SYNTHETIC APPROACHES TO PREPHENATE ANALOGUES AND PODOPHYLLOTOXIN

by

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To my mother

This thesis was my own composition and unless otherwise stated the results described are original. They have not been previously submitted, in whole or in part, for any degree at this or any other university.

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The provision of a Research Studentship by the Science and Engineering Research Council is gratefully acknowledged.

Finally, I wish to thank Victoria for her patience and support.

Courses Attended

While working on this thesis I attended the following courses:

Spectroscopy	Various Lecturers
Application of X-ray Crystallography	Various Lecturers
Carbohydrates	Professor R. Ramage
Modern Synthetic Methods in Organic Chemistry	Dr. G. Tennant
Nuclear Magnetic Resonance Spectroscopy	Dr. I. Sadler
Current Topics in Organic Chemistry	Various Lecturers
Organic Departmental Seminars	Various Lecturers

Abstract

Attempts to synthesize analogues of prephenate which are potentially capable of acting as substrate inhibitors are described. These involved a general route in which the α-keto acid side-chain was protected until late in the synthesis as an ylidenedioxolanone group. A synthetic approach to the cytotoxic agent podophyllotoxin is also described. A number of esters of 2,3-epoxy-3-(3,4-methylenedioxyphenyl)propan-1-ol were prepared and their potential for undergoing intramolecular epoxide opening with ring closure to form lactones was examined. Such cyclizations were found to be effective in the case of β-keto esters when sodium hydride was used as a base.

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P A R T A

SYNTHETIC APPROACHES TO PREPHENATE ANALOGUES

Chapter 1

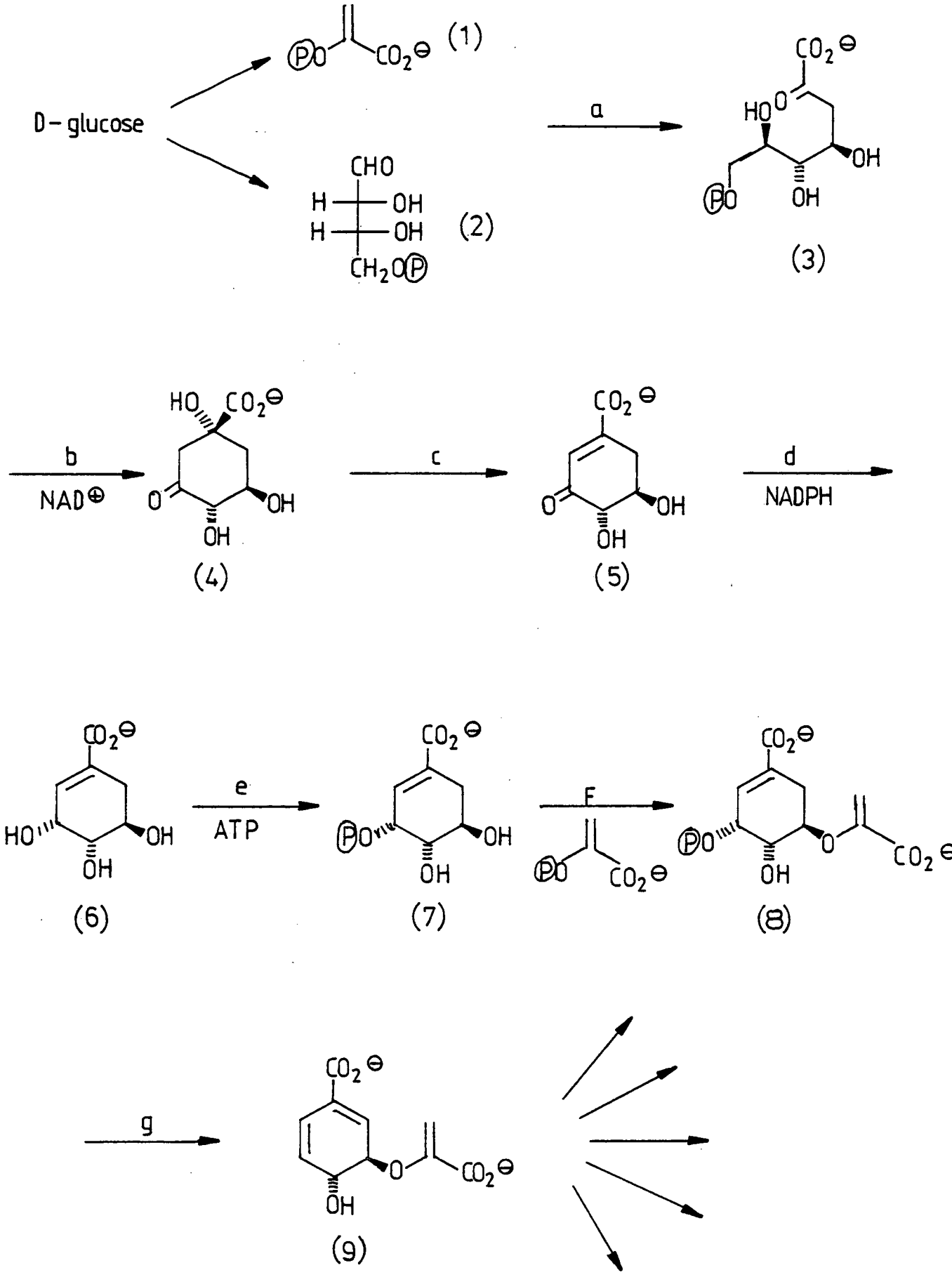
INTRODUCTION

1.1 The Shikimate Pathway

The shikimate pathway (Scheme 1) occurs in plants and micro-organisms and is an important source of a vast variety of aromatic compounds in nature[1-3]. The pathway transforms glucose, in an eight step sequence known as the common pathway, to chorismate (9), from which five major biosynthetic routes diverge. In three of these the aromatic amino acids phenylalanine (15), tyrosine (16) and tryptophan (18) are formed, and the other two lead to the isoprenoid quinones (which are involved in respiratory and photosynthetic electron transport) and the folate coenzymes (which are involved in biosynthetic one carbon fragment transfers). The route has been established over the past thirty-five years, beginning with experiments by Davis[4] with auxotrophic mutants, and it derives its name from shikimic acid (6), the intermediate which was the first to be identified as a member of the pathway[5].

In the first step phosphoenolpyruvate (1) and D-erythrose-4-phosphate (2), both derived from D-glucose, are condensed to form 3-deoxy-D-arabinoheptulosonic acid (DAHP) (3) which then undergoes a formal intramolecular aldol condensation to give 3-dehydroquinate (4). This, the first cyclic intermediate, is dehydrated to 3-dehydroshikimate (5) which is reduced to shikimate (6) and then phosphorylated to shikimate-3-phosphate (7). The next step, reaction with a unit of phosphoenolpyruvate to give 5-enolpyruvyl-shikimate-3-phosphate (EPSP) (8), has attracted considerable attention because the enzyme responsible, EPSP synthetase, is selectively and powerfully inhibited by the commercial

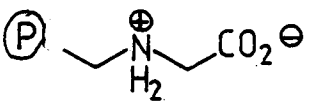
Scheme 1



(cont. on Page 3)

Scheme 1 (cont.)

a) DAHP synthetase
b) 3-dehydroquinate synthetase
c) 3-dehydroquinate dehydratase
d) 3-dehydroshikimate reductase
e) shikimate kinase
F) 5-enolpyruvylshikimate-3-phosphate synthetase
g) chorismate synthetase

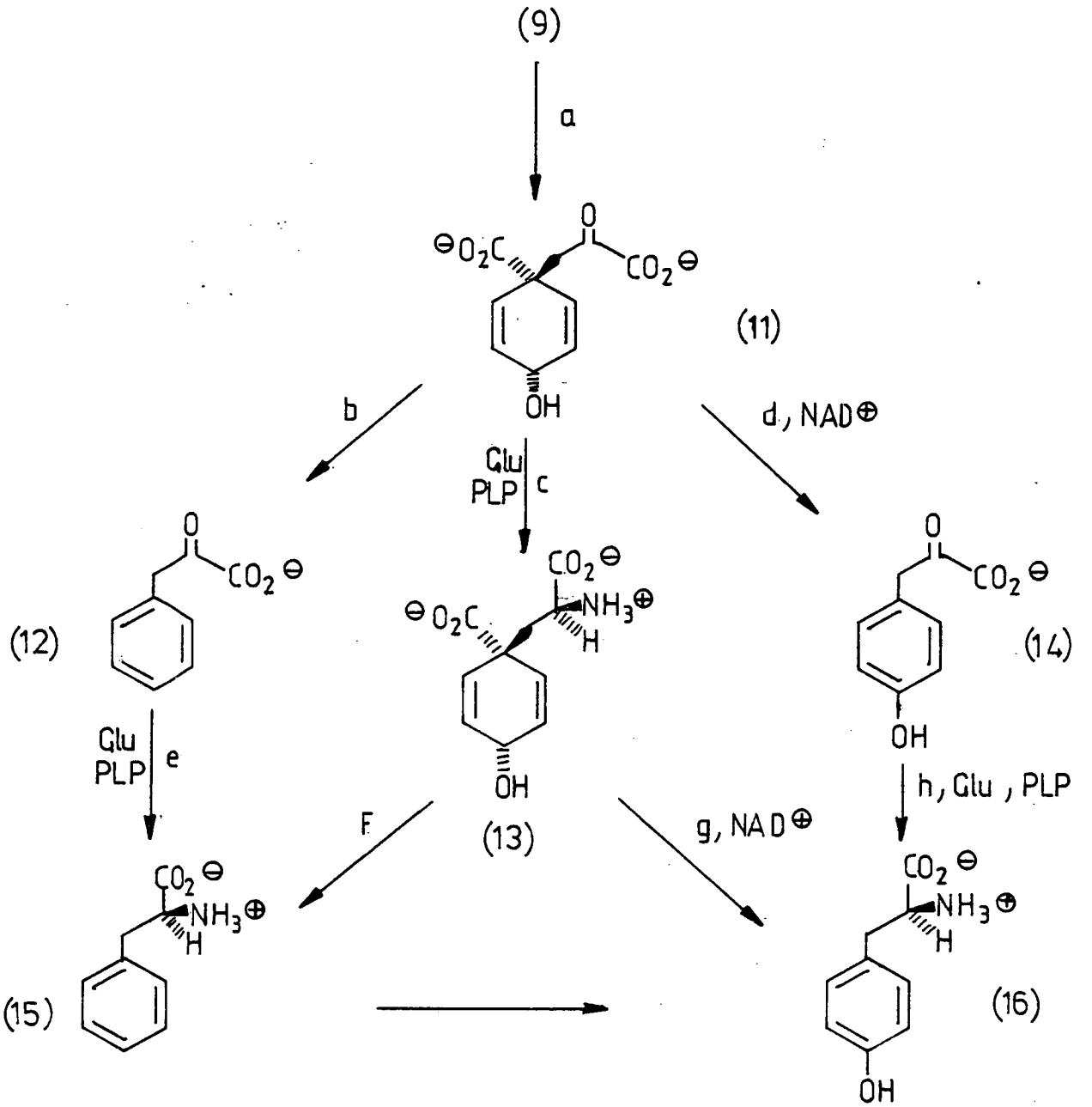


(10)

herbicide glyphosphate (10). In the next step a 1,4-elimination affords the branch point intermediate chorismate (9), which must rank as one of the most significant compounds in intermediary metabolism. The part of the pathway leading to phenylalanine (15) and tyrosine (16) proceeds via an initial [3,3]-sigmatropic rearrangement catalysed by chorismate mutase to give prephenate (11), and thus a molecule with a plane of symmetry is generated from one which is optically active. In most organisms prephenate is converted to phenylalanine by a decarboxylative dehydration (mediated by prephenate dehydratase) to give phenylpyruvic acid (12). This process also proceeds rapidly *in vitro* in acid. Transamination then gives phenylalanine (15), but reversal of this sequence has occasionally been observed, i.e. transamination of prephenate to give arogenate (13), followed by decarboxylative dehydration. Some higher plants and most micro-organisms synthesize tyrosine (16) by oxidative decarboxylation of prephenate to give p-hydroxyphenylpyruvic acid (14) (mediated by prephenate dehydrogenase) which undergoes transamination, but again reversal of this sequence has been observed, i.e. transamination to give arogenate (13) followed by oxidative decarboxylation. Also, plants and micro-organisms derive tyrosine by hydroxylation of phenylalanine (Scheme 2). The remaining aromatic amino acid, tryptophan (18), is formed from chorismate in several stages via anthranilate (17) (Scheme 3).

The most important regulation point in the common pathway is the first reaction, formation of DAHP (3),

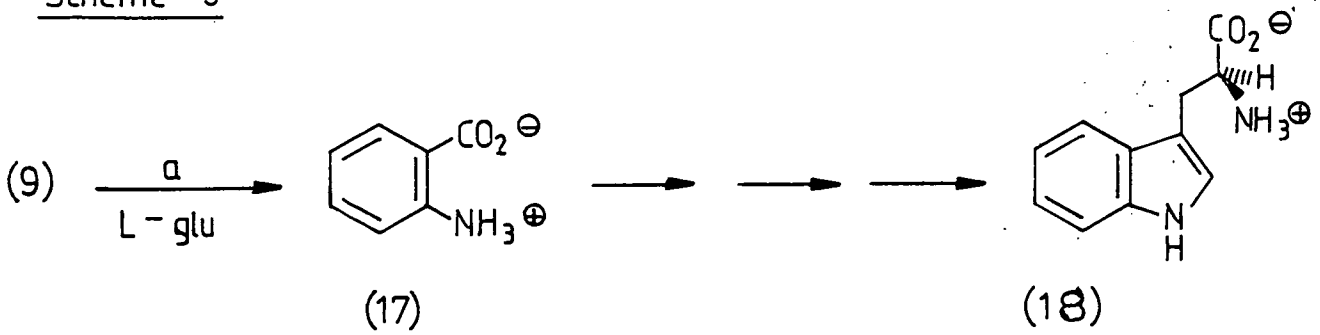
Scheme 2



PLP = pyridoxal 5'-phosphate
Glu = glutamate

a) chorismate mutase
b) prephenate dehydratase
c) prephenate aminotransferase
d) prephenate dehydrogenase
e) phenylpyruvate aminotransferase
F) arogenate dehydratase
h) 4-hydroxyphenylpyruvate aminotransferase
g) arogenate dehydrogenase

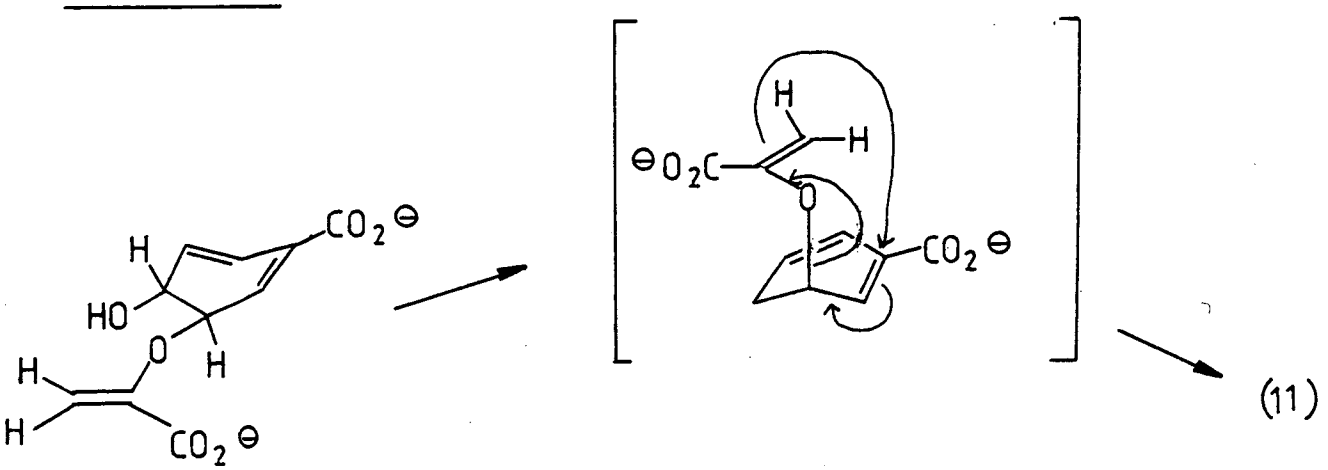
Scheme 3



(17) (18)

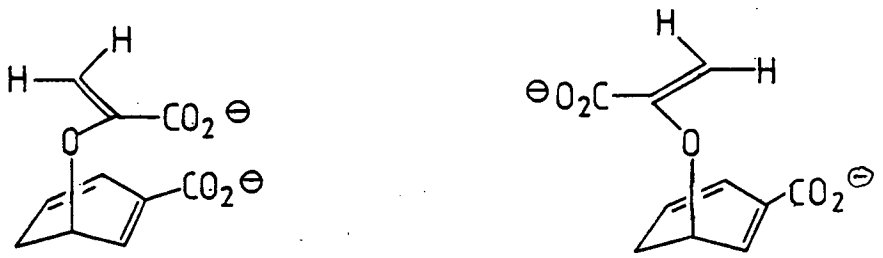
a) anthranilate synthetase

Scheme 4



(19)

Scheme 5



Boat Chair

which in general is catalysed by three DAHP synthetase isoenzymes. Each of these is subject to feedback inhibition by one of phenylanaline, tyrosine or tryptophan. Normally the rest of the common pathway is not controlled by later intermediates, but the metabolism of chorismate (9) into the aromatic amino acids is very closely regulated by the levels of these end products (see Section 1.2).

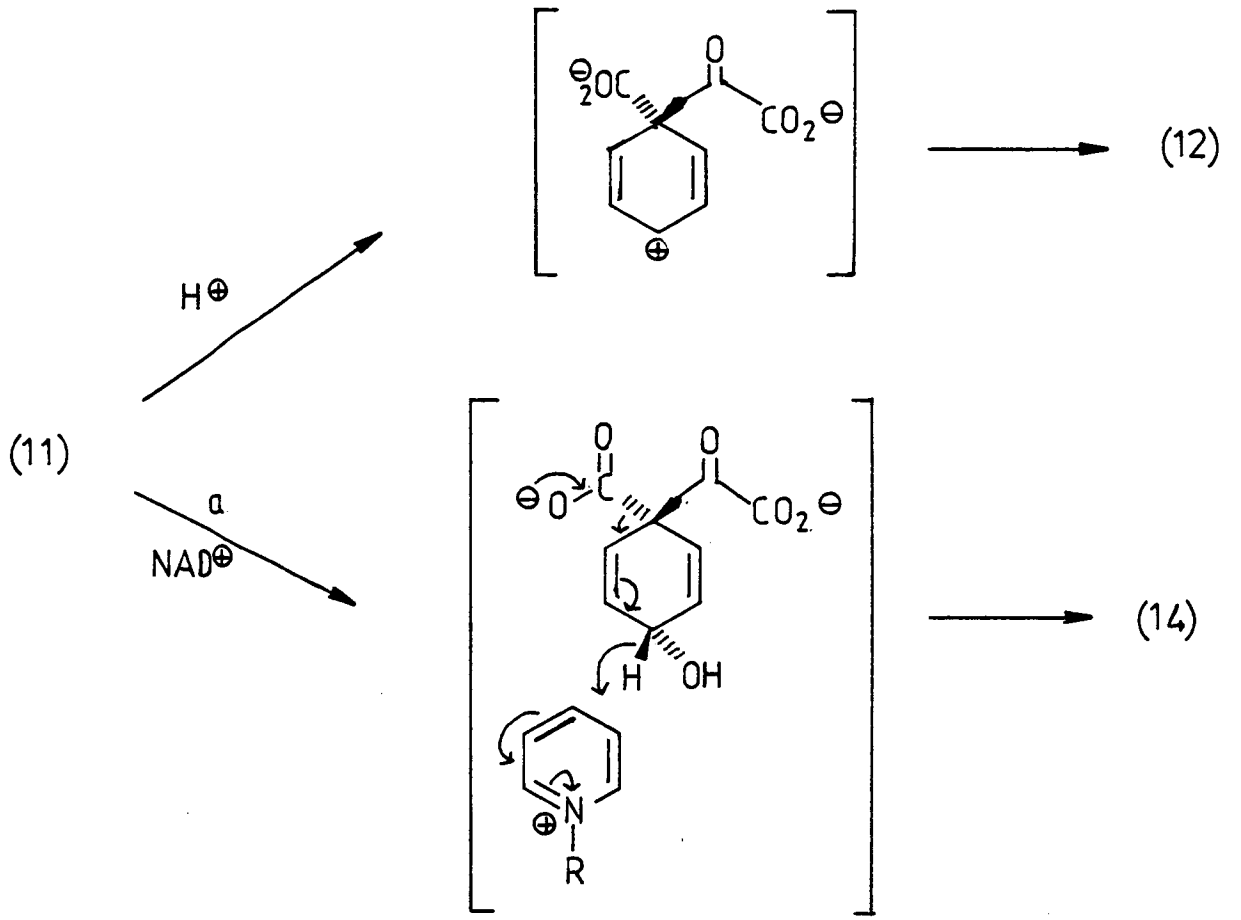
Reviews on the enzymology[6] and biosynthetic aspects[7] of the pathway have recently appeared.

1.2 Enzymology of Prephenate Metabolism

The Claisen rearrangement in which chorismate (9) is transformed into prephenate (11) is very facile even in free solution, but chorismate mutase accelerates it by a factor of 1.9×10^6 [8]. Recent work, particularly by Knowles[9], suggests that chorismate binds to the enzyme in its more stable equatorial conformation (19) and then, in a slow step, undergoes a conformational change in which the enolpyruvyl group is placed in a pseudoaxial position for subsequent bond rearrangement (Scheme 4). Further work done independently by Knowles[10,11] and Floss[12] has shown that both the enzyme-catalysed and thermal reactions proceed via a chair transition state (Scheme 5). The non-enzymatic, acid-catalysed decarboxylation of prephenate (11) has been shown to be a stepwise process[13] with a carbonium ion intermediate , whereas the enzymatic conversion to p-hydroxyphenylpyruvate (14) appears to be a concerted process (Scheme 6)[13].

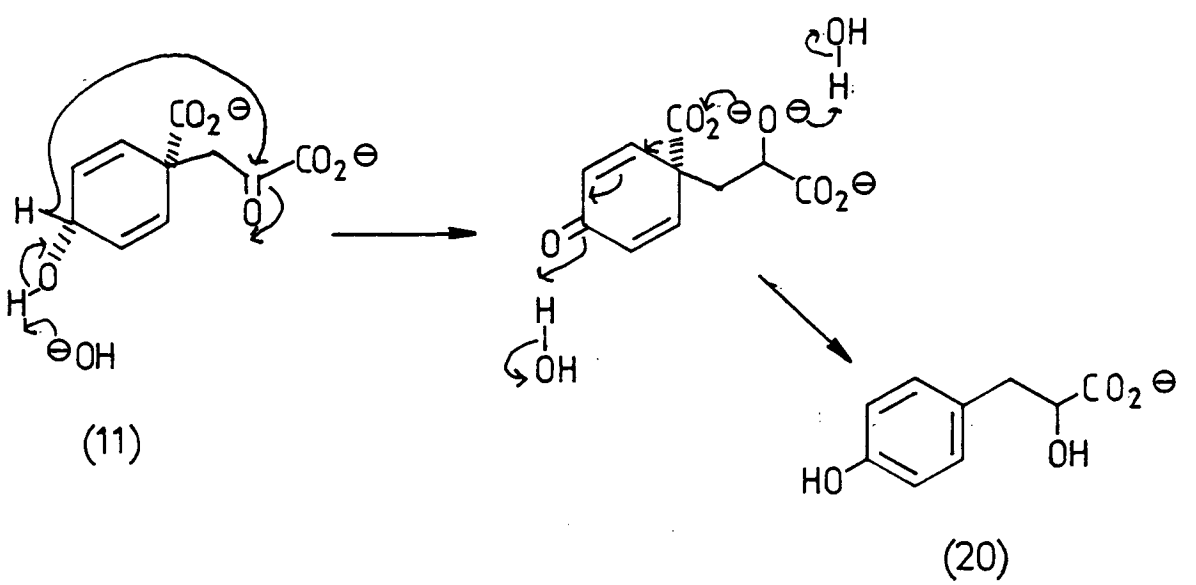
The nature and regulation of the enzymes which convert chorismate (9) into phenylalanine (15) and tyrosine (16) varies somewhat between species. In *Escherisichia coli*, *Salmonella typhimurium* and *Aerobacter aerogenes* enzyme complexes catalyse the first two steps, the P-protein forming phenylpyruvate (12) and the T-protein 4-hydroxy-phenylpyruvate (14). The P-protein is a single, bifunctional enzyme with distinct and separate sites for chorismate mutase and prephenate dehydrogenase activities. Both of these are subject to feedback control by phenyl-alanine in *S.typhimurium* and *A.aerogenes*, but only the

Scheme 6



a) 4-hydroxyphenylpyruvate dehydrogenase

Scheme 7



latter activity is affected in *E.coli*. Phenylalanine also represses P-protein synthesis in *E.coli* and *A.aerogenes*. Prephenate (11) has been shown to dissociate from the enzyme in *E.coli;* it then reassociates prior to decarboxylation[14]. The T-protein is also a single, bifunctional enzyme, but here the active sites are very close and may overlap. Tyrosine inhibits only the dehydrogenase activity in *E.coli* and *A.aerogenes*, but in *S.typhimurium* the mutase activity is also diminished. Synthesis of the T-protein in *E.coli* and *A.aerogenes* is also repressed by tyrosine.

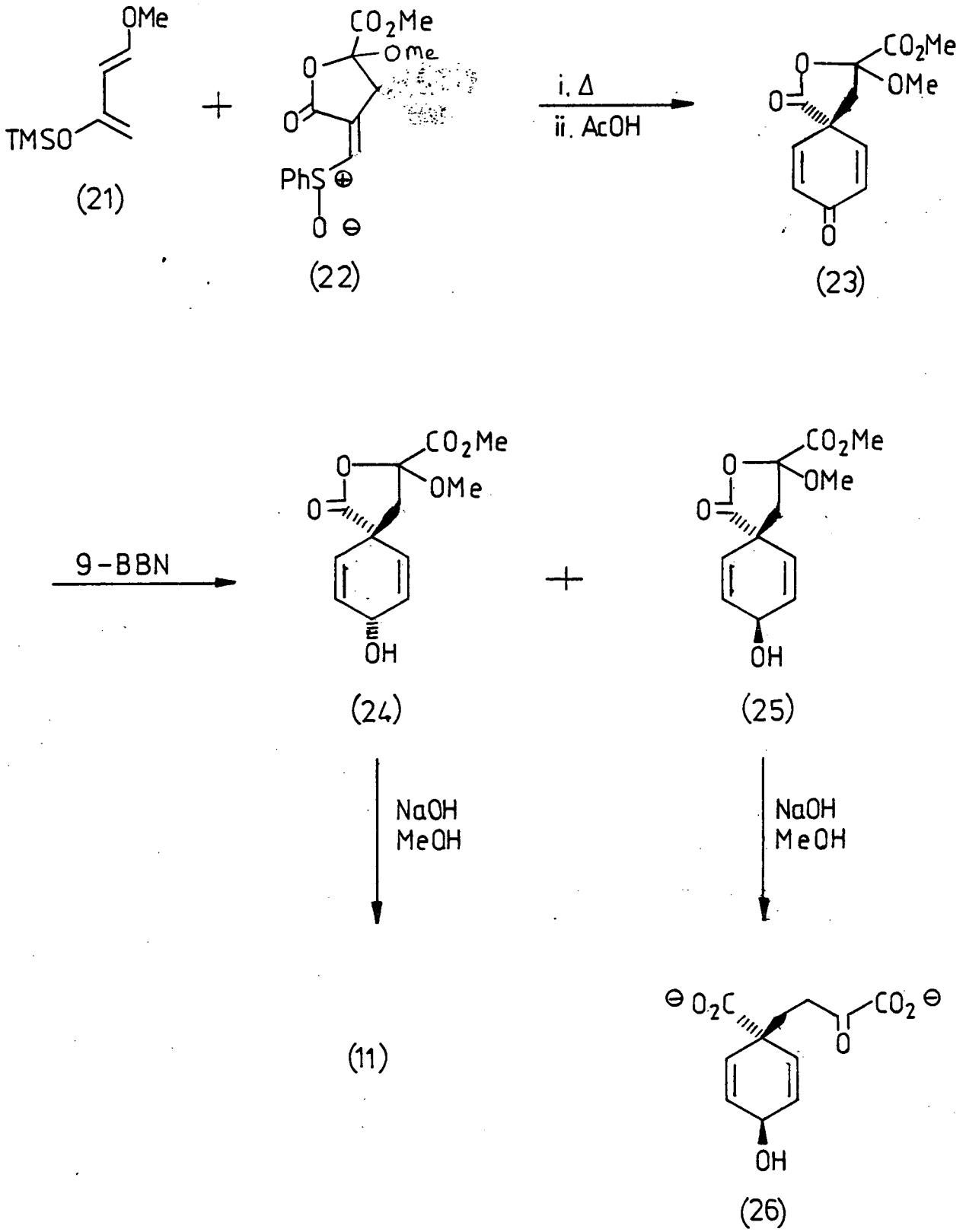
In some organisms the enzymes utilizing chorismate and prephenate are separable. *Neurospora crussa* contains a single chorismate mutase which is uncomplexed with either of the prephenate enzymes. Its activity is inhibited by phenylalanine and tyrosine and enhanced by tryptophan (18). In yeast there are two chorismate mutases, both of which are separable from their respective prephenate dehydratase and prephenate dehydrogenase activities. The latter enzymes are subject to inhibition by phenylalanine and tyrosine respectively.

1.3 Synthesis of Prephenate

Prephenic acid (11) was first isolated from *E.coli* mutants which were unable to carry out its aromatization[15]. Its structure was assigned in 1954 by Davis and Weiss[15], with the relative stereochemistry being deduced by Plieninger[16] in 1961; the cis relationship between the 1-carboxyl and 4-hydroxyl groups has since been confirmed by X-ray work[17]. As already mentioned decarboxylation occurs very rapidly even in mild acid[18], and although it is more stable under basic conditions heating in dilute alkali results in formation of 4-hydroxyphenyllactic acid (20). The latter reaction has been demonstrated to involve a 1,6-hydride transfer[17] (Scheme 7).

Only four total syntheses of prephenate (11) have appeared since Plieninger's[19] preparation of impure barium prephenate in 1962. The acid labile nature of the molecule dictates that the final step must be carried out under basic conditions, the salt thus being isolated. Thus the synthesis of Danishefsky[17] led to a final stage in which a cyclic acylhemiacetal group, which protected both the side-chain keto and quaternary carboxyl groups, was removed by mild saponification (Scheme 8). The cyclohexadiene ring system was constructed via a Diels Alder reaction between a functionalized diene (21) and a dienophile (22) in which the protected side-chain is already present. The cycloadduct was subjected to *in situ* elimination and acidolysis to yield the cyclohexadienone (23), and reduction with 9-BBN gave a mixture of epimeric alcohols (24) and (25) in the ratio 3:2. These were

Scheme 8

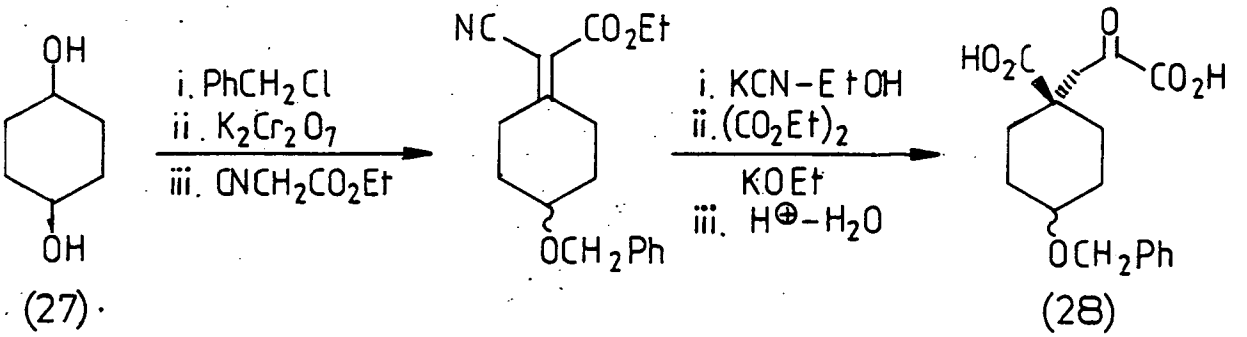

OMe
TMSO
(21)
CO2Me
OMe
O
O
PhS⊕
O ⊖
(22)
i. Δ
ii. AcOH
CO2Me
OMe
O
O
(23)
9-BBN
CO2Me
OMe
O
O
OH
(24)
CO2Me
OMe
O
O
OH
(25)
NaOH
MeOH
NaOH
MeOH
(11)
⊖ O2C
CO2 ⊖
O
OH
(26)

separated chromatographically and individually deprotected using methanolic sodium hydroxide to give disodium prephenate (11) and epiprephenate (26) respectively.

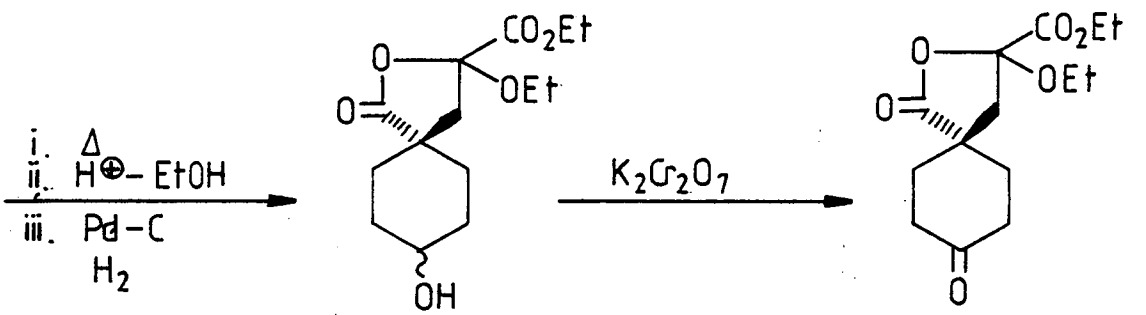
Plieninger[20] (Scheme 9) used exactly the same protecting group strategy in an alternative synthesis, which started with 1,4-cyclohexanediol (27). This was transformed over several stages into the keto diacid (28), which formed the protected lactol (29) on heating and treatment with acidic ethanol, followed by deprotection of the alcohol. After oxidation to the ketone (30) two consecutive selenations and selenoxide eliminations gave the cyclohexadienone (31). As in Danishefsky's route this could be reduced by 9-BBN and the resulting epimeric alcohols separately deprotected to give the disodium salts of prephenate (11) and epiprephenate (26).

The synthesis of Berchtold et al[21] differs from the others in that it is biomimetic, the final prephenate precursor arising from a synthetic chorismate derivative (Scheme 10). Thus bisallylic bromination of methyl cyclohexanecarboxylate (32) followed by debromination gave the 1,3-cyclohexadiene (33). This was oxidized to give an epimeric mixture of epoxides (34) which were isomerized together to the epoxy alcohol (35), from which the malonate (36) was obtained. The enol ether (37) was formed via the Mannich base, which was quaternized and eliminated, and then regioselective epoxide opening with phenylselenide followed by selenoxide elimination gave dimethyl chorismate (38). This underwent thermal rearrangement to dimethyl prephenate (39), and saponification gave disodium prephenate (11).

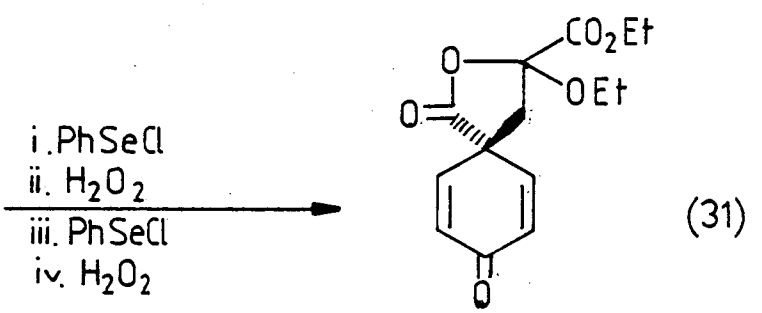
Scheme 9



(27) (28)



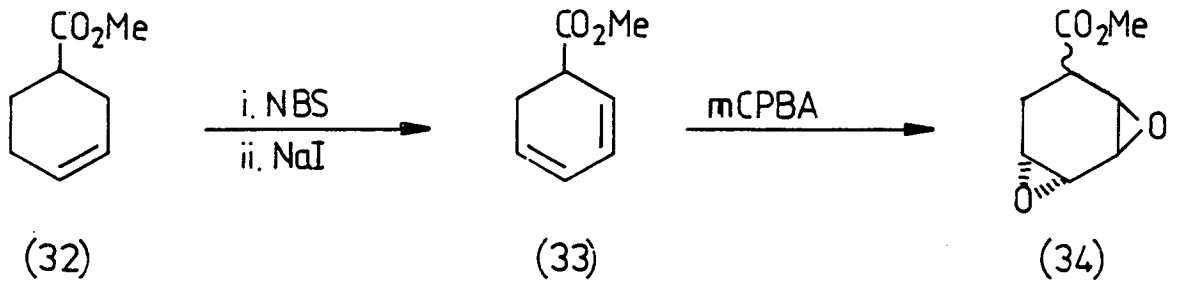
(29) (30)



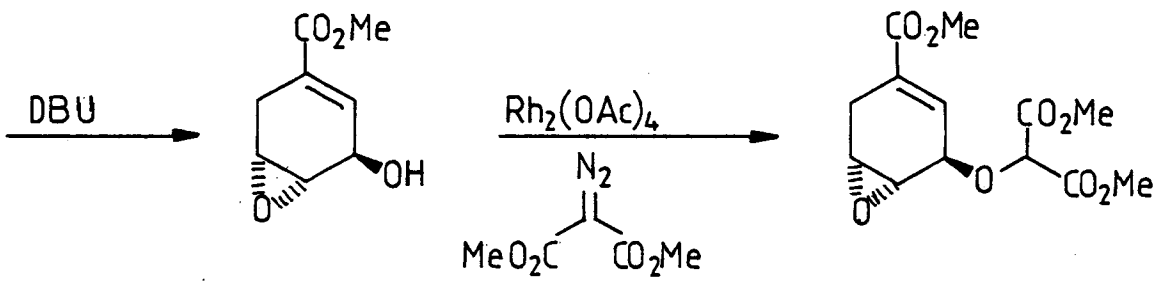
(31)

(11) (26)

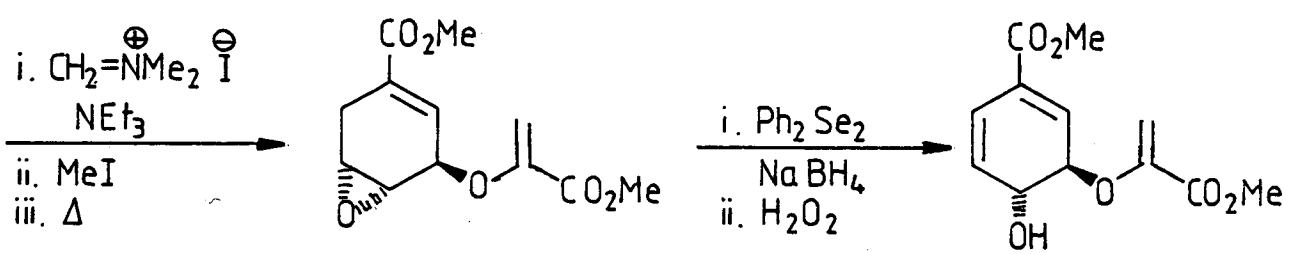
Scheme 10



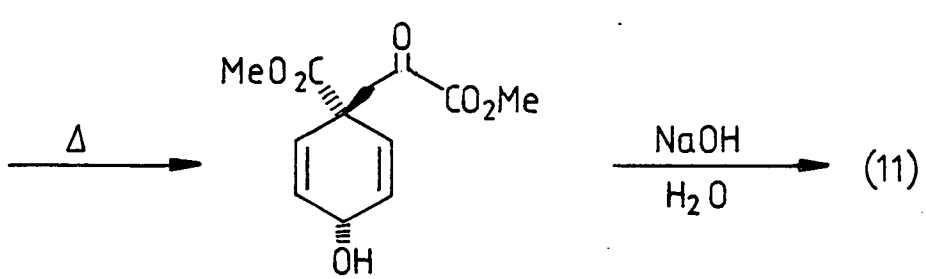
(32) (33) (34)



(35) (36)



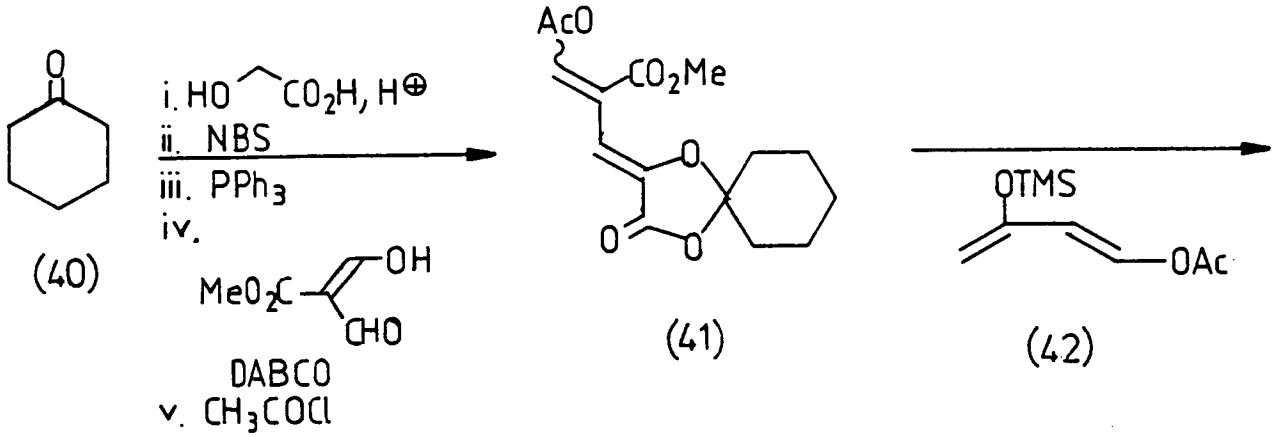
(37) (38)

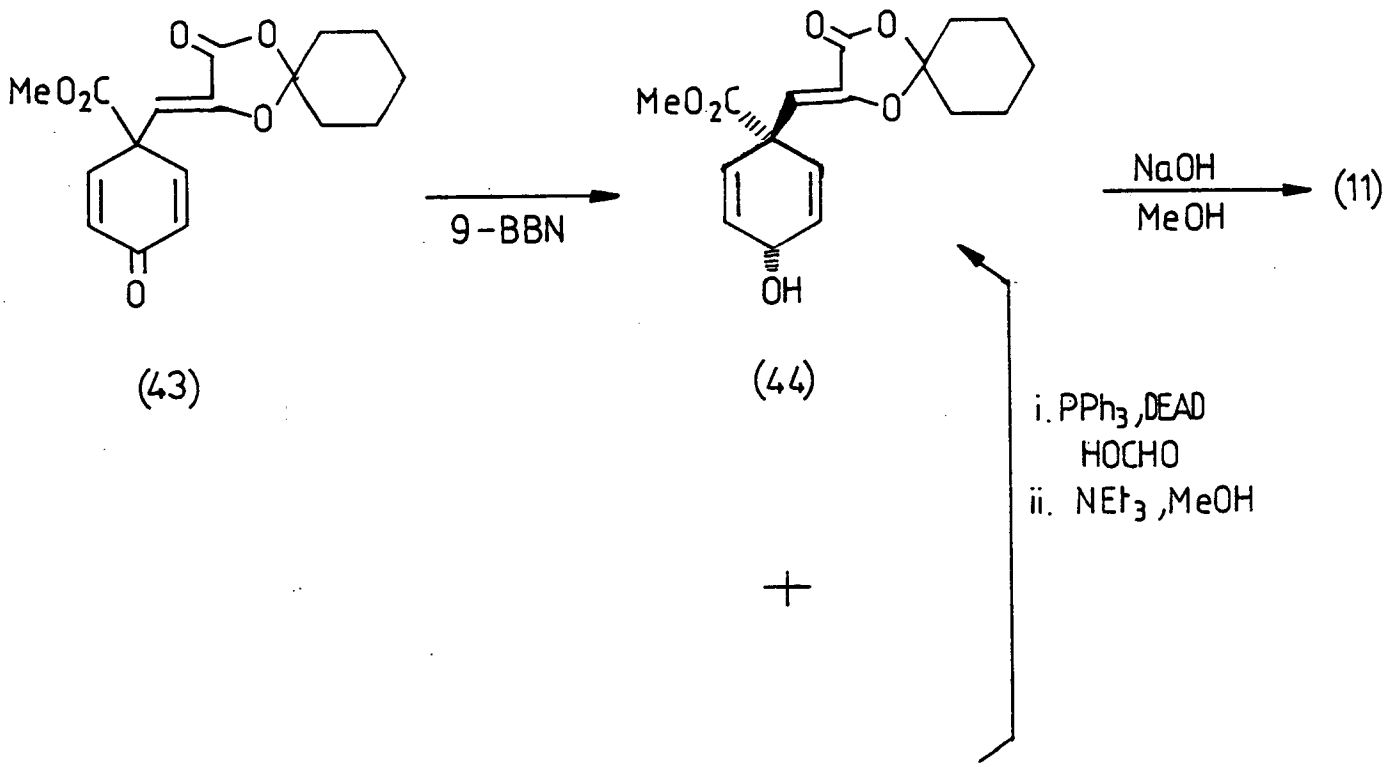


(39) (11)

The most recently published synthesis is that of Ramage and MacLeod[22]. Here the α-keto acid side chain function was protected as an ylidenedioxolanone, a group which is suitably base-labile for the final deprotection (Scheme 11). As in Danishefsky's route[17] the cyclohexadiene ring was constructed using a Diels Alder reaction. The dienophile fragment (41) carrying the masked side chain was formed from cyclohexanone (40), but reaction with Danishefsky's diene (21) gave a disappointing yield of cyclohexadienone (43). This was attributed to incomplete methanol elimination from the initially formed cycloadduct. Use of the acetoxydiene (42), however, gave subsequent efficient elimination of two equivalents of acetic acid from the cycloadduct to afford the cyclohexadienone (43) which was reduced with 9-BBN to give a 3:5 mixture of epimeric alcohols (44) and (45). These were individually hydrolysed to disodium prephenate (11) and epiprephenate (26) respectively. The yield of the former could be increased by subjecting the protected epiprephenate precursor alcohol (45) to a Mitsonobu inversion, thus forming more of the epimer (44) required for deprotection to prephenate.

Scheme 11

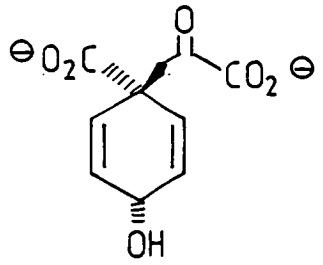

(40)
i. HO CO2H, H⊕
ii. NBS
iii. PPh3
iv.
MeO2C OH
CHO
DABCO
v. CH3COCl
AcO
CO2Me
(41)
OTMS
OAc
(42)


MeO2C
(43)
9-BBN
MeO2C
OH
(44)
NaOH
MeOH
(11)
i. PPh3, DEAD
HOCHO
ii. NEt3, MeOH
MeO2C
OH
(45)
NaOH
MeOH
(26)

Chapter 2

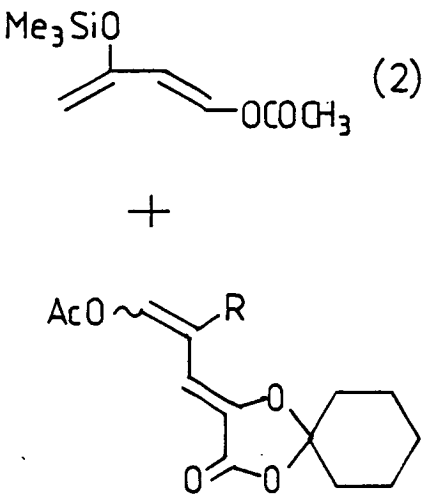
DISCUSSION

There is currently intense interest in designing syntheses of primary metabolites of the shikimate pathway which can be adapted to prepare structural analogues capable of inhibiting the enzymes of the pathway. This has arisen largely because it is recognized that since the pathway is utilized by plants and micro-organisms, but not by mammals, there is considerable potential for developing selective herbicidal and bacteriocidal agents which are non-toxic to animals[23]. Among the many important end-products of the pathway are the amino acids phenylalanine and tyrosine, which are obtained by aromatization of the common intermediate prephenate (1), processes mediated by the enzymes prephenate dehydratase and prephenate dehydrogenase respectively (see Chapter 1, Scheme 2). Our aim was to synthesize compounds related to prephenate (1) which may act as inhibiting substrate analogues, and to achieve this by modification of the route by which Ramage and MacLeod recently prepared[22] disodium prephenate itself (see Chapter 1, Scheme 11). This involved protection of the α-keto acid group in the side-chain until late in the synthesis as a base-labile ylidenedioxolanone group. The cyclohexadiene ring was constructed using a Diels Alder reaction between the suitably functionalized diene (2) and a dienophile (3) carrying both the protected side-chain and the eventual spiro carboxylate group (Scheme 1). Based on this the targets selected for synthesis were those in which the ring carboxylate was replaced either by a methyl phosphonate (6) or by a tetrazole (7), and that in which the hydroxyl was replaced by an amino group (8). The



(1)

Scheme 1

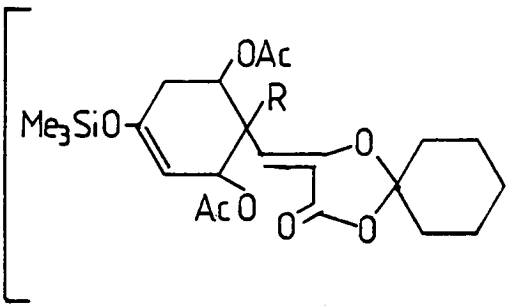


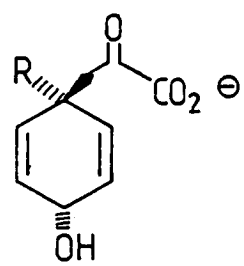
(2)

(3) R = $-CO_2Me$

(4) R = $-P(=O)(OMe)OMe$

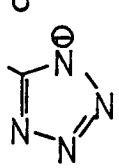
(5) R = $-CN$

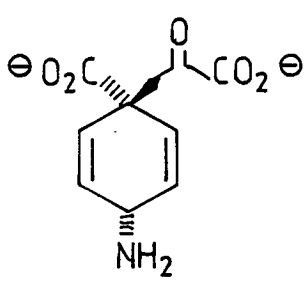




(1) R = $-CO_2Me$

(6) R = $-P(=O)(O^{\ominus})OMe$

(7) R = 

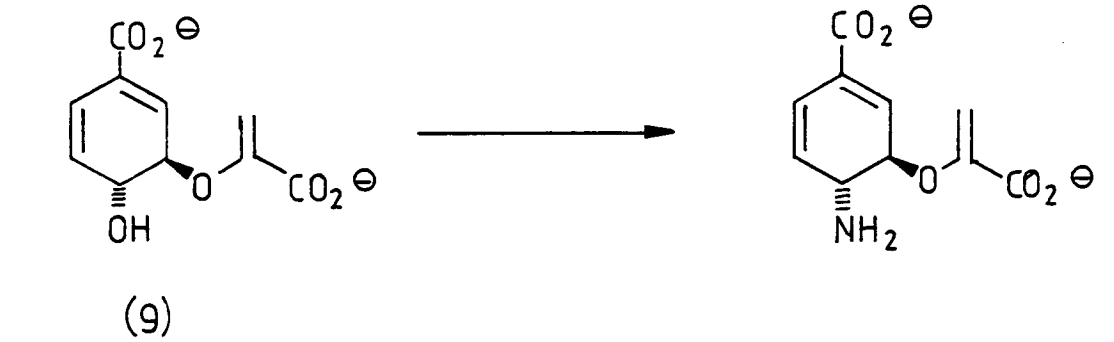


(8)

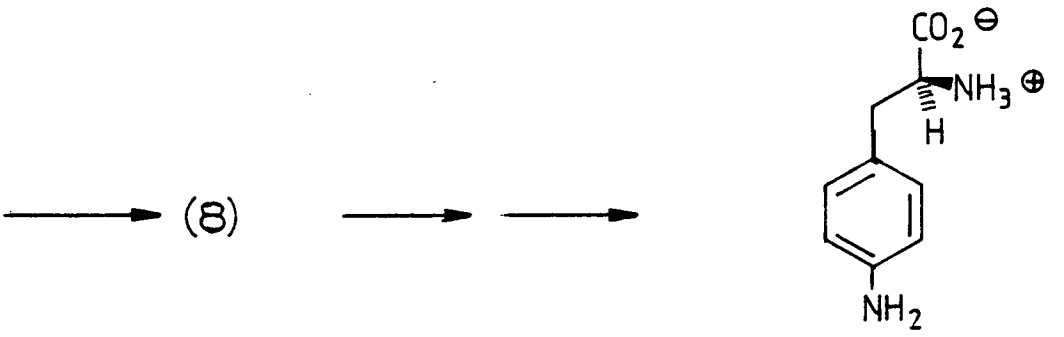
surrogate groups in analogues (6) and (7) have already seen use as carboxylate mimics[24,25], and (8) is of further interest as recent enzyme studies[26] strongly suggest that it is an intermediate in a biosynthetic sequence leading from chorismate (9) to 4-aminophenylalanine (10) (Scheme 2). The latter is a precursor of the broad spectrum antibiotic chloramphenicol (11) in *Streptomyces venezuelae*.

It was hoped that access to the first target, the phosphonate monoester (6), could be achieved by using the phosphonate diester dienophile (4) instead of the corresponding carboxylate ester (3) in the Diels Alder reaction with diene (2). The synthesis of the key intermediate (4) was envisaged as involving formylation and subsequent O-acetylation of the allylic phosphonate (12). The latter was prepared in five stages from cyclohexanone by a route developed by Ramage and MacLeod[27] (Scheme 3). Acid-catalysed condensation of glycolic acid and cyclohexanone gave the dioxolanone (13) in 35% yield, and bromination of this with N-bromosuccinimide, followed by immediate treatment of the intermediate bromide with triphenylphosphine gave the phosphonium salt (14) in 66% yield. Wittig reaction between the phosphorane (15), generated using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base, and acetaldehyde gave the ethylidenedioxolanone (16) as a *ca.* 2:1 mixture of E and Z geometrical isomers. These underwent bromination together using N-bromosuccinimide to give a 7:1 mixture of Z and E isomers of bromide (17). Some double bond isomerization must have occurred in this reaction, but the isomers were not separated, instead being

Scheme 2

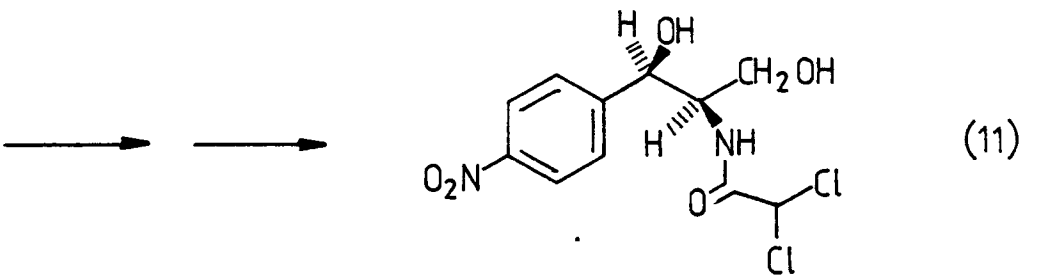


(9)



(8)

(10)



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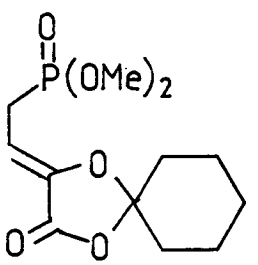
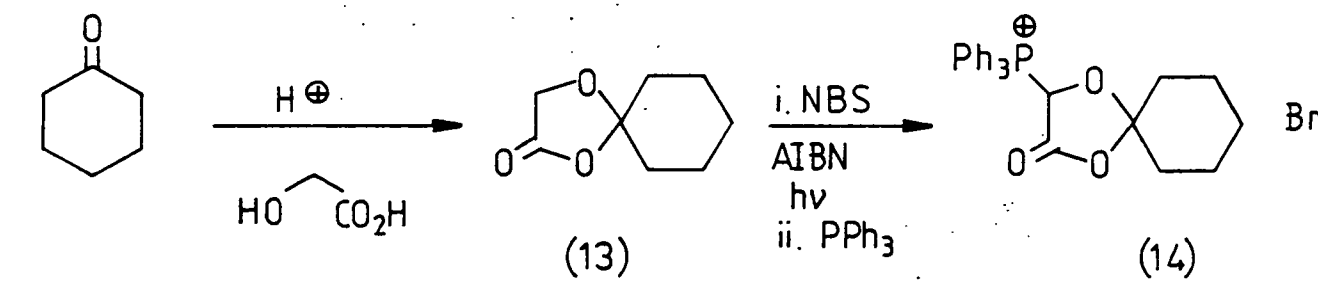
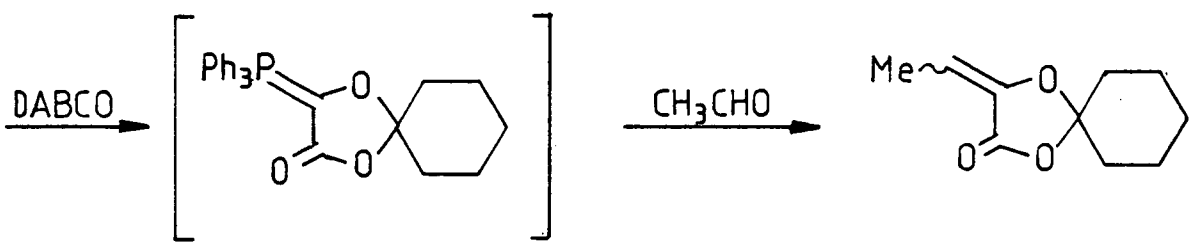


(12)

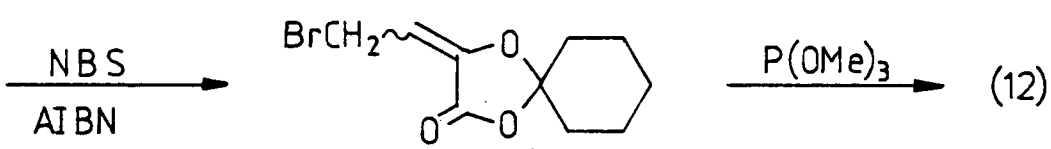
Scheme 3



(13) (14)



(15) (16)



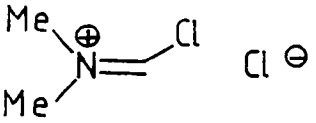
(12)

(17)

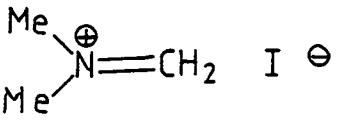
subjected together to an Arbuzov reaction with trimethylphosphite to afford, upon recrystallization, the phosphonate (12) as a single, Z, isomer in 46% yield.

Attempted formylation of (12) with acetic formic anhydride under both basic (LDA-THF) and acidic (boron trifluoride etherate-benzene) conditions gave no observable reaction. When LDA was used as a base in THF or THF-HMPA no reaction was observed with the Vilsmeier formylating reagent (18), but use of this with sodium hydride in DMF resulted in a mixture of starting material and an unidentified product in which the phosphonate group was absent. Reaction between Eschenmoser's salt (19) and the phosphonate (12) in the presence of sodium hydride gave a similar mixture, and an attempt to investigate the formation of the sodium salt of (12) by a deuterium exchange experiment also gave the same result. A substantial proportion of the recovered starting material in the latter, however, had undergone monodeuteration at the allylic position. A similar experiment using LDA as a base gave clean recovery of starting material in which a high level of deuterium exchange had again occurred, and it would appear therefore that the lithium salt of (12) is not reactive.

As the intermediate (12) could not be acylated or alkylated an alternative approach was attempted. The 1-acylalkylphosphonates (20) and (21) are known compounds[28] and it was hoped that the diformyl derivative (22) could be prepared and condensed in a Wittig reaction with the phosphorane (15). Trimethylsilyl dimethyl phosphonoacetate (23) and the corresponding carboxylic acid (24) were



(18)



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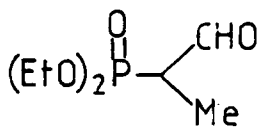
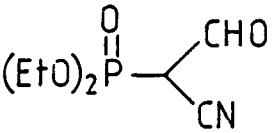
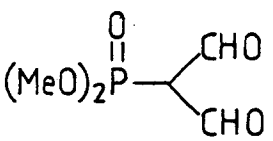


(20)

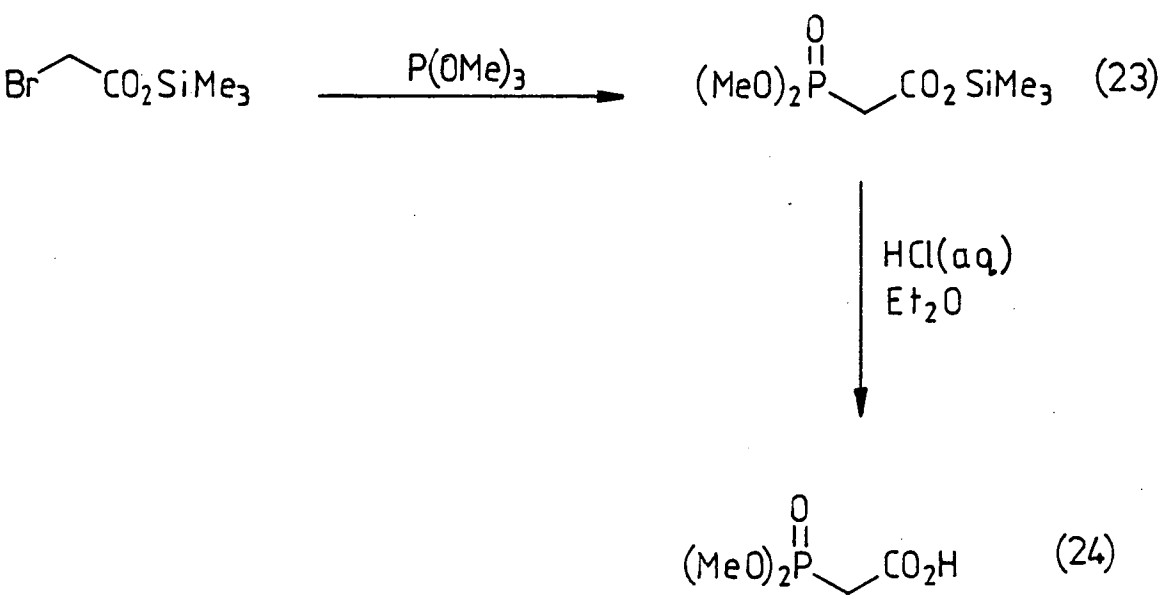


(21)



(22)

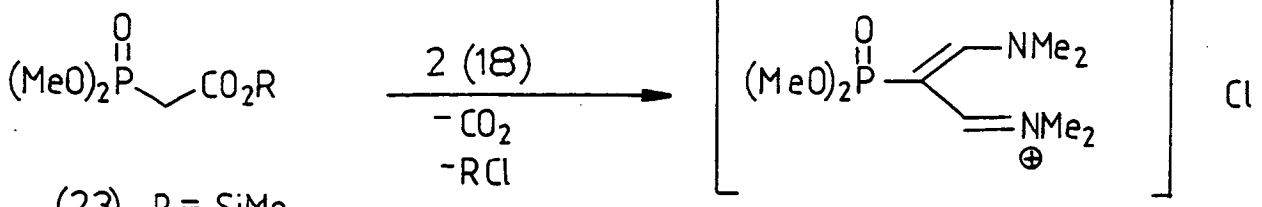
Scheme 4



prepared from trimethylsilyl bromoacetate by the method of Lombardo and Taylor[29,30] (Scheme 4), but attempts to convert either of these into the diformylmethanephosphonate (22) by Vilsmeier diformylation with concomitant decarboxylation (Scheme 5) failed. This procedure has been used in the successful conversion of monomethyl malonate into methyl diformylacetate (37)[31] (see later). In the present case however, very low yields of unidentified material were obtained, ms showing high m/e value ions suggestive of oligomers. It seemed that the reaction products were very water-soluble and thus were lost in the workup, so attempts were made to acetylate any (22) formed *in situ* to produce the enol acetate (25). This would be expected to be less water soluble and could be used in a Wittig condensation with the phosphorane (15) to give the desired dienophile (4) directly. However, again low yields of complex mixtures of products were obtained, and at this point attempts to prepare the phosphonate analogue (6) of prephenate were abandoned.

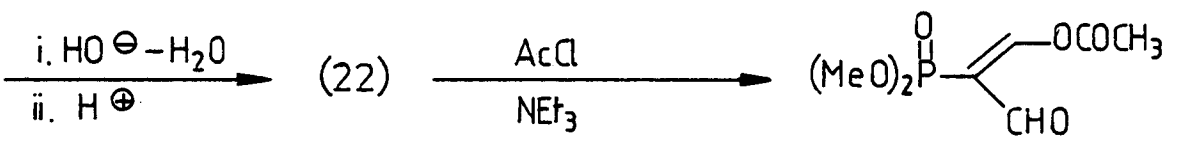
The required dienophile for preparation of the tetrazole analogue (7) of prephenate is the nitrile (5). Work by Ramage and MacLeod[27b] had already shown that the allylic nitrile (26) exhibits a lack of reactivity similar to that of the allylic phosphonate (12), and so it was planned instead to synthesize (5) via a Wittig condensation between the dioxolanone ylid (15) and the known compound diformylacetonitrile (27). Preparation of the latter was described by Trofimenko[32], who claimed that catalytic hydrogenation of cyanoform (28) in the presence of water gave 3-amino-2-

Scheme 5

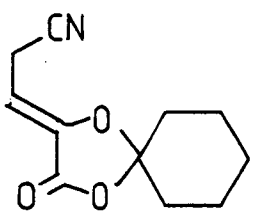


(23) R = $SiMe_3$

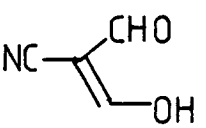
(24) R = H



(25)



(26)

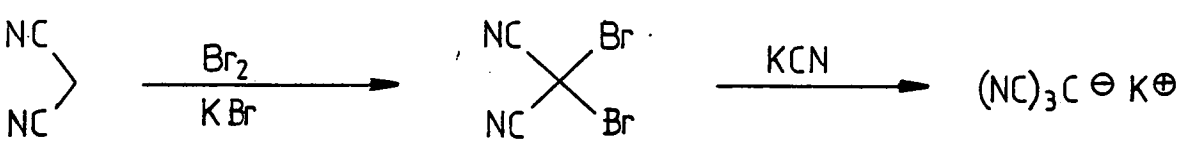


(27)

$HC(CN)_3$

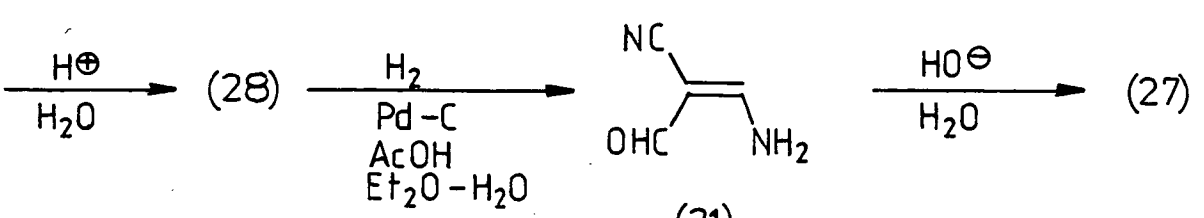
(28)

Scheme 6



(29)

(30)

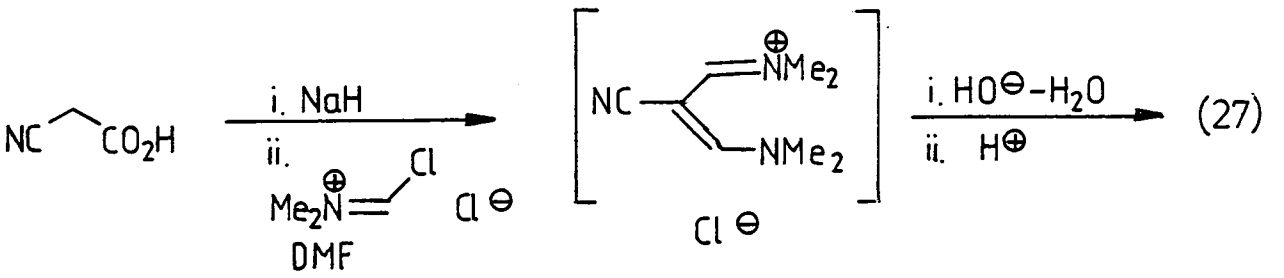


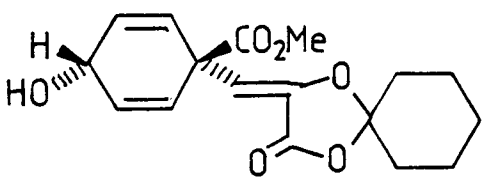
(31)

cyanoacrolein (31). This could be isolated and hydrolysed by alkali to afford (27) (Scheme 6). Cyanoform was prepared by the method of Trofimenko et al[33]. Thus potassium tricyanomethanide (30) was prepared from malonitrile via dibromomalononitrile (29) and was treated with aqueous sulphuric acid to generate cyanoform. This was not isolated but was subjected *in situ* to catalytic hydrogenation at 40psi. It appeared that hydrogen absorption ceased after 30 min, but workup afforded only a solid which was insoluble in most solvents (the exact solubility properties varied according to the precise workup procedure used) and contained no strong carbonyl absorption in the ir spectrum, in contrast to that reported[32]. It was assumed that the product was polymeric and another approach was adopted. This involved the diformylation-decarboxylation of cyanoacetic acid (Scheme 7), but as with the attempted synthesis of the diformylmethanephosphonate (22) only a very low yield of product was isolated. Although ^{1}H nmr and ms indicated that a minor component may have been the desired nitrile (27) it was decided at this stage to abandon approaches to the tetrazole analogue (7) of prephenate.

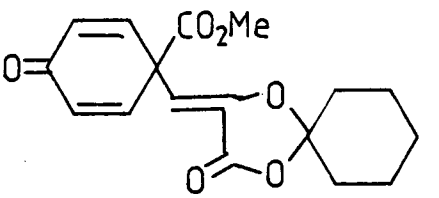
It was intended to synthesize the final analogue, 4-amino-4-deoxyprephenate (8), via a Mitsonobu reaction[34] of the major isomeric alcohol product (32) arising from hydride reduction of the cyclohexadienone (33). The stereospecific formation of azides from secondary alcohols by this method has been reported[35], hydrazoic acid (34) being used as the nucleophilic component in the reaction. The resulting azide (35) in this case would then need to be selectively

Scheme 7





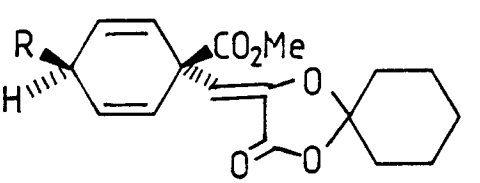
(32)



(33)

N_3H

(34)



(35) R = N_3

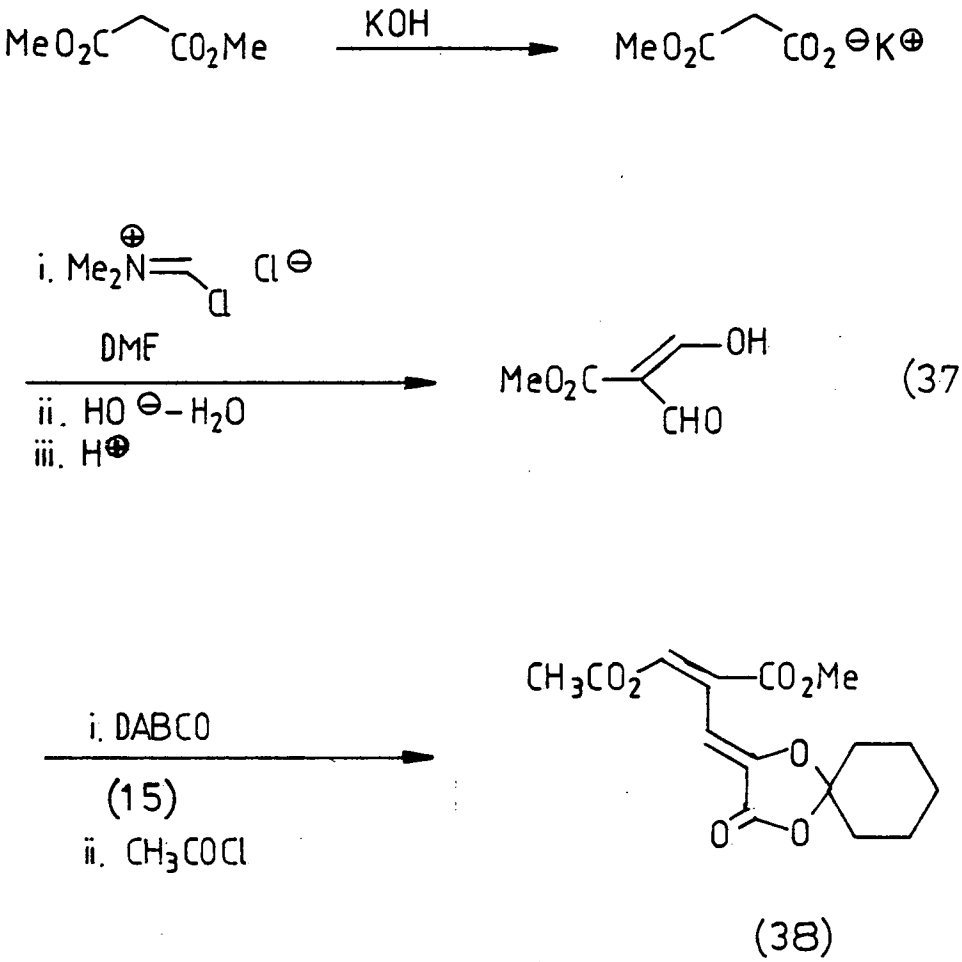
(36) R = NH_2

reduced to the amine (36), base-catalysed deprotection of which would afford the desired prephenate analogue (8).

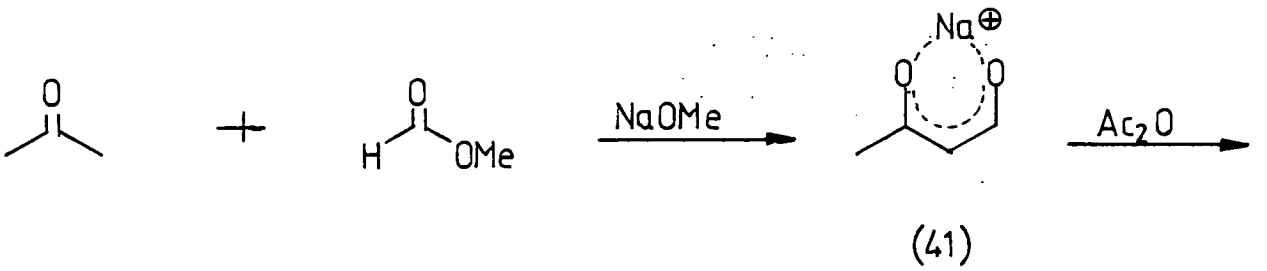
The alcohol (32) was prepared using the route developed by Ramage and MacLeod[22]. Methyl diformylacetate (37) was formed from dimethyl malonate using the procedure of Nakau et al[31], the overall yield over two steps being 33% (Scheme 8). The ylidenedioxolanone (38) was prepared using a Wittig reaction which involved addition of this aldehyde to the phosphorane (15) generated *in situ* from the phosphonium salt (14) in the presence of two equivalents of DABCO. Quenching of the reaction with acetyl chloride afforded the acetoxy dienophile (38), but the yield (11%) was very poor compared to that reported[22], and only the E/Z isomer of (3) was isolated in this case.

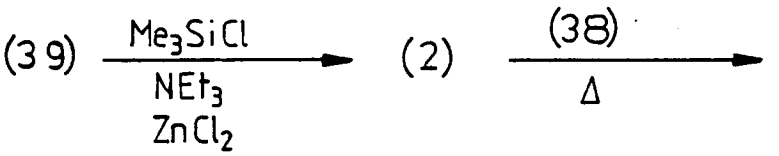
Ramage and MacLeod[22] prepared the acetoxydiene (2) by O-silylation of 1-acetoxybut-1-en-3-one (39). This they prepared by formylation of acetone using methyl formate, followed by quenching of the reaction with acetyl chloride[38]. On repeating this, however, low yields of impure E enol acetate (39) were obtained, a major contaminant being the Z isomer (40). A reasonable yield (47%) of the pure E isomer (39) could be obtained, however, when the sodium salt of formylacetone (41) was acetylated instead with acetic anhydride under carefully controlled conditions[37] (Scheme 9). Reaction with trimethylsilyl chloride then gave the diene (2) in 33% yield. Diels Alder reaction of this with dienophile (38), followed by hydrolysis of and elimination of acetic acid from the cycloadduct (42), gave the cyclohexadienone (33) in good yield. Reduction with

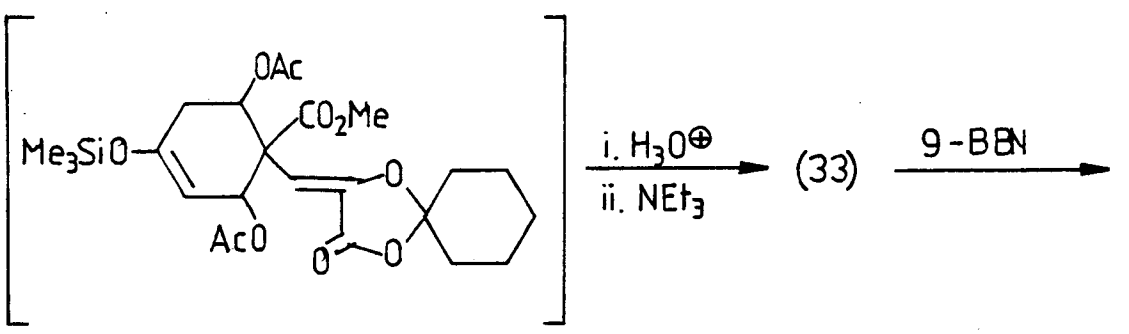
Scheme 8

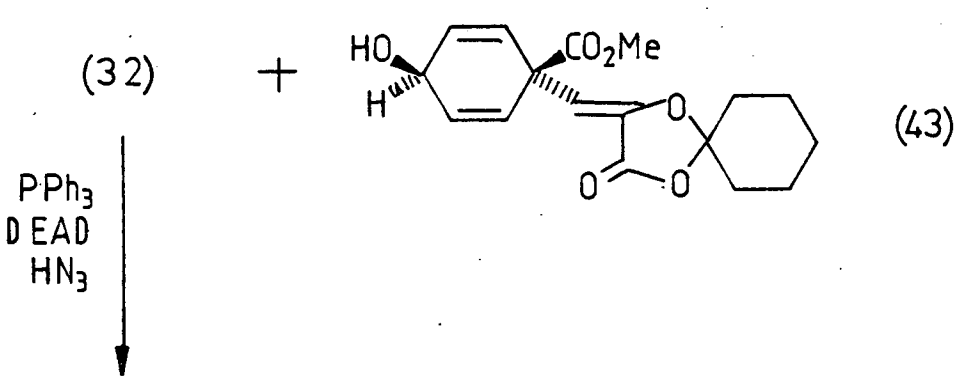

MeO2C CO2Me
KOH
MeO2C CO2⊖K⊕
i. Me2N=CHCl Cl⊖
DMF
ii. HO⊖ – H2O
iii. H⊕
MeO2C OH CHO
(37)
i. DABCO
(15)
ii. CH3COCl
CH3CO2 CO2Me
O
O
O
(38)
O
OCOCH3
(39)
O
OCOCH3
(40)

Scheme 9


NaOMe
Ac2O
(41)


(39)
Me3SiCl
NEt3
ZnCl2
(2)
(38)
Δ

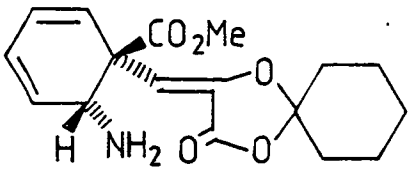

OAc
CO2Me
Me3SiO
AcO
i. H3O⊕
ii. NEt3
(33)
9-BBN
(42)


(32)
HO
H
CO2Me
(43)
PPh3
DEAD
HN3
CO2Me
H
N3
(35)
(44)

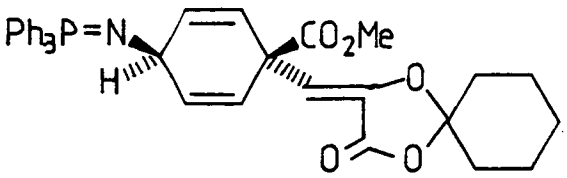
9-borobicyclo[3.3.1]nonane (9-BBN) then gave a mixture of the epimeric alcohols (32) and (43) in a *ca.*2:1 ratio (73% yield); these could be separated by chromatography.

Reaction of the major isomer (32) under modified Mitsonobu conditions[35] (triphenylphosphine-diethylazodicarboxylate (DEAD)-hydrazoic acid) gave two products, however (Scheme 9). One resulted from direct S_N2 substitution of the activated hydroxyl group to give the desired azide (35), but an allylic rearrangement also occurred to give the conjugated isomer (44). As the latter presumably arises from a S_N2' reaction, which would involve a cis relationship between the attacking nucleophile and the leaving group, the relative stereochemistry was assigned as shown, with the azide cis to the adjacent ylidenedioxolanone group. The isomeric azides were virtually identical by chromatography on silica and separation was not attempted at this stage. It was hoped that reduction of both together would lead to a mixture of amines (36) and (45) of significantly different polarities, so that separation could then be effected.

Reduction was first attempted with triphenylphosphine[39]. Use of an excess of this reagent in dichloromethane led to the formation of the phosphinimes (46) and (47), as indicated by evolution of a gas, development of a red colour in the solution and disappearance of the azide absorption (2100 cm^{-1}) in the ir spectrum. These, however, proved resistant to hydrolysis under conditions compatible with the protection in the rest of the molecule. Dilute aqueous hydrochloric acid or p-toluenesulphonic acid failed to give an amine, although the ester and dioxolanone functions remained

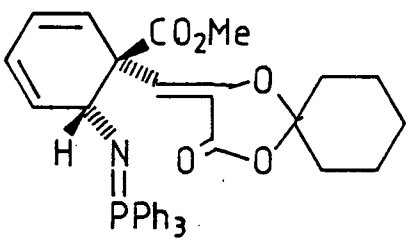


(45)

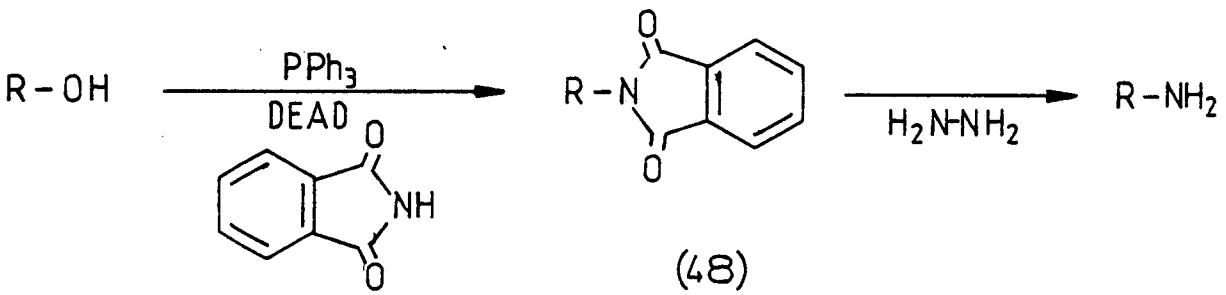


(46)

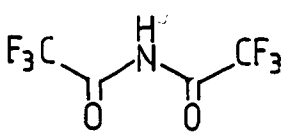
(47)



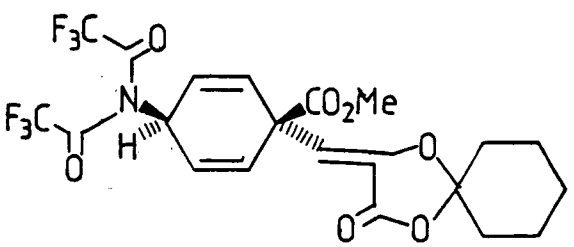
Scheme 10



(48)



(49)



(50)

essentially intact. Use of one equivalent of triphenylphosphine in wet THF at room temperature gave the phosphinimine mixture as before; heating the red reaction product with three equivalents of sodium hydroxide in methanol then gave, upon workup, a brown solid which may have contained a very low level of the desired hydrolysis product (8) (by ^{1}H nmr).

Some other reduction methods were also attempted. Transfer hydrogenation[40] (ammonium formate-palladium on charcoal) failed to give any reaction, propane-1,3-dithiol[41] resulted in attack upon the dioxolane group (no amine product was detected) and aluminium amalgum[42] gave only baseline material by tlc. As yet the successful selective reduction of the azides has still to be accomplished.

Conclusion

Of the three prephenate analogues (6)-(8) whose synthesis has been attempted the aminodeoxy derivative (8) appears to show most promise. The azide precursor (35) has been prepared, albeit as a mixture with the structural isomer (44). Reduction selectively to the amine (36) still has to be achieved, but methods such as the use of sodium borohydride[43] or catalytic hydrogenation employing Lindlar's catalyst[44] should be investigated. Another method which has been used to convert secondary alcohols to primary amines with inversion involves use of phthalimide as the nucleophilic component in a Mitsonobu reaction[34]. This affords N-substituted phthalimides (48) which can be

converted into amines by treatment with hydrazine (Scheme 10). The latter conditions are incompatible with the ylidene-dioxolanone protection, but an alternative to be considered is use of 2,2,2,2',2',2'-hexafluorodiacetamide (49), a known compound[45], as the nucleophile in the Mitsonobu reaction. This should give rise to the N,N-bis(trifluoroacetyl)amino-cyclohexadiene (50) which would be expected to undergo transacylation to afford the amine (36) under very mild conditions.

Chapter 3

EXPERIMENTAL

Melting points were taken in open capillary tubes on an electrically heated Büchi 510 melting point apparatus and are uncorrected, or on a Reichert hot stage microscope. Thin layer chromatography was carried out on commercial silica gel 60 F_{254} (Merck) plates; visualization of compounds was achieved by ultraviolet absorption at 254 nm. Microanalyses were determined by the microanalytical laboratories in the Departments of Chemistry at UMIST and Edinburgh University. Ultraviolet spectra were measured on a Varian Cary 210 spectrometer; extinction coefficients are quoted in units of $dm^3 mole^{-1} cm^{-1}$. Infrared spectra were measured in solution on a Perkin Elmer 781 double beam instrument. Proton nuclear magnetic resonance spectra were obtained on Varian EM360 (60 MHz), Bruker WP-80-SY (80 MHz) and Bruker WP-200-SY (200 MHz) instruments; chemical shifts are quoted in ppm downfield from tetramethylsilane. Signals are described as singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). Phosphorous-31 nuclear magnetic resonance spectra were recorded on a Jeol FX-60-Q (24.2 MHz) instrument; chemical shifts are quoted in ppm relative to external 85% aqueous phosphoric acid. Mass spectra were measured on a Kratos MS-45 machine; relative abundance of ions are quoted. High resolution mass spectra were measured on a Kratos MS-50 machine; relative abundances (and deviation in ppm of measured accurate mass from the calculated accurate mass) of ions are quoted. High performance liquid chromatography was carried out on a Waters system comprising an M-45 pump, a UCK injection system, a 15 cm x 3.9 mm 5µl

spherical silica column and a uv detector (model 450). Isochratic solvent systems were used at 1 ml min^{-1} and detection of samples was at 254 nm. Toluene, benzene and diethyl ether were dried over sodium wire. Dichloromethane, diisopropylamine and triethylamine were dried by distillation from calcium hydride. Dimethylformamide (DMF) was dried by distillation from calcium hydride at reduced pressure. Methanol, ethanol and ethyl acetate were distilled before use. Tetrahydrofuran (THF) was dried by distillation from potassium benzophenone ketyl immediately before use. Petrol refers to the fraction of petroleum ether boiling in the range 40-60°C and was distilled before use. Dry-flash chromatography was performed on 'Merck' Kieselgel 60H. The technique involved filling a cylindrical glass sinter (porosity 3) with silica, then applying suction, agitating and compressing until the silica was compact. The column was solvated with the least polar solvent component and sucked dry. The mixture to be separated was loaded onto the column in solution with a minimum of the least polar solvent mixture required for dissolution, and was eluted with solvent mixtures of increasing polarity. The polarity of fractions was generally increased in steps of 5-10% every alternate fraction. Flash chromatography refers to the technique developed by Still.[46]

Cyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (13).- This was prepared by the method of Ramage et al[27a].
A solution of cyclohexanone (21.0 mmol, 0.2 mol) and p-toluenesulphonic acid hydrate (50 mg, 0.27 mmol) in toluene (90 ml) was heated and strongly stirred at reflux while glycolic acid (12.2 g, 0.16 mmol) in water (6 ml) was added over a period of 4h. Water was removed by a Dean-Stark collector. After a further 2.5h heating the mixture was cooled to room temperature and anhydrous sodium acetate (75 mg, 1.0 mmol) was added and stirring was continued for 40 min. The solid was removed by filtration and the filtrate evaporated *in vacuo* to leave a yellow oil which was purified by distillation (twice), leaving a clear liquid which solidified on standing. M.p. 25-31°C (lit.[22a] 30-31°C); B.p. 77°C (0.5 mmg) [lit.[27a] 70°C (0.55 mmHg)]; ν_{max} (CH_2Cl_2) 2950, 1795, 1372, 1224, 1107 cm^{-1}. This data was in agreement with the literature[27a].

5'-Oxocyclohexanespiro-2'-(1',3'-dioxolan)-4'-yltriphenylphosphonium Bromide (14).- This was prepared by the method of Ramage et al[27a].
Cyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (13) (18.0 g, 0.12 mol) was dissolved in carbon tetrachloride (175 ml) and N-bromosuccinimide (21.8 g, 0.12 mol) was added. The mixture was brought to reflux and azobisisobutyronitrile (50 mg, 0.3 mmol) was added, the red solution then was irradiated with a 500w tungsten lamp causing a vigorous reaction and a white precipitation. After 30 min reaction the suspension was cooled to 0°C, filtered and the filtrate evaporated under

reduced pressure to leave a pale yellow oil. This was dissolved in toluene (230 ml) and stirred at room temperature while triphenylphosphine (30.3 g, 0.12 mol) in toluene (115 ml) was added over 1h. Stirring was continued for a further 22h, then the mixture was filtered and the filtrate washed with toluene and ether. Recrystallization from ethanol : ether afforded a white solid (37.7 g, 66%); M.p. 198-200°C (lit.[27a] 198°C); ν_{max} (CH_2Cl_2) 2950, 1790, 1438, 1204, 1113 cm^{-1}; δ_H (80MHz, $CDCl_3$) 1.05-2.35 (10H, m), 7.40-8.23 (15H, m), 9.25 (1H, d, J=2Hz). This data was in agreement with literature[27a] except that in the latter the nmr spectrum, recorded in $(CD_3)_2CO$-D_2O, contained the signal corresponding to that at δ9.25 within a multiplet at δ7.85-8.15 which integrated for 16H.

5'-Ethylidenecyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (16).- This was prepared by the method of Ramage et al.[27a] 5'-Oxocyclohexanespiro-2'-(1',3'-dioxolan)-4'-yltriphenylphosphonium bromide (14) (37.7 g, 75.8 mmol) was stirred as a suspension in toluene (180 ml) at 90°C and 1,4-diazabicyclo[2.2.2]octane (8.8 g, 78.5 ml) in toluene (120 ml) was added under nitrogen, followed 3 min later by acetaldehyde (10.6 ml, 189.6 mmol) in toluene (30 ml). After a further 45 min stirring the mixture was filtered and the filtrate concentrated to a white residue. This was triturated with petrol (4 x 100 ml) and the combined triturates were evaporated *in vacuo* to afford a pale-yellow oil. Purification by dry-flash chromatography on silica (ether:petrol, 0:1-1:4) followed by distillation

gave the title compound as a clear oil (9.1 g, 79%). The E:Z ratio was *ca.* 2:1. B.p. 52-60°C (0.6 mmHg) [lit.[27a] 95°C (0.04 mmHg)]; ν_{max} 2945, 1779, 1695, 1681, 1226, 1135 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 1.25-1.90 (10H, m, both isomers), 1.75 (d, J=7Hz, Z isomer) and 2.00 (d, J=8Hz, E isomer) (total of 3H), 5.54 (q, J=8Hz, E isomer) and 5.61 (q, J=7Hz, Z isomer) (total of 1H). The spectral data was consistent with the literature[27a].

5'-(2-Bromoethylidene)cyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (17).- 5'-Ethylidenecyclohexane-2'-(1',3'-dioxolan)-4'-one (16) (9.13 g, 49.9 mmol), N-bromosuccinimide (9.73 g, 54.7 mmol) and azobisisobutyronitrile (30 mg, 0.18 mmol) in carbon tetrachloride (240 ml) were heated at reflux temperature for 20h whilst irradiated by a 500w tungsten lamp. The mixture was then chilled to 0°C and filtered, the filtrate evaporated and the residue distilled to give the title compound (5.03 g, 38%) as a Z and E mixture in the ratio *ca.* 7:1. B.p. 80°C (0.05 mmHg) [reported[27b], 100°C (0.1 mmHg)]; δ_H (60 MHz, $CDCl_3$) 1.20-2.04 (10H, m), 4.04 (d, J=9Hz, Z-isomer) and 4.52 (d, J=9Hz, E-isomer) (total of 2H), 5.61 (t, J=9Hz, E-isomer) and 5.68 (t, J=9Hz, Z-isomer) (total of 1H). This data was in agreement with that previously reported[27b].

Dimethyl 5'-Oxocyclohexanespiro-2'-(1',3'-dioxolan)-4'-2"-ethylidenephosphonate (12).- 5'-(2-Bromoethylidene)-cyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (17) (3.20 g, 12.3 mmol) was stirred under nitrogen, trimethyl phosphite

(2.6 ml, 22.0 mmol) was added and the resulting solution was stirred at room temperature for 65h, then distilled in a Kugelrohr (180°C oven temperature, 0.02 mmHg). The least volatile product, a clear oil, was dissolved in ether (5 ml) and chilled (-20°C), giving the title compound as white crystals (1.65 g, 46%). M.p. 68-69°C (reported[27b] 68°C): Found: C, 49.50; H, 6.62, $C_{12}H_{19}O_6P$ requires C, 49.66; H, 6.60; λ_{max} (EtOH) 246 nm (ε9920); ν_{max} (CH_2Cl_2) 2955, 1786, 1695, 1437, 1268, 1034 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 1.25-2.00 (10H, m), 2.74 (2H, dd, J=23, 8Hz), 3.74 (6H, d, J=11Hz), 5.55 (1H, td, J=8,7Hz); δ_P (24.2 MHz, $CDCl_3$) 27.8; m/z 290 (M^+), 6.2%. Hplc (EtOAc) 2.5 min.

Deuteration of Dimethyl 5'-Oxocyclohexanespiro-2'-(1',3'-dioxolan)-4'-2"-ethylidenephosphonate (12).- A solution of diisopropylamine (54 µl, 0.38 mmol) in THF (0.5 ml) was stirred at -78°C and n-butyllithium (1.0M in THF, 0.24 ml, 0.38 mmol) was added. After 10 min stirring a solution of dimethyl 5'-oxocyclohexanespiro-2'-(1',3'-dioxolan)-4'-2"-ethylidenephosphonate (12) (100 mg, 0.38 mmol) in THF (1 ml) was added and the deep yellow solution was stirred at -78°C for a further 17 min. Deuterium oxide (0.5 ml) was added and stirring was continued as the temperature was gradually raised. At room temperature the mixture was extracted with ether (2 x 10 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated, leaving a clear oil (58 mg). The ^1H nmr was similar to that of the starting material, but the signal at δ2.74 (dd) was of

reduced intensity and a broadened triplet (J=*ca.*8Hz) now appeared at δ5.55. Monodeuteration at the allylic position appeared to have occurred almost quantitatively.

Dimethyl Trimethsilyloxycarbonylmethanephosphonate (23).- This was prepared by the method of Lombardo and Taylor[29]. Trimethylsilyl bromoacetate (2.7 ml, 16.4 mmol) was stirred at 80°C while trimethylphosphite (3.0 ml, 25.4 ml) was slowly added. The mixture was stirred at this temperature for 3h and then distilled to afford a clear liquid (2.8 g, 71%). B.p. 92-96°C (1 mmHg); δ_H (80 MHz, $CDCl_3$) 0.24 (9H, s), 2.92 (2H, d, J=22Hz), 3.73 (6H, d, J=11Hz).

Dimethyl Carboxymethanephosphonate (24).- This was prepared by the method of Lombardo and Taylor[30]. Dimethyl trimethylsilyloxymethanephosphonate (23) was dissolved in ether (10 ml) and aqueous hydrochloric acid solution (1.0M, 0.5 ml) was added. The mixture was stirred at room temperature for 1h and then the organic layer was separated and the aqueous layer was washed thoroughly with more ether (6 x 5 ml). The combined ethereal solutions were dried ($MgSO_4$) and evaporated under reduced pressure, leaving a pale oil (0.32 g, 49%). ν_{max} (CH_2Cl_2) 3400-2300 (br), 2955, 1727, 1220, 1035 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 3.14 (2H, d, J=22Hz), 3.93 (6H, d, J=12Hz), 8.87 (1H, br s).

Methyl Diformylacetate (37).- This was prepared by the method of Nakau et al[31]. Phosphoryl chloride (90.0 ml, 0.97 moles) was added to DMF (380 ml, 4.91moles) at such a rate that the temperature of the mixture remained in the range 23-28°C. Potassium monomethylmalonate (50.3 g, 0.30 moles) was then added portionwise and the reaction was subsequently stirred at 90°C for 4h. The solvent was removed *in vacuo* and the residue poured onto ice (1 Kg) and stirred while saturated aqueous sodium carbonate solution was slowly added (vigorous frothing!) until the pH of the solution reached 9.5. Stirring was continued at room temperature for 65h and the mixture was then saturated with potassium chloride, washed with ether (2 x 500 ml) and acidified to pH 1 with ice-cold aqueous hydrochloric acid solution (6.0M). The solution was then extracted with ether (4 x 500 ml) and the combined ethereal layers were washed with saturated aqueous potassium chloride solution (1000 ml), dried (Na_2SO_4) and concentrated to 100 ml, redried and evaporated to dryness *in vacuo*. The residual red-brown liquid was purified by distillation, affording a clear liquid (16.0 g, 41%) which solidified on storage at 0°C. B.p. 47°C (2 mmHg) [lit.[36] 58-61°C, 2 mmHg]; ν_{max} (CH_2Cl_2) 3300-2700 (br), 2980, 1720, 1660, 1585, 1440, 1244, 1110 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 3.80 (3H, s), 9.11 (2H, s), 12.88 (1H, br s, exchanges with D_2O). This data was in agreement with the literature[36],

5'-[2-(Acetoxy-(E)-methylidene)-2-methoxycarbonyl-(Z)-ethylidene]cyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (38).- This was prepared by the method of Ramage and MacLeod[22]. 5'-Oxocyclohexanespiro-2'-(1',3'-dioxolan)-4'-yltriphenylphosphonium bromide (14) (24.10 g, 48.5 mmol) and 1,4-diazabicyclo[2.2.2]octane (11.92 g, 106.2 mmol) were stirred in benzene (60 ml) under nitrogen for 10 min at room temperature. Methyl diformylacetate (37) (6.22 g, 47.8 mmol) in benzene (25 ml) was slowly added and stirring was continued for 30 min, then acetyl chloride (3.8 ml, 53.8 mmol) was slowly added. After a further 15 min ether (100 ml) was added and precipitated solid was removed by filtration. The filter was washed with more ether (50 ml) and the combined filtrates were evaporated under reduced pressure. The residue was dissolved in dichloromethane (15 ml) and filtered through a 1" bed of silica, then purified by dry-flash chromatography on silica (ether:petrol). This gave a solid which was recrystallized (twice) from ether:petrol, affording the pure desired product (1.69 g, 11%). M.p. 103°C (lit.[22] 101°C); ν_{max} (CH_2Cl_2) 3050, 2955, 1780, 1720, 1637, 1369, 1228, 1188, 1163, 1126, 1093 cm^{-1}. δ_H (80 MHz, $CDCl_3$) 1.25-1.98 (10H, m), 2.23 (3H, s), 3.78 (3H, s), 6.19 (1H, d, J=1Hz), 8.24 (1H, d, J=1Hz). This was consistent with the published data[22] for the E/Z isomer (38). No Z/Z isomer was detected in the present preparation, however, in contrast to the published procedure.

(E)-1-Acetoxybut-1-en-3-one (39)

Method A: This was prepared by the method of Bockstahler et al[37]. Sodium (4.49 g, 0.19 mol) was added to methanol (60 ml) and when the reaction was complete the excess methanol was removed *in vacuo* (final azeotropic removal using benzene). The resulting white solid was dried *in vacuo* and then suspended in benzene (125 ml). Acetone (14.1 ml, 0.19 mol) and methyl formate (12.0 ml, 0.19 mol) were slowly added at 55°C and the thick creamy mixture was stirred at ambient temperature for 3.5h. It was then filtered and the pale yellow solid which was collected was dried *in vacuo*. Ether (80 ml) was added and the suspension was stirred while acetic anhydride (13.9 ml, 0.15 mol) was slowly added, causing a mild exotherm. The suspension thickened and was stirred mechanically at 35-38°C for 3.5h and then at 30°C for 18h. The solid was removed by filtration and the filtrate was evaporated to leave a red liquid which was distilled, affording a colourless liquid (8.31 g, 47% based on acetic anhydride). B.p. 54-59°C (0.5 mmHg) [lit.[37] 60-61 (0.4 mmHg)]; ν_{max} (CH_2Cl_2) (*inter alia*) 3035, 2965, 1783, 1670, 1625, 1372, 1190, 1128 cm^{-1}. δ_H (80 MHz, $CDCl_3$) 2.20 (3H, s), 2.24 (3H, s), 5.95 (1H, d, J=13Hz), 8.20 (1H, d, J=13Hz).

Method B: Preparation was attempted by the method of Burness[38]. The product ratio was variable; a typical procedure is given. Sodium (5.28 g, 0.23 mol) was dissolved in methanol (200 ml) under nitrogen and the solution was evaporated to leave solid sodium methoxide. Ether (500 ml) was added and the suspension was stirred in

a water bath while acetone (17.5 ml, 0.24 mol) and methyl formate (0.31 mol) were added. The mixture was stirred for 1h and left to stand for 3h, then filtered and the collected white solid suspended in ether (125 ml). Acetyl chloride (17.0 ml, 0.24 mol) was slowly added at 0°C and after 10 min stirring the mixture was filtered and the filtrate was evaporated. The residue (6.90 g, an oil which darkened on standing) consisted of a mixture of the title compound (38), (Z)-1-acetoxybut-1-en-3-one (40) (in a *ca.*1:1 ratio) and unidentified impurities. This could not be effectively purified by distillation.
δ_H (60MHz, $CDCl_3$) (*inter alia*) 2.00 (3H, s), 2.07 (3H, s), 5.49 (1H, d, J=4Hz), 7.84 (1H, d, J=4Hz), plus signals due to the E isomer (39).

1-Acetoxy-3-trimethylsilyloxybut-1,3-diene (2).- This was prepared by the method of Ramage and MacLeod[22]. Zinc chloride (0.35 g, 2.6 mmol) and triethylamine (15.0 ml, 107.6 mmol) were stirred in benzene (6 ml) under nitrogen at room temperature for 16h, the 1-acetoxybut-1-en-3-one (39) (6.29 g, 49.1 mmol) was added, followed by more benzene (6 ml). The mixture was cooled to 0°C and trimethylsilyl chloride (12.0 ml, 94.6 mmol) was slowly added and stirring was continued at 0°C for 15 min, then at room temperature for 89h. It was then poured onto ether:petrol (1:1, 200 ml). After 10 min stirring the suspension was filtered through Celite and the filtrate was evaporated to afford a blood-red residue which was distilled, giving a clear liquid (4.33 g, 44%).

B.p. 75-78°C (2 mmHg) [lit.[22] 115°C (30 mmHg)]; ν_{max} (CH_2Cl_2) 1755, 1657, 1593, 1372, 1215, 1110, 1022 cm^{-1}. δ_H (60MHz, $CDCl_3$) 0.03 (9H, s), 1.94 (3H, s), 4.11 (2H, s), 5.72 (1H, d, J=12Hz), 7.41 (1H, d, J=12Hz). This was in full agreement with the published data[22].

5'-[(1-Methoxycarbonyl-4-oxocyclohexa-2,5-dien-1-yl)-(Z)-methylidene]cyclohexane-2'-(1',3'-dioxolan)-4'-one (33).- This was prepared by the method of Ramage and MacLeod[22]. 1-Acetoxy-3-trimethylsilyloxybut-1,3-diene (2) (2.63 g, 12.7 mmol) and 5'-[2-(acetoxy-(E)-methylidene)-2-methoxycarbonyl-(Z)-ethylidene]cyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (38) (1.83 g, 6.5 mmol) were stirred together at 80°C under nitrogen for 65h and then excess diene was removed *in vacuo*. The residue was stirred in THF (27 ml) and aqueous hydrochloric acid solution (0.1M, 3.5 ml) for 35 min and then ether (80 ml) was added. The organic layer was washed with saturated aqueous sodium bicarbonate solution (25 ml), brine (25 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Triethylamine (1.53 ml, 11.0 mmol) and dichloromethane (35 ml) were added and the solution stirred at room temperature for 24h, then filtered through florisil and the filtrate stirred with charcoal (140 mg), filtered and evaporated *in vacuo* to leave a dark oil. This was purified by flash chromatography on silica (ether:petrol, 1:1-1:0) followed by recrystallization from ether:petrol. Colourless crystals (1.17 g, 67%) was obtained. M.p. 94-95°C (lit.[22] 90-91°C); ν_{max} (CH_2Cl_2) 3050, 2953, 1790, 1741, 1670, 1420, 1220 cm^{-1}. δ_H (200MHz, $CDCl_3$)

1.30-1.98 (10H, m), 3.78 (3H, s), 5.76 (1H, s), 6.38 (2H, d, J=10Hz), 6.98 (2H, d, J=10Hz). This data was in full accord with the literature[22].

5'-[(4α-Hydroxy-1β-methoxycarbonylcyclohexa-2,5-dien-1-yl)-(Z)-methylidene]cyclohexane-2'-(1',3'-dioxolan)-4'-one (32). This was prepared by the method of Ramage and MacLeod[22]. The cyclohexadienone (33) (590 mg, 1.75 mmol) was dissolved in THF (9 ml) and stirred at 0°C under nitrogen while 9-borabicyclo [3.3.1]nonane (0.5M in THF, 8.6 ml, 4.3 mmol) was slowly added. The temperature was gradually raised to room temperature and then methanol (6 ml) was added and stirring was continued for 5 min. The mixture was poured onto water (90 ml) and extracted with dichloromethane (3 x 90 ml), then the organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to leave a clear oil. This was purified by dry-flash chromatography on silica (toluene:ether), affording the title compound as a clear oil (229 mg, 39%). R_f 0.41. ν_{max} (CH_2Cl_2) 3580, 3050, 2950, 1788, 1736, 1687, 1348, 1337, 1218 cm^{-1}. δ_H (80MHz, $CDCl_3$) 1.15-1.98 (10H, m), 3.70 (3H, s), 4.49 (1H, br m), 5.73 (1H, s), 6.02 (4H, m), plus 5'-[(4α-hydroxy-1α-methoxycarbonylcyclohexa-2,5-dien-1-yl)-(Z)-methylidene]cyclohexane-2'-(1',3'-dioxolan)-4'-one (43) as a clear oil (11%). R_f (ether) 0.38; ν_{max} (CH_2Cl_2) 3580, 3050, 2950, 1789, 1736, 1367, 1336, 1220 cm^{-1}. δ_H (80MHz, $CDCl_3$) 1.05-1.90 (10H, m), 3.73 (3H, s), 4.48 (1H, br m), 5.68 (1H, s), 6.02 (4H, m), plus fractions containing both of the above isomers (23%,not purified further). This data was in agreement with the literature[22].

Mitsonobu Reaction of 5'-([4α-Hydroxy-1β-methoxycarbonyl-cyclohexa-2,5-dien-1-yl]-(Z)-methylidene)cyclohexane-2'-(1',3'-dioxolan)-4'-one (32) using Hydrazoic Acid.- The title alcohol (32) (32 mg, 99.9 μmol) and triphenylphosphine (29 mg, 110.6 μmol) were stirred in benzene (0.5 ml) under nitrogen and hydrazoic acid (1.41M in benzene, 78 μl, 110.0 μmol) was added. Diethyl azodicarboxylate (18 μl, 114.3 μmol) in benzene was slowly added, the mixture was stirred at room temperature for 1.5h and then evaporated under reduced pressure. The residual pale-yellow solid was recrystallized from ether:petrol to remove diethyl hydrazinecarboxylate and the filtrate was evaporated under reduced pressure to leave a yellow oil. This was purified by flash chromatography on silica (ether) affording a clear oil (140 mg, 80%), identified as a 1:1 mixture of 5'-[(4α-azido-1α-methoxycarboxylcyclohexa-2,5-dien-1-yl)-(Z)-methylidene]cyclohexan -2'-(1',3'-dioxolan)-4'-one (35) (isomer A) and 5'-[(2α-azido-1α-methoxycarbonylcyclohexa-3,5-dien-1-yl)-(Z)-methylidene]cyclohexane-2'-(1',3'-dioxolan)-4'-one (44) (isomer B). ν_{max} (CH_2Cl_2) 3050, 2950, 2100, 1788, 1740, 1688, 1337, 1220 cm^{-1}. δ_H (200MHz, $CDCl_3$) 1.10-1.95 (10H, m, both isomers), 3.73 (s) and 3.79 (s) (total of 3H, both isomers), 4.04 (br m, isomer A) and 4.09 (dd, J=6,1Hz, isomer B) (total of 1H), 5.67 (s) and 5.70 (s) (total of 1H, both isomers), 5.86 (0.5H, dd, J=9,6Hz, isomer B), 5.98 (dd, J=10,3Hz, isomer A) and 6.00 (m, isomer B) (total of 1.5H), 6.17 (1.0H, dd, J=10, 1Hz, isomer A), 6.32 (1.0H, m, isomer B). Hrms 345.1329 ($C_{17}H_{19}N_3O_5$, M^+), 4% (1.36); 302 (M^+-N_3). Hplc (dichloromethane) 4.9 and 6.0 min.

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P A R T B

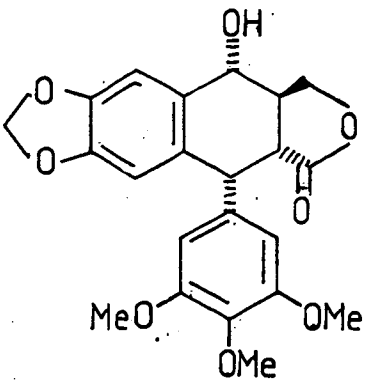
SYNTHETIC APPROACHES TO PODOPHYLLOTOXIN

Chapter 4

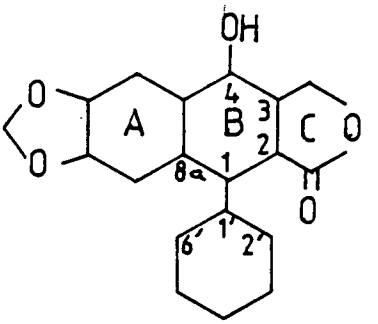
INTRODUCTION

4.1 Historical

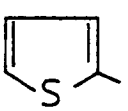
Podophyllotoxin (1) is an example of the lignan family of natural products, a class of compounds widespread among higher plants[1] and recently isolated from animals[2]. Podophyllotoxin itself was isolated originally from the roots and rhizomes of *Podophyllum peltatum* and *Podophyllum emodi*, perennial herbs found in the eastern parts of the United States and in the Himalayas respectively. Crude resinous extracts ('podophyllin') obtained from the former have a long history of use, particularly as a purgative, and since 1942 the resin obtained from both sources has been used to treat condyloma acuminatum ('ano-genital warts')[3]. Further study of the cytotoxic effects of podophyllin showed it to be effective against a variety of tumour systems; podophyllotoxin was identified as the major active ingredient and has been demonstrated to act as a mitotic poison. Clinical development of podophyllotoxin did not meet with success, but studies with many derivatives and analogues have led to the development of VM-26 (2) and VP-14-213 (3) as agents used clinically against small cell lung cancer and testicular cancer[4]. These latter drugs, incidentally, appear to arrest cell development during the G_2 phase rather than during mitosis, in contrast to podophyllotoxin, and they are synthesized from naturally derived podophyllotoxin.


OH
O
O
O
O
MeO
OMe
OMe

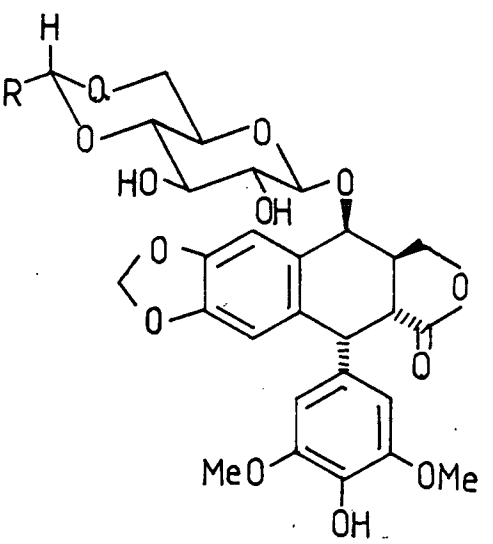
(1)


OH
O
O
A
B
C
O
4
3
2
1
8a
O
6'
1'
2'

(1a)

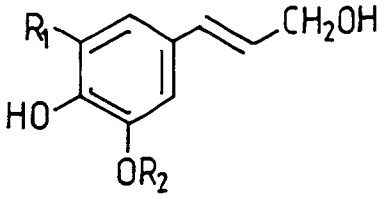
(2) R = 
S

(3) R = CH_3


H
R
O
O
O
O
HO
OH
O
O
O
O
MeO
OMe
OH

4.2 Lignans - Classification and Biosynthesis

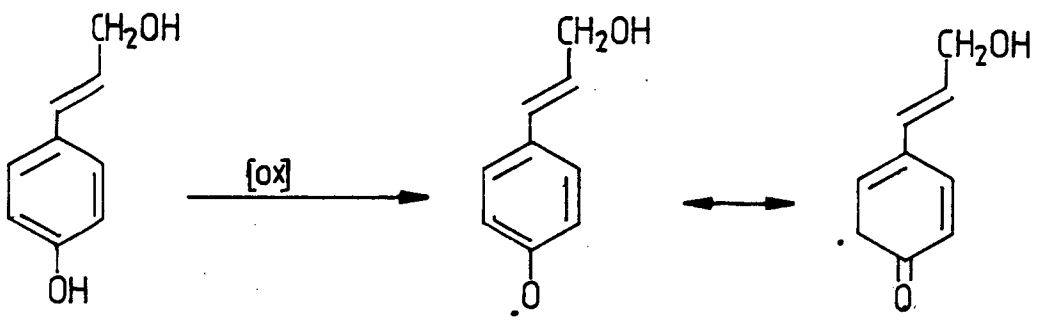
The term 'lignan' was originally introduced by Haworth[5] to describe naturally occurring compounds consisting of two C_6C_3 (phenylpropane) units linked at the central (β) carbon atoms of the side chains. Their formation is attributed to the oxidative dimerization of monomeric C_6C_3 phenols via the radical mechanism originally proposed by Pummerer[6]. For example, p-coumaryl alcohol (4) may undergo radical oxidation and the radical thus formed may exist in the mesomeric forms (7a-d). There are in theory ten possible dimeric combinations of these, but the most common in nature results from the coupling of two (7c) forms to give the β-β linkage common to lignans. The term 'neolignan' was introduced by Gottlieb[7] to describe congeners arising from any of the alternative couplings possible. During lignan biosynthesis the dimerization is accompanied by modification of the resulting methinequinone, such as (8), in a number of ways, e.g. selective reduction, formation of an oxygen bridge or bridges to form furan derivatives, or intramolecular cyclization to give arylnaphthalene derivatives[8]. Thus a wide variety of skeletal types is formed, for which a consistent classification system has been devised by Freudenberg and Weinges[9]. Podophyllotoxin (1) is hereby classified as one of the 'cyclolignans', all of which contain the arylnaphthalene nucleus (or its partially hydrogenated form). The numeration system normally applied to these compounds is illustrated in (1a), although this convention has not always been observed in the literature.



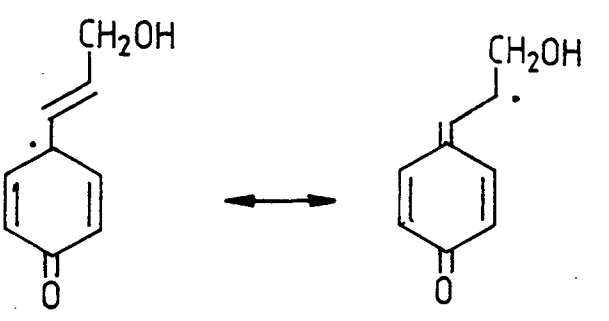
(4) $R_1 = R_2 = H$

(5) $R_1 = H$, $R_2 = Me$

(6) $R_1 = R_2 = Me$



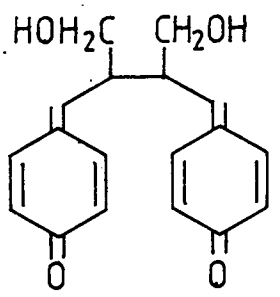
(4) (7a) (7b)



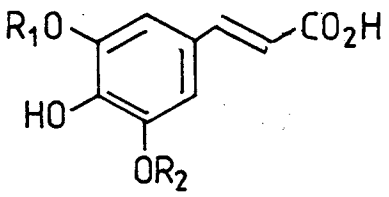
(7d) (7c)

The aromatic rings of the lignans usually contain two, and often three, oxygenated groups, usually -3,4 or -3,4,5 to the C_3 side chain, and these are frequently methylated, or may be methylenated. Inspection of structures suggests that the most common precursor units are p-coumaryl alcohol (4), coniferyl alcohol (5) and sinapyl alcohol (6) (or their oxidized or reduced counterparts), but biosynthetic work in this field has been very limited[21b]. The origin of podophyllotoxin (1) has been one of the most investigated areas, with a number of useful radiochemical labelling studies. Ayres[11] has reported that labelled phenylalanine and p-coumaric acid (9) are incorporated while tyrosine and acetate are not. Incorporation of two C_6C_3 monomers was indicated. Recent studies by Jackson and Dewick[10] have shown that cinnamic acid and ferulic acid (10) are precursors of podophyllotoxin, but sinapic acid (11) and 3,4,5-trimethoxycinnamic acid are not, and also that ferulic acid was incorporated equally into both halves of the lignan dimer. It thus appears that the substitution pattern of the pendant aromatic ring is assembled after the coupling of two phenylpropane units, both of which probably have the 4-hydroxy-3-methoxy substitution pattern. The same authors have also demonstrated[12] that deoxypodophyllotoxin (12) is hydroxylated to podophyllotoxin (1), which is in turn further oxidized to podophyllotoxone (13) (Scheme 1). The existence of such of pathway invalidates a number of hypothetical biosynthetic sequences which require introduction of the 4-hydroxyl soon after oxidative coupling of the C_6C_3 units[8].

2 x (7c) ⟶



(8)

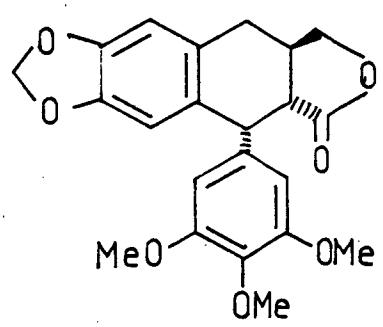


(9) $R_1 = R_2 = H$

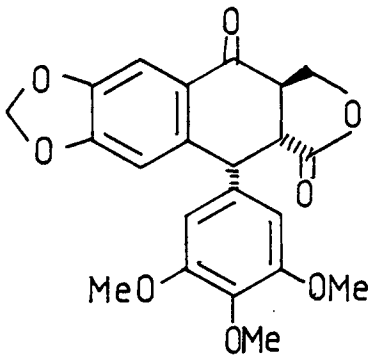
(10) $R_1 = H$, $R_2 = Me$

(11) $R_1 = R_2 = Me$

Scheme 1



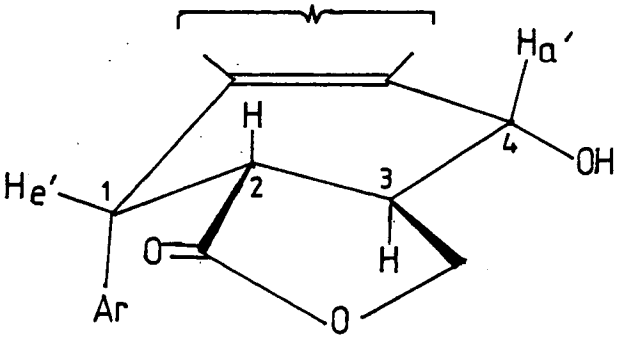
⟶ (1) ⟶



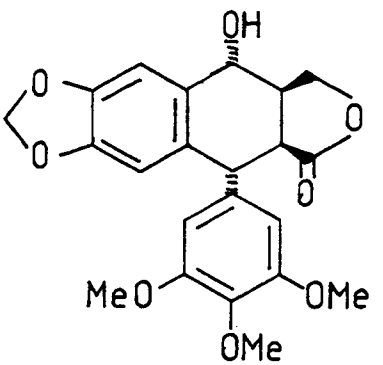
(12) (13)

4.3 Structure and Properties of Podophyllotoxin

By 1956 the structure, relative and absolute configurations of podophyllotoxin had been established[3], and an X-ray study of 2'-bromopodophyllotoxin has since confirmed the stereochemistry[13]. Podophyllotoxin (1) is a 1-aryl-4-tetralol with a 2,3-fusion to a γ-lactone. The overall relative configuration is cis-1,2-trans-2,3-trans-3,4 and the absolute configuration is (1R,2R,3R,4R). Examination of a scale model of podophyllotoxin suggests that it is held in a highly rigid and strained half-chair conformation, and that the C-1 pendant aromatic ring maintains a pseudo-axial orientation, with the C-4 hydroxyl pseudoequatorial (14). Rotation of the aromatic ring about the 1,1'-axis also appears to be restricted due to interaction with the substituent at C-2. This is in contrast to the C-2 epimer, picropodophyllin (15), which contains a cis-fused lactone and as a result has much more conformational freedom. Podophyllotoxin is readily converted into picropodophyllin by weak bases[3], and an investigation by Gensler and Gationis into the podophyllotoxin-picropodophyllin equilibrium in 0.1M piperidine in t-butanol showed that the equilibrium constant at 31°C was 37±0.5[14]. The standard enthalpy change was -1.3 kcal $mole^{-1}$ and the standard entropy change was +2.9 e.u., indicating that at room temperature *ca.*40% of the free energy value favouring picropodophyllin was due to the entropy factor, i.e. the greater flexibility of the cis-fused system and the greater rotational freedom of the pendant aromatic ring.



(14)



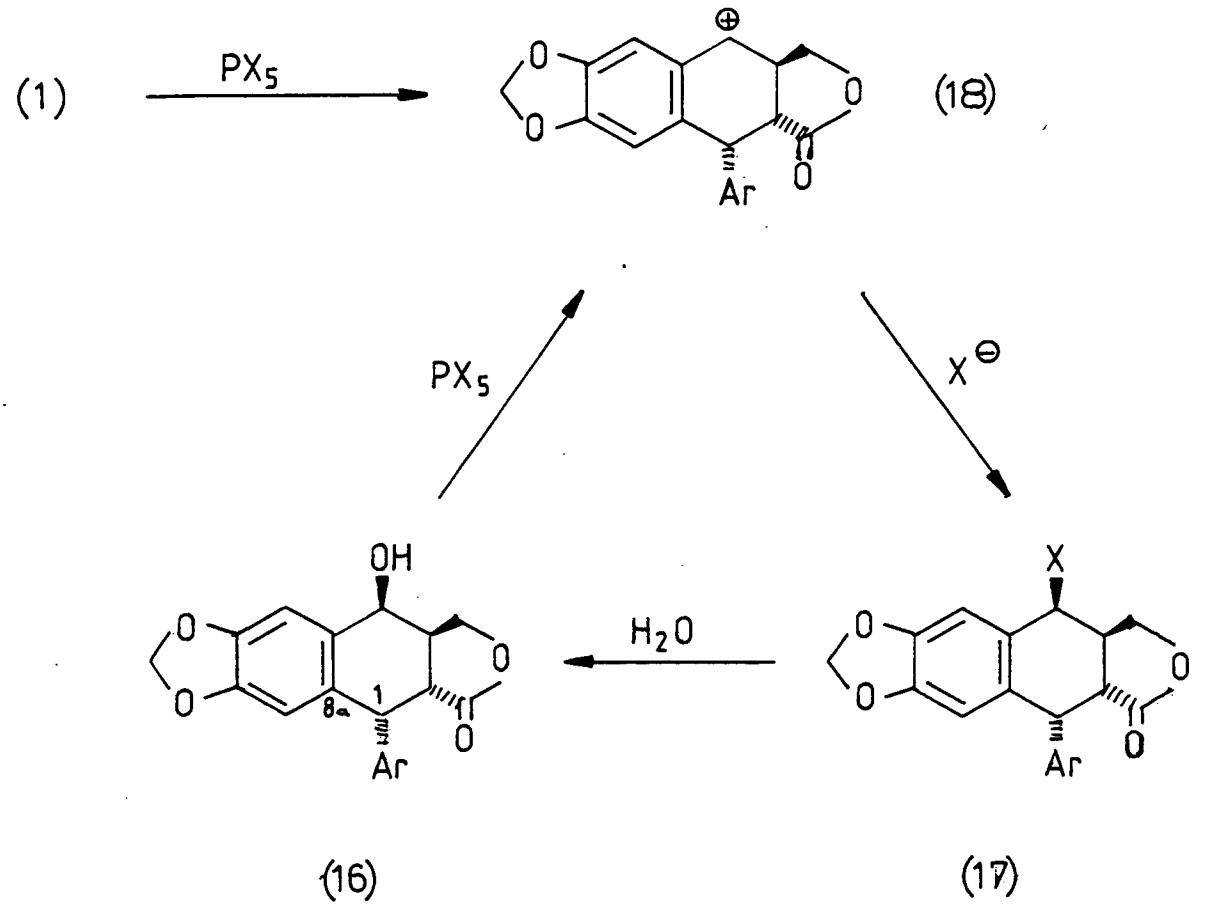
(15)

Nuclear magnetic resonance spectra of podophyllotoxin and related compounds have been interpreted in terms of conformational analysis of the cyclohexene ring[15] with the aid of a modified form of the Karplus equation, which takes into account substituent electronegativity effects[16]. Work has also been done on the carbon-13 nmr[17] and ultra-violet[18] spectroscopic behaviour of podophyllotoxin and related compounds, the latter particularly with regard to analysis of Cotton effects in optical rotational dispersion and circular dichroism spectra in terms of stereochemistry and conformation.

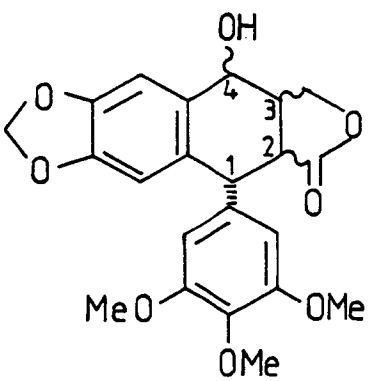
The conformational demands and high degree of steric crowding in the podophyllotoxin series of compounds have a significant effect upon their chemistry[19,20]. For example, all four diastereoisomers of podophyllotoxone (13) are reduced by $ZnBH_4$ to yield alcohols of α-configuration at C-4 (as in podophyllotoxin)[20], while halogen donors such as phosphorous pentahalides react with both podophyllotoxin (1) and epipodophyllotoxin (16) to give the β-halides (17). These can be hydrolysed by base to the β-alcohol (16). In each case nucleophilic attack is directed onto the less crowded β-face of either a ketone or the common carbonium ion intermediate (18) (Scheme 2).

Finally, all naturally occurring compounds related to podophyllotoxin have the same α-configuration at C-1 and this is arbitrarily designated the L-configuration[20a]. All eight diastereoisomers of L-podophyllotoxin (1) are known and most of them result from synthetic interconversions

Scheme 2



Table



(1)	podophyllotoxin	(2α,3β,4α)
(16)	epipodophyllotoxin	(2α,3β,4β)
(15)	picropodophyllin	(2β,3β,4α)
(19)	epipicropodophyllin	(2β,3β,4β)
(20)	isopodophyllotoxin	(2β,3α,4β)
(21)	epiisopodophyllotoxin	(2β,3α,4α)
(22)	isopicropodophyllin	(2α,3α,4β)
(23)	epiisopicropodophyllin	(2α,3α,4α)

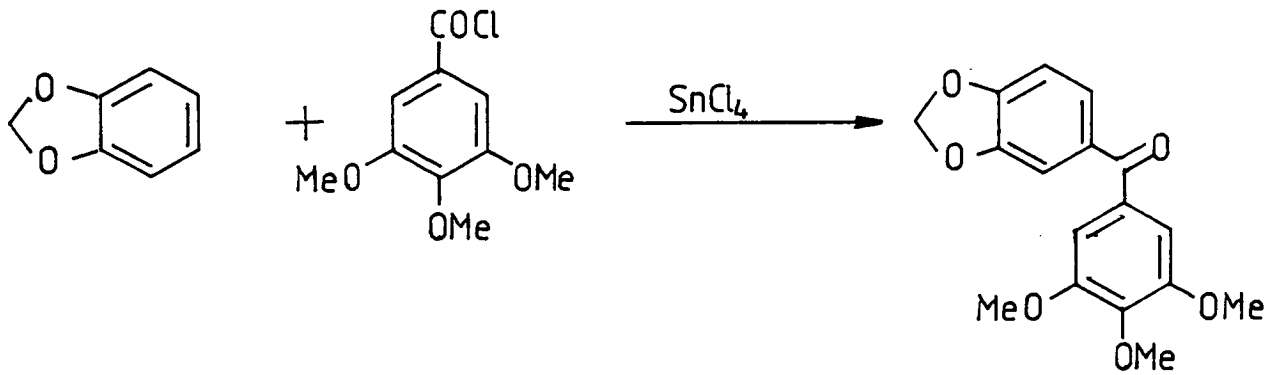
using the types of epimerization, reduction and solvolysis reactions mentioned above. The series is summarised in the Table.

4.4 Synthesis of Podophyllotoxin

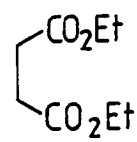
There has been a great deal of interest in the synthesis of podophyllotoxin (1) as a result of the successful development of two of its synthetic derivatives into the clinically useful antitumour agents VM-26 and VP-14-213. There has also been a substantial effort directed towards synthesis of aryltetralins in general, and this has been reviewed recently[21]. This section will survey the approaches which have so far been used in the total synthesis of podophyllotoxin and closely related compounds, with particular attention being paid to the stereochemical factors involved.

A successful and efficient synthesis of podophyllotoxin must overcome the conformational difficulties described in Section 1.3, namely construction of the highly strained trans B/C ring junction and correct disposition of the pendant aromatic ring in the thermodynamically disfavoured pseudoaxial orientation, cis to the substituent at C-2. The orientation of the hydroxyl group at C-4 can be more easily manipulated and is therefore less of a problem. The earliest, and until recently only, synthesis partially circumvented these difficulties by proceeding via the more accessible isomer picropodophyllin (15), which could then be epimerized under conditions of kinetic control. This pioneering route was developed by Gensler[22] (Scheme 3). A Friedel Crafts reaction gave the benzophenone (24) which underwent a Stobbe condensation with diethyl succinate to give, after hydrolysis, a 1:1 mixture of the itaconic acids (25) and (26). Upon hydrogenation and dehydration only

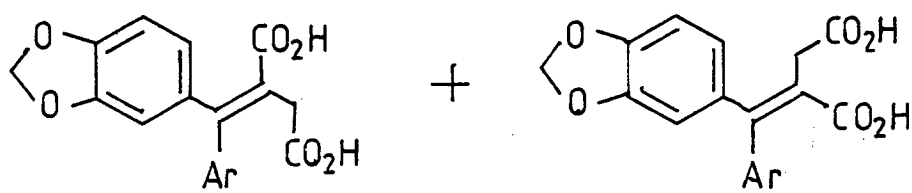
Scheme 3



(24)

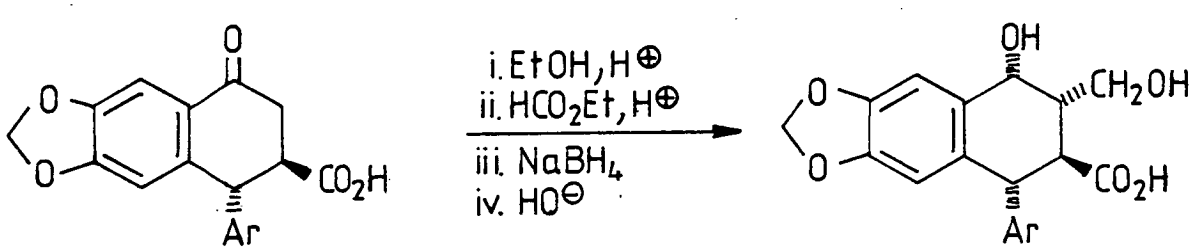
i. 

ii. $H_3O^{\oplus}$



(25) (26)

i. H_2
ii. AcCl
iii. $SnCl_4$



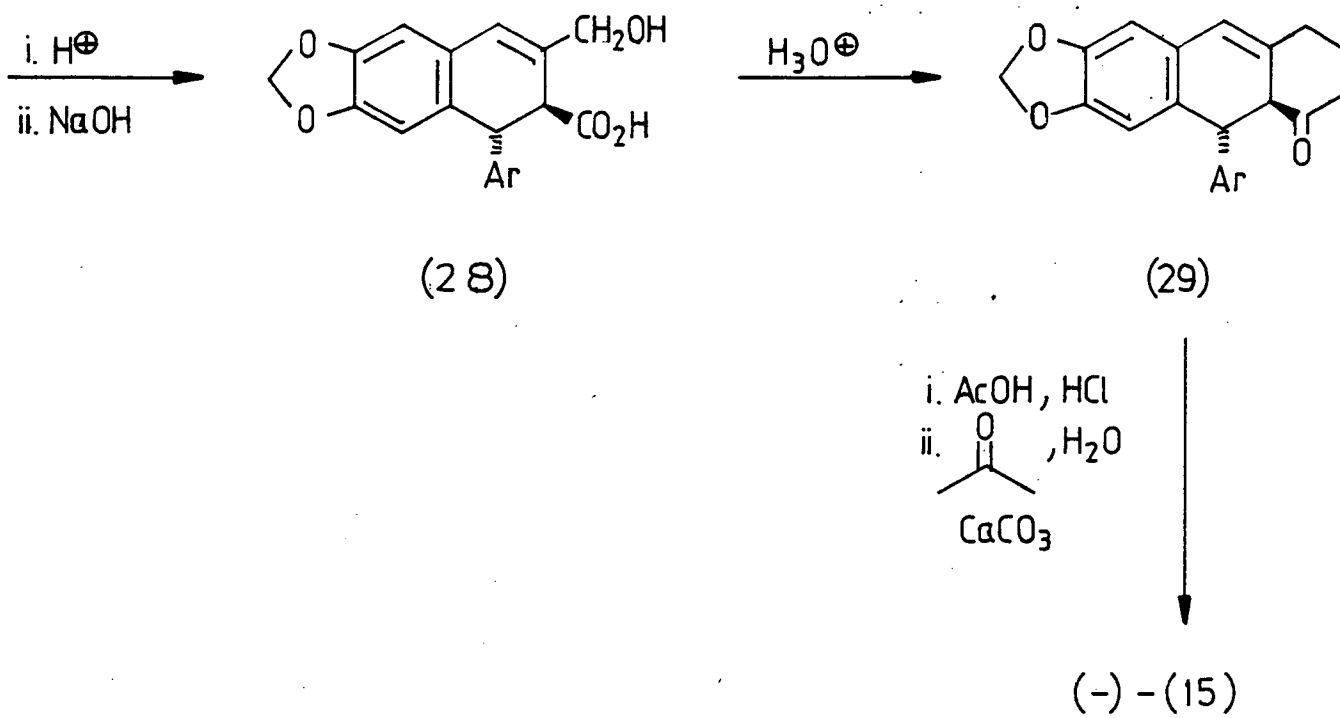
(27)

cont. Page 67

the adduct from (25) gave a satisfactory cyclization to the tetralin (27). Also, cyclization occurred specifically onto the ring shown because the 3,4-methylenedioxy group is a more effective stabilizer of the resulting Wheland intermediate than the 3,4,5-trimethoxy substitution pattern. After esterification, formylation, reduction and hydrolysis resolution was carried out via the quinine salt of α-apopodophyllic acid (28). Lactonization occurred on acidification to give (29). The great drawback of the synthesis was the final step, as hydration of (29) resulted in only a *ca.* 2% yield of L-(-)-picropodophyllin [(-)-(15)]. Picropodophyllin was then converted to podophyllotoxin by a kinetically controlled reprotonation of the enolate (31) formed by the action of triphenylmethyl sodium on the tetrahydropyranyl ether of picropodophyllin[22b] (30) (Scheme 4). The protecting group was removed in dilute acid without affecting the chiral centres and yielded, after separation by crystallization, picropodophyllin (15) and podophyllotoxin (1) in 51% and 38% yieldsrespectively. This gave a greater proportion of podophyllotoxin than is thermodynamically preferred[14] because the β-face of the enolate is less crowded than the α-face.

Gensler's synthesis was completed in 1966 and it was not until 1977 that the next formed synthetic route was presented. Kende[23] used a strategy in which the tetralone (27) again was a key intermediate, but this time it was obtained via a phenolic oxidative coupling reaction. The approach is thus to some extent biomimetic (Scheme 5). The phenol (33), obtained from homopiperonyl mesylate (32)

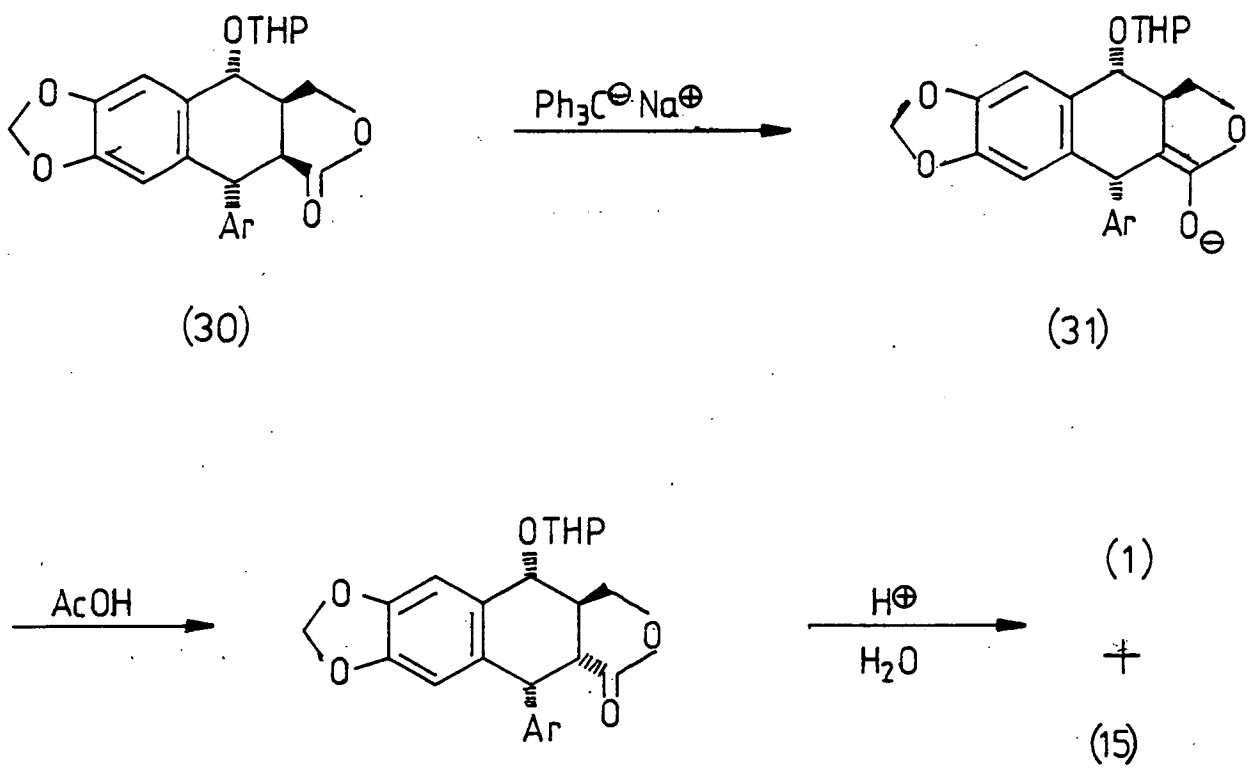
Scheme 3 (cont)



(28) (29)

(-) - (15)

Scheme 4



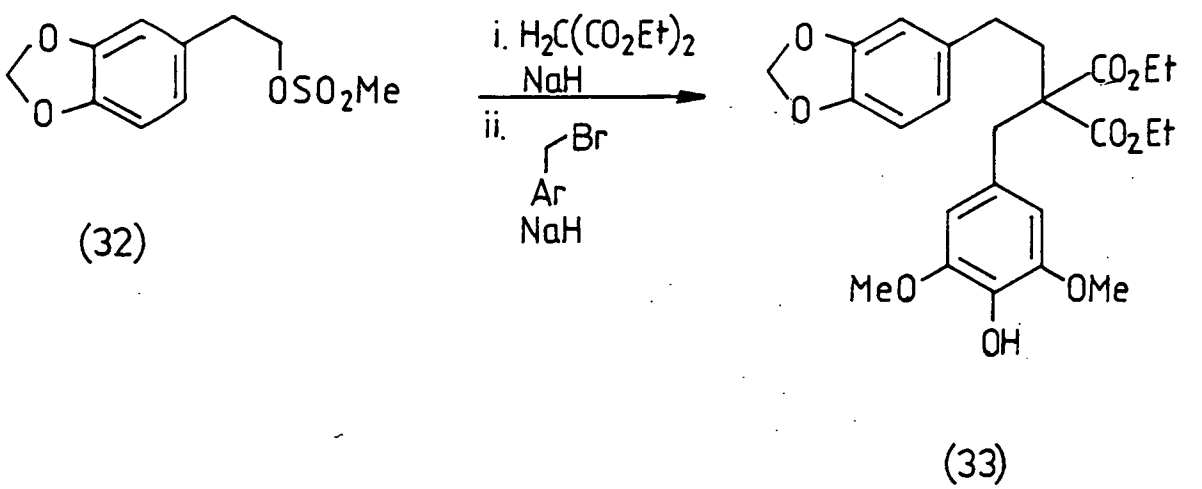
(30) (31)

(30)

by successive alkylations was oxidized with thallium trifluoroacetate (TTFA), and reductive work-up followed by *in situ* methylation gave the tetralin (34). This was further elaborated, via (27) to picropodophyllone (35), the overall yield from phenol (33) being 13%. As picropodophyllone can be reduced to picropodophyllin by $ZnBH_4$ [24] this constitutes a formal synthesis of podophyllotoxin in which the inefficient hydration step present in Gensler's is avoided.

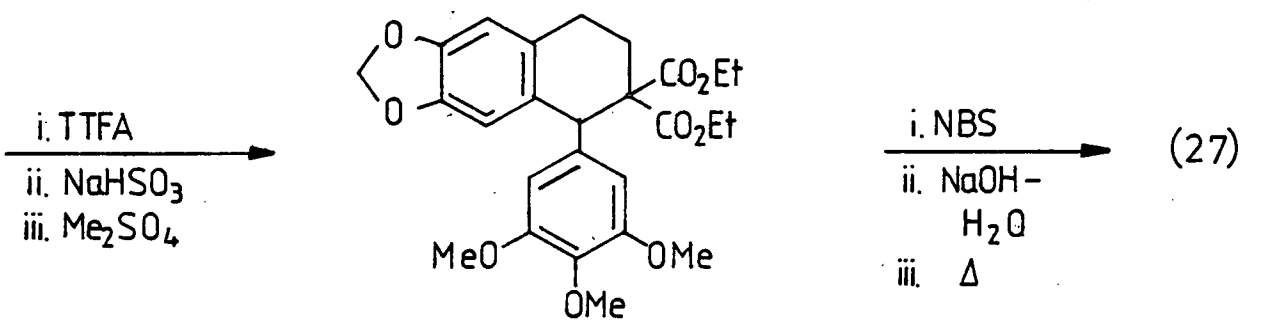
Kende[25] later developed an alternative route to the tetralone (27) in which the oxygen function at C-4 was automatically incorporated early in the synthesis; the oxidation of (34) to the ketone which was earlier reported[23] apparently is unreliable on scales greater than 50 mg [25]. The organolithium reagent (37), prepared in three steps from piperonal (36), was reacted in a Michael fashion with the arylidenemalonate (38), the resulting enolate being trapped intramolecularly to yield the tetralin (39). This was then converted to the tetralone (27) which was transformed to picropodophyllin as before[23]. The Gensler enolate quenching procedure[22b] was improved upon by protecting the hydroxyl group as a t-butyldimethylsilyl ether and generating the enolate with LDA. The kinetically controlled reprotonation was achieved using freshly prepared pyridine hydrochloride to give picropodophyllin and podophyllotoxin silyl ethers in 34% and 36% yields respectively. The latter was deprotected to give podophyllotoxin (1), the overall yield being 4.5% in twelve steps from piperonal (36) (Scheme 6).

Scheme 5



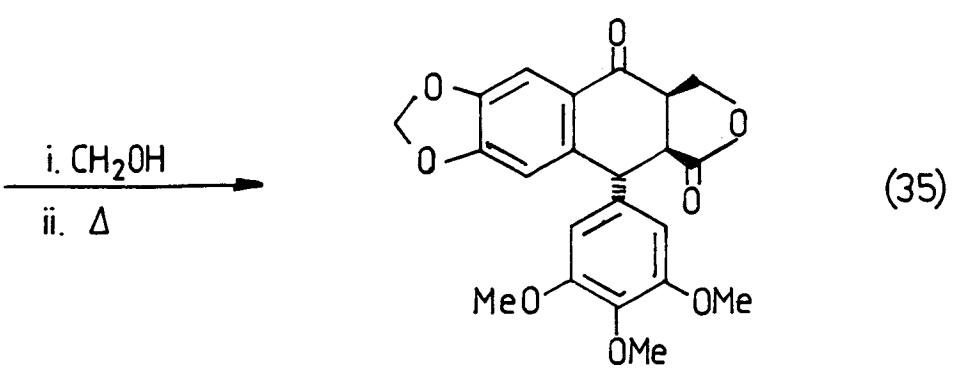
(32)

(33)



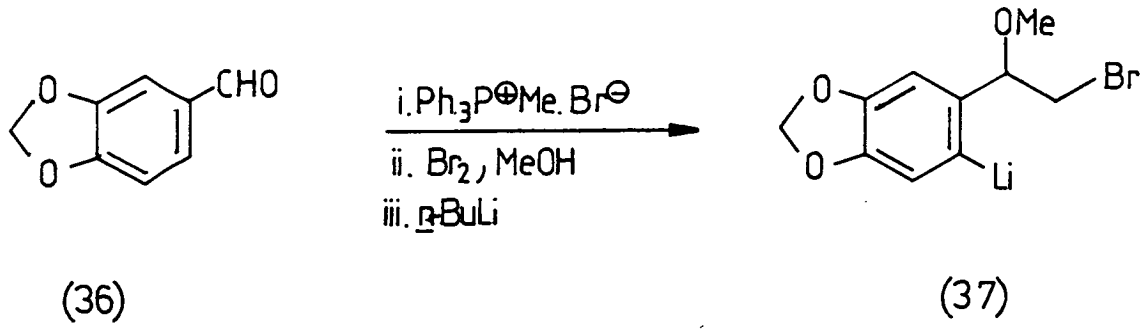
(34)

(27)

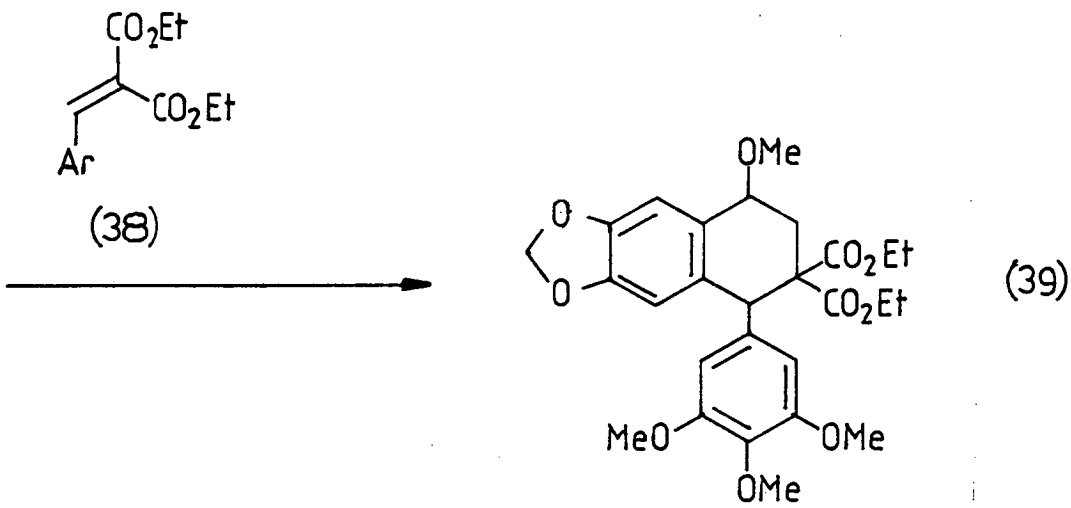


(35)

Scheme 6



(36) (37)



(39)

i. KOH – EtOH
ii. $H_3O^{\oplus}$
iii. CrO_3

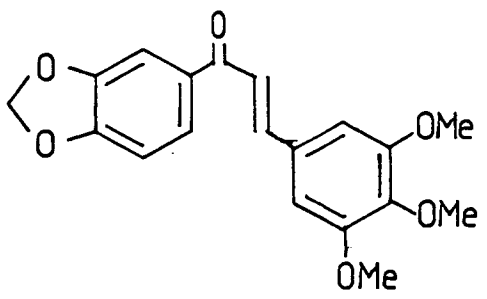
(27) → → (15)

i. TBDMS – Cl
ii. LDA
iii. pyrHCl
iv. $Et_3N.HF$

(1)

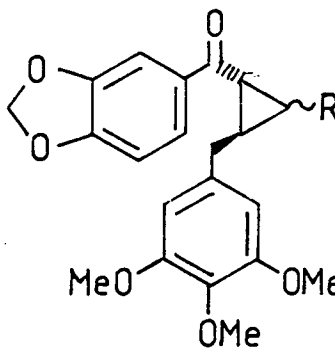
A short route to the ethyl ester of tetralone (27) has been published by Murphy[26], starting from the chalcone (40) (Scheme 7). Reaction with dimethylsulphonium ethoxycarbonylmethylide afforded a 1:1 mixture of the epimeric cyclopropane esters (41), both of which gave the tetralone (43) with tin (IV) chloride or boron trifluoride etherate. The cyclization was studied in detail and is thought to proceed in a stepwise manner as shown. The intermediate carbonium ion (42b) is destabilized by the net electron withdrawing effect of the 3,4,5-trimethoxy substitution[22a] and so the equilibrium normally favours the oxonium ion (42a), which can, however, undergo side-reactions. As a result the reaction is very solvent dependent and nitromethane is required for tetralone (43) formation, presumably due to a shift in the equilibrium towards (42b). The deactivating effect of the benzoyl carbonyl group also probably contributes to the overall slowness of the reaction. Vyas et al[27] at Bristol-Myers have very recently published a synthesis of epipodophyllotoxin (16) in which Murphy's procedure for preparation of tetralone (43) is modified by incorporating two equivalents of acetic anhydride in the rearrangement step. This improves the yield and reduces the reaction time; presumably a transient enol acetate forms, preventing the formation of oxonium ion (42a) and removing the deactivating carbonyl group. A novel route was then used to transform the tetralone (43) into epipodophyllotoxin (Scheme 8). The 1,2-transdisubstituted dihydronaphthalene (44) was formed in four steps and was epimerized at C-2 by another kinetically controlled

Scheme 7



(40)

$\overset{\oplus\ominus}{Me_2SCHCO_2Et}$

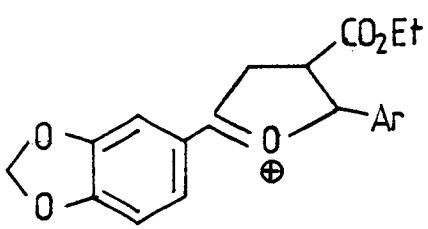


(41a) R = α-CO_2Et

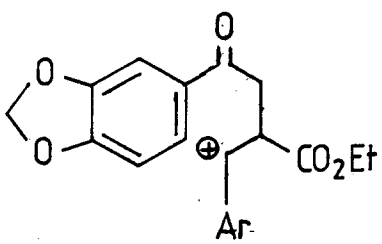
(41b) R = β-CO_2Et

$SnCl_4$-MeOH

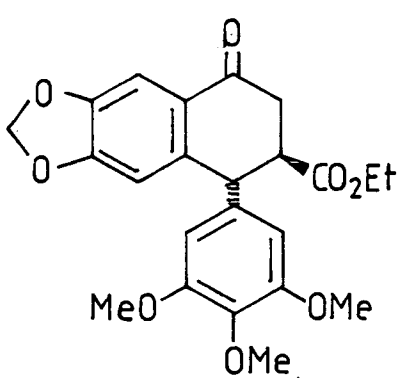
or BF_3-Et_2O



(42a)

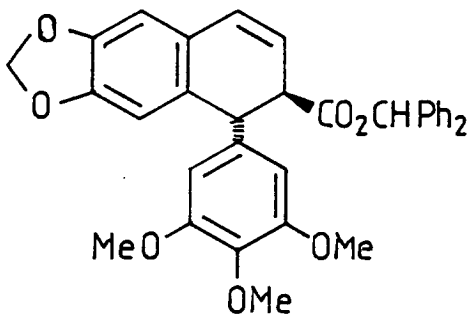


(42b)

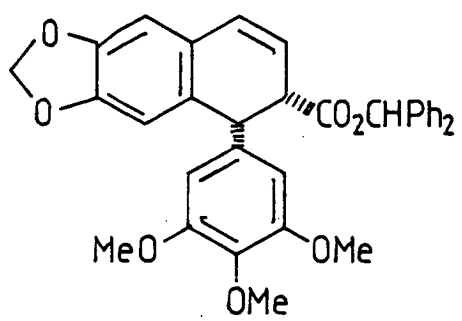


(43)

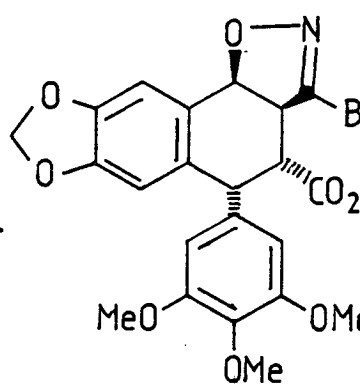
Scheme 8

(43) —(i. KOH–MeOH; ii. $NaBH_4$; iii. pTSA; iv. Ph_2CHOH)→ 

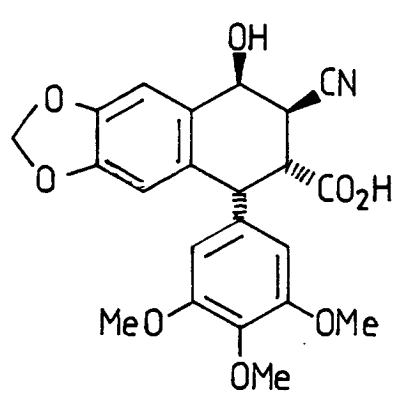
(44)

(44) —(i. LDA; ii. HCl)→ 

(45)

(45) —($KHCO_3$; Br_2CNOH)→ 

(46)

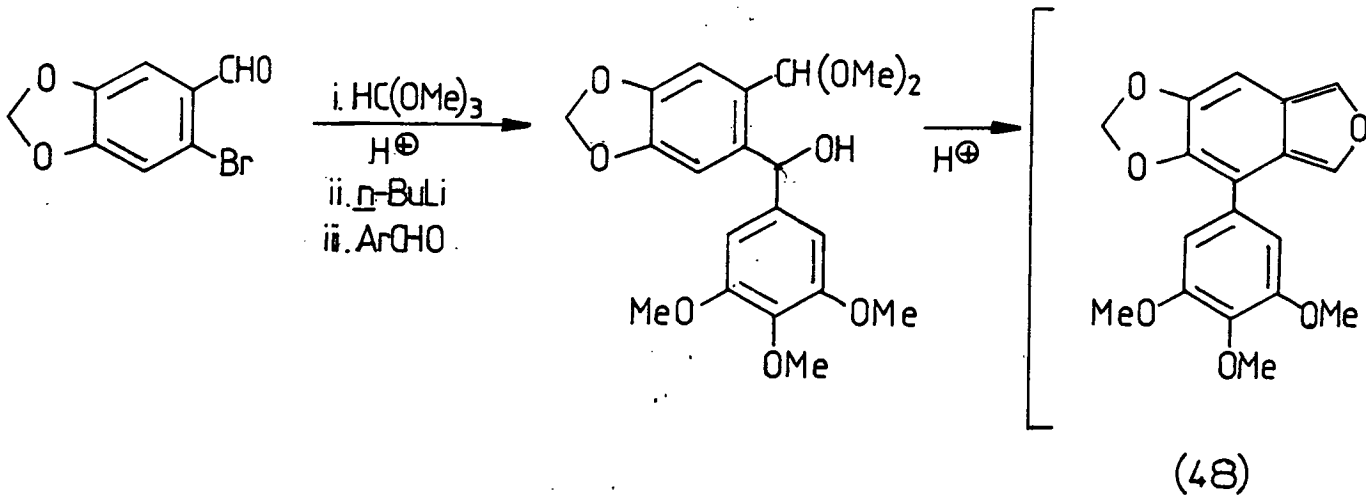
(47) —(i. $H^{\oplus}$–MeOH; ii. RaNi)→ 

(47) —(i. $LiAlH_4$; ii. $NaNO_2$, AcOH, H_2O)→ (16)

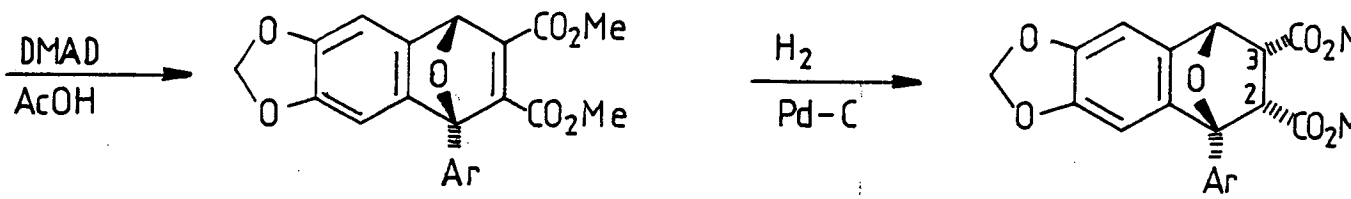
enolate quenching to give the 1,2-cis isomer (45). This underwent a [3+2] cycloaddition with *in situ* generated bromonitrile oxide, giving the tricyclic system (46) with the desired stereochemistry. Hydrolysis of the ester was followed by reductive cleavage of the isoxazole ring, yielding the hydroxynitrile (47). This was lactonized in one pot by $LiAlH_4$ reduction followed by diazotization of the resulting amine, affording epipodophyllotoxin (16). The overall yield was *ca.*25%.

Subtle exploitation of the conformational properties of podophyllotoxin-related aryltetralins has led to other syntheses which do not depend on the epimerization of picropodophyllin as the final step. Thus Rodrigo and Rajapaksa [28] prepared the oxygen-bridged dihydronaphthalene (49) by a Diels Alder reaction between an *in situ* generated isobenzofuran derivative (48) and dimethylacetylene dicarboxylate (DMAD) in the presence of a catalytic amount of a carefully chosen acid (Scheme 9). This was selectively hydrogenated, giving the endo-ester (50) which was epimerized selectively at C-3. The resulting 1,2-cis-2,3-trans product was selectively reduced at the C-3 ester by the sterically demanding reducing agent $LiEt_3BH$. Hydrogenation of the resulting ester alcohol (51) with Raney nickel gave methyl epipodophyllate (52) which was converted into the acetonide (53) whose ester function could be saponified without inversion to afford (54). Conformational analysis of the decalin-type system present in (53) indicates that the most stable conformer is (53b), which contains the ester group equatorial and which suffers less of the interference

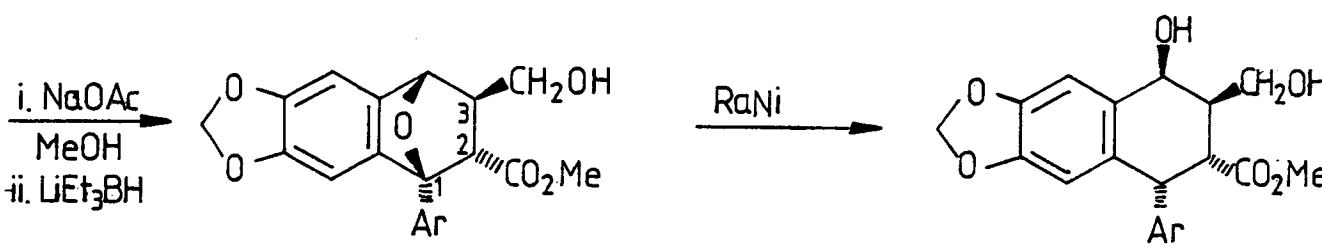
Scheme 9



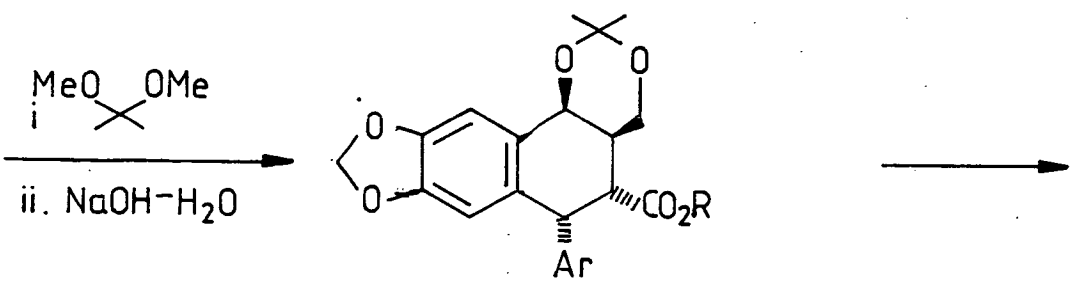
(48)



(49) (50)



(51) (52)



(53) R = Me
(54) R = H

cont.
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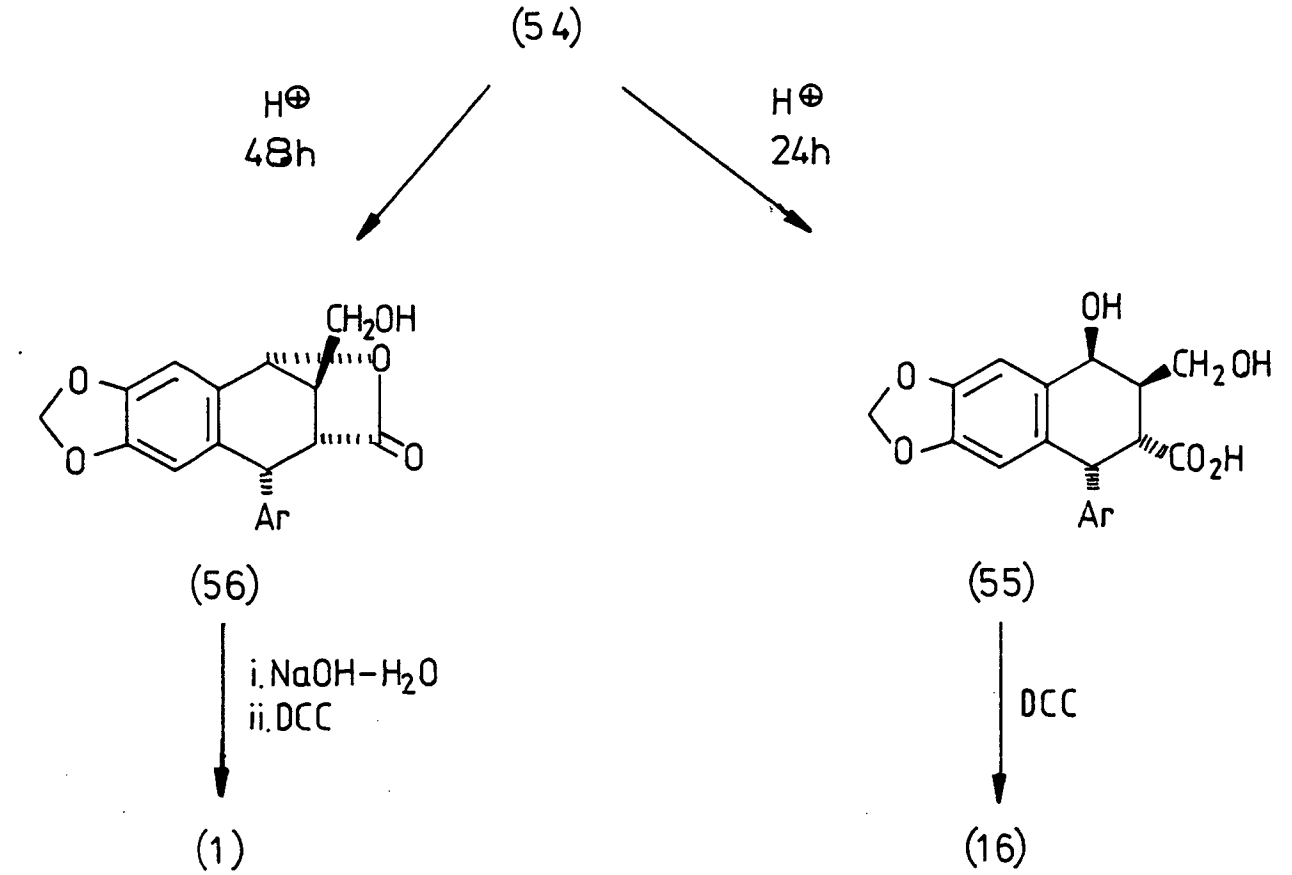
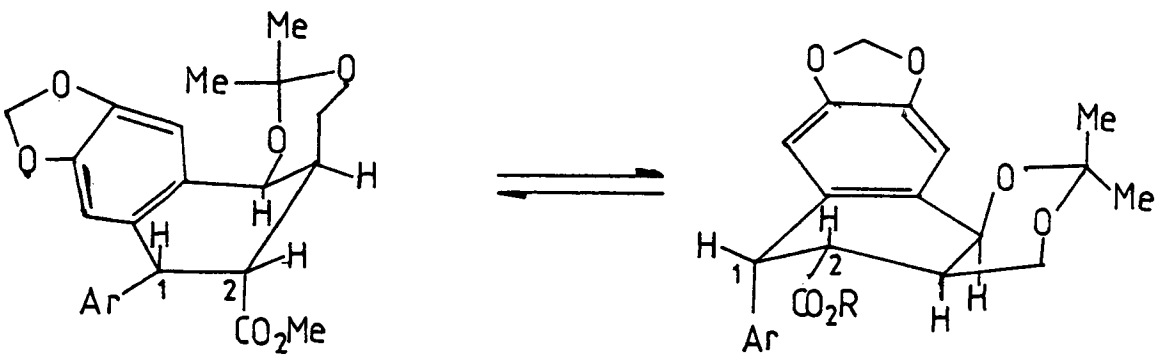
Scheme 9 (cont.)

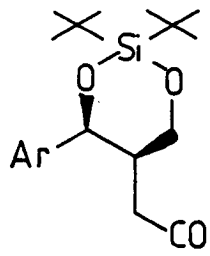




between the aromatic group at C-1 and the axial methyl group of the ketal that occurs in (53a). There is thus no inversion at C-2. Dilute acid removed the ketal and the product depended on the time allowed for hydrolysis. Whereas 24-hour exposure yielded epipodophyllic acid (55), which could be lactonized with dicyclohexylcarbodiimide (DCC) to give epipodophyllotoxin (16), 48-hour exposure gave neopodophyllotoxin (56), which upon careful saponification followed by lactonization gave podophyllotoxin (1). The overall yield from 2-bromopiperonal to podophyllotoxin was 9.4% in twelve steps.

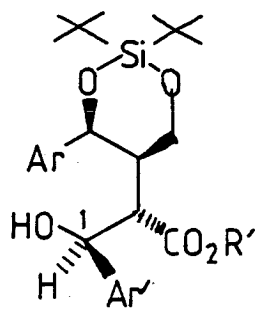
Another example in which conformational factors are employed to good advantage is the very recent synthesis of epipodophyllotoxin (16) by Vandewalle et al[29] (Scheme 10). This is the only synthesis in which the C1-8a bond is the last carbon-carbon bond formed, and the stereochemical outcome obtained contrasts with previous ring closures of this type which have been reported[30,31]. First, cyclic silylene derivatives of type (57) were synthesized and subjected to aldol condensation with 3,4,5-trimethoxybenzaldehyde. Studies of this reaction showed that the stereocontrol was very sensitive to the conditions employed. Most usefully, preparation of the lithium enolate of the trimethylsilyl ester (57, R = $SiMe_3$) in THF resulted in a 4:5 mixture of diastereomeric acids (58a) and (59a). Ester alcohols of type (58b) and (59b) failed to cyclize to give the desired tetralins under a variety of Lewis acid conditions, but it was found that treatment with mesyl chloride gave clean ring closure. Inversion at C-1

Scheme 10



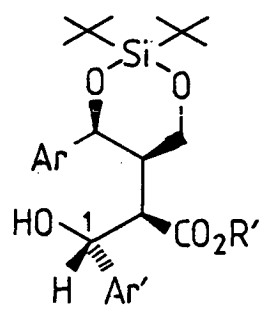
(57)

R = TMS
i. LDA-THF
ii. Ar'CHO
iii. AcOH-EtOH



(58) a R = H
b R = alkyl

+



(59) a R = H
b R = alkyl

(58a) → (60)

R' = H
i. TMS-Cl
ii. $MeSO_2Cl$
NEt_3
iii. H_2O

(60) → (16)

i. TBAF
THF
ii. DCC

Ar' = 3,4,5-trimethoxyphenyl

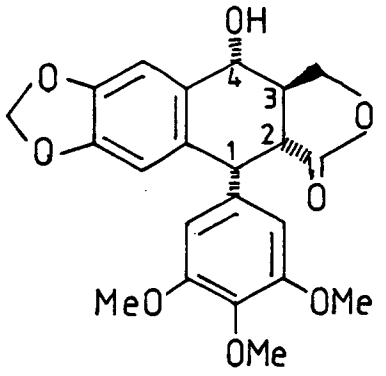
occurred, implying an S_N 2-type displacement. Thus the acid (58a) was protected *in situ* with a trimethylsilyl group and treated with mesyl chloride followed by an aqueous work up to give tetralin (60). The silylene group was removed and lactonization with DCC gave epidophyllotoxin (16).

Chapter 5

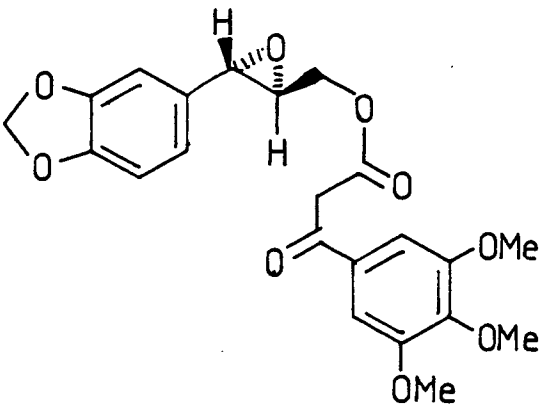
DISCUSSION

None of the synthetic schemes described in the Introduction (Section 1.4) represent entirely satisfactory approaches to podophyllotoxin (1), but they illustrate the problems to be overcome in developing a synthesis. Gensler[22], Kende[23,25], Murphy[26] and Vyas[27] all achieve the disfavoured 1,2-cis-2,3-trans relative configuration of the substituents on the lactone by kinetically controlled epimerizations at the C-2 position of thermodynamically favoured intermediates. Rodrigo[28], Vandewalle[29] and Vyas[27] all carry the oxygen function at C-4 in the undesired β-configuration, and thus require an epimerization at this position at some stage. Moreover, unless a resolution is carried out late in any of these syntheses the final product is racemic.

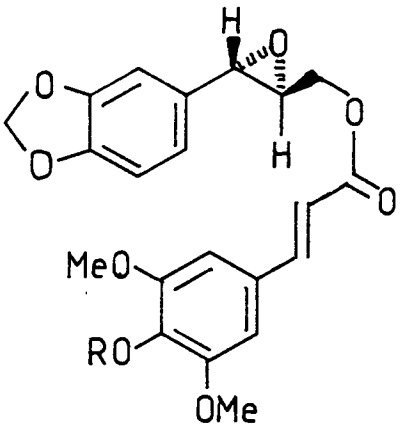
Our intention was to develop a chiral synthesis of podophyllotoxin by making use of the asymmetric epoxidation reaction recently introduced by Sharpless[32] in which allylic alcohols are converted to epoxy alcohols with a high degree of predictable enantioselectivity. The strategy chosen incorporates such an epoxy alcohol function within epoxy esters such as (2)-(4). These each contain a nucleophilic carbon centre which is capable of opening the epoxide in an intramolecular fashion, as shown, to generate in a stereospecific manner the γ-lactone ring of podophyllotoxin (1). Intramolecular ring opening of epoxides is a common synthetic device for forming cyclic compounds[33], and the ready availability of chiral epoxy alcohols resulting from Sharpless' work has made the use of suitable derivatives (such as carbamates and carbonates) which can be so cyclized very



(1)



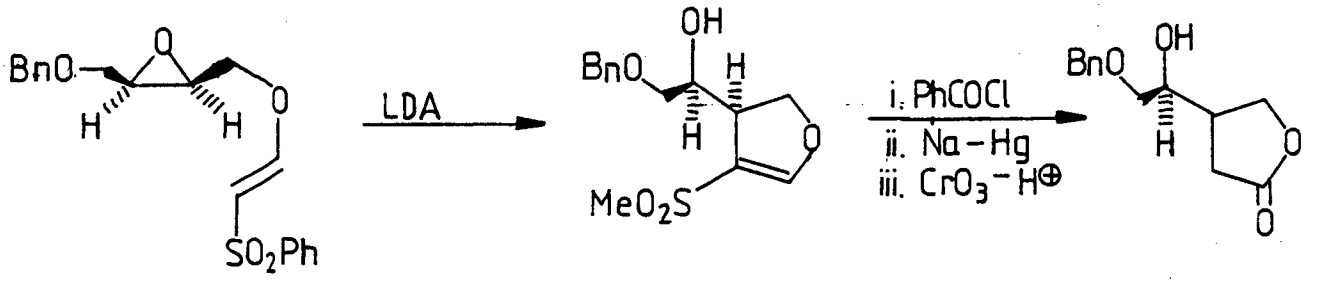
(2)



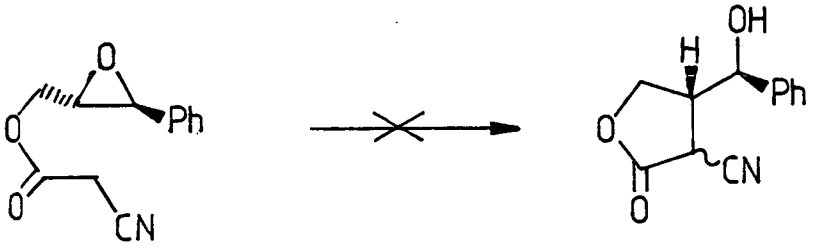
(3) R = Me

(4) R = H

Scheme 1



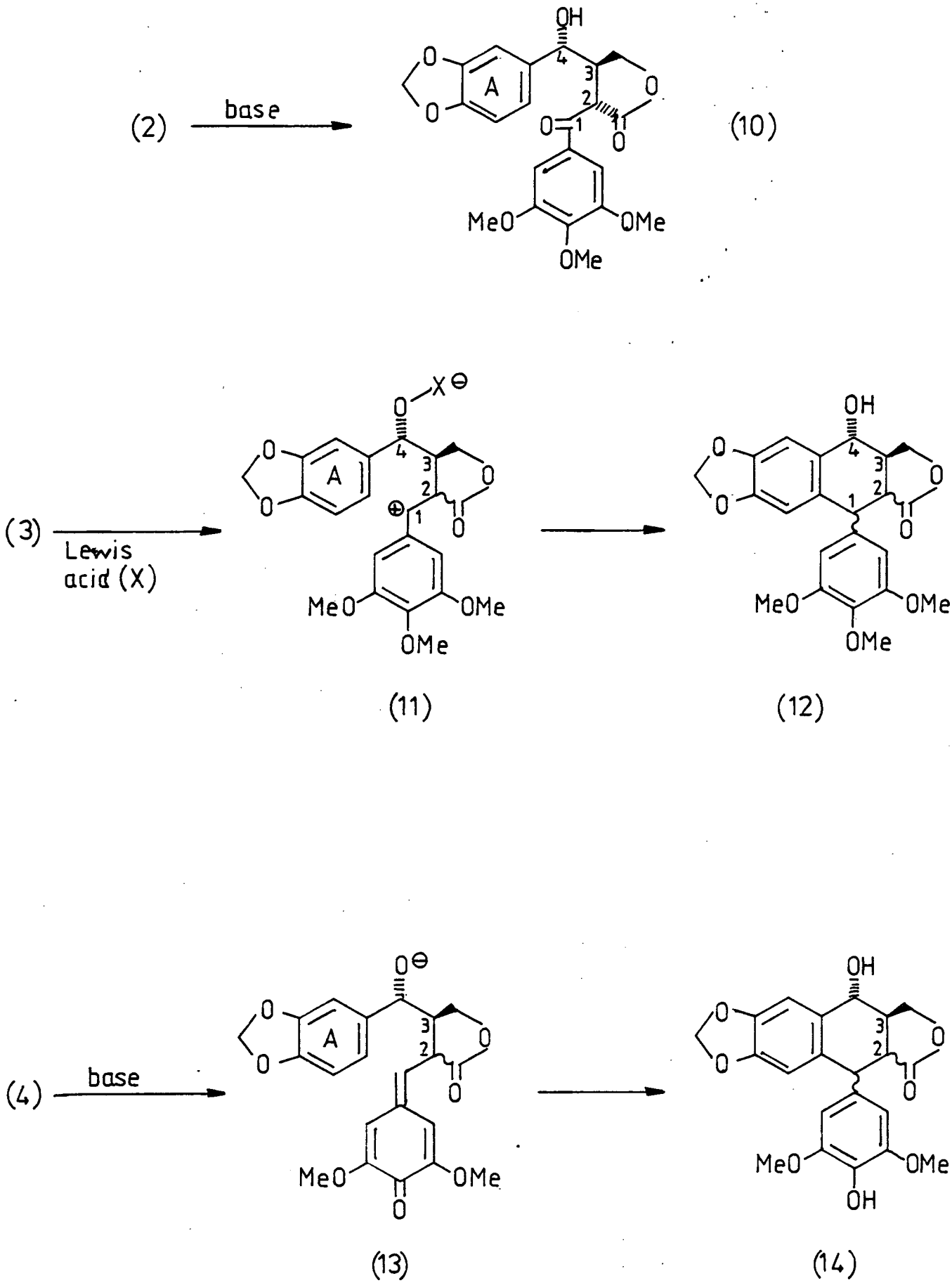
(5) (6) (7)



(8) (9)

attractive in natural product synthesis[34]. However, it is only very recently that an example has appeared in which the internal nucleophile is a carbon atom[35] (Scheme 1). In this case the cyclic product (6) could be elaborated further to the lactone (7), but it was found that the cyanoester (8) did not cyclize to the corresponding lactone (9). The ring closure of (5) occurred to give a five-membered ring, as appears to be the usual case for epoxy alcohol derivatives under both acidic and basic conditions[34].

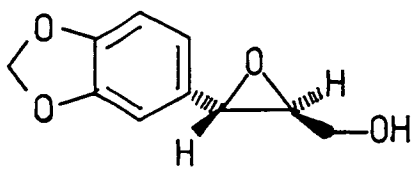
Formation of carbocyclic rings with epoxide opening normally involves intramolecular attack of the carbon nucleophile either as a carbanion generated by a strong base, or as an olefin, in which case the reaction is usually Lewis acid-catalysed[33]. Approaches employing each of these types of cyclization reaction were considered. Thus in the former category the synthesis and cyclization of β-keto esters such as (2) was studied; successful cyclization to the γ-lactone (10) would not only result in the correct absolute configurations at positions C-3 and C-4 but would also automatically incorporate a 3,4,5-trimethoxybenzoyl substituent at C-2. Equilibration of this to give the trans-disubstituted lactone present in podophyllotoxin should occur under the basic reaction conditions (Scheme 2). The possibilities for stereoselective coupling of ring A to C-1 in (10) will be discussed later. In the alternative type of intramolecular epoxide opening reaction, for which use of ester (3) was considered, the regioselectivity of the acid-catalysed cyclization may require careful investigation. The strong electron-donating character of


(2)
base
(10)
(3)
Lewis acid (X)
(11)
(12)
(4)
base
(13)
(14)

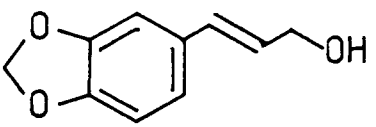
the 3,4-methylenedioxyphenyl group may have an influence in determining whether a γ- or δ-lactone (formed by attack at C-4) is formed. The carbonium ion (11) which would result from attack by the olefin could, among other possibilities, undergo electrophilic substitution onto ring A to form the tetralin system (12). The stereochemical course of the entire process at C-1 and C-2 would depend on factors such as the concertedness of the two bond-forming steps as well as on the geometry of the ester starting material.

As an alternative to an acid-catalysed intramolecular reaction between an olefin and an epoxide it was considered that under basic conditions the phenol (4) may be able to undergo cyclization via the quinonemethide (13) (Scheme 2). As with carbonium ion (11), this may then be able to undergo further cyclization onto ring A to give the tetralin (14). This approach is biomimetic in the sense that it is proposed that in nature construction of the C2-3 bond results in formation of a quinonemethide similar to (13)[8].

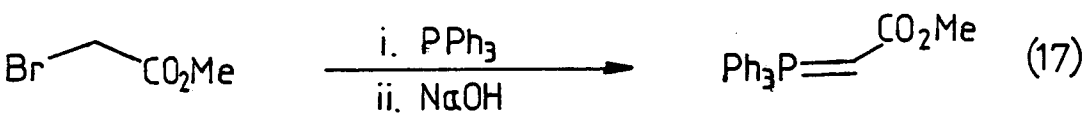
The Sharpless asymmetric epoxidation reaction converts allylic alcohols into chiral epoxy alcohols and so the esters (2)-(4) must all be formed by the coupling of (2R,3S)-epoxy alcohol (15) with appropriate acids. The required substrate for asymmetric epoxidation here then is the trans-cinnamyl alcohol (16), and this was obtained via a stereoselective Wittig reaction. Thus the stabilized phosphorane (17) was prepared in 87% yield from methyl bromoacetate and was reacted with piperonal (18), giving the cinnamate ester (19) in 88% yield (Scheme 3).



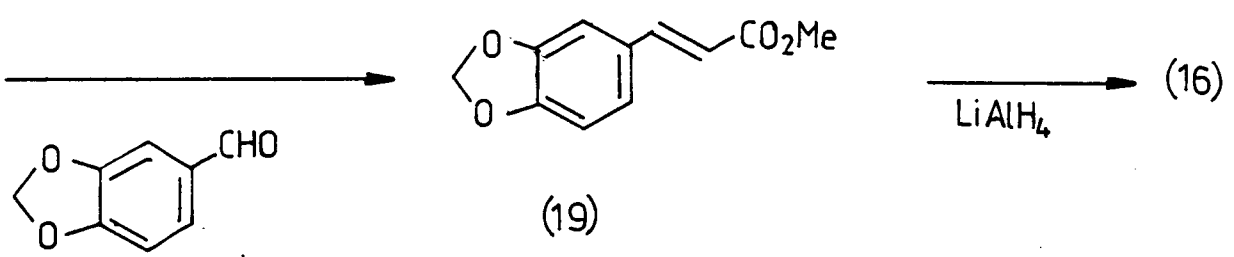
(15)

(16) 

Scheme 3



(17)



(16)

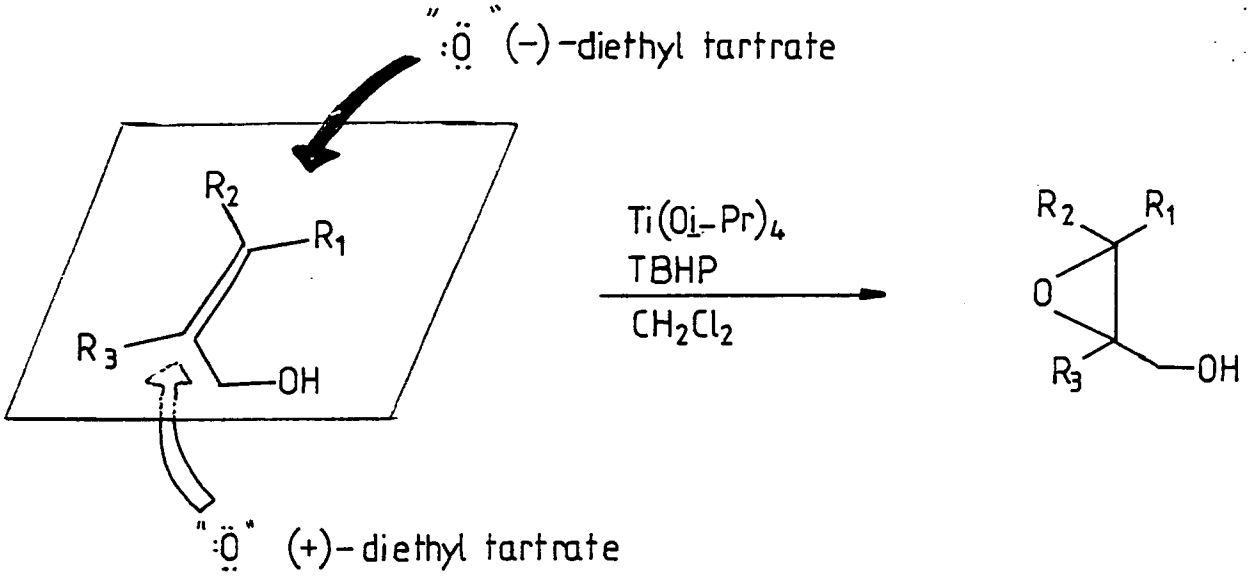
(19)

(18)

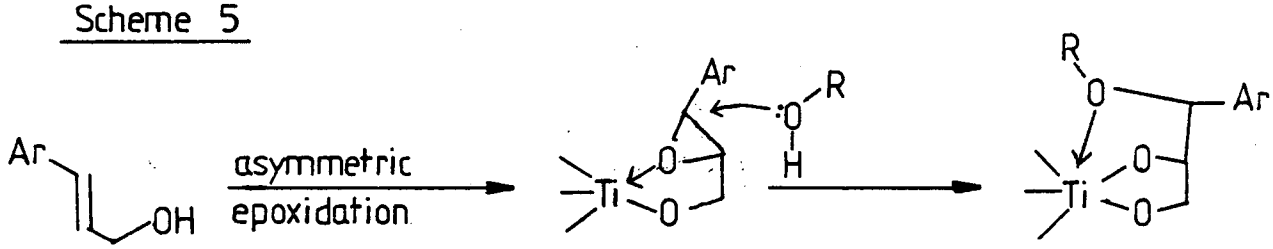
Selective reduction of the ester function with lithium aluminium hydride[36] gave the cinnamyl alcohol (16) in 78% yield.

Asymmetric epoxidation by the Sharpless method[32,37a] involves oxidation of the double bond by t-butyl hydroperoxide (TBHP) in the presence of titanium tetraisopropoxide and a chiral tartrate ester. The enantioselectivity is controlled by the chirality of the tartrate employed, and it may be predicted as shown in Scheme 4. The reliability of this rule is quite remarkable[37b] and the mechanism of the reaction has been the subject of intense investigation and speculation[37c]. (+)-Diethyl tartrate was therefore chosen in order to produce epoxy alcohol (15) from allylic alcohol (16). The conversion was first attempted at -20°C using the olefin and oxidizing mixture (TBHP, titanium tetraisopropoxide and (+)-diethyl tartrate) in a stoichiometric ratio, but no epoxy alcohol was isolated. While results were variable, in general the reaction had a tendency not to reach completion (starting material was usually recovered) and any conversion only gave complex mixtures of products which could not be resolved, even when purification was attempted on acetylated material. Recent studies by Sharpless[37d,38] suggest that the epoxides obtained from cinnamyl alcohols are sensitive to opening under the reaction conditions. As a Lewis acid the titanium (IV) species catalyses not only epoxidation but also opening of the epoxide due to nucleophilic attack by isopropanol, TBHP, allylic alcohol or epoxy alcohol (Scheme 5). Moreover, the resulting diol ether is a strong chelating

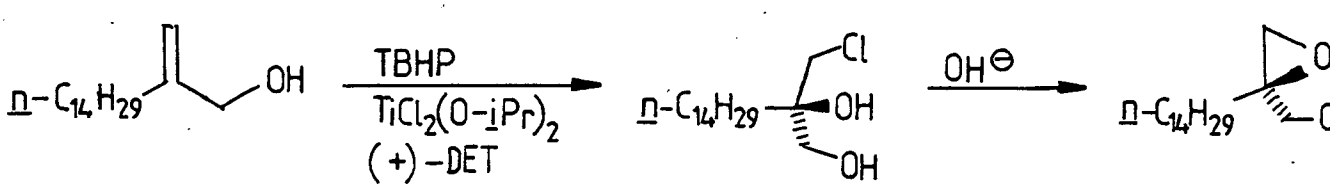
Scheme 4



Scheme 5

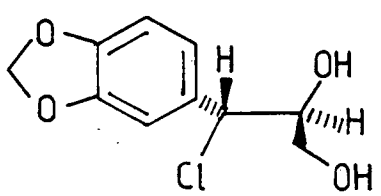


Scheme 6

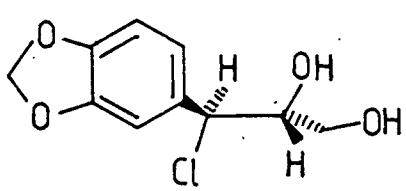


(20)

(21)



(22)



(23)

agent and so the titanium is deactivated as a catalyst; this may account for the incomplete conversion observed with (16).

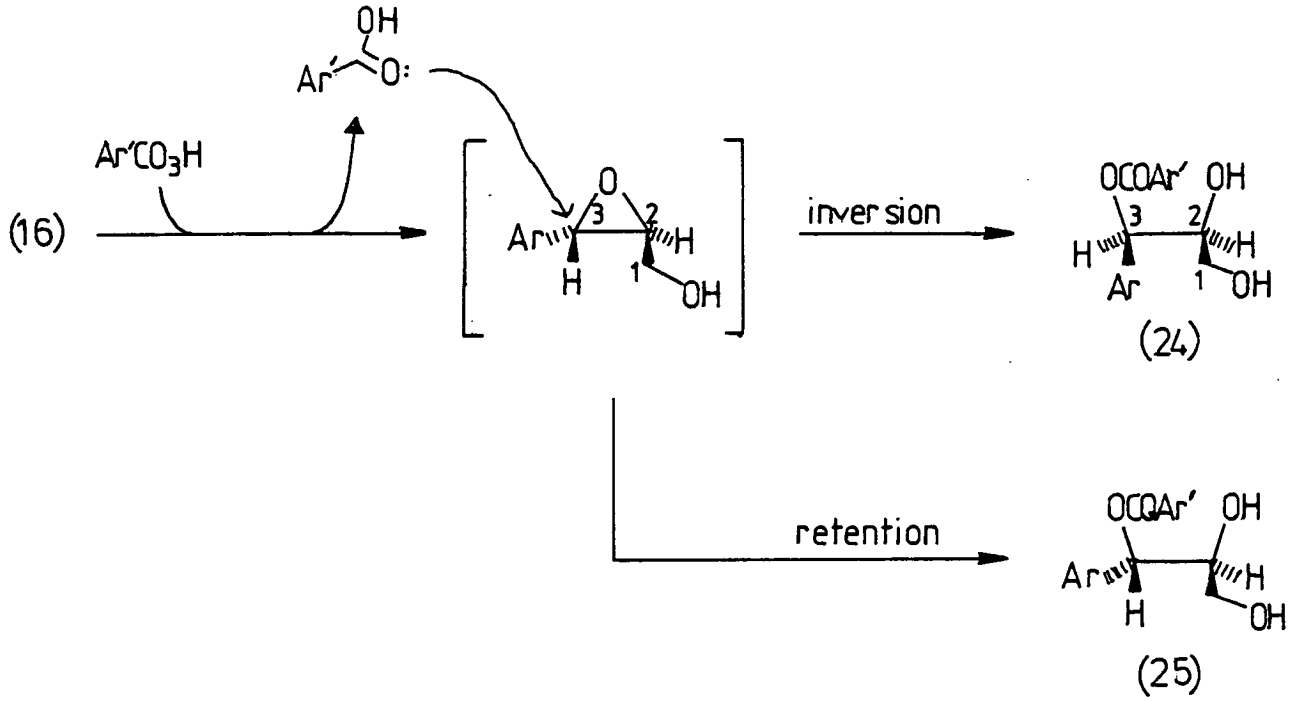
Two approaches were used in an attempt to overcome this problem. First, it has been suggested by Sharpless[38] that sensitive epoxy alcohols such as (15) can be trapped *in situ* in a selective manner by substituting titanium dichlorodiisopropoxide for titanium tetraisopropoxide in the asymmetric epoxidation reaction. This has been shown to lead in certain cases, such as (20), where the standard process gave a poor yield, to a single chlorodiol which could be closed to the epoxide, (21), on exposure to base (Scheme 6). The enantioselectivity of the transformation involving use of titanium dichlorodiisopropoxide was found to be the inverse of that described for the titanium tetraisopropoxide-catalysed reaction. In order to obtain the desired epoxide (15) via chlorodiol (22) use of unnatural (-)-diethyl tartrate would therefore be necessary. Trial reactions, however, using (+)-diethyl tartrate failed to give chlorodiol (23), once again resulting in complex mixtures of products. Attempts to carry out *in situ* base-catalysed ring closure (aqueous sodium carbonate-ether) similarly failed.

The other approach was an attempt to exploit the recent finding by Sharpless that when the standard asymmetric epoxidation reaction is carried out in the presence of molecular sieves only catalytic (<10%) quantities of titanium tetraisopropoxide and diethyl tartrate are required[39]. It was suggested that this modification would then reduce the

risk of the undesired epoxide opening, but in practice it was found that only a minimal (<10%) conversion of the cinnamyl alcohol (16) occurred, although hplc indicated that this may have been to the desired epoxy alcohol (15).

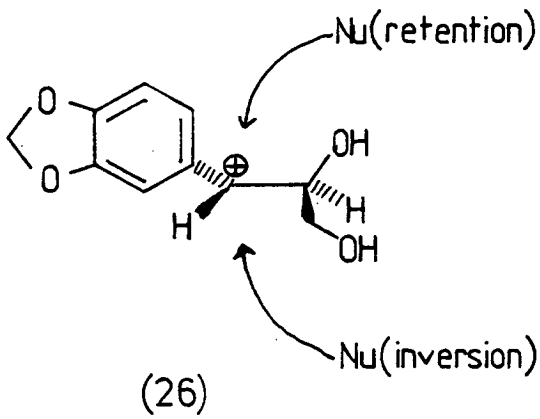
As no success was forthcoming in the asymmetric epoxidation reaction, synthesis of racemic epoxy alcohol (15) was considered, both for characterisation purposes and for a 'back up' non-chiral route. First, use of m-chloroperbenzoic acid (mCPBA) under standard conditions[40] was examined, but the crude product of the reaction did not contain any of the desired epoxide. Instead, only a mixture of adducts (24) and (25) arising from nucleophilic attack on it by m-chlorobenzoic acid generated during the reaction (Scheme 7) were present. The position of attachment of the benzoyloxy group was deduced from the chemical shifts in the ^{1}H nmr spectrum, assignments being confirmed by use of selective double irradiation, but it was not possible on the basis of the data available to distinguish between the two diastereoisomers. Formation of the product with retained configuration at C-3 must involve either the fully formed carbonium ion (26) or neighbouring group participation, as in (27)[41]. The ratio of the isomers was *ca.*7:3 and the outcome of attempted chromatographic separation on silica depended on the conditions employed. Dry-flash chromatography gave a product considerably enriched in the major isomer, but preparative tlc involving overnight extraction of the separated bands with dichloromethane led to a mixture now containing (24) and (25) as minor components. The new,

Scheme 7

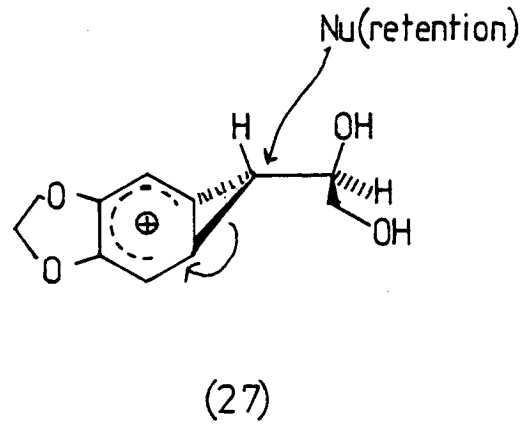


Ar = 3,4-methylenedioxyphenyl

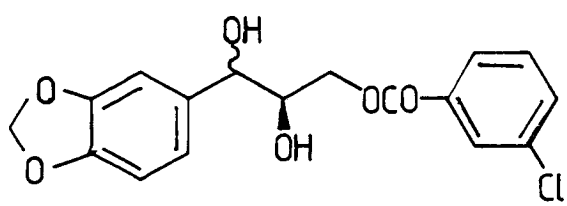
Ar' = 3-chlorophenyl



(26)



(27)



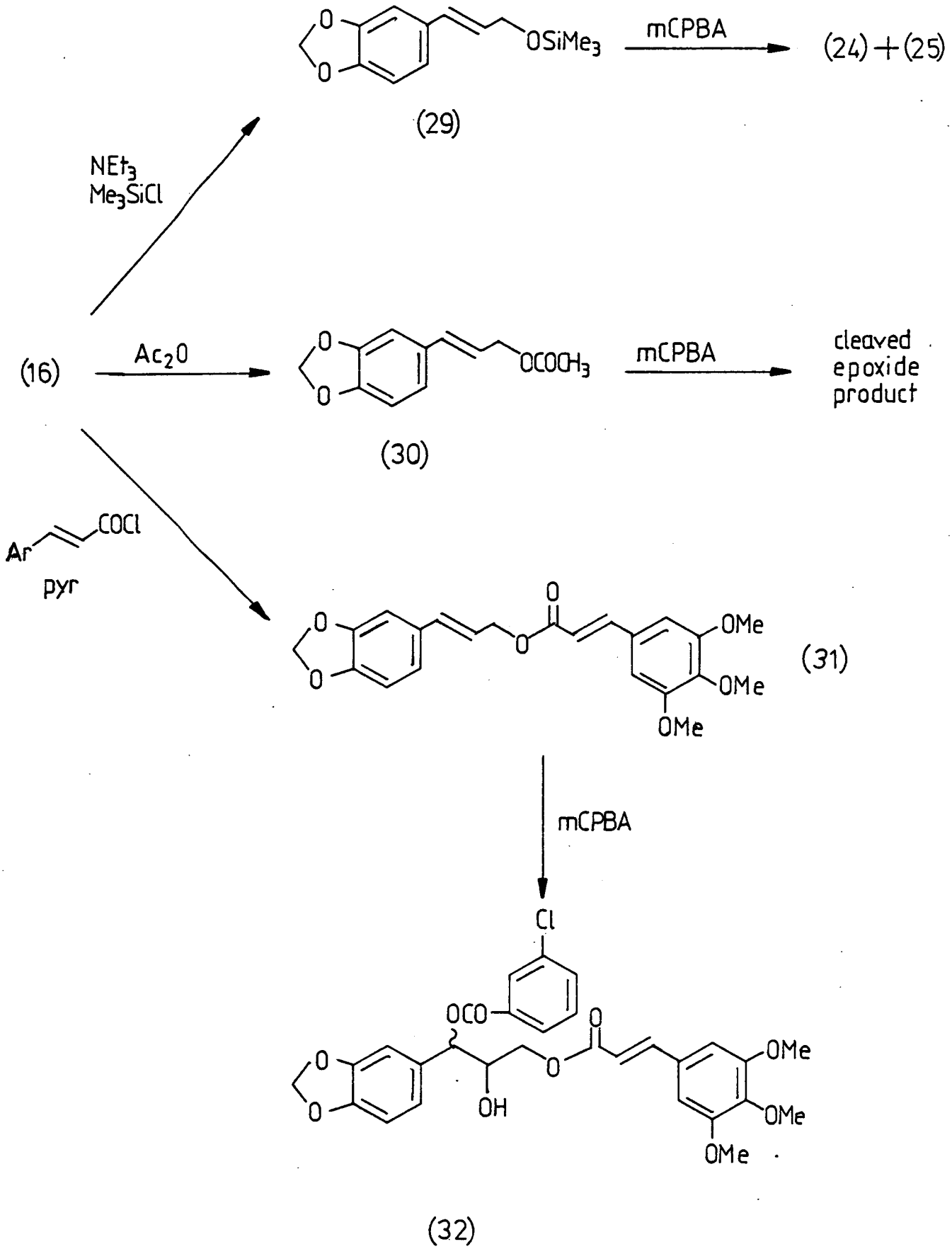
(28)

major, product was assigned on the basis of its ^1H nmr spectrum as the isomer (28) (of undetermined stereochemistry), arising from a 1,3-shift of the benzoyl group onto the thermodynamically preferred primary position.

Further study of the m-chloroperbenzoic acid epoxidation showed that the olefin was oxidized very rapidly but the subsequent cleavage reaction was also very fast. Thus when the reaction was stopped after 90 seconds only starting material and cleaved epoxide were obtained, in a *ca* 1:1 ratio. It was hoped that by providing a suitable buffering medium the acid-catalysed epoxide opening might be prevented, but use of pyridine or a two-phase system with aqueous sodium bicarbonate[42] resulted in the same benzoate ester cleavage products as before, while triethylamine retarded the epoxidation reaction and virtually no olefin conversion was noted after 1 hour.

The hydroxyl group in allylic alcohols is well-known to exert a directing and accelerating influence in peracid epoxidations and this is thought to be due to its participation in the highly ordered transition state for the reaction[43]. As it may similarly affect the cleavage reactions the m-chloroperbenzoic acid epoxidations of some protected allylic alcohols were studied (Scheme 8). The trimethylsilyl ether (29) and the acetate and cinnamate esters (30)[44] and (31)[36] were prepared in 100%, 65% and 66% yields respectively. Use of the silyl ether (29) demonstrated the accelerating effect of the hydroxyl group, as after 60 seconds no reaction was observed. After 1.5 hours no olefin remained but the products, after aqueous

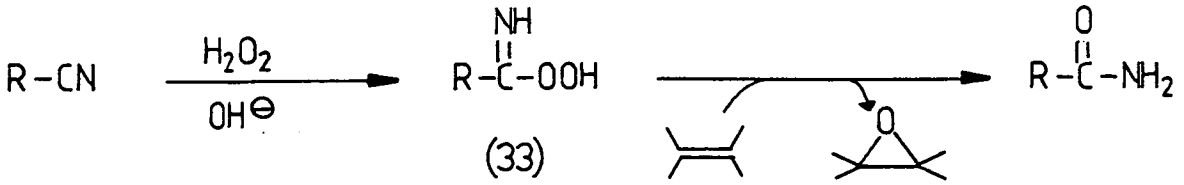
Scheme 8


OSiMe3
mCPBA
(24) + (25)
(29)
NEt3
Me3SiCl
(16)
Ac2O
OCOCH3
mCPBA
cleaved epoxide product
(30)
ArCOCl
pyr
OMe
OMe
OMe
(31)
mCPBA
Cl
OCO
OH
OMe
OMe
OMe
(32)

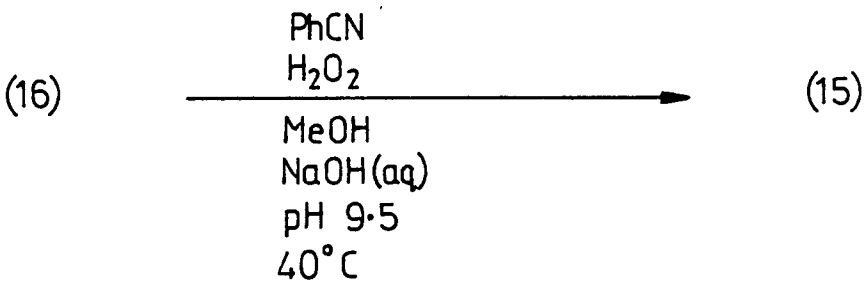
workup, were the same benzoate esters (24) and (25) obtained with the alcohol (16). The acetate (30) also reacted relatively slowly and after 1.5 hours reaction workup gave only a 7:3 mixture of cleaved epoxide products and starting material. Successful formation of the epoxide from the cinnamyl cinnamate (31) would give the key epoxy ester (3), but with m-chloroperbenzoic acid the only product isolated (in 35% yield) was the benzoate ester (32) of predominantly one diastereoisomeric form.

In view of the acid-labile nature of the epoxide the method of Payne[45] was considered whereby a perimidic acid (33) is generated *in situ* by the action of hydrogen peroxide in base. This then delivers an oxygen atom to a carbon-carbon double bond and is itself reduced to a non-nucleophilic amide (Scheme 9). Following considerable optimization of conditions, involving use of different bases, nitriles, solvents, pH's and temperatures it was found that the conditions summarized in Scheme 10 were effective for almost quantitative conversion of allylic alcohol (16) into epoxy alcohol (15). An excess of benzonitrile and hydrogen peroxide, a pH of 9.5 (as indicated by a pH meter) and a temperature of 40°C were necessary for complete reaction with minimum side-reactions. Potassium bicarbonate could also be used as the base[46] but gave a reduced yield and the reaction was sluggish, while changing the solvent to isopropanol resulted in no reaction. Use of other nitriles, e.g. acetonitrile, trichloroacetonitrile, either led to quantitative recovery of starting material or unidentified mixtures, depending

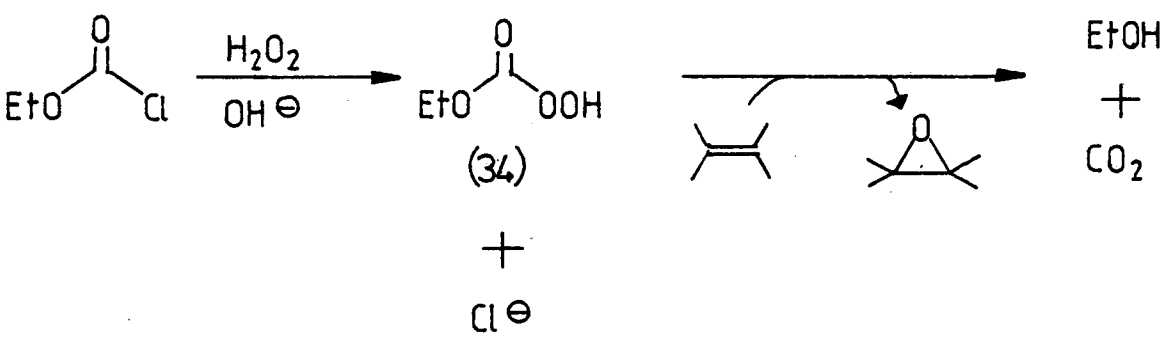
Scheme 9



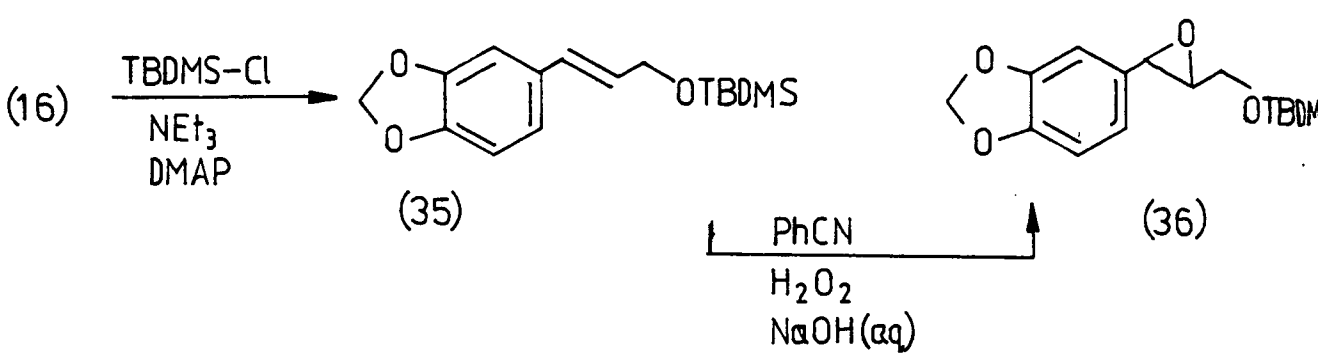
Scheme 10



Scheme 11



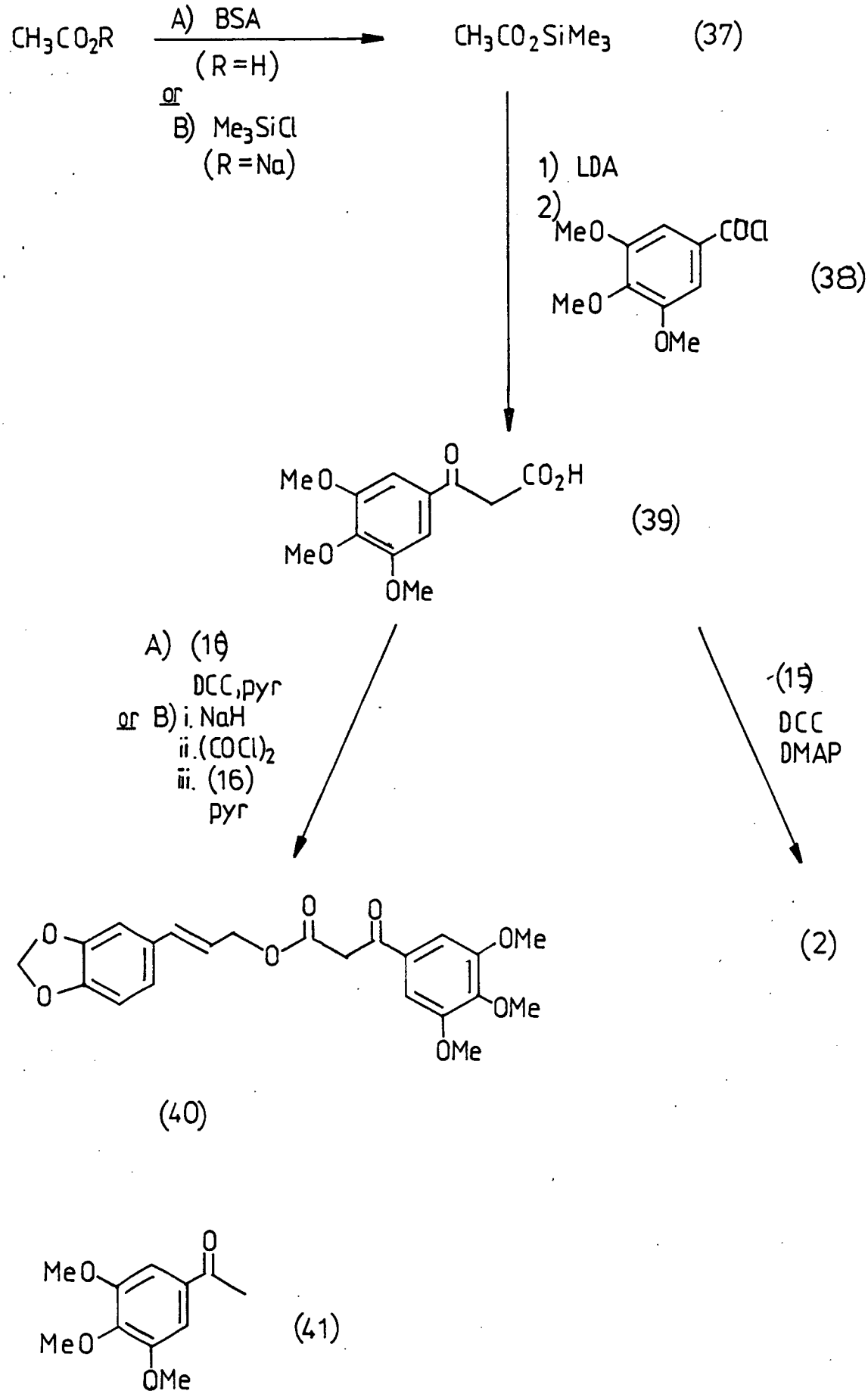
Scheme 12



on the conditions. Similar results were obtained with ethyl chloroformate, which in basic hydrogen peroxide is reported[47] to form O-ethylpercarbonic acid (34) which is then reduced by an olefin to easily removable carbon dioxide and ethanol (Scheme 11). This would have helped overcome the problem of purification of (15), which was unstable to chromatography and did not crystallize. Another attempt to obtain pure (15) involved subjecting the t-butyldimethylsilyl ether (35) to a perimidic acid epoxidation in the hope that the resulting epoxide (36) would be stable to chromatography. In practice (35), which was obtained from the alcohol (16) in 58% yield, showed little reactivity towards the benzonitrile-hydrogen peroxide mixture, although ^{1}H nmr suggested a minimal (<10%) conversion to the epoxide (36) may have occurred (Scheme 12). Similar attempts to epoxidize the cinnamyl cinnamate ester (31) using hydrogen peroxide and benzonitrile or trichloroacetonitrile also gave no reaction. Fortunately the impurities contaminating the epoxy alcohol (15) (consisting mainly of benzamide) could be removed at the next stage.

Epoxy alcohol (15) was next coupled with various acid functions to give esters of type (2)-(4). The first target was β-keto ester (2), for which it was decided to prepare the acid (39) by the method of Cowan and Rathke[48]. Acetic acid was O-silylated by bis(trimethylsilyl)acetamide (BSA) (Method A, yield 94%) or sodium acetate by trimethylsilyl chloride (Method B, yield 42%) to give trimethylsilyl acetate (37). The lithium enolate of this was acylated

Scheme 13


CH3CO2R
A) BSA
(R=H)
or
B) Me3SiCl
(R=Na)
CH3CO2SiMe3
(37)
1) LDA
2)
MeO
COCl
MeO
OMe
(38)
MeO
CO2H
MeO
OMe
(39)
A) (16)
DCC, pyr
or B) i. NaH
ii. (COCl)2
iii. (16)
pyr
(15)
DCC
DMAP
OMe
OMe
OMe
(2)
(40)
MeO
MeO
OMe
(41)

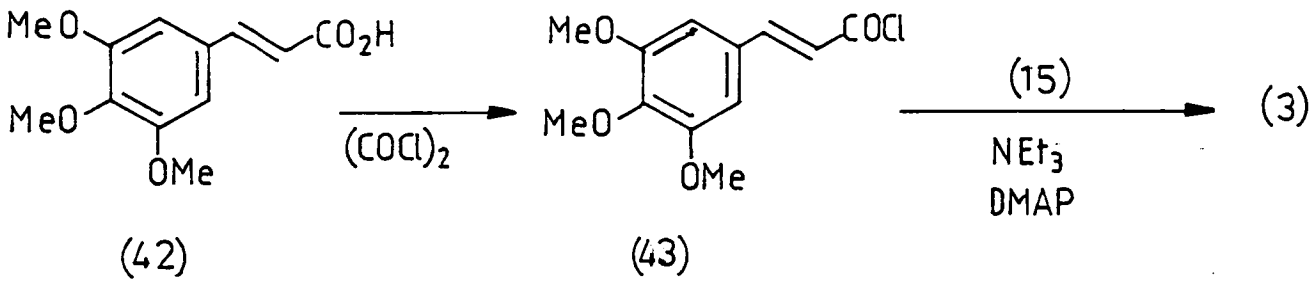
with 3,4,5-trimethoxybenzoyl chloride (38) to give, after careful workup, the desired β-keto acid (39) (Scheme 13). The best yield (53%) was obtained when (37), LDA and (38) were used in the ratio 1.5:2:1. Model studies using the cinnamyl alcohol (16) and the β-keto acid (39) showed that coupling could be achieved by use of dicyclohexylcarbodiimide (DCC), giving the ester (40) in 35% yield (not optimized) after chromatography (Scheme 13). Alternatively the sodium salt of (39) could be treated with oxalyl chloride at 0°C and the alcohol (16) added after 1 hour's stirring at room temperature. This gave the ester (40) in 18% yield (not optimized), plus the aryl ketone (41) as a major side-product. The DCC coupling method was used to esterify the epoxy alcohol (15) with β-keto acid (39), giving the ester (2) in yields ranging from 20 to 35%. The poor, variable yield is mainly a reflection of the stability of the ester towards chromatography on silica, the method used for its purification; for example, in one experiment material of purity >90% was obtained after initial chromatography of the crude product, but after a further column the yield dropped to 20% of very pure (2). In the absence of the catalyst 4-dimethylaminopyridine (DMAP) no ester (2) was obtained.

Attempting to couple the epoxy alcohol (15) with 3,4,5-trimethoxycinnamic acid (42) using DCC failed to produce the next desired ester, the epoxy cinnamate (3), in appreciable yield, but use of the acid chloride (43) was slightly more promising (Scheme 14). Upon reaction with the alcohol in the presence of triethylamine base

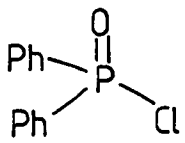
and a catalytic amount of DMAP the ester was obtained in 12% yield; other bases, e.g. guanidine, pyridine, diisopropylamine-polystyrene gave inferior results. The best method, however, was application of the peptide coupling reagent diphenylphosphinyl chloride[49] (DppCl) (44). Reaction of this with a carboxylic acid (RCO_2H) results in formation of a carboxylic phosphinic mixed anhydride (45), and in peptide synthesis this undergoes attack by an amino component selectively at the carboxylic centre to give an amide (peptide), plus diphenylphosphinic acid by-product. In order to synthesize the ester (3) using this methodology 3,4,5-trimethoxycinnamic acid (42) and DppCl were mixed together at 0°C and then the alcohol (15), triethylamine and DMAP catalyst were added. Eventual workup and purification by chromatography afforded the ester (3) in 45% yield (Scheme 15). The reaction could be studied by following the fate of the phosphorous by ^{31}P nmr. Thus it was found that the formation of the mixed anhydride was complete within 2 minutes, while only 5 minutes was required for the alcohol to completely react. The use of DMAP in the second stage of the process was essential; in its absence the yield of (3) dropped to 12%.

The preparation of (3) required one equivalent of DppCl to form the mixed anhydride (46), but it was envisaged that preparation of the phenol ester (4) would demand two equivalents in order to affect *in situ* protection of the phenolic hydroxyl group as a phosphinate ester (47) (cf. tyrosine protection in peptide synthesis[50]). However, reaction of sinapic acid (48) in this manner followed by

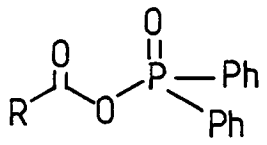
Scheme 14



(42) (43)

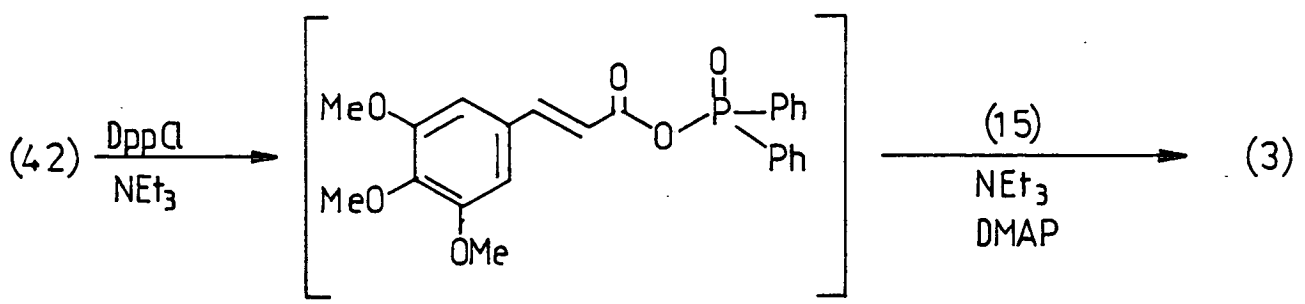


(44)

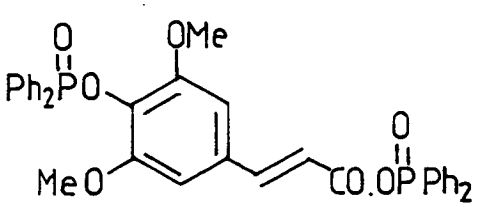


(45)

Scheme 15

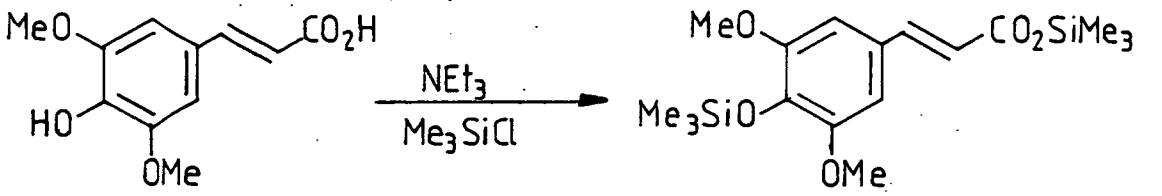


(46)

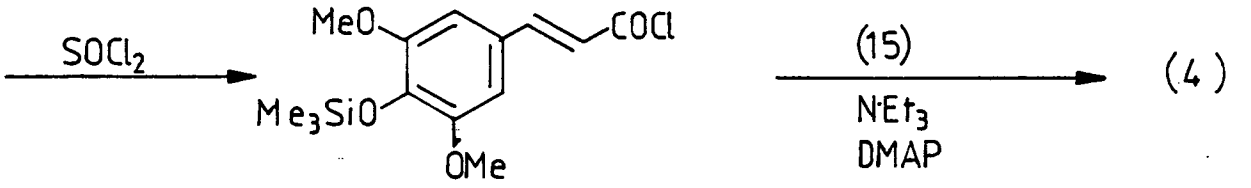


(47)

Scheme 16

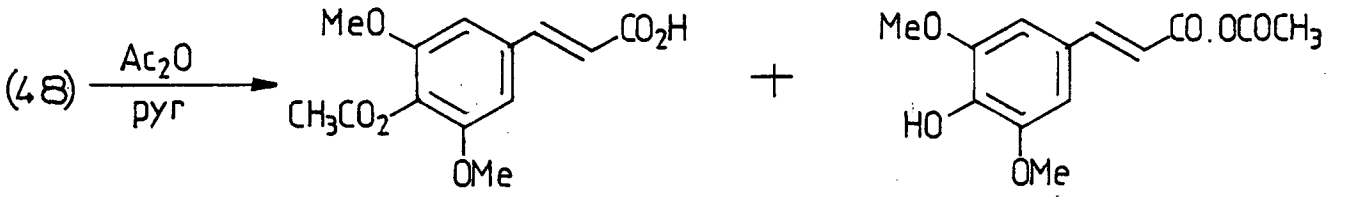


(48) (49)

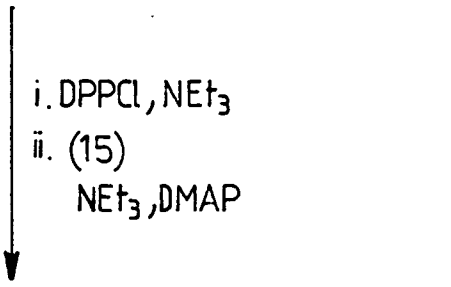


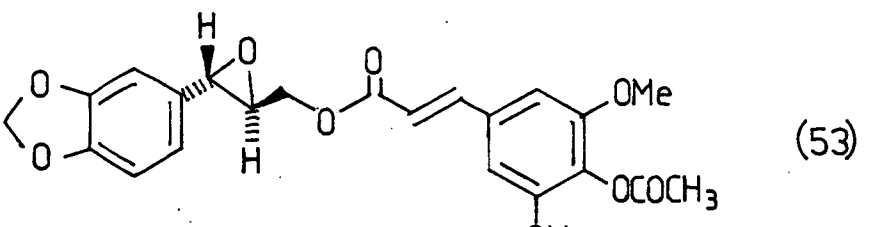
(50)

Scheme 17



(51) (52)





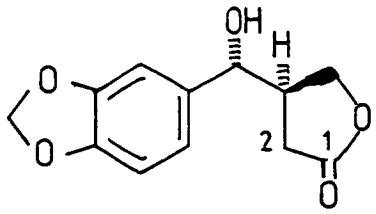
(53)

addition of epoxy alcohol (15) as before gave no isolable ester. The method of Kricheldorf et al[51] however was successful. Here two equivalents of trimethylsilyl chloride were reacted with the acid to give the silyl ether silyl ester (49) which was converted into the acid chloride (50) with thionyl chloride. Reaction of (50) with the epoxy alcohol (15) in the presence of triethylamine and DMAP gave the phenol ester (4) (Scheme 16), but the overall yield from sinapic acid dropped from 61% after preliminary chromatographic purification to only 13% of pure product after a further two columns.

As difficulty was encountered with the preparation of the phenol ester (4) the synthesis and use of its acetate (53) was considered. Under suitable conditions this may constitute a 'pro' form of (4), removal of the acetyl group by a basic nucleophile revealing the phenolate *in situ* prior to cyclization. Acetylsinapic acid (51) was prepared[52] in poor (26%) yield, the main product of acetylation of sinapic acid (48) being the mixed anhydride (52) (52% yield) (Scheme 17). The former product was treated with DppCl (one equivalent) followed by the epoxy alcohol (15) as before to give the diester (53) in 55% yield after chromatography. Epoxy esters (2)-(4) and (53) were each obtained as solids, but no solvent systems could be found in which any of them could be recrystallized.

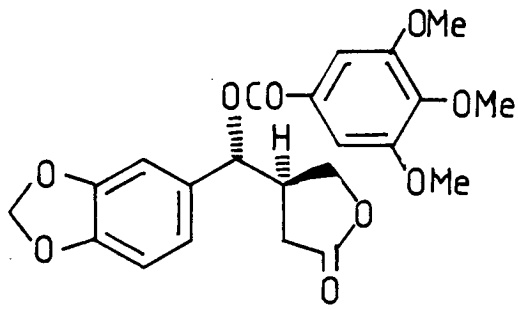
The epoxide openings of esters (2)-(4) and (53) were next investigated. The β-keto ester (2) gave no reaction in the presence of n-butyllithium in THF, but when mixed with potassium carbonate in DMF (2) was completely

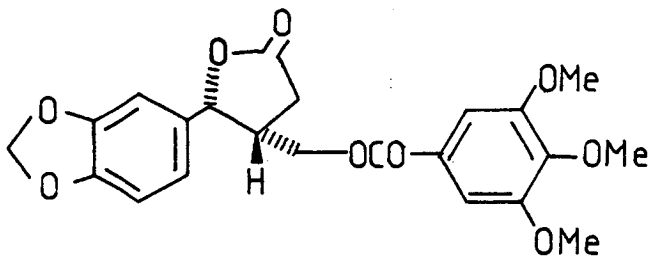
consumed even at room temperature. A weak band at 1772 cm^{-1} in the ir spectrum suggested some lactonization had occurred, but nmr showed a complex mixture. After further experimentation it was found that clean conversion into lactonized material could be achieved by use of sodium hydride in DMF. At temperatures up to 100°C no reaction took place, while at 160°C the product profile varied according to the quantity of base employed. When one equivalent of sodium hydride was used (54), (55) and (56) were obtained in a 9:2:1 molar ratio, following separation by chromatography; the yield of (54) was 48%. When two equivalents of sodium hydride were used only (54) and (55) were obtained, in a 5:1 ratio; the yield of (54) here was 55%. The structures (53)-(55) were assigned on the basis of ir, nmr (with appropriate decoupling) and ms analysis, and the structure of (54) was confirmed by acetylation to give the acetate (57). Mild conditions (acetic anhydride-pyridine) were necessary for this acetylation since more vigorous ones (acetyl chloride-triethylamine) afforded no identifiable product. The rearrangement products (55) and (56) could not be distinguished spectroscopically and the assignments shown were made by comparison with the spectral properties of acetate (57), but are only tentative. Confirmation by chemical means, e.g. ester elimination or hydrogenation was not attempted. A likely route from the ester (2) to products (54)-(56) is shown in Scheme 18. The initial intermediate (58) arising from cyclization with inversion at C-4 was not isolated, and neither was the postulated C-acyl rearranged lactone



(54)

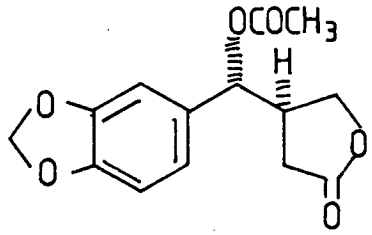
(55)



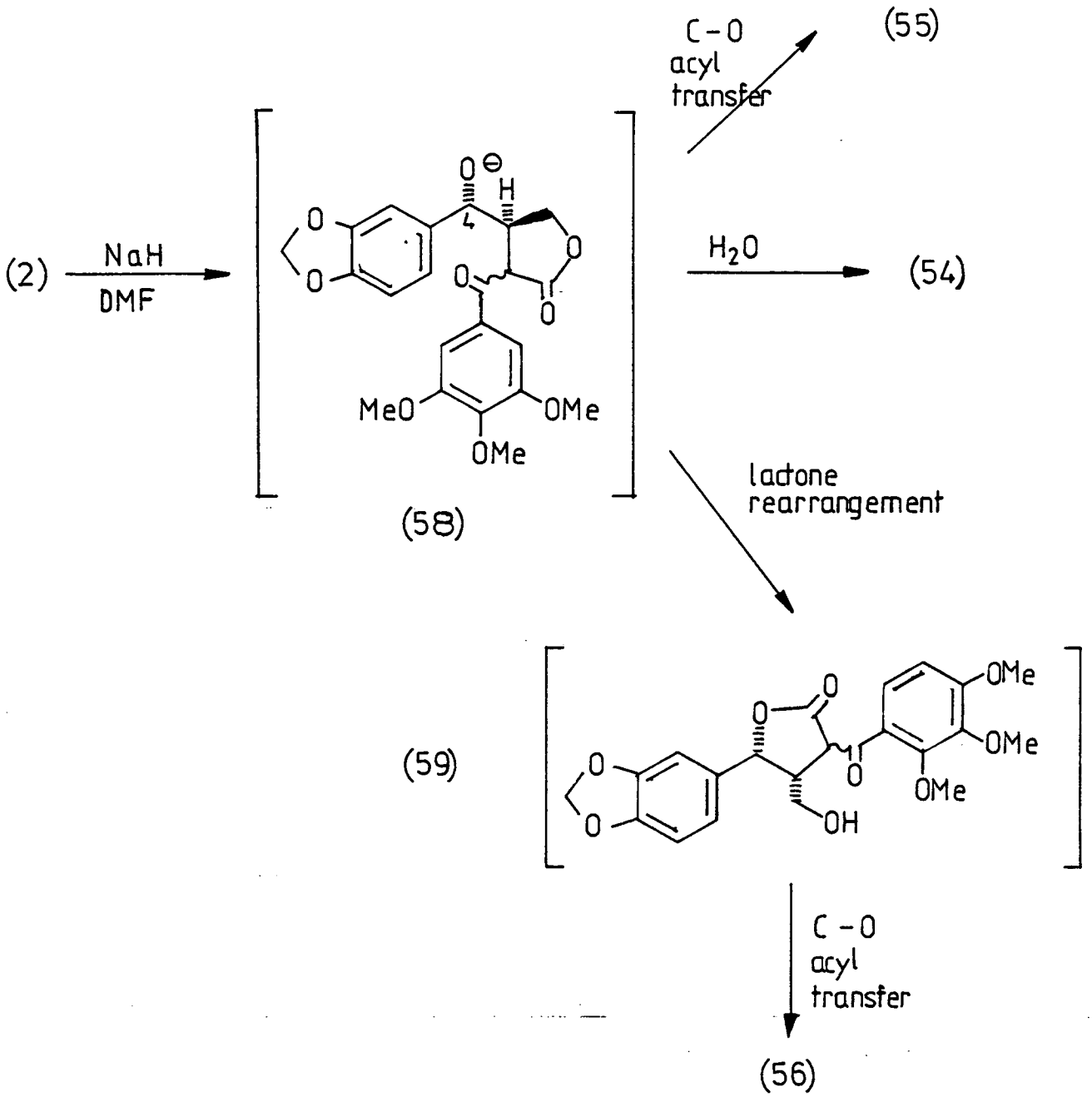


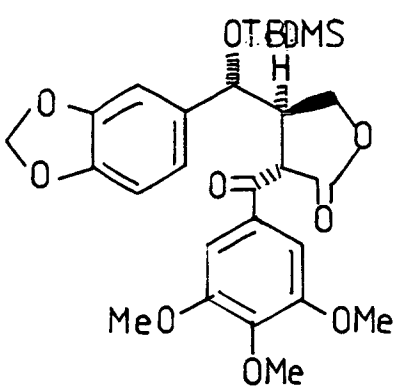
(56)

(57)



Scheme 18


(2)
NaH
DMF
C-O
acyl
transfer
(55)
H_2O
(54)
lactone
rearrangement
(58)
(59)
C-O
acyl
transfer
(56)
MeO
OMe
OMe
OH

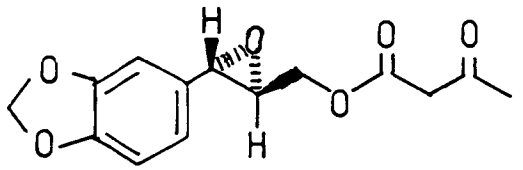

OTBDMS
H
MeO
OMe
OMe

(60)

(59). An attempt was made to trap the proposed intermediate (58) by forming the t-butyldimethysilyl derivative (60) *in situ* , but a mixture again resulted in which the major isolated product (42% yield) was the deacylated lactone (54).

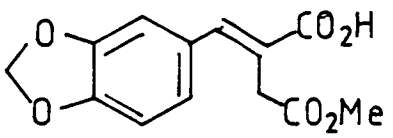
The desired benzoylated lactone (10) was thus not directly available by this route, and it seemed likely that a simpler route to (54), which could then be protected and substituted at C-2, would involve cyclization of the acetoacetate ester (61). This was synthesized by reaction of epoxy alcohol (15) with diketene[53], but once again the epoxy ester was unstable to chromatography on silica. The crude reaction product was largely the desired material, but purification over two columns led to a yield of only 17% of pure (61) as a fluid oil. Cyclization of this epoxy ester with sodium hydride in DMF again gave results dependent on the temperature and quantity of base used. At 120°C no lactonization occurred and only unreacted starting material was recovered, although facile deuterium exchange at the methylene position of the acetoacetate group could be demonstrated. When the reaction was carried out at 150°C in the presence of one equivalent of sodium hydride the only isolated product (in 20% yield) was the acetate (57) arising from a C-O acyl transfer. Use of two equivalents of sodium hydride led to the deacylated lactone (54) and acetate (57) in 28% and 11% yields respectively. No product analogous to the rearranged lactone (56) was obtained by cyclization of the acetoacetate ester.

The cyclization of the other epoxy esters proved less successful. The 3,4,5-trimethoxycinnamate (3) appeared to

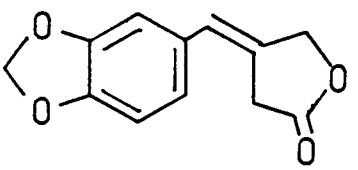


(61)

Scheme 19

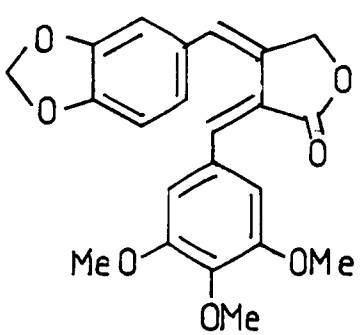


(62)

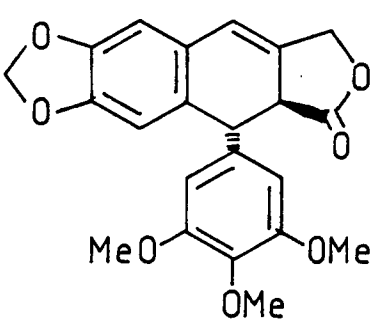


(63)

ArCHO



(64)



(65)

(1)

be stable in the presence of diethylaluminium chloride and tin(IV) chloride. In one experiment use of boron trifluoride etherate at 0°C in dichloromethane gave a product containing strong ir absorption at 1774 cm^{-1}, indicating γ-lactonization, but this could not be repeated and subsequent attempts gave unchanged starting material. Use of excess boron trifluoride etherate at dichloromethane reflux temperature gave a complex mixture of products in which no γ-lactone was detected. The phenol ester (4) gave no reaction with sodium hydride in several solvent systems, e.g. DMF, DMF-HMPA, DMF-18-crown-6, DME, nor with n-butyllithium in THF-HMPA. Use of the latter base in DME resulted in a complex mixture of products in which no γ-lactone was observed. Irradiation with ultraviolet light similarly resulted in no reaction (C_6D_6, sodium hydride-DMF) or a complex mixture of products (acetone) containing no γ-lactone. Finally the acetylsinapate (53) gave no reaction with potassium carbonate in aqueous acetone or sodamide in benzene. Sodamide in hot DMF gave a complex mixture of products in which the acetyl moiety had been removed from the cinnamate group, but no γ-lactone was isolated.

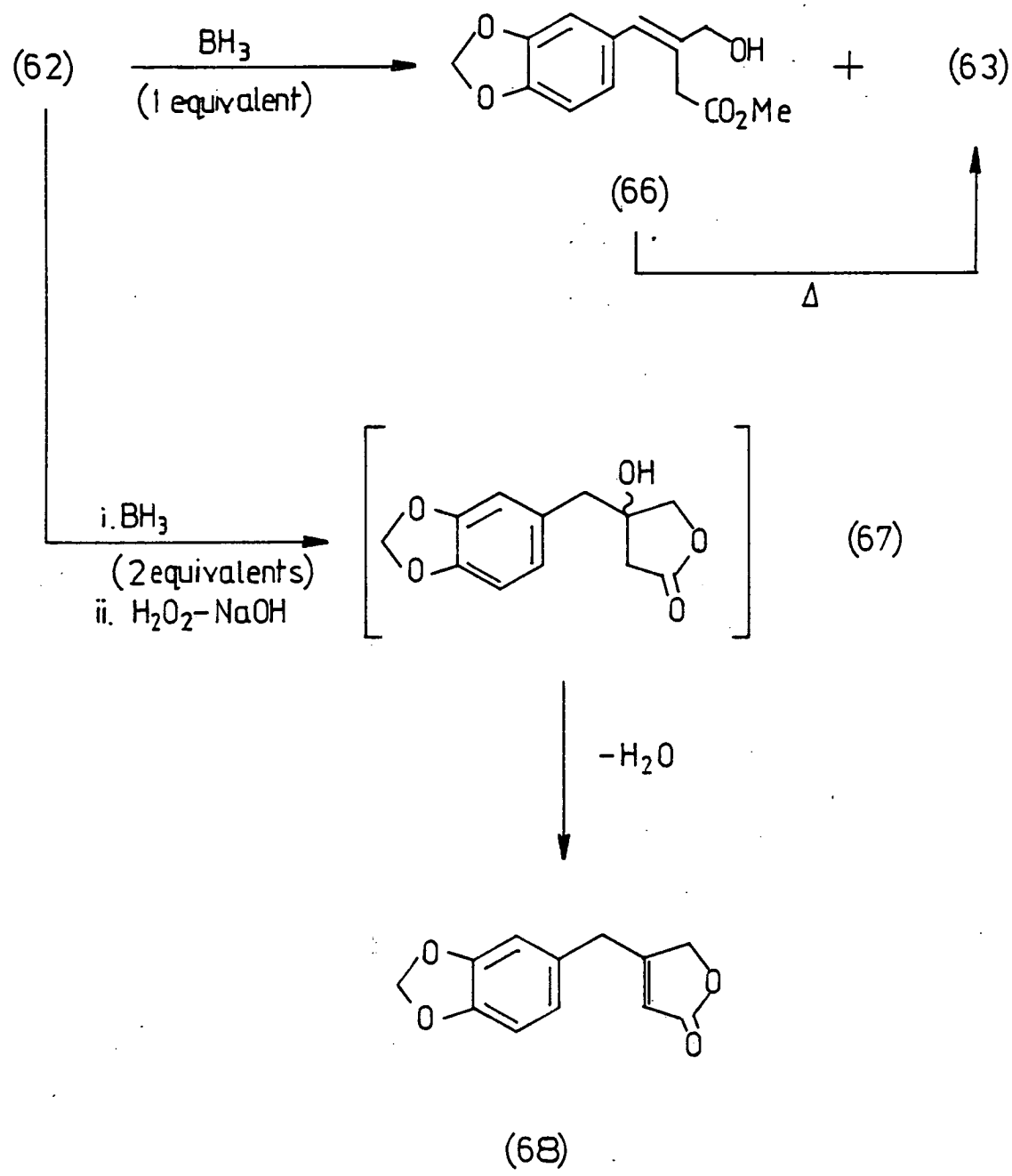
An alternative synthetic approach to podophyllotoxin (1) was also considered (Scheme 19). Here it was envisaged that the itaconic acid half-ester (62), which is available from piperonal[54] (18), would be converted into the arylidene γ-lactone (63) which could then be condensed with 3,4,5-trimethoxybenzaldehyde to give the bisarylidene γ-lactone (64). There is some precedent for the

transformation of such systems into trans-1,2-dihydronaphthalene derivatives via an electrocyclic reaction[55]. In this case the double bond of the resulting α-apopicropodophyllin (65) must then be hydrated[22a,56] and the overall stereocontrol in the synthesis would require careful examination.

The reaction of acid (62) with borane in THF was studied. In the presence of one equivalent of borane and under neutral workup conditions a 95% yield of the ester alcohol (66), contaminated by lactone (63), was obtained (Scheme 20). The latter was the major product when a basic workup was used and it could also be obtained by heating (66) at 90°C. When two equivalents of borane were used and a basic oxidative workup (hydrogen peroxide-sodium hydroxide) was employed the α,β-unsaturated lactone (68) was obtained, presumably via the alcohol (67). A small amount of material with strong absorption bands at 3600 and 1780 cm^{-1} in the ir spectrum, consistent with structure (67), was also isolated. Condensation of lactone (63) with 3,4,5-trimethoxybenzaldehyde resulted in no reaction when sodium hydride was used as a base, but with LDA very little starting material was recovered and the ir spectrum of the crude product contained a major absorption band at 1750 cm^{-1}, consistent with the bisarylidene lactone (64). Tlc and nmr showed a multicomponent mixture, however. The anion of lactone (63) is an ambident nucleophile and the regioselectivity, as well as stereoselectivity, of the reaction may need investigation.

Finally, a thermal intramolecular cycloaddition reaction

Scheme 20

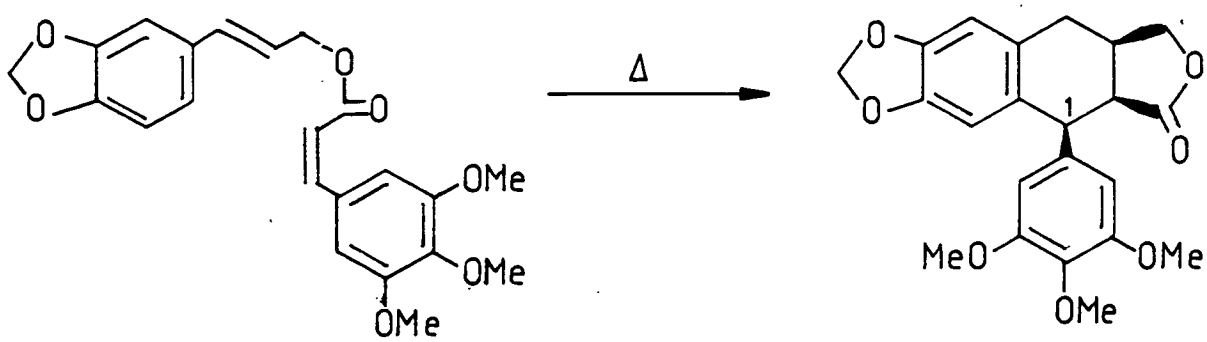

(62)
BH3
(1 equivalent)
OH
CO2Me
+
(63)
(66)
Δ
i. BH3
(2 equivalents)
ii. H2O2-NaOH
OH
(67)
-H2O
(68)

of the (E)-cinnamyl (Z)-cinnamate (69) has been reported[57] to lead to the direct formation of deoxyisopicropodophyllin (70) (Scheme 21). The (E),(E)-isomer (31) was reported to be unreactive. In an attempt to produce the C-1 epimeric tetralin, deoxypicropodophyllin (71), reaction of ester (31) was attempted in the presence of a Lewis acid catalyst (boron trifluoride). However, although the starting material completely reacted only polymerized product was obtained (ions with high m/e values were detected by ms), even when the reaction was carried out at high dilution.

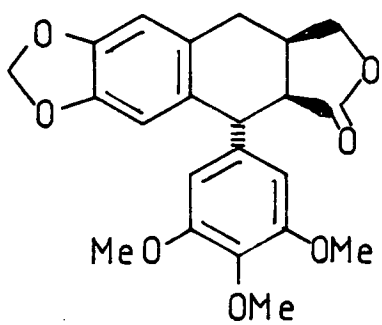
Conclusion

A route to the podophyllotoxin precursor (54) has thus been developed, but in order to be viable the problem of the yield loss on purification of the β-keto ester (61) must be overcome and the conditions for the intramolecular epoxide opening lactonization should be further optimized. Following suitable protection of the hydroxyl function the C-2 position of the lactone (54) next needs to be derivatized in order that the tetralin system of podophyllotoxin (1) may be formed. Hydroxybenzylation of lactones such as (72) is precedented[58], but subsequent formation of the C1-8a bond by a Lewis acid-catalysed electrophilic substitution onto ring A gives the undesired tetralin stereoisomer (74) (containing the substituent at C-1 in the β-configuration) with both of the epimeric alcohols

Scheme 21

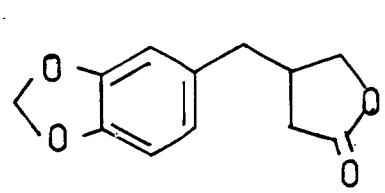


(69) (70)

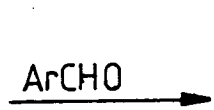


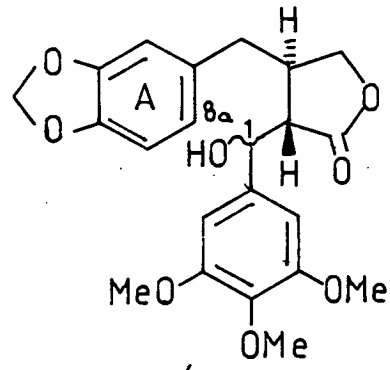
(71)

Scheme 22

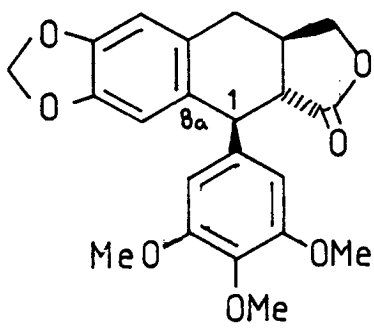


(72)

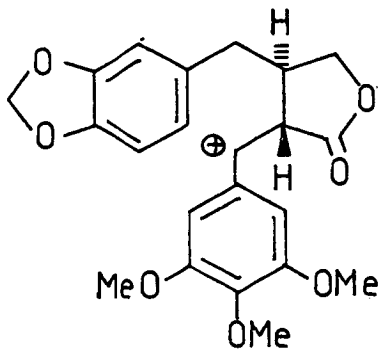




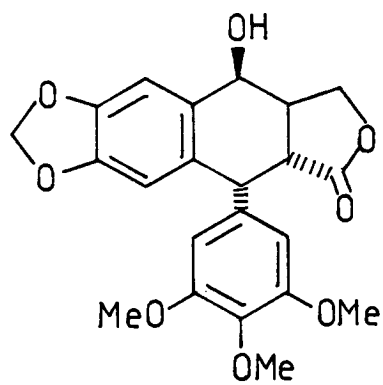
(73)



(74)



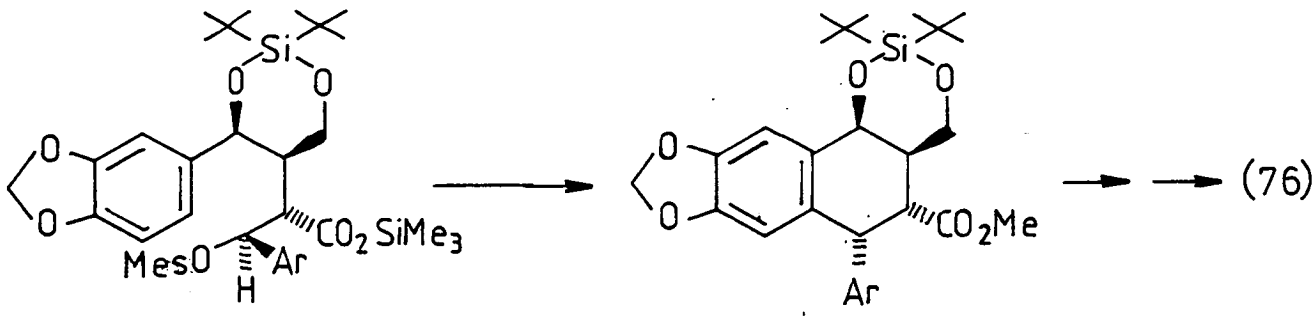
(75)



(76)

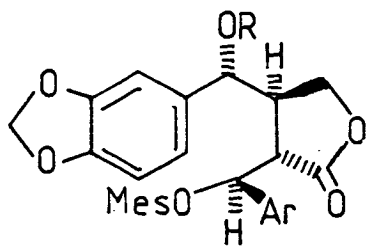
(73)[30]. This reaction has been demonstrated to proceed via the carbonium ion (75)[59]. In the synthesis of epipodophyllotoxin (76) by Vandewalle et al[29] the mesylate (77) was shown to cyclize to the tetralin (78) via an S_N2-type process (Scheme 23), and cyclization of the mesylate (79) should be similarly considered. Another approach would involve the novel cyclization of a benzylstannane (81) in the presence of a radical initiator; substitution by carbon nucleophiles at carbon-metal centres normally proceeds with retention[60]. Formation of (81) from the arylidene (80) and lithium tributylstannane would be expected to proceed diastereoselectively with respect to positions C-1 and -2[60], and the bulky substituent at C-3 may direct the hydrostannylation to give the desired diastereoisomer (81) (Scheme 24).

Scheme 23



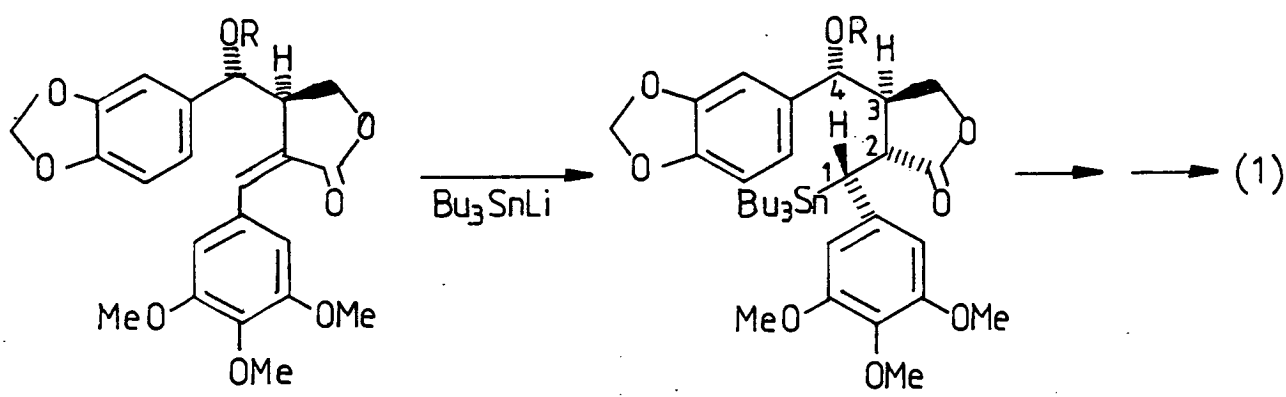
(77) (78)

Ar = 3,4,5 – trimethoxyphenyl



(79)

Scheme 24



(80) (81)

Chapter 6

EXPERIMENTAL

Instrumentation, purification of solvents and techniques were as described in Chapter 3. In addition proton nuclear magnetic resonance spectra were also obtained on Perkin Elmer R12A (60 MHz), Perkin Elmer R34 (220 MHz) and Bruker WH 360 (360 MHz) instruments. Carbon-13 nuclear magnetic resonance spectra were obtained on a Bruker WH360 (90.56 MHz) instrument; chemical shifts are quoted in ppm downfield from tetramethylsilane. Chloroform was distilled before use and acetonitrile and pyridine were dried by distillation from calcium hydride. A Radiometer autotitrator was used for the maintenance of constant pH.

Methoxycarbonylmethylenetriphenylphosphorane (17).- Triphenylphosphine (70.0 g, 0.27 mol) was dissolved in toluene (150 ml) and methyl bromoacetate (25.0 ml, 0.26 mol) was added dropwise. The resulting white suspension was stirred at room temperature for 18h and the solid collected by filtration. It was then dissolved in a two-phase system consisting of dichloromethane (350 ml) and water (110 ml) and a few drops of phenolphthalein were added. The solution was shaken while aqueous sodium hydroxide solution (1·0M) was slowly added until the indicator remained pink. The organic layer was separated and the aqueous layer was washed with dichloromethane (200 ml). The combined organic layers were washed with water (200 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was recrystallized from dichloromethane:petrol to afford a white solid (75.7 g, 87%). M.p. 167-168°C (lit.[61] 162-163°C); ν_{max} (CH_2Cl_2) 1619, 1347, 1127, 1105 cm^{-1}. δ_H (60MHz, $CDCl_3$) 3.00 (1H, br s), 3.51 (3H, s), 7.31-7.92 (15H, m).

Methyl (E)-3-(3,4-Methylenedioxyphenyl)prop-2-enoate (19).- Methoxycarbonyltriphenylphosphorane (17) (74.3 g, 0.22 mol) and piperonal (33.0 g, 0.22 mol) were stirred in refluxing dichloromethane (500 ml) under an argon atmosphere for 3h. The solvent was removed under reduced pressure and the remaining white solid was recrystallized from chloroform: petrol (39.7 g, 88%). M.p. 129-30°C (lit.[62] 133-34°C); ν_{max} 1710, 1632, 1615, 1605, 1502, 1489, 1172, 1040 cm^{-1}. δ_H (220MHz, $CDCl_3$) 3.80 (3H, s), 6.01 (2H, s), 6.27 (1H,

d, J=16Hz), 6.83 (1H, d, J=8Hz), 7.00 (dd, J=8,2Hz) and 7.04 (br s) (total of 2H), 7.63 (1H, d, J=16Hz).

(E)-3-(3,4-Methylenedioxyphenyl)prop-2-en-1-ol (16).- Lithium aluminium hydride (1.50 g, 40.0 mmol) was suspended in ether (200 ml), cooled to -5°C and stirred mechanically while methyl (E)-3-(3,4-methylenedioxyphenyl)prop-2-enoate (19) (3.50 g, 17.0 mmol) was added portionwise. The mixture was stirred at room temperature for 1h and then water (50 ml) was added. The ethereal solution was decanted from the resulting slurry and dried ($CaCl_2$) and evaporated *in vacuo*, leaving a white solid which was recrystallized from chloroform:petrol (2.35 g, 78%). M.p. 77-78°C (lit.[36] 75°C). Found: C, 67.62; H, 5.32. $C_{10}H_{10}O_3$ requires C, 67.41; H, 5.66. λ_{max} (EtOH) 205 (ε34,070), 264 (15,080) and 304nm (7,700). ν_{max} (CH_2Cl_2) 3590, 2880, 1606, 1488, 1040 cm^{-1}. δ_H (220MHz, $CDCl_3$) 2.08 (1H, br s, removed by D_2O), 4.27 (2H, dd, J=6,2Hz), 5.94 (2H, s), 6.17 (1H, dt, J=16,6Hz), 6.52 (1H, dt, J=16,2 Hz), 6.77 (d, J=8Hz) and 6.82 (dd, J=8,2Hz) (total of 2H), 6.92 (1H, d, J=2Hz). m/z 178 (M^+), 76.0%. Hplc (hexane: ethyl acetate, 7:3) 2.6 min.

Reaction between (E)-3-(3,4-Methylenedioxyphenyl)prop-2-en-1-ol (16) and m-Chloroperbenzoic Acid.- A solution of (E)-3-(3,4-methylenedioxyphenyl)prop-2-en-1-ol (16) (200 mg, 1.1 mmol) was added to a solution of m-chloroperbenzoic acid (80-90%, 260 mg, 1.1-1.2 mmol) in dichloromethane (4 ml) at 0°C. The resulting white suspension was stirred

at 0°C for 3h, then 10% aqueous sodium sulphite solution (2 ml) was added. After 10 min stirring at 0°C the organic solution was washed with saturated aqueous sodium bicarbonate solution (2 ml) and brine (2 ml), dried (Na_2SO_4) and evaporated under reduced pressure to afford a colourless oil (225 mg). This was a 7:3 mixture of isomers A and B, assigned as (2R,3S),(2S,3R)- and (2R,3R),(2S,3S)-3-(3-chlorobenzoyloxy)-3-(3,4-methylenedioxyphenyl)-propane-1,2-diol, (24) and (25), respectively (not distinguishable), contaminated with a small amount (*ca.*10%) of starting olefin. R_f ($CHCl_3$:MeOH, 9:1) 0.51, 0.47. ν_{max} 3600, 3050, 2975, 2895, 1726, 1504, 1488, 1240, 1040 cm^{-1}. δ_H (200MHz, $CDCl_3$) 2.57 (2H, br s, removed by D_2O, both isomers), 3.44 (0.7H, dd, J=12,6Hz, isomer A), 3.57 (0.7H, dd, J=12,4Hz, isomer A), 3.66 (0.3H, dd, J=12,6Hz, isomer B), 3.80 (3H, dd, J=12,3Hz isomer B), 4.05 (1H, m, both isomers), 5.86 (0.3H, d, J=7Hz, isomer B), 5.94 (2.7H, m, both isomers), 6.55-7.00 (3H, m, both isomers), 7.38 (1H, t, J=8Hz, both isomers), 7.53 (1H, m, both isomers), 7.85-8.10 (2H, m, both isomers). m/z 350 (M^+), 42%; 332 (M^+-H_2O), 12%; 194 ($M^+-C_7H_5ClO_2$), 3.2%. Hrms 350.0568 ($C_{17}H_{15}ClO_6$), 23% (2.98).

Purification of an 80 mg sample of this oil was attempted by preparative tlc on silica (ethyl acetate:petrol, 1:1). The products were extracted from the separated silica bands by stirring in dichloromethane at room temperature for 16h. The major product was a pale oil, which was a mixture consisting predominantly of (24), (25) and 1-(3-chlorobenzoyloxy)-3-(3,4-methylenedioxyphenyl)propane-2,3-diol (28) in a *ca.*1:1:3 ratio (23 mg). R_f (EtOAc, petrol, 1:1) 0.23, 0.32.

ν_{max} (CH_2Cl_2) as for A,B mixture, apart from some minor intensity variations. δ_H (200MHz, $CDCl_3$) (*inter alia*) 2.35 (2H, vbr, removed by D_2O), 4.05 (1H, m), 4.34 (1H, dd, J=12,6Hz), 4.59 (1H, dd, J=12,4Hz), 4.60 (1H, d, J=7Hz), 5.92 (2H, s), 6.71-6.99 (3H, m), 7.36 (1H, t, J=8Hz), 7.53 (1H, m), 7.80-8.08 (2H, m), plus signals due to (24) and (25). Hrms 350.0564 ($C_{17}H_{15}ClO_6$, M^+), 25% (1.97).

(E)-3-(3,4-Methylenedioxyphenyl)-1-trimethylsilyloxyprop-2-ene (29).- (E)-3-(3,4-Methylenedioxyphenyl)prop-2-en-1-ol (16) (1.00 g, 5.6 mmol) was dissolved in dichloromethane (20 ml) and triethylamine (0.8 ml, 5.7 mmol) and trimethylsilyl chloride (0.8 ml, 6.3 mmol) were added with stirring at 0°C. Stirring was continued at this temperature for 16h, then the solvent was removed *in vacuo* and the residue was washed with ether (20 ml) and filtered to remove insoluble material. The filtrate was evaporated under reduced pressure to afford a clear oil (1.40 g, 100%). Found: C, 62.1; H, 7.0; Si, 10.6. $C_{13}H_{18}O_3Si$ requires C, 62.4; H, 7.2; Si, 11.2. λ_{max} (EtOH) 265 (ε10,610) and 306 nm (5660). ν_{max} (CH_2Cl_2) 2890, 1605, 1502, 1486, 1040 cm^{-1}. δ_H (220MHz, $CDCl_3$) 0.10 (9H, s), 4.22 (2H, d, J=5Hz), 5.85 (2H, s), 6.05 (1H, dt, J=17,5Hz), 6.44 (1H, d, J=17Hz), 6.67 (d, J=8Hz) and 6.75 (d, J=8Hz) (total of 2H), 6.86 (1H, s). m/z 250 (M^+); 235 (M^+-CH_3),; 177 ($M^+-C_3H_9Si$); 161 ($M^+-C_3H_9OSi$).

(E)-1-Acetoxy-3-(3-4-Methylenedioxyphenyl)prop-2-ene (30). (E)-3-(3,4-Methylenedioxyphenyl)prop-2-en-1-ol (16) (0.50 g, 2.8 mmol) was dissolved in acetic anhydride (1 ml) and heated at reflux temperature for 2.5h, then thrown onto ice-water (5 ml) and stirred at room temperature for 1h. The mixture was partitioned between chloroform (10 ml) and 10% aqueous potassium carbonate solution (10 ml) and the organic layer was then washed with water (10 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica (chloroform), affording a pale yellow oil (0.40 g, 65%). ν_{max} (CH_2Cl_2) 2873, 1732, 1654, 1606, 1485, 1018 cm^{-1}. δ_H (60MHz, $CDCl_3$) 2.08 (3H, s), 4.70 (2H, d, J=6Hz), 5.94 (2H, s), 6.22 (1H, t, J=6Hz), 6.47 (1H, s), 6.79 (2H, m), 6.94 (1H, s).

Reaction between (E)-1-Acetoxy-3-(3,4-Methylenedioxyphenyl)-prop-2-ene (30) and m-Chloroperbenzoic Acid.- A solution of m-chloroperbenzoic acid (80-90%, 0.25 g, 1.1-1.2 mmol) in dichloromethane (5 ml) was stirred at 0°C and (E)-1-acetoxy-3-(3,4-methylenedioxyphenyl)prop-2-ene (30) (0.25 g, 1.1 mmol) in dichloromethane (1 ml) was added. The mixture was stirred at 0°C for 1.5h and then washed with 10% aqueous sodium hydrogen sulphite solution, dried (Na_2SO_4) and the solvent removed *in vacuo*. This left a clear colourless oil (0.24 g) which was a 7:3 mixture of cleaved epoxide product and starting material. ν_{max} (CH_2Cl_2) 3595, 2895, 1730, 1656, 1611, 1487, 1040 cm^{-1}; δ_H (60MHz, $CDCl_3$) 2.18 (3H, s), 2.92 (1H, br s, removed by D_2O), 3.84-4.36 (3H, m), 5.98 (2H, s), 6.12

(1H, d, J=5Hz), 6.92 (3H, m), 7.47 (2H, m), 8.08 (2H, m), plus signals due to (30).

3-(3,4-Methylenedioxyphenyl)prop-2-en-1-yl 3-(3,4,5-trimethoxyphenyl)prop-2-enoate (31).- This was prepared by the method of Klemm et al[36].

3-(3,4,5-Trimethoxyphenyl)prop-2-enoic acid (1.50 g, 6.3 mmol), thionyl chloride (0.50 ml, 6.7 mmol) and pyridine (3 drops) were heated at reflux temperature in benzene (7.5 ml) for 5.5h and then left to stand overnight at room temperature. The solvent was removed *in vacuo* and then benzene (5 ml) and pyridine (12.5 ml) were added, followed by 3-(3,4-methylenedioxyphenyl)prop-2-en-1-ol (16) (1.25 g, 7.0 mmol). The solution was stirred at room temperature for 20 min and then at reflux temperature for 16h. Solid material was then removed by filtration and the filtrate was evaporated *in vacuo* to leave a gummy yellow solid. This was recrystallized from ethanol, affording white prisms (1.76 g, 66%). M.p. 119-121°C (lit.[36] 119-120°C); ν_{max} (CH_2Cl_2) 2935, 1706, 1637, 1583, 1505, 1490, 1128, 1040 cm^{-1}; δ_H (220MHz, $CDCl_3$) 3.88 (9H, s), 4.85 (2H, d, J=6Hz), 5.96 (2H, s), 6.20 (1H, dt, J=17,6Hz), 6.40 (1H, d, J=16Hz), 6.62 (1H, d, J=17Hz), 6.72-7.00 (5H, m), 7.66 (1H, d, J=16Hz).

Reaction between 3-(3,4-Methylenedioxyphenyl)prop-2-en-1-yl 3-(3,4,5-Trimethoxyphenyl)prop-2-enoate (31) and m-Chloroperbenzoic Acid.- 3-(3,4-Methylenedioxyphenyl)prop-2-en-1-yl 3-(3,4,5-trimethoxyphenyl)prop-2-enoate (31) (200 mg, 0.50

mmol) in dichloromethane (4 ml) was added to m-chloroperbenzoic acid (80-90%, 240 mg, 1.1-1.3 mmol) in dichloromethane (4 ml) at 0°C. After stirring at 0°C for 15 min the mixture was allowed to warm to room temperature and was then stirred for 9h. 10% Aqueous sodium sulphite solution (2 ml) was added and the mixture was stirred for 15 min, then the organic solution was washed with saturated aqueous sodium bicarbonate solution (4 ml), brine (2 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* left a pale brown oil which was purified by flash chromatography on silica (ethyl acetate:petrol, 1:2). This gave a clear viscous oil, 3-(3-chlorobenzoyloxy)-2-hydroxy-3-(3,4-methylenedioxyphenyl)prop-1-yl 3-(3,4,5-trimethoxyphenyl)-prop-2-enoate (32) (100 mg, 35%). Starting ester (31) (80 mg, 40%) was also recovered. ν_{max} (CH_2Cl_2) 3580, 2890, 1720, 1635, 1585, 1503, 1125, 1035 cm^{-1}. δ_H (220MHz, $CDCl_3$) 2.75 (1H, v br s, removed by D_2O), 3.90 (9H, s), 4.22 (1H, dd, J=15,6Hz), 4.35 (2H, m), 5.94 (2H, s), 6.06 (1H, d, J=7Hz), 6.38 (1H, d, J=16Hz), 6.77 (s) and 6.81 (d, J=8Hz) (total of 3H), 6.96 (d, J=8Hz) and 6.98 (s) (total of 2H), 7.39 (1H, t, J=8Hz), 7.56 (1H, d, J=8Hz), 7.62 (1H, d, J=16Hz), 7.99 (1H, d, J=8Hz), 8.08 (1H, s); m/z 570 (M^+), 414 ($M^+-C_7H_5ClO_2$).

(2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)-propan-1-ol (15).-

Method A: (E)-3-(3,4-Methylenedioxyphenyl)prop-2-en-1-ol (16) (2.00 g, 5.6 mmol) and benzonitrile (1.2 ml, 11.8 mmol) were stirred in methanol (12 ml) at 40°C. The pH of the solution

was monitored by a pH meter. Hydrogen peroxide (30%, 2.4 ml, 11.8 mmol) was added slowly with stirring, followed by careful addition of aqueous sodium hydroxide solution (1.0M) by an autotitrator to give an indicated pH of 9.50. This was maintained throughout the reaction, base being added automatically as required. After 3h water (50 ml) was added and the resulting emulsion was extracted with ether (3 x 50 ml). The organic washings were combined, dried (Na_2SO_4) and the ether removed at reduced pressure, leaving a pale brown semi-solid. Benzamide was removed by crystallization from chloroform:petrol and the mother liquor was evaporated under reduced pressure to afford a clear oil which smelt strongly of benzonitrile. The latter impurity was removed by Kugelrohr distillation (100°C oven temperature, 0.1 mmHg), leaving a pale yellow, viscous oil (2.14 g, approximate yield 98%). λ_{max} (EtOH) 235 (ε5750) and 289 nm (2570); ν_{max} (CH_2Cl_2) *(inter alia)* 3600, 2890, 1504, 1488, 1444, 1240, 1040 cm^{-1}. δ_H (200MHz, $CDCl_3$-D_2O) 3.13 (1H, dt, J=4,2Hz), 3.69 (1H, dd, J=13,4Hz), 3.80 (1H, d, J=2Hz), 3.95 (1H, dd, J=13,2Hz), 5.92 (2H, s), 6.67 (1H, s), 6.75 (2H, s); signals in the range 7.3-7.8 were assigned to impurities. δ_H (200MHz, $CDCl_3$) 2.69 (1H, br t, J=7Hz); otherwise as in $CDCl_3$-D_2O but less well resolved in the region 3.5-4.0. Hrms 194.0583 ($C_{10}H_{10}O_4$, M^+), 55% (2.1). Hplc (hexane:ethyl acetate, 7:3) 2.7 (unknown), 6.7 (15) and 21.7 min ($PhCONH_2$).

Method B: A mixture of (E)-3-(3,4-methylenedioxyphenyl)-prop-2-en-1-ol (16) (0.25 g, 1.4 mmol), benzonitrile (0.30 ml, 2.9 mmol) and potassium bicarbonate (50 mg, 0.5 mmol)

in methanol (2 ml) was stirred in a water bath at room temperature and hydrogen peroxide (9.8M, 0.30 ml, 2.9 mmol) was slowly added. The mixture was stirred at room temperature for 18h, and then worked up using the procedure described in Method A to yield a pale yellow oil (0.12, 44%). Hplc indicated that this was a 99:1 mixture of the desired epoxy alcohol (15) and starting olefin (16), contaminated with low levels of the same impurities obtained before. ^{1}H Nmr showed that the product was the epoxy alcohol (15) plus those impurities; no starting olefin (16) was detected.

(E)-1-t-Butyldimethylsilyloxy-3-(3,4-methylenedioxyphenyl)-prop-2-ene (35).- A dichloromethane (7 ml) solution of (E)-3-(3,4-methylenedioxyphenyl)prop-2-en-1-ol (16) (0.65 g, 3.6 mmol), t-butyldimethylsilyl chloride (0.60 g, 4.0 mmol), triethylamine (0.61 ml, 4.4 mmol) and 4-dimethyl-aminopyridine (18 mg, 0.14 mmol) was stirred at room temperature under argon for 14h, then washed with water (2 x 7 ml) and saturated aqueous ammonium chloride solution (7 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a brown oil which was purified by dry-flash chromatography on silica (chloroform:petrol, 1:5-1:0), affording a clear oil (0.62 g, 58%). λ_{max} (EtOH) 265 nm (ε7680); ν_{max} (CH_2Cl_2) 2956, 2933, 2892, 1607, 1505, 1490, 1040 cm^{-1}. δ_H (60MHz, $CDCl_3$) 0.12 (6H, s), 0.98 (9H, s), 4.39 (2H, d, J=5Hz), 6.00 (2H, s), 6.29 (1H, t, J=5Hz), 6.49 (1H, s), 6.85 (2H, s), 7.00 (1H, s). Hrms 292.1491 ($C_{16}H_{24}O_3Si$, M^+), 30% (-1.37); 235 ($M^+-C_4H_9$), 28%.

Trimethylsilyl Acetate (37)

Method A: Bis(trimethylsilyl)acetamide (8.0 ml, 32.4 mmol) was slowly added to acetic acid (2.1 ml, 36.7 mmol) and the exothermic reaction stirred at room temperature for 45 min. The product was collected by distillation as a clear liquid (4.0 g, 94%). B.p. 20°C (20 mmHg) [lit.[63] 30-31°C (35 mmHg)]. Found: C, 45.2; H, 9.3; Si, 20.8. $C_5H_{12}O_2Si$ requires C, 45.4; H, 9.2; Si, 21.2. ν_{max} (CH_2Cl_2) 2955, 1727, 1370, 1260, 1020 cm^{-1}. δ_H (60MHz, $CDCl_3$) 0.28 (9H, s), 2.05 (3H, s); m/z 132 (M^+), 0.1%; 117 (M^+-CH_3), 40.1%; 59 ($M^+-C_3H_9Si$), 5.1% 43 ($M^+-C_3H_9OSi$), 17.2%.

Method B: Sodium acetate (8.0 g, 97.5 mmol) was suspended in dry ether (40 ml) and trimethylsilyl chloride (6.0 ml, 47.3 mmol) was slowly added. The mixture was stirred at room temperature for 8h, filtered and the ether removed *in vacuo* to leave a clear oil which was distilled. The clear liquid product (2.7 g, 42%) was identical to an authentic sample of the title compound.

3-Oxo-3-(3,4,5-Trimethoxyphenyl)propanoic Acid (39).- n-Butyllithium (1.4M in hexane, 26.0 ml, 36.4 mmol) was cooled to 0°C under a nitrogen atmosphere and diisopropylamine (5.1 ml, 36.4 mmol) was slowly added. The stirred mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure, leaving a white solid. Tetrahydrofuran (20 ml) was added, the solution was cooled to -78°C and trimethylsilyl acetate (37) (3.50 g, 26.3 mmol) was added with stirring. After 15 min at

-78°C 3,4,5-trimethoxybenzoyl chloride (4.20 g, 18.2 mmol) in tetrahydrofuran (20 ml) was added and the temperature of the reaction mixture was allowed to reach room temperature. After a further 15 min stirring the solvent was removed *in vacuo* and the residual brown oil was dissolved in dichloromethane (20 ml). Ice-cold aqueous hydrochloric acid solution (6.0M) was added until approximately pH 1 was attained. The aqueous layer was washed with more dichloromethane (3 x 10 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residual oil was dissolved in saturated aqueous sodium bicarbonate solution (15 ml), washed with ether (20 ml) and acidified to pH 1 with ice-cold aqueous hydrochloric acid solution (6.0M). Chloroform (30 ml) was added and the organic layer was dried ($MgSO_4$) and concentrated to approximately one-third volume, then warmed gently while sufficient petrol was added to cause initial precipitation. After chilling the resulting white solid was collected by filtration (2.44 g, 53%) and identified as the title compound, slightly contaminated by 3',4',5'-trimethoxyacetophenone. M.p. 95-96°C (with effervescence). Found: C, 56.5; H, 5.8. $C_{12}H_{14}O_6$ requires C, 56.7; H, 5.6. λ_{max} (EtOH) 219 (ε22590) and 285 nm (10710). ν_{max} (CH_2Cl_2) 3350-2500 (v br), 1759, 1725, 1679, 1646, 1585, 1505, 1450, 1425, 1338, 1133 cm^{-1}. ν_{max} (ether) 3400-2400 (v br), 1745, 1686, 1629, 1584, 1332 cm^{-1}. δ_H (80MHz, $CDCl_3$) 3.90 (6H, s), 3.92 (3H, s), 4.03 (2H, s), 7.21 (2H, s), 8.11 (1H, v br s, removed by D_2O); a signal at δ5.64 (s) indicated the presence of the enol tautomer (ketone:enol *ca.*9:1); m/z 210 (M^+-CO_2), 75.0%.

3-(3,4-Methylenedioxyphenyl)prop-2-en-1-yl 3-Oxo-(3,4,5-trimethoxyphenyl)propanoate (40).-

Method A: 3-Oxo-3-(3,4,5-trimethoxyphenyl)propanoic acid (39) (140 mg, 0.55 mmol) and 3-(3,4-methylenedioxyphenyl)-prop-2-en-1-ol (16) (105 mg, 0.59 mmol) were stirred together in acetonitrile (3 ml) and pyridine (90 µl, 1.1 mmol) and dicyclohexylcarbodiimide (170 mg, 0.82 mmol) were added at 0°C. Stirring was continued at this temperature for 24h. Aqueous acetic acid was added and the mixture was stirred at room temperature for 15 min, then filtered to remove a precipitated white solid. The aqueous phase in the filtrate was washed with ether (2 x 20 ml) and the combined organic solutions were dried (Na_2SO_4) and evaporated under reduced pressure, leaving a granular brown oil. This was purified by flash chromatography on silica (ethyl acetate:petrol, 1:1), yielding a white solid (80 mg, 35%). M.p. 78-81°C. Found: C, 63.38; H, 5.32. $C_{22}H_{22}O_8$ requires C, 63.76; H, 5.35. λ_{max} (EtOH) 216 (ε33840), 272 (15420) and 295 nm (14710); ν_{max} (CH_2Cl_2) 2925, 1735, 1675, 1584, 1500, 1487, 1323, 1125, 1040 cm^{-1}. δ_H (80MHz, $CDCl_3$) 3.98 (6H, s), 3.91 (3H, s), 3.99 (2H, s), 4.77 (2H, dd, J=6,1Hz), 5.94 (2H, s), 6.15 (1H, t, J=6Hz), 6.46 (1H, br s), 6.62-6.97 (3H, m), 7.21 (2H, s); a signal at δ5.64 indicated the presence of the enol tautomer (ketone:enol *ca.*8:1). m/z 414 (M^+).

Method B: 3-Oxo-3-(3,4,5-trimethoxyphenyl)propanoic acid (39) (100 mg, 0.39 mmol) was suspended in benzene (1.5 ml) and sodium hydride (50% dispersed in oil, 20 mg, 0.42 mmol) was added. This was stirred for 15 min, resulting in a

thin yellow suspension, and was added to a stirred solution of oxalyl chloride (35 µl, 0.41 mmol) in benzene (1.4 ml) at 0°C. After 10 min stirring the mixture was allowed to warm to room temperature and after a further 1h 3-(3,4-methylenedioxyphenyl)prop-2-en-1-ol (16) (70 mg, 0.39 mmol) in pyridine (0.5 ml) was added slowly, with external cooling by a water bath, resulting in some precipitation. The mixture was then stirred at room temperature for 1.5h, concentrated, dissolved in chloroform (5 ml) and washed in turn with cold aqueous hydrochloric acid solution (2.0M, 10 ml), aqueous sodium hydroxide solution (1.0M, 5 ml) and water (10 ml). The organic solution was dried (Na_2SO_4) and evaporated *in vacuo* to leave a brown oil. Purification by preparative tlc on silica (ethyl acetate:petrol, 4:1) gave a pale brown gum (30 mg, 18%) which had identical characterisation properties (tlc, ir, nmr) as an authentic sample of the title compound.

(2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)-prop-1-yl 3-Oxo-3-(3,4,5-trimethoxyphenyl)propanoate (2).- (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)-propan-1-ol (15) (1.80 g, 9.3 mmol) was dissolved in dichloromethane (10 ml) and added to a solution of 3-oxo-3-(3,4,5-trimethoxyphenyl)propanoic acid (39) (2.35 g, 9.2 mmol) in dichloromethane (30 ml) at 0°C. Immediately dicyclohexylcarbodiimide (1.91 g, 9.3 mmol) in dichloromethane (10 ml) was added followed by 4-dimethylaminopyridine (50 mg, 0.41 mmol), and the mixture was allowed to warm to room temperature. Stirring was continued for 17h, then the precipitated white solid was removed by filtration

and the filtrate evaporated. Flash chromatographic purification of the residue on silica (ether) gave an oil which was dissolved in hot ethyl acetate and chilled, giving a precipitate. Filtration and evaporation of the filtrate left a pale yellow oil which was purified by flash chromatography on silica (ether:petrol, 7:3-1:0) affording a white amorphous solid (0.79 g, 20%). This failed to recrystallize. M.p. 109-110°C. Found: C, 61.34; H, 5.07. $C_{22}H_{22}O_9$ requires C, 61.39; H, 5.15. λ_{max} (EtOH) 289 nm (ε12030). ν_{max} (CH_2Cl_2) 3050, 2940, 1746, 1680, 1589, 1505, 1450, 1412, 1377, 1238, 1130, 1040 cm^{-1}. δ_H (200MHz, $CDCl_3$) 3.18 (1H, ddd, J=5,3,2Hz), 3.70 (1H, d, J=2Hz), 3.90 (s) and 3.91 (s) (total of 9H), 4.03 (2H, s), 4.16 (1H, dd, J=12,5Hz), 4.55 (1H, dd, J=12,3Hz), 5.94 (2H, s), 6.65 (1H, s), 6.75 (2H, s), 7.20 (2H, s); signals at δ3.28 (br m), 3.79 (br d), 4.20 (br m), 4.58 (br m), 5.67 (s), 6.72 (s), 6.78 (s) and 7.03 (s) indicated the presence of the enol tautomer (ketone;enol *ca.*7:1). Hrms 430.1265 ($C_{22}H_{22}O_9$, M^+), 48.0% (0.2).

(2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl (E)-3-(3,4,5-Trimethoxyphenyl)prop-2-enoate (3).- Method A: 3-(3,4,5-Trimethoxyphenyl)prop-2-enoic acid (130 mg, 0.55 mmol) was dissolved in dichloromethane (2.5 ml), chilled to 0°C and triethylamine (80 µl, 0.57 mmol) and diphenylphosphinyl chloride (130 mg, 0.55 mmol) were added. After 12 min stirring at 0°C a solution of (2R,3S),(2S,3R)-2,3-epoxy-3-(3,4-methylenedioxyphenyl)propan-1-ol (16) (100 mg, 0.51 mmol) and triethylamine (0.25 ml, 1.8 mmol)

in dichloromethane (1 ml) was added. The mixture was stirred at 0°C for 30 min and saturated aqueous sodium bicarbonate solution (4 ml) was added, then the organic layer was washed with brine (4 ml), dried (Na_2SO_4) and evaporated, leaving a pale yellow oil. This was purified by flash chromatography on silica (ethyl acetate:petrol, 1:1) to afford a pale oil (96 mg, 45%) which solidified on prolonged storage at -20°C. The product failed to recrystallize. M.p. 119-120°C (softens at 95°C). Found: C, 63.61; H, 5.29. $C_{22}H_{22}O_8$ requires C, 63.76; H, 5.35; λ_{max} 235 (ε18550) and 297 nm (14960). ν_{max} (CH_2Cl_2) 2940, 1725, 1639, 1586, 1506, 1239, 1130, 1040 cm^{-1}. δ_H (200MHz, $CDCl_3$) 3.28 (1H, ddd, J=6,3,2Hz), 3.78 (1H, d, J=2Hz), 3.87 (s) and 3.88 (s) (total of 9H), 4.20 (1H, dd, J=12,6Hz), 4.59 (1H, dd, J=12,3Hz), 5.95 (2H, s), 6.38 (1H, d, J=16Hz), 6.67-6.83 (5H, m), 7.65 (1H, d, J=16Hz); m/z 414 (M^+), 221 ($M^+-C_{10}H_9O_4$). Hrms 414.1302 ($C_{22}H_{22}O_8$, M^+), 16.0% (-2.94).

Method B: 3-(3,4,5-Trimethoxyphenyl)prop-2-enoic acid (1.23 g, 5.2 mmol) was dissolved in dichloromethane (10 ml) and benzene (10 ml) and stirred at 0°C while oxalyl chloride (1.2 ml, 13.8 mmol) was added. The solution was allowed to warm to room temperature and stirred for 2.5h, then the solvent and excess oxalyl chloride were removed *in vacuo*. The pale yellow residue was dissolved in dichloromethane (10 ml) and added to a solution of (2R,3S),(2S,3R)-2,3-epoxy-3-(3,4-methylenedioxyphenyl)propan-1-ol (16) (1.00 g, 5.1 mmol), triethylamine (7.2 ml, 51.7 mmol) and 4-dimethyl-aminopyridine (30 mg, 0.24 mmol) in dichloromethane (10 ml),

external cooling for the exothermic reaction being provided by a water bath. After 18h stirring ether (100 ml) was added and the resulting white precipitate was removed by filtration. The filtrate was washed with saturated aqueous sodium bicarbonate solution (25 ml), water (50 ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. This afforded a pale yellow oil (256 mg, 12%) which crystallized on prolonged storage at -20°C and displayed identical characterization properties (tlc, ir, nmr) to an authentic sample of the title compound.

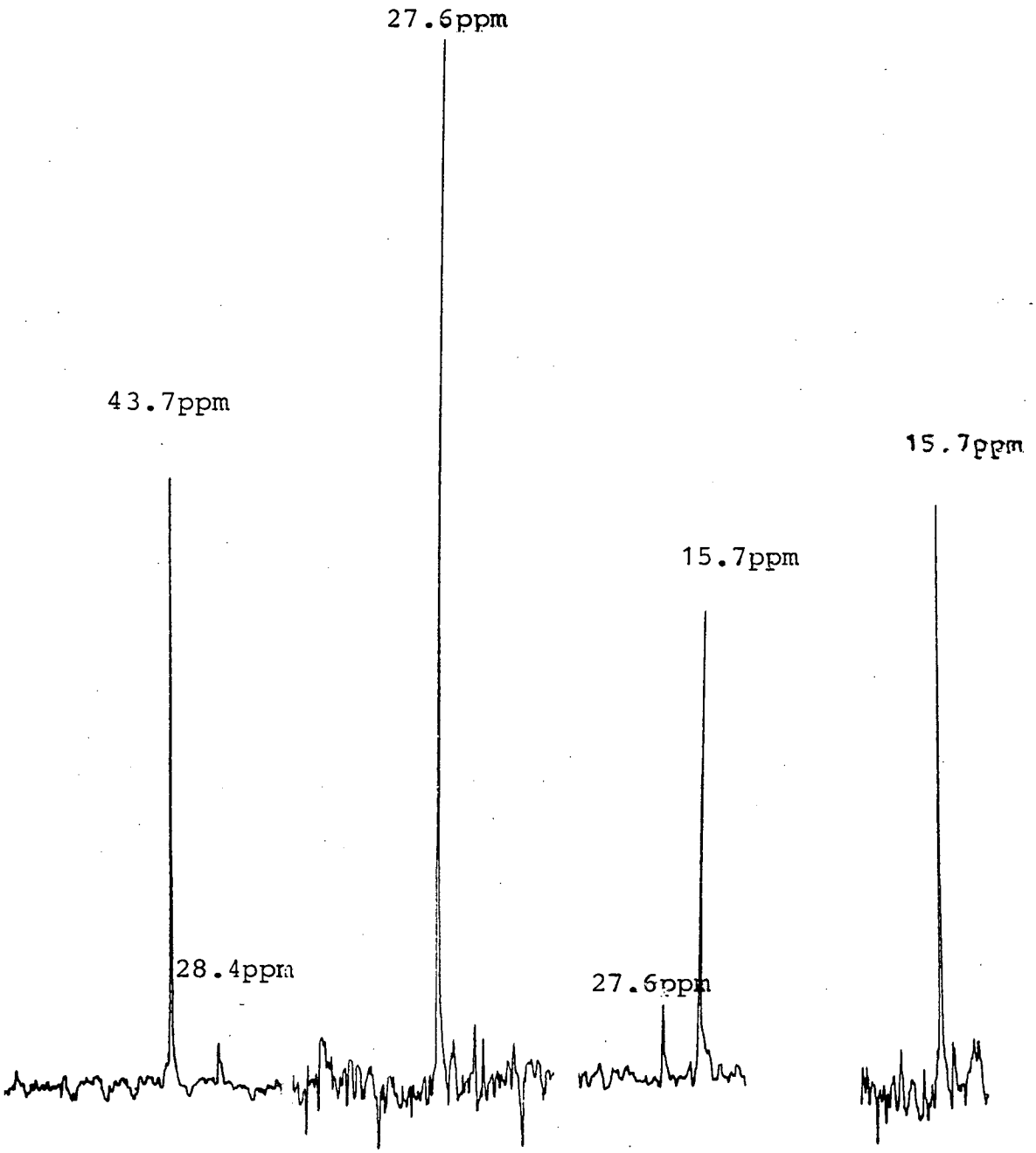
^{31}P Nmr Study of Coupling of (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)propan-1-ol (15) and 3,4,5-Trimethoxycinnamic Acid with Diphenylphosphinyl Chloride.- Diphenylphosphinyl chloride (34.7 g, 0.15 mmol) in dichloromethane (0.55 ml) was cooled to 0°C in a 5mm nmr tube and its ^{31}P nmr spectrum recorded. A peak at 43.7 ppm was present (plus a minor peak at 28.4 ppm due to symmetrical anhydride $[Ph_2P(O)]_2O$). A solution of 3,4,5-trimethoxycinnamic acid (35 mg, 0.15 mmol) and triethylamine (21 µl, 0.15 mmol) in dichloromethane (0.5 ml) was added and the reaction was continued at 0°C. A spectrum recorded 2 min after mixing showed complete disappearance of the peak at 43.7 ppm and appearance of a new peak at 27.6 ppm, which was assigned to the carboxylic phosphinic mixed anhydride (46). This was unchanged after 7 min, and after 8 min a solution of (2R,3S),(2S,3R)-2,3-epoxy-3-(3,4-methylenedioxyphenyl)propan-1-ol (15) (30 mg, 0.15 mmol), triethylamine (70 µl, 0.50 mmol) and 4-dimethylaminopyridine (2 mg,

16.4 μmol) was added. Reaction was continued at 0°C, and after 3 min a spectrum was recorded and showed a major peak at 15.7 ppm (assigned to $Ph_2\underline{P}O_2^{\ominus}$) plus a minor peak at 27.6 ppm. After 5 min reaction only the former peak was detectable, indicating complete reaction. Spectra recorded after 27 and 55 min showed no changes. See page 134.

Trimethylsilyl 3-(3,5-Dimethoxy-4-trimethylsilyloxyphenyl)-prop-2-enoate (49).- 3-(3,5-Dimethoxy-4-hydroxyphenyl)-prop-2-enoic acid (sinapic acid) (1.51 g, 6.7 mmol) was suspended in toluene (15 ml) and trimethylsilyl chloride (1.8 ml, 14.2 mmol) was added. Triethylamine (2.1 ml, 15.1 mmol) was slowly added and the mixture was refluxed for 5h, then filtered to remove a colourless solid. The filtrate was concentrated and ether (30 ml) was added. The resulting precipitate was removed by filtration and the filtrate was evaporated under reduced pressure, leaving a colourless oil (2.52 g) which solidified below 0°C. This was not purified further but was used crude in the next stage. ν_{max} (CH_2Cl_2) 2960, 1684, 1629, 1583, 1507, 1410, 1130 cm^{-1}. δ_H (60MHz, $CDCl_3$) 0.50 (9H, s), 0.60 (9H, s), 3.80 (6H, s), 6.46 (1H, d, J=16Hz), 6.93 (2H, s), 7.30 (1H, d, J=16Hz).

3-(3,5-Dimethoxy-4-trimethylsilyloxyphenyl)prop-2-enoyl Chloride (50).- The freshly prepared trimethylsilyl 3-(3,5-dimethoxy-4-trimethylsilyloxyphenyl)prop-2-enoate (49) (2.52 g, crude) was dissolved in dichloromethane (10 ml) and thionyl chloride (0.65 ml) was added. The

^{31}P Nmr Study of Coupling of (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)propan-1-ol (15) and 3,4,5-Trimethoxycinnamic Acid with Diphenylphosphinyl Chloride



solution was refluxed for 2.5h and then evaporated to dryness under reduced pressure, leaving a pale orange solid (1.71 g). This was not purified further but was used crude in the next stage. ν_{max} (CH_2Cl_2) 3045, 2865, 1749, 1610, 1580, 1506, 1349, 1134 cm^{-1}.

(2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl (E)-3-(3,5-Dimethoxy-4-hydroxyphenyl)prop-2-enoate (4).- The freshly prepared 3-(3,5-dimethoxy-4-trimethylsilyloxyphenyl)prop-2-enoyl chloride (50) (1.71 g, crude) was dissolved in dichloromethane (10 ml) and cooled to 0°C. (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)-propan-1-ol (15) (1.47 g, 21.5 mmol) and triethylamine (3.0 ml, 21.5 mmol) in dichloromethane (10 ml) were added dropwise, followed immediately by 4-dimethylaminopyridine (50 mg, 0.41 mmol). The mixture was stirred at 0°C for 30 min and then at room temperature for 30 min. After filtration through Celite removal of the solvent *in vacuo* left an orange gum which was purified by flash chromatography on silica (three times). This gave the product as a white foam (271 mg, 13% from sinapic acid). λ_{max} (EtOH) 241 (ε11770), 297 (6560) and 332 nm (10590). ν_{max} (CH_2Cl_2) 3522, 2890, 1709, 1638, 1610, 1505, 1446, 1248, 1155, 1120, 1040 cm^{-1}. δ_H (200MHz, $CDCl_3$) 1.58 (1H, s, removed by D_2O), 3.27 (1H, m), 3.78 (1H, d, J=2Hz), 3.91 (6H, s), 4.20 (1H, dd, J=12,6Hz), 4.58 (1H, dd, J=12,3Hz), 5.95 (2H, s), 6.34 (1H, d, J=16Hz), 6.65-6.90 (5H, s), 7.64 (1H, d, J=16Hz). Hrms 400.1166 ($C_{21}H_{20}O_8$, M^+), 13% (0.8).

(E)-3-(4-Acetoxy-3,5-dimethoxyphenyl)prop-2-enoic Acid (51).- 3-(3,5-Dimethoxy-4-hydroxyphenyl)prop-2-enoic acid (2.00 g, 8.9 mmol), acetic anhydride (4.0 ml, 42.4 mmol) and pyridine (6.0 ml, 74.2 mmol) were heated together at reflux temperature for 1h, then evaporated *in vacuo* to leave a white solid. This was purified by dry-flash chromatography on silica (chloroform:ethyl acetate, 1:0-0:1). The more polar component was recrystallized from chloroform:petrol to give a white solid (0.61 g, 26%), identified as the title compound. M.p. 192-194°C (lit.[52] 188-192°C). ν_{max} (CH_2Cl_2) 3350-2340 (v br), 1766, 1688, 1632, 1598, 1503, 1458, 1197, 1133 cm^{-1}. δ_H (60MHz, $CDCl_3$) 2.44 (3H, s), 3.96 (6H, s), 6.05 (1H, d, J=16Hz), 6.92 (2H, s), 7.87 (1H, d, J=16Hz), 9.42 (1H, br s). m/z 266 (M^+). The less polar component, a white solid (430 mg, 52%), was tentatively assigned as acetic (E)-3-(3,5-dimethoxy-4-hydroxyphenyl)prop-2-enoic anhydride (52). ν_{max} (CH_2Cl_2) 3680, 3050, 2972, 1765, 1712(w), 1628, 1596, 1199, 1133, 1080 cm^{-1}. δ_H (60MHz, $CDCl_3$) 2.38 (3H, s), 3.85 (6H, s), 6.48 (1H, d, J=16Hz), 6.83 (2H, s), 7.82 (1H, d, J=16Hz). Hrms 266.0788 ($C_{13}H_{14}O_6$, M^+), 7.6% (-0.74); 224 ($C_{11}H_{12}O_3$, $M^+-C_2H_2O$), 100.0% (-1.13).

(2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)-prop-1-yl 3-(4-Acetoxy-3,5-dimethoxyphenyl)prop-2-enoate (53).- 3-(4-Acetoxy-3,5-dimethoxyphenyl)prop-2-enoic acid (51) (100 mg, 0.38 mmol) and trimethylamine (60 µl, 0.43 mmol) in dichloromethane (0.5 ml) were cooled to 0°C and diphenylphosphinyl chloride (92 mg, 0.39 mmol) in dichloromethane (1.3 ml) was added. The mixture was

stirred at 0°C for 10 min and then a solution of (2R,3S), (2S,3R)-2,3-epoxy-3-(3,4-methylenedioxyphenyl)propan-1-ol (15) (74 mg, 0.38 mmol) and triethylamine (160 µl, 1.15 mmol) in dichloromethane (0.5 ml) was added, followed immediately by 4-dimethylaminopyridine (3 mg, 24.5 µmol). The mixture was stirred at 0°C for a further 25 min and then filtered through a bed of Kieselgohr which was further washed with ethyl acetate:petrol (1:1). The combined filtrates were concentrated *in vacuo* and purified by dry-flash chromatography on silica (ethyl acetate:petrol, 1:1), yielding a white solid (91 mg, 55%) which failed to recrystallize. M.p. 51-56°C. Found: C, 62.20; H, 5.06. $C_{23}H_{22}O_9$ requires C, 62.44; H, 5.01. λ_{max} (EtOH) 231 (ε14210) and 295 nm (14210); ν_{max} (CH_2Cl_2) 3050, 2965, 1767, 1714, 1639, 1599, 1507, 1133, 1039 cm^{-1}. δ_H (80MHz, $CDCl_3$) 2.33 (3H, s), 3.28 (1H, ddd, J=6,3,2Hz), 3.78 (1H, d, J=2Hz), 3.84 (6H, s), 4.20 (1H, dd, J=12,6Hz), 4.60 (1H, dd, J=12,3Hz), 5.94 (2H, s), 6.41 (1H, d, J=16Hz), 6.71 (1H, s), 6.77 (s) and 6.78 (s) (total of 4H), 7.67 (1H, d, J=16Hz). m/z 442 (M^+).

Cyclization of (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl 3-Oxo-3-(3,4,5-trimethoxyphenyl)-propanoate (2).- (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl 3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (2) (200 mg, 0.46 mmol) was dissolved in DMF (5 ml) and sodium hydride (50% dispersed in oil, 24 mg, 0.50 mmol) was added. The mixture was stirred under nitrogen at an oil-bath temperature of 160°C for 1h and the

resulting dark solution was then allowed to cool to room temperature. Water (20 ml) and ethyl acetate (15 ml) were added and the aqueous layer was washed with more ethyl acetate (3 x 15 ml). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to leave a brown oil (169 mg). This was purified by preparative tlc on silica (chloroform), giving as the major product threo-4,5-dihydro-4-[hydroxy(3,4-methylenedioxyphenyl)methyl]furan-2(3H)-one (54) (51 mg, 0.22 mmol, 48%). λ_{max} (EtOH) 286 nm (ε4166); ν_{max} (CH_2Cl_2) 3600, 3450 (br), 2900, 1778, 1503, 1487, 1240, 1178, 1040 cm^{-1}. δ_H (200MHz, $CDCl_3$) 1.67 (1H, br s, removed by D_2O), 2.23 (1H, dd, J=18,8Hz), 2.39 (1H, dd, J=18,9Hz), 2.81 (1H, m), 4.39 (2H, d, J=7Hz), 4.53 (1H, d, J=8Hz), 5.96 (2H, s), 6.76 (s) and 6.77 (s) (total of 2H), 6.82 (1H, s). δ_C (90.56MHz, $CDCl_3$) 31.2, 42.4, 70.3, 74.9, 101.1, 106.1, 108.2, 119.5, 135.7, 147.5, 148.1, 176.8. m/z 236 (M^+), 29.6%; 218 (M^+-H_2O), 5.2%. Hrms 236.0686 ($C_{12}H_{12}O_5$, M^+), 5.1% (0.42). The minor component (32 mg, 16%) was purified further by preparative tlc on silica (ether), giving two products. These were tentatively assigned as threo-4,5-dihydro-4-[(3,4-methylenedioxyphenyl)(3,4,5-trimethoxybenzoyloxy)methyl]furan-2(3H)-one (55) (5 mg, 11.6 μmol, 3%). ν_{max} (CH_2Cl_2) 3050, 2940, 1782, 1720, 1590, 1504, 1332, 1218, 1130 cm^{-1}. δ_H (200MHz, $CDCl_3$) 2.37 (1H, dd, J=17,6Hz), 2.62 (1H, dd, J=17,9Hz), 3.13 (1H, m), 3.89 (s) and 3.90 (s) (total of 9H), 4.39 (d, J=6Hz) and 4.40 (d, J=7Hz) (total of 2H), 5.86 (1H, d, J=7Hz), 5.96 (2H, s), 6.80 (1H, s), 6.82 (2H, s), 7.27 (2H, s). m/z 430 (M^+); 212 ($M^+-C_{10}H_{12}O_5$) and threo-4,5-dihydro-5-

(3,4-methylenedioxyphenyl)-4-(3,4,5-trimethoxybenzoyloxymethyl)furan-2(3H)-one (56) (9 mg, 209 μmol, 5%). ν_{max} (CH_2Cl_2) 3050, 2943, 1785, 1715, 1590, 1504, 1335, 1223, 1130 cm^{-1}. δ_H (360MHz, $CDCl_3$) 2.70 (1H, dd, J=17,3 Hz), 2.95 (1H, dd, J=17,9Hz), 3.10 (1H, m), 3.91 (3H, s), 3.93 (6H, s), 3.95 (1H, dd, J=12,7Hz), 4.07 (1H, dd, J=12,5Hz), 5.67 (1H, d, J=6Hz), 5.93 (2H, s), 6.75 (3H, s), 7.22 (2H, s). m/z 430 (M^+); 212 ($M^+-C_{10}H_{12}O_5$).

threo-4,5-Dihydro-4-[acetoxy(3,4-methylenedioxyphenyl)-methyl]furan-2(3H)-one (57).- Pyridine (0.15 ml, 1.85 mmol) was added dropwise to a stirred solution of threo-4,5-dihydro-4-[hydroxy(3,4-methylenedioxyphenyl)methyl]-furan-2(3H)-one (54) (14 mg, 0.063 mmol) and acetic anhydride (60 μl, 0.64 mmol) in chloroform (0.3 ml), with external cooling being provided by a water bath. Stirring was continued for 23h and then the solvent and excess reagents were removed *in vacuo*. The residue was dissolved in dichloromethane (1 ml), washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to leave a pale brown oil (9 mg, 55%), consisting predominantly of the title compound. λ_{max} (EtOH) 287 (ε2900) and 235 nm (2810). ν_{max} (CH_2Cl_2) 3050, 2982, 1784, 1745, 1503, 1233, 1042 cm^{-1}. δ_H (200MHz, $CDCl_3$) *(inter alia)* 2.07 (3H, s), 2.23 (1H, dd, J=18,8Hz), 2.44 (1H, dd, J=18,9Hz), 3.03 (1H, m), 4.21 (1H, dd, J=10,6Hz), 4.38 (1H, dd, J=10,8Hz), 5.61 (1H, d, J=8Hz), 5.96 (2H, s), 6.77 (3H, s). m/z 278 (M^+), 85%; 218 ($M^+-C_2H_4O_2$), 19%. Hrms 278.0791 ($C_{14}H_{14}O_6$, M^+), 84.7% (0.32).

(2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)-prop-1-yl 3-Oxobutanoate (61).- (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)propan-1-ol (15) (4.10 g, 21.2 mmol) was dissolved in chloroform (12.5 ml) and triethylamine (42 µl, 0.30 mmol) was added. The solution was stirred under nitrogen, while diketene (1.65 ml, 21.1 mmol) was added then stirring was continued at reflux temperature for 30 min. The resulting green solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica (ethyl acetate:petrol, 1:1) (twice) to afford a pale yellow oil (1.00 g, 17%). Found: C, 60.12; H, 4.83. $C_{14}H_{14}O_6$ requires C, 60.43, H, 5.07. λ_{max} (EtOH) 240 (ε6760) and 288 nm (3930). ν_{max} (CH_2Cl_2) 3050, 2980, 2895, 1748, 1720, 1504, 1442, 1236, 1040 cm^{-1}. δ_H (80MHz, $CDCl_3$) 2.27 (3H, s), 3.20 (1H, ddd, J=6,3,2Hz), 3.51 (2H, s), 3.74 (1H, d, J=2Hz), 4.15 (1H, dd, J=12,6Hz), 4.53 (1H, dd, J=12,3Hz), 5.94 (2H, s), 6.69 (1H, s), 6.77 (s) and 6.78 (s) (total of 3H); signals at 1.97 (s) and 5.05 (s) indicated the presence of the enol tautomer (ketone:enol *ca.*9:1). δ_C (90.56MHz, $CDCl_3$) 29.6, 49.1, 55.8, 58.3, 64.2, 100.8, 105.2, 107.8, 119.5, 129.6, 147.5, 147.6, 166.4, 199.8. m/z 278 (M^+).

Deuteration of (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl 3-Oxobutanoate (61).- (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl 3-oxopropanoate (61) (10 mg, 35.9 µmol) was dissolved in DMF (0.25 ml) and sodium hydride (50% dispersed in oil, 3.4 mg, 70.9 µmol) was added. The solution was stirred

under nitrogen for 30 min and then ethyl acetate (1 ml) and deuterium oxide (1 ml) were added. The organic layer was separated and the aqueous layer was washed with more ethyl acetate (2 x 1 ml). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, leaving a pale brown oil. The ^1H nmr of this was identical to that of the starting material apart from contamination by DMF and a reduction in the relative intensity of the signal at δ3.51. Inspection of integral ratios indicated *ca.*50% monodeuteration to form (2R,3S),(2S,3R)-2,3-epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl 2-deuterio-3-oxopropanoate had occurred.

Cyclization of (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl 3-Oxobutanoate (61).- (2R,3S),(2S,3R)-2,3-Epoxy-3-(3,4-methylenedioxyphenyl)prop-1-yl 2-oxobutanoate (100 mg, 0.36 mmol) was dissolved in DMF (2.5 ml) and sodium hydride (50% dispersed in oil, 35 mg, 0.73 mmol) was added. The temperature was raised to 150°C and the mixture was stirred for 1h and then allowed to cool to room temperature. Water (10 ml) and ethyl acetate (10 ml) were added and the aqueous layer was washed with more ethyl acetate (3 x 10 ml). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to leave a brown oil (83 mg). This was purified by preparative tlc on silica (ether), giving threo-4,5-dihydro-4-[hydroxy-(3,4-methylenedioxyphenyl)methyl]furan-2(3H)-one (54) (24 mg, 0.10 mmol, 28%) and threo-4,5-dihydro-4-[acetoxy(3,4-methylenedioxyphenyl)methyl]furan-2(3H)-one (57) (11 mg, 39.5 μmol, 11%), both identical (tlc, ir, nmr) to authentic samples.

(E)-2-Methoxycarbonylmethyl-3-(3,4-methylenedioxyphenyl)-prop-2-en-1-ol (66).- (E)-2-Methoxycarbonylmethyl-3-(3,4-methylenedioxyphenyl)prop-2-enoic acid (1.00 g, 4.2 mmol) was dissolved in THF (10 ml) and borane (1.0M in THF, 4.2 ml, 4.2 mmol) was added slowly at 0°C. The yellow solution was stirred at room temperature for 1h and then the solvent was removed under reduced pressure. Ether (30 ml) and brine (30 ml) were added to the residue and the aqueous phase was washed with more ether (4 x 50 ml). The combined ethereal solutions were dried ($MgSO_4$) and evaporated *in vacuo*, leaving a clear oil (0.85 g, 95%). This was identified as the title compound, with slight (<10%) contamination by 4,5-dihydro-4-[(3,4-methylenedioxyphenyl)-(E)-methylidene]furan-2(3H)-one (63). Any attempt at purification led to further lactonization.
ν_{max} 3600, 1730, 1605, 1487, 1038 cm^{-1}. δ_H (60MHz, $CDCl_3$) 2.40 (1H, v br s), 3.33 (2H, s), 3.74 (3H, s), 4.24 (2H, s), 5.99 (2H, s), 6.71 (1H, s), 6.81 (3H, s).

4,5-Dihydro-4-(3,4-methylenedioxyphenyl-(E)-methylidene)-furan-2(3H)-one (63).- (E)-2-Methoxycarbonylmethyl-3-(3,4-methylenedioxyphenyl)prop-2-enoic acid (5.00 g, 20.8 mmol) was dissolved in THF (50 ml) and borane (1.0M in THF, 21.0 ml, 21.0 mmol) was added slowly at 0°C. The yellow solution was stirred at room temperature for 1h and then evaporated *in vacuo*. The residual oil was partitioned between brine (100 ml) and ether (4 x 50 ml) and the ethereal layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure. This left a pale yellow semi-solid

which was identified as a mixture of the title compound, ester alcohol (66) and starting material. It was dissolved in chloroform (50 ml) and aqueous sodium hydroxide solution (2.0M, 10 ml) was added, the organic layer was washed with brine (25 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was heated at 90°C (15 mmHg) for 2h, then recrystallized from chloroform:petrol, affording a white microcrystalline solid (1.50 g, 32%). M.p. 151-152°C. Found: C, 66.08; H, 4.70. $C_{12}H_{10}O_4$ requires C, 66.05; H, 4.62. λ_{max} (EtOH) 273 nm (ε6590). ν_{max} (CH_2Cl_2) 2880, 1782, 1487, 1184, 1040 cm^{-1}. δ_H (80MHz, $CDCl_3$) 3.39 (1H, d, J=2Hz), 3.45 (1H, d, J=2Hz), 4.95 (1H, d, J=2Hz), 5.00 (1H, d, J=2Hz), 5.97 (2H, s), 6.35 (1H, quintet, J=2Hz), 6.60-6.90 (3H, m). δ_C (90.56 MHz, $CDCl_3$) 32.9, 73.1, 100.4, 107.8, 108.4, 122.4, 123.6, 127.9, 129.7, 147.1, 148.0, 175.0. Hrms 218.0578 ($C_{12}H_{10}O_4$, M^+), 94.6% (-0.55).

3-(3,4-Methylenedioxyphenyl)methylfuran-2(5H)-one (68).- (E)-2-Methoxycarbonylmethyl-3-(3,4-methylenedioxyphenyl)-prop-2-enoic acid (0.50 g, 2.1 mmol) was dissolved in THF (5 ml) and borane (1.0M in THF, 4.2 ml, 4.2 mmol) was added at 0°C. The solution was stirred at room temperature for 2.5h and then sufficient water was added to decompose excess borane, followed by ether (25 ml) and hydrogen peroxide (27.5%, 0.5 ml) in aqueous sodium hydroxide solution (2.0M, 2 ml). The mixture was stirred overnight and then the aqueous phase was separated and washed with

ether (25 ml), and the combined ethereal layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by dry-flash chromatography (chloroform:methanol, 1:0-4:1) gave a clear oil (0.21 g, 46%). λ_{max} (EtOH) 287 (ε3350) and 214 nm (7410). ν_{max} (CH_2Cl_2) 2895, 1782, 1755, 1642, 1490, 1038 cm^{-1}. δ_H (80MHz, $CDCl_3$) 3.64 (2H, br s), 4.69 (2H, d, J=2Hz), 5.83 (1H, quintet, J=2Hz), 5.95 (2H, s), 6.53-6.80 (3H, m). Hrms 218.0577 ($C_{12}H_{10}O_4$, M^+), 74.6% (-1.15).

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