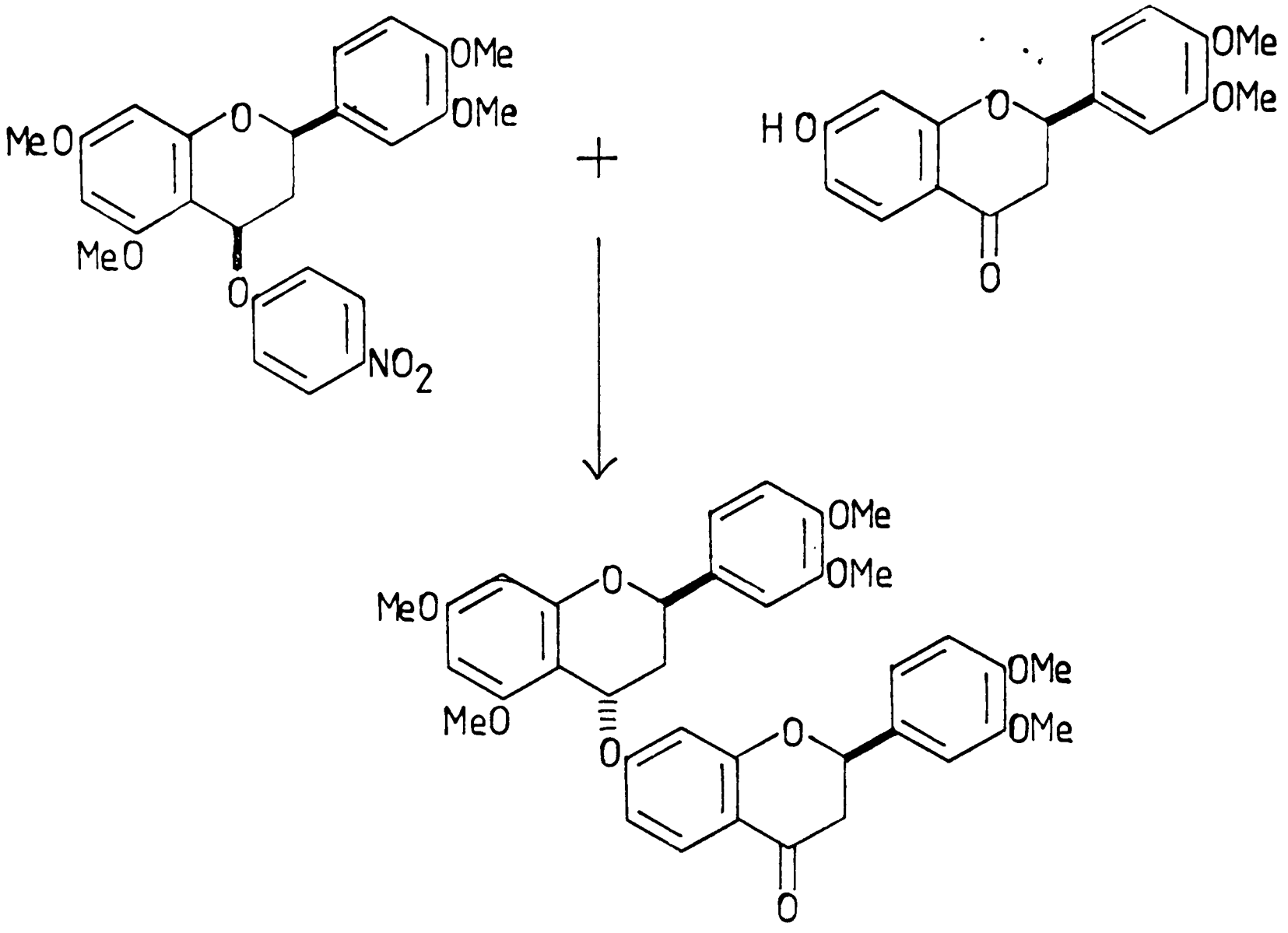
It remains to be shown in this thesis that the stable phenolic flavanoids (CLXI) and (CLXXXIV) can be converted by one of the methods used to synthesise 4-aryloxyflavans into ether-linked flavanoid dimers.



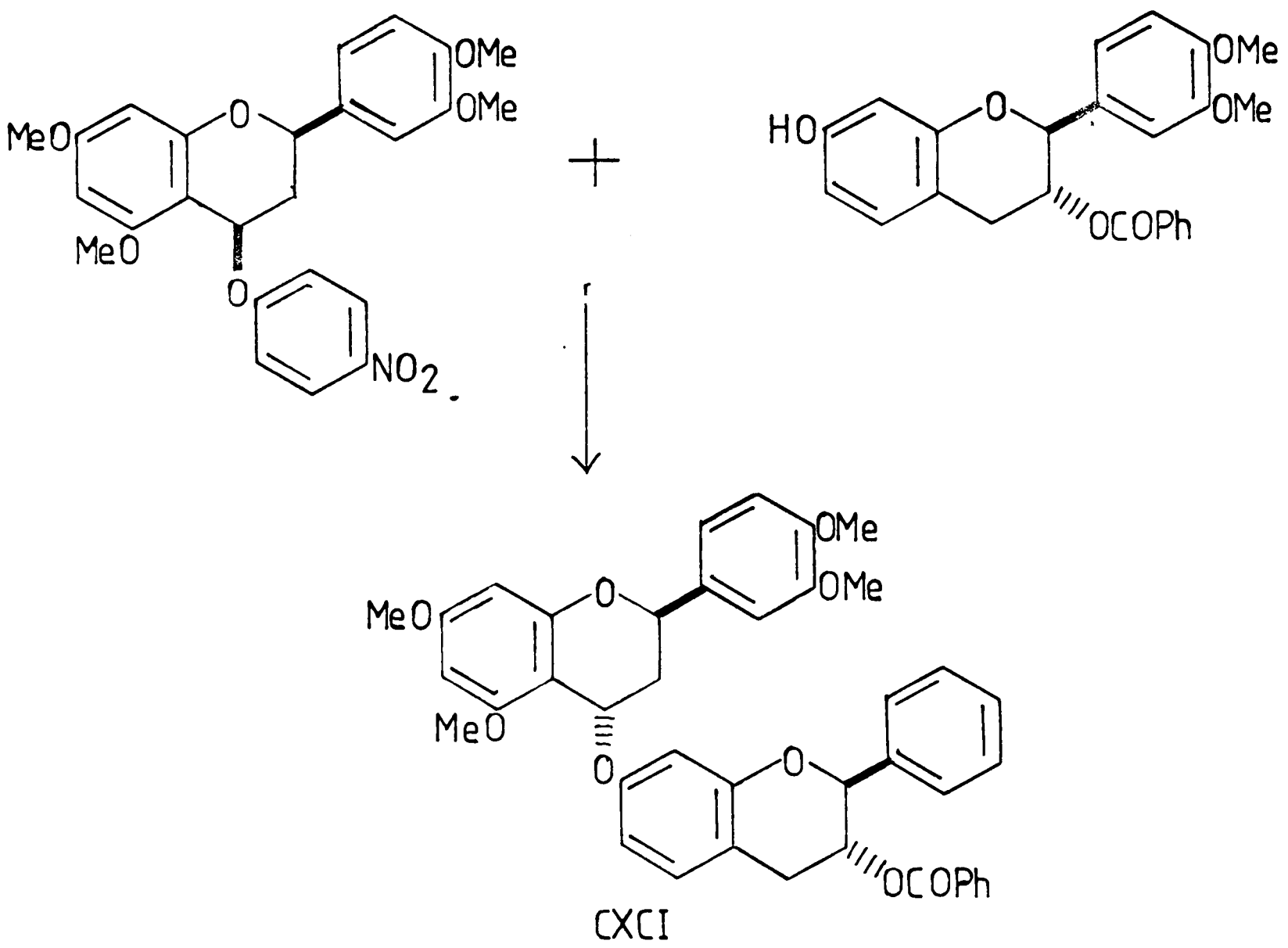
CLXI



CLXXXIV



CLXXXVIII



CXCI

Scheme 46

CHAPTER 4

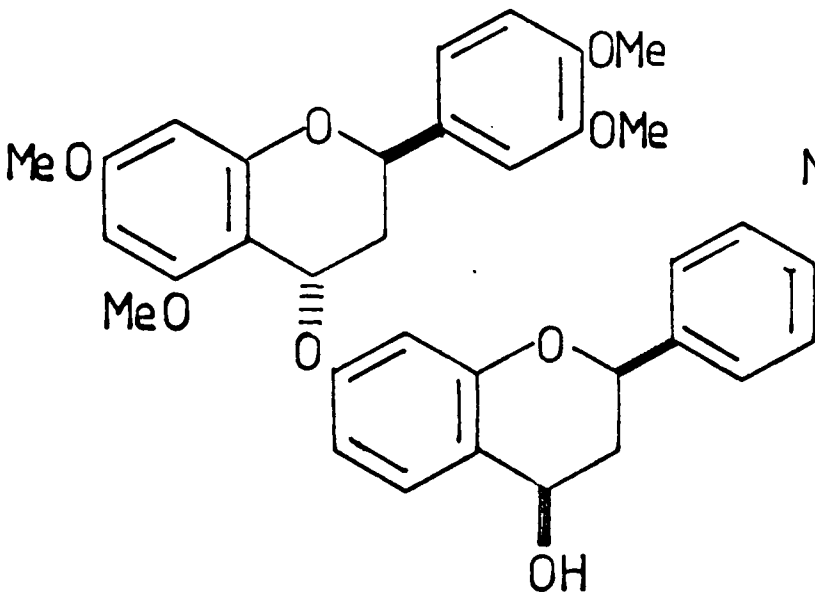
Synthesis of ether-linked flavanoid dimers

Of the methods described in this thesis for the preparation of 4-aryloxyflavanoids, the one requiring the mildest conditions is the synthesis which employs 4β-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (CL) in pyridine for 3 days at 40° (Chapter 2). Because of the sensitivity to base of 2,3-trans-3,4-cis-dibenzoyloxy-3',4'-dimethoxyflavan-7-ol (CLXXII) and, presumably, of 7-hydroxy-3',4'-dimethoxyflav-3-ene (CLXXXII), it seemed unwise to attempt the synthesis of ether-linked flavanoid dimers in pyridine from these phenolic flavanoids. It was decided instead to use the two stable phenolic flavanoids (CLXI) and (CLXXXIV) (scheme 46).

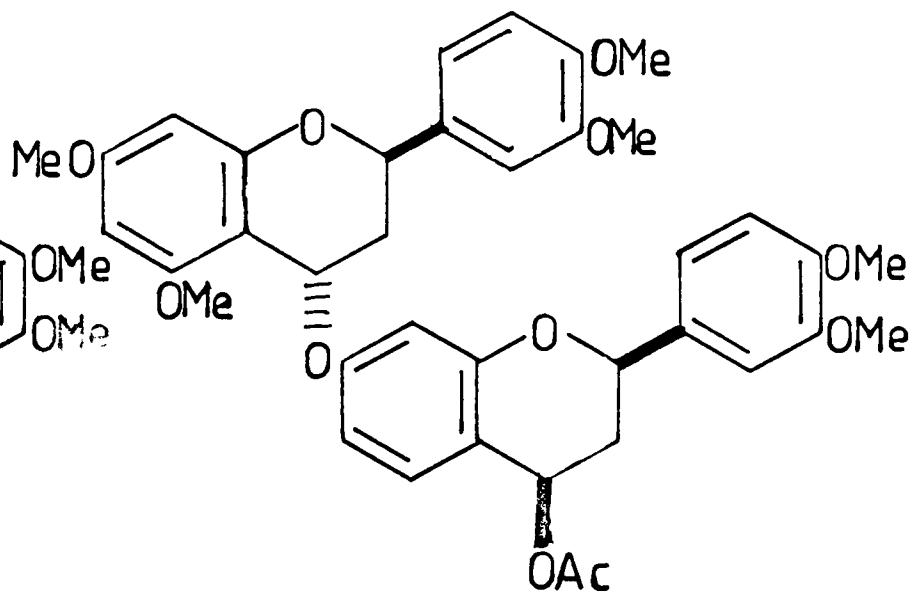
7-Hydroxy-3',4'-dimethoxyflavanone (CLXI) was expected to be a stronger acid than phenol, because of the mesomeric electron-withdrawing effect of the 4-keto function which would stabilise the phenate anion relative to the phenol, and hence a better leaving group, as mentioned in Chapter 2. This would make the expected dimer (CLXXXVIII) particularly reactive and difficult to isolate. It was therefore decided to treat the crude reaction product with sodium borohydride and isolate the dimeric flavan-4-ol (CLXXXIX). The high isolated yield (92%) of the flavan-4β-ol formed by sodium borohydride reduction of 7,3',4'-trimethoxyflavanone suggested that the latter reduction was stereospecific and that reduction of the dimeric flavanone (CLXXXVIII) would also give specifically the dimeric flavan-4β-ol (CLXXXIX).

Since both the flavanoid species being joined in the dimer were racemic, it was expected that a mixture of diastereo-

isomers would be formed. The formula (CLXXXIX) is therefore inaccurate because it represents only one (the 2S:2S form) of the possible relative configurations of the two flavanoid nuclei joined in the dimer. This form and the corresponding 2R:2S, 2S:2R and 2R:2R forms make up two diastereomeric pairs of enantiomers. The formulae (CLXXXVIII) to (CXCI) must therefore be taken as representative of mixtures of diastereo-isomers.



CLXXXIX



CXC

When the reaction was carried out as planned, 7-(5,7,3',4'-tetramethoxyflavan-4α-yloxy)-3',4'-dimethoxyflavan-4β-ol (CLXXXIX) was isolated as a chromatographically homogeneous oil in 52% yield. A satisfactory elemental analysis was not obtained, but the proton magnetic resonance spectrum shows signals as expected due to both "upper" and "lower" flavan nuclei. The presence of the 4-hydroxyl group of the lower flavan is indicated by the shift of ca. 1.2τ in the position of the 4-H resonance of the lower flavan when (CLXXXIX) was acetylated to obtain (CXC). The width of this 4-H signal in

the spectrum of the acetate (CXC) gives the sum of the coupling constants $\underline{J}_{3,4}+\underline{J}_{3*,4}=16$Hz, confirming the 4β-configuration of the lower flavan. The 4α-configuration of the upper flavan is indicated by the width of the 4-H resonances of this flavan in both (CLXXXIX) and (CXC) which give $\underline{J}_{3,4}+\underline{J}_{3*,4}=6$Hz.

The mass spectra of these two compounds also show that two flavanoid nuclei are present. Peaks at 328 and 327 are due to the upper flavan, while peaks at 284 and 283 are caused by the intact lower flavan skeleton. The molecular ion peak of the dimer was not, however, observed.

The preparation of 2,3-trans-3-benzoyloxy-7-(5,7,3',4'-tetramethoxyflavan-4α-yloxy)-3',4'-dimethoxyflavan (CXCI) was accomplished in the same way from 4β-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (CL) and 2,3-trans-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol (CLXXXIV). The dimer (CXCI) was, however, left overnight on a silica chromatographic plate which caused partial decomposition. The yield of the dimer isolated after further preparative thin layer chromatography as an analytically pure gum was therefore only 10%. The proton magnetic resonance spectrum of the dimer (CXCI) is consistent with its expected structure, but it is not possible to confirm the expected 4α-stereochemistry of the upper flavan nucleus because the relevant 4-H signal coincides with the 3-H signal of the lower flavan.

The mass spectrum of the dimer (CXCI) was run under conditions of chemical ionisation (C.I.). The method involves proton transfer to the species under investigation and mass peaks one unit higher than the corresponding peaks from electron impact ionisation are common. This method was chosen in the

hope that it would allow observation of the molecular ion peak from (CXCI),[104] but this peak (at 735) was not observed. The signals at 285 and 284 result from the lower flavan (after loss of the 3-benzoyloxy group) while that at 329 is due to the upper flavan.

These results have demonstrated that the rationale and one of the methods suggested for the synthesis of 4-aryloxy-flavans may be extended to the synthesis of ether-linked flavanoid dimers. The hypothesis that ether-linked polyphenolic flavanoid polymers are labile precursors of carbon-carbon linked tannins might be further investigated by synthesising ether-linked dimers with free phenolic hydroxyl groups. The ortho-nitrobenzyl group might prove a valuable way of protecting these phenolic hydroxyl groups during the dimerisation, because of its ready removal under non-acidic conditions. The study of the synthesis of ether-linked flavanoid dimers, nevertheless, will require considerable further work on protecting groups for phenols and the preparation of flavanoids substituted at the 4-position with a variety of leaving groups, along the lines suggested in this thesis.

EXPERIMENTAL SECTION

General Information

Melting points were determined on a Kofler block and are corrected. Microanalyses were performed by Dr. F.B. Strauss and staff, Oxford. Proton magnetic resonance spectra were recorded at 90 or 100MHz (unless otherwise indicated) and coupling constants and chemical shifts were measured on the assumption of first-order behaviour. Where appropriate, the protons at the flavanoid 3-position are distinguished as 3-H and 3*-H, the latter being in the pseudo-axial position.

N.m.r. spectra are reported in the form: chemical shift and then, in parentheses, integral, observed splitting pattern and assignment. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; b, broad.

Mass spectra were recorded by Dr. R.T. Aplin and staff using electron impact ionisation except where otherwise indicated. Inlet temperatures and intensities are given in parentheses.

Alumina for column chromatography was Laporte type H (neutral), and for preparative thin layer chromatography was Merck (type E), PF_{254}. Chromatographic plates were as supplied by Mr. R. Prior and, unless otherwise indicated, were coated with Merck $HF_{254+366}$ or $PF_{254+366}$ silica. Chromatograms were examined under u.v. light or by being sprayed with a 1% solution of isovanillin in sulphuric acid which, on heating, gives a bright colour with flavanoids and polyphenols. Redistilled acetone was used to strip products from preparative plates, which had 1mm thickness of adsorbent and were eluted with redistilled acetone before use.

Molecular sieve was type 3A, dried at 150°. Pyridine was stored over potassium hydroxide; light petroleum and dimethyl sulphate were redistilled. Dichloromethane was washed successively with sulphuric acid, water, aqueous sodium hydroxide and water. It was dried over calcium chloride, distilled from calcium hydride and stored over molecular sieve.

Other reagents were used without purification except where indicated in the text.

Methanol and ethanol were dried by distillation from magnesium methoxide and ethoxide, respectively. Tetrahydrofuran and dioxan were obtained dry by distillation from sodium, after being boiled under reflux with sodium until the addition of benzophenone gave a persistent blue colour. Ether, benzene and toluene were dried over sodium wire.

Dimethylsulphoxide was dried by passage over alumina and distillation (reduced pressure) from calcium hydride. Dimethylformamide was dried over anhydrous potassium carbonate. Both solvents were stored over molecular sieve.

Sodium hydride dispersion was as supplied by Koch-Light Ltd., containing 50% sodium hydride. "Acetic anhydride mixture" refers to acetic anhydride containing 25 mole percent of acetic acid. The concentration was monitored by n.m.r. spectroscopy in chloroform solution. Acetic anhydride absorbs at 7.80τ and acetic acid at 7.92τ.

Organic extracts were dried with anhydrous magnesium sulphate and evaporated on a rotary film evaporator.

Chapter 1

2'-Hydroxy-3,4-dimethoxychalcone

To a solution of o-hydroxyacetophenone (17g) and veratraldehyde (25g) in methylated spirit (150ml) at 10° was added potassium hydroxide (20g) in water (20ml). Water (60ml) was added after 12h to dissolve the precipitate and the mixture was left for a further 24h.

It was diluted with water (150ml), cooled to 0° and neutralised with dilute hydrochloric acid. The resulting yellow mass solidified overnight and separated from methylated spirit as a mixture of orange and yellow crystals (23g), m.p. 95-122°, thought to be the desired chalcone (lit.,[105] m.p. 115°) contaminated with 3',4'-dimethoxyflavanone (lit.,[105] m.p. 125°).

3',4'-Dimethoxyflavanone

Crude 2'-hydroxy-3,4-dimethoxychalcone (30g) in methylated spirit (500ml) and 2N hydrochloric acid (100ml) was boiled under reflux for 36h. The mixture was cooled and the precipitate collected. The filtrate was boiled for a further 18h, diluted with water (200ml) and cooled. It was again filtered and the combined solid was recrystallised from ethyl acetate to furnish pale yellow prisms of 3',4'-dimethoxy-flavanone (14.5g, 48%), m.p. 123-124° (lit.,[105] 123-125°).

3',4'-Dimethoxyflavan-4β-ol (XXXIV)

3',4'-Dimethoxyflavanone (10.0g) in chloroform (100ml) and methanol (150ml) was treated with sodium borohydride (3.5g) at -10° for 3h.

Water (700ml) was added, the mixture was separated and the aqueous phase was extracted with chloroform (3 x 100ml). The

combined organic extracts were washed with water (2 x 100ml), dried and evaporated. Crystallisation of the solid residue from methylated spirit/water furnished 3',4'-dimethoxyflavan-4β-ol (9.2g, 91%) as colourless rods, m.p. 157.5-158.5° (lit.,[47] 154-155°).

2,6-Dihydroxyacetophenone[106]

Resorcinol (178g) was condensed with ethyl acetoacetate (211g) in sulphuric acid (1.6l). After 24h dilution with water gave a solid which was dissolved in 5% aqueous sodium hydroxide, filtered and re-precipitated with acid to furnish 7-hydroxy-4-methylcoumarin (158g, 55%). A sample crystallised from ethanol as tiny rods, m.p. 187-189° (lit.,[106] 185°).

7-Hydroxy-4-methylcoumarin (286g) was heated under reflux with acetic anhydride (530ml). After 90 min the mixture was cooled briefly and poured into ice/water to precipitate 7-acetoxy-4-methylcoumarin (XXXII) (314g, 85%). A sample crystallised from ethanol as needles, m.p. 150-151° (lit.,[106] 150-151°).

7-Acetoxy-4-methylcoumarin (140g) mixed with powdered anhydrous aluminium chloride (320g) was heated from 120° to 170° during 2h. It was cooled, treated with aqueous acid and heated to 100° for 30 min. After cooling, the precipitate was recrystallised from methylated spirit, yielding yellow-green prisms of 7-hydroxy-8-acetyl-4-methylcoumarin (XXXIII) (110g, 79%), m.p. 158-163° (lit.,[106] 162-163°). This product was heated on a water bath for 5h under nitrogen with 12% aqueous sodium hydroxide (850ml). The solution was acidified and the

precipitate recrystallised from aqueous methylated spirit to furnish 2,6-dihydroxyacetophenone (58g, 80%), m.p. 154-158° (lit.,[106] 154-155°).

2-Hydroxy-6-methoxyacetophenone[107]

2,6-Dihydroxyacetophenone (34g) with anhydrous potassium carbonate (60g) and dimethyl sulphate (23ml) in dry benzene (350ml) was boiled under reflux for 11h. Water (300ml) was added and the organic phase separated. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with benzene (2 x 100ml). The combined organic solutions were extracted with 2N sodium hydroxide solution (4 x 80ml), the alkaline extract was acidified with dilute hydrochloric acid and the precipitate was filtered, dried and recrystallised from methanol. Pale yellow prisms of 2-hydroxy-6-methoxyacetophenone were obtained (28.5g, 77%), m.p. 56-58° (lit.,[106] 60°).

2'-Hydroxy-3,4,6'-trimethoxychalcone

2-Hydroxy-6-methoxyacetophenone (10.0g) and veratraldehyde (14.0g) in methylated spirit (100ml) were treated with potassium hydroxide (10g) in water (20ml). After 48h, the orange solution was diluted with water (100ml) and cooled in ice/salt while it was neutralised with dilute hydrochloric acid. The precipitate was crystallised twice from methylated spirit giving orange prisms of 2'-hydroxy-3,4,6'-trimethoxychalcone (16.0g, 82%), m.p. 119-121°. Chandorkar *et al.*[108] report m.p. 120-121°; Seshadri and Venkateswarlu[109] report m.p. 131-132°.

5,3',4'-Trimethoxyflavanone

2'-Hydroxy-3,4,6'-trimethoxychalcone (12.0g) in methanol (1.0l) and 2N hydrochloric acid (200ml) was boiled under reflux for 60h. Sodium hydroxide solution (2N, 100ml) was added and the methanol was removed under reduced pressure. The resulting solid separated from benzene as colourless plates of 5,3',4'-trimethoxyflavanone (6.8g, 57%), m.p. 194-196° (decomp.). Oliverio and Schiavello[110] report m.p. 186° (decomp.); Seshadri and Venkateswarlu[109] report m.p. 145-147°.

5,3',4'-Trimethoxyflavan-4β-ol (XXXV)

Sodium borohydride (0.5g) was added to a solution of 5,3',4'-trimethoxyflavanone (5.0g) in chloroform (120ml) and methanol (120ml) at -10°. The mixture was left overnight at 0° then poured into water (300ml). The organic layer was separated and the aqueous phase was extracted with ether (3 x 100ml). The combined organic extract was washed with water (100ml) and dried.

Removal of the solvent left an oil which separated from toluene as prisms of 5,3',4'-trimethoxyflavan-4β-ol (3.8g, 76%), m.p. 139-142°. A sample recrystallised from methanol had m.p. 142-143° (lit.,[40] 140-141°).

2-Hydroxy-4-methoxyacetophenone[111]

2,4-Dihydroxyacetophenone (125g) in methanol (1.1l) was boiled under reflux for 19h with methyl iodide (48ml) and potassium hydroxide (48g).

Hydrochloric acid was added until the mixture was neutral and the methanol was removed under reduced pressure. The

organic matter was extracted into ethyl acetate (3 x 150ml), washed with water and extracted with sodium hydroxide solution (2N; 4 x 100ml). The alkaline extract was acidified with dilute hydrochloric acid and extracted with ether (4 x 100ml).

The ethereal solution was washed with brine and dried. Removal of the solvent gave an oil which separated from aqueous ethanol as colourless rods of 2-hydroxy-4-methoxy-acetophenone (49g, 36%), m.p. 47-49° (lit.,[111] 50°).

2'-Hydroxy-3,4,4'-trimethoxychalcone

To a solution of 2-hydroxy-4-methoxyacetophenone (10.0g) and veratraldehyde (14.0g) in methylated spirit (100ml) was added potassium hydroxide (10g) in water (10ml). After 3 days, the solution was diluted with water (150ml), neutralised with 2N hydrochloric acid and filtered. The solid crystallised from acetone as yellow rods of 2'-hydroxy-3,4,4'-trimethoxy-chalcone (11.6g, 61%), m.p. 160-162°. Shah et al.[112] report m.p. 156°; MacBride[113] gives m.p. 162-164°.

7,3',4'-Trimethoxyflavanone

2'-Hydroxy-3,4,4'-trimethoxychalcone (9.0g) in methanol (1.0l) and 2N hydrochloric acid (200ml) was boiled under reflux for 3 days. The solution was cooled to room temperature and unreacted chalcone was filtered off. Further cooling furnished crude 7,3',4'-trimethoxyflavanone which was recrystallised twice from ethyl acetate giving colourless prisms (4.2g, 47%), m.p. 118-120° (lit.,[114] 118-120°).

7,3',4'-Trimethoxyflavan-4β-ol (XXXVI)

Sodium borohydride (0.7g) was added to a solution of 7,3',4'-trimethoxyflavanone (2.0g) in chloroform (25ml) and methanol (50ml) at -10°. The mixture was left at 0° overnight then poured into water (150ml) and chloroform (50ml).

The chloroform layer was separated and the aqueous phase was extracted with ether (3 x 50ml). The combined organic extract was washed with water (50ml) and dried. Removal of the solvent left a solid which separated from toluene as needles of 7,3',4'-trimethoxyflavan-4β-ol (1.85g, 92%), m.p. 138-140°. A sample recrystallised from methanol had m.p. 139-140° (Found: C,68.5; H,6.45. $C_{18}H_{20}O_5$ requires: C,68.35; H,6.35%). N.m.r. (τ,$CDCl_3$): 2.64 (1H, d, 5-H), 2.98-3.12 (3H, m, B-ring), 3.40-3.60 (2H, m, 6-H and 8-H), 4.94 (1H, dd, 2-H), 5.02 (1H, partly obscured dd, 4-H), 6.12 (6H, s, 2 x -OMe), 6.26 (3H, s, -OMe), 7.56 (1H, ddd, 3-H), 7.88 and 7.82 (2H, m and s at 7.82 exchanges with D_2O, 3*-H and hydroxyl); $J_{2,3}$=2.2Hz, $J_{2,3*}$=11.4Hz, $J_{3,3*}$=12.8Hz, $J_{3,4}$=6.4Hz, $J_{3*,4}$=10.0Hz.

2,4,6-Trihydroxyacetophenone[115]

Phloroglucinol (dried at 110°, 140g) was treated with acetonitrile (91g) in dry ether (550ml) in the presence of anhydrous zinc chloride (28g) and dry hydrogen chloride at 0° for 4 days. The yellow precipitate was washed by decantation with ether and then added to water (4l) and heated under reflux for 2h. On cooling, 2,4,6-trihydroxyacetophenone was deposited (159g, 85%), m.p. 219-222° (lit.,[115] 218-219°).

2-Hydroxy-4,6-dimethoxyacetophenone

A solution of 2,4,6-trihydroxyacetophenone (50g) in Analar acetone (200ml) and dry benzene (750ml) was boiled under reflux

for 6h with anhydrous potassium carbonate (170g) and dimethyl sulphate (60ml). The mixture was filtered and the solid was washed well with hot benzene (300ml).

The combined filtrate was washed with 2N hydrochloric acid (100ml) and water (100ml) and extracted with 2N sodium hydroxide solution (6 x 200ml). The alkaline extract was acidified at 0° with dilute hydrochloric acid. Recrystallisation of the precipitate from methylated spirit afforded 2-hydroxy-4,6-dimethoxyacetophenone (39g, 67%) as colourless plates, m.p. 79-81°, raised to 80-81° on recrystallisation from methanol (Found: C,61.25; H,6.15. Calculated for $C_{10}H_{12}O_4$: C,61.2; H,6.15%). Friedländer and Schnell[116] report m.p. 85-88°.

2'-Hydroxy-3,4,4',6'-tetramethoxychalcone

To a solution of 2-hydroxy-4,6-dimethoxyacetophenone (32g) and veratraldehyde (36g) in methylated spirit (300ml), vigorously stirred, was added a solution of potassium hydroxide (31g) in water (30ml). The mixture was stirred at room temperature until all solid had dissolved (18h). After 4 days it was diluted with water (200ml) and neutralised with 2N hydrochloric acid. The precipitate was filtered, dried and recrystallised from acetone to furnish orange needles of 2'-hydroxy-3,4,4',6'-tetramethoxychalcone (49g, 87%), m.p. 156-158° (lit.,[117] 157°).

5,7,3',4'-Tetramethoxyflavanone

2'-Hydroxy-3,4,4',6'-tetramethoxychalcone (10.0g) in methanol and 2N hydrochloric acid (200ml) was boiled under

reflux for 3 days. The mixture was cooled to 18° and the precipitated starting material filtered off. The filtrate was cooled to -5° and crude 5,7,3',4'-tetramethoxyflavanone (5g) was collected. It was dried and recrystallised several times from ethyl acetate furnishing colourless needles of the flavanone, m.p. 162-163° (lit.,[118] 159-160°). By recycling the recovered starting material, 31g of the chalcone was converted into 23g (74%) of 5,7,3',4'-tetramethoxyflavanone and 3g (10%) of a mixture of the chalcone and flavanone.

5,7,3',4'-Tetramethoxyflavan-4β-ol (XXXVII)[43]

5,7,3',4'-Tetramethoxyflavanone (5.1g) in chloroform (100ml) and methanol (100ml) was treated at 0° with sodium borohydride (2.5g). After 2h, the mixture was shaken with water (300ml) and the organic phase separated. The aqueous phase was extracted with ether (3 x 100ml) and the combined organic solutions were washed with water (100ml) and brine and dried.

Removal of the solvent left an oil which separated from methylated spirit containing a little potassium hydroxide as colourless prisms of 5,7,3',4'-tetramethoxyflavan-4β-ol (4.1g, 80%), m.p. 113-116° (lit.,[43] 116-117°).

2'-Hydroxy-4',6'-dimethoxychalcone

2-Hydroxy-4,6-dimethoxyacetophenone (9.7g) and benzaldehyde (7.8g) in methylated spirit (100ml) was stirred vigorously for 20min as a solution of potassium hydroxide (10g) in water (10ml) was added.

The mixture was stirred for a further 4h then kept at 0°

for 2 days. It was diluted with water and neutralised with dilute hydrochloric acid at 0°. Two recrystallisations of the orange precipitate from methanol gave 2'-hydroxy-4',6'-dimethoxychalcone (7.1g, 51%) as orange needles, m.p. 90-91° (lit.,[119] 91-92°).

5,7-Dimethoxyflavanone[134]

2'-Hydroxy-4',6'-dimethoxychalcone (10.0g) in hot methylated spirit was poured into warm 1.5% sodium hydroxide solution (300ml). The mixture was left overnight and filtered. The filtrate was acidified with dilute hydrochloric acid, heated to the boiling point, allowed to cool and filtered again.

The solid collected from the two filtrations crystallised from methanol as colourless needles of 5,7-dimethoxyflavanone (7.8g, 78%), m.p. 145-147° (lit.,[120] 146-147°).

5,7-Dimethoxyflavan-4β-ol (XXXVIII).

To a solution of 5,7-dimethoxyflavanone (1.00g) in chloroform (15ml) and methanol (40ml) at 0° was added sodium borohydride (0.5g).

The mixture was left overnight at 0°, poured into water (100ml) and extracted with ether (4 x 50ml). The ethereal extract was washed with water (50ml) and dried. Removal of the solvent gave a colourless oil which separated very slowly from dichloromethane/light petroleum (b.p. 60-80°) as needles of 5,7-dimethoxyflavan-4β-ol (650mg, 65%), m.p. 74-80°. The substance could be recrystallised only with great difficulty and was therefore used without further purification.

O'Neill[22] reports m.p. 76-77°; Kamat *et al.*[40] report m.p. 89-90°. N.m.r. (τ, CCl_4) : 2.60-2.80 (5H, m, B-ring), 4.00 (2H, s, 6-H and 8-H), 4.90 (1H, dd, 4-H), 5.08 (1H, dd, 2-H), 6.20 (3H, s, -OMe), 6.30 (3H, s, -OMe), 7.48-8.02 (2H, m, 3-H and 3*-H); $J_{2,3}$=2.4Hz, $J_{2,3*}$=11.6Hz, $J_{3,4}$=7.2Hz, $J_{3*,4}$=9.8Hz.

4β-Acetoxy-3',4'-dimethoxyflavan (XXXIX)

3',4'-Dimethoxyflavan-4β-ol (1.00g) was treated with dry pyridine (4ml) and acetic anhydride (4ml) at room temperature for 22h. Volatile matter was removed at 40° on a rotary oil pump. The resulting solid separated from dichloromethane/light petroleum (b.p. 60-80°) as colourless rods of 4β-acetoxy-3',4'-dimethoxyflavan (1.04g, 92%), m.p. 116-118° (lit.,[49] 118.5-119.5°).

4β-Acetoxy-5,3',4'-trimethoxyflavan (XL)

5,3',4'-Trimethoxyflavan-4β-ol (500mg) was treated with dry pyridine (2ml) and acetic anhydride (2ml) at room temperature. After 42h, volatile matter was removed at 30° on a rotary oil pump. The resultant oil separated from dichloromethane/light petroleum (b.p. 60-80°) as colourless needles of 4β-acetoxy-5,3',4'-trimethoxyflavan (490mg, 86%), m.p. 137-139° (Found: C,67.2; H,6.0. $C_{20}H_{22}O_6$ requires: C,67.0, H,6.2%). N.m.r. (τ,$CDCl_3$) : 2.80 (1H, t, J=8Hz, 7-H), 3.00-3.12 (3H, m, B-ring), 3.38 and 3.52 (2H, 2bd, J=8Hz, A-ring), 3.68 (1H, t, 4-H), 4.88 (1H, dd, 2-H), 6.10 (6H, bs, 2 x -OMe), 6.20 (3H, s, -OMe), 7.22-7.90 (2H, m, 3-H and 3*-H), 8.08 (3H, s, acetyl); $J_{2,3}$=3.2Hz, $J_{2,3*}$=9.4Hz, $J_{3,4}$=7.2Hz, $J_{3*,4}$=7.2Hz.

4β-Acetoxy-7,3',4'-trimethoxyflavan (XLI)

7,3',4'-Trimethoxyflavan-4β-ol (400mg) was treated with dry pyridine (1.5ml) and acetic anhydride (1.5ml) at room temperature for 20h. Volatile matter was removed on a rotary oil pump at 35°. The resulting gum separated from dichloromethane/light petroleum (b.p. 60-80°) as prisms of 4β-acetoxy-7,3',4'-trimethoxyflavan (425mg, 94%), m.p. 101-103° (Found: C,67.1; H,6.15. $C_{20}H_{22}O_6$ requires: C,67.0; H,6.2%). N.m.r. (τ,$CDCl_3$) : 2.80-3.52 (6H, m, aromatic), 3.82 (1H, bdd, 4-H), 4.86 (1H, dd, 2-H), 6.10 (6H, s, 2 x -OMe), 6.20 (3H, s, -OMe), 7.24-7.90 (2H, m, 3-H and 3*-H), 7.88 (3H, s, acetyl); $J_{2,3}$=2.2Hz, $J_{2,3*}$=11.2Hz, $J_{3,4}$=6.6Hz, $J_{3*,4}$=10.0Hz.

4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (XLII)

5,7,3',4'-Tetramethoxyflavan-4β-ol (3.0g) was treated with dry pyridine (8ml) and acetic anhydride (8ml) for 3 days at 0°. Volatile matter was removed at 35° on a rotary oil pump.

The resulting gum after several crystallisations from dichloromethane/light petroleum (b.p. 60-80°) furnished 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (2.6g, 77%) as colourless needles, m.p. 125-127° (Found: C,64.95; H,6.3. $C_{21}H_{24}O_7$ requires: C,64.95; H,6.25%). N.m.r. (τ,$CDCl_3$): 2.98-3.10 (3H, m, B-ring), 3.74 (1H, t, 4-H), 3.82 and 3.90 (2H, 2d, A-ring), 4.90 (1H, dd, 2-H), 6.10 and 6.12 (6H, 2s, 2 x -OMe), 6.22 (6H, s, 2 x -OMe), 7.24-7.90 (2H, m, 3-H and 3*-H), 8.10 (3H, s, acetyl); $J_{2,3}$=3.2Hz, $J_{2,3*}$=9.2Hz, $J_{3,4}$=7.4Hz, $J_{3*,4}$=7.4Hz.

4α-Acetoxy-5,7,3',4'-tetramethoxyflavan (XLIII)

5,7,3',4'-Tetramethoxyflavan-4β-ol (500mg) was heated to

90° for 2h in dry pyridine (1ml) and acetic anhydride (1ml). The volatile matter was then removed at 50° on a rotary oil pump leaving a colourless gum.

Two crystallisations from dichloromethane/light petroleum (b.p. 60-80°) furnished 4α-acetoxy-5,7,3',4'-tetramethoxyflavan (360mg, 64%) as colourless needles, m.p. 124-126.5° (Found: C,65.0; H,6.35. $C_{21}H_{24}O_7$ requires: C,64.95; H,6.25%). N.m.r. (τ,$CDCl_3$) : 2.96-3.08 (3H, m, B-ring), 3.78-3.92 (3H, m, 4-H and A-ring), 4.90 (1H, dd, 2-H), 6.08 and 6.10 (6H, 2s, 2 x -OMe), 6.20 and 6.22 (6H, 2s, 2 x -OMe), 7.70-7.90 (5H, m overlapping s at 7.90 , 3-H, 3*-H and acetyl); $J_{2,3}$=4.4Hz, $J_{2,3*}$=9.8Hz, $J_{3,4} + J_{3*,4} < 11$Hz.

4β-Acetoxy-5,7-dimethoxyflavan (XLIV)

5,7-Dimethoxyflavan-4β-ol (240mg) was treated with dry pyridine (1ml) and acetic anhydride (1ml) at 0° for 2 days. Volatile matter was removed on a rotary oil pump at 30°, leaving an oil which separated from light petroleum (b.p. 60-80°) as colourless prisms of 4β-acetoxy-5,7-dimethoxyflavan (172mg, 62%), m.p. 96-98° (Found: C,69.6; H,6.25. $C_{17}H_{20}O_5$ requires: C,69.5; 6.15%). N.m.r. (τ,$CDCl_3$) : 2.66 (5H, bs, B-ring), 3.74-3.94 (3H, m, 4-H and A-ring), 4.78 (1H, dd, 2-H), 6.22 (3H, s, -OMe), 6.26 (3H, s, -OMe), 7.28-8.00 (2H, m, 3-H and 3*-H), 8.24 (3H, s, acetyl); $J_{2,3}$=4.2Hz, $J_{2,3*}$=8.2Hz, $J_{3,4} + J_{3*,4}$=13Hz.

Equilibration of 4β- and 4α-acetoxy-5,7,3',4'-tetramethoxyflavans, (XLII) and (XLIII).

Separate samples (65mg each) of 4α- and 4β-acetoxy-5,7,3',4'-tetramethoxyflavan in dry pyridine (0.5ml), acetic

anhydride (0.5ml) and acetic acid (1 drop) were heated to 90° for 2h. The solvent was removed on a rotary oil pump at 80° and the residue dried in vacuo over potassium hydroxide.

The n.m.r. spectrum of each sample resembled that of 4α-acetoxy-5,7,3',4'-tetramethoxyflavan with an extra peak at 8.10τ due to the 4β-isomer. Comparison of the integrated intensity of this peak with the corresponding (acetyl) peak of the 4α-isomer or with the signal due to 2-H (4.90τ), showed that in each sample the proportion of the 4β-isomer was 5-10%.

The effect of hot acetic anhydride/pyridine/acetic acid on 5,7,3',4'-tetramethoxyflav-3-ene

5,7,3',4'-Tetramethoxyflav-3-ene (100mg, preparation described in Chapter 2) in dry pyridine (0.5ml) and acetic anhydride (0.5ml) with acetic acid (1 drop) was heated to 90° for 3h. Volatile matter was removed on a rotary oil pump and the residual gum was dissolved in ether. 5,7,3',4'-Tetramethoxyflav-3-ene (80mg, 80%) separated as prisms, m.p. and m.m.p. 121-122°.

Reaction of 4β- and 4α-acetoxy-5,7,3',4'-tetramethoxyflavan, (XLII) and (XLIII), with methanolic potassium hydroxide.

a) 4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (125mg) was added to a boiling solution of potassium hydroxide (80mg) in dry methanol (5ml). After a few minutes the mixture was allowed to cool, diluted with ether (50ml), washed with water (10ml) and brine and dried. Removal of the solvent left an oil which was applied to 2 x 20cm silica p.l.c. plates and eluted with ether.

The faster band (60mg, 52%) separated from methanol as

needles of 4α,5,7,3',4'-pentamethoxyflavan (48mg), m.p. 98.5-100° (Found: C,66.6; H,6.9. $C_{20}H_{24}O_6$ requires: C,66.65; H,6.7%). N.m.r. (τ, $CDCl_3$): 2.92-3.16 (3H, m, B-ring), 3.88 (2H, s, 6-H and 8-H), 4.76 (1H, dd, 2-H), 5.42 (1H, t, 4-H), 6.08, 6.10 and 6.12 (9H, 3s, 3 x -OMe), 6.22 (3H, s, -OMe), 6.50 (3H, s, 4-OMe), 7.68 (1H, dt, 3-H), 8.10 (1H, 8 lines, 3*-H); $J_{2,3}$=2.2Hz, $J_{2,3*}$=12.4Hz, $J_{3,3*}$=13.6Hz, $J_{3,4}$=2.6Hz, $J_{3*,4}$=2.6Hz.

The slower band (27mg, 24%) separated from methanol as prisms of 5,7,3',4'-tetramethoxyflavan-4β-ol (14mg), m.p. 111-118°. N.m.r. identical to that of an authentic sample.

b) 4α-Acetoxy-5,7,3',4'-tetramethoxyflavan (120mg) treated as in (a) also yielded two bands on chromatography.

The faster band (48mg, 48%) separated from methanol as needles of 4α,5,7,3',4'-pentamethoxyflavan (38mg), m.p. 96.5-98.5°, m.m.p. with authentic sample 96.5-99°.

The slower band (35mg, 32%) separated from methanol as prisms of 5,7,3',4'-tetramethoxyflavan-4α-ol (23mg), m.p. 82-87°. N.m.r. identical to that of authentic sample (see below).

The action of heat on 4β-acetoxy-5,7,3',4'-tetramethoxyflavan in pyridine

4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (100mg) in dry pyridine (1ml) was heated to 80° for 2h. Evaporation of the solvent left a gum which separated from dichloromethane/light petroleum (b.p. 60-80°) as needles of 4β-acetoxy-5,7,3',4'-tetramethoxyflavan (81mg, 81%), m.p. and m.m.p. 125-127°.

The relative reactivities of variously substituted 4β-acetoxyflavans.

The 4β-acetoxyflavans were treated with one or more of the following reagents:

reagent (i): 1:1 acetic anhydride mixture/pyridine at 65°

reagent (ii): 1:1 acetic anhydride mixture/pyridine at 80° or 90° (temperature specified in text).

reagent (iii): acetic anhydride mixture at 60°

reagent (iv): acetic anhydride mixture at 90°

The reaction mixtures were worked up by evaporation of volatile matter at 0.2 torr and the residues were examined immediately by n.m.r. or the products were isolated by crystallisation from dichloromethane/light petroleum (b.p. 60-80°) and identified as described in the text.

a) 4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (XLII)

The acetoxyflavan (50mg) treated with reagent (i) (1ml) for 1h gave a 1:1 mixture of 4α- and 4β-acetoxy-5,7,3',4'-tetramethoxyflavan, identified by n.m.r.

Treatment of the acetoxyflavan (103mg) with reagent (ii) (1ml) at 80° for 2h, yielded 4α-acetoxy-5,7,3',4'-tetramethoxyflavan (62mg, 60%), m.p. and m.m.p. 124.5-126.5° (depressed on admixture with 4β-isomer).

b) 4β-Acetoxy-5,7-dimethoxyflavan (XLIV)

Treatment of the acetoxyflavan (30mg) with reagent (i) (1ml) for 1h gave a 1:1 mixture of 4α- and 4β-acetoxy-5,7-dimethoxyflavan, identified by n.m.r.

The acetoxyflavan (106mg) with reagent (ii) (1ml) at 80° for 2h furnished 4α-acetoxy-5,7-dimethoxyflavan (XLVI) (60mg, 57%) as rods, m.p. 123-125° (Found: C,69.4; H,6.25. $C_{17}H_{20}O_5$ requires: C,69.5; H,6.15%). N.m.r. (τ,$CDCl_3$): 2.58 (5H, bs, B-ring), 3.78-3.90 (3H, m, A-ring and 4-H), 4.84 (1H, dd, 2-H), 6.20 (6H, bs, 2 x -OMe), 7.70-7.92 and 7.90 (5H, m and s, 3-H, 3*-H and acetyl); $J_{2,3}$=3.8Hz, $J_{2,3*}$=11.2Hz, $J_{3,4}+J_{3*,4}$<11Hz.

c) 4β-Acetoxy-7,3',4'-trimethoxyflavan (XLI)

The acetoxyflavan (115mg) was heated to 90° with reagent (ii) (1ml) for 2h. The standard work up furnished prisms of the starting material (105mg, 91%), m.p. 100-103° identified by its n.m.r. spectrum.

Treatment of this acetoxyflavan (76mg) with reagent (iii) (1ml) for 2h afforded 4α-acetoxy-7,3',4'-trimethoxyflavan (XLVII) (26mg, 34%) as prisms m.p. 119-121° (Found: C,67.25; H,6.15; $C_{20}H_{22}O_6$ requires: C,67.0; H,6.15%). N.m.r. (τ,$CDCl_3$): 2.70 (1H, d, 5-H), 2.90-3.08 (3H, m, B-ring), 3.36-3.54 (2H, d and bs, A-ring), 4.02 (1H, t, 4-H), 4.82 (1H, t, 2-H), 6.08 and 6.10 (6H, 2s, 2 x -OMe), 6.22 (3H, s, -OMe), 7.64-7.80 (2H, m, 3-H and 3*-H), 7.90 (3H, s, acetyl); $J_{2,3}$=7.2Hz, $J_{2,3*}$=7.2Hz, $J_{3,4}$=3.0Hz, $J_{3*,4}$=3.0Hz.

d) 4β-Acetoxy-5,3',4'-trimethoxyflavan (XL)

The acetoxyflavan (74mg) treated with reagent (ii) (1ml) at 80° for 2h was recovered unchanged (69mg, 93%), m.p. and m.m.p. 138-139°.

Treatment of the acetoxyflavan (70mg) with reagent (iii) (1ml) for 2h also yielded recovered starting material (62mg, 89%),

m.p. and m.m.p. 137-139°.

Treatment of the acetoxyflavan (79mg) with reagent (iv) for 2h afforded 4α-acetoxy-5,3',4'-trimethoxyflavan (XLVIII) (46mg, 59%) as needles, m.p. 138-140° (m.m.p. with starting material 115-135°) (Found: C,67.25; H,5.95. $C_{20}H_{22}O_6$ requires C,67.0; H,6.2%). N.m.r. (τ,$CDCl_3$): 2.78 (1H, t, 7-H), 3.00-3.18 (3H, m, B-ring), 3.42 and 3.56 (2H, 2bd, A-ring), 3.78 (1H, t, 4-H), 4.92 (1H, dd, 2-H), 6.08 and 6.10 (6H, 2s, 2 x -OMe), 6.18 (3H, s, -OMe), 7.70-7.96 and 7.90 (5H, m overlapping s, 3-H, 3*-H and acetyl); $J_{2,3}$=4.2Hz, $J_{2,3*}$=10.0Hz, $J_{3,4}$=3.0Hz, $J_{3*,4}$=3.0Hz.

e) 4β-Acetoxy-3',4'-dimethoxyflavan (XXXIX)

The acetoxyflavan (96mg) treated with reagent (iv) (1.0ml) for 2h was recovered unchanged (83mg, 86%), m.p. and m.m.p. 116-118°.

5,3',4'-Trimethoxyflavan-4α-ol (LIII) by acid-catalysed epimerisation of 5,3',4'-trimethoxyflavan-4β-ol

5,3',4'-Trimethoxyflavan-4β-ol (320mg) was stirred with water (20ml), acetonitrile (10ml) and 2N hydrochloric acid (1ml) until the solid had dissolved. After 24h, the mixture was poured into ethyl acetate (50ml), washed with 2N aqueous sodium hydroxide solution (10ml), water (10ml) and brine and dried. Removal of the solvent left a solid which was recrystallised from benzene and then aqueous methanol to furnish colourless prisms of 5,3',4'-trimethoxyflavan-4α-ol (150mg, 47%), m.p. 121-123°. (Found: C,68.55; H,6.55. $C_{18}H_{20}O_5$ requires: C,68.35; H,6.35%). N.m.r. (τ,$CDCl_3$): 2.72-3.20 (4H, m, 7-H and B-ring),

7.38 and 7.54 (2H, 2d, A-ring), 4.82-5.00 (2H, dd obscuring t, 2-H and 4-H), 6.12 (9H, bs, 3 x -OMe), 7.26 (1H, bs exchanges with D_2O, hydroxyl), 7.60-8.00 (2H, m, 3-H and 3*-H); $J_{2,3}$=3Hz, $J_{2,3*}$=11Hz, $J_{3,4}+J_{3*,4}$<10Hz.

7,3',4'-Trimethoxyflavan-4α-ol (LXVI)

7,3',4'-Trimethoxyflavan-4β-ol (510mg) was stirred with water (40ml), acetonitrile (40ml) and 2N hydrochloric acid (1.5ml) until the solid had dissolved. Water (300ml) was added in portions during 24h, the mixture was cooled to 0° and the precipitate was collected. Several recrystallisations from benzene furnished 7,3',4'-trimethoxyflavan-4α-ol (155mg, 30%) as rods, m.p. 128-130° (Found: C,68.3; H,6.25. $C_{18}H_{20}O_5$ requires: C,68.35; H,6.35%). N.m.r. (τ,$CDCl_3$): 2.66-3.20 (4H, m, B-ring and 5-H), 3.42-3.52 (2H, m, 6-H and 8-H), 4.82 (1H, dd, 2-H), 5.24 (1H, t, 4-H), 6.12 (6H, s, 2 x -OMe), 6.26 (3H, s, -OMe), 7.80-7.96 (3H, m, 3-H, 3*-H and hydroxyl (exchanges with D_2O)); $J_{2,3}$=4.0Hz, $J_{2,3*}$=10.0Hz, $J_{3,4}$=3.0Hz, $J_{3*,4}$=3.0Hz.

5,7,3',4'-Tetramethoxyflavan-4α-ol (LV) by acid catalysed epimerisation of 5,7,3',4'-tetramethoxyflavan-4β-ol

5,7,3',4'-Tetramethoxyflavan-4β-ol (1.00g) in benzene (30ml) and ether (100ml) was stirred for 28h with water (20ml) and 2N hydrochloric acid (1ml). The mixture was diluted with ether (100ml) and the ethereal layer was separated, washed with sodium bicarbonate solution (2 x 30ml) and dried. Removal of the solvent left an oil which separated from ethanol as clusters of needles of 5,7,3',4'-tetramethoxyflavan-4α-ol (LV) (0.62g, 62%), m.p. 80-90°. N.m.r. identical to that of a pure sample prepared

by reduction with lithium aluminium hydride of 4α-acetoxy-5,7,3',4'-tetramethoxyflavan (see below).

Acetylation of 5,3',4'-trimethoxyflavan-4α-ol and 7,3',4'-trimethoxyflavan-4α-ol

a) 5,3',4'-Trimethoxyflavan-4α-ol (200mg) treated with dry pyridine (1ml) and acetic anhydride (1ml) for 44h furnished, after evaporation at 0.2 torr and crystallisation of the residue from dichloromethane/light petroleum (b.p. 60-80°), needles of 4α-acetoxy-5,3',4'-trimethoxyflavan (195mg, 86%), m.p. and m.m.p. 138-140°.

b) 7,3',4'-Trimethoxyflavan-4α-ol (93mg) treated with dry pyridine (0.5ml) and acetic anhydride (0.5ml) for 24h and worked up as in (a) furnished 4α-acetoxy-7,3',4'-trimethoxyflavan (90mg, 86%) m.p. and m.m.p. 120-121°.

5,7,3',4'-Tetramethoxyflavan-4α-ol (LV) by lithium aluminium hydride reduction of 4α-acetoxy-5,7,3',4'-tetramethoxyflavan

To a solution of 4α-acetoxy-5,7,3',4'-tetramethoxyflavan (145mg) in dry ether (25ml) and dry tetrahydrofuran (7ml) at 0° was added lithium aluminium hydride (70mg). The mixture was stirred at room temperature for 5h, then treated with wet ether until effervescence ceased, and 2N aqueous sodium hydroxide (0.3ml).

The mixture was filtered and the filtrate evaporated. The resulting oil crystallised from ether. Recrystallisation from ether/light petroleum (b.p. 60-80°) afforded 5,7,3',4'-tetramethoxyflavan-4α-ol (62mg, 48%) as colourless needles, m.p. 126.5-128.5° (Found: C,65.7; H,6.4. $C_{19}H_{22}O_6$ requires: C,65.9; H,6.4%). N.m.r. (τ,$CDCl_3$): 2.90-3.20 (3H, m, B-ring), 3.86 and

3.92 (2H, 2d, A-ring), 4.88 and 4.98 (2H, dd and t, 2-H and 4-H), 6.10 (6H, s, 2 x -OMe), 6.14 (3H, s, -OMe), 6.22 (3H, s, -OMe), 7.40 (1H, bs, exchanges with D_2O, hydroxyl), 7.62-8.26 (2H, m, 3-H and 3*-H); $J_{2,3}$=2.4Hz, $J_{2,3*}$=11.0Hz, $J_{3,4}+J_{3*,4}$=4Hz.

<u>4α-Ethoxy-5,3',4'-trimethoxyflavan (LXVII) and 5,3',4'-trimethoxyflavan-4α-ol (LIII) from 4-bromo-5,3',4'-trimethoxyflavan</u>

a) Phosphorus tribromide (0.50ml) was added to a stirred solution of 5,3',4'-trimethoxyflavan-4β-ol (1.0g) in dry ether (100ml) and dry benzene (10ml) at 0°. After 2h, the mixture was poured into water. The aqueous phase was separated and extracted with ether (2 x 100ml), and the combined organic extracts were washed with aqueous sodium acetate and water and dried.

Removal of the solvent under reduced pressure at 30° left a pink solid. A sample (170mg) crystallised from dry ether as colourless needles of 4-bromo-5,3',4'-trimethoxyflavan, m.p. 108° (decomp.) (lit.,[40] 113° (decomp.)) which turned pink on standing. The remainder of the crude 4-bromo-5,3',4'-trimethoxyflavan was heated under reflux for 2h with potassium hydroxide (1.8g) in ethanol (60ml). Evaporation of the solvent and dilution with water gave a precipitate which crystallised from ethanol as needles of <u>4α-ethoxy-5,3',4'-trimethoxyflavan</u> (570mg), m.p. 86-88° (Found: C,69.55; H,6.85. $C_{20}H_{24}O_5$ requires: C,69.75; H,7.0%). N.m.r. (τ,$CDCl_3$): 2.78-3.20 (4H, m, 7-H and B-ring), 3.44 and 3.54 (2H, 2d, A-ring), 4.76 (1H, dd, 2-H), 5.30 (1H, t, 4-H), 6.10, 6.12 and 6.14 (9H, 3s, 3 x -OMe), 6.26 (2H, bq, -OEt), 7.70 (1H, 2t, 3-H), 8.08 (1H, 8 lines, 3*-H), 8.72 (3H, t, -OEt); $J_{2,3}$=2.4Hz, $J_{2,3*}$=12.0Hz, $J_{3,3*}$=14.0Hz,

$J_{3,4}$=2.6Hz, $J_{3*,4}$=3.0Hz.

b) 4-Bromo-5,3',4'-trimethoxyflavan was again prepared as in (a) from 5,3',4'-trimethoxyflavan-4β-ol (1.0g). Dioxan (40ml) and aqueous potassium hydroxide (350mg in 40ml) were added and the solution was boiled under reflux for 2h. Dilution of the mixture with water and cooling gave a solid which was crystallised twice from methanol to afford colourless prisms of 5,3',4'-trimethoxyflavan-4α-ol (740mg, 74%), m.p. and m.m.p. 121-123°.

Equilibration of 4α- and 4β-acetoxy-5,7-dimethoxyflavans, (XLVI) and (XLIV)

Separate samples of 4α- and 4β-acetoxy-5,7-dimethoxyflavan (50mg) in dry pyridine (0.5ml) and acetic anhydride mixture (0.5ml) were heated to 80° for 3h. Volatile matter was removed on a rotary oil pump and the resulting gums were dried *in vacuo* over potassium hydroxide.

The n.m.r. spectrum of each sample was that of 4α-acetoxy-5,7-dimethoxyflavan with a peak at 8.24τ whose integral indicated the presence of 6-7% of 4β-acetoxy-5,7-dimethoxyflavan.

Reaction of thiophenol in aqueous dioxan with flavan-4β-ol and 4'-methoxyflavan-4β-ol

Samples of flavan-4β-ol (230mg) and 4'-methoxyflavan-4β-ol (250mg), prepared by previous workers, were separately heated under reflux in dioxan (12ml), 0.50N hydrochloric acid (12ml) and thiophenol (1.0ml). T.l.c. (elution with 50% ether/light petroleum, b.p. 40-60°) indicated formation of 4α-thiophenoxyflavan and 4'-methoxy-4α-thiophenoxyflavan at the same rate.

After 75min only a small amount of the flavan-4-ols remained.

Each mixture was diluted with ether (50ml), washed with water (20ml) and 2N aqueous sodium hydroxide (3 x 20ml), dried and evaporated. The residues were crystallised from ethanol.

a) From flavan-4β-ol was obtained 4α-thiophenoxyflavan (LXXII) as colourless plates (194mg, 60%), m.p. 124-125° (lit.,[27] 127-128°). N.m.r. (τ,$CDCl_3$): 2.44-3.18 (14H, m, aromatic), 4.48 (1H, dd, 2-H), 5.42 (1H, t, 4-H), 7.68-7.82 (2H, m, 3-H and 3*-H); $J_{2,3}$=6Hz, $J_{2,3*}$=7Hz, $J_{3,4}=J_{3*,4}$=3Hz.

Evaporation of the mother liquor and crystallisation of the residue from ether/light petroleum (b.p. 60-80°) furnished flavan-4α-ol (LVII) (38mg, 16%) as needles, m.p. 118-120° (lit.,[121] 119°); m.m.p. with authentic sample of m.p. 117-119° was 117-119°.

b) From 4'-methoxyflavan-4β-ol was obtained 4α-thiophenoxy-4'-methoxyflavan (LXXI) (219mg, 64%) as colourless plates, m.p. 103-105° (lit.,[27] 104-105°).

Evaporation of the mother liquor and crystallisation of the residue from ether/light petroleum (b.p. 60-80°) furnished 4'-methoxyflavan-4α-ol (LIX) (24mg, 10%) as needles, m.p. 130-132° (lit.,[41] 131-132°), undepressed when mixed with an authentic sample.

2,3-Trans-3-hydroxy-5,7,3',4'-tetramethoxyflavanone (LXXVII)[22]

(+)-Dihydroquercetin (LXXVI) (supplied by Koch-Light Ltd., 5.8g) in Analar acetone (200ml) was heated under reflux with vigorously stirred anhydrous potassium carbonate (40g). Dimethyl sulphate (22ml) was added during 30min and the mixture

was boiled with stirring for a further 12h.

The solid residue was collected and washed well with hot acetone (2 x 100ml). The combined filtrate was evaporated giving a solid which crystallised from methylated spirit as prisms of 2,3-trans-3-hydroxy-5,7,3',4'-tetramethoxyflavanone (LXXVII) (3.9g, 57%), m.p. 173-176°, $[\alpha]_{589}^{20} = -6°$ (c=1 in $CHCl_3$).

For the optically active, partially racemised hydroxyflavanone, Clark-Lewis and Korytnyk[54] report m.p. 165-168°, $[\alpha]_{589}^{20} = -23.4°$ (c=2.3 in $CHCl_3$). For the racemate, Hergert and Coad[122] give m.p. 169-170°.

Reduction of 2,3-trans-3-hydroxy-5,7,3',4'-tetramethoxyflavanone with sodium borohydride[30]

To a solution of 2,3-trans-3-hydroxy-5,7,3',4'-tetramethoxyflavanone (1.74g) in boiling methanol (250ml) was added sodium borohydride (1.0g). The mixture was allowed to cool and treated with more sodium borohydride (0.3g). After 3h, the solution was evaporated to a volume of 50ml, diluted with water (400ml) and cooled to 0°. Recrystallisation of the precipitate from methanol furnished racemic 2,3-trans-3,4-trans-5,7,3',4'-tetramethoxyflavan-3,4-diol (XX) (395mg, 23%), m.p. 208-210° (lit.,[30] 205.5-206.5°).

The alkaline filtrate was neutralised with acetic acid. The precipitate, on recrystallisation from methanol, furnished racemic 2,3-trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (LXXVIII) (630mg, 36%), $[\alpha]_{589}^{20} = -1.5°$ (c=1 in $CHCl_3$), m.p. 167-169° (lit.,[30] 165.5-166.5°). For a single enantiomer of this diol Brown and MacBride[123] report m.p. 189-190°, $[\alpha]_{589}^{20} = +32°$.

2,3-Trans-3,4-cis-diacetoxy-5,7,3',4'-tetramethoxyflavan (LXV)

2,3-Trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (800mg) was treated with dry pyridine (8ml) and acetic anhydride (8ml) at room temperature for 42h. Removal of volatile matter on a rotary oil pump at 40° left a gum which separated from ether as colourless prisms of 2,3-trans-3,4-cis-diacetoxy-5,7,3',4'-tetramethoxyflavan (950mg, 96%), m.p. 159-161° (lit.,[30] 155-156°). N.m.r. (τ,$CDCl_3$, 60MHz): 2.96-3.02 (3H, m, aromatic), 3.50 (1H, d, 4-H), 3.86 (2H, s, A-ring), 4.52 (1H, dd, 3-H), 4.88 (1H, d, 2-H), 6.08 (6H, s, 2 x -OMe), 6.18 and 6.20 (6H, 2s, 2 x -OMe), 7.86 (3H, s, acetyl), 8.16 (3H, s, acetyl); $J_{2,3}$=11Hz, $J_{3,4}$=3.5Hz.

2,3-Trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (LXXIII)

2,3-Trans-3,4-trans-5,7,3',4'-tetramethoxyflavan-3,4-diol (400mg) in dry pyridine (4ml) was treated with acetic anhydride (4ml) for 46h. Removal of volatile matter at 40° on a rotary oil pump left a gum which separated from ether as prisms of 2,3-trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (390mg, 79%), $[\alpha]_{589}^{20}$ = 0° (C=1 in $CHCl_3$), m.p. 133-136° (lit.,[30] 132.5-133.5°).

The effect of acetic anhydride mixture/pyridine and acetic anhydride mixture alone on 2,3-trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan

a) 2,3-Trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (100mg) in dry pyridine (1ml) and acetic anhydride mixture (1ml) was heated to 80° for 2h. Removal of volatile matter on a rotary oil pump left an oil which separated from ether as

colourless prisms of the starting material, (81mg, 81%), m.p. and m.m.p. 133-136°.

b) 2,3-Trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan (129mg) in acetic anhydride mixture was heated to 60° for 2h. Work-up as in (a) furnished 2,3-trans-3,4-cis-diacetoxy-5,7,3',4'-tetramethoxyflavan (90mg, 70%) as prisms, m.p. and m.m.p. 158.5-160°.

Equilibration of 2,3-trans-3,4-trans- and 2,3-trans-3,4-cis-diacetoxy-5,7,3',4'-tetramethoxyflavan

Samples of 2,3-trans-3,4-trans- (80mg) and 2,3-trans-3,4-cis-diacetoxy-5,7,3',4'-tetramethoxyflavan (100mg) were heated separately to 70° for 2.5h in acetic anhydride mixture (1ml). The solvent was removed on a rotary oil pump and the products were dried in vacuo over potassium hydroxide.

The n.m.r. spectra of the two samples were identical and indicated the presence of a mixture of the 2,3-trans-3,4-trans- and 2,3-trans-3,4-cis-diacetates, (LXXIII) and (XXV). Comparison of the intensity of the acetyl resonances due to each isomer showed that each sample contained 14-18% of 2,3-trans-3,4-trans-diacetoxy-5,7,3',4'-tetramethoxyflavan.

Chapter 2

4α-Phenoxy-5,7,3',4'-tetramethoxyflavan (CVII)

a) 4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (101mg) was heated to 40° with phenol (300mg) in dry pyridine (0.5ml). After 5 days, the mixture was diluted with ether (60ml), washed with 2N aqueous sodium hydroxide (3 x 10ml) and water (10ml) and dried. Removal of the solvent left an oil which separated from ethanol containing a little potassium hydroxide as colourless plates of 4α-phenoxy-5,7,3',4'-tetramethoxyflavan (66mg, 60%), m.p. 137-139° (lit.,[22] 132-133°) (Found: C,70.75; H,6.0. Calculated for $C_{25}H_{26}O_6$: C,71.05; H,6.2%). N.m.r. (τ,$CDCl_3$): 2.62-3.22 (8H, m, aromatic), 3.84 and 3.90 (2H, 2d, A-ring), 4.42 (1H, t, 4-H), 4.72 (1H, dd, 2-H), 6.12 and 6.14 (6H, 2s, 2 x -OMe), 6.26 (6H, s, 2 x -OMe), 7.58 (1H, dt, 3-H), 7.98 (1H, 8 lines, 3*-H); $J_{2,3}$=2.4Hz, $J_{2,3*}$=11.8Hz, $J_{3,3*}$=14.6Hz, $J_{3,4}$=2.4Hz, $J_{3*,4}$=2.8Hz. m/e(40°): 422(M^+,1), 329(100), 175 (77), 328(63), 327(31), 94(29), 330(20).

b) 4α-Acetoxy-5,7,3',4'-tetramethoxyflavan (112mg) with phenol (300mg) in dry pyridine (0.5ml) was heated to 40° for 9 days. Work up as in (a) furnished plates of 4α-phenoxy-5,7,3',4'-tetramethoxyflavan (72mg, 59%), m.p. and m.m.p. 136-139°.

4α-Phenoxy-5,7-dimethoxyflavan (CV)

4β-Acetoxy-5,7-dimethoxyflavan (150mg) and phenol (500mg) in dry pyridine were heated to 40° for 8 days. The mixture was diluted with ether (100ml), washed with 2N aqueous sodium hydroxide (3 x 10ml) and water (10ml) and dried. Removal of the ether and pyridine left a colourless oil which separated from light petroleum (b.p. 60-80°) as needles of 4α-phenoxy-5,7-dimethoxyflavan (79mg, 48%), m.p. 114-116° (Found: C,76.35;

H,6.25. $C_{23}H_{22}O_4$ requires: C,76.2; H,6.1%). N.m.r. (τ,$CDCl_3$): 2.56-3.10 (10H, m, aromatic), 3.82 and 3.88 (2H, 2d, A-ring), 4.42 (1H, t, 4-H), 4.64 (1H, dd, 2-H), 6.24 (6H, s, 2 x -OMe), 7.58 (1H, dt, 3-H), 8.00 (1H, 8 lines, 3*-H); $J_{2,3}$=2.4Hz, $J_{2,3*}$=12.2Hz, $J_{3,3*}$=15.0Hz, $J_{3,4}$=2.4Hz, $J_{3*,4}$=2.8Hz. m/e(60°): 362(M^+,trace), 269(100), 270(19), 91(14), 268(11), 115(8), 191(8).

m-Methoxyphenol (CVIII)[124]

Resorcinol (110g) in 3N aqueous potassium hydroxide (600ml) was stirred for 2h with dimethyl sulphate (100ml). The mixture was acidified with concentrated hydrochloric acid and extracted with benzene (3 x 200ml). Extraction with 2N aqueous sodium hydroxide, acidification and extraction into benzene (3 x 200ml) gave, after drying and evaporation of the solvent, an oil. Distillation under reduced pressure furnished liquid m-methoxyphenol (50g, 41%), b.p. 112-114°/7 torr (lit.,[124] 115-119°/7.5 torr). N.m.r. (τ,$CDCl_3$, 60MHz): 2.80-3.08 (1H, bt, aromatic), 3.50-3.72 (3H, m, aromatic), 4.50 (1H, s, exchanges with D_2O, hydroxyl), 6.30 (3H, s, methoxyl).

4α-(m-Methoxyphenoxy)-5,7,3',4'-tetramethoxyflavan (CX)

4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (150mg) in dry pyridine (1ml) with m-methoxyphenol (500mg) was heated to 40° for 5 days. The reaction mixture was poured into ether (80ml), washed with 2N aqueous sodium hydroxide (3 x 10ml) and water (10ml) and dried.

Removal of the solvent left an oil which, after several crystallisations from ethanol containing a little potassium hydroxide, furnished 4α-(m-methoxyphenoxy)-5,7,3',4'-tetramethoxyflavan (80mg, 46%) as colourless prisms, m.p. 123-125°

(Found: C,69.15; H,6.3. $C_{26}H_{28}O_7$ requires: C,69.0; H,6.25). N.m.r. (τ,$CDCl_3$): 2.70-3.50 (7H, m, aromatic), 3.80 and 3.86 (2H, 2d, A-ring), 4.40 (1H, t, 4-H), 4.70 (1H, dd, 2-H), 6.10 and 6.12 (6H, 2s, 2 x -OMe), 6.20 (9H, bs, 3 x -OMe), 7.56 (1H, dt, 3-H), 7.96 (1H, 8 lines, 3*-H); $J_{2,3}$=2.4Hz, $J_{2,3*}$=11.8Hz, $J_{3,3*}$=14.4Hz, $J_{3,4}$=2.8Hz, $J_{3*,4}$=3.0Hz. m/e(160°): 452(M^+,9), 328(100), 329(60), 327(48), 175(48), 124(36), 191(32).

Resorcinol monobenzoate (CIX)[125]

A solution of resorcinol (11.0g) in water (200ml) was stirred while 10% sodium hydroxide solution (1.0eqt., 40ml) and benzoyl chloride (1.1eqt., 12.5ml) were added dropwise at such a rate that the solution remained approximately at pH 8.

The mixture was cooled to 0° overnight and the precipitate was filtered and dissolved in ether (400ml). The ethereal solution was washed with sodium bicarbonate solution (2 x 50ml) and water (50ml) and dried. Evaporation of the solvent left a solid which crystallised from dichloromethane/carbon tetrachloride as colourless prisms of resorcinol monobenzoate (9.6g, 45%), m.p. 132.5-134.5° (lit.,[125] 132°; 135-136°[126]) (Found: C,72.9; H,4.8. Calculated for $C_{13}H_{10}O_3$: C,72.9; H,4.7%).

4α-(m-Benzoyloxyphenoxy)-5,7,3',4'-tetramethoxyflavan (CXI)

4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (500mg) and resorcinol monobenzoate (3.0g) were dissolved in dry pyridine and heated to 40° for 9 days. The mixture was diluted with ether (200ml), washed with 2N aqueous sodium hydroxide (3 x 15ml) and water (15ml) and dried. The solvent was removed and the resultant oil crystallised from ether. Recrystallisation from acetone/methanol furnished 4α-(m-benzoyloxyphenoxy)-5,7,3',4'-

tetramethoxyflavan (355mg, 51%) as prisms, m.p. 134-136° (Found: C,70.75; H,5.65. $C_{32}H_{30}O_8$ requires: C,70.85; H,5.55%). N.m.r. (τ,$CDCl_3$): 1.76-1.86 (2H, m, aromatic), 2.38-2.76 (4H, m, aromatic), 2.96-3.20 (6H, m, aromatic), 3.82 and 3.88 (2H, 2d, A-ring), 4.40 (1H, t, 4-H), 4.70 (1H, dd, 2-H), 6.10 and 6.12 (6H, 2s, 2 x -OMe), 6.22 (6H, s, 2 x -OMe), 7.54 (1H, dt, 3-H), 7.92 (1H, 8 lines, 3*-H); $J_{2,3}$=2.2Hz, $J_{2,3*}$=12.0Hz, $J_{3,3*}$=14Hz, $J_{3,4}$=2.6Hz, $J_{3*,4}$=2.6Hz. m/e(170°): 542(M^+,trace), 105(100), 328(92), 77(29), 327(28), 329(22), 313(17).

3,5-Dimethoxyphenol (CXII)[127]

A solution of phloroglucinol (dried at 110°; 24g) in dry methanol (140ml) was saturated with dry hydrogen chloride at room temperature. After 12 days, the solvent was removed and chloroform (200ml) was added. The solution was washed with aqueous sodium carbonate, dried and evaporated.

The residue was distilled under reduced pressure, furnishing as the main fraction 3,5-dimethoxyphenol (14.5g, 49%), b.p. 158-161°/8 torr (lit.,[128] 172-175°/17 torr). On standing, the oil solidified to a mass of colourless crystals, m.p. 35-42° (lit.,[129] 44.5°). N.m.r. (τ,$CDCl_3$, 60MHz): 3.90 (3H, s, aromatic), 4.42 (1H, s, exchanges with D_2O, hydroxyl), 6.26 (6H, s, 2 x -OMe).

4α-(3,5-Dimethoxyphenoxy)-5,7,3',4'-tetramethoxyflavan (CXIII)

4β-Acetoxy-5,7,3',4'-tetramethoxyflavan (400mg) in dry pyridine (3ml) with 3,5-dimethoxyphenol (1.2g) was heated to 40° for 7 days. The mixture was then diluted with ether (200ml), washed with 2N aqueous sodium hydroxide (4 x 20ml) and water

(20ml) and dried. Removal of the solvent left an oil which deposited crystals (95mg) from methanol containing a little potassium hydroxide. Two recrystallisations from acetone/methanol furnished 4α-(3,5-dimethoxyphenoxy)-5,7,3',4'-tetramethoxyflavan (43mg, 9%) as colourless plates, m.p. 143-145° (Found: C,67.0; H,6.25. $C_{27}H_{30}O_8$ requires: C,67.2; H,6.25%). N.m.r. (τ,$CDCl_3$): 2.98-3.22 (3H, m, B-ring), 3.72 (2H, d, J=2Hz, D-ring), 3.82-3.92 (3H, m, aromatic), 4.44 (1H, t, 4-H), 4.74 (1H, dd, 2-H), 6.12 and 6.14 (6H, 2s, 2 x -OMe), 6.24 (12H, bs, 4 x -OMe), 7.56 (1H, dt, 3-H), 7.98 (1H, 8 lines, 3*-H); $J_{2,3}$=2.2Hz, $J_{2,3*}$=11.8Hz, $J_{3,3*}$=14Hz, $J_{3,4}$=2.6Hz, $J_{3*,4}$=2.6Hz. m/e (60°): 482(M^+,8), 328(100), 327(60), 154(54), 125(31), 329(29), 313(19).

4β-Benzoyloxy-7,3',4'-trimethoxyflavan (CXIX)

7,3',4'-Trimethoxyflavan-4β-ol (800mg) in dry pyridine (5ml) was treated at room temperature with benzoyl chloride (0.37ml, 1.3eqt.). After 2h, the supernatant solution was decanted from the solid pyridinium chloride and diluted with ethyl acetate (150ml). It was washed with aqueous sodium bicarbonate (15ml) and brine and dried. Removal of the solvent left an oil which separated from ether as colourless prisms of 4β-benzoyloxy-7,3',4'-trimethoxyflavan (440mg, 42%), m.p. 158.5-160° (Found: C,71.4; H,5.75. $C_{25}H_{24}O_6$ requires: C,71.4; H,5.75%). N.m.r. (τ,$CDCl_3$): 1.92-2.04 (2H, m, aromatic ortho to carbonyl group), 2.40-3.52 (9H, m, aromatic), 3.60 (1H, dd, 4-H), 4.74 (1H, dd, 2-H), 6.10 (6H, s, 2 x -OMe), 6.22 (3H, s, -OMe), 7.24 (1H, ddd, 3-H), 7.58 (1H, 8 lines, 3*-H); $J_{2,3}$=1.8Hz, $J_{2,3*}$=11.0Hz, $J_{3,3*}$=13.0Hz, $J_{3,4}$=6.8Hz, $J_{3*,4}$=9.2Hz.

Reaction of 4β-benzoyloxy-7,3',4'-trimethoxyflavan with pyridine/acetic anhydride mixture

4β-Benzoyloxy-7,3',4'-trimethoxyflavan (125mg) in dry pyridine (0.5ml) and acetic anhydride mixture (0.5ml) was heated to 90° for 3h. Volatile matter was removed at 60° on a rotary oil pump and the residue was dissolved in ethyl acetate (50ml). It was washed with aqueous sodium bicarbonate (10ml) and brine and dried. Removal of the solvent left an oil which crystallised from ether/light petroleum (b.p. 60-80°). Several recrystallisations from light petroleum furnished 4α-acetoxy-7,3',4'-trimethoxyflavan (32mg, 30%) as prisms, m.p. 118-120°, undepressed when mixed with authentic sample (m.p. 120-121°).

4α-Phenoxy-7,3',4'-trimethoxyflavan (CXVIII)

4β-Benzoyloxy-7,3',4'-trimethoxyflavan (210mg) in dry pyridine (2ml) with phenol (400mg) was heated to 75° for 9 days. The mixture was diluted with ether (100ml), washed with 2N sodium hydroxide solution (3 x 10ml) and water (10ml) and dried. The solvent was evaporated leaving an oil which crystallised from ether. Recrystallisation from methanol furnished 4α-phenoxy-7,3',4'-trimethoxyflavan (77mg, 39%), m.p. 97-99° (Found: C,73.45; H,6.15. $C_{24}H_{24}O_5$ requires: C,73.6; H,6.1%). N.m.r. (τ,$CDCl_3$): 2.60-3.22 (9H, m, aromatic), 3.40-3.52 (2H, m, 6-H and 8-H), 4.66 (1H, t, 4-H), 4.74 (1H, dd, 2-H), 6.12 and 6.14 (6H, 2s, 2 x -OMe), 6.24 (3H, s, -OMe), 7.40-8.00 (2H, m, 3-H and 3*-H); $J_{2,3}$=2.6Hz, $J_{2,3*}$=9Hz, $J_{3,4}=J_{3*,4}$=2.6Hz. m/e (50°): 392(M^+, trace), 299(100), 175(28), 300(20), 161(19), 298(13), 268(10).

5,7,3',4'-Tetramethoxyflav-3-ene (CXXII)[51,22]

2'-Hydroxy-3,4,4',6'-tetramethoxychalcone (12.0g) was stirred in dry ethanol (200ml) at 65° with sodium borohydride (3.0g) until the orange colour of the chalcone disappeared. After cooling for 1h with stirring, the solvent was removed. Chloroform (200ml) was added with swirling to dissolve the solid, then acetic acid (Analar; 10ml) in chloroform (100ml), and the mixture was boiled under reflux for 2h.

2N Potassium carbonate solution (50ml) was added cautiously with shaking and the organic layer was separated, dried and evaporated. The resultant red oil separated from methylated spirit as pale brown prisms of 5,7,3',4'-tetramethoxyflav-3-ene (9.0g, 79%), m.p. 121-122°. Clark-Lewis and Jemison[51] report m.p. 119.5°; O'Neill[22] gives m.p. 121-122°.

N-Methylmorpholine-N-oxide[69]

N-Methylmorpholine (35ml) was heated to 50° and hydrogen peroxide (100vol. strength; 28ml) was added dropwise with stirring at such a rate that the temperature remained between 60° and 70°. The mixture was heated to 75° for a further 4h and then evaporated at 90°/20 torr.

The oily residue separated from acetone as colourless deliquescent needles of hydrated N-methylmorpholine-N-oxide, which were dried at 20° over silica gel (26g, 74%). N.m.r. (in pyridine) showed the presence of amine oxide (multiplet, 5.8-7.6τ) and water (singlet, 5.3τ) in the mole ratio 1:1.3.

2,3-Trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (LXXVIII)

a) To a solution of 5,7,3',4'-tetramethoxyflav-3-ene (12.0g)

in dichloromethane (300ml) at 0° was added anhydrous sodium acetate (1.0g) in acetic acid (Analar, 20ml) and 40% peracetic acid (7.5ml).

The mixture was kept at 0° for 30h, then poured into methanol (400ml) containing potassium hydroxide (40g). The dichloromethane was removed by distillation at atmospheric pressure and the resulting brown solution was poured into brine (1l). It was extracted with ethyl acetate (5 x 200ml), washed with brine and dried. Removal of the solvent left a solid which separated from methanol containing potassium hydroxide as colourless needles of 2,3-trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (4.5g, 34%), m.p. 165-168°, raised on recrystallisation to 167-169°, undepressed on admixture with a sample (m.p. 167-169°) prepared by reduction of 2,3-trans-3-hydroxy-5,7,3',4'-tetramethoxyflavanone.

The preparation was repeated on a smaller scale with m-chloroperbenzoic acid (1-2 equivalents) as the oxidant. It was performed at 0° and at room temperature; in the presence and absence of aqueous sodium bicarbonate; in benzene, dichloromethane or tetrahydrofuran as solvent; and it was worked up with potassium hydroxide in methanol or in aqueous dioxan. Consistent yields of 20-30% were obtained.

b) 5,7,3',4'-Tetramethoxyflav-3-ene (10.0g) was stirred in tetrahydrofuran (100ml) and water (70ml) with N-methylmorpholine-N-oxide (1.3 hydrate; 5.0g) and osmium tetroxide (25mg).

After 24h, the mixture was poured into ice/water (1l). Recrystallisation of the precipitate from methanol furnished

2,3-trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (8.6g, 78%) as colourless needles, m.p. 168-170°; m.m.p. 167-170° with authentic sample (m.p. 167-169°) prepared by reduction of 2,3-trans-3-hydroxy-5,7,3',4'-tetramethoxyflavanone.

After a preparation by the same method on a smaller scale (3.3g 5,7,3',4'-tetramethoxyflav-3-ene), extraction of the aqueous mother liquor with ethyl acetate (3 x 50ml), evaporation and crystallisation of the residue from the methanolic mother liquor furnished a solid (285mg). P.l.c. on silica (1 x 1m plate, eluted 3 times with 30% ethyl acetate in benzene) afforded 2,3-cis-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (131mg, 4%) as colourless needles, m.p. 153-156° (from ethanol) unchanged by further crystallisation (Found: C,62.9; H,6.05. Calculated for $C_{19}H_{22}O_7$: C,62.95; H,6.1%) (lit.,[55] m.p. 161-162°). N.m.r. (τ,$CDCl_3$): 2.74-3.18 (3H, m, B-ring), 3.80 and 3.88 (2H, 2d, A-ring), 4.84 (1H, d, 4-H), 5.10 (1H, bs, 2-H), 5.74 (1H, s, exchanges with D_2O, hydroxyl), 5.78 (1H, bd, 3-H), 6.10 (3H, s, -OMe), 6.12 (6H, 2s, 2 x -OMe), 6.26 (3H, s, -OMe), 7.02 (1H, bs, exchanges with D_2O, hydroxyl); $J_{2,3}$=1Hz; $J_{3,4}$=4.6Hz.

2,3-Trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (CXX)

2,3-Trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (1.00g) in dry pyridine (10ml) was treated with benzoyl chloride (0.76ml, 1.2 equivalents). After 5h, the mixture was diluted with ethyl acetate (350ml), washed with water (2 x 50ml), aqueous sodium bicarbonate (50ml) and brine and dried. Removal of the solvent left an oil which separated from toluene/light petroleum (b.p. 60-80°) as needles of 2,3-trans-3,4-cis-

dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (1.26g, 80%), m.p. 173-178°. A sample recrystallised from the same solvent had m.p. 176-178° (Found: C,69.65; H,5.3. $C_{33}H_{30}O_9$ requires: C,69.45; H,5.3%). N.m.r. (τ,$CDCl_3$): 1.92-2.04 (2H, m, aromatic), 2.24-3.24 (12H, m, aromatic and 4-H), 3.78 and 3.86 (2H, 2d, A-ring), 4.26 (1H, dd, 3-H), 4.60 (1H, d, 2-H), 6.20 (9H, s, 3 x -OMe), 6.26 (3H, s, -OMe); $J_{2,3}$=10.8Hz, $J_{3,4}$=3.6Hz.

Reaction of 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan with pyridine/acetic anhydride mixture and acetic anhydride mixture alone

a) 2,3-Trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (150mg) in dry pyridine (0.5ml) and acetic anhydride mixture (0.5ml) was heated to 90° for 4h. The mixture was diluted with ether (90ml), washed with 2N aqueous sodium hydroxide (20ml) and water (20ml) and dried. Removal of the solvent left a gum which separated from ether as (impure) crystals of 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (51mg, 34%), m.p. 168-174°, identified by n.m.r.

The mother liquor was applied to 3 x 20cm silica p.l.c. plates and eluted 6 times with 50% ether/light petroleum (b.p. 40-60°). The faster band furnished impure starting material (32mg, 12%), m.p. 156-163°, identified by n.m.r.

The slower band furnished 2,3-trans-3,4-cis-3-benzoyloxy-4-acetoxy-5,7,3',4'-tetramethoxyflavan (37mg, 28%), as an oil, identified by its n.m.r. spectrum (see below).

b) 2,3-Trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (150mg) in acetic anhydride mixture (1.5ml) was heated to 60° for 2h. The mixture was poured into ether (100ml), washed with 2N sodium hydroxide solution (2 x 15ml) and water

(15ml) and dried. Removal of the solvent left an oil which separated from benzene as colourless prisms of 2,3-trans-3,4-cis-3-benzoyloxy-4-acetoxy-5,7,3',4'-tetramethoxyflavan (75mg, 56%), m.p. 194-196° (Found: C,66.25; H,5.45. $C_{28}H_{28}O_9$ requires: C,66.15; H,5.55%). N.m.r. (τ,$CDCl_3$): 2.18 (2H, m, aromatic, ortho to carbonyl group), 2.48-3.22 (6H, m, aromatic), 3.38 (1H, d, 4-H), 3.86 (2H, bs, 6-H and 8-H), 4.38 (1H, dd, 3-H), 4.74 (1H, d, 2-H), 6.18 and 6.20 (12H, 2s, 4 x -OMe), 7.92 (3H, s, acetyl); $J_{2,3}$=11.0Hz, $J_{3,4}$=3.2Hz. m/e (60°): 508(M^+,1), 449(1), 448(2), 387,386 (not observed), 105(100), 327(77), 77(26), 328(19), 43(13).

Reaction of 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan with phenol in toluene

2,3-Trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (700mg) and phenol (2.0g) in dry toluene (6ml) were heated to 75° for 30h. The mixture was diluted with ether (250ml), washed with 2N sodium hydroxide solution (2 x 15ml) and water (15ml), dried and evaporated.

The resulting oil was applied to 2 x 1m silica p.l.c. plates and eluted twice with 75% ether/light petroleum (b.p. 40-60°). Four bands were removed. The band with the second greatest R_f was further resolved into two components (denoted B and C) on 2 x 20cm silica plates eluted twice with chloroform.

Band A (170mg, 25%) yielded crystals from ether. Recrystallisation from acetone/ethanol furnished 2,3-trans-3,4-cis-3-benzoyloxy-4-phenoxy-5,7,3',4'-tetramethoxyflavan (CXXVI) (97mg, 15%) as colourless prisms, m.p. 150.5-152.5° (Found:

C,70.8; H,5.65. $C_{32}H_{30}O_8$ requires: C,70.85; H,5.5%). N.m.r. (τ,$CDCl_3$): 2.48-3.30 (13H, m, aromatic), 3.82 and 3.88 (2H, 2d, A-ring), 3.96 (1H, bs, 4-H), 4.40 (2H, bs, 2-H and 3-H), 6.16 (3H, s, -OMe), 6.20 (6H, s, 2 x -OMe), 6.26 (3H, s, -OMe).

The mother liquor from band A contained other compounds (detected by n.m.r.) which could not be separated chromatographically nor induced to crystallise.

Band B (36mg, 5%) crystallised from ethanol as prisms of 2,3-trans-3,4-trans-3-benzoyloxy-4-(o-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXVII) (29mg), m.p. 182-184° (Found: C,70.7; H,5.65. $C_{32}H_{30}O_8$ requires: C,70.85; H,5.55%). N.m.r. (τ,$CDCl_3$): 1.98 (2H, dd, aromatic ortho to carbonyl), 2.44-2.78 (4H, m, aromatic and hydroxyl (exchanges with D_2O)), 3.04-3.50 (5H, m, aromatic), 3.58-3.92 (4H, m, aromatic), 4.16 (1H, dd, 3-H), 4.50 (1H, bd, J=4.4Hz, 2-H or 4-H), 5.42 (1H, bd, J=3.2Hz, 2-H or 4-H), 6.18, 6.28, 6.40 and 6.54 (12H, 4s, 4 x -OMe); $J_{2,3}$=3.2 or 4.4Hz, $J_{3,4}$=3.2 or 4.4Hz. m/e(200°): 542(M^+, not observed), 420(100), 105(41), 91(32), 151(31), 421(28), 327(23).

Band C (23mg, 3%) crystallised from ethanol as prisms of 2,3-trans-3,4-cis-3-benzoyloxy-4-(o-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXVIII) (14mg), m.p. 215-218° (decomp.) (Found: C,70.6; H,5.65%). N.m.r. (τ,$CDCl_3$): 2.34 (2H, dd, aromatic ortho to carbonyl), 2.56-3.46 (10H, m, aromatic), 3.76 and 3.90 (2H, 2d, A-ring), 4.28 (1H, dd, 3-H), 4.80 (1H, d, 4-H), 4.86 (1H, d, 2-H), 5.1 (1H, bs, exchanges with D_2O hydroxyl), 6.20, 6.24, 6.30 and 6.42 (12H, 4s, 4 x -OMe); $J_{2,3}$=10.2Hz, $J_{3,4}$=5.8Hz.

Band D (47mg, 7%) crystallised from ether. Recrystallisation

from methanol furnished prisms of 2,3-trans-3,4-cis-3-benzoyloxy-4-(p-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXIX) (32mg), m.p. 182-184° (Found: C,70.55; H,5.65%). N.m.r. (τ,$CDCl_3$): 2.30 (2H, dd, aromatic ortho to carbonyl), 2.52-2.84 (3H, m, aromatic), 3.00-3.40 (7H, m including 2d at 3.06 and 3.34 integrating to 4H, J=9Hz, aromatic) 3.78 and 3.90 (2H, 2d, A-ring), 4.40 (1H, dd, 3-H), 4.96 (1H, d, 2-H), 5.26 (1H, d, 4-H), 6.20, 6.22, 6.30 and 6.42 (12H, 4s, 4 x -OMe); $J_{2,3}$=10.6Hz, $J_{3,4}$=5.8Hz.

Band E (145mg, 22%) crystallised from methanol/acetone as colourless prisms of 2,3-trans-3,4-trans-3-benzoyloxy-4-(p-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXX) (130mg), m.p. 170-172° (Found: C,70.9; H,5.6%). N.m.r. (τ,$CDCl_3$): 2.16 (2H, dd, aromatic ortho to carbonyl group), 2.50-2.76 (3H, m, aromatic), 3.08-3.60 (1H, m, aromatic), 3.72 and 3.92 (2H, 2d, A-ring), 4.28 (1H, dd, 3-H), 4.46 (1H, s, exchanges with D_2O, hydroxyl), 4.92 (1H, d, 2-H), 5.70 (1H, d, 4-H), 6.20, 6.26, 6.34 and 6.58 (12H, 4s, 4 x -OMe); $J_{2,3}$=7.4Hz, $J_{3,4}$=6.4Hz.

2,3-Trans-3,4-cis-4-phenoxy-5,7,3',4'-tetramethoxyflavan-3-ol (CXXXI) and 3-acetate, and 2,3-trans-3,4-trans-4-phenoxy-5,7,3',4'-tetramethoxyflavan-3-ol (CXXXII)

2,3-Trans-3,4-cis-3-benzoyloxy-4-phenoxy-5,7,3',4'-tetramethoxyflavan (CXXVI) (42mg) was boiled for 10min in methanol (3ml) with potassium hydroxide (90mg). On cooling, 2,3-trans-3,4-cis-4-phenoxy-5,7,3',4'-tetramethoxyflavan-3-ol (CXXXI) (30mg) separated as needles, m.p. 169-171° (Found: C,68.5; H,6.1. $C_{25}H_{26}O_7$ requires: C,68.5; H,6.0%). N.m.r. (τ,$CDCl_3$): 2.64-3.18 (8H, m, aromatic), 3.90 and 4.00 (2H, 2d, A-ring), 4.38 (1H, d, 4-H), 4.86 (1H, d, 2-H), 5.86 (1H, 8 lines

collapsing to dd with D_2O, 3-H), 6.10 and 6.12 (6H, 2s, 2 x -OMe), 6.28 and 6.52 (6H, 2s, 2 x -OMe), 7.96 (1H, d exchanges with D_2O, hydroxyl); $J_{2,3}$=10.4Hz, $J_{3,4}$=3.6Hz. m/e (40°): 438(M^+, trace), 94(100), 316(70), 301(25), 344(23), 178(19), 317(16).

Acetylation of the flavan-3-ol (CXXXI) [illegible]idine (0.5ml) and acetic anhydride (0.5ml) at 50° for 30min and evaporation on a rotary oil pump gave 2,3-trans-3,4-cis-3-acetoxy-4-phenoxy-5,7,3',4'-tetramethoxyflavan (CXXXVII) (22mg) as colourless needles, m.p. 136-139° (from ethanol) (Found: C,67.8; H,5.8. $C_{27}H_{28}O_8$ requires: C,67.5, H,5.85%). N.m.r. (τ,$CDCl_3$): 2.64-3.20 (8H, m, aromatic), 3.90 (2H, bs, A-ring), 4.12 (1H, d, 4-H), 4.54 (1H, d, 2-H), 4.74 (1H, dd, 3-H), 6.12 (6H, s, 2 x -OMe), 6.26 and 6.28 (6H, 2s, 2 x -OMe), 8.60 (3H, s, acetyl); $J_{2,3}$=11.0Hz, $J_{3,4}$=2.8Hz.

The mother liquor from band A of the previous experiment was concentrated and treated with potassium hydroxide (80mg) in methanol (5ml) at 50° for 30min. The mixture was diluted with ether (40ml), washed with water (2 x 10ml), dried and evaporated. The resulting gum (30mg) was chromatographed on 1 x 20cm silica p.l.c. plate, eluted with chloroform. 2,3-Trans-3,4-trans-4-phenoxy-5,7,3',4'-tetramethoxyflavan-3-ol (CXXXII) (6mg, 1%), was obtained as prisms, m.p. 150.5-152.5° (from acetone/light petroleum, b.p. 60-80°) (Found: C,68.55; H,6.05. $C_{25}H_{26}O_7$ requires: C,68.5; H,6.0%). N.m.r. (τ,$CDCl_3$): 2.62-3.18 (8H, m, aromatic), 3.78 and 3.86 (2H, 2d, A-ring), 4.46 (1H, d, 4-H), 4.98 (1H, d, 2-H), 5.58 (1H, 8 lines collapsing to dd with D_2O, 3-H), 6.12 (3H, s, -OMe), 6.20 (6H,

s, 2 x -OMe), 6.36 (3H, s, -OMe), 8.06 (1H, d, exchanges with D_2O, hydroxyl; $J_{2,3}$=7.4Hz, $J_{3,4}$=5.4Hz. m/e(65°): 438(M^+,3), 345(100), 94(92), 316(90), 191(65), 167(42), 151(38).

Hydrolysis of the isomers of 2,3-trans-3-benzoyloxy-4-hydroxyphenyl-5,7,3',4'-tetramethoxyflavan (CXXVII) to (CXXX)

a) 2,3-Trans-3,4-trans-3-benzoyloxy-4-(o-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXVII) (41mg) was heated to 50° for 30min with potassium hydroxide (80mg) in methanol (3ml). The mixture was poured into ethyl acetate, washed with 0.5N hydrochloric acid (10ml), water (10ml) and brine and dried. Removal of the solvent left a solid which separated from ethanol/acetone as prisms of 2,3-trans-3,4-trans-4-(o-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan-3-ol (CXXXIII) (19mg), m.p. 232-233° (Found: C,68.25; H,6.15. $C_{25}H_{26}O_7$ requires: C,68.5; H,6.0%). N.m.r. (τ,$CDCl_3$+$(CD_3)_2SO$): 1.26 (1H, bs, exchanges with D_2O, hydroxyl), 2.98-3.22 (5H, m, aromatic), 3.36-3.40 (2H, m, aromatic), 3.82 and 3.92 (2H, 2d, A-ring), 5.36 (1H, d, 2-H), 5.54 (1H, d, 4-H), 5.98 (1H, bdd, sharpens with D_2O, 3-H), 6.14 (6H, s, 2 x -OMe), 6.22 (3H, s, -OMe), 6.58 (3H, s, -OMe), 7.06 (1H, bs, exchanges with D_2O, hydroxyl); $J_{2,3}$=9.0Hz, $J_{3,4}$=7.8Hz.

b) 2,3-Trans-3,4-cis-3-benzoyloxy-4-(o-hydroxyphenyl)-5,7,-3',4'-tetramethoxyflavan (CXXVIII) (18mg) hydrolysed as in (a) furnished 2,3-trans-3,4-cis-4-(o-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan-3-ol (CXXXIV) (10mg), m.p. 250-254° (decomp.) (from acetone/ethanol) (Found: C,68.3; H,6.05%). N.m.r. (τ,$CDCl_3$+$(CD_3)_2SO$): 0.8 (1H, bs, exchanges with D_2O, hydroxyl), 2.82-3.30 (7H, m, aromatic), 7.84 and 7.92 (2H, 2d, A-ring),

5.0 (1H, bs, exchanges with D_2O, hydroxyl), 5.06 (1H, d, 4-H), 5.34 (1H, d, 2-H), 5.70 (1H, dd, sharpens with D_2O, 3-H), 6.18 (6H, s, 2 x -OMe), 6.22 (3H, s, -OMe), 6.42 (3H, s, -OMe); $J_{2,3}$=10.0Hz, $J_{3,4}$=5.4Hz.

c) 2,3-Trans-3,4-cis-3-benzoyloxy-4-(p-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXIX) (35mg) hydrolysed as in (a) yielded 2,3-trans-3,4-cis-4-(p-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan-3-ol (CXXXV) (26mg) as prisms from ethanol, m.p. 120° (solvent expelled), resolidifies, m.p. 208-209° (Found after drying at 120°: C,68.5; H,5.9%). N.m.r. (τ,$CDCl_3$): 2.96 (2H, d, J=9Hz, D-ring), 3.10-3.16 (3H, m, B-ring), 3.30 (2H, d, J=9Hz, D-ring), 3.82 and 3.92 (2H, 2d, A-ring), 4.48 (1H, bs, exchanges with D_2O, hydroxyl), 5.32 (1H, d, 2-H), 5.54 (1H, d, 4-H), 5.88 (1H, bdd, sharpens with D_2O, 3-H), 6.18 (6H, s, 2 x -OMe), 6.24 (3H, s, -OMe), 6.42 (3H, s, -OMe), 8.30 (1H, bs, exchanges with D_2O, hydroxyl); $J_{2,3}$=9.8Hz, $J_{3,4}$=5.8Hz.

Acetylation with pyridine/acetic anhydride at 50° for 30min and evaporation on a rotary oil pump furnished 2,3-trans-3,4-cis-3-acetoxy-4-(p-acetoxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXXVIII) as plates from acetone/ethanol, m.p. 172.5-174° (Found: C,66.7; H,5.9. $C_{29}H_{30}O_9$ requires: C,66.65; H,5.8%). N.m.r. (τ,$CDCl_3$): 2.96 (4H, bs, D-ring), 3.14 (3H, bs, B-ring), 3.82 and 3.94 (2H, 2d, A-ring), 4.60 (1H, dd, 3-H), 5.08 (1H, d, 2-H), 5.34 (1H, d, 4-H), 6.16 (6H, s, 2 x -OMe), 6.24 (3H, s, -OMe), 6.44 (3H, s, -OMe), 7.72 (3H, s, acetyl), 8.24 (3H, s, acetyl); $J_{2,3}$=10.4Hz, $J_{3,4}$=5.8Hz.

d) 2,3-Trans-3,4-trans-3-benzoyloxy-4-(p-hydroxyphenyl)-5,7,-3',4'-tetramethoxyflavan (CXXX) (55mg) hydrolysed as in (a)

afforded 2,3-trans-3,4-trans-4-(p-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan-3-ol (CXXXVI) (17mg), m.p. 222-224° (Found: C,68.2; H,6.0. $C_{25}H_{26}O_7$ requires: C,68.5; H,6.0%). N.m.r. (τ,$CDCl_3$+$(CD_3)_2SO$): 1.50 (1H, s, exchanges with D_2O, hydroxyl), 2.96-3.22 (5H, m including d at 3.08 having J=8Hz, aromatic), 3.36 (2H, d, J=8Hz, D-ring), 3.86 and 3.98 (2H, 2d, A-ring), 5.40 (1H, dd, J=2.0Hz and 7.2Hz, 2-H), 6.04-6.30 (11H, m+2s at 6.16 and 6.28, 3-H, 4-H and 3 x -OMe), 6.62 (3H, s, -OMe).

Acetylation as in (c) furnished 2,3-trans-3,4-trans-3-acetoxy-4-(p-acetoxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXXIX) as needles, m.p. 176-178° (from ethanol) (Found: C,66.7; H,5.7. $C_{29}H_{30}O_9$ requires: C,66.65; H,5.8%). N.m.r. (τ,$CDCl_3$): 3.00-3.38 (7H, m including 2d at 3.12 and 3.24 having J=7Hz, aromatic), 3.72 and 3.92 (2H, 2d, A-ring), 4.48 (1H, dd, 3-H), 5.02 (1H, d, 2-H), 5.82 (1H, d, 4-H), 6.20 and 6.22 (9H, 2s, 3 x -OMe), 6.60 (3H, s, -OMe), 7.78 (3H, s, acetyl), 8.16 (3H, s, acetyl); $J_{2,3}$=7.4Hz, $J_{3,4}$=6.6Hz.

Reaction of 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan with phenol in pyridine

2,3-Trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan (320mg) and phenol (1.4g) in dry pyridine (3ml) were heated to 90° for 23h. The mixture was poured into ether (100ml), washed with 2N aqueous sodium hydroxide (3 x 10ml) and water (10ml) and dried. T.l.c. of the mixture (eluted with 75% ether/light petroleum, b.p. 40-60°) resembled that of the reaction of 2,3-trans-3,4-cis-dibenzoyloxy-5,7,3',4'-tetramethoxyflavan with phenol in toluene (above), with one extra product which gave a yellow colour with isovanillin.

The mixture was concentrated and treated with potassium hydroxide (250mg) in methanol (10ml) overnight. It was diluted with ether (100ml), washed with water (2 x 5ml), dried, concentrated and applied to 1 x 1m alumina p.l.c. plate, eluted 7 times with 40% ether/light petroleum (b.p. 40-60°). The major band separated from ether as needles of 2,3-trans-3,4-cis-4-phenoxy-5,7,3',4'-tetramethoxyflavan-3-ol (20mg, 8%), m.p. 159-166°, raised on recrystallisation from methanol to 167-169°, undepressed on admixture with authentic sample of m.p. 169-171°.

Effect of phenol and benzoic acid in toluene on 2,3-trans-3,4-cis-3-benzoyloxy-4-phenoxy-5,7,3',4'-tetramethoxyflavan (CXXVI) and 2,3-trans-3,4-trans-3-benzoyloxy-4-(p-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXX)

a) 2,3-Trans-3,4-cis-3-benzoyloxy-4-phenoxy-5,7,3',4'-tetramethoxyflavan (CXXVI) (10mg) was heated to 75° for 24h with phenol (180mg) and benzoic acid (12mg) in dry toluene (0.5ml). The mixture was diluted with ether (30ml) and washed with 2N aqueous sodium hydroxide (2 x 4ml). T.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated the presence of the starting material and a mixture of 3-benzoyloxy-4-(hydroxyphenyl)-5,7,3',4'-tetramethoxyflavans.

b) 2,3-Trans-3,4-trans-3-benzoyloxy-4-(p-hydroxyphenyl)-5,7,3',4'-tetramethoxyflavan (CXXX) treated as in (a) was shown by t.l.c. to be unchanged.

4β,3',4'-Trimethoxyflavan (CXLV)

a) To a solution of 3',4'-dimethoxyflavan-4β-ol (290mg) in dry tetrahydrofuran (12ml) was added phenyllithium (2M; 0.8ml, 1.6eqt.) then methyl iodide (0.1ml). After 1h at room

temperature, t.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated the presence of the starting material but no product. After warming to 40° for 6h t.l.c. indicated that almost complete reaction had occurred.

Ether (100ml) was added and the mixture was washed with water (2 x 15ml) and dried. Removal of the solvent left a yellow oil which crystallised from methanol as colourless prisms of 4β,3',4'-trimethoxyflavan (170mg, 56%), m.p. 99-101° (Found: C,72.1; H,6.65. $C_{18}H_{20}O_4$ requires: C,72.0; H,6.7%). N.m.r. (τ,$CDCl_3$): 2.52(1H, bd, A-ring), 2.72-3.20 (6H, m, aromatic), 4.94 (1H, dd, 2-H), 5.24 (1H, dd, 4-H), 6.10 and 6.12 (6H, 2s, 2 x -OMe), 6.50 (3H, s, 4-OMe), 7.48(1H, 8 lines, 3-H), 7.88 (1H, 8 lines, 3*-H); $J_{2,3}$=2.0Hz, $J_{2,3*}$=11.8Hz, $J_{3,3*}$=13.0Hz, $J_{3,4}$=6.2Hz, $J_{3*,4}$=10.4Hz.

b) 3',4'-Dimethoxyflavan-4β-ol (280mg) in dry tetrahydrofuran (18ml) was stirred for 2h with sodium hydride dispersion (185mg). Methyl iodide (0.3ml) was added. After 1h at room temperature, t.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated that reaction was almost complete.

4β,5,7,3',4'-Pentamethoxyflavan (CXLVI)

5,7,3',4'-Tetramethoxyflavan-4β-ol (340mg) was stirred in dry dimethylformamide (10ml) with sodium hydride dispersion (250mg). After 15min, methyl iodide (0.5ml) was added and the mixture was stirred for a further 2h. T.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated almost complete reaction.

After 6h, ether (150ml) was added and the mixture was

washed with water (3 x 20ml) and dried. Removal of the solvent left an oil which crystallised from ether. Recrystallisation from methanol furnished colourless needles of 4β,5,7,3',4'-pentamethoxyflavan (210mg, 60%), m.p. 109.5-111.5° (Found: C,66.55; H,6.7. $C_{20}H_{24}O_6$ requires: C,66.65; H,6.7%). N.m.r. (τ,$CDCl_3$): 3.00-3.20 (3H, m, B-ring), 3.90 (2H, s, 6-H and 8-H), 5.02 (1H, dd, 2-H), 5.22 (1H, t, 4-H), 6.10 and 6.12 (6H, 2s, 2 x -OMe), 6.18 and 6.24 (6H, 2s, 2 x -OMe), 6.68 (3H, s, 4-OMe), 7.38-7.82 (2H, m, 3-H and 3*-H); $J_{2,3}$=3.2Hz, $J_{2,3*}$=9.6Hz, $J_{3,4}$=$J_{3*,4}$=7.4Hz.

A sample crystallised unchanged after being boiled for a few minutes with methanolic potassium hydroxide.

4β,7,3',4'-Tetramethoxyflavan (CXLVII)

7,3',4'-Trimethoxyflavan-4β-ol (310mg) was stirred for 10min with sodium hydride dispersion (65mg) in dry dimethylformamide (10ml). Methyl iodide (0.2ml) was added and the mixture was stirred for 2h then poured into ether (100ml).

The ethereal solution was washed with water (3 x 15ml), dried and evaporated. The resultant oil crystallised from ether/light petroleum (b.p. 40-60°). Recrystallisation from methanol afforded colourless needles of 4β,7,3',4'-tetramethoxyflavan (220mg, 65%), m.p. 90-92° (Found: C,69.05; H,6.65. $C_{19}H_{22}O_5$ requires: C,69.05; H,6.7%). N.m.r. (τ,$CDCl_3$): 2.64 (1H, bd, 5-H), 2.98-3.18 (3H, m, B-ring), 3.40-3.60 (2H, m, 6-H and 8-H), 4.96 (1H, dd, 2-H), 5.26 (1H, dd, 4-H), 6.10 and 6.12 (6H, 2s, 2 x -OMe), 6.24 (3H, s, -OMe), 6.52 (3H, s, 4-OMe), 7.50 (1H, 8 lines, 3-H), 7.94 (1H, 8 lines, 3*-H); $J_{2,3}$=2.0Hz, $J_{2,3*}$=11.6Hz, $J_{3,3*}$=12.4Hz, $J_{3,4}$=6.6Hz, $J_{3*,4}$=10.6Hz.

4β-(p-Nitrophenoxy)-3',4'-dimethoxyflavan (CXLVIII)

3',4'-Dimethoxyflavan-4β-ol (860mg) in dry dimethylsulphoxide (8ml) was added to a solution prepared from sodium hydride dispersion (250mg) and dry dimethylsulphoxide (10ml). After 5min, p-fluoronitrobenzene (0.6ml) was added with stirring. After 30min the mixture was poured into ethyl acetate (150ml), washed with water (3 x 20ml) and brine and dried. Removal of the solvent left an oil which separated from acetone as pale yellow prisms of 4β-(p-nitrophenoxy)-3',4'-dimethoxyflavan (960mg, 79%). A sample recrystallised from benzene had m.p. 189-191° (Found: C,67.9; H,5.15; N,3.5. $C_{23}H_{21}NO_6$ requires: C,67.8; H,5.2; N,3.45%). N.m.r. (τ,$CDCl_3$): 1.90 (2H, bd, J=10Hz, aromatic ortho to nitro-group), 2.58-3.10 (9H, m, aromatic), 4.14 (1H, dd, 4-H), 4.78 (1H, dd, 2-H), 6.10 (6H, s, 2 x -OMe), 7.34 (1H, 8 lines, 3-H), 7.64 (1H, 8 lines, 3*-H); $J_{2,3}$=2.4Hz, $J_{2,3*}$=11.6Hz, $J_{3,3*}$=13.4Hz, $J_{3,4}$=6.4Hz, $J_{3*,4}$=10.0Hz.

4β-(p-Nitrophenoxy)-7,3',4'-trimethoxyflavan (CXLIX)

7,3',4'-Trimethoxyflavan-4β-ol (630mg) in dry dimethylsulphoxide (6ml) was added to a solution prepared from sodium hydride dispersion (200mg) and dry dimethylsulphoxide (8ml).[74] p-Fluoronitrobenzene (0.8ml) was added with stirring.

After 30min, the mixture was poured into ethyl acetate (150ml), washed with water (3 x 20ml) and brine and dried. Removal of the solvent left an oil which crystallised from acetone. Recrystallisation from acetone furnished 4β-(p-nitrophenoxy)-7,3',4'-trimethoxyflavan (550mg, 63%) as yellow prisms, m.p. 149-151° (Found: C,66.2; H,5.25; N,3.05.

$C_{24}H_{23}NO_7$ requires: C,65.9; H,5.3; N,3.2%). N.m.r. (τ,$CDCl_3$): 1.80 (2H, d, $\underline{J}$=10Hz, aromatic ortho to nitro-group), 2.68-3.10 (6H, m, aromatic), 3.38-3.50 (2H, m, 6-H and 8-H), 4.20 (1H, dd, 4-H), 4.80 (1H, dd, 2-H), 6.10 (6H, s, 2x-OMe), 6.20 (3H, s, -OMe), 7.24-7.82 (2H, m, 3-H and 3*-H); $\underline{J}_{2,3}$=1.8Hz, $\underline{J}_{2,3*}$=11.8Hz, $\underline{J}_{3,4}$=6.0Hz, $\underline{J}_{3*,4}$=10.0Hz.

4β-(p-Nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (CL)

5,7,3',4'-Tetramethoxyflavan-4β-ol (345mg) in dry dimethylsulphoxide (3ml) was added to a solution prepared from sodium hydride dispersion (100mg) and dry dimethylsulphoxide (5ml).[74] After 2min, p-fluoronitrobenzene (0.4ml) was added and the mixture was stirred for 10min then diluted with ethyl acetate (80ml).

It was washed with water (3 x 15ml) and brine and dried. The solvent was evaporated leaving an oil which separated from acetone as colourless needles (turning yellow in light) of 4β-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (304mg, 65%), m.p. 117-119° (decomp.) (Found: C,64.05; H,5.35; N,2.85. $C_{25}H_{25}NO_8$ requires: C,64.25; H,5.4; N,3.0%). N.m.r. (τ,$CDCl_3$): 1.86 (2H, d, $\underline{J}$=10Hz, aromatic ortho to nitro-group), 3.02-3.20 (3H, m, B-ring), 3.78 and 3.88 (2H, 2d, A-ring), 4.14 (1H, t, 4-H), 4.78 (1H, dd, 2-H), 6.10 (3H, s, -OMe), 6.20 (6H, s, 2 x -OMe), 6.32 (3H, s, -OMe), 7.30-7.48 (2H, m, 3-H and 3*-H); $\underline{J}_{2,3}$=4.4Hz, $\underline{J}_{2,3*}$=7.8Hz, $\underline{J}_{3,4}$=$\underline{J}_{3*,4}$=6.2Hz.

4β-(2,4-Dinitrophenoxy)-3',4'-dimethoxyflavan (CLI)

a) 3',4'-Dimethoxyflavan-4β-ol (285mg) in dry dimethylsulphoxide (3ml) was added to a solution prepared from sodium hydride dispersion (80mg, 1.6eqt.) and dry dimethylsulphoxide [74]

(5ml). 2,4-Dinitrofluorobenzene (0.28ml, 2.2eqt) was added after 5min.

After 4h, the mixture was diluted with ethyl acetate (70ml), washed with water (3 x 10ml) and brine and dried. Removal of the solvent left an oil which crystallised from acetone. Recrystallisation from acetone yielded colourless needles of 3',4'-dimethoxyflavan-4β-ol (120mg, 42%), m.p. and m.m.p. 157-158°.

b) To a solution of 3',4'-dimethoxyflavan-4β-ol (560mg) in dry tetrahydrofuran (15ml) was added phenyllithium (2M; 1.1ml, 1.1eqt.), then 2,4-dinitrofluorobenzene (0.30ml, 1.2eqt.).

After 3h, the mixture was diluted with ethyl acetate (100ml), washed with aqueous sodium bicarbonate (2 x 20ml) and brine and dried. Removal of the solvent left an oil which separated from benzene as colourless rods of 4β-(2,4-dinitrophenoxy)-3',4'-dimethoxyflavan (680mg, 74%), m.p. 110-113° (Found: C,61.25; H,4.55; N,5.95. $C_{23}H_{20}N_2O_8$ requires: C,61.05; H,4.45; N,6.2%). N.m.r. (τ,$CDCl_3$): 1.20 (1H, d, J=2.8Hz, D-ring), 1.46 (1H, dd, J=9.4, and 2.8Hz, D-ring), 2.04 (1H, d, J=9.4Hz, D-ring), 2.54-3.12 (7H, m, aromatic), 3.64 (1H, dd, 4-H), 4.64 (1H, dd, 2-H), 6.20 (6H, s, 2 x -OMe), 7.10-7.90 (2H, m, 3-H and 3*-H); $J_{2,3}$=1Hz, $J_{2,3*}$=11.2Hz, $J_{3,4}$=6.2Hz, $J_{3*,4}$=9.8Hz.

Attempted preparation of 4β-(2,4-dinitrophenoxy)-7,3',4'-trimethoxyflavan

a) 7,3',4'-Trimethoxyflavan-4β-ol (320mg) in dry dimethylsulphoxide (3ml) was added to a solution prepared from sodium hydride dispersion (95mg) and dry dimethylsulphoxide (5ml).[74]

After 30min, 2,4-dinitrofluorobenzene (0.30ml, 2.5eqt.) was added and the mixture was stirred for 2h.

It was diluted with ethyl acetate (80ml), washed with water (3 x 15ml), dried and evaporated. Removal of the solvent left an oil which separated from benzene as prisms of 7,3',4'-trimethoxyflavan-4β-ol (105mg, 33%), identified by n.m.r.

b) 7,3',4'-Trimethoxyflavan-4β-ol (470mg) in dry tetrahydrofuran (10ml) was treated with phenyllithium (2M; 0.90ml, 1.2eqt.) and then 2,4-dinitrofluorobenzene (0.25ml, 1.3eqt.). After 90min, the mixture was diluted with ether (200ml), washed with 2N aqueous sodium hydroxide (20ml), water (2 x 20ml) and brine and dried. Removal of the solvent left an oil which could not be induced to crystallise. T.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated the presence of little starting material and many products.

Attempted preparation of 4β-(2,4-dinitrophenoxy)-5,3',4'-trimethoxyflavan

5,3',4'-Trimethoxyflavan-4β-ol (315mg) in dry tetrahydrofuran (5ml) was treated with phenyllithium (2M; 0.7ml, 1.4eqt.) and then 2,4-dinitrofluorobenzene (0.22ml, 1.8eqt.). After 2h, the mixture was poured into ether (150ml), washed with 2N aqueous sodium hydroxide (20ml) and water (2 x 20ml) and dried. Removal of the solvent left an oil which separated from benzene/ether as prisms of 4β-(2,4-dinitrophenoxy)-5,3',4'-trimethoxyflavan (210mg, 44%), m.p. 78-83°. N.m.r. (τ,$CDCl_3$, 60MHz): 1.34 (1H, d, D-ring), 1.58 (1H, dd, D-ring), 2.54-3.12 (5H, m, aromatic), 3.36 and 3.48 (2H, 2bd, 6-H and 8-H), 3.94 (1H, t, 4-H), 4.86 (1H, dd, 2-H), 6.12 (6H, s,

2 x -OMe), 6.40 (3H, s, -OMe), 7.12-7.42 (2H, m, 3-H and 3*-H); $J_{2,3}$=5Hz, $J_{2,3*}$=8Hz, $J_{3,4}=J_{3*,4}$=7.5Hz.

Recrystallisation of the sample from benzene/light petroleum (b.p. 60-80°) lowered its purity. N.m.r. showed extra signals in the region 1-2τ and 6.0-6.2τ.

Reaction of 4β-(p-nitrophenoxy)-7,3',4'-trimethoxyflavan with phenol in pyridine

4β-(p-Nitrophenoxy)-7,3',4'-trimethoxyflavan (100mg) and phenol (200mg) in dry pyridine (1ml) were heated to 75°. T.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated that reaction was incomplete after 2 days, but complete after 3 days.

The mixture was then diluted with ether (100ml), washed with 2N sodium hydroxide solution (3 x 15ml) and water (15ml) and dried. Evaporation of the solvent left an oil which separated from methanol as prisms of 4α-phenoxy-7,3',4'-trimethoxyflavan (38mg, 43%), m.p. and m.m.p. 97-99°.

Reaction of 4β-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan with phenol in pyridine

4β-(p-Nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (100mg) and phenol (200mg) in dry pyridine (1ml) were heated to 40°. After 3 days, t.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated that reaction was complete.

The mixture was diluted with ether (100ml), washed with 2N aqueous sodium hydroxide (3 x 15ml) and water (15ml) and dried. Removal of the solvent left an oil which crystallised from ethanol containing a little potassium hydroxide.

Recrystallisation furnished 4α-phenoxy-5,7,3',4'-tetramethoxyflavan (45mg, 50%), m.p. 135-139°. A sample recrystallised from ethanol/potassium hydroxide had m.p. and m.m.p. 137-139°.

2,3-Trans-3,4-cis-di-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (CLIII)

2,3-Trans-3,4-cis-5,7,3',4'-tetramethoxyflavan-3,4-diol (360mg) in dry dimethylsulphoxide (8ml) was added to a solution prepared from sodium hydride dispersion (250mg) and dry dimethylsulphoxide (8ml).[74] After 5min, p-fluoronitrobenzene (0.8ml) was added with stirring.

After 45min, the mixture was diluted with ethyl acetate (150ml), washed with water (3 x 20ml) and brine and dried. Removal of the solvent left an oil which crystallised from acetone/ether. Recrystallisation from acetone/light petroleum (b.p. 60-80°) furnished 2,3-trans-3,4-cis-di-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (395mg, 66%) as pale yellow prisms, m.p. 182-184° (decomp.) (Found: C,62.0; H,4.7; N,4.65. $C_{31}H_{28}N_2O_{11}$ requires: C,61.75; H,4.65; N,4.65%). N.m.r. (τ,$CDCl_3$): 1.92 (2H, d, J=9Hz, aromatic ortho to nitro group), 2.06 (2H, d, J=9Hz, aromatic ortho to nitro group), 2.86-3.02 (3H, m, B-ring), 3.20 (2H, d, J=9Hz, aromatic meta to nitro group), 3.44 (2H, d, J=9Hz, aromatic meta to nitro group), 3.80 and 3.88 (2H, 2d, A-ring), 3.98 (1H, d, 4-H), 4.46 (1H, d, 2-H), 5.08 (1H, dd, 3-H), 6.18 (6H, s, 2 x -OMe), 6.22 (3H, s, -OMe), 6.30 (3H, s, -OMe); $J_{2,3}$=10.2Hz, $J_{3,4}$=3.0Hz.

Effect of alcoholic alkali on 4β-(p-nitrophenoxy)-7,3',4'-trimethoxyflavan

Separate samples of 4β-(p-nitrophenoxy)-7,3',4'-trimethoxy-

flavan (50mg) were boiled under reflux for 2h in methanol (5ml) containing potassium hydroxide (100mg) and in ethanol (5ml) to which had been added sodium (ca. 50mg). T.l.c. (elution with 75% ether/light petroleum, b.p. 40–60°) indicated that each mixture contained the starting material and no 7,3',4'-trimethoxyflavan-4β-ol.

Chapter 3

2-Hydroxy-4-methoxymethoxyacetophenone (CLXIII)

2,4-Dihydroxyacetophenone (22.5g) in Analar acetone (200ml) was stirred for 3h with anhydrous potassium carbonate (80g) and methoxymethyl chloride (11ml, 1.0eqt.). The mixture was filtered and the solid was washed well with acetone.

Evaporation of the acetone and distillation of a sample of the residual oil under reduced pressure gave a product, b.p. 118-128°/0.5torr, shown by t.l.c. (elution with 50% ether/light petroleum, b.p. 40-60°) to be contaminated with 2,4-dihydroxyacetophenone; (for 2-hydroxy-4-methoxymethoxyacetophenone, Bellini and Venturella[93] report b.p. 118-122°/0.2torr).

Steam distillation of the crude oil furnished chromatographically pure 2-hydroxy-4-methoxymethoxyacetophenone (18g, 62%). N.m.r. (τ,$CDCl_3$): -3.4 (1H, s, exchanges with D_2O, hydroxyl), 2.32 (1H, d, aromatic), 3.32-3.52 (2H, m, aromatic), 4.80 (2H, s, $-OCH_2O-$), 6.52 (3H, s, -OMe), 7.44 (3H, s, acetyl).

7-Methoxymethoxy-3',4'-dimethoxyflavanone (CLX)

2-Hydroxy-4-methoxymethoxyacetophenone (13.5g) and veratraldehyde (16g) in methylated spirit (150ml) were treated with potassium hydroxide (10g) in water (10ml). After 5 days, the solution was neutralised with 10% acetic acid in water (*ca.* 100ml), diluted with water (50ml) and cooled to 0°. The precipitate was recrystallised twice from acetone to furnish 7-methoxymethoxy-3',4'-dimethoxyflavanone (6.0g, 25%) as colourless rods, m.p. 120-122° (Found: C,66.1; H,5.75. $C_{19}H_{20}O_6$ requires: C,66.25; H,5.85%). N.m.r. (τ,$CDCl_3$): 2.16 (1H, d, 5-H), 2.96-3.36 (5H, m, aromatic), 4.58 (1H, dd, 2-H), 4.80 (2H,

s, $-OCH_2O-$), 6.08 (3H, s, -OMe), 6.10 (3H, s, -OMe), 6.52 (3H, s, -OMe), 6.78-7.30 (2H, m, 3-H and 3*-H); $J_{2,3}$=4.0Hz, $J_{2,3*}$=12.0Hz.

Concentration of the mother liquor and crystallisation from methylated spirit afforded 2'-hydroxy-4'-methoxymethoxy-3,4-dimethoxychalcone (5.2g, 22%) as yellow prisms, m.p. 99-100° (lit.,[93] 104-105°). N.m.r. (τ,$CDCl_3$): -3.3 (1H, s, exchanges with D_2O, hydroxyl), 2.04-2.20 (2H, m, 6-H and β-H), 2.50-2.86 (3H, m, B-ring and α-H), 3.08 (1H, d, 5-H), 3.36-3.46 (2H, m, 3'-H and 5'-H), 6.78 (2H, s, $-OCH_2O-$), 6.02 (3H, s, -OMe), 6.06 (3H, s, -OMe), 6.50 (3H, s, -OMe).

7-Hydroxy-3',4'-dimethoxyflavanone (CLXI)

7-Methoxymethoxy-3',4'-dimethoxyflavanone (4.0g) in acetic acid (50ml) was treated with toluene-p-sulphonic acid (60mg) at room temperature overnight. The mixture was diluted with ethyl acetate (300ml), washed repeatedly with aqueous sodium carbonate and then brine and dried. Removal of the solvent left a solid which crystallised from acetone as colourless prisms of 7-hydroxy-3',4'-dimethoxyflavanone (2.55g, 73%), m.p. 198-204° (decomp.) (Found: C,68.2; H,5.6. $C_{17}H_{16}O_5$ requires: C,68.0; H,5.35%). N.m.r. (τ,$CDCl_3$+$(CD_3)_2SO$): -0.3 (1H, exchanges with D_2O, hydroxyl), 2.28 (1H, d, 5-H), 2.86-3.02 (3H, m, aromatic), 3.32-3.60 (2H, m, aromatic), 4.56 (1H, dd, 2-H), 6.14 (6H, s, 2 x -OMe), 6.52-7.24 (2H, m, 3-H and 3*-H); $J_{2,3}$=4Hz, $J_{2,3*}$=12Hz.

o-Nitrobenzyl bromide[130]

o-Nitrotoluene (175g, 150ml), N-bromosuccinimide (178g) and dibenzoyl peroxide (65% paste; 1.5g) were stirred vigorously

in carbon tetrachloride (500ml) and heated under reflux for 10h. The mixture was cooled to 0° and filtered and the solid collected was washed with carbon tetrachloride. The combined filtrate was washed with aqueous iron (II) sulphate, dried and evaporated at 20 torr. Unchanged o-nitrotoluene was removed on a rotary oil pump at 90° and the residue was crystallised from ethanol to yield colourless rods of o-nitrobenzyl bromide (56g, 26%), m.p. 44.5-46° (lit.,[130] 46-47°).

2-Hydroxy-4-(o-nitrobenzyloxy)-acetophenone (CLXV)

2,4-Dihydroxyacetophenone (3.0g) and o-nitrobenzyl bromide (1.0 eqt., 4.3g) in Analar acetone (30ml) and dry benzene (30ml) were stirred for 10h with anhydrous potassium carbonate (7g). The mixture was then stirred for a further 2h while being heated under reflux and filtered while hot. The solid was washed with hot acetone and the combined filtrate was cooled to 0° to furnish 2-hydroxy-4-(o-nitrobenzyloxy)-acetophenone (4.5g, 80%), m.p. 151-153° (Found: C,62.8; H,4.7; N,4.9. $C_{15}H_{13}NO_5$ requires: C,62.7; H,4.55; N,4.9%). N.m.r. (τ,$CDCl_3$): -3.3 (1H, s, exchanges with D_2O, hydroxyl), 1.84 (1H, dd, aromatic ortho to nitro group), 2.12-2.62 (3H, m, aromatic), 3.40-3.54 (2H, m, aromatic), 4.50 (2H, s, $-OCH_2-$), 7.46 (3H, s, acetyl).

2'-Hydroxy-4'-(o-nitrobenzyloxy)-3,4-dimethoxychalcone (CLXVI)

a) 2',4'-Dihydroxy-3,4-dimethoxychalcone (15.0g) and o-nitrobenzyl bromide (1.0eqt., 11.0g) in Analar acetone (500ml) were heated under reflux for 2h while being vigorously stirred with anhydrous potassium carbonate (30g). The mixture was filtered. The solid collected was shaken with water and the undissolved chalcone was collected, dissolved in hot acetone and added to

the original filtrate. On cooling, 2'-hydroxy-4'-(o-nitrobenzyloxy)-3,4-dimethoxychalcone (13.9g, 64%) separated as orange-yellow prisms, m.p. 164-169°, raised on recrystallisation from acetone to 168-170° (Found: C,66.25; H,4.9; N,3.15. $C_{24}H_{21}NO_7$ requires: C,66.2; H,4.85; N,3.2%). N.m.r. (τ,$CDCl_3$): -3.4 (1H, s, exchanges with D_2O, hydroxyl), 1.86 (1H, bd, aromatic ortho to nitro group), 2.10-2.90 (8H, m, aromatic, α-H and β-H), 3.14 (1H, d, J=9Hz, 6'-H), 3.40-3.50 (2H, m, 3'-H and 5'-H), 4.50 (2H, bs, $-OCH_2-$), 6.06 and 6.10 (6H, s, 2 x -OMe).

b) 2-Hydroxy-4-o-nitrobenzyloxyacetophenone (2.9g) and veratraldehyde (2.2g) in methylated spirit (30ml) were stirred with potassium hydroxide (2.0g) in water (7ml) until the precipitate dissolved (ca. 30min).

After 2 days, water (20ml) was added and the dark brown mixture was neutralised with 2N hydrochloric acid. The resulting oil was extracted with chloroform (2 x 100ml), washed with water (30ml) and dried. Removal of the solvent left an oil which deposited a small amount of solid from acetone/methylated spirit. Recrystallisation from acetone furnished yellow prisms of 2'-hydroxy-4'-(o-nitrobenzyloxy)-3,4-dimethoxychalcone (50mg, 1.1%), m.p. and m.m.p. 168-170°.

7-(o-Nitrobenzyloxy)-3',4'-dimethoxyflav-3-ene (CLXVII)

2'-Hydroxy-4'-(o-nitrobenzyloxy)-3,4-dimethoxychalcone (12.0g) stirred at 70° in dry ethanol (350ml) was treated with sodium borohydride (3.5g, added in portions during 90min). The solution was evaporated to dryness and chloroform (300ml) and Analar acetic acid (12ml) were added.

The mixture was boiled under reflux for 2h, washed with 2N aqueous sodium hydroxide (100ml) and brine and dried over anhydrous potassium carbonate. Removal of the solvent left an oil which was dissolved in benzene and applied to a short column of alumina (100g). Elution with benzene (700ml) and evaporation of the eluant furnished an oil which separated from ethanol/acetone as pale yellow needles of 7-(o-nitrobenzyloxy)-3',4'-dimethoxyflav-3-ene (6.6g, 58%), m.p. 90-92° (Found: C,68.8; H,5.1; N,3.35. $C_{24}H_{21}NO_6$ requires: C,68.7; H,5.05; N,3.35%). N.m.r. (τ,$CDCl_3$): 1.90 (1H, bd, aromatic ortho to nitro group), 2.12-2.70 (3H, m, aromatic), 3.00-3.24 (4H, m, aromatic), 3.48-3.60 (3H, m, 6-H, 8-H and 4-H), 4.20 (1H, dd, 2-H), 4.36 (1H, dd, 3-H), 4.60 (2H, s, $-OCH_2-$), 6.16 (6H, s, 2 x -OMe); $J_{2,3}$=3.6Hz, $J_{2,4}$=1.4Hz, $J_{3,4}$=10.0Hz.

2,3-Trans-3,4-cis-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan-3,4-diol (CLXVIII)

7-(o-Nitrobenzyloxy)-3',4'-dimethoxyflav-3-ene (3.0g) was stirred in tetrahydrofuran (30ml) and water (30ml) with N-methylmorpholine-N-oxide (1.3 hydrate; 1.1g) and osmium tetroxide (10mg). After 12h, the mixture was diluted with ice/water (300ml). Recrystallisation of the precipitate from ethanol/acetone afforded 2,3-trans-3,4-cis-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan-3,4-diol (2.7g, 84%) as colourless needles, m.p. 170-172° (Found: C,63.65; H,5.3; N,3.15. $C_{24}H_{23}NO_8$ requires: C,63.55; H,5.1; N,3.1%). N.m.r. (τ,$CDCl_3$+$(CD_3)_2SO$): 1.92 (1H, bd, aromatic ortho to nitro group), 2.14-2.62 (3H, m, aromatic), 2.74 (1H, d, 5-H), 2.94-3.20 (3H, m, aromatic), 3.40 (1H, dd, 6-H), 3.52 (1H, d, 8-H), 4.60 (2H, s, $-OCH_2-$), 5:02 (1H, d, 2-H), 5.10 (1H, bs, exchanges with

D_2O, hydroxyl), 5.40-5.58 (2H, m, collapses to d integrating to 1H with D_2O, 4-H and hydroxyl), 6.04 (1H, dd, 3-H), 6.18 (6H, s, 2 x -OMe); $J_{2,3}$=9.0Hz, $J_{3,4}$=3.4Hz.

2,3-Trans-3,4-cis-3',4'-dimethoxyflavan-3,4,7-triol (CLXIX)

2,3-Trans-3,4-cis-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan-3,4-diol (120mg) in dry dioxan (15ml) in a pyrex tube was irradiated in a 300nm Rayonet apparatus. After 30h, t.l.c. (elution with ether) indicated that some starting material remained. After 48h, no starting material remained. The solvent was evaporated and the residue was chromatographed on 2 x 20cm silica plates, eluted 3 times with ether. The major band separated from acetone/light petroleum (b.p. 60-80°) as very pale yellow needles of 2,3-trans-3,4-cis-3',4'-dimethoxyflavan-3,4,7-triol (44mg, 53%), m.p. 186-191° (decomp.) (Found: C,64.2; H,5.8. $C_{17}H_{18}O_6$ requires: C,64.15; H,5.7%). N.m.r. (τ,$CDCl_3$+$(CD_3)_2SO$): 1.0 (1H, bs, exchanges with D_2O, hydroxyl), 2.84-3.20 (4H, m, aromatic), 3.58 (1H, dd, 6-H), 3.70 (1H, d, 8-H), 5.06 (1H, d, 2-H), 5.3 (1H, bs, exchanges with D_2O, hydroxyl), 5.44 (1H, bs, sharpens to d with D_2O, 4-H), 5.7-6.1 (2H, m, collapses with D_2O to dd at 6.0 integrating to 1H, 3-H and hydroxyl), 6.18 (6H, s, 2 x -OMe); $J_{2,3}$=9.6Hz, $J_{3,4}$=3.6Hz.

2,3-Trans-3,4-cis-dibenzoyloxy-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan (CLXX)

2,3-Trans-3,4-cis-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan-3,4-diol (450mg) in dry pyridine (5ml) was treated with benzoyl chloride (2eqt., 0.5ml) for 18h at room temperature and then heated to 60° for 2h. The mixture was diluted with

ethyl acetate (80ml), washed with 2N hydrochloric acid (2 x 10ml), water (10ml), 2N aqueous sodium hydroxide (10ml), water (10ml) and brine and dried. Evaporation of the solvent left a gum which was triturated with water and extracted with ethyl acetate. The solution was dried and the solvent removed, leaving an oil which crystallised from acetone/ethanol as needles of 2,3-trans-3,4-cis-dibenzoyloxy-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan (420mg, 62%), m.p. 82-84° (Found: C,68.9; H,4.7; N,2.0. $C_{38}H_{31}NO_{10}$ requires: C,69.0; H,4.75; N,2.1%). N.m.r. (τ,$CDCl_3$): 1.82-3.02 (17H, m, aromatic), 3.16-3.38 (3H, m, aromatic), 3.46 (1H, d, 4-H), 4.18 (1H, dd, 3-H), 4.44-4.54 (3H, m, 2-H and $-OCH_2-$), 6.18 (6H, s, 2 x -OMe); $J_{2,3}$=9.6Hz, $J_{3,4}$=3.6Hz.

2,3-Trans-3,4-cis-diacetoxy-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan (CLXXI)

2,3-Trans-3,4-cis-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan-3,4-diol (215mg) in dry pyridine (2ml) was treated with acetic anhydride (2ml) for 3 days. The mixture was evaporated on an oil pump at 40° and the residue was dissolved in ethanol. 2,3-Trans-3,4-cis-diacetoxy-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan (183mg, 72%) separated as needles, m.p. 132-135°, raised on recrystallisation from ethanol to 134-136° (Found: C,62.75; H,5.1; N,2.4. $C_{28}H_{27}NO_9$ requires: C,62.55; H,5.05; N,2.6%). N.m.r. (τ,$CDCl_3$): 1.88 (1H, bd, aromatic ortho to nitro group), 2.14-2.84 (4H, m, aromatic), 2.96-3.50 (5H, m, aromatic), 3.86 (1H, d, 4-H), 4.46-4.60 (3H, m, 3-H and $-OCH_2-$), 4.82 (1H, d, 2-H), 6.14 (6H, s, 2 x -OMe), 7.88 (3H, s, acetyl), 8.16 (3H, s, acetyl); $J_{2,3}$=10.2Hz, $J_{3,4}$=3.6Hz.

Attempted removal of the o-nitrobenzyl group from 2,3-trans-3,4-cis-dibenzoyloxy- and 2,3-trans-3,4-cis-diacetoxy-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan (CLXX) and (CLXXI)

a) 2,3-Trans-3,4-cis-dibenzoyloxy-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan (60mg) in dry dioxan (5ml) in a pyrex tube was irradiated for 12h in a 300nm Rayonet apparatus. Removal of the solvent left an oil which was chromatographed on 1 x 20cm silica p.l.c. plate (eluted with ether). The major band was found by t.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) to be composed of several compounds which gave a red colour with isovanillin.

b) 2,3-Trans-3,4-cis-diacetoxy-7-(o-nitrobenzyloxy)-3',4'-dimethoxyflavan (63mg) irradiated as in (a) but for 18h and worked up in the same way also yielded a mixture (40mg) of compounds which gave a red colour with isovanillin.

2-Hydroxy-4-tetrahydropyranyloxyacetophenone

Resacetophenone (76g) was treated with dihydropyran (90ml, 2.0eqt.) and toluene-p-sulphonic acid monohydrate (0.5g) in dry ether (350ml). After 8h, the reaction was quenched with triethylamine (0.5ml) and the solution was washed with 2N aqueous sodium carbonate (2 x 30ml), dried over anhydrous sodium carbonate and evaporated. The product separated from methanol as prisms of 2-hydroxy-4-tetrahydropyranyloxyacetophenone, (91g, 77%), m.p. 76-78° (lit.,[131] 76-78°).

2'-Hydroxy-4'-tetrahydropyranyloxy-3,4-dimethoxychalcone

2-Hydroxy-4-tetrahydropyranyloxyacetophenone (70g) and veratraldehyde (70g) were stirred in methylated spirit (700ml)

with potassium hydroxide (75g) in water (75ml) until the solid dissolved. After 4 days the mixture was neutralised with 10% acetic acid in water (800ml) and cooled to 0°. The precipitate was recrystallised twice from acetone to furnish orange prisms of 2'-hydroxy-4'-tetrahydropyranyloxy-3,4-dimethoxychalcone (84g, 74%), m.p. 156-158° (Found: C,68.85; H,6.3. $C_{22}H_{24}O_6$ requires: C,68.75; H,6.3%). N.m.r. (τ,$CDCl_3$): -3.3 (1H, s, exchanges with D_2O, hydroxyl), 2.14 (2H, 2d, β-H and 5H), 2.56 (1H, d, α-H), 2.70-2.86 (2H, m, B-ring), 3.10 (1H, d, J=8Hz, B-ring), 3.30-3.46 (2H, m, 3'-H and 5'-H), 4.50 (1H, t, tetrahydropyranyl), 6.04 and 6.08 (6H, 2s, 2 x -OMe), 6.1-6.5 (2H, m, tetrahydropyranyl), 7.95-8.46 (6H, m, tetrahydropyranyl); $J_{\alpha,\beta}$=15.8Hz.

2',4'-Dihydroxy-3,4-dimethoxychalcone

2'-Hydroxy-4'-tetrahydropyranyloxy-3,4-dimethoxychalcone (50g) was dissolved in warm tetrahydrofuran (350ml). Acetic acid (250ml), water (30ml) and toluene-p-sulphonic acid (0.5g) were added and the mixture was stirred for 3h, then poured into ice/water (1.5l).

The precipitate was recrystallised from acetone to furnish 2',4'-dihydroxy-3,4-dimethoxychalcone (34g, 86%) as yellow prisms, m.p. 219-222° (decomp.) (lit.,[132] 203°) (Found: C,68.15; H,5.5. Calculated for $C_{17}H_{16}O_5$: C,68.0; H,5.35%). N.m.r. (τ,$CDCl_3$+$(CD_3)_2SO$): -3.5 (1H, bs, exchanges with D_2O, hydroxyl), 2.04-2.80 (5H, m, aromatic, α-H and β-H), 3.08 (1H, d, 5-H), 3.50-3.66 (2H, m, 3'-H and 5'-H), 6.06 and 6.10 (7H, 2s, 2 x -OMe and hydroxyl).

7-Tetrahydropyranyloxy-3',4'-dimethoxyflav-3-ene (CLXXVII)

2'-Hydroxy-4'-tetrahydropyranyloxy-3,4-dim[illegible]chalcone (11.5g) was stirred with sodium borohydride (2.5g) in dry ethanol (120ml) at 65° until the solution was colourless (ca. 40min). The solvent was evaporated and the solid residue was dried in vacuo over potassium hydroxide and then dissolved in chloroform (150g). Analar acetic acid (8ml) was added cautiously with swirling and the mixture was boiled under reflux for 2h.

After cooling, it was washed with 2N aqueous sodium hydroxide (2 x 40ml), dried and evaporated. The resulting oil was dissolved in benzene and applied to a short column of alumina (150g) made up in benzene. Elution with benzene furnished as the first product from the column 7-tetrahydropyranyloxy-3',4'-dimethoxyflav-3-ene (9.0g, 82%) as a colourless oil which solidified very slowly to a mass of oil and crystals, m.p. 76-82° (Found: C,71.95; H,6.55. $C_{22}H_{24}O_5$ requires: C,71.7; H,6.55%). N.m.r. (τ,$CDCl_3$): 3.00-3.24 (4H, m, aromatic), 3.40-3.60 (3H, m, 6-H, 8-H and 4-H), 4.20 (1H, dd, 2-H), 4.36 (1H, dd, 3-H), 4.68 (1H, bs, tetrahydropyranyl), 6.14 (6H, s, 2 x -OMe), 6.2-6.6 (2H, m, tetrahydropyranyl), 8.00-8.38 (6H, m, tetrahydropyranyl); $J_{2,3}$=3.4Hz, $J_{2,4}$=1.8Hz, $J_{3,4}$=9.4Hz.

5,6-Dihydro-4-methoxy-2H-pyran (CLXXVIII)[100]

2-Chloropropionyl chloride (435 g) was added cautiously to anhydrous aluminium chloride (640g) and dichloromethane (480ml). Ethylene was passed into the liquid until it was no longer absorbed then the mixture was poured into dichloromethane

(450ml), ice (900g) and 2N hydrochloric acid (900ml), the temperature being kept below 20°. The organic phase was separated, washed with water (4 x 500ml), dried and evaporated to leave crude 1,5-dichloropentan-3-one as a brown oil (570g).

Crude 1,5-dichloropentan-3-one (310g) was added during 75min to a vigorously stirred mixture of sodium dihydrogen orthophosphate (dihydrate; 620g), orthophosphoric acid (88%; 115ml) and water (1.2l) at 100°. After a further 2h at 100°, the mixture was cooled and neutralised with sodium hydroxide (260g) in water (650ml). The aqueous layer was decanted and extracted repeatedly with dichloromethane. Evaporation of the solvent furnished tetrahydro-γ-pyrone (CLXXIX) (74g). N.m.r. (τ,$CDCl_3$, 60MHz): 6.10 (2H, t), 7.62 (2H, t); J=6Hz.

Tetrahydro-γ-pyrone (140g) and toluene-p-sulphonic acid (monohydrate; 0.8g) in dry methanol (60ml) were heated under reflux for 30min during the addition of trimethyl orthoformate (190ml). After a further 15min heating, excess of sodium methoxide was added and the mixture was distilled to furnish 4,4-dimethoxytetrahydropyran (142g), b.p. 70-71°/16 torr (lit.,[100] 61-63°/10-11 torr).

4,4-Dimethoxytetrahydropyran (35g) with toluene-p-sulphonic acid (100mg) and trimethyl orthoformate (0.2ml) were distilled through a Nester-Faust NFA-200 spinning band fractionating column until the head temperature reached 125°. Triethylamine (0.3ml) was added to the cooled mixture and distillation afforded 5,6-dihydro-4-methoxy-2H-pyran (CLXXVIII) (19g), b.p. 47°/11 torr (lit.,[100] 50.5°/10-11 torr). N.m.r. (τ,$CDCl_3$, 60MHz): 5.40 (1H, m), 5.80 (2H, t), 6.20 (2H, t), 6.48 (3H, s), 7.80 (2H, m).

2-Hydroxy-4-(4-methoxytetrahydropyranyloxy)-acetophenone (CLXXX)

2,4-Dihydroxyacetophenone (3.0g) and 5,6-dihydro-4-methoxy-2H-pyran (4.0ml, 2eqt.) in dry ether (20ml) were treated with toluene-p-sulphonic acid (monohydrate; 30mg). The solution was shown by t.l.c. (elution with 30% acetone/light petroleum, b.p. 60-80°) to contain a considerable proportion of 2,4-dihydroxyacetophenone after 2h and no detectable decrease after 12h.

The mixture was then washed with aqueous sodium carbonate, dried over sodium carbonate and evaporated to leave an oil which separated from methanol/water as prisms of 2-hydroxy-4-(4-methoxytetrahydropyranyloxy)-acetophenone (1.5g, 29%), m.p. 97-100°, raised on recrystallisation to 99-101° (Found: C,63.05; H,6.7. $C_{14}H_{18}O_5$ requires: C,63.15; H,6.8%). N.m.r. (τ,$CDCl_3$, 60MHz): -2.6 (1H, s, exchanges with D_2O, hydroxyl), 2.34 (1H, d, aromatic), 3.10-3.40 (2H, m, aromatic), 6.28 (4H, bt, tetrahydropyranyl), 6.62 (3H, s, -OMe), 7.46 (3H, s, acetyl), 8.00 (4H, bt, tetrahydropyranyl).

Attempted preparation of 2'-hydroxy-4'-(4-methoxytetrahydropyranyloxy)-3,4-dimethoxychalcone (CLXXXI)

2-Hydroxy-4-(4-methoxytetrahydropyranyloxy)-acetophenone (2.7g) and veratraldehyde (2.2g) in methylated spirit (30ml) were treated with potassium hydroxide (2.0g) in water (2ml). After 4 days the mixture was cooled to 0° and neutralised with 10% acetic acid in water. The resulting yellow gum (4.7g) could not be induced to crystallise. A sample subjected to p.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) afforded a yellow gum which could not be induced to crystallise and was found by t.l.c. (elution with 75% ether/light petroleum,

b.p. 40-60°) to be impure. N.m.r. (τ,$CDCl_3$): 0.2 (1H, s, exchanges with D_2O, hydroxyl), 2.08-2.28 (2H, m, 5-H and β-H), 2.50-3.60 (6H, m, aromatic and α-H), 6.04 and 6.06 (6H, 2s, 2 x -OMe), 6.22 (4H, bt, tetrahydropyranyl), 6.04 and 6.06 (3H, s, -OMe), 7.92 (4H, m, tetrahydropyranyl).

Attempted preparation of 7-Hydroxy-3',4'-dimethoxyflav-3-ene (CLXXXII)

7-Tetrahydropyranyloxy-3',4'-dimethoxyflav-3-ene (120mg) in methanol (5ml) was treated with 2N hydrochloric acid (1 drop). After 10min, t.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated that starting material was absent and one major product had been formed. Dilution with ether (30ml), washing with water (3 x 5ml), drying and evaporation of the solvent furnished an oil which rapidly turned red in air, consisting chiefly of 7-hydroxy-3',4'-dimethoxyflav-3-ene. N.m.r. (τ,$CDCl_3$, 60MHz): 2.86-3.20 (5H, m, aromatic and hydroxyl), 3.36-3.68 (3H, m, aromatic and 4-H), 4.10-4.44 (2H, m, 3-H and 4-H), 6.12 (6H, s, 2 x -OMe).

A sample subjected to p.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) was found not to be significantly purer (t.l.c.).

2,3-Trans-3,4-cis-7-tetrahydropyranyloxy-3',4'-dimethoxyflavan-3,4-diol (CLXXXIII)

7-Tetrahydropyranyloxy-3',4'-dimethoxyflav-3-ene (4.9g) in acetone (50ml) was stirred for 3h with water (40ml), N-methylmorpholine-N-oxide (1.3 hydrate, 2.0g) and osmium tetroxide (40mg).

Water (100ml) and a little sodium sulphite was added and

the mixture was extracted with ethyl acetate (100ml + 3 x 50ml). The organic extract was washed with water (50ml) and brine and dried. Removal of the solvent left a solid which separated from acetone/light petroleum (b.p. 60-80°) as colourless, chromatographically pure needles of 2,3-trans-3,4-cis-7-tetrahydropyranyloxy-3',4'-dimethoxyflavan-3,4-diol (3.6g, 68%), m.p. 143-158°. A sample crystallised from methanol had m.p. 160-164° (Found: C,65.85; H,6.55. $C_{22}H_{26}O_7$ requires: C,65.65; H,6.5%). N.m.r. (τ,$CDCl_3$): 2.78 (1H, d, 5-H), 2.94-3.36 (5H, m, aromatic), 6.64 (1H, bs, tetrahydropyranyl), 5.06 (1H, d, 2-H), 5.32 (1H, t collapses to d with D_2O, 4-H), 6.02 and 6.12 (7H, m and s, 4-H and 2 x -OMe), 6.32-6.44 (2H, m, tetrahydropyranyl), 7.12 (1H, d, exchanges with D_2O, 4-hydroxyl), 7.52 (1H, d, exchanges with D_2O, 3-hydroxyl), 8.02-8.52 (6H, m, tetrahydropyranyl); $J_{2,3}$=9.6Hz, $J_{3,4}$=3.6Hz.

2,3-Trans-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol (CLXXXIV)

2,3-Trans-3,4-cis-7-tetrahydropyranyloxy-3',4'-dimethoxyflavan-3,4-diol (2.6g) in ethyl acetate (100ml) was hydrogenated at atmospheric pressure over 10% palladium on charcoal (1.0g) for 26h. T.l.c. (elution with ether) showed that one major product had been formed.

The catalyst was filtered off and washed with ethyl acetate (2 x 100ml). The organic solution was washed with 2N aqueous sodium hydroxide (20ml), water (20ml) and brine and dried. Removal of the solvent left an oil which was dissolved in dry pyridine (5ml) and dry ether (5ml) and treated with benzoyl chloride (1.0ml) for 24h.

The mixture was diluted with ethyl acetate (300ml),

washed with water (25ml), 2N hydrochloric acid (2 x 25ml), water (25ml) and brine and dried. Removal of the solvent left an oil which was shaken with methanol (30ml) and 2N hydrochloric acid (0.5ml) until it dissolved (ca. 10min). Water (2ml) was added and after a further 20min, the mixture was diluted with ethyl acetate (200ml), washed with water (3 x 30ml) and brine and dried. The solvent was evaporated to leave an oil which was applied to 5 x 1m p.l.c. plates and eluted with 75% ether/ light petroleum, b.p. 40-60°. The major band furnished 2,3-trans-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol (1.85g, 71%) as a colourless oil which could not be induced to crystallise (Found: C,70.75; H,5.5. $C_{24}H_{22}O_6$ requires: C,70.9; H,5.45%). N.m.r. (τ,$CDCl_3$): 2.12 (2H, bd, aromatic ortho to carbonyl), 2.42-2.80 (3H, m, aromatic), 3.00-3.30 (4H, m, aromatic), 3.48-3.64 (2H, m, 6-H and 8-H), 4.46 (1H, bq, 3-H), 4.80 (1H, d, 2-H), 4.9 (1H, bs, exchanges with D_2O, hydroxyl), 6.18 and 6.20 (6H, 2s, 2 x -OMe), 6.74-7.22 (2H, m, 2 x 4-H); $J_{2,3}$=6.6Hz, average $J_{3,4}$=6.0Hz.

2,3-Trans-3',4'-dimethoxyflavan-3,7-diol (CLXXXV)

2,3-Trans-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol (ca. 50mg) and potassium hydroxide (80mg) in methanol (2ml) were heated to 50° for 10min. Acetic acid (0.1ml) was added and the solution was cooled. The precipitate was recrystallised from methanol/ acetone to yield prisms of 2,3-trans-3',4'-dimethoxyflavan-3,7-diol, m.p. 234-235° (Found: C,67.3; H,6.05. $C_{17}H_{18}O_5$ requires: C,67.55; H,6.0%). N.m.r. (τ,$CDCl_3$+$(CD_3)_2SO$): 1.1 (1H, bs, exchanges with D_2O, hydroxyl), 3.00-3.26 (4H, m, aromatic), 3.60-3.78 (2H, m, aromatic), 5.20 (1H, d, exchanges with D_2O, hydroxyl), 5.34 (1H, d, 2-H), 6.0 (1H, 6 lines, 3-H), 6.96-7.34

(2H, m, 2 x 4-H); $J_{2,3}$=7.8Hz, $J_{3,4}$=5.6, 7.8Hz.

2,3-Trans-7,3',4'-trimethoxyflavan-3-ol (CLXXXVI)

A sample of 2,3-trans-3',4'-dimethoxyflavan-3,7-ol (ca. 25mg) in Analar acetone (5ml) stirred with anhydrous potassium carbonate (150mg) and dimethyl sulphate (0.3ml) was heated under reflux for 6h. Dilution with ether (40ml), washing with water (5ml) and 2N aqueous sodium hydroxide (5ml), drying and evaporation of the solvent furnished an oil which was chromatographed on 1 x 20cm p.l.c. plate (eluted with ether). The major band furnished 2,3-trans-7,3',4'-trimethoxy-flavan-3-ol as an oil (ca. 15mg) identified by its n.m.r. spectrum.[28] N.m.r. (τ,$CDCl_3$): 2.96-3.10 (4H, m, aromatic), 3.44-3.54 (2H, m, 6-H and 8-H), 5.32 (1H, d, 2-H), 5.94 (1H, m, 3-H), 6.12 (6H, s, 2 x -OMe), 6.26 (3H, s, -OMe), 6.8-7.24 (2H, m, 2 x 4-H), 8.4 (1H, bs, hydroxyl); $J_{2,3}$ = 8 Hz.

2,3-Trans-3,4-cis-dibenzoyloxy-3',4'-dimethoxyflavan-7-ol (CLXXII)

2,3-Trans-3,4-cis-7-tetrahydropyranyloxy-3',4'-dimethoxy-flavan-3,4-diol (400mg) in dry pyridine (5ml) was treated with benzoyl chloride (1.5eqt., 0.35ml) at 50° for 30min then left overnight at 20°. T.l.c. (elution with 75% ether/light petroleum, b.p. 40-60°) indicated the formation of a single product.

The mixture was diluted with ethyl acetate (40ml), washed with water (10ml), N hydrochloric acid (2 x 10ml) and brine and dried. The solution was passed through a column of chromato-graphic alumina (30g), washed with N hydrochloric acid (2 x 5ml) and water (5ml) and dried. Removal of the solvent left a

chromatographically pure oil (ca. 500mg).

A sample of this oil (ca. 50mg) in methanol (2ml) containing toluene-p-sulphonic acid (1.0mg) was found by t.l.c. (elution with ether) after 12h to have reacted almost completely to form one major product. The mixture was diluted with toluene (30ml), washed with water (3 x 5ml) and brine and dried. Removal of the solvent left an oil shown by n.m.r. to be composed chiefly of 2,3-trans-3,4-cis-dibenzoyloxy-3',4'-dimethoxyflavan-7-ol. N.m.r. (τ,$CDCl_3$): 1.90-3.02 (13H, m, aromatic), 3.20 (1H, d, 5'-H), 3.46-3.58 (3H, m, 6-H, 8-H and 4-H), 4.22 (1H, dd, 3-H), 4.46 (1H, s, exchanges with D_2O, hydroxyl), 4.52 (1H, d, 2-H), 6.20 (6H, s, 2 x -OMe); $J_{2,3}$=10.0Hz, $J_{3,4}$=3.4Hz.

Rapid p.l.c. on silica (elution with ether) did not bring about further purification, as judged by t.l.c.

Chapter 4

Reaction of 4β-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan with 7-hydroxy-3',4'-dimethoxyflavanone

4β-(p-Nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (250mg) and 7-hydroxy-3',4'-dimethoxyflavanone (1.0g) in dry pyridine (5ml) were heated to 40° for 3 days. The mixture was diluted with ether (200ml), washed with 2N aqueous sodium hydroxide (3 x 20ml) and water (20ml) and dried.

The solvent was evaporated and the résidual gum was dissolved in chloroform (10ml) and methanol (10ml), cooled to -15° and treated with sodium borohydride (0.3g). After 12h at 0°, the solution was poured into water (50ml), extracted into ether (4 x 20ml), washed with water (10ml), dried and evaporated. The resulting gum was applied to 1 x 1m alumina p.l.c. plate and eluted twice with ether. The major band furnished 7-(5,7,3',4'-tetramethoxyflavan-4α-yloxy)-3',4'-dimethoxyflavan-4β-ol (175mg, 52%) as a colourless foam (Found: C,69.15; H,6.4. $C_{36}H_{38}O_{10}$ requires: C,68.55; H,6.05%). N.m.r. (τ,$CDCl_3$): 2.60 (1H, d, J=9Hz, 5-H), 3.02-3.40 (8H, m, aromatic), 3.88 and 3.92 (2H, 2d, A-ring of upper flavan), 4.48 (1H, bt, $J_{3,4}+J_{3*,4}$=6Hz, 4-H of upper flavan), 4.78 (1H, dd, $J_{2,3}$=2Hz, $J_{2,3*}$=12Hz, 2-H), 4.86-5.12 (2H, m, heterocyclic rings), 6.18 (12H, s, 4 x -OMe), 6.28 (6H, s, 2 x -OMe), 7.46-8.20 (5H, m, 4 x 3-H and hydroxyl (exchanges with D_2O)). m/e (110°): 328(100), 284(90), 164(79), 327(59), 283(48), 253(31).

A sample of this flavanol (58mg) in dry pyridine (0.5ml) was treated with acetic anhydride (0.5ml) for 16h. Removal of volatile matter on a rotary oil pump at 50° left a gum which was chromatographed on 1 x 20cm silica p.l.c. plate (eluted

with ether) to furnish 7-(5,7,3',4'-tetramethoxyflavan-4α-yloxy)-4β-acetoxy-3',4'-dimethoxyflavan (CXC) (60mg) as a colourless foam (Found: C,68.4; H,6.3. $C_{38}H_{40}O_{11}$ requires: C,67.85; H,6.0%). N.m.r. (τ,$CDCl_3$): 2.66-3.38 (9H, m, aromatic), 3.78-3.94 (3H, m, A-ring of upper flavan and 4-H of lower flavan, $J_{3,4}+J_{3^*,4}$=16Hz), 4.46 (1H, bt, $J_{3,4}+J_{3^*,4}$=6Hz, 4-H of upper flavan), 4.78 and 4.90 (2H, 2 overlapping dd, 2 x 2-H), 6.14 (12H, bs, 4 x -OMe), 6.24 (6H, s, 2 x -OMe), 7.28-8.02 (7H, m overlapping s at 7.80, 4 x 3-H and acetyl). m/e (110°): 328(100), 327(48), 284(32), 191(28), 313(25), 297(23).

Reaction of 4β-(p-nitrophenoxy)-5,7,3',4'-tetramethoxyflavan with 2,3-trans-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol

4β-(p-Nitrophenoxy)-5,7,3',4'-tetramethoxyflavan (330mg) and 2,3-trans-3-benzoyloxy-3',4'-dimethoxyflavan-7-ol (1.7g) in dry pyridine (4ml) were heated to 40° for 3 days. The mixture was diluted with ether (200ml), washed with 2N aqueous sodium hydroxide (3 x 20ml), water (20ml) and brine and dried. Removal of the solvent left an oil which was applied to 2 x 1m silica p.l.c. plates and eluted 3 times with 60% ether/light petroleum (b.p. 40-60°). The major band (195mg) was left on the plate overnight and then found to have undergone partial decomposition (t.l.c.). Chromatography on 2 x 20cm p.l.c. plates (eluted with chloroform) furnished 2,3-trans-3-benzoyloxy-7-(5,7,3',4'-tetramethoxyflavan-4α-yloxy)-3',4'-dimethoxyflavan (CXCI) as a colourless gum (51mg, 10%) (Found: C,70.25; H,6.0. $C_{43}H_{42}O_{11}$ requires: C,70.3; H,5.75%). N.m.r. (τ,$CDCl_3$): 2.08 (2H, bd, aromatic ortho to carbonyl group), 2.42-2.78 (4H, m, aromatic), 2.92-3.34 (8H, m, aromatic), 3.82 and 3.88 (2H, 2d,

A-ring of upper flavan), 4.44 (2H, bs, 4-H of upper flavan + 3-H of lower flavan), 4.64-4.82 (2H, m, 2 x 2-H), 6.12, 6.14, 6.16, 6.20, 6.22 and 6.24 (18H, 6s, 6 x -OMe), 6.80-7.00 (2H, m, 2 x 4-H of lower flavan), 7.42-7.96 (2H, m, 3H and 3*-H of upper flavan). m/e (C.I. by methane): 285(100), 123(90), 151(51), 105(41), 284(27), 329(21).

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