"The Synthesis of Furofuranoid Lignans".

by

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Contents

Abstract.

An approach to the synthesis of 2,6-diaryl-8-oxo-3,7-dioxabicyclo [3,3,0] octane lignan lactones is presented and then used in the synthesis of the natural products aptosimon and styraxin. The structure of aptosimon has now been confirmed as having a 2,6-diaryl structure rather than the 2,4-diaryl structure which has been postulated in the literature. A germination inhibitor MEL, isolated from Aegilops ovata, has also been synthesised.

A key ring closing reaction in this strategy was a Lewis acid catalysed directed aldol reaction between a silyl enol ether and an acetal. A review of similar ring closures in the literature is presented.

The use of α-arylidene lactones as intermediates in lignan synthesis has also been investigated. The stereochemistry of products from reactions used in this strategy was determined and as a result it was possible to successfully design a stereochemically controlled synthesis of dihydrosesamin.

Acknowledgements

Firstly, I would like to thank my supervisor in this work, Don Whiting, for his constant help and guidance without which this thesis would not have been possible.

I would also like to thank the excellent technical staff within the department. Special thanks must go to Bob and Margaret in the NMR department and also Mike and Tony in the mass spectroscopy department.

Thanks also go to everyone that I had the pleasure of working with in Lab C29 for helping to make my time in Nottingham so enjoyable.

Finally, I would like to thank Linda Gibson for her patience in typing this thesis.

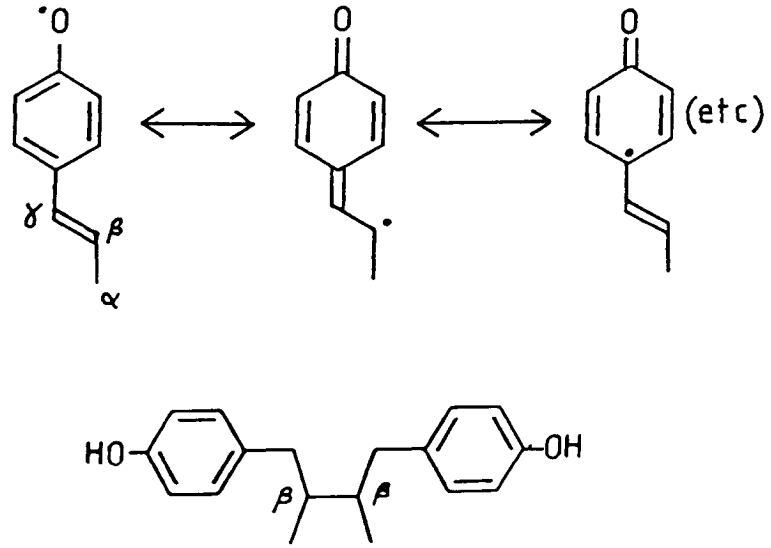
Abbreviations

DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DIBAL	Diisobutylaluminium hydride
FAB	Fast atom bombardment
DMF	Dimethylformamide
IR	Infra red
LDA	Lithium diisopropylamide
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance
nOe	nuclear Overhauser effect
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethanesulphonate

Introduction

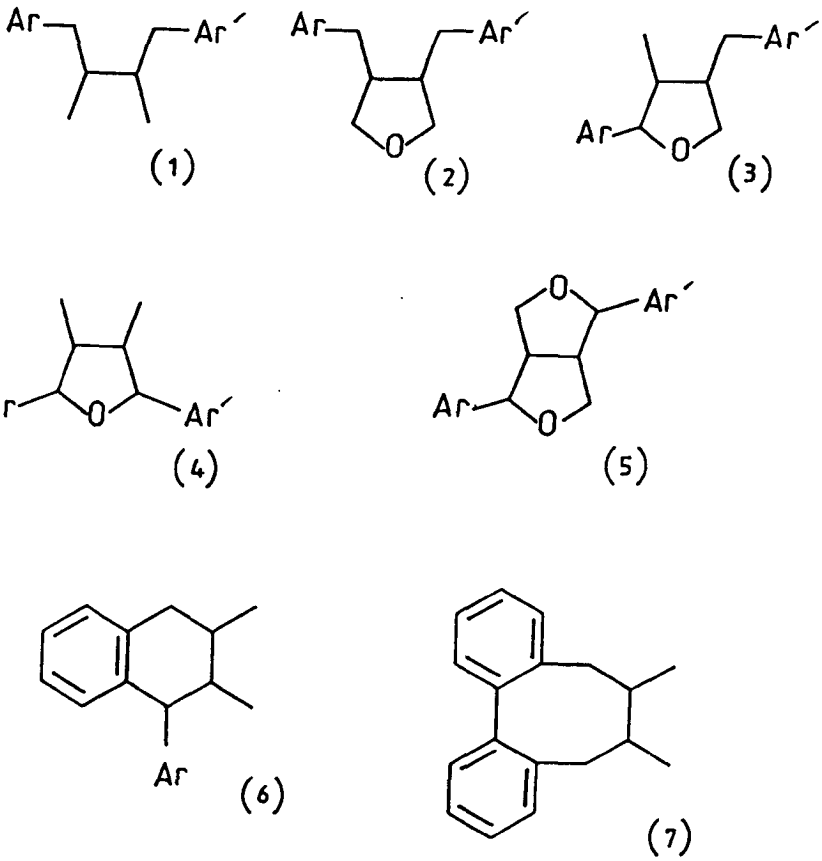
(a) (i) General background

Lignans are a large and important class of natural compounds. The name was first used by Haworth[1] in 1936 who applied the term to phenylpropane (C_6C_3) dimers where there is a carbon-carbon bond between the central or β-atoms of the propane side chain. Their biosynthesis is believed to arise from the dimerisation of phenolic radicals as shown in scheme 1. (Dimers of such radicals that do not contain a β-β bond have been termed neolignans by Gottlieb[2]).



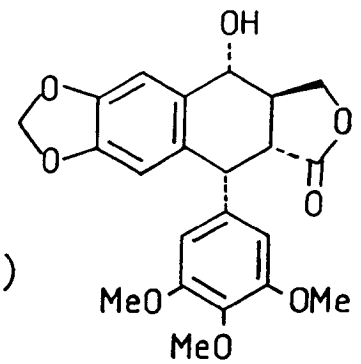
SCHEME 1

Other carbon-carbon bonds may be present as well as ether linkages and other oxygen functions. Examples of lignan type structures are shown in scheme 2. Examples of actual lignans are shown in scheme 3.



SCHEME 2

Lignans have attracted much interest in the literature in recent years and several reviews have appeared. The most notable publication is a collection of reviews, "The Chemistry of Lignans", edited by Rao[3] which is a thorough survey of the literature of lignans to the mid 1970's. Synthetic approaches to lignans were reviewed by Ward[4] in 1982. Update reviews to both of these works have been produced by Whiting[5,6] and cover the literature to the end of 1985.



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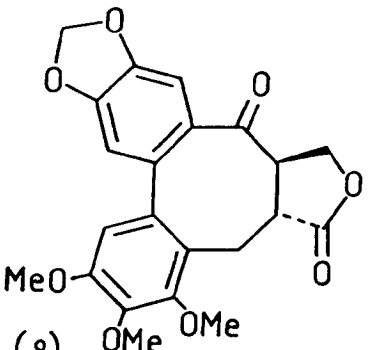

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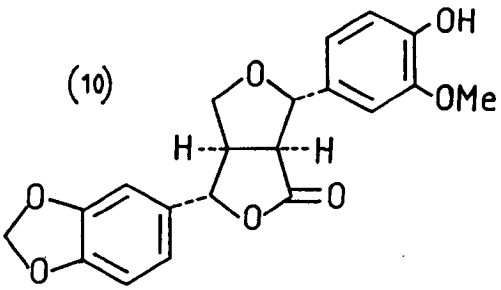

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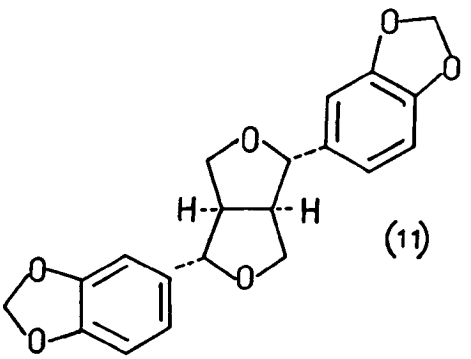

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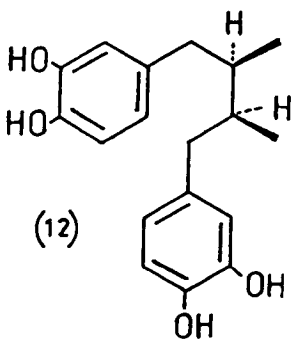

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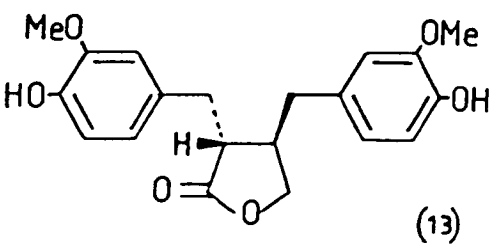

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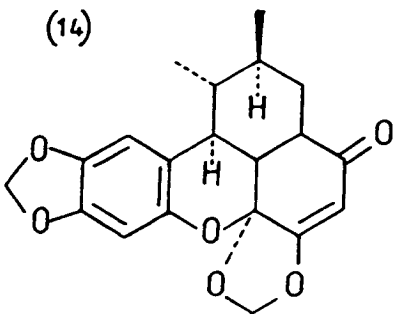

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SCHEME 3

An earlier review appeared by Hearon and MacGregor[7] in 1955 which covered all aspects of the literature to that date.

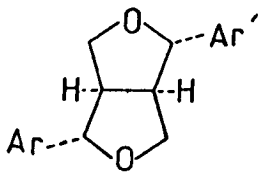
The most comprehensive review of biological activities of the lignans was by MacRae and Towers[8] and covers the entire spectrum of activities displayed by these compounds. Other reviews on activities have been published by Mabry[9] and also by Swain[10].

(ii) Distribution and Biological Activities[7]

The occurrence of lignans in plants has been reviewed by Cole and Wiedhopf[11] and lignans have been shown to occur in almost every part of plants such as bark, resin, leaves, roots, flowers, fruits and heartwoods. More recently, lignans have been isolated from mammalian sources, however the origin and role of these compounds is not well understood.

One of the most notable activities of naturally occuring lignans is the anti-cancer properties shown by many compounds. Derivatives of podophyllotoxin (8) are clinically important[12] although members of other families show activity as well for example steganone (9) and styraxin (10).

Other activities that have attracted interest are the insecticide synergist properties of sesamin (11) and its epimer asarinin. nordihydroguaiaretic acid (12) has been used commercially as a food anti-oxidant. Many other activities have been identified



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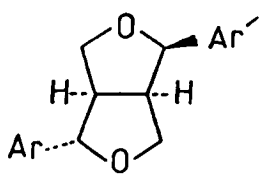

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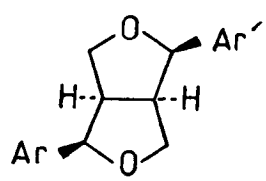

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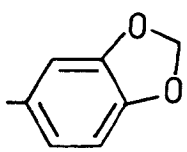
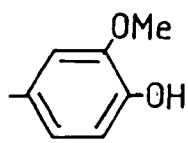
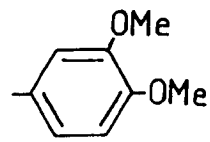
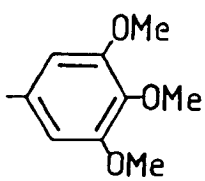
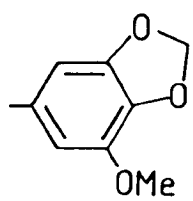
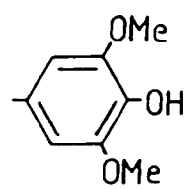












SCHEME 4

including anti-viral activity, the inhibition of DNA and RNA synthesis, enzyme inhibition and both cardiac stimulation and relaxation.

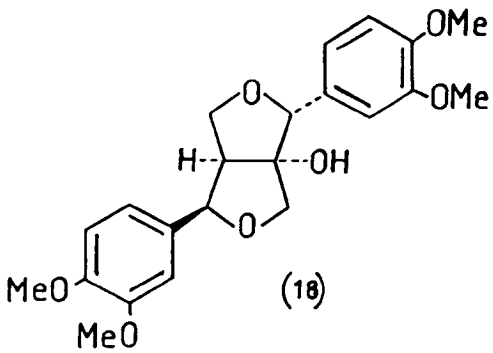
The diverse range of structures and biological activities have helped to stimulate the ever increasing interest in lignans as synthetic targets for organic chemists.

(b) Substituted furofurans

The diaryl-3,7-dioxabicyclo[3,3,0] octanes represent one of the largest groups of lignans and have been reviewed by Pelter and Ward[13]. This review has been updated in the later works by Whiting[5,6] and only a very brief survey of these compounds is presented here.

The three basic structures which have been shown to occur naturally can be represented by structures (15), (16) and (17). Several different aromatic groups have been found in these compounds and the aromatic groups at the 2 and 6-positions may be the same or different. A selection of some commonly found aromatic groups is shown in scheme 4.

Various oxygen functions have been found to occur on the bicyclic nucleus as exemplified by gmelinol (18) which is hydroxylated at the 1-position and 4-hydroxysesamin (19). Diols that exist include arboreol (20), gummadiol (21) wodeshiol (22) and 4,8-dihydroxy



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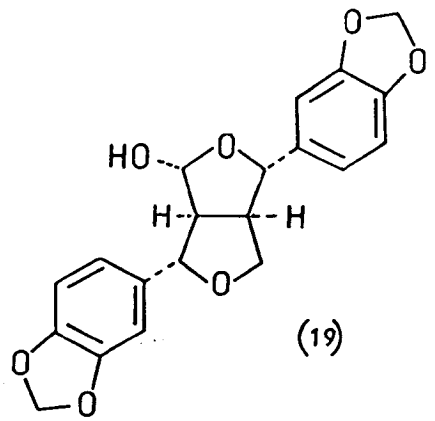

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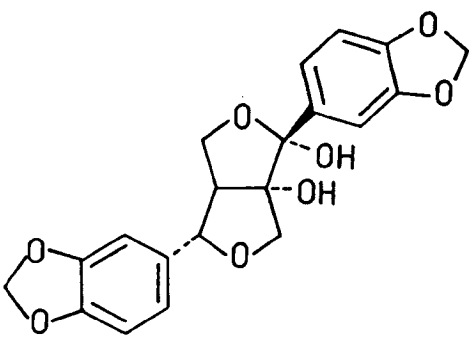

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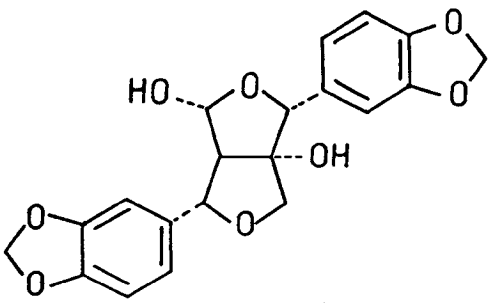

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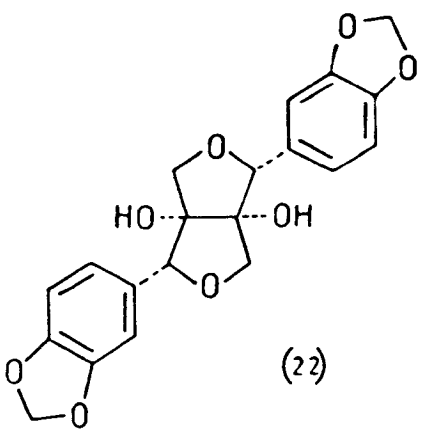

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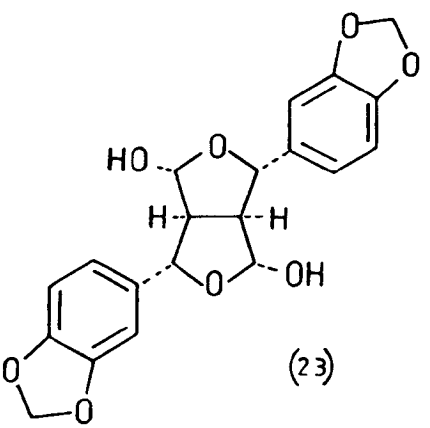
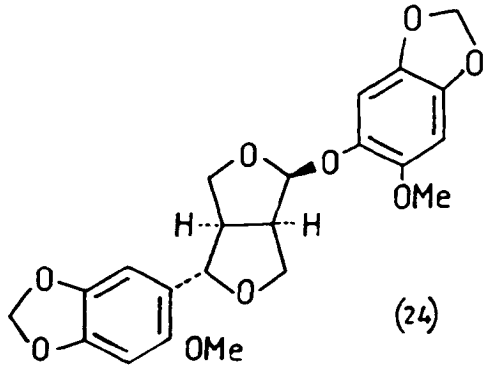


(23)

sesamin (23).

Phrymarolin (24) is an example of a lignan where an oxygen has inserted between the bicyclic nucleus and an aromatic group.

One of the earlier members of a new family of lignan lactones was aptosimon which was first reported as a 2,4-diaryl structure (25) but was however re-assigned a 2,6-diaryl structure (26). Other members of this family, some with interesting biological activites have been isolated from natural sources and their synthesis is the subject of chapters 2 and 3 in this thesis. In chapter 1, a summary of published synthetic strategies to diaryl-3,7-dioxa bicyclo [3,3,0] octane lignans is presented.



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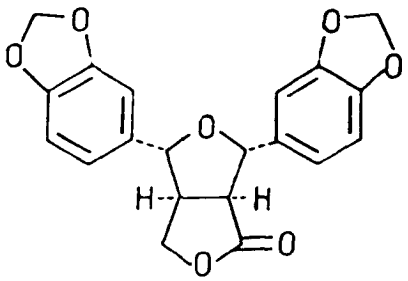

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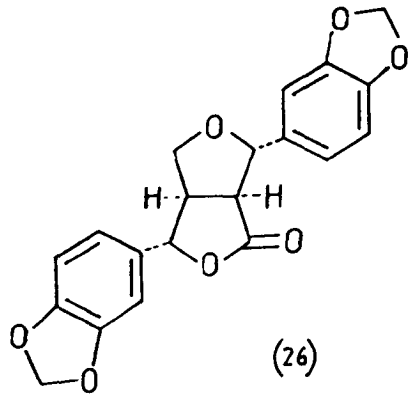

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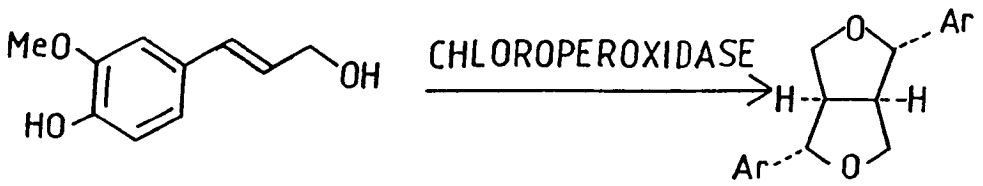
Chapter 1



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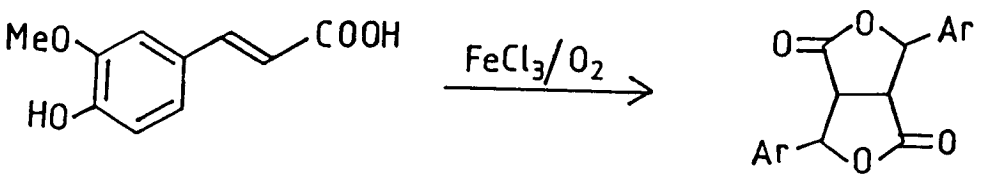
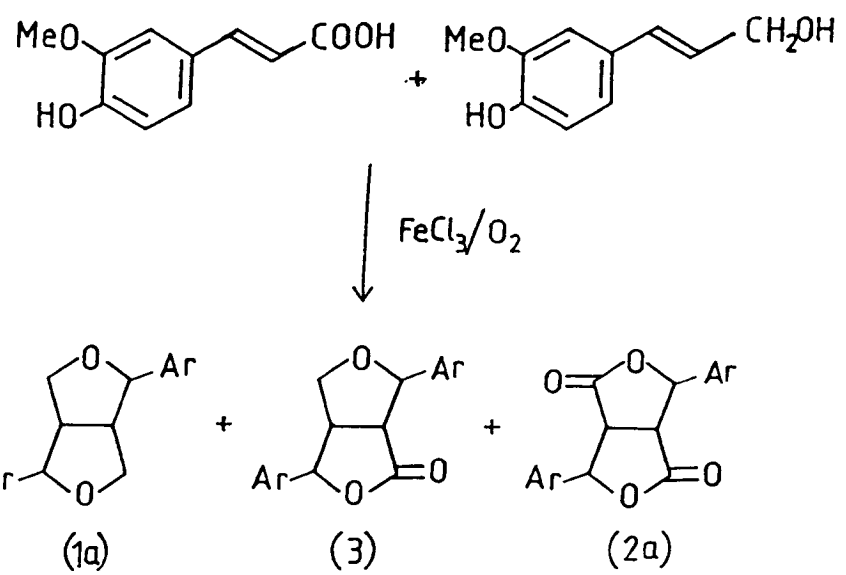


SCHEME 2 (2a)



(1a) (3) (2a)

SCHEME 3

The Synthesis of Diaryl-3,7-dioxabicyclo[3,3,0]octane Lignans.

The diaryl-3,7-dioxabicyclo[3,3,0]octane lignans are a large and important class of natural products and there have been a number of syntheses reported in the literature[1]. Lignan syntheses in general have been reviewed by Ward[2] in 1982 and later updates have been included in reviews by Whiting[3].

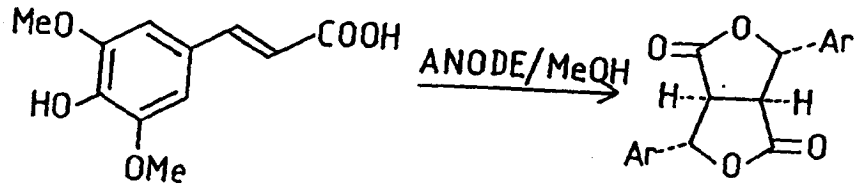
The intention here is only to outline the type of strategies that have been used and as far as possible, syntheses of a similar nature have been grouped together.

a) Oxidative Couplings

The most direct entry into the diaryl-3,7-dioxabicyclo[3,3,0] octane lignans is the oxidative coupling of phenolic and non-phenolic cinnamic acids and alcohols. This has been achieved both enzymatically and chemically.

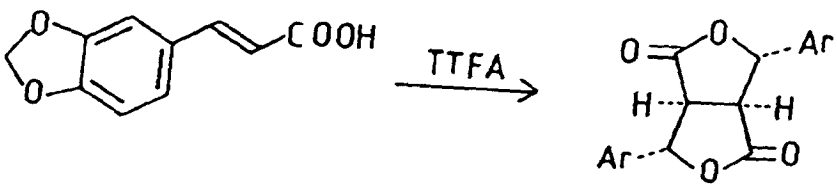
Enzymatic coupling of phenolic cinnamyl alcohols[4] (scheme 1) produced a complex variety of structures from which 2,6-diaryl-bis-tetrahydrofurans (eg (1a)) were isolated whereas chemical oxidative coupling[5] ($FeCl_3/O_2$) of cinnamic acids gave rise to the corresponding bis-lactone structure (2a)(scheme 2).

When phenolic cinnamic acids and alcohols were cross coupled ($FeCl_3/O_2$) a complex mixture of compounds was produced (scheme 3) which included the bis-tetrahydrofuran (1a), the monolactone (3)



+ COMPLEX MIXTURE

SCHEME 4



SCHEME 5

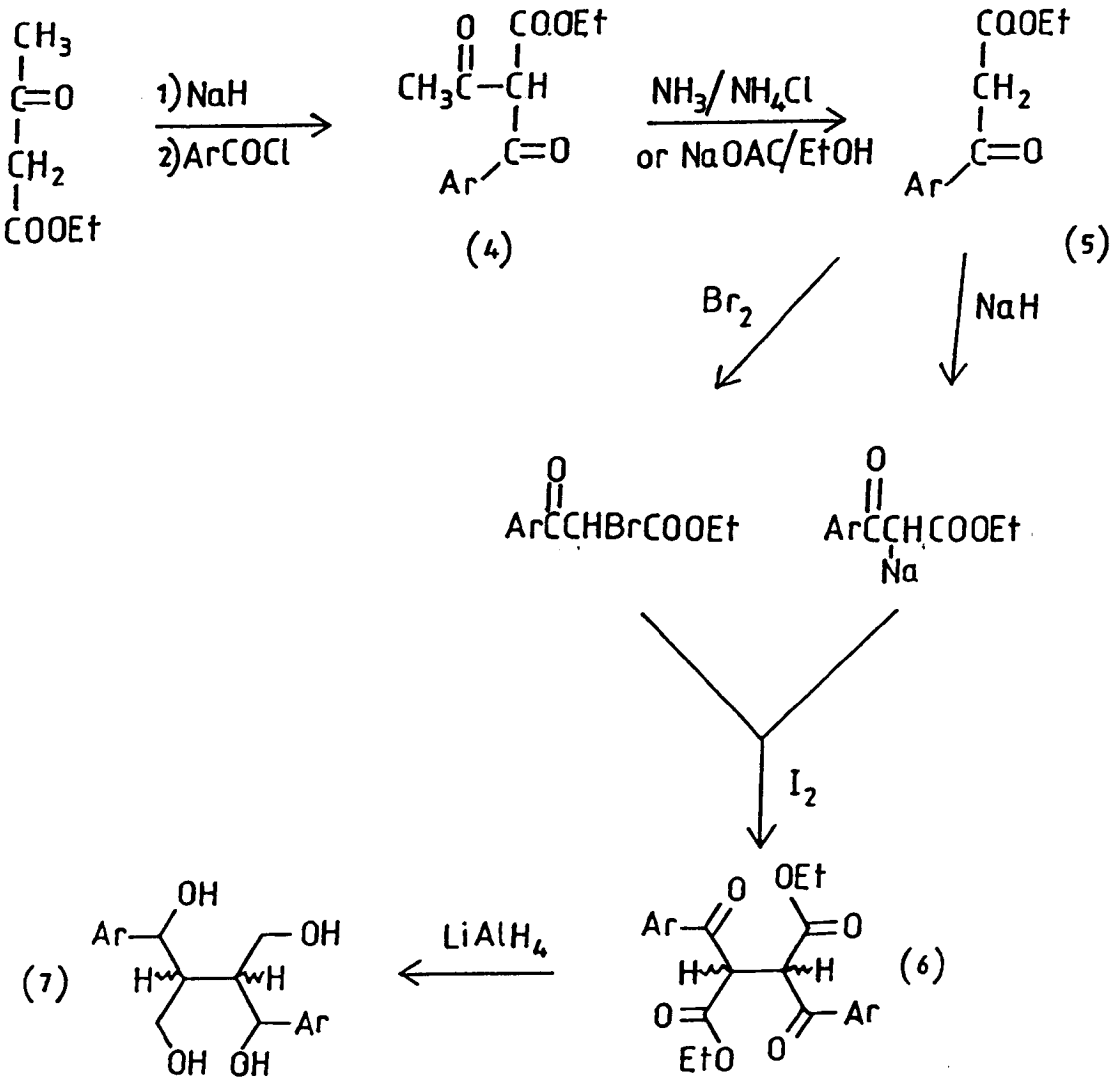
and the bis-lactone (2)[6].

Anodic oxidation[7] (scheme 4) of cinnamic acids gave rise to a mixture of compounds from which bis-lactone lignan type structures were isolated.

More recently[8], non-phenolic dimerisations have been performed (useful for example when Ar = 3,4-methylenedioxyphenyl) using thallium (III) trifluoroacetate (scheme 5). Reported yields were quite reasonable for this type of reaction (up to 54%). An electron transfer mechanism was proposed with an aryl stabilised radical carbocation as an intermediate. The reaction was extremely vigorous and must be quenched immediately the reagents have been mixed. Interestingly, following research groups have had difficulties in repeating these yields[9].

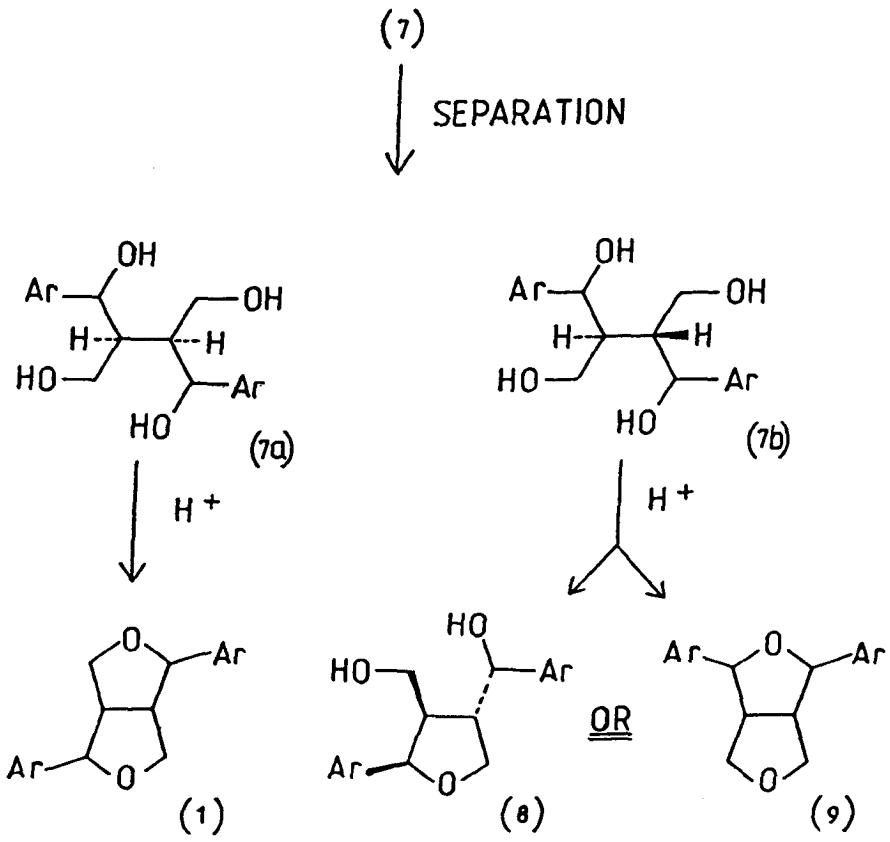
b) Substituted Ethyl Benzoyl Acetates[10]

A very popular route to 3,7-dioxabicyclo[3,3,0] octanes has used ethylacetoacetate as a starting material (scheme 6). Condensation with the substituted benzoyl chloride of choice produced the diketone ester (4) which can be decomposed to the ethyl benzoyl acetate (5). Coupling of these units has been effected by converting one unit to the halide (iodide or bromide) and reacting this with the sodium salt of another. The resulting diastereoisomeric mixture (6) was reduced to the tetrol (7) with lithium aluminium hydride and the isomers were separated.



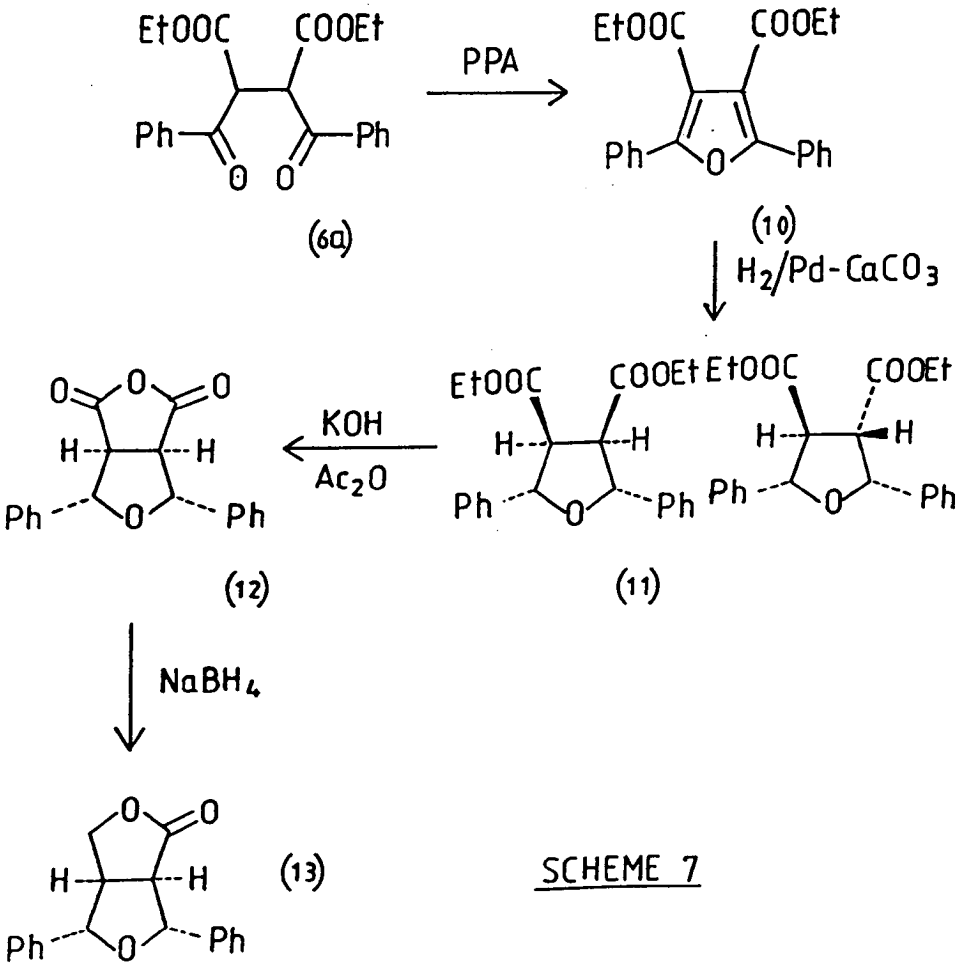
SCHEME 6

One isomer (7a) can be cyclised (acid catalysis) to the bis-tetrahydrofuran (1). The other isomer (7b) has been reported to cyclise to form a tetrahydrofuran diol (8) and more recently the same isomer has been reported to have cyclised to a 2,4-diaryl bicylic structure (9). The product was confirmed by x-ray analysis.



SCHEME 6
(continued)

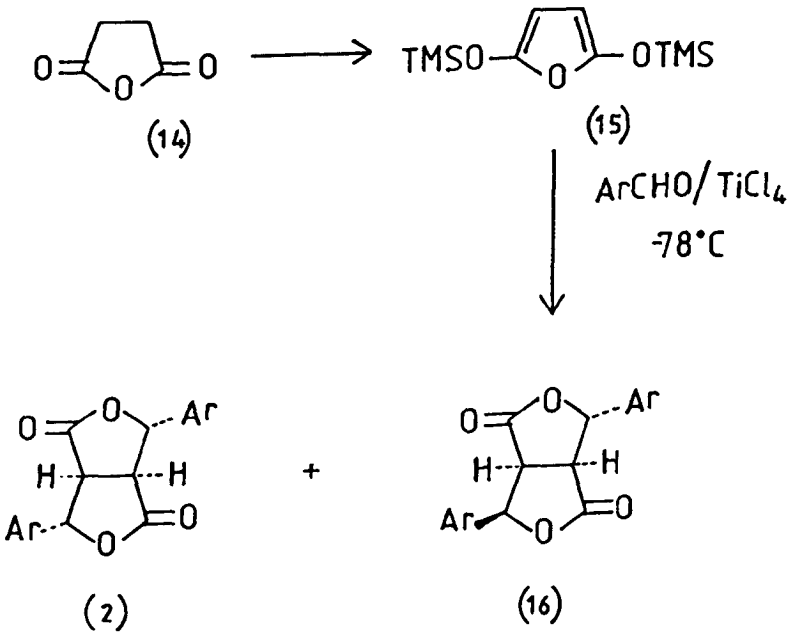
Cooper and Lavie[6] have used a similar intermediate (6a) to unambiguously synthesise 2,4-diaryl lignans (scheme 7), the key step being the formation of the furan (10) by polyphosphoric acid catalysed cyclisation. Hydrogenation gave a mixture of diesters, one of which (11) after hydrolysis and acetic anhydride dehydration was cyclised to the anhydride (12). Sodium borohydride reduction gave the lactone (13) which was identified by x-ray crystallography.



SCHEME 7

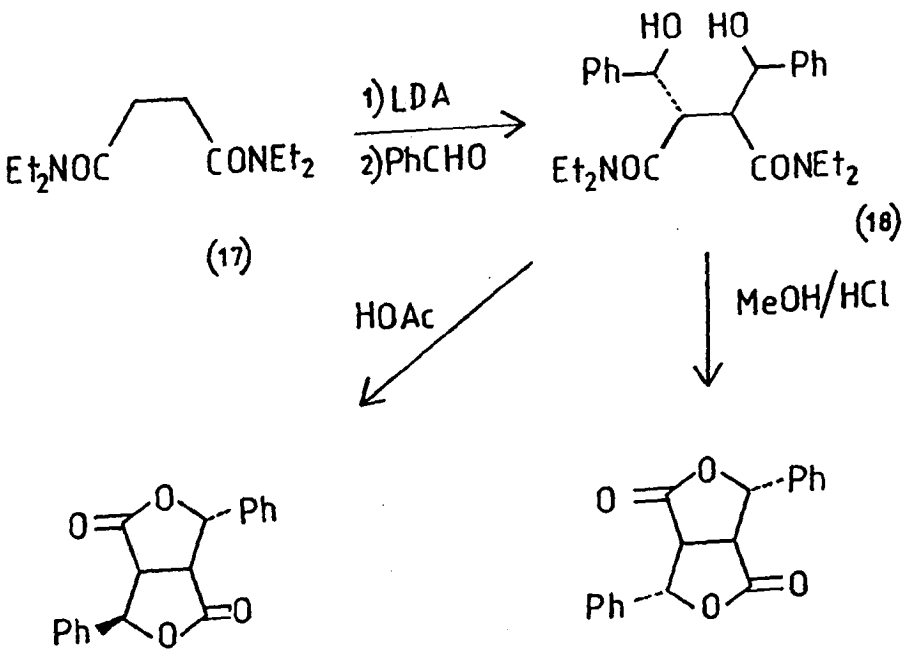
c) bis-(Trimethylsiloxy) Furans[11]

Brownbridge and Chan have used succinic anhydride (14) as a starting material and converted it to the bis-silyl enol ether (15) (scheme 8). Condensation of this with an aromatic aldehyde gave different products depending on the stoichiometry of titanium tetrachloride used. When an excess (2.0 equivalents) was used the symmetrical diequatorial dilactone (2) was produced exclusively in 70% yield whereas when 1.0 equivalents was used 12% of the diequatorial isomer was isolated as well as the equatorial/axial isomer (16) in 58%

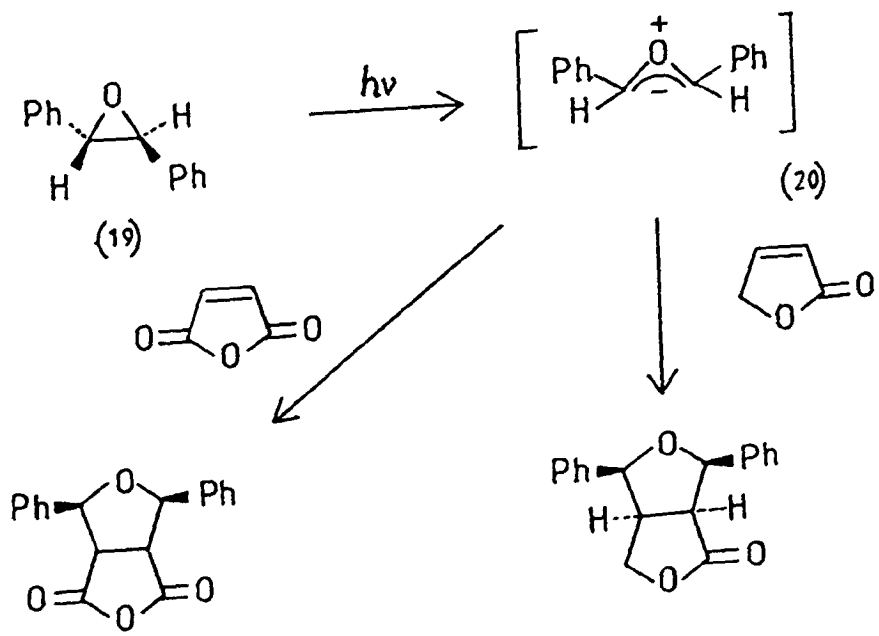


SCHEME 8

eq $TiCl_4$	ratio (2):(16)
1·0	12 : 58
2·0	100 : 0



SCHEME 9



SCHEME 10

yield. This strategy gives a very rapid entry to the bis-lactone skeleton.

d) Dimetalated Tertiary Succinamides

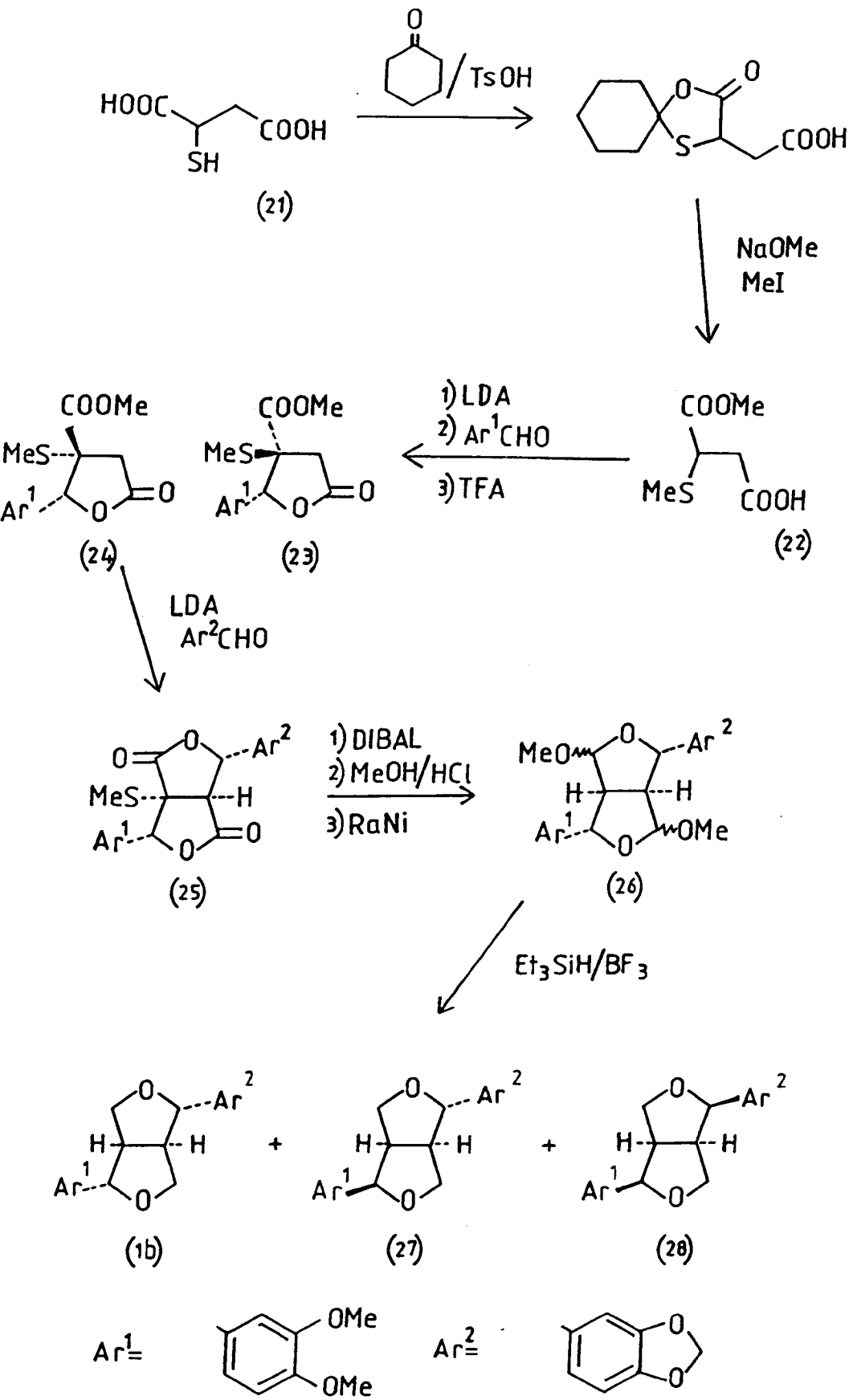
Snieckus and his co-workers[12] have gained entry to the bis-lactone series starting with a 2,3-dibenzylated succinamide (scheme 9). Lithiation of N,N-diethylsuccinamide (17) followed by condensation with benzaldehyde gave predominantly the syn-anti-syn isomer (18) as confirmed by x-ray studies. Refluxing the major diastereoisomer in acetic acid gave the trans-diaryl-bis-lactone in 85% yield whereas refluxing with methanol/hydrochloric acid gave the corresponding cis-compound in 65% yield.

e) Carbonyl Ylides

Continued interest in unambiguous 2,4-diaryl-3,7-dioxabicyclo[3,3,0]octane synthesis led to the use of carbonyl ylides (20) as intermediates[13]. The Ylide (generated photochemically from a trans-stilbene oxide (19)) was added across the double bond of a buteneolide or maleic anhydride (scheme 10). This gave rise to 1,4-diaryl bicyclic lactones and anhydrides respectively. It is now generally accepted that there are no known naturally occuring lignans having these or similar general structures.

f) Unsymmetrical Synthesis

It is important in a general synthesis of

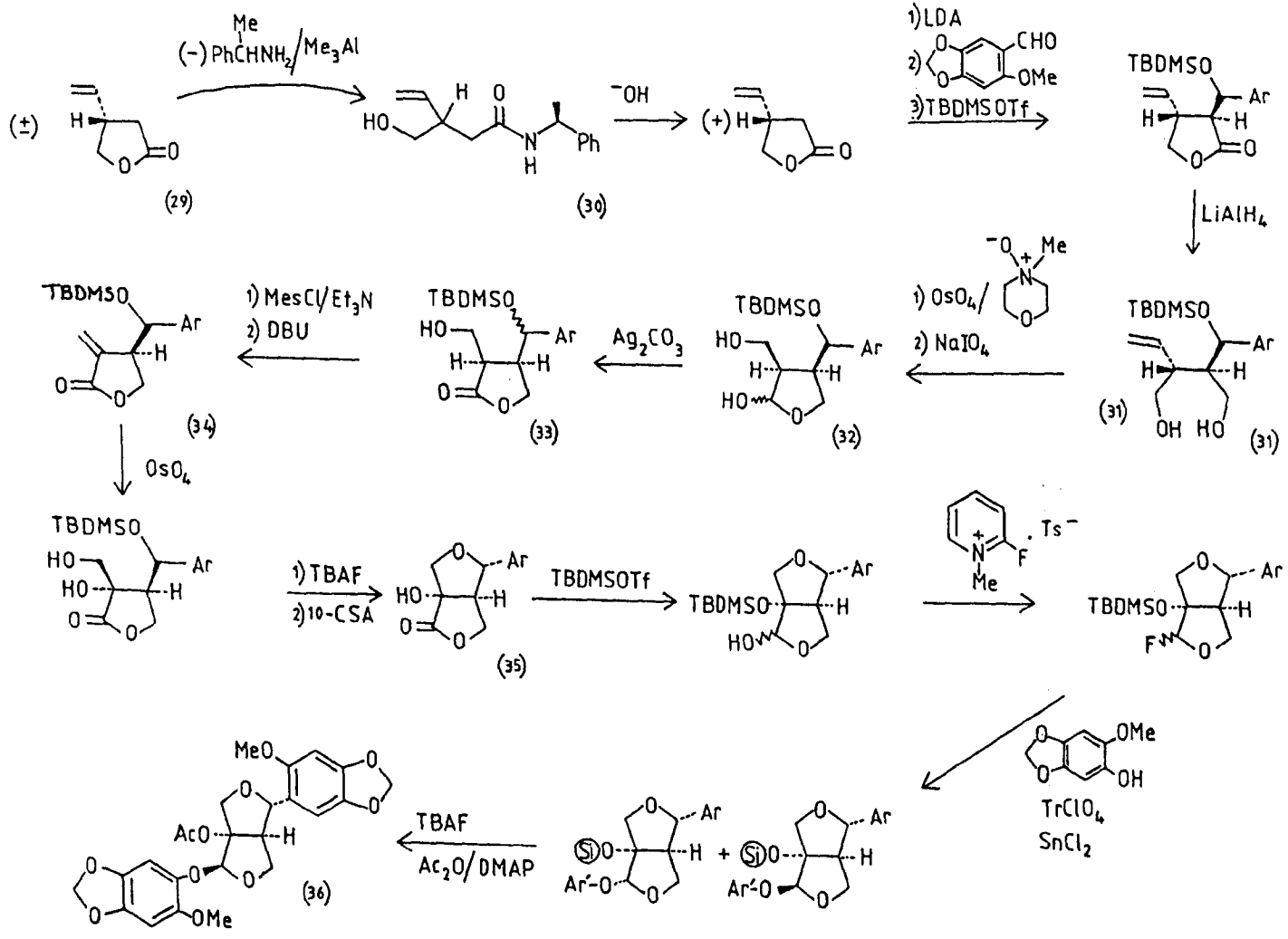

HOOC
COOH
SH
(21)
TsOH
COOH
NaOMe
MeI
COOMe
MeS
COOH
(22)
1) LDA
2) Ar1CHO
3) TFA
COOMe
MeS
Ar1
(23)
(24)
LDA
Ar2CHO
MeS
H
(25)
1) DIBAL
2) MeOH/HCl
3) RaNi
MeO
OMe
(26)
Et3SiH/BF3
(1b)
(27)
(28)
Ar1=
OMe
OMe
Ar2=

SCHEME 11

2,6-diaryl-3,7-dioxabicyclo[3,3,0]octane lignans that there can be different aromatic groups in the molecule. To this end, Pelter, Ward and co-workers[14] have devised a route whereby the aromatic groups are introduced individually and in definitely known positions. Starting from mercaptosuccinic acid (21) the chemistry is outlined in scheme 11. The key intermediate is the methylsulphide monoester (22). Metallation (LDA) of this key intermediate produced a carbanion α- to the methyl ester which was then trapped by an aromatic aldehyde to produce a mixture of the two lactones (23) and (24). Only one isomer of the lactone (24) had the correct stereochemistry for ring closure to occur when it was reacted with LDA followed by an aromatic aldehyde. All attempts at desulphuristion of the formed dilactone (25) were unsuccessful. The dilactone was reduced with DIBAL to the hemi-acetal which was in turn converted to the methyl acetal. This resulting compound was desulphurised (Raney nickel) in 49% yield (26). The methoxy groups were cleaved using triethylsilane and boron trifluoride which produced a mixture of three isomers (1b), (27) and (28) in 35.4%, 18.4% and 17.4% yields respectively. (If the methoxy group cleavage and the desulphurisation steps were reversed, the major isomer produced was (1b)).

g) Enantioselective Syntheses

i) (+)-Phrymarolin (34) is a somewhat unusual lignan in that an oxygen atom has inserted between an aromatic ring and the

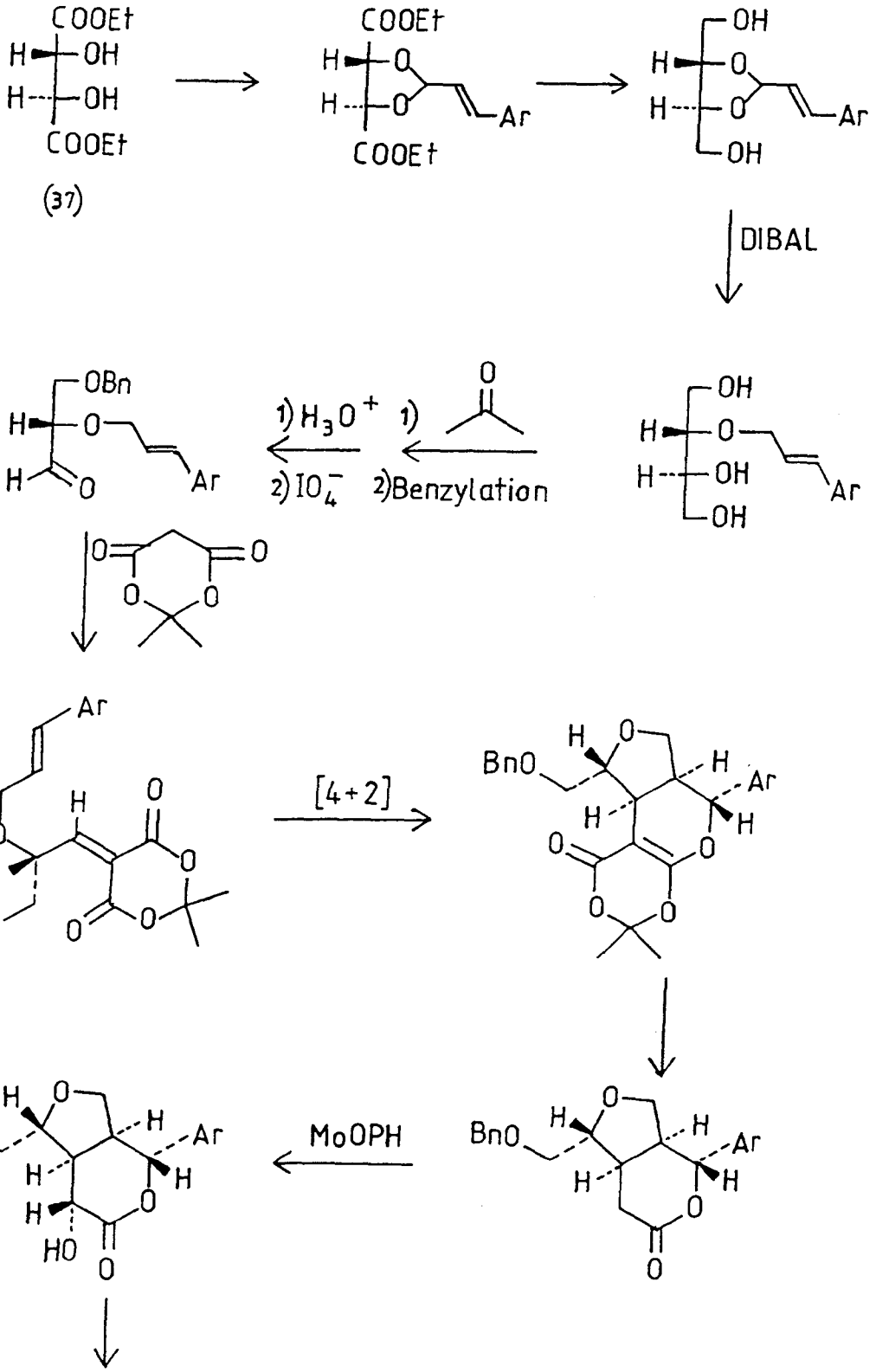

(±)
(29)
(-) PhCHNH2/Me3Al
(30)
⁻OH
(+)
1) LDA
2)
3) TBDMSOTf
CHO
OMe
TBDMSO
Ar
LiAlH4
(31)
1) OsO4/
2) NaIO4
(32)
Ag2CO3
(33)
1) MesCl/Et3N
2) DBU
(34)
OsO4
1) TBAF
2) 10-CSA
(35)
TBDMSOTf
Ts⁻
TrClO4
SnCl2
TBAF
Ac2O/DMAP
(36)
MeO
AcO
OMe
OH

SCHEME 12

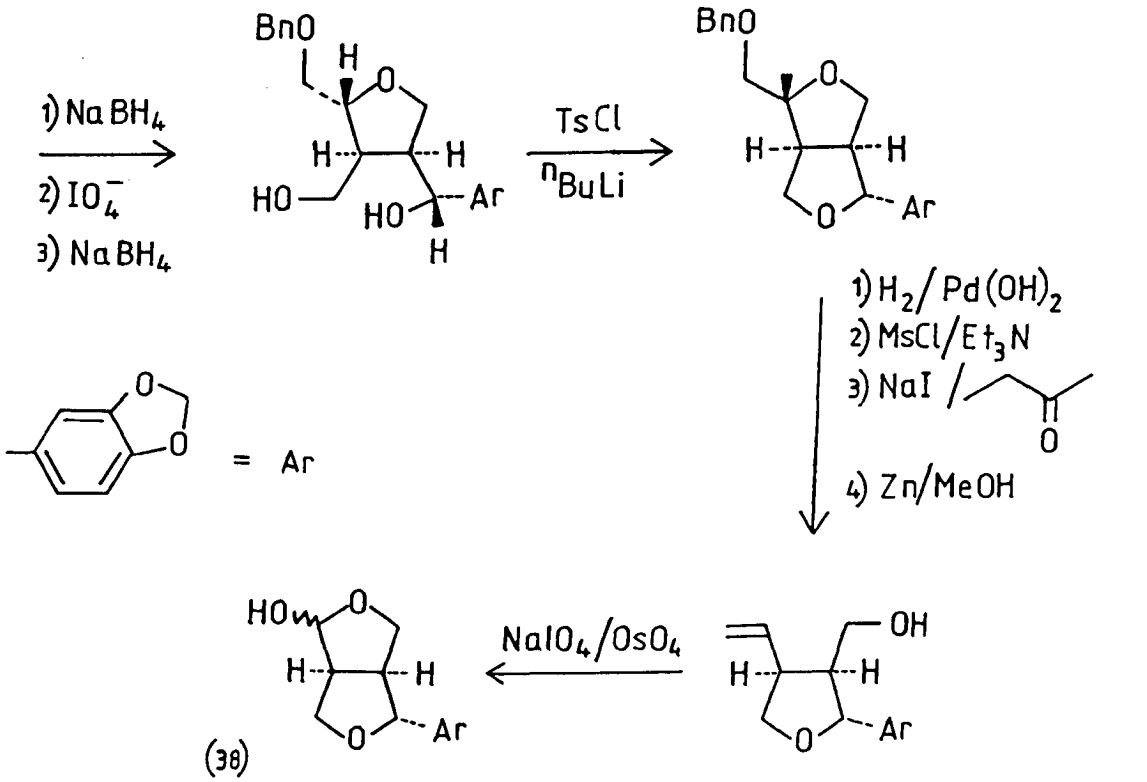
bicyclic system. A lengthy but nevertheless chiral synthesis has been published by Ishibashi and Taniguchi[15]. (±)- β -Vinyl-α-butyrolactone (29) was resolved by conversion to the diastereomeric amides (30) by reaction with (-)- α -phenylethylamine and trimethylaluminium (scheme 12). These were separated chromatographically and the lactone was regenerated by alkaline hydrolysis followed by azeotropic removal of water.

The lithium enolate of the lactone was generated using LDA and was trapped with 2-methoxy-4,5-methylenedioxybenzaldehyde. Silylation (tert-butyldimethylsilyl trifluoromethanesulphonate /2,6-lutidine) of the alcohol function and lithium aluminium hydride reduction gave a diol (31). The double bond was cleaved to the aldehyde (osmium tetroxide followed by sodium periodate) which gave a lactol (32). Silver carbonate oxidation gave the lactone (33). The remaining free alcohol function was mesylated and treated with base (DBU) to furnish the α -methylenelactone (34). Osmium tetroxide catalysed diol formation occurred in a stereoselective manner. Fluoride ion cleavage of the silyl protecting group followed by 10-camphorsulphonic acid catalysed dehydrative cyclisation gave the bicyclic skeleton (35). Further functional group transformations led to the natural product (36) of approximately 81% ee.

ii) Diels Alder Approach


COOEt
H
OH
H
OH
COOEt
(37)
COOEt
H
O
H
O
Ar
COOEt
OH
H
O
H
O
Ar
OH
DIBAL
OBn
H
O
H
O
Ar
1) H_3O^+
2) IO_4^-
O
1)
2) Benzylation
OH
H
O
H
OH
OH
Ar
O
O
O
O
Ar
H
O
O
O
H
BnO
O
O
[4+2]
BnO
H
O
H
Ar
H
H
O
O
O
O
BnO
H
O
H
Ar
H
H
O
O
MoOPH
BnO
H
O
H
Ar
H
H
H
O
HO
O

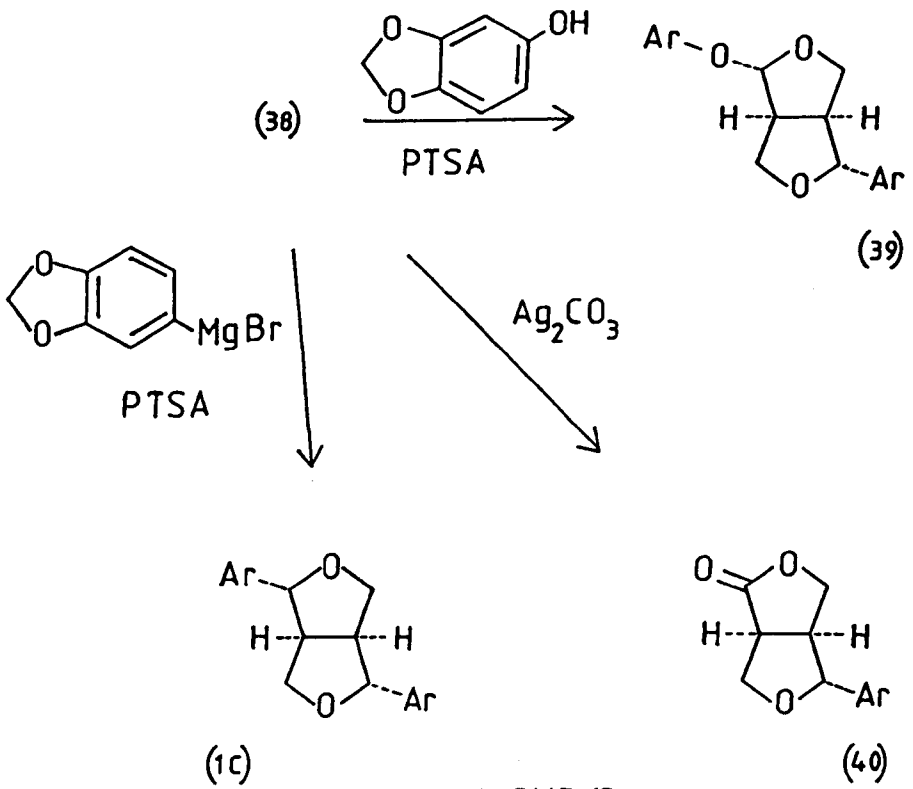
Diethyl tartrate (37) has been used recently by Takano and co-workers[16] in an elaborate synthesis (scheme 13) of (-)-sesamin, (-)-sesamolin and (-)-acuminatolide. The key step in this sequence is a highly diastereoselective intramolecular hetero [4+2] cyclisation. This very lengthy sequence does however produce natural products of high optical purity. The bicyclic lactol intermediate (38) was readily converted to the natural products (-)-sesamin (1c) and (+)-sesamolin (39) in high ee. (-)-Acuminatolide (40) was of lower optical purity, however it was clearly identified by its ^1H NMR spectrum.



SCHEME 13

(continued)

P.T.O. →



SCHEME 13a

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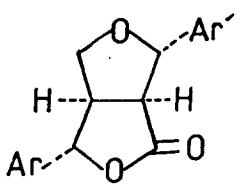
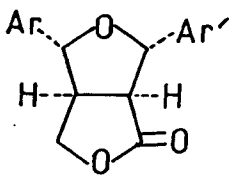
Chapter 2



(1)



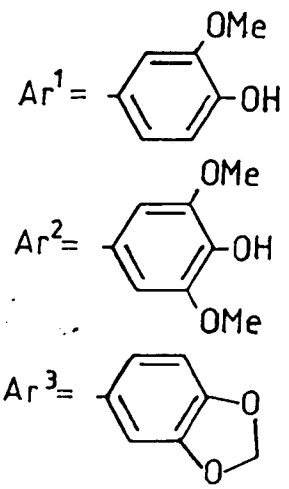
(2)

a) $Ar = Ar' = Ar^1$

b) $Ar = Ar^2$ $Ar' = Ar^1$

c) $Ar = Ar' = Ar^3$

d) $Ar = Ar^3$ $Ar' = Ar^1$



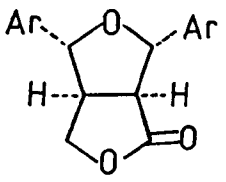
The Synthesis of

2,6-Diaryl-8-oxo-3,7-dioxabicyclo[3,3,0]octane Lignans.

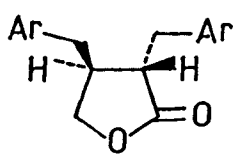
As described in earlier chapters, there has been discovered in recent years a new family of lignan lactones having general structure (1). This is currently a small class and to the authors knowledge, only four members have been reported to date from natural sources. These include a germination inhibitor MEL[1] (1a), (MonoEpoxyLignanolide) reported by Lavie et al. isolated from Aegilops ovata along with a co-occurring methoxy derivative (1b). Also reported in the literature have been aptosimon[2] (1c) by Brieskorn and Huber as well as styraxin[3] (1d) an antitumour compound reported by Ulubelen et al.

MEL (1a) was initially reported to possess a 2,4-diaryl structure (2a) and aptosimon (1c) was later reported to have a similar structure (2c). Both halves of these molecules are isolated from each other in a ^{1}H and ^{13}C NMR sense by the two bridging oxygens and similar chemical shifts and multiplicities might be expected from isomers (1) and (2) in each case. Aptosimon was assigned a 2,4-diaryl structure by Brieskorn and Huber[2] on the basis of a weak mass spectral fragment.

Evidence that these compounds should be revised to 2,6-diaryl structures came from a number of sources. There are no known

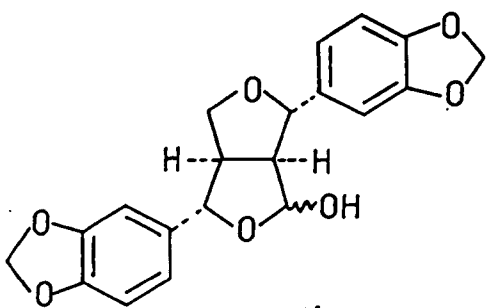


(3)



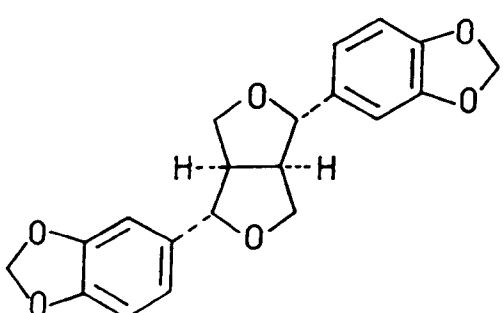
(4)

[PLANT] ⟶ (1)



(5)

CrO_3 ⟶ (1)

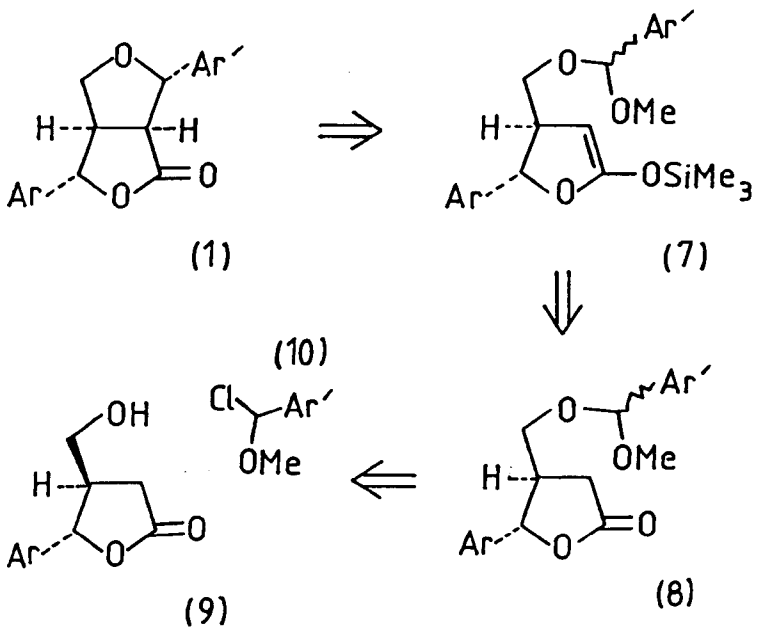


(6)

2,4-diaryl compounds (3) in the corresponding bis-tetrahydrofuran[4] series while the corresponding dibenzylbutyrolactones[5] (4) invariably have a trans configuration so that it would not be biosynthetically straightforward to insert an oxygen atom and form two five membered rings.

Styraxin was reported to have a 2,6-diaryl structure which was confirmed by X-ray crystallography. It was then possible to compare the reported ^{1}H NMR data and mass spectral fragmentation with both MEL and aptosimon casting doubts over their structural assignments. 4-Hydroxysesamin (5) has been reported by Pelter and Ward[6] and its structural assignment is based on the similarity of its ^{1}H NMR spectrum with that of sesamin (6), a well known natural compound. Chromium trioxide oxidation of the hemi-acetal (5) gave a compound which correlated very closely with aptosimon (1c). Lavie has since reassigned MEL as having a 2,6-diaryl structure[1c].

In the absence of X-ray analyses, one answer to structural problems of this sort would be unambiguous chemical synthesis. No satisfactory synthesis for lignans of this type has been reported (oxidative coupling generally gives poor results and still leaves some doubt over the final position of the aromatic groups). Interesting biological activities are also displayed within the class. We thus considered these lactones to be worthwhile synthetic targets. Moreover the carbonyl


Ar'
O
H
H
Ar
O
O
(1)
Ar'
O
OMe
H
Ar
O
OSiMe3
(7)
(10)
Cl
Ar'
OMe
OH
H
Ar
O
O
(9)
Ar'
O
OMe
H
Ar
O
O
(8)

SCHEME 1

group in the lactone represents a convenient synthetic handle in the molecule for its own synthesis; further, it is easy to envisage a reduction of this to a corresponding tetrahydrofuran ring and hence give entry to a large number of other natural lignans.

A satisfactory synthesis of lignan lactones (1) must fulfil a number of requirements.

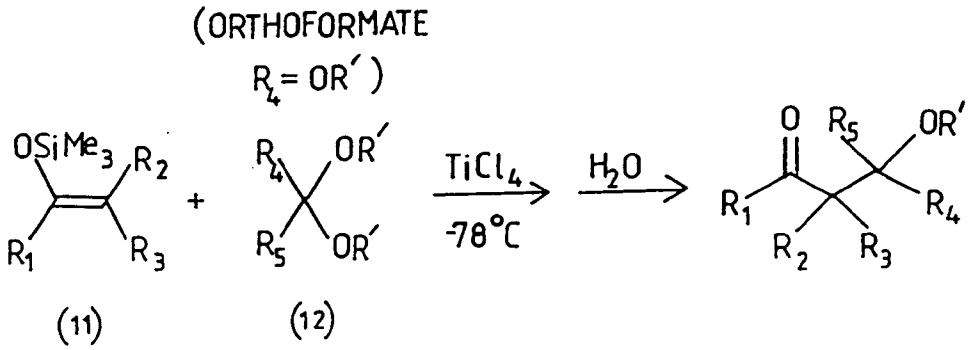
(a) The two aromatic groups must be introduced in separate, discrete stages and the exact postion of each aromatic group in the bicyclic nucleus must be determinable. This requirement is currently satisfied only by one approach reported by Pelter and Ward[7] . (See last chapter, page 12)

(b) It must be possible to impress a cis junction between the two five membered rings.

(c) Considerable control over the stereochemistry of the two aromatic groups is required.

(d) The synthesis should be as short as possible.

Analysing the basic skeleton retrosynthetically (scheme 1) we can see that the C_1-C_2 bond might be formed using a Lewis acid catalysed, directed aldol reaction between a silyl enol ether (a silyl ketene acetal in this example) and an acetal; a


(ORTHOFORMATE
R4 = OR′)
OSiMe3
R2
R1
R3
+
R4
OR′
R5
OR′
TiCl4
-78°C
H2O
O
R5
OR′
R1
R4
R2
R3
(11)
(12)

SCHEME 2

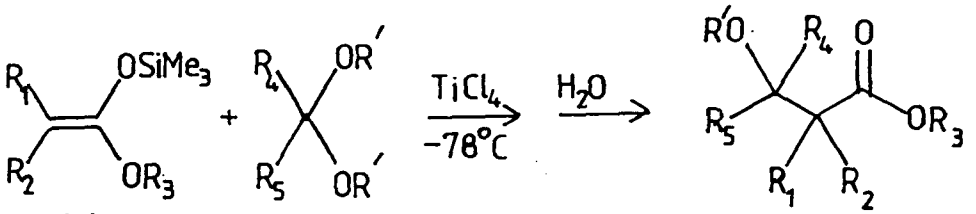
reaction of a type first reported by Mukaiyama[8]. Furthermore, the silyl ketene acetal (7) would derive from the lactone (8) and the acetal could be formed from the reaction between an alcohol (9) and an α-chloro-benzyl ether (10).

The key step in this scheme is clearly the final carbon-carbon bond formation and it is useful at this point to review similar ring closures that have been reported in the literature.

The Mukaiyama Acetal Directed Aldol Reaction and its use in Ring Closures.

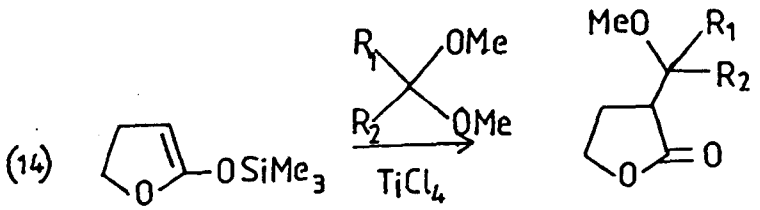
Mukaiyama first reported the reaction in 1974, between a silyl enol ether (11) and an acetal or orthoformate (12) catalysed by a Lewis acid, titanium tetrachloride (scheme 2).

Since this first reaction was reported several modifications and different conditions have been described[9]. Titanium tetrachloride remains the favourite Lewis acid but other Lewis acids have been used successfully. These include $BF_3.OEt_2$[10], trimethylsilyl trifluoromethanesulphonate[11], $ZnCl_2$[12], $ZnBr_2$[13,12a] TMSI[14], ZnI_2[15], $Ph_3C^+ClO_4^-$[16] and $SnCl_4$[17]. It is frequently difficult to predict which catalyst will be most effective for a particular reaction and trial and error is often the only resort to finding successful conditions. A Lewis acid giving a good yield in one particular case may be ineffective in



(13)

SCHEME 3



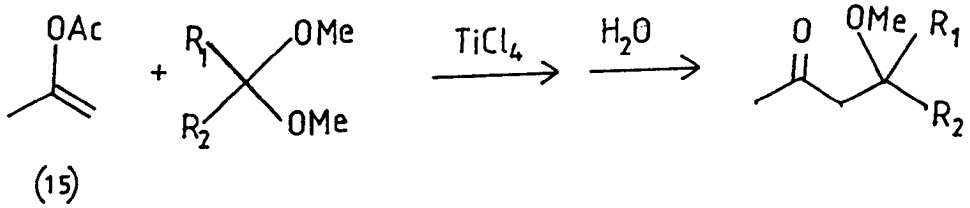
SCHEME 4

another whereas an alternative acid in the new case may give satisfactory results.

The reaction has also been successful where silyl ketene acetals have been used, and derivatives of both esters[18] (13) and lactones (14) have been employed. (schemes 3 and 4)

Other enolates and enolate equivalents have also been reported in the literature;

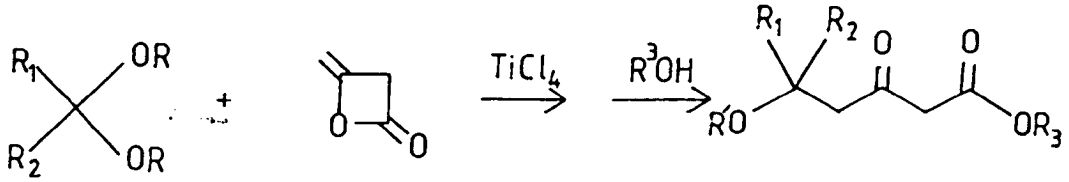
(a) Enol acetates[19] (15) (scheme 5).



(15)

SCHEME 5

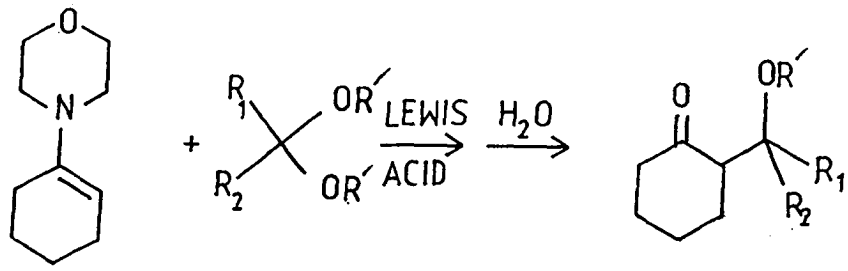
(b) Diketene[20] (16) (scheme 6).



(16)

SCHEME 6

(c) Enamines[21] (17) (scheme 7).



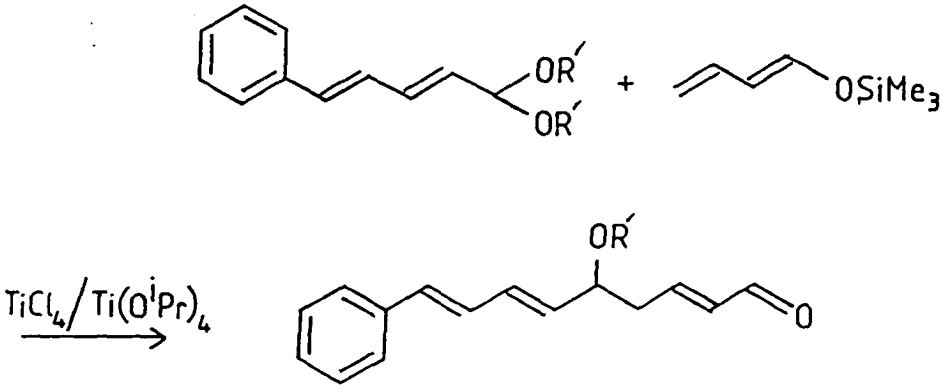
(17)

ORTHOFORMATE $R_1 = OR'$

LEWIS ACID = $TiCl_4$, BF_3OEt_2, $SnCl_4$ or $ZnCl_2$.

SCHEME 7

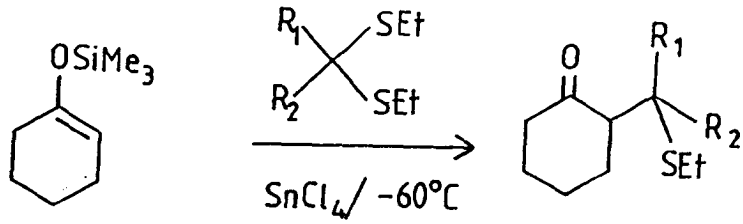
(d) The reaction has even been extended in the vinylogous sense[22] (scheme 8).



SCHEME 8

This chemistry has been used in total synthesis of Vitamin A.

Sulphur acetals[22] (18) are useful when softer Lewis acids are used (eg scheme 9) such as tin tetrachloride.



SCHEME 9

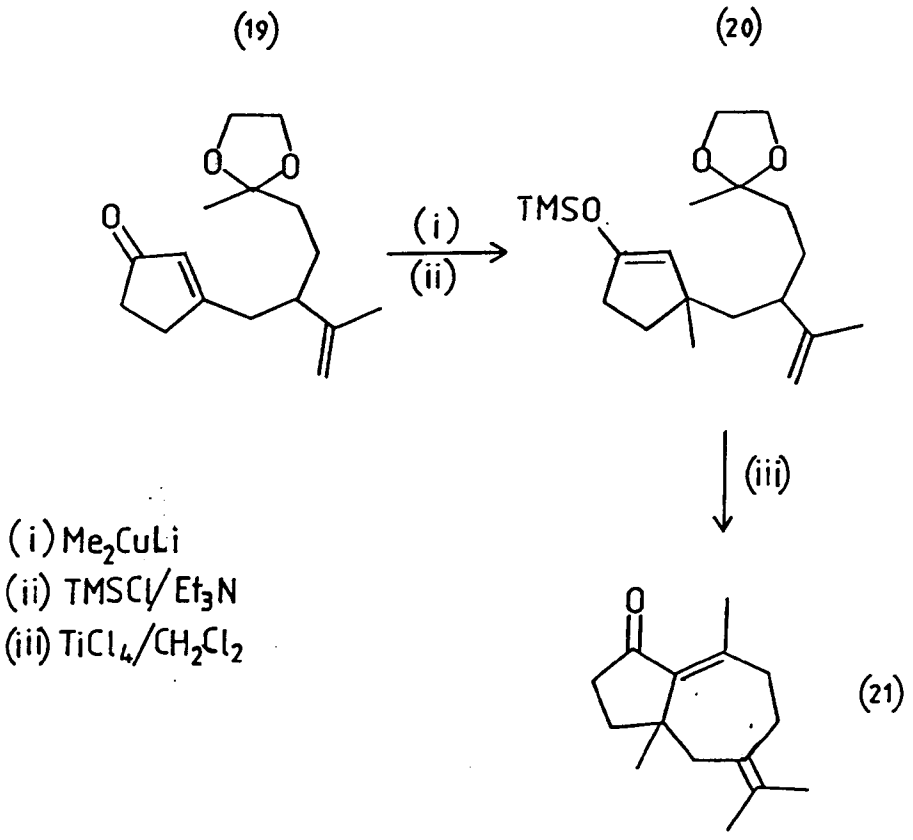
Intramolecular Ring Closures.

One of the successes of the intramolecular version of this reaction is in the formation of medium and large size rings. This reaction is frequently useful where other reactions have failed, for example usual acid or base catalysed aldol reactions between carbonyl compounds. The advantages of the acetal aldol reaction are;

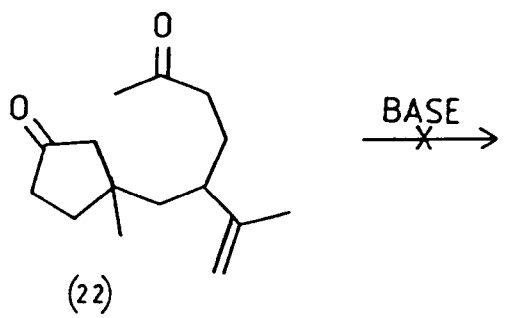
(a) It is usually unambiguous as to which carbon-carbon bond will be formed.

(b) The reaction is irreversible and usually rapid unlike many aldol reactions where unfavourable equilibria frequently exist.

(c) The conditions for the reactions are usually very mild, even strong Lewis acids are usually used at low temperatures (eg titanium tetrachloride at -78°C).



SCHEME 10



SCHEME 11

(d) Given optimum conditions, moderate to high yields can be obtained.

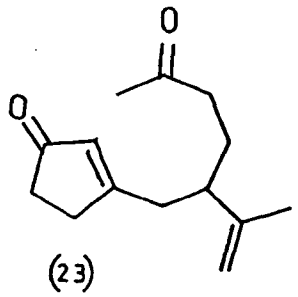
(e) Unlike many medium or large ring closures, high dilution techniques are not required, 0.05 - 0.10 M concentrations are typical.

The first reported example of a ring closure using an acetal directed aldol reaction was made by Posner in his synthesis of pseudoguaianes[24].

The silyl enol ether (20) was formed by Michael addition of a methyl lithium cuprate to a cyclopentenone (19) and subsequently trapping the enolate with trimethylsilyl chloride (scheme 10). Ring closure was effected using titanium tetrachloride with an internal cyclic acetal and this followed by hydrolytic work-up gave a bicyclic product (21) in good yield (60%). The acid conditions also caused a double bond migration.

In this case an attempted base catalysed aldol reaction using a diketone (22) failed, presumably due to an unfavourable equilibrium in forming a seven membered ring (scheme 11a).

An alternative ring closure was effected using various methyl metallic species on the diketone (23) equivalent of the acetal (19) but generally gave poor yields (scheme 12).

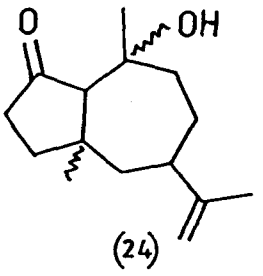


(23)

Me-Metal

THF

0°C



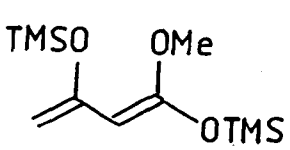
(24)

Me-METAL = 2eq MeCuLi -10%

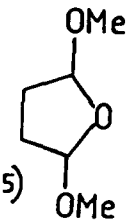
" +10% $CuBr.Me_2S$ -15%

" + eq $CuBr.Me_2S$ -25%

SCHEME 12

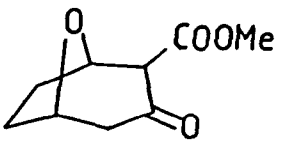


+



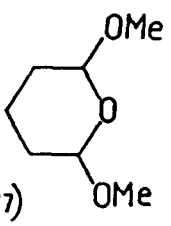
(25)

$TiCl_4$



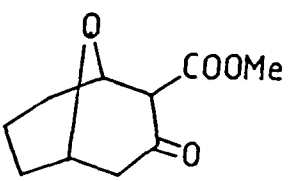
(26)

(24) +



(27)

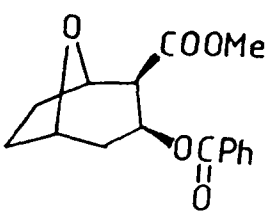
$TiCl_4$



(28)

SCHEME 13

(26) $\xrightarrow[PhCOCl]{NaBH_4}$



(29)

SCHEME 14

Isolation of compound (22) provided more evidence of the previous unfavourable equilibrium.

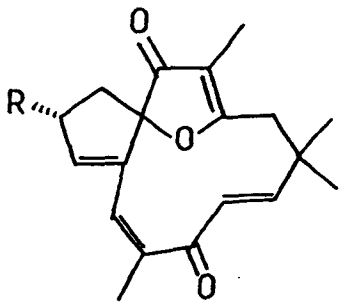
Brownbridge and Chan[25] have used a reaction closely related to the general procedure involving the bis-silyl enol ether of methyl acetoacetate , 2,5-dimethoxytetrahydrofuran (25) and 2,6-dimethoxytetrahydropyran (27). Condensation was effected using titanium tetrachloride to produce bicyclic products (26) and (28) in good yields, 79% and 74% respectively (scheme 13).

The bicyclic product (26) was later reduced ($NaBH_4$) to the alcohol which was condensed with benzoyl chloride to give an oxo analogue of cocaine (29). ^1H NMR spectroscopy showed that coupling constants in this molecule were almost identical to natural cocaine.

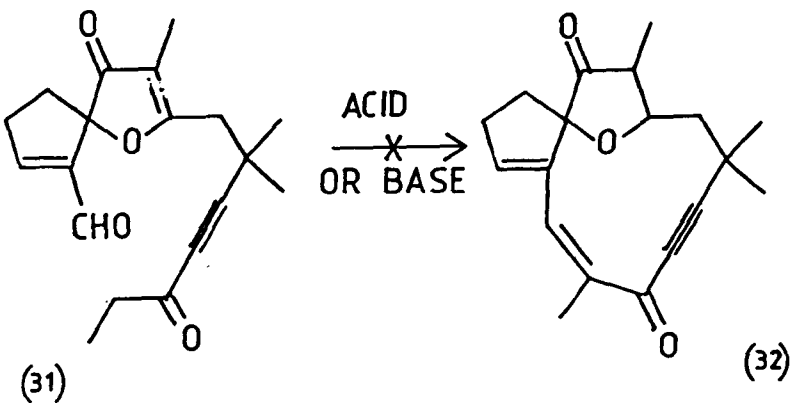
Smith et al[26] turned to the reaction in their synthesis of normethyljatrophone (30a). The antitumour diterpene jatrophone (30b, R = CH_3) contains a macrocyclic ring.

Early attempts to synthesise the eleven membered ring (32) (with an 8-9 acetylenic bond) involved acid and base catalysed aldol reaction (scheme 15), however this proved completely fruitless.

(30)

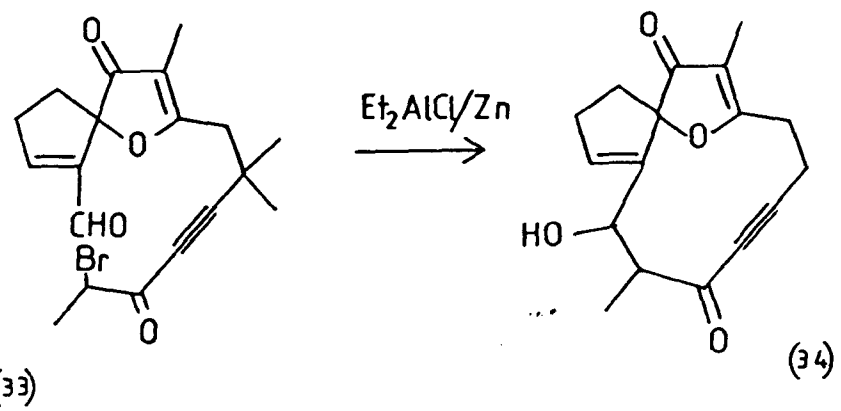


(a) R=H
(b) R=CH_3



(31) (32)

SCHEME 15

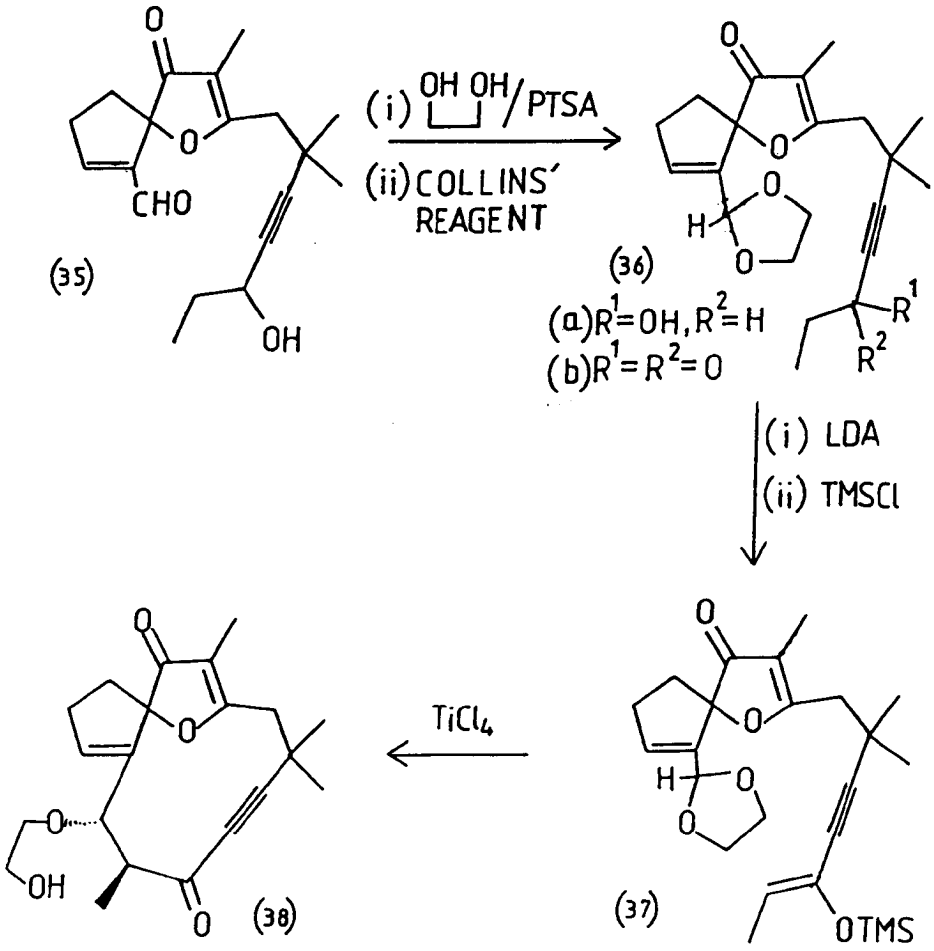


(33) (34)

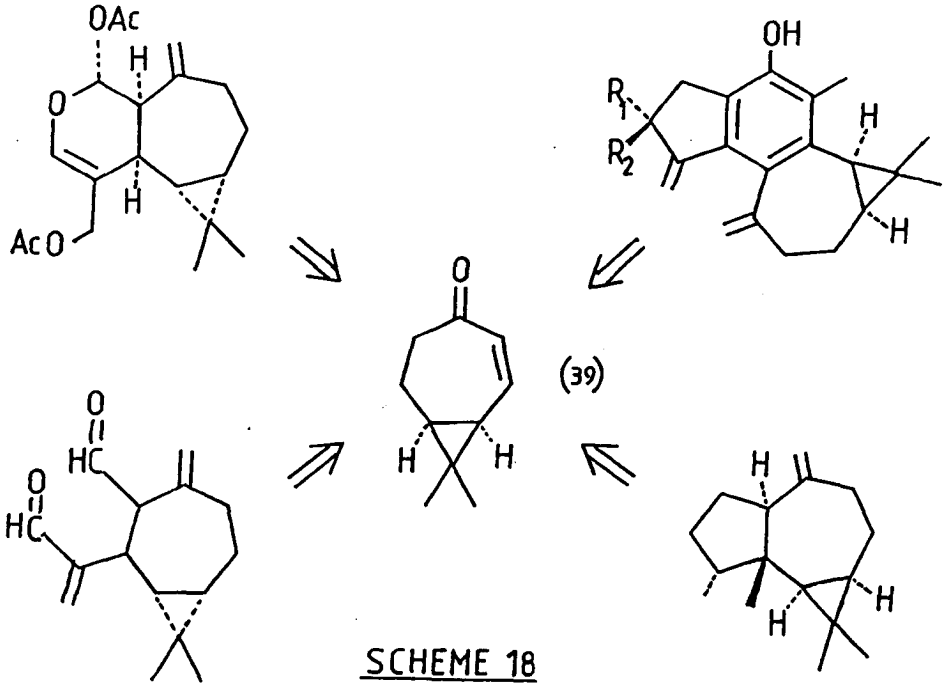
SCHEME 16

An alternative approach with somewhat more success involved α-bromination of the ketone ((31)--->(33)) followed by Yamamota "Reformatski like" aldol reaction (scheme 16). However, the ring closed product (34) was reported to revert to the ring opened dicarbonyl compound (31) "with ease" probably explaining the failure of earlier efforts.

A much more satisfactory approach was the use of the Mukaiyama reaction. The aldehyde (35) was converted to the acetal (36a, 100%) and the alcohol function was then oxidised to the corresponding ketone (36b, 85%). (scheme 17)



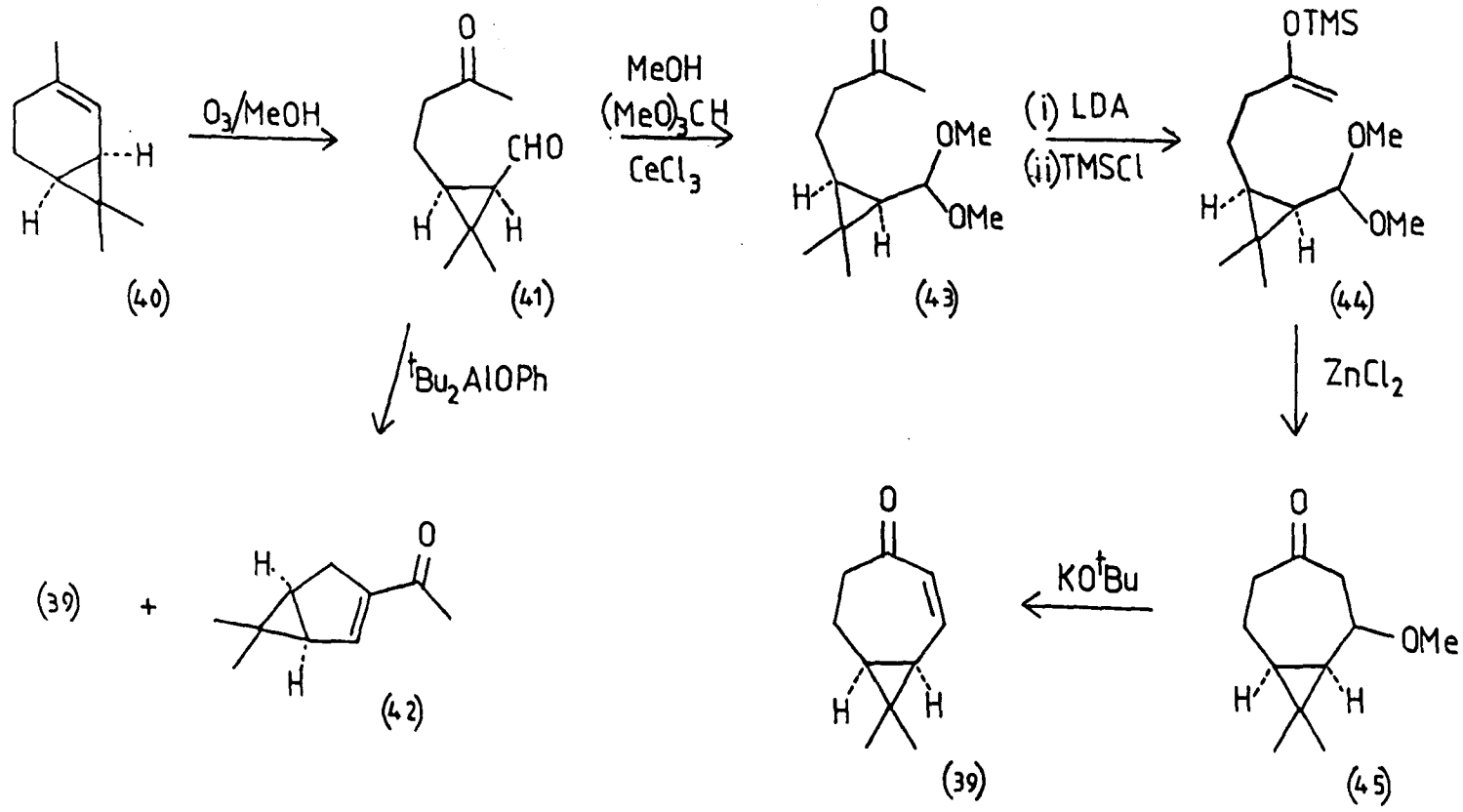
SCHEME 17



SCHEME 18

Formation of the silyl enol ether (37) followed by titanium tetrachloride catalysed cyclisation gave the desired aldol product (38) in 47% yield as a 2:1 mixture of diastereoisomers. The advantage of the reaction in this case is again its irreversibility. Smith[12] has also adopted a somewhat similar approach to a very different system. 8,8-Dimethylbicyclo[5,1,0]oct-2-en-4-one (39) was seen to be a major structural component common to a number of sesqui- and di-terpenes (scheme 18).

A chiral synthesis of this compound was completed using (-)-2-carene (40) as a starting material. Ozonolysis produced the corresponding chiral diketone (41). Using standard aldol chemistry, five rather than seven membered rings were formed preferentially. Even when the reaction was tried using


O3/MeOH
MeOH
(MeO)3CH
CeCl3
(i) LDA
(ii)TMSCl
ZnCl2
KOtBu
tBu2AlOPh
(40)
(41)
(43)
(44)
(45)
(39)
(42)
(39)
+

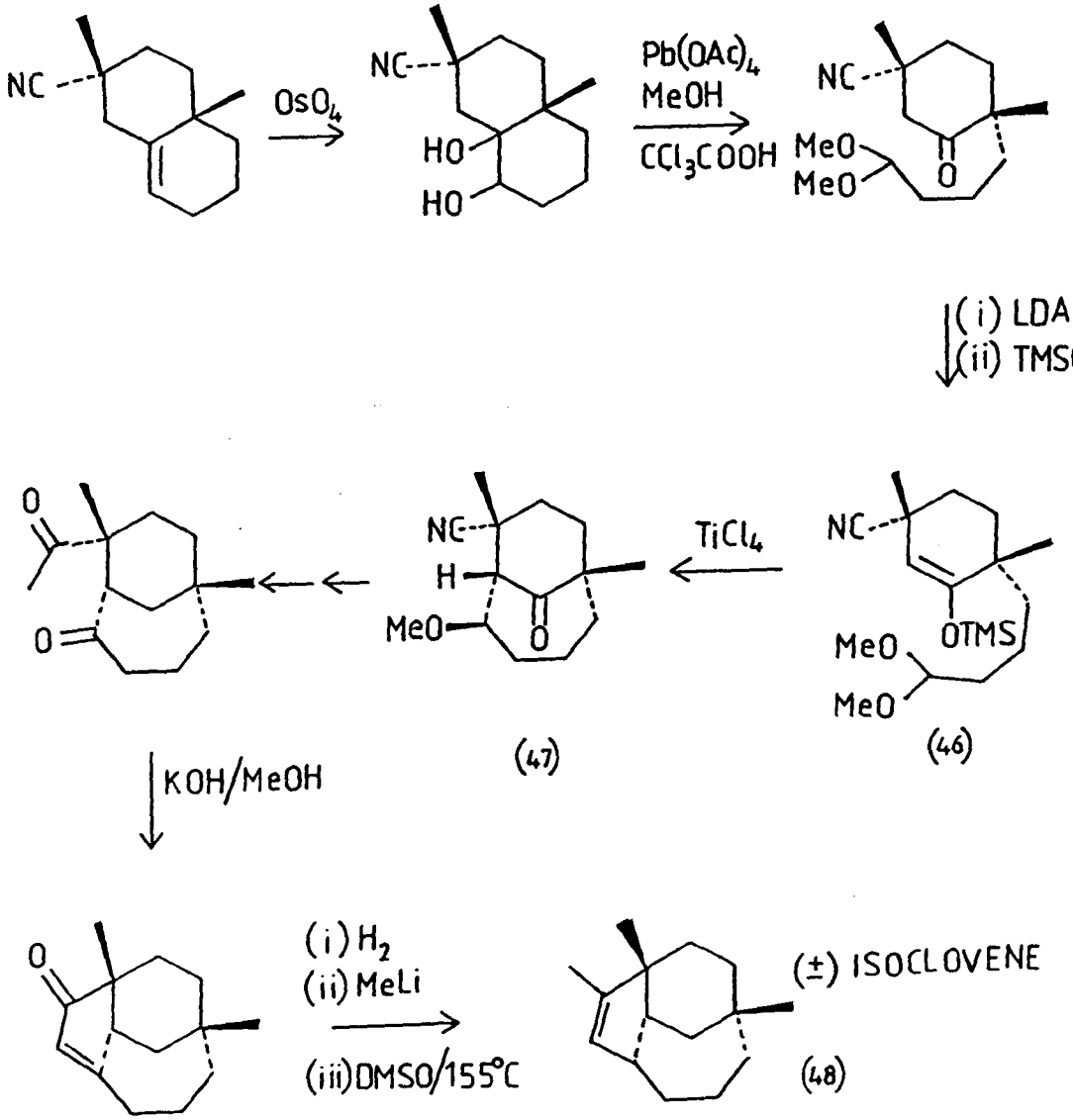
SCHEME 19

diisobutylaluminium phenoxide (reported to form enolates specifically from methyl ketones) it gave a mixture of seven and five membered rings (scheme 19).

Formation of the dimethyl acetal (43) selectively over the ketal was effected using cerium(III) chloride catalysis. The silyl enol ether (44) was formed as usual, however using titanium tetrachloride as the Lewis acid catalyst (CH_2Cl_2, -78°C) gave only very low yields (10%) of the required ring closed product (45), decomposition being the major reaction. Milder catalysis was required and after much experimentation, zinc chloride proved to be the most effective (59% yields). The required olefin (39) was formed by the action of potassium tert-butoxide in ether (27% overall from (-)-2-carene).

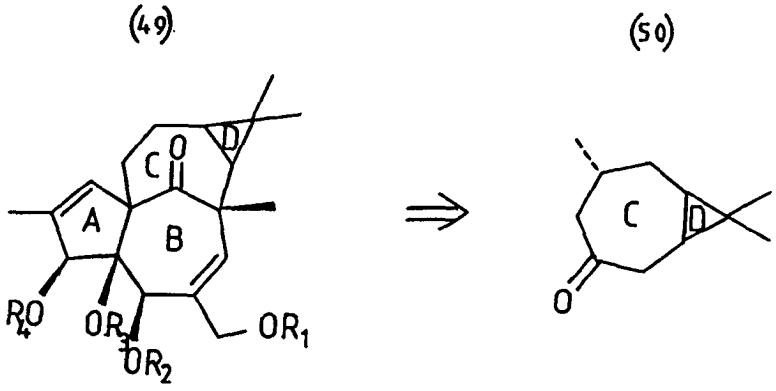
Isoclovene[27] (48) is a rearrangement product of caryophyllene and has been the subject of a reported synthesis by Kellner and Loewenthal. As a key step in this synthesis there was an intramolecular aldol reaction to form a seven membered ring. ((46)--->(47)). The methods used are outlined (scheme 20) and again use titanium tetrachloride as the catalyst which gave excellent yields in the aldol reaction.

Ingenol esters (49) are tetracyclic diterpenes found in the Euphorbiaceae family of plants and are responsible for the considerable variety of biological activities (cytotoxic, irritant, cocarcinogenic, antileukemic and piscicidal) observed. Yamakawa[28] has reported a synthesis of the C/D ring


NC
OsO4
HO
HO
Pb(OAc)4
MeOH
CCl3COOH
MeO
MeO
O
(i) LDA
(ii) TMSCl
OTMS
TiCl4
H
(47)
(46)
KOH/MeOH
(i) H2
(ii) MeLi
(iii) DMSO/155°C
(±) ISOCLOVENE
(48)

SCHEME 20

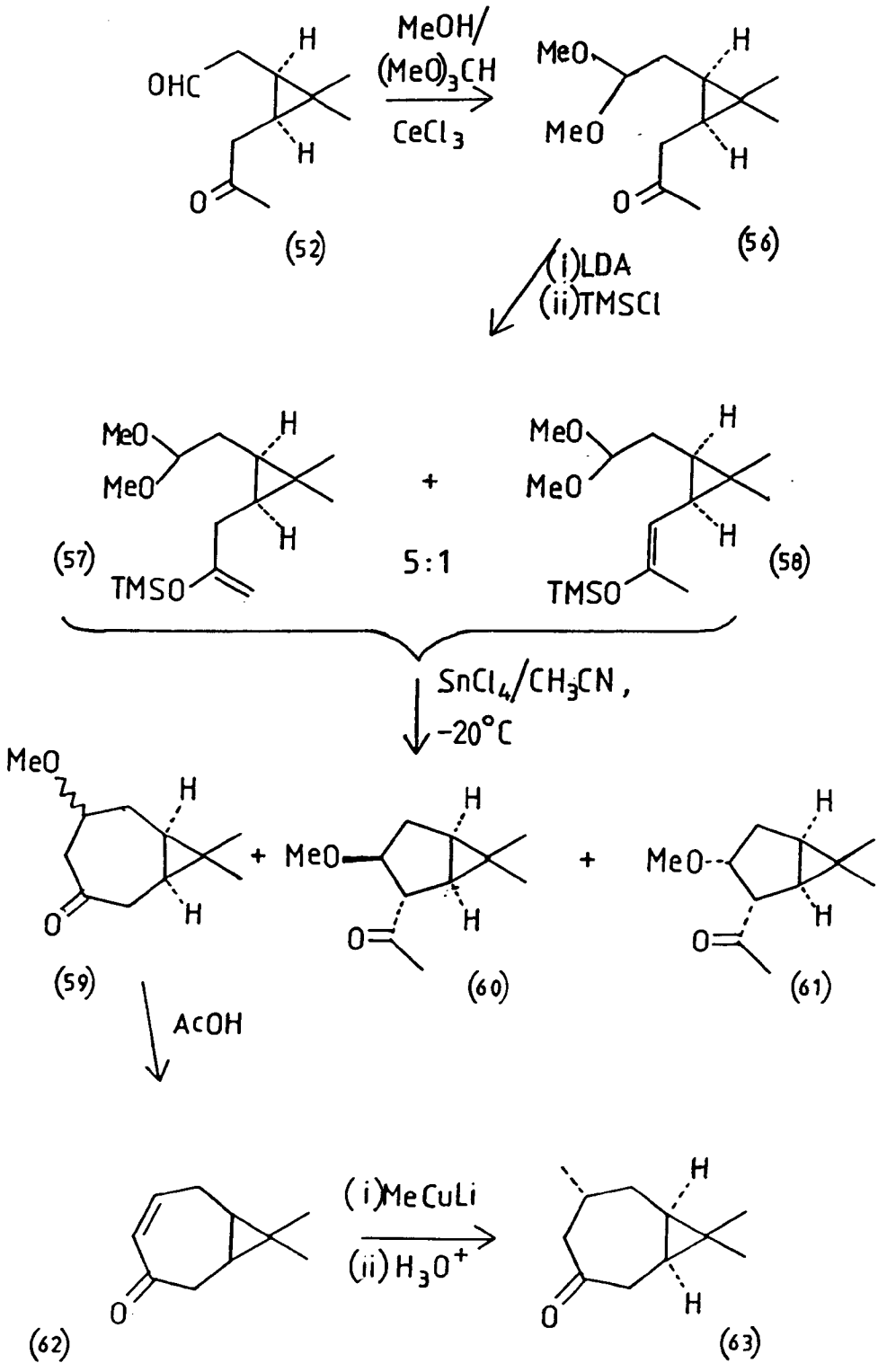
moiety in the molecule (50) using (+)-3-carene (51) as a starting material. (scheme 21)



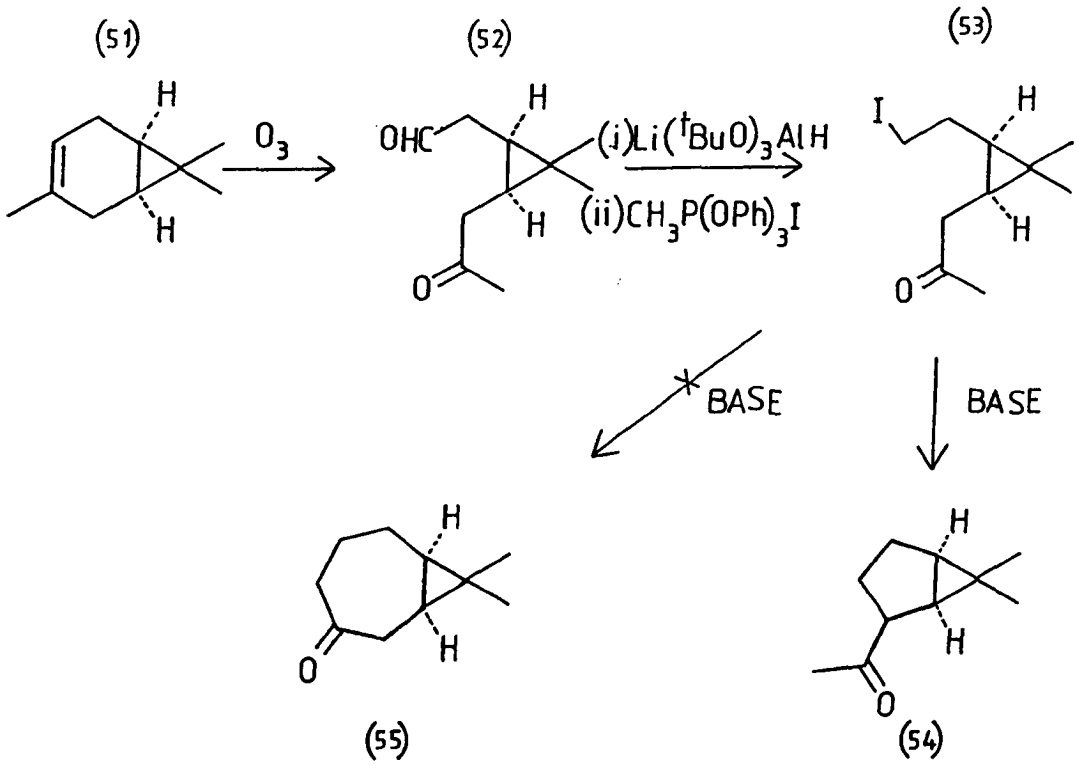
R_{1-4} = H, $COCH_3$, $COCH_2CH_3$, $COCH(CH_3)_2$.

SCHEME 21

(+)-3-Carene (51) was converted to the dicarbonyl compound (52) using ozonolysis and the aldehyde group was converted to the iodide (53) following selective reduction with lithium tri-tert-butoxy aluminium hydride and reaction with triphenylphosphite methiodide. Reaction of this compound with a range of strong, hindered bases (lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilylazide) gave 26-65% yields of the cyclopropane (54) derivative rather than the much less favoured cycloheptanone (55) (scheme 22).


MeOH/
(MeO)3CH
CeCl3
(52)
(56)
(i)LDA
(ii)TMSCl
(57)
5:1
(58)
SnCl4/CH3CN,
-20°C
(59)
(60)
(61)
AcOH
(i)MeCuLi
(ii)H3O+
(62)
(63)

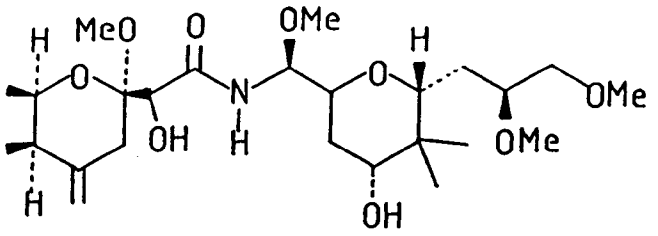
SCHEME 23



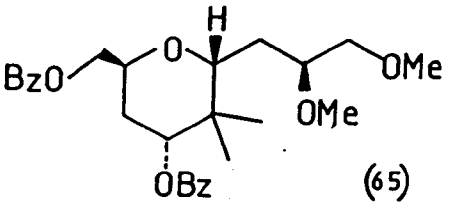
SCHEME 22

Again recourse was made to the acetal directed aldol reaction. The aldehyde (52) was converted to the dimethyl acetal (56) using trimethyl orthoformate / methanol (85%) and the ketone was converted to a (5:1) mixture of silyl enol ethers (57) and (58) in 97% yield. A variety of Lewis acids ($TiCl_4$, $ZnBr_2$, $ZnCl_2$, $BF_3.OEt_2$, $SnCl_4$, TMS triflate) were tried but only tin(IV) chloride worked and acetonitrile was found to be the best solvent at -20°C. The seven membered ring (59) was formed in 66% yield as a mixture of diastereoisomers. Two epimers of the cyclopentanone (60) and (61) were also formed in 15% yield (scheme 23).

Treatment of the diastereoisomers (59) with refluxing acetic

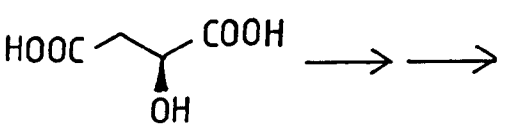


(64)

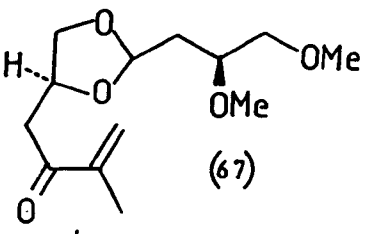


(65)

SCHEME 24

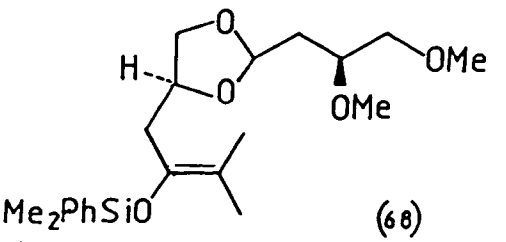


(66)



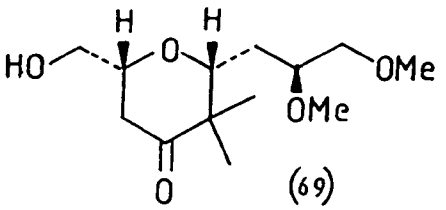
(67)

$PhMe_2SiH/(Ph_3P)RhCl$



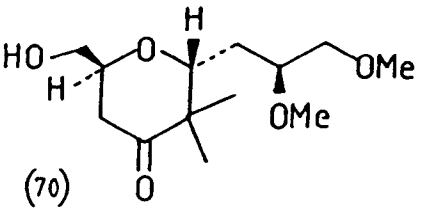
(68)

$TiCl_4$



(69)

+



(70)

(i) BENZOYLATION
(ii) $NaBH_4$
(iii) BENZOYLATION

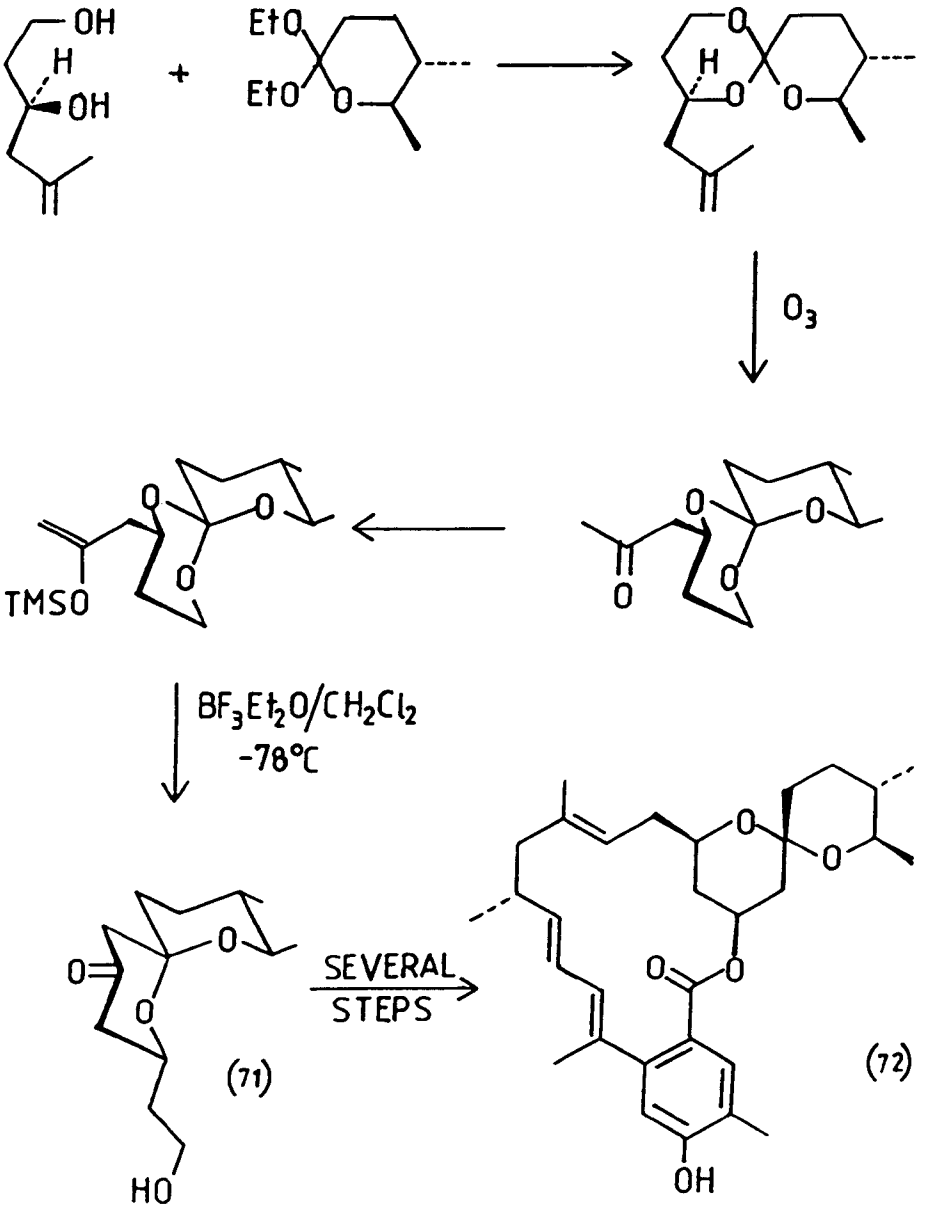
(65)

SCHEME 25

acid gave the desired enone (62, 48%) and unchanged starting material (45.5%). The enone was readily converted, using lithium dimethyl cuprate, to the required compound (63) in 84% yield.

Pederin (64) is a powerful vesicant (blister causing agent) found in the defence secretion of the East African beetle Paederus fuscipes. A key intermediate in the synthisis of this compound as suggested by Kocienski et al[29] is pederol dibenzoate (65). (scheme 24) . This highly oxygenated fragment was made using a directed aldol reaction to construct the corresponding tetrahydropyran-4-one. The chiral starting material in this synthesis was (S)-malic acid (66) which was converted to the key cyclic acetal (67) in a number of steps. The enone in this molecule underwent smooth, rhodium catalysed hydrosilylation to produce silyl enol ether (68) in 90% yield. This compound subsequently on reaction with titanium tetrachloride at -78°C gave a complex mixture of products from which the tetrahydropyran-4-ones (69, 38%) and (70, 11%) could be isolated (scheme 25).

The minor isomer turned out to have the required stereochemistry and was easily converted to the required compound (65) using standard chemistry. This reaction is interesting because the system has been set up so that the intramolecular aldol reaction leaves an oxygen in the ring.


OH
H
OH
+
EtO
EtO
O
H
O
O
O
O_3
O
O
O
TMSO
BF_3Et_2O/CH_2Cl_2
-78°C
O
O
O
HO
(71)
SEVERAL
STEPS
O
O
O
O
OH
(72)

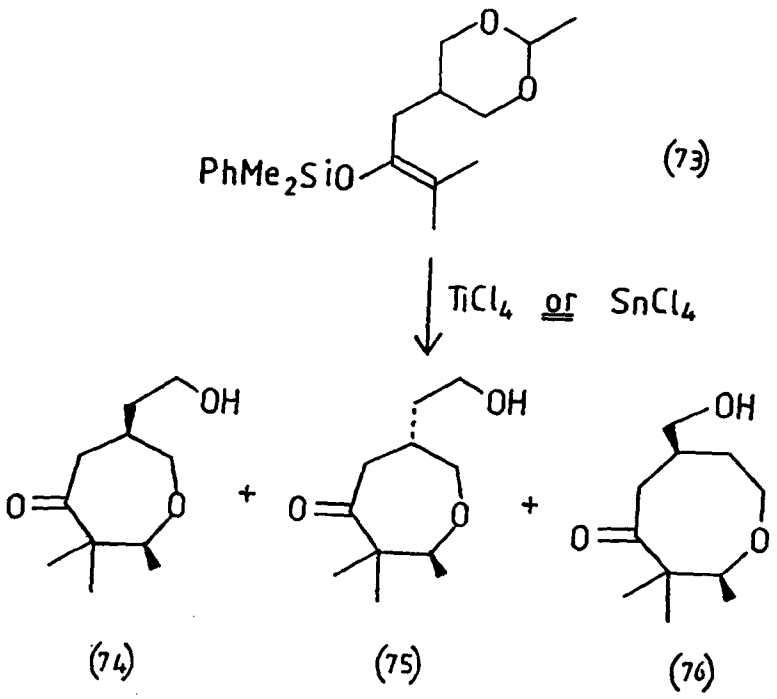
SCHEME 26

It is important to note that only the six membered ring was isolated and none of the thermodynamically less favoured seven which might also be envisaged as a possible reaction product.

Kocienski has also used Mukaiyama type chemistry in a very different reaction involving a bicyclic orthoether in a synthesis of the antiparasitic macrocycle (+)-milbemycin β_3 (72) . The system was set up as outlined (scheme 26).

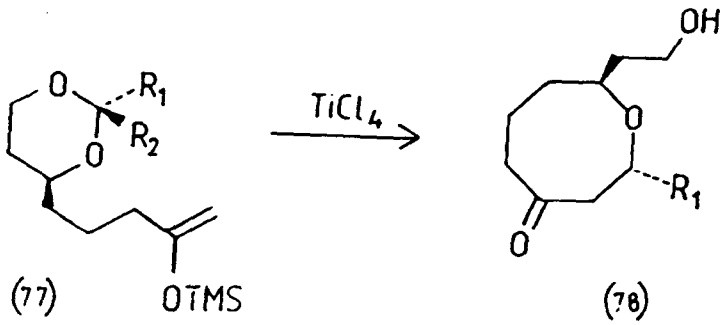
The yield of 36% with boron trifluoride as catalyst was probably quite disappointing but since the product (71) was formed as a single diastereoisomer this was a major advantage. Other products were polymeric and easily removed by chromatography.

Kocienski has studied a number of related ring closures where cyclic acetals have been used such that medium sized rings containing oxygen have been formed[31]. In addition to the reaction previously described where pederol dibenzoate (65) was prepared, a number of other sequences have been tried where seven and eight membered rings (traditionally very difficult to form) may be readily prepared without the need for high dilution techniques. (eg scheme 27). The reaction shows a clear preference for closing the smallest possible ring. In both cases the eight membered ring product (76) was formed as a single diastereoisomer. To try to examine the reaction further the system (77) was set up (scheme 28). Only



7 : 6 : 4
(74) : (75) : (76)

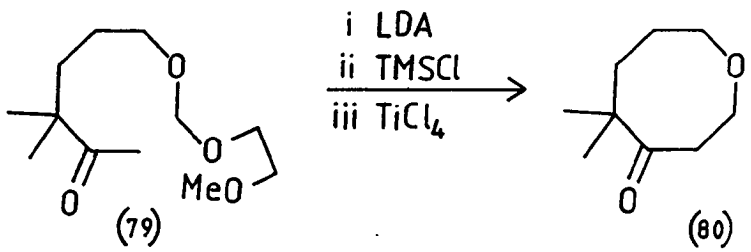
SCHEME 27



SCHEME 28

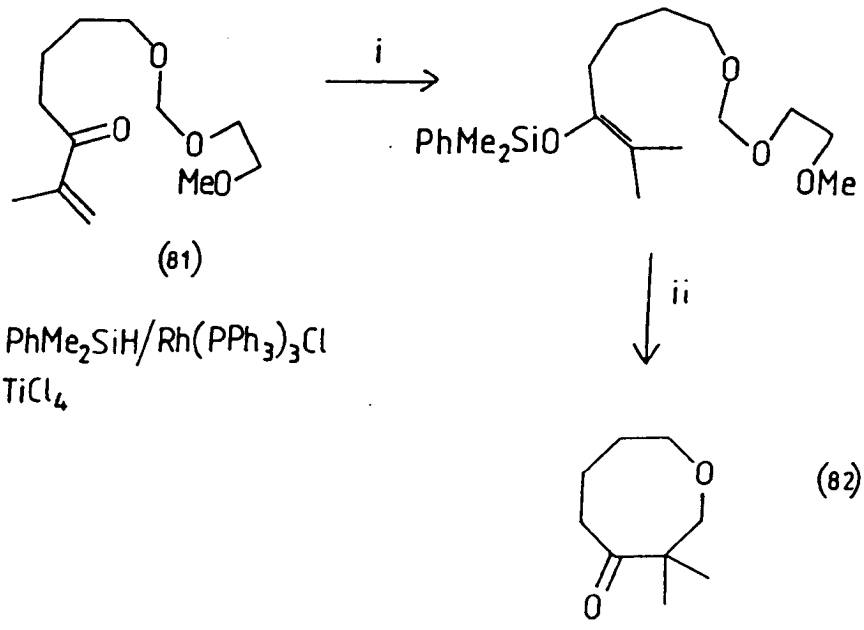
one diastereoisomer (78) was isolated and none of the possible 10-membered ring was formed.

As another model to eliminate the "regiochemical ambiguity" in the acetal cleavages, methoxyethoxymethyl acetals were used ie (79) and (81). These on reaction with titanium tetrachloride gave products (80) and (82), (schemes 29 and 30).



(79) (80)

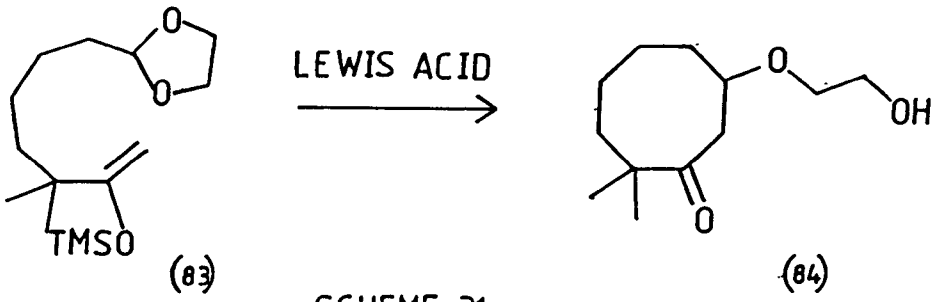
SCHEME 29



(81) (82)

i. $PhMe_2SiH/Rh(PPh_3)_3Cl$
ii. $TiCl_4$

SCHEME 30



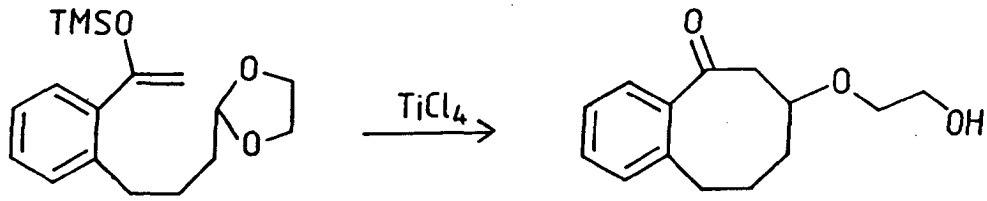
(83) (84)

SCHEME 31

Lewis Acid	Temp/°C	Time	Yield (84)/%
$TiCl_4$	-78	15 min	43
$TlCl_2(OPr^i)_2$	-78 -> 25	20 hours	45
BF_3 - OEt_2	-78 -> 25	20 hours	48
$ZnBr_2$	25	7 days	41
$SnCl_4$	-40	20 hours	35
TMSOTf	-78 -> 25	20 hours	16

It was suggested that the titanium had a template effect such that oxygen atoms from the enol ether and the acetal are co-ordinated to the metal in an intermediate and the steric constraints imposed on the intermediate determine the stereochemistry of the product.

In a concurrent study[32] investigating the synthesis of β -alkoxy cyclo-octanones a variety of carbocyclic compounds were prepared. In this study a number of Lewis acids were tested on a variety of systems (eg (83) and (85)) and typical results are shown (scheme 31, table 1 and scheme 32).

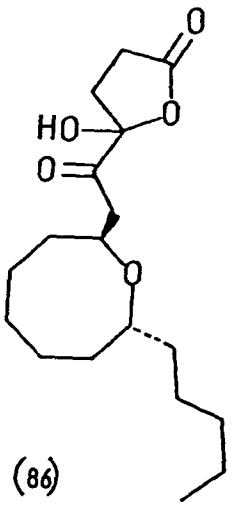


(85)

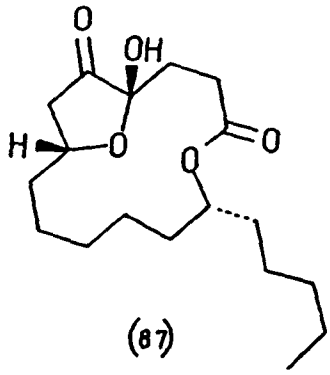
SCHEME 32

These results show quite clearly that it is possible to synthesise medium size rings in acceptable yields without high dilution techniques having to be used.

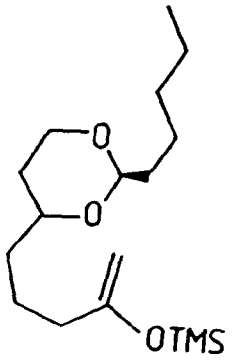
Early 1987 showed a noticeable increase in publications where the intramolecular directed acetal aldol reaction has been exploited. Kocienski[33] has again figured in these and has



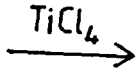
(86)

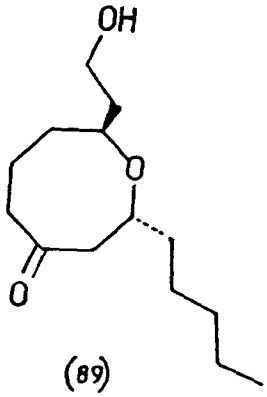


(87)



(88)





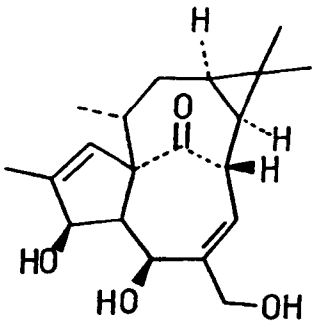
(89)

SCHEME 33

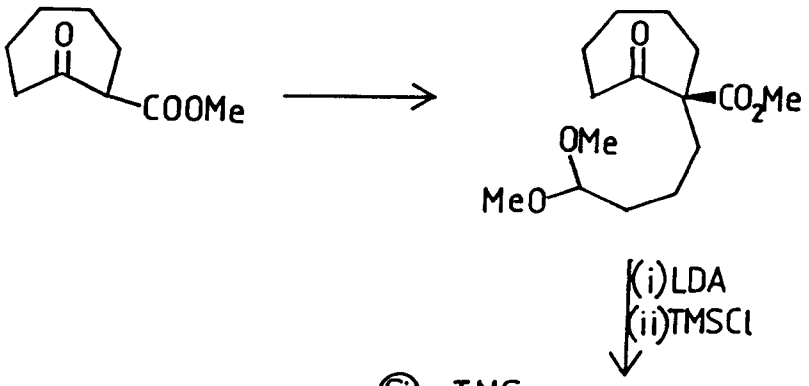
used chemistry that he had developed earlier in his synthesis of pseudo-gloeosporone (86). Gloeosporone (a seed germination inhibitor from the fungal spores of Colletotrichum gloeosporioides) was originally assigned structure (86) however synthetic studies[34] have showed that this is incorrect. Single crystal X-ray studies have showed that the correct structure is in fact (87). The key reaction in this synthesis was the aldol reaction (scheme 33) to form the oxocan-4-one, ((88)--->(89)). Again, the low yield was compensated for by the formation of a single diastereoisomer which was easily separated chromatographically from the reaction mixture.

The ingenane ring system represented here by ingenol (90) continues to attract synthetic interest and again the Mukaiyama reaction has been used, this time in the construction of the ABC ring as reported by Mehta[35]. The strategy that was used is outlined (scheme 34). The aldol yield was good (66%) and the mixture of diastereoisomers (91) formed was of no consequence since the methoxy group was subsequently converted to the alcohol and oxidised to the ketone (92).

Pattenden[36] has used the reaction in studies towards the synthesis of forskolin (94) (a highly pharmacologically active diterpene isolated from the roots of the Indian plant Coleus forskohlii) in tandem with a radical cyclisation (scheme 35).

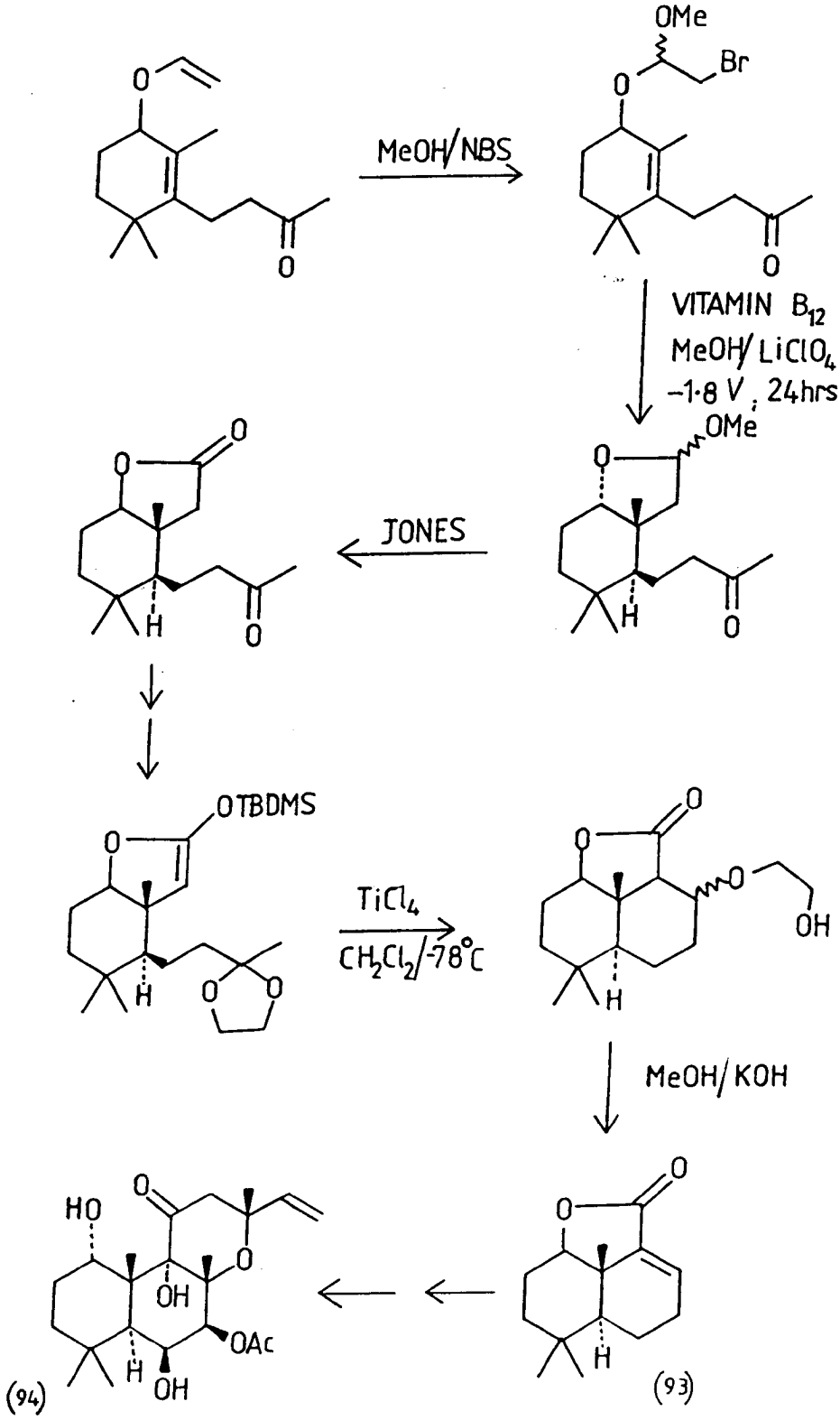


(90)

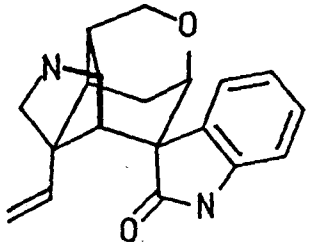


(92)

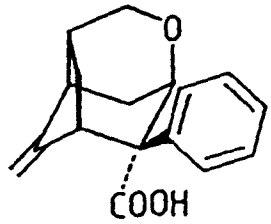
SCHEME 34


OMe
Br
MeOH/NBS
VITAMIN B_{12}
MeOH/ $LiClO_4$
−1·8 V ; 24hrs
OMe
JONES
OTBDMS
$TiCl_4$
CH_2Cl_2/-78°C
OH
MeOH/KOH
HO
OH
OAc
OH
(94)
(93)

SCHEME 35



(95)



(96)

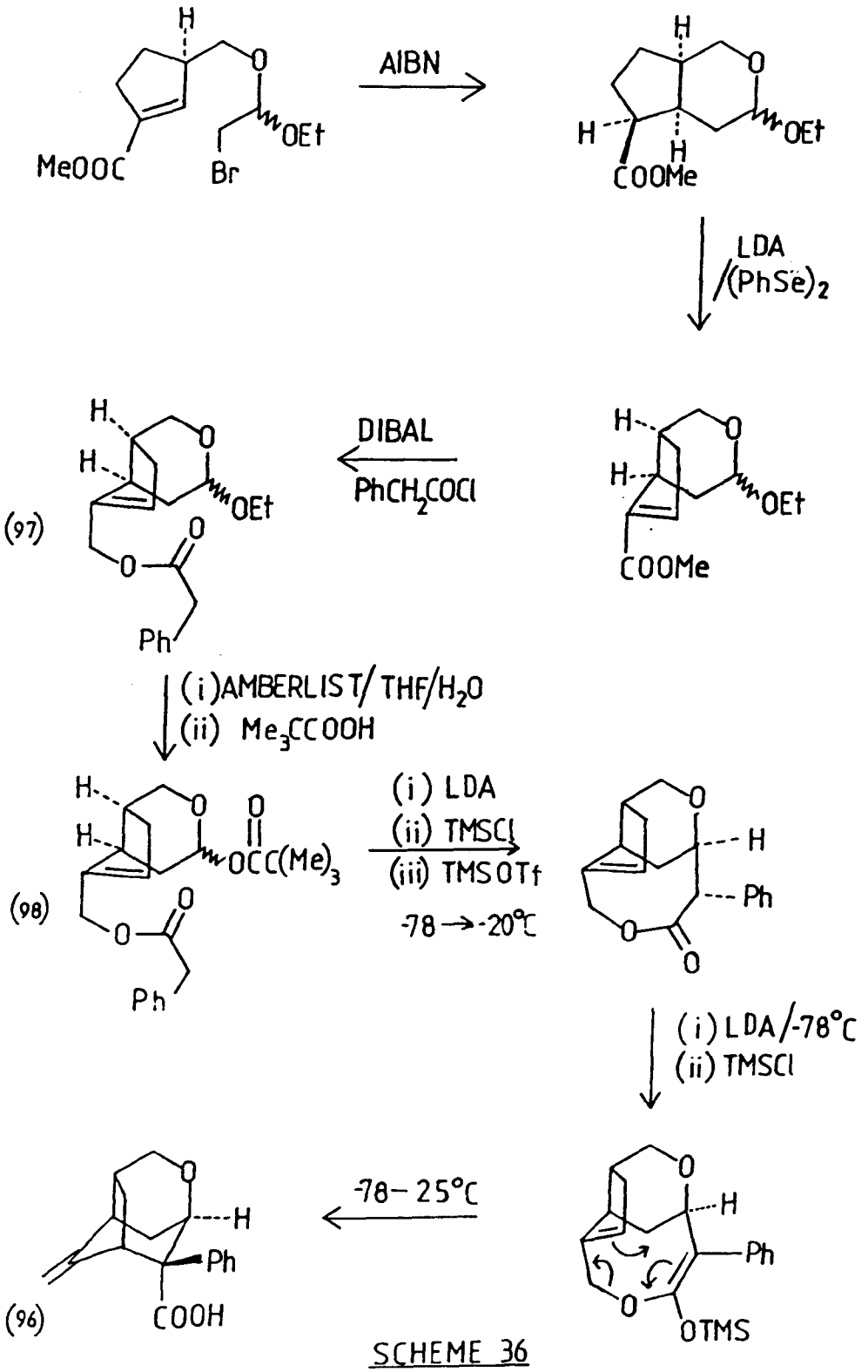
It is now hoped to convert the "advanced precursor" (93) shown here to forskolin (94) itself.

Interestingly, Stork[37] has also combined both radical and Mukaiyama chemistry in a synthetic sequence reported at a similar time in studies towards the alkaloid gelsemine (95). As a model the acid (96) was synthesised using the following strategy (scheme 36) culminating with a Claisen enolate rearrangement.

It is interesting to note before this aldol reaction that the ethoxy group of the acetal (97) was replaced by a more activated leaving group. In this new molecule (98) containing the trimethylacetate group, the Lewis acid has the option of co-ordinating to the electron rich carbonyl group.

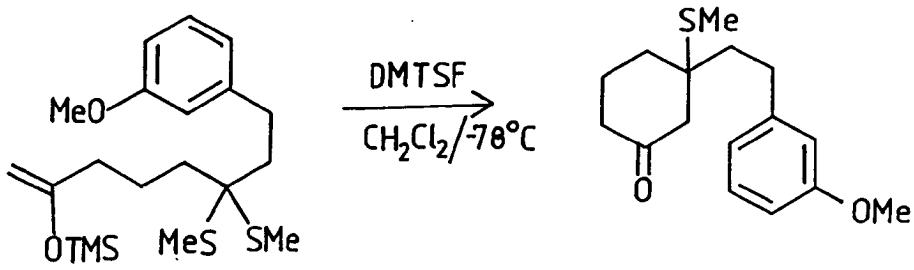
Trost in 1982 extended the horizons of the intramolecular aldol reaction when he used a sulphur ketal (99) in a synthesis of the phenanthrene nucleus[38]. The Lewis acid in this case was dimethyl(methylthio)sulphonium tetrafluoroborate (92) used at -78°C and gives very good yields of the ring closed product (91). The key step is shown (scheme 37).

Clearly now the Lewis acid catalysed directed aldol reaction between a silyl enol ether (or a silyl ketene acetal) and an acetal is a firmly established and reliable method for

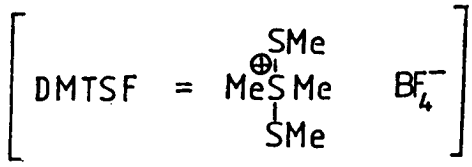

AIBN
LDA
/(PhSe)2
DIBAL
PhCH2COCl
(97)
(i)AMBERLIST/ THF/H2O
(ii) Me3CCOOH
(98)
(i) LDA
(ii) TMSCl
(iii) TMSOTf
-78 → -20°C
(i) LDA/-78°C
(ii) TMSCl
-78 – 25°C
(96)

SCHEME 36

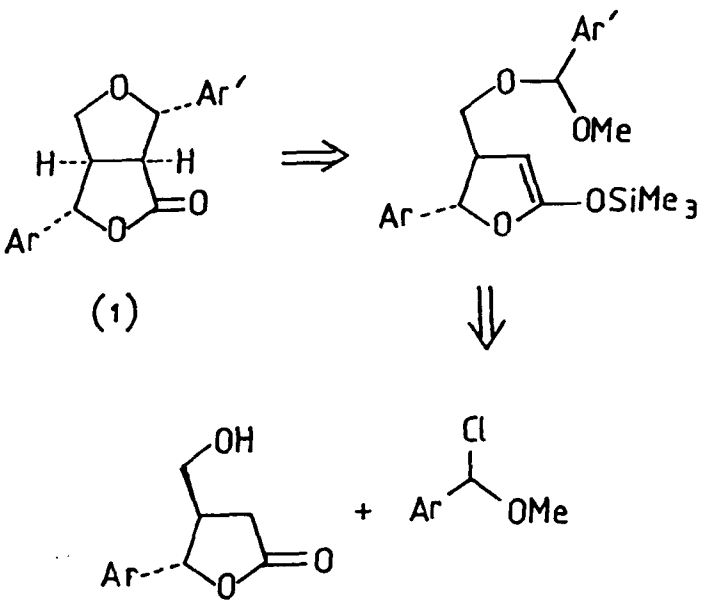
carbon-carbon bond formation and we should expect to see it continuing to be used in organic chemistry in many future syntheses.



(99)



SCHEME 37

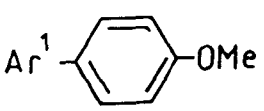


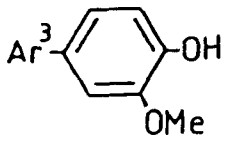
SCHEME 1

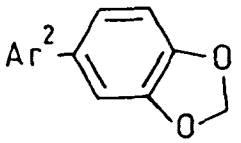
(a) Ar = Ph $Ar' = Ar^1$

(b) $Ar = Ar' = Ar^2$

(c) $Ar = Ar^2$ $Ar' = Ar^3$







The Synthesis of (±)-Aptosimon, (±)-Asarinin, (±)-Styraxin and (±)-Pluviatilol.

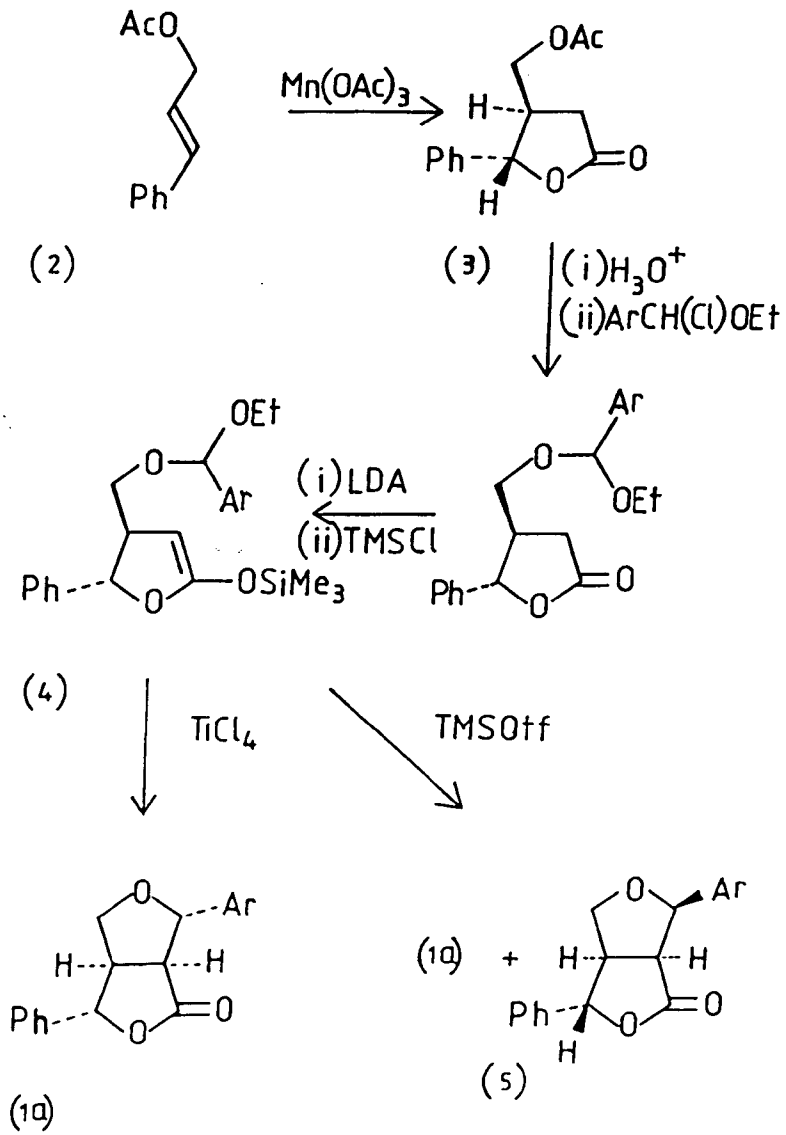
Our original synthetic strategy for these lignans (see page 20) has been summarised in scheme 1. Some earlier work has been performed on these ideas which has been reported by Whiting and Till[39].

The chemistry used to create the lactone (3) involved, manganese (III) induced radical addition of acetic acid to cinnamyl acetate (2). This and the chemistry to form the ring closed bicyclic lactone is shown in scheme 2.

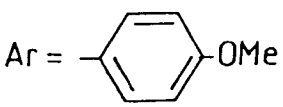
The lactone (3) formation took place with the isolation of only the trans-isomer as expected. When titanium tetrachloride was used as the aldol catalyst on the silyl enol ether/acetal system (4) only one isomer (1a) was formed which was shown to be the 2-exo-6-exo isomer. When trimethylsilyl trifluoromethanesulphonate was used as the Lewis acid catalyst two isomers were identified, (1a) and also the 2-endo-6-exo-isomer (5).

These results were very promising and with a view to extending this work towards natural products it was decided to repeat some of this earlier chemistry.

Manganese (III) acetate dihydrate[40] is readily available in

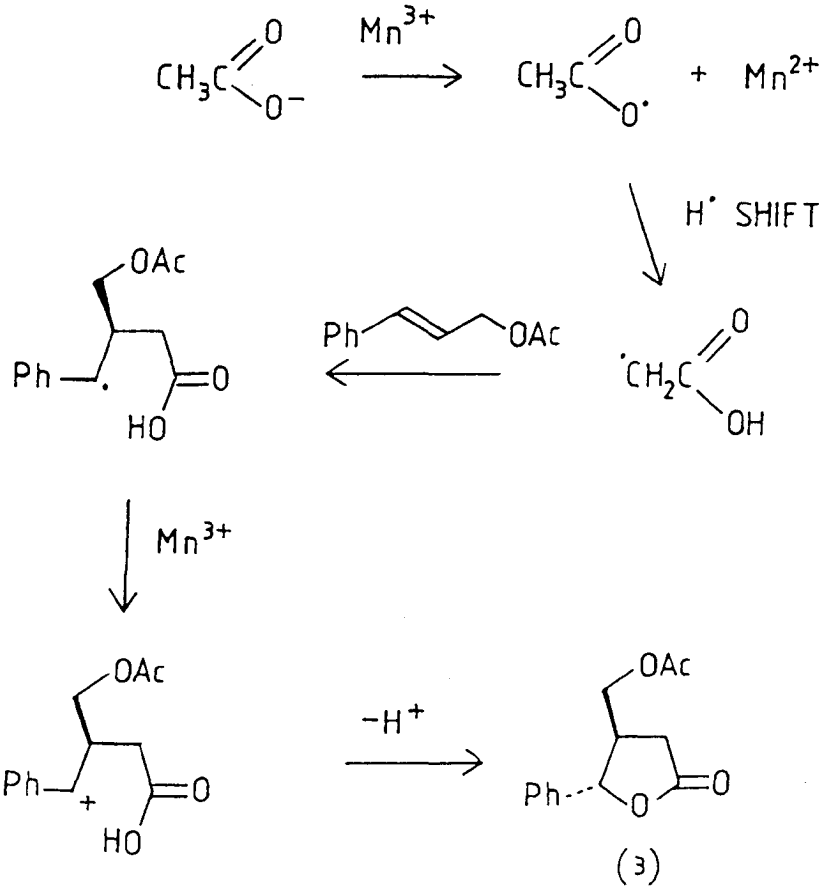

AcO
Ph
(2)
Mn(OAc)3
OAc
H
Ph
O
O
H
(3)
(i)H3O+
(ii)ArCH(Cl)OEt
OEt
O
Ar
Ph
O
OSiMe3
(i)LDA
(ii)TMSCl
Ar
O
OEt
Ph
O
O
(4)
TiCl4
TMSOtf
O
Ar
H
H
Ph
O
O
(1a)
(1a) + H
O
Ar
H
Ph
O
O
H
(5)

SCHEME 2

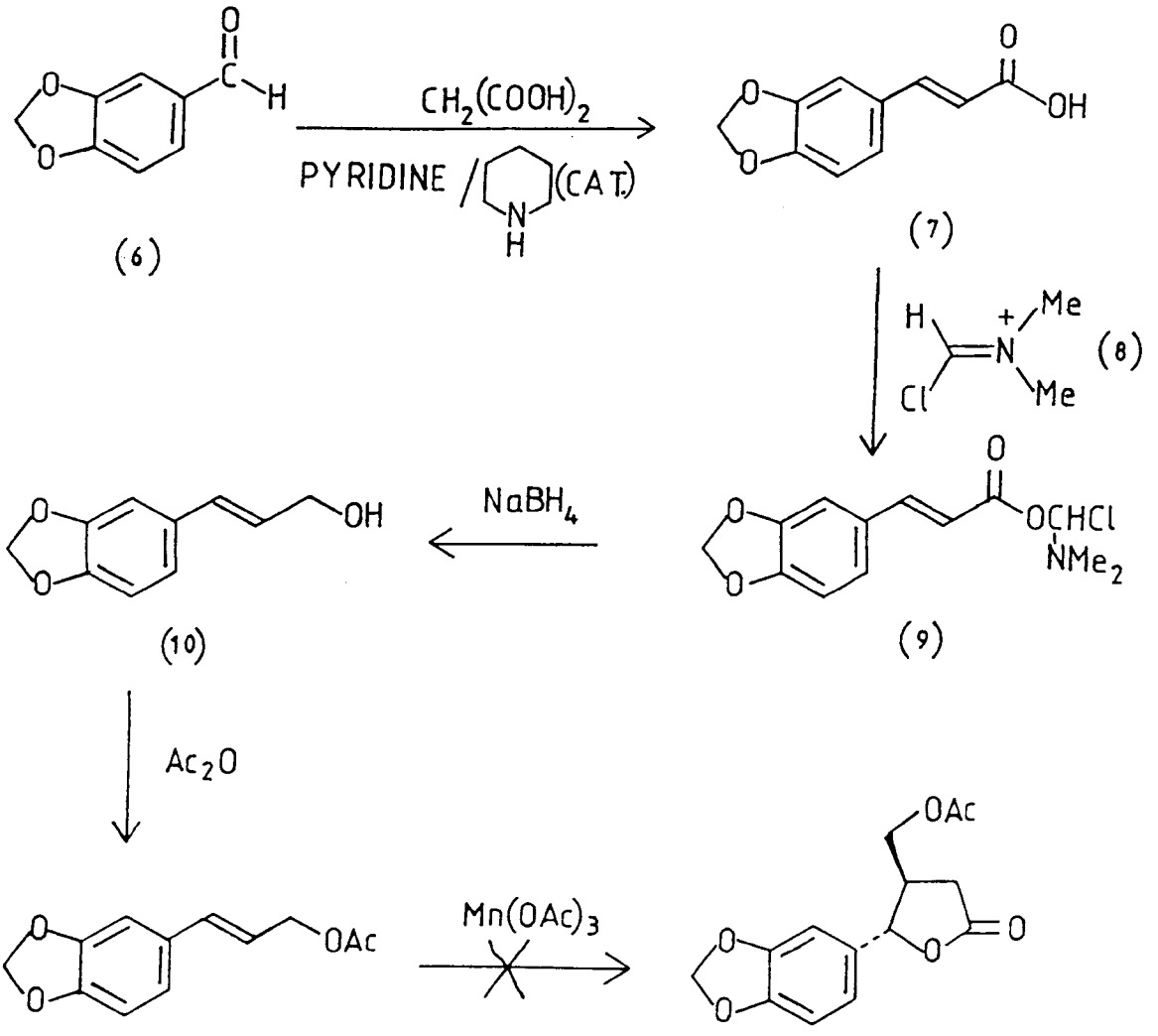

Ar =
OMe

high yield from the reaction between manganese (II) acetate tetrahydrate and potassium permanganate in refluxing acetic acid and can be prepared in large quantities (50 -> 500 g).

Cinnamyl acetate (2) was prepared from the alcohol using standard conditions[41] (acetic anhydride/pyridine) and this in turn reacted with manganese (III) acetate according to Heibas' conditions in refluxing glacial acetic acid, to give the expected trans lactone (3) in 42% chromatographically pure yield. The mechanism is believed to be a radical one and a possibe route is shown (scheme 3).



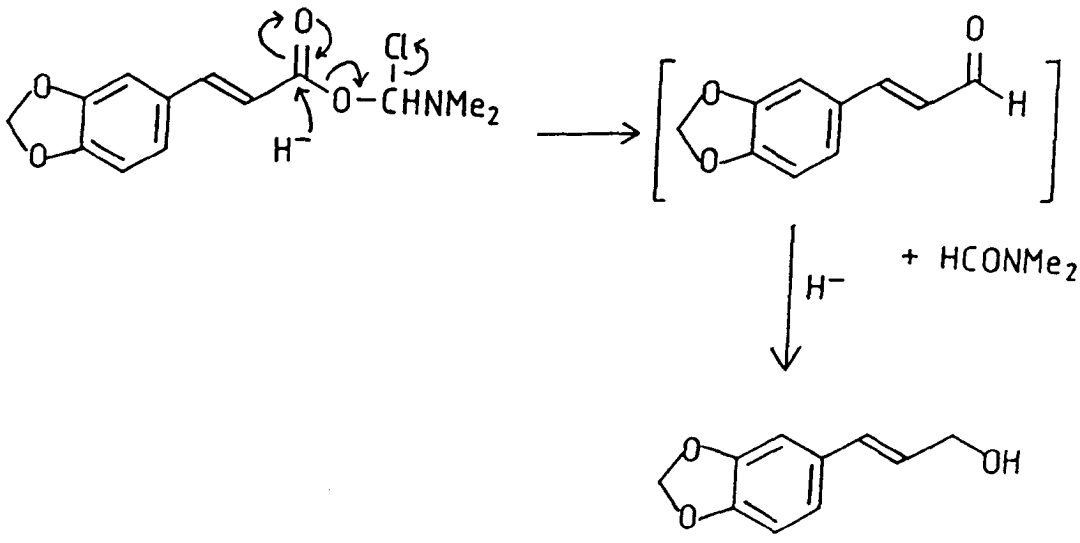
SCHEME 3



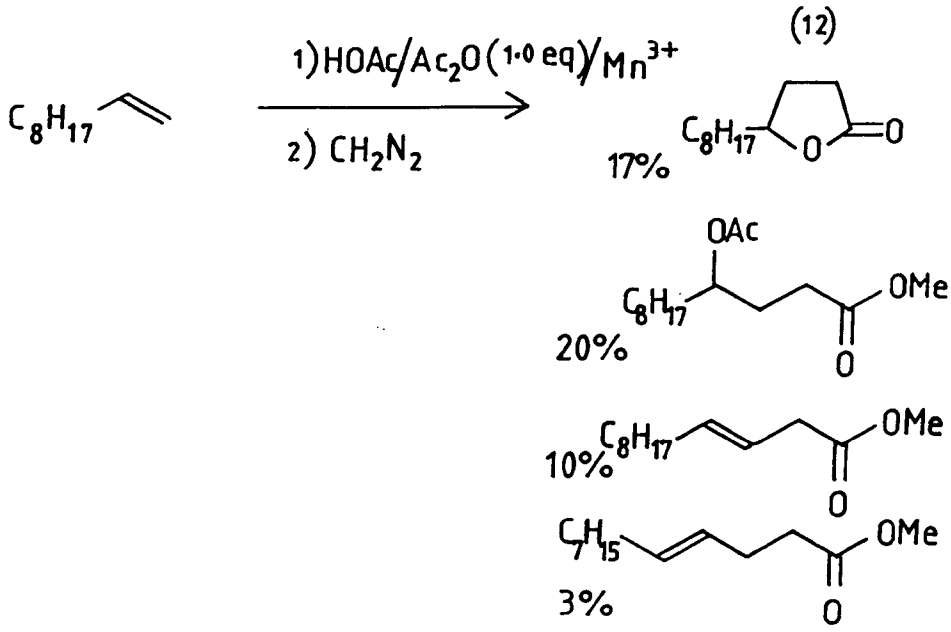
SCHEME 4

To extend this reaction to produce lactones which might be of value in synthesising naturally occurring lignans, aromatic rings with oxygenated functions were needed in place of the phenyl group. For the synthesis of aptosimon (1b) and styraxin (1c) a 3,4-methylenedioxyphenyl group was required and so the corresponding cinnamyl alcohol was synthesised (scheme 4).

The Doebner modification of the Knoevenagel reaction with piperonal (6) proceeded in high yield and gave the acid (7) as a very pure product which could be used after drying without further purification[42]. Reaction of dimethyl formamide with oxalyl chloride in chloroform under anhydrous conditions gave (chloromethylene)dimethylammonium chloride (8) as an air sensitive, yellow powder in essentially quantitative yield.



SCHEME 5



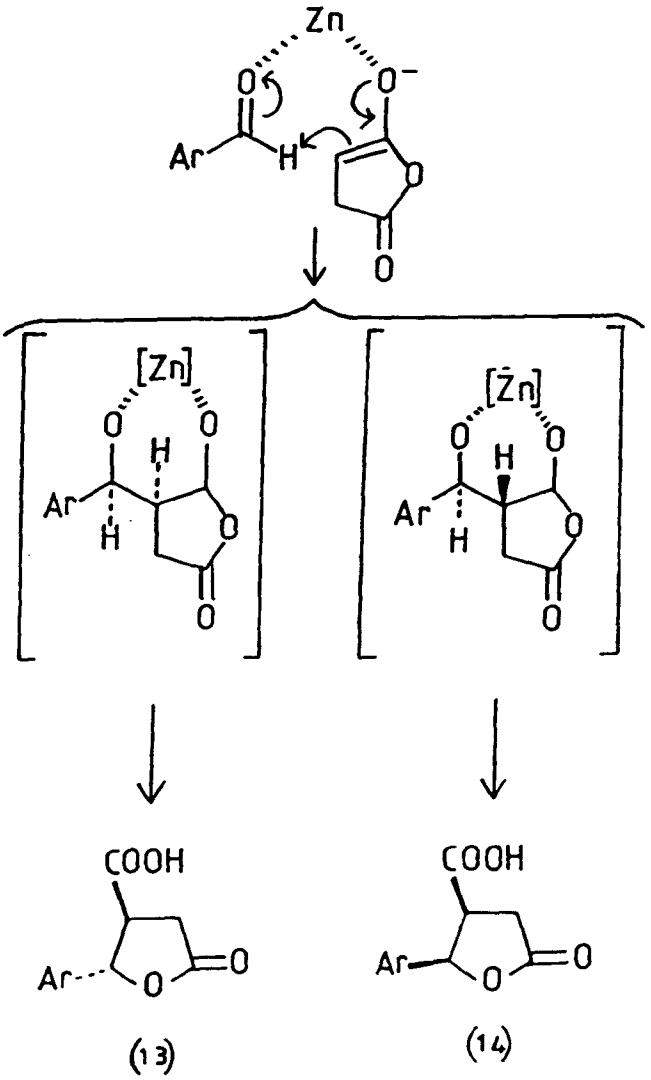
SCHEME 6

This was dissolved in a mixed tetrahydrofuran/acetonitrile solvent at low temperature (-10°C) and the substituted cinnamic acid was added which dissolved as ester (9) formation took place. Further cooling (-30°C) and the addition of sodium borohydride in dimethylformamide solution, gave the corresponding alcohol (10) in good (71%) yield after purification[43,44]. In this reaction it is possible to conceive dimethylformamide as a stable leaving group (scheme 5). Again the acetate (11) of this alcohol was formed using standard conditions (acetic anhydride/pyridine) in high yield.

Treatment of this olefinic acetate (11) as before with manganese (III) acetate did not give the expected lactone but on reaching reflux temperature, a deep brown/black unidentifiable product was formed.

Fristad[45] has reported "optimum conditions" for lactone formation in this type of reaction as being olefin 1.0 eq, manganese (III) acetate 2.5 eq and potassium acetate 5.0 eq and also states that the addition of acetic anhydride as in Heibas' conditions frequently results in dramatically reduced yields. The anhydride frequently interferes with the reaction and Fristadt showed that products due to its presence can be formed (scheme 6).

When no acetic anhydride is present only the lactone (12) was isolated. When the reaction was repeated on cinnamyl acetate



(13) (14)

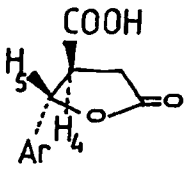
SCHEME 7

with no acetic anhydride present, virtually identical yields of the lactone (6) were isolated (40%). The same conditions for 3,4-methylenedioxycinnamyl acetate (11) still however gave no identifiable products at reflux temperature. Lower temperatures (60°C) gave no reaction detectable by TLC and gently warming the solution further to reflux over a number of hours gave only a transition from starting mater ial to polymeric base line rubbish by TLC with no intermediate compounds being detected.

An alternative synthetic route to lactone alchols was clearly needed. Lawlor[46] has published a synthesis of 4-aryl substituted paraconic acids using a variation of the Stobbe condensation. This involves reaction of an aromatic aldehyde with succinic anhydride in the presence of zinc chloride /triethylamine complex to produce a cis/trans mixture of acids in moderate to high yield (36 - 98%). The mechanism proposed by Lawlor involves the trapping of the enolate formed from succinic anhydride by the aldehydic carbonyl with the zinc ion acting as a template for two oxygen atoms to co-ordinate to (scheme 7). Presumably, the cis/trans ratio of the final products is defined by the ratio of the two intermediate complexes formed.

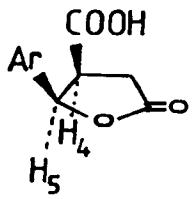
Using piperonal, (3,4-methylenedioxybenzaldehyde) as the aromatic aldehyde, the acids (13) and (14) were obtained in 50 - 75% overall yields, typically in a trans/cis ratio of 3:2.

(13)



NO ENHANCEMENTS

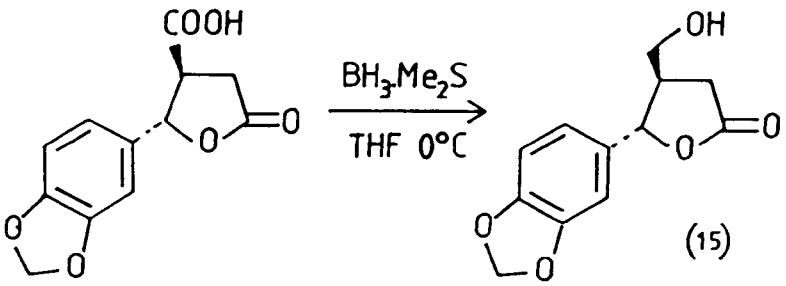
(14)



$H_4 \rightarrow H_5$ 10·7%

$H_5 \rightarrow H_4$ 11·3%

nOe EFFECTS

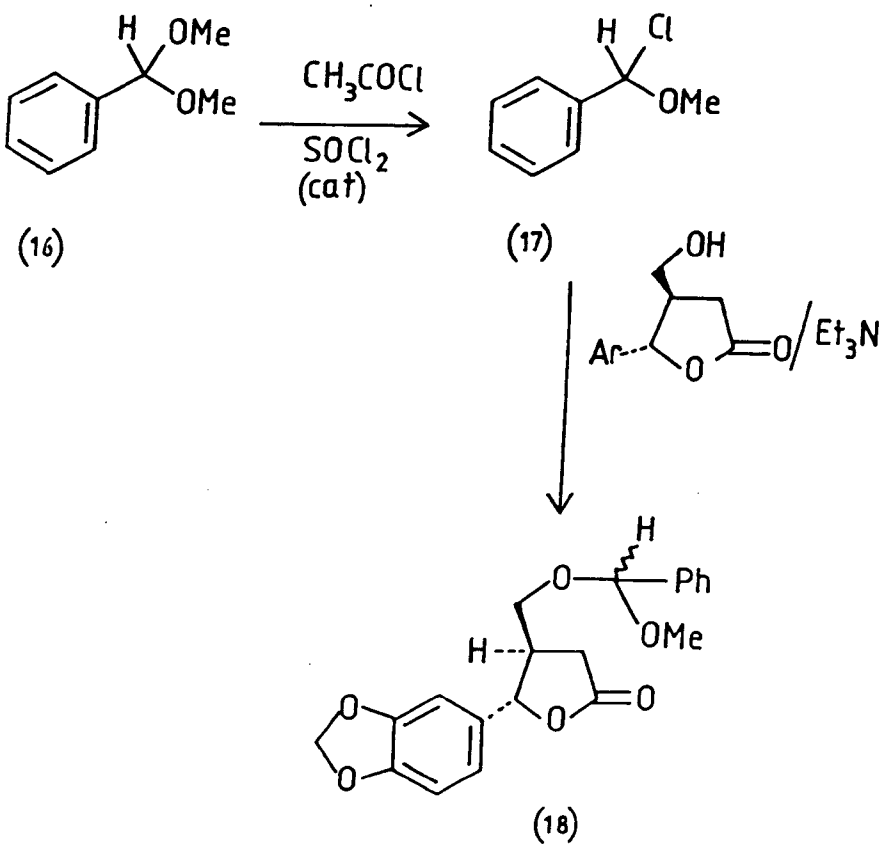


(15)

SCHEME 8

The isomers could be separated by trituration with ether or by fractional recrystallisation from ethyl acetate or ethyl acetate/hexane mixtures. Pure samples of both isomers were obtained and characterised. It was found that freshly distilled solvents and triethylamine were essential to producing easily purified products. The zinc chloride used in the reaction was dried first by fusing for a short period in a crucible with a Bunsen or, more easily and with better results, by crushing and stirring with freshly distilled thionyl chloride. Excess thionyl chloride was readily removed in vacuo when drying was complete.

The stereochemistry of the acids was demonstrated by the use of the nuclear Overhauser enhancement technique in the proton NMR spectrum. Difference spectra showed no mutual enhancements for signals for H_4 and H_5 in the trans-isomer (13) but in the cis-isomer (14) enhancements of 10.7% and 11.3% were observed. The ^1H NMR spectra also correlated well with those reported by Crombie and Reynolds[47] in a different study. Reduction of the trans isomer of the acid (13) to the alcohol (15) was effected using borane-methyl sulphide[48] complex in tetrahydrofuran solvent at 0°C, 24 hours being necessary for complete reduction (scheme 8). The reaction was very clean, no reduction of the lactone was ever observed and high yields (86%) of very pure products could be obtained after standard work-up.

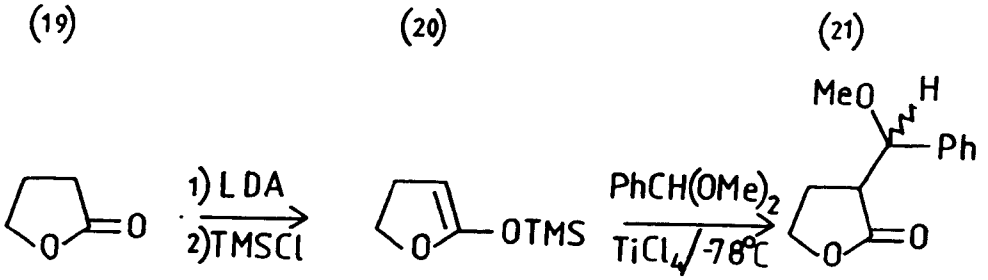

H
OMe
OMe
CH3COCl
SOCl2
(cat)
H
Cl
OMe
(16)
(17)
OH
Ar
O
O
Et3N
H
O
Ph
OMe
H
O
O
O
O
O
(18)

SCHEME 9

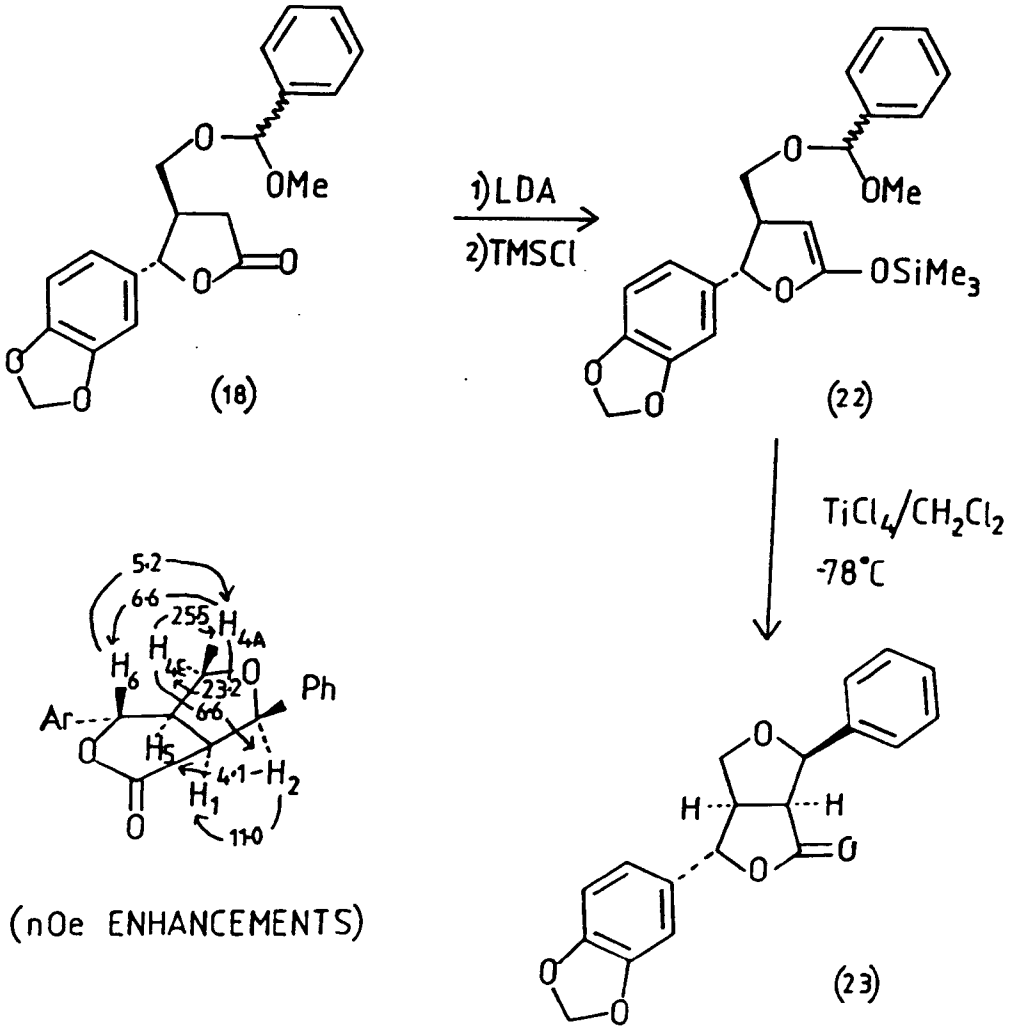
Attention was then turned towards the α-chloro benzyl methyl ether (17) which has been synthesised from the reaction between benzaldehyde dimethyl acetal (16) and acetyl chloride using a trace of thionyl chloride as catalyst[49]. Initial attempts at this transformation proved unreliable. For good yields of the chloroether, strictly anhydrous conditions are essential and the acetyl chloride must be freshly distilled immediately before required. When these precautions were taken, quantitative yields of the desired product (17) could be reliably obtained (scheme 9).

Coupling of the lactone alcohol (15) and the α-chloroether (17) took place very readily in dichloromethane solvent in the presence of triethylamine at 0°C. Excellent yields (92%) were obtained of the mixed acetal (18), which could be readily purified by column chromatography to give a stable, white solid. ^{1}H NMR showed that the product was a mixture of ~~diastereoisomers~~ epimers at the acetal centre.

Before attempting to ring close the valuable acetal, a model study was undertaken. Butyrolactone (19) was treated with lithium diisopropylamide at -78°C in tetrahydrofuran solvent and the enolate formed was quenched with trimethylsilyl chloride. Isolation of the formed silyl ketene acetal (20) and reaction with benzaldehyde dimethyl acetal using titanium tetrachloride as catalyst gave the expected condensation product (21) in 43% overall yield (two steps), as a 1:1



SCHEME 10

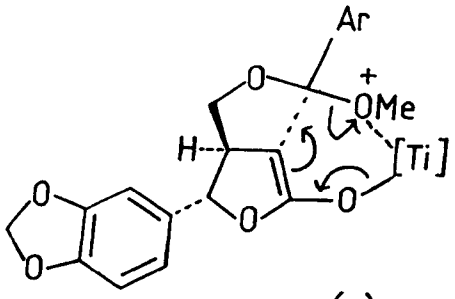


SCHEME 11

mixture of diastereoisomers (scheme 10).

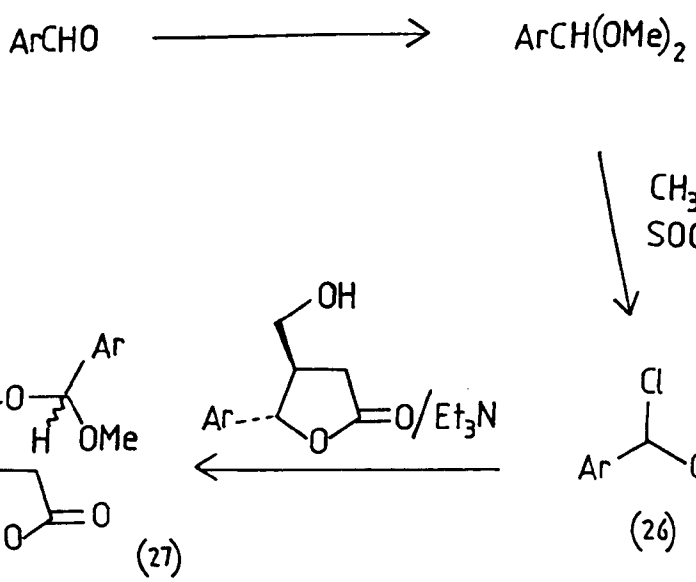
The mixed acetal (18) was then subjected to the same reactions. The silyl ketene acetal (22) was formed from the reaction between the lactone acetal and lithium diisopropylamide followed by trimethylsilyl chloride as usual. These species can be very water sensitive and because of this, it was decided that a non aqueous work up was the safest way of isolating the product. This involved evaporation of the solvent in vacuo, followed by digestion of the residue in dry ether and filtration of the insoluble inorganics. Treatment of the product with titanium tetrachloride at -78°C in dichloromethane solution gave a single bicyclic stereoisomer (23) in 27% yield (scheme 11). The nuclear Overhauser enhancement technique was used to determine the stereochemistry and it was possible to unambiguously assign a 2-endo-6-exo-diaryl structure to the compound.

The other products that could be isolated from the reaction were benzaldehyde and the starting lactone alcohol. This result was surprising because Whiting and Till[39] in earlier experiments (scheme 2) had also produced a single diastereoisomer (1a) only. In their case however, a 2-exo-6-exo-diaryl structure had been unambiguously assigned. The differences between the two syntheses are at first sight very minor with respect to the aldol reaction, i.e. different aromatic groups and a change from ethoxy to methoxy leaving



(24)

(25)

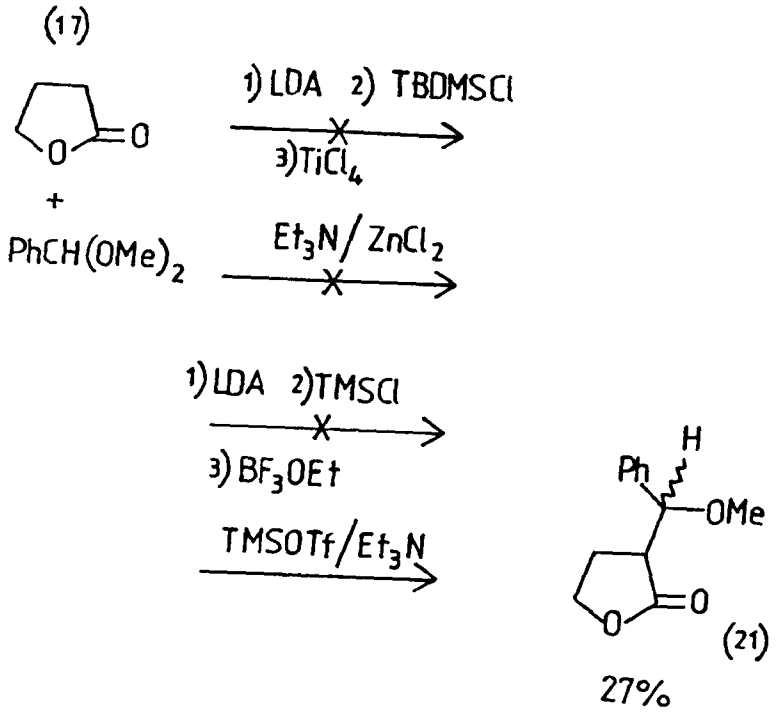


(1b)

SCHEME 12

groups. In both examples only one stereoisomer was produced and it would seem likely that the titanium plays a vital role in the transition state. A six membered ring containing the titanium can be drawn (24) but it is by no means clear why two very different stereochemistries should result from such seemingly similar systems. However, one possible reason for this difference could be due to the electronic effect of the 4-methoxy aryl substituent providing much greater stabilisation to the incipient benzylic carbocation. The (presumably) more stable stereochemistry of (1a) could indeed arise by rapid product equilibrium, as well as by a change in reaction profile bringing transition state closer to products. It is clear (see below page 51) that there is only a small energy difference between exo-endo and exo-exo isomers in these compounds.

The next step taken was to try to extend the synthesis to natural systems, even though this last example had given an unnatural stereochemistry. The only way to test the outcome of the reaction where a natural lignan might be formed was to set up the aldol system and try the reaction. Logically the first lignan to try and synthesise was aptosimon[2] (1b) since no protection of the aromatic phenol groups was required (scheme 12). The relevant α-chloroether (26) was prepared from piperonal. The dimethyl acetal (25) was formed using trimethylorthoformate and one drop of conc. sulphuric acid as catalyst[50]. By using the orthoformate as solvent, complete

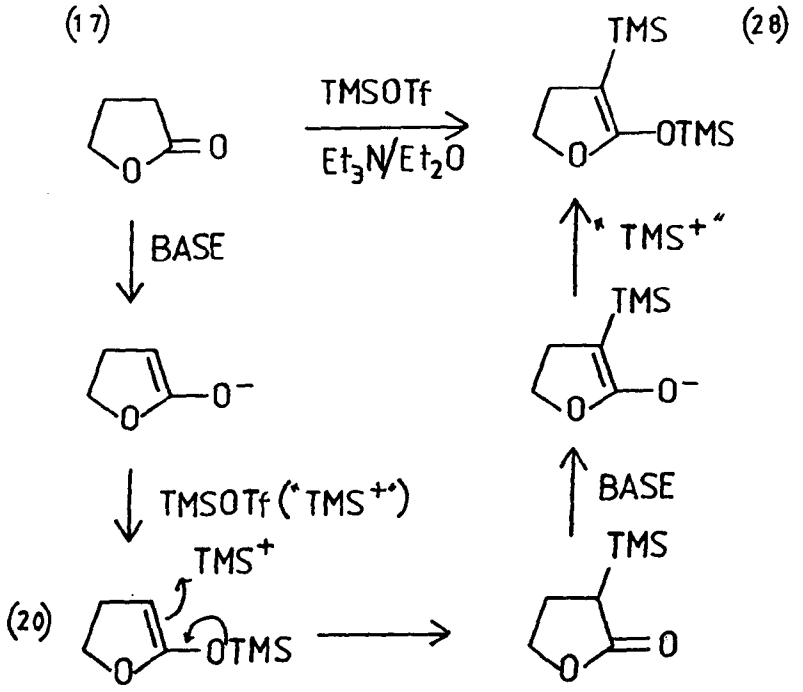

(17)
1) LDA 2) TBDMSCl
3) TiCl4
+
PhCH(OMe)2
Et3N / ZnCl2
1) LDA 2) TMSCl
3) BF3OEt
TMSOTf / Et3N
Ph
H
OMe
O
O
(21)
27%

SCHEME 13

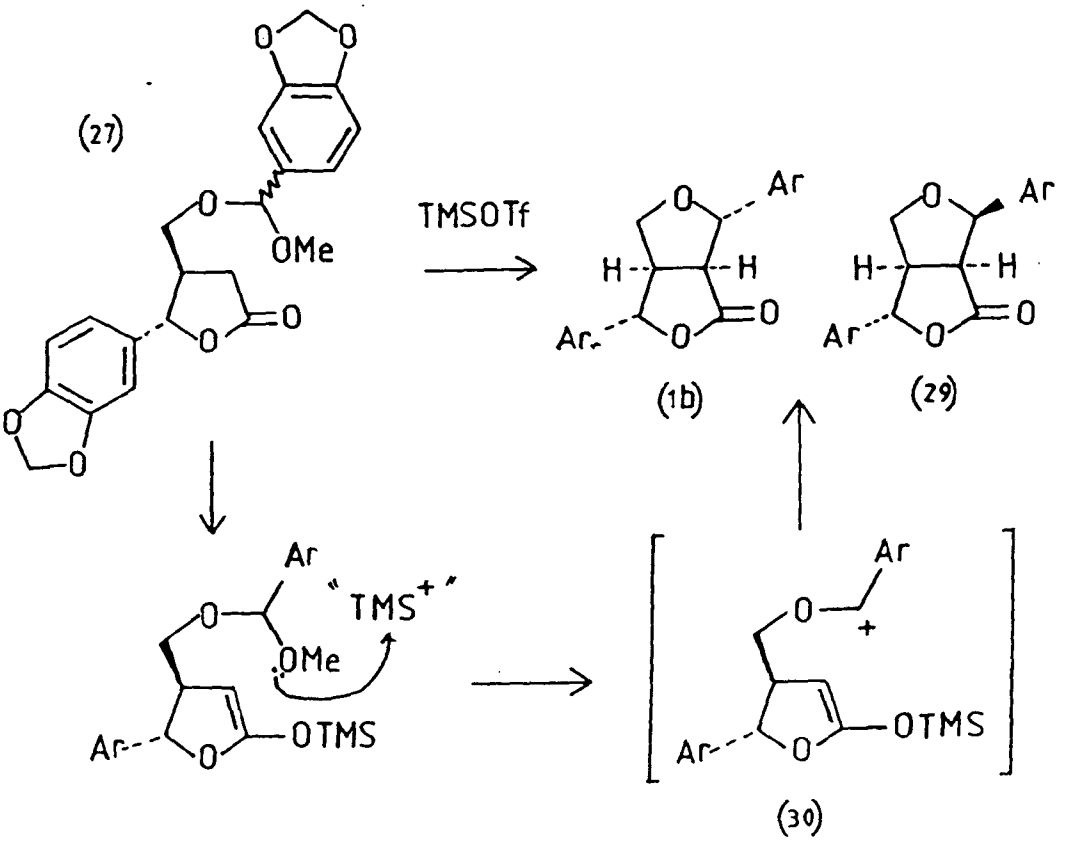
conversion of the aldehyde to the acetal was possible and distillation gave good (89%) yields of very pure product as an oil. This was subsequently transformed into the α-chloro ether (26) as before by dissolving in freshly distilled acetyl chloride with a trace of thionyl chloride catalyst under an inert (N_2) atmosphere. The mixed acetal (27) was prepared by reaction of lactone alcohol (15) with α-chloroether (26) in dichloromethane solvent in the presence of triethylamine to give a very high yield (93%) after chromatography. This mixed acetal proved to be much more acid/moisture sensitive than the corresponding benzaldehyde derivative (18) and more care needed to be taken in its purification. Using a short column of neutral alumina and keeping the eluant (ether/40 - 60 petrol) slightly basic with a trace of triethylamine proved satisfactory.

All attempts at ring closure using the procedure developed before (LDA/trimethylsilyl chloride then titanium tetrachloride) proved unsuccessful. The reasons for this are by no means clear though possibly the increased lability of the acetal may be significant.

An alternative ring closure catalyst appeared to be needed and so model studies were tried again using butyrolactone (17) and benzaldehyde dimethyl acetal. The reactions tried are outlined (scheme 13).



SCHEME 14

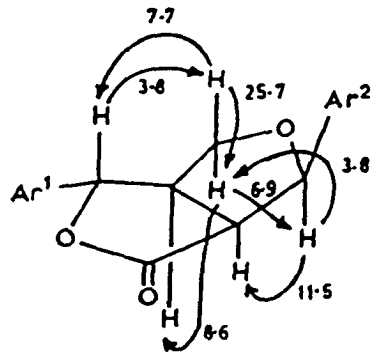


SCHEME 15

The only successful reaction was in the use of trimethylsilyl trifluoromethane sulphonate[11] as both silylating agent and Lewis acid. The reaction between butyrolactone and trimethylsilyl trifluromethanesulphonate[51] has been reported to form the bis-silylated compound (28). The mechanism for the reaction is open to speculation, but one possible route is suggested here. (scheme 14).

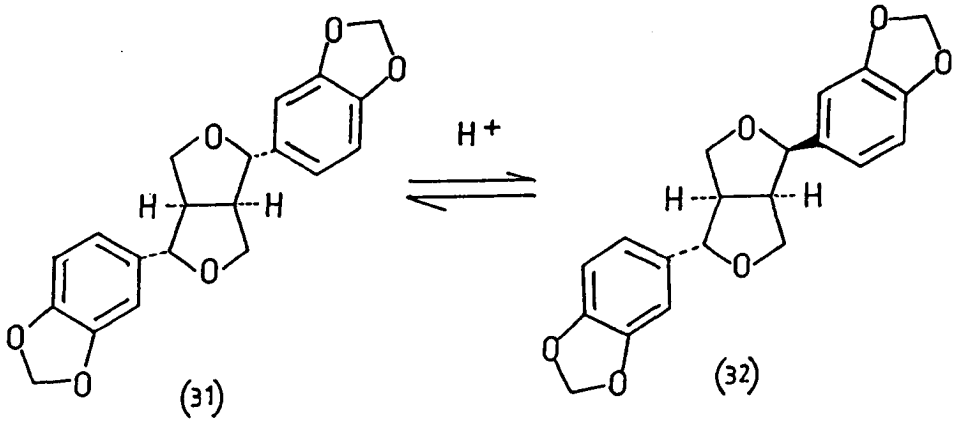
No silicon appears in the product from the model reaction and so possibly the silyl ketene acetal (20) is trapped by a molecule of acetal before another trimethylsilyl group.

The same conditions for the aldol reaction were tried on the mixed acetal (27) (tetrahydrofuran was added to aid in solvation) and two ring closed compounds aptosimon (1b, 19%) and 2-epi-aptosimon (29, 28%) were isolated (scheme 15).



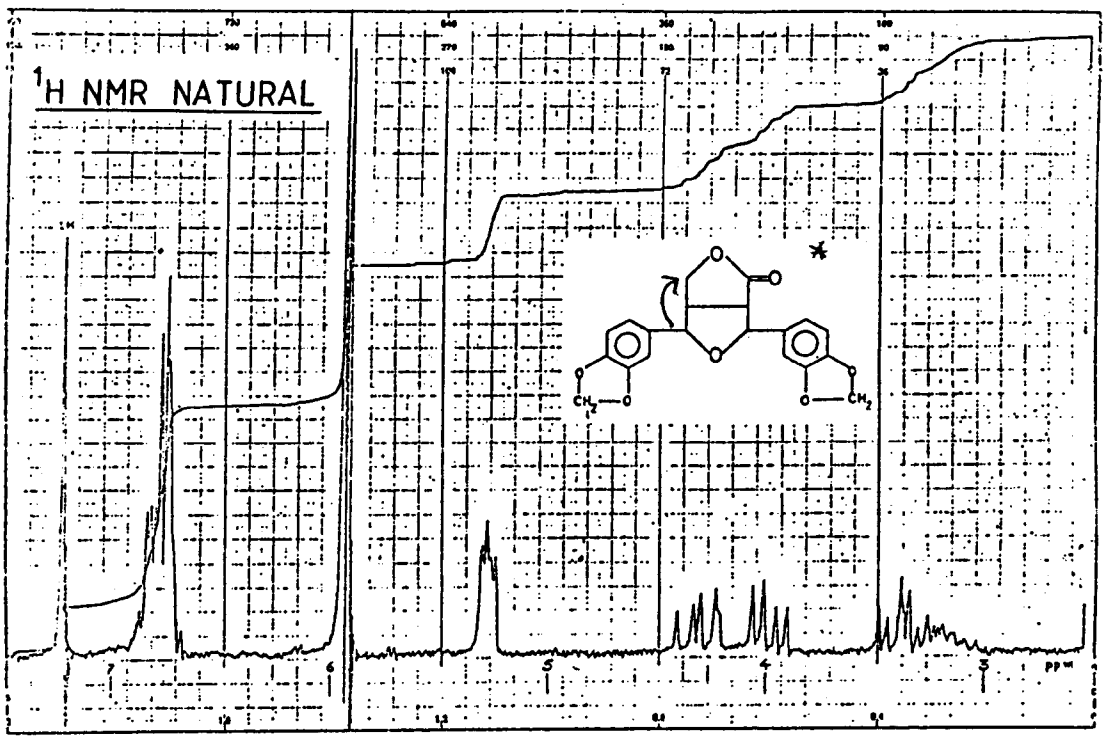
nOe data for epiaptosimon

Again it is interesting to note that the 2-endo-6-exo isomer is formed preferentially to the 2-exo-6-exo isomer. This could be for thermodynamic or kinetic reasons. One possible explanation of this could be the formation of a planar, carbocationic species (30) in the transition state of the reaction which then undergoes cyclisation to produce two different stereoisomers. It is very likely that the two isomers are of very similar free energies. These two isomers can be compared with sesamin (31) and asarinin (32) which are also epimers (scheme 16).

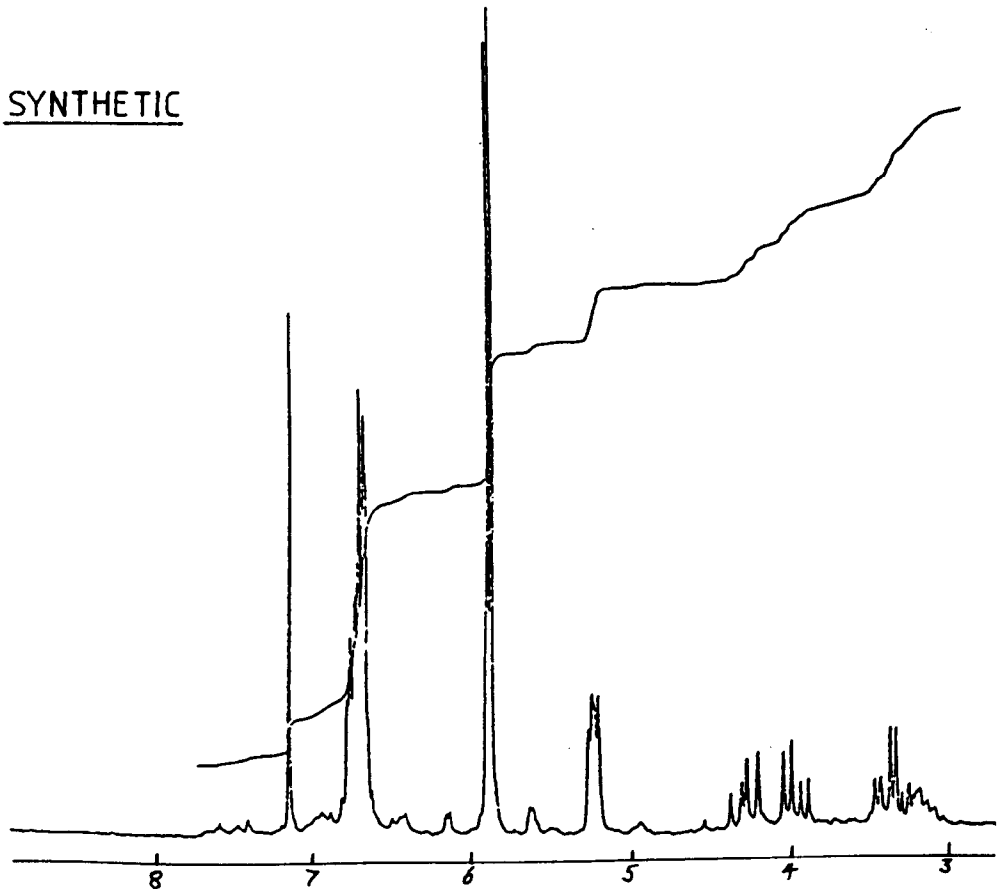


SCHEME 16

An alcoholic (methanol or ethanol) solution of asarinin or sesamin containing hydrochloric acid, when refluxed produces an equilibrium mixture of both asarinin and sesamin[52] (and also the diaxial isomer, diasesamin in tiny yields) and so it might not be unreasonable to expect on thermodynamic grounds for both aptosimon and 2-epi -aptosimon to be formed, having very similar energies, from the same intermediate carbocation (30).

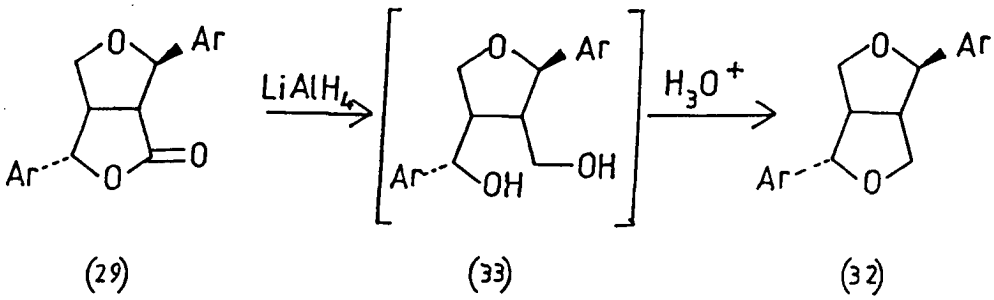


* THIS STRUCTURE IS SHOWN AS IT WAS ORIGINALLY ASSIGNED



The stereochemistry of 2-epi-aptosimon was convincingly deduced from nuclear Overhauser enhancement experiments. The 2-exo-6-exo isomer was identical to naturally occuring aptosimon by 90 MHz ^{1}H NMR and mass spectral data and also gave a carbon-13 NMR spectrum consistent with the proposed structure. We thank Prof. Brieskorn for the ^{1}H NMR and mass spectra.

This synthesis coupled with other evidence from the literature means that there can no longer be any reasonable doubt that aptosimon has a 2,6-diaryl structure.

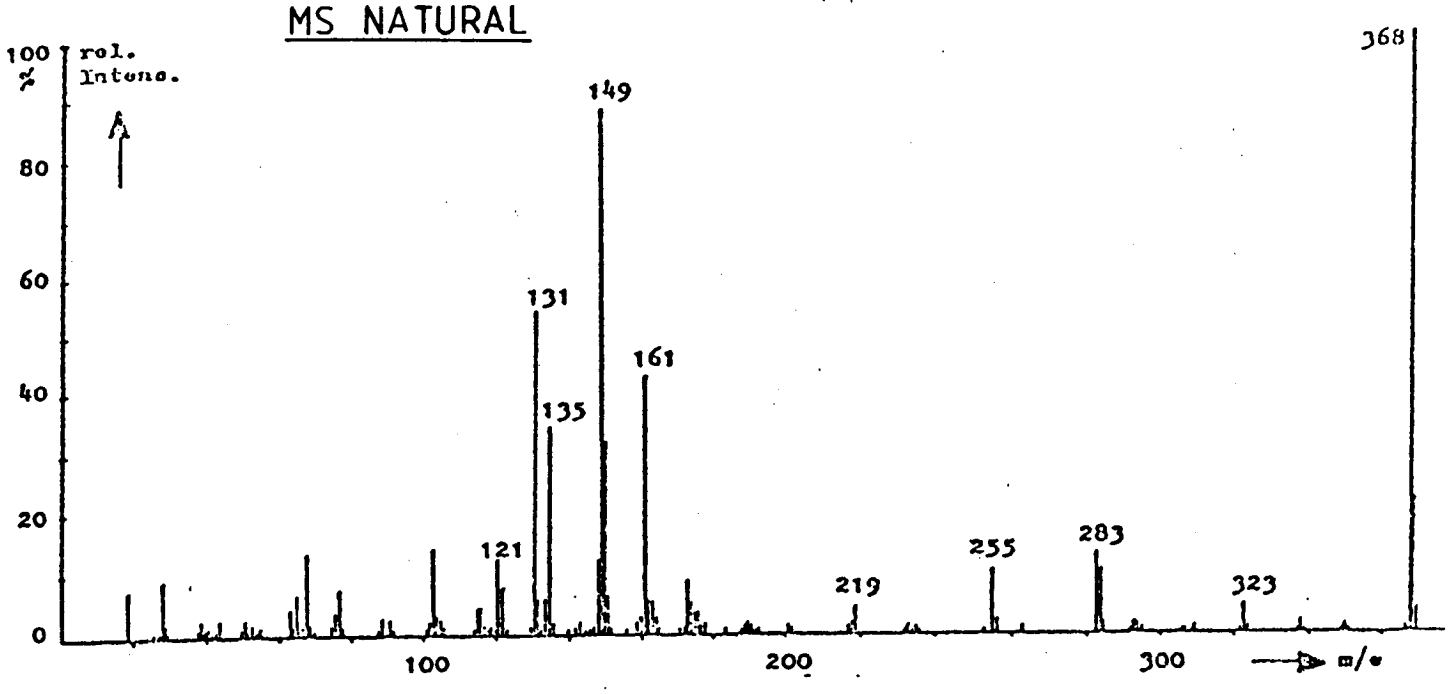


(29) (33) (32)

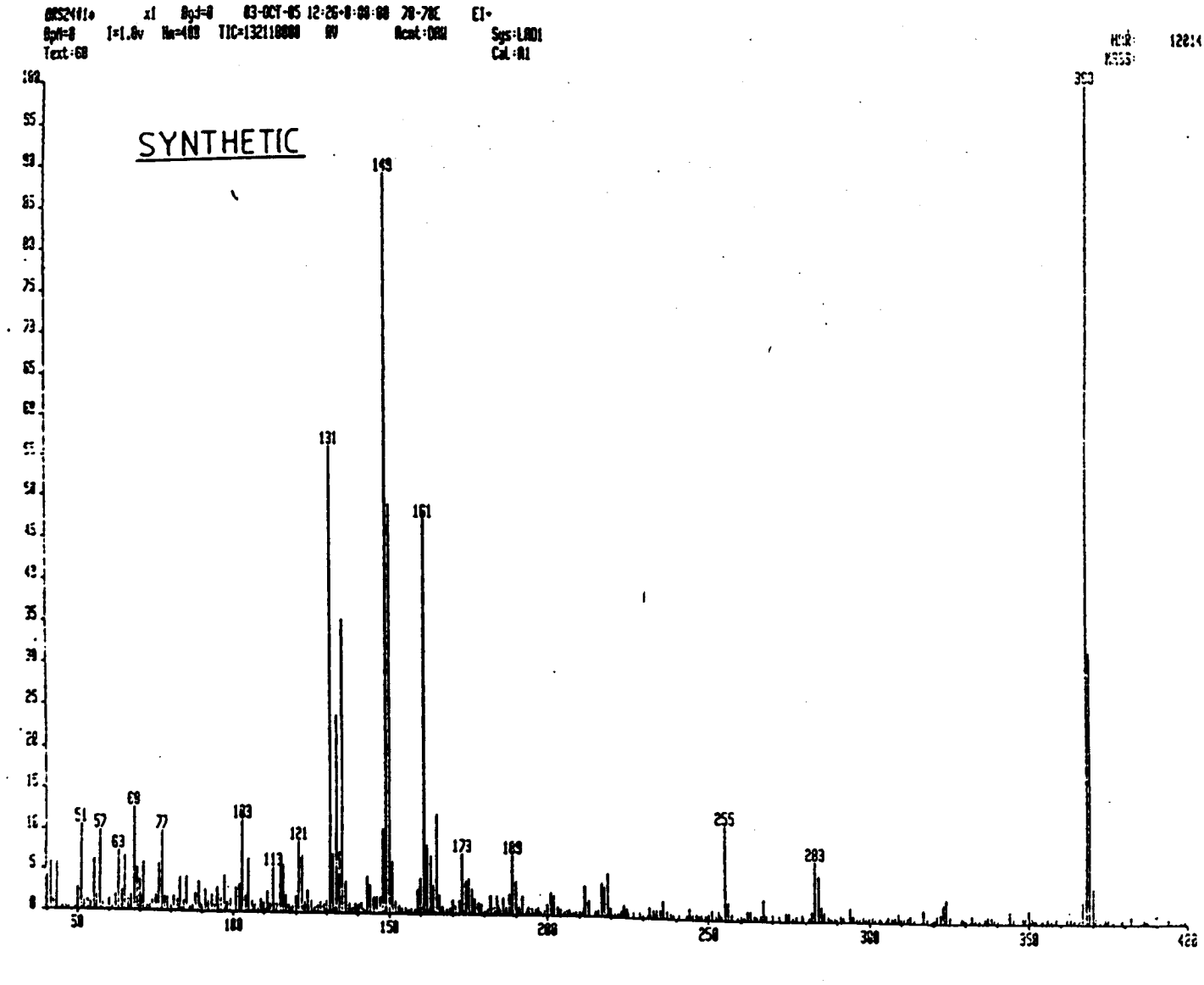
SCHEME 17

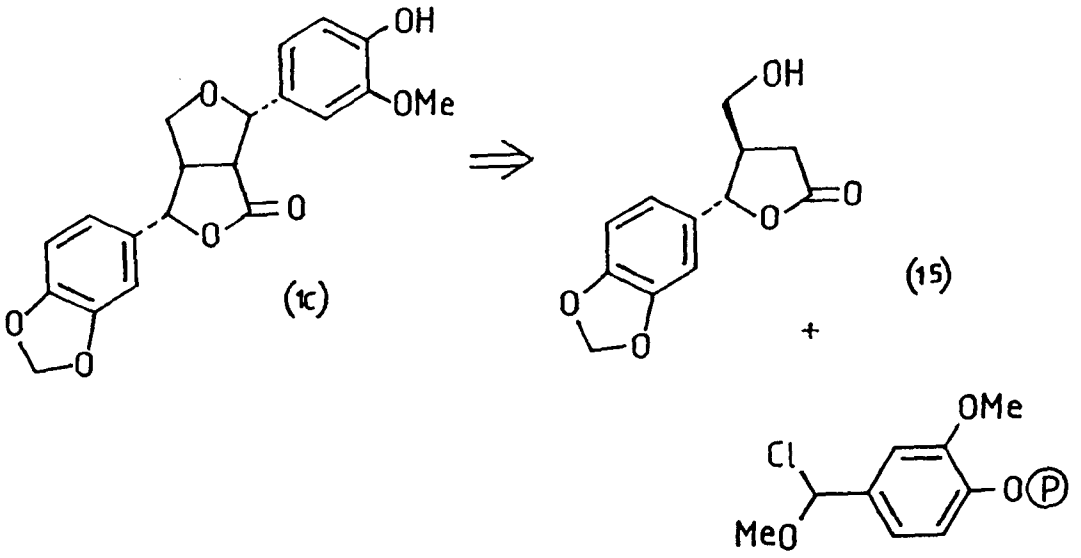
2-epi-Aptosimon (29) is not known to be naturally occurring. However, the lactone ring was reduced using lithium aluminium hydride and then exposed to an acid work-up to ring close the subsequently formed diol (33) (scheme 17). The 250 MHz ^{1}H NMR spectrum of this compound (±)-(32) was superimposable on that

MS NATURAL



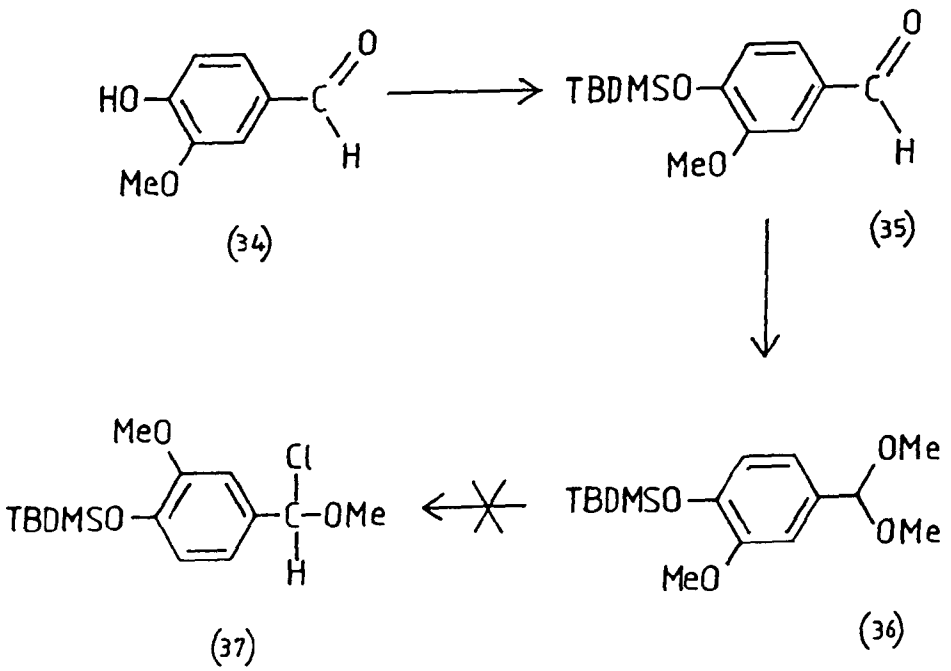
SYNTHETIC





P = PROTECTING GROUP

SCHEME 18



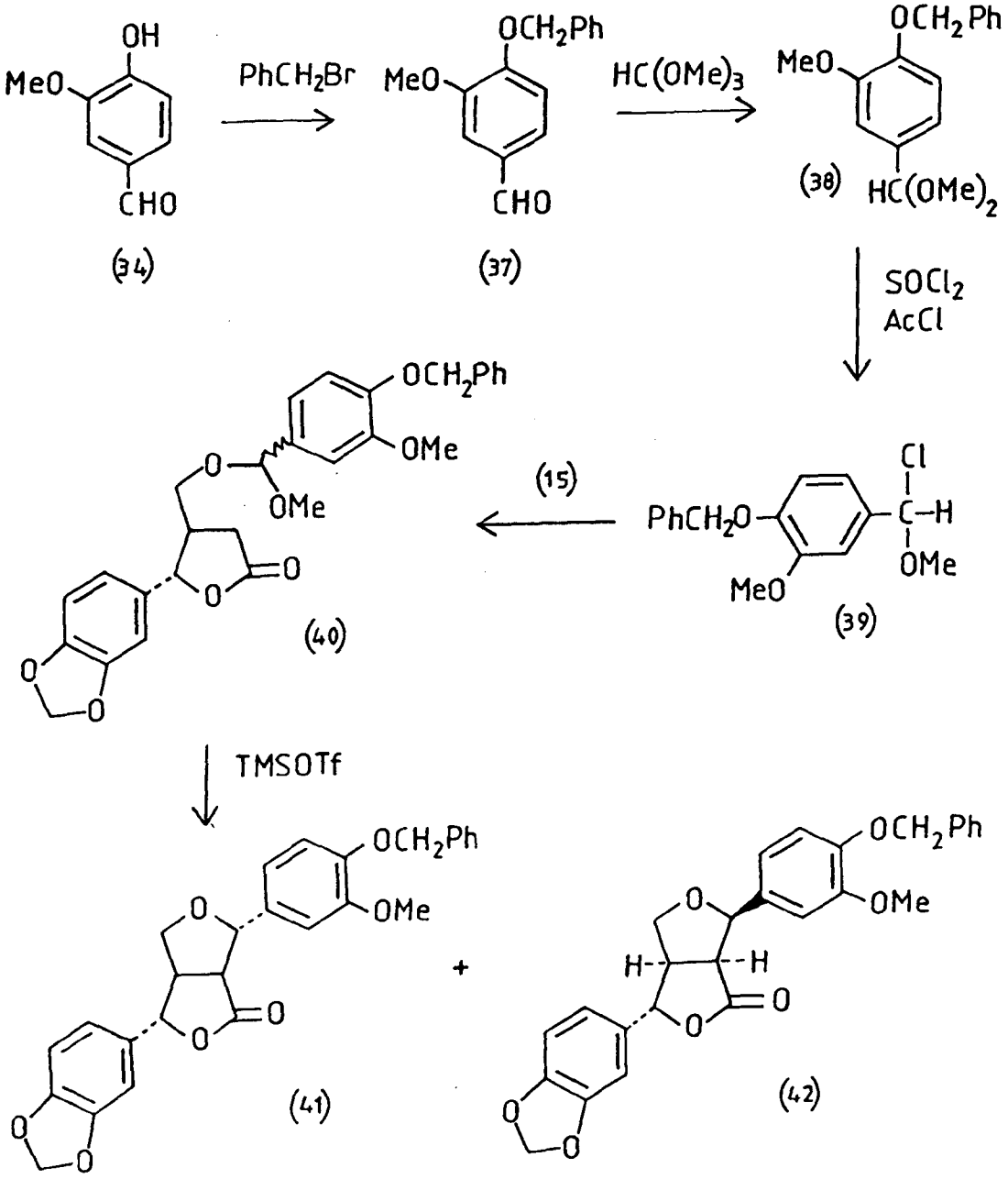
SCHEME 19

of a sample of natural (-)-asarinin , a well known and characterised lignan. We thank Prof. L. Crombie for this sample.

We now wanted to show that the reaction scheme was compatible with protected phenolic functions and styraxin (1c) was chosen. This target would require the same lactone alcohol (15) intermediate as aptosimon but would require protection in the chloroether formation (scheme 18).

Vanillin (4-hydroxy-3-methoxy benzaldehyde) (34) was readily protected using t-butyldimethylsilyl chloride under standard conditions[53], in 50% yield and this compound (35) subsequently gave the dimethyl acetal (36) as before in 52% yield after distillation. Attempts to form the α-chloroether (37) however were unsucessful, presumably because the reaction conditions (acetyl chloride/thionyl chloride catalyst) were too acidic for silicon protecting group to survive and the free phenol could then react with the α-chloroether to form a polymer (scheme 19).

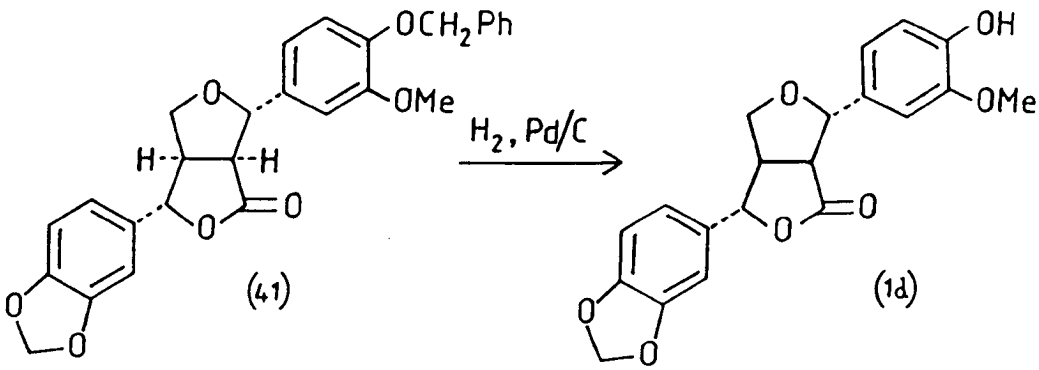
A protecting group more stable to acidic conditions was required and so vanillin (34) was protected using benzyl bromide in refluxing dry acetone in the presence of potassium carbonate and potassium iodide[54] (scheme 20). Benzyl vanillin (37) was produced in high (92%) yield which readily formed the dimethyl acetal (38) using trimethyl orthoformate in 91%


OH
MeO
CHO
(34)
PhCH2Br
OCH2Ph
MeO
CHO
(37)
HC(OMe)3
OCH2Ph
MeO
(38)
HC(OMe)2
SOCl2
AcCl
Cl
PhCH2O
C–H
OMe
MeO
(39)
(15)
OCH2Ph
OMe
O
OMe
O
O
O
O
(40)
TMSOTf
OCH2Ph
OMe
O
O
O
O
O
(41)
+
OCH2Ph
OMe
O
H
H
O
O
O
O
(42)

SCHEME 20

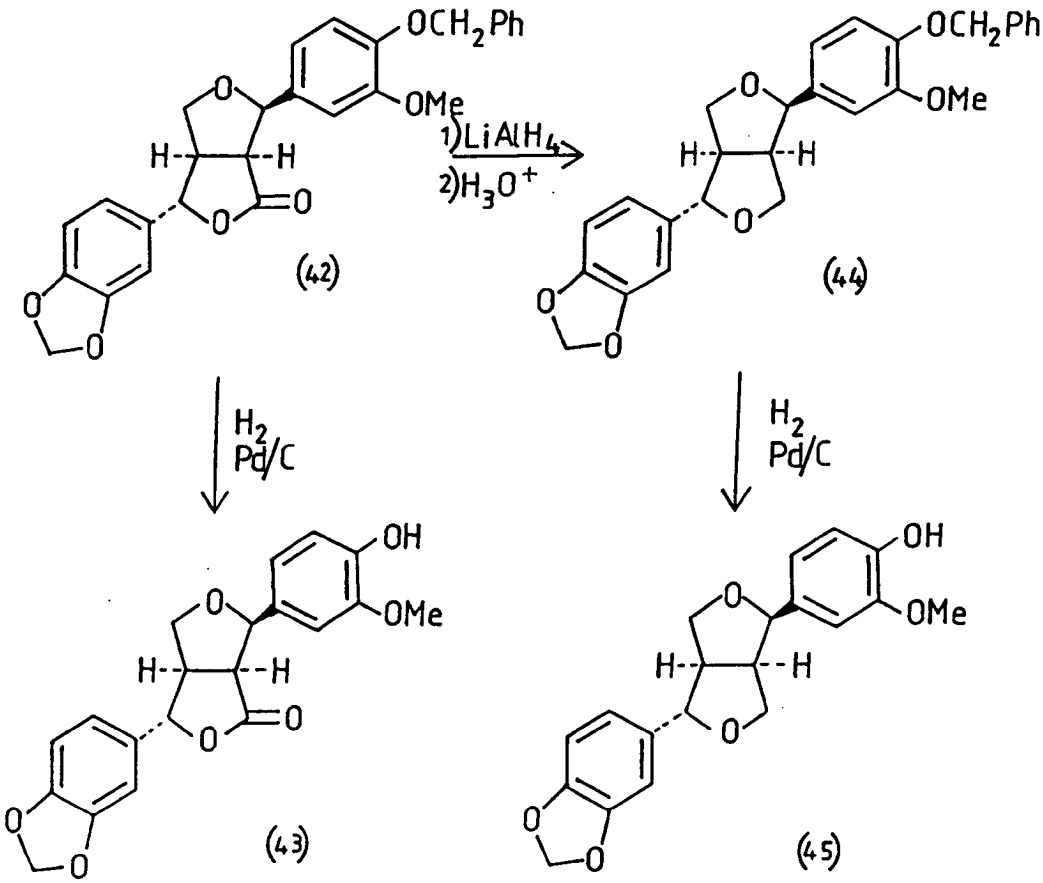
yield. Formation of the α-chloroether (39) took place in essentially quantitative yields and this in turn coupled with the lactone alcohol (15) to produce the mixed acetal (40) in reasonable yield (59%). Ring closure of this mixed acetal using trimethylsilyl trifluoromethanesulphonate in the presence of triethylamine in mixed tetrahydrofuran/ether solvent gave (±)-benzyl styraxin (41) and (±)-benzyl-2-epi-styraxin (42) in 12% and 22% yields respectively. Again it is interesting to note that the 2-endo-isomer predominates over the 2-exo-isomer. The isomers were clearly identified by comparison of both ^{1}H and ^{13}C NMR spectra with those of aptosimon (1b) and 2-epi aptosimon (29).

Catalytic hydrogenolysis (10% Pd on carbon) of benzyl styraxin (42) gave (±)-styraxin (1c) in 98% yield (scheme 21). This was identical to a sample of natural styraxin by TLC, 400 MHz ^{1}H NMR and mass spectral data. The sample of (-)-styraxin was kindly supplied by Prof. Ulubelen.



SCHEME 21

The 2-endo-isomer also readily underwent hydrogenolysis to give 2-epi-styraxin (43) in 96% yield (scheme 22).



SCHEME 22

Reduction of benzyl-2-epi-styraxin (43) with lithium aluminium hydride followed by acid work up gave the corresponding tetrahydrofuran (44) as expected. Debenzylation involving catalytic hydrogenolysis again gave (±)-pluviatilol[55] (45) in 81% yield with spectral data identical to that reported for

the natural compound.

In summary, we have developed a short synthesis of the lignan lactones (±)-aptosimon and (±)-styraxin with known relative regio- and stereochemistries and have shown that these correspond to naturally occuring (-)-aptosimon and styraxin. From these results we are forced to conclude that the structure for aptosimon must be revised from a 2,4- to a 2,6-diaryl structure.

Experimental Generalisations

TLC (analytical and preparative) used silica HF_{254}. Infra red spectra were recorded on a Pye Unicam SP3-100 machine.

Chemical shifts are reported relative to an internal TMS standard as δ values. These were recorded at 90 MHz using Perkin Elmer R32 or Jeol FX90Q (^{13}C at 22.5 MHz) spectrometers. Shifts were also determined at 250 MHz using a Brucker WM 250 (^{13}C at 63 MHz) and 400 MHz using a Brucker AM 400 (^{13}C at 100 MHz). ^{13}C NMR spectra at 20 MHz were recorded using a Brucker WP 80 SY spectrometer.

Accurate masses were measured at 70 ev.

Melting points were recorded using a Kofler hot stage apparatus and are uncorrected.

Microanalyses were performed in the chemistry department at Nottingham University. No reaction conditions were optimised. THF was dried at reflux over sodium metal and benzophenone. Dichloromethane was dried by distillation from P_2O_5. Ether was dried over sodium wire. Diisopropylamine was distilled from sodium hydroxide and stored over molecular sieve (3 or 4 A) before use. Other solvents were dried using standard techniques where applicable.

Experimental Section.

Manganese (III) acetate dihydrate[40].

Manganese (II) acetate tetrahydrate (51.45 g, 0.210 mol) was dissolved in glacial acetic acid (360 ml) in a three necked flask fitted with a condenser and stirrer. The temperature was maintained at 110°C and potassium permanganate (8.29 g, 0.0525 mol) was added slowly down the condenser to maintain the temperature below 114°C. The mixture was then refluxed for an hour and left to cool. Water (90 ml) was added and the mixture left overnight to crystallise. The brown solid was filtered off, washed with ether and dried in air to leave manganese (III) acetate dihydrate (53.35 g, 0.199 mmol, 76%).

trans-1-Acetoxy-3-phenyl-2-propene (2). (Cinnamyl acetate)[41].

trans-3-Phenyl-2-propen-1-ol (10.58 g, 79.0 mmol) was dissolved in pyridine (110 ml) and acetic anhydride (8.1 ml, 8.76 g, 85.9 mmol) was then added. The solution was stirred overnight and was then partitioned between ethyl acetate and hydrochloric acid. The organic phase after drying ($MgSO_4$) and chromatography (silca, ethyl acetate/hexane) gave cinnamyl acetate (12.55 g, 71.3 mmol, 90%) as a colourless oil; ν max 3050, 2950, 1745, 1680 and 1245 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 2.04 (3H, s, CH_3), 4.71 (2H, d, J 6 Hz, CH_2), 6.30 (1H, dt, J 16 and 6 Hz, 2-H), 6.65 (1H, d, J 16 Hz, 3-H), 7.38 (5H, s, Ar-H).

trans-4-Acetoxymethyl-5-phenyl dihydro-2(3H)-furanone (3).

Cinnamyl acetate (1.00 g, 5.67 mmol), manganese (III) acetate dihydrate (3.80 g, 14.2 mmol, 2.5 eq) and potassium acetate (2.78 g, 28.3 mmol, 5 eq) were dissolved in glacial acetic acid (25 ml) and were refluxed for four hours. When the brown colour had disappeared, the solution was cooled and ethyl acetate (50 ml) was added. The mixture was washed with water (twice), sodium carbonate solution and brine. Drying ($MgSO_4$), evaporation and chromatography (silica, ethyl acetate/hexane) gave the title compound (0.53 g, 2.26 mmol, 40%) as a colourless oil; (Found: M^+, 234.0887. $C_{13}H_{14}O_4$ requires M^+, 234.0891); νmax (thinfilm) 3050, 2950, 1795, 1745, 1680, 1460, 1380, 1240 cm^{-1}; δ (90 MHz, $CDCl_3$) 2.06 (3H, s, $-CH_3$), 2.40-2.95 (3H, m, 3-H_2, 4-H), 4.26 (2H, d, J 5 Hz, CH_2OAc), 5.31 (1H, d, J 6.5 Hz, 5-H), 7.44 (5H, s, Ar-H); m/z 234 (M^+, V. Weak), 174 (72), 146 (80), 131 (13), 115 (10), 107 (24), 105 (100), 86 (22), 77 (18), 68 (25).

3-(3,4-Methylenedioxyphenyl)propenoic acid (7).

3,4-(Methylenedioxy)benzaldehyde (10.0 g, 66.6 mmol), malonic acid (15.0 g, 144 mmol) and piperidine (1 ml) were dissolved in pyridine (30 ml) and the solution was refluxed for 90 minutes. The solution was cooled and poured into 2M hydrochloric acid (200 ml) and the resulting precipitate was filtered, washed with water, a little ethanol and dried in

vacuo. This gave white crystals of the title compound (11.90 g, 61.9 mmol, 94%); m.p.246°C (Lit[42] 247°C).

(Chloromethylene)dimethylammonium chloride[43] (8).

Dry dimethylformamide (5.0 ml, 4.72 g, 64.6 mmol) was added to dry chloroform (40 ml) under nitrogen. Oxalyl chloride (6.2 ml, 9.02 g, 71.1 mmol, 1.1 eq) was added dropwise at 0°C and the solution was stirred for an hour. Solvent and volatiles were removed using a high vacuum oil pump to leave an air sensitive, yellow powder (8.26 g, ~ 100%) used without further purification.

3-(3,4-Methylenedioxyphenyl)-2-propen-1-ol (10).

A solution of (chloromethylene)dimethylammonium chloride (2.62 g, 20.5 mmol) in dry acetonitrile (30 ml) and dry THF (60 ml) under a nitrogen atmosphere was cooled to -10°C. 3-(3,4-Methylenedioxyphenyl)propenoic acid (3.92 g, 20.5 mmol) was added in portions to the solution. The mixture was stirred for one hour as the acid dissolved on reaction. The solution was then cooled further to -30°C, when a suspension of sodium borohydride (2.0 g, 53 mmol) in dimethylformamide (20 ml) was added and stirred. The reaction was allowed to warm to room temperature over an hour and was then stirred for another hour. Ethyl acetate and hydrochloric acid (dropwise) were added to work up the reaction. The organic layer was washed

with water and brine and then dried ($MgSO_4$). Column chromatography (silica, ethyl acetate/hexane) gave the alcohol (2.60 g, 14.6 mmol, 71%) as a pale yellow solid; m.p. 78.5-79°C (ethyl acetate/hexane) (Lit[56] m.p. 77-77.8°C), δ_H (90 MHz, $CDCl_3$) 1.72 (1H, s, -OH), 4.28 (2H, dd, J 5.5, 0.9 Hz, 1-CH_2), 5.95 (2H, s, -OCH_2O-), 6.19 (1H, dt, J 15.8 and 5.5 Hz, 2-CH), 6.51 (1H, d, J 15.8 Hz, 3-CH) 6.77-6.92 (3H, m, Ar-H).

1-Acetoxy-3-(3,4-methylenedioxyphenyl)-2-propene (11).

The alcohol (10) (0.81 g, 4.55 mmol) was dissolved in pyridine (10 ml) and acetic anhydride (0.52 ml, 0.56 g, 5.46 mmol, 1.1 eq) was added. The solution was stirred overnight before ethyl acetate (30 ml) was added and the mixture was then washed with hydrochloric acid (20 ml x 3) and brine (20 ml). Drying ($MgSO_4$) and chromatography (silica, ethyl acetate /hexane) gave the title compound (0.79 g, 3.59 mmol, 79%) as a colourless oil; δ_H (90 MHz, $CDCl_3$) 2.12 (3H, s, -CH), 4.71 (2H, d, J 6 Hz, 1-H_2), 5.99 (2H, s, -OCH_2O-), 6.18 (1H, dd, J 16 and 6 Hz, 2-H), 6.53 (1H, d, J 16 Hz, 3-H), 6.79-7.00 (3H, m, Ar-H).

4-Carboxy-5-(3,4-methylenedioxyphenyl)-dihydro-2(3H)-furanone[46] ((13) and (14)).

In a typical procedure, to powderd zinc chloride (18.15 g 133.2 mmol) dried *in situ* with thionyl chloride, was added dry dichloromethane (80 ml), 3,4-(methylenedioxy)benzaldehyde (16.0 g, 66.6 mmol) and succinic anhydride (10.0 g, 100 mmol) under a nitrogen atmosphere. Triethylamine (21.2 ml, 13.5 g, 133 mmol) was added dropwise over a 30 minute period *via* a rubber septum using a syringe, whereupon the mixture became warm and nearly homogenous. Stirring was continued overnight before 2M hydrochloric acid (80 ml) was added and the solution was extracted with ethyl acetate. The organic layer was washed with hydrochloric acid and brine, and was extracted with saturated sodium bicarbonate solution (3 x 100 ml). The combined extracts were washed with chloroform until no more colour dissolved in the organic layer. Acidification (conc. hydrochloric acid) of the aqueous layer gave the *title compound* (8.3-12.4 g, 50-75%; cis:trans 2:3) as a mixture of isomers. The isomers could be separated by trituration with ether followed by recrystallisation from ethyl acetate/hexane, methanol/water or chloroform to give the acids as pure white solids.

trans-*Isomer* (13); m.p. 160-161°C (Lit[47] for sample made by another route, 164-165°C) (Found: C, 57.3; H, 4.1%; M^+ 250.0477. $C_{12}H_{16}O_6$ requires C, 57.6; H, 4.0%; M^+ 250.0477);

ν_{max}^{KBr} 2900-3300, 1740, 1720, 1500, 1255, 1225, 1180 1160, 1035 and 965 cm^{-1}; δ_H (250 MHz, CD_3COCD_3) 2.98 (2H, m, 3-H_2), 3.50-3.60 (1H, m, 4-H), 5.55 (1H, d, J 8.5 Hz, 5-H), 6.04 (2H, s, $-OCH_2O-$), 6.85-7.02 (3H, m, Ar-H); δ_c(80 MHz, CD_3COCD_3) 32.7 (CH_2-3), 48.9 (CH-4), 83.2 (CH-5), 102.3 ($-OCH_2O-$), 107.4, 108.9, 121.3 (Ar-CH), 133.5 (Ar-C_1'), 149.2 (2 signals ?, Ar-C_3', C_4'), 172.5, 174.7 (C=O, COOH) ; m/z 250 (M^+, 34), 207 (21), 161 (41), 151 (72), 131 (100), 103 (69), 77 (33).

cis-Isomer (14); m.p. 163-165°C (Lit[47], 160-163°C (d)) (Found: C, 57.5; H, 4.0%, M^+, 250.0450. $C_{12}H_{10}O_6$ requires C, 57.6; H, 4.0%; M^+, 250.0477); ν_{max}^{KBr} 3410, 1770, 1740, 1690, 1500, 1450, 1260, 1090, 1040, 930, 825 cm^{-1}; δ_H(400 MHz, CD_3COCD_3) 2.90-2.91 (2H, m, 3, 3'-H), 3.80 (1H, td, J 7.3 and 5.4 Hz, 4-H), 5.80 (1H, d, J 7.4 Hz, 5-H), 5.99 (2H, 2 x d, J 2.6 and 1.0 Hz, $-OCH_2O-$), 6.78-6.92 (3H, m, Ar-H), δ_c(250 MHz, CD_3COCD_3) 32.9 (CH_2-3), 47.4 (CH-4), 81.8 (CH-5), 102.2 ($-OCH_2O-$), 107.3, 108.8, 120.6 (CH-Ar), 131.0 (C_1'-Ar), 148.5, 148.8, (C_3', C_4'-Ar), 172.1, 175.8 (C=O, COOH); m/z 250 (M^+, 30), 206 (12), 151 (100), 150 (38), 149 (30), 131 (19), 121 (6), 113 (7), 163 (14), 93 (26).

trans-4-Hydroxymethyl-5-(3,4-methylenedioxyphenyl)-dihydro-2(3H)-furanone (15).

Lactone acid (13) (4.75 g, 19.0 mmol) was dissolved in dry THF (80 ml) under nitrogen and was cooled to 0°C. A 2M solution of borane/methyl sulphide complex (14.25 ml, 28.5 mmol, 1.5 eq) was added dropwise over ten minutes. The ice bath and the reaction were allowed to warm to room temperature overnight. Excess reagent was destroyed by dropwise addition of methanol (20 ml) and the solution was evaporated. Brine (50 ml) and ethyl acetate (50 ml) were added to the residue and the organic layer was separated. This was washed with sodium bicarbonate solution (2 x 20 ml) and dried ($MgSO_4$). Evaporation of the solvent gave the alcohol as an oil which on the addition of a small quantity of ether and stirring, gave the title alcolol (15) (3.85 g, 16.3 mmol, 86%) as a white solid; m.p. 82-83°C (ethyl acetate/40-60 petrol, square plates); (Found: C, 61.2, H, 5.1%; M^+, 236.0685. $C_{12}H_{12}O_5$ requires C, 61.0 ; H, 5.1%, M^+ 236.0683); ν_{max}^{KBr} 3440, 2890, 1745, 1505, 1210, 1039, 973, 934, 827, 709, cm^{-1}; δ_H(250 MHz, $CDCl_3$) 2.33 (1H, br s, -OH), 2.59-2.75 (3H, m, 3-H_2, 4-H), 3.72-3.74 (2H, m, -CH_2OH), 5.28 (1H, d, J 6.6 Hz, 5-H) 5.97 (2H, s, -OCH_2O-), 6.79-6.81 (3H, m, Ar-H); δ_c (80 MHz, $CHCl_3$) 31.5 (CH_2-3), 46.1 (CH-4), 61.2 (-CH OH), 83.2 (CH-5), 101.4 (-OCH_2O-), 106.3, 108.4, 119.7 (Ar-CH), 132.5 (Ar-C_1'), 148.0, 148.2 (Ar-C_3', C_4'), 176.8 (C=O); m/z 236 (M^+, 56), 222 (7), 151 (100), 150 (43), 149 (49), 131 (12), 121 (10), 93 (32), 77 (11), 65 (17).

3-(α -Methoxybenzyl)dihydro-2(3H)-furanone (21).

($TiCl_4$ method).

Lithium diisopropylamide (12.8 mmol) was prepared by adding n-butyl lithium (8.0 ml of a 1.6M solution in hexane, 12.8 mmol) to a solution of diisopropylamine (1.30 g, 1.80 ml, 12.8 mmol) in dry THF at 0°C under a nitrogen atmosphere. The solution was cooled to -78°C and a solution of γ-butyro lactone (1.00 g, 11.6 mmol) in dry THF (3 ml) was added dropwise over five minutes. The reaction was stirred for 30 minutes and then quenched with trimethylsilyl chloride (1.60 ml, 1.37 g, 12.6 mmol) and warmed to room temperature. The solution was evaporated to dryness and the residue was mixed with dry pentane (20 ml). The insoluble inorganics were filtered to leave a pale yellow solution which on evaporation to dryness gave a pale yellow oil. The oil was dissolved in dry dichloromethane (30 ml) under nitrogen and cooled to -78°C. Benzaldehyde dimethyl acetal (1.77 g, 11.6 mmol) was added followed by dropwise addition of titanium tetrachloride (1.41 ml, 2.43 g, 12.8 mmol). The resulting solution was stirred for 30 minutes before water (20 ml) was added to quench the reaction. The organic layer was separated, washed with sodium bicarbonate solution and brine, and then dried ($MgSO_4$). Solvent was removed by rotary evaporation and the residue was chromatographed (silica, 40-60 petrol/ether, 3:1) to give pure samples of two diastereoisomers (1.03 g total yield, 43%, isomeric ratio, 1:1) as colourless oils (isomer A,

first off column and isomer B).

Isomer A (Found: C, 69.6; H, 7.1%; M^+, 206.0944. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%; M^+ 206.0943); νmax 3100-2840, 1770, 1455, 1380, 1160, 1030, 770, 710 cm^{-1}; δ_H(250 MHz $CDCl_3$) 1.80 (1H, m, 4-H), 2.32 (1H, m, 4'-H), 2.60 (1H, td, J 9.3 and 2.55 Hz, 3-H), 3.13 (3H, s,-OMe), 3.97 (1H, dt, J 8.5 and 7.6 Hz, 5-H), 4.19 (1H, td, J 8.7 and 3.9 Hz, 5'-H), 4.64 (1H, d, J 2.5 Hz, -CH(Ph)OMe), 7.08-7.24 (5H, m, Ph-H); δ_c(80 MHz, $CDCl_3$) 21.8 (CH_2-4), 47.4 (CH-3), 57.6 ($-OCH_3$), 67.0 (CH_2-5), 80.7 (CH(OMe)Ph), 127.1, 127.8, 128.7 (CH-Ar), 139.5 (C_1-Ar), 177.4 (C=O); m/z 206 (M^+,1), 191 (2), 121 (100), 115 (6), 105 (11), 91 (20), 77 (28).

Isomer B; (Found: C, 70.2; H, 7.0% M^+, 206.0934. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%; M^+, 206.0943); ν max 3050, 2885, 2830, 1770, 1470, 1395, 1220, 1110, 1040, 980, 735, 720 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 2.03-2.28 (2H, m, 4, 4'-H) 3.17 (1H, ddd, J 9.3, 8.1 and 4.5 Hz, 3-H), 3.32 (3H, s,-OMe), 3.77 (1H, td, J 8.6 and 5.15 Hz, 5-H), 4.07 (1H, td, J 8.8 and 7.6 Hz, 5-H), 4.72 (1H, d, J 4.4 Hz, -CH(OMe)Ph), 7.26-7.41 (5H, m, Ph-H); δ_c(80 MHz, $CDCl_3$), 23.9 (CH_2-4), 45.9 (CH-3), 57.1 ($-OCH_3$), 67.0 (CH_2-5), 81.8 (-CH(OMe)Ph), 127.2, 128.3, 128.5 (CH-Ph), 137.4 (C_1-Ph), 176.6 (C=O); m/z 206 (M^+, 1), 121 (100), 115 (4), 105 (8), 91 (13), 77 (20).

3-(α-Methoxybenzyl)dihydro-2(3H)furanone (21).

(TMSOTf method).

Butyrolactone (200 mg, 2.32 mmol) and benzaldehyde dimethyl acetal (353 mg, 2.32 mmol, 1.0 eq) were dissolved in dry ether (30 ml) at 0°C under a nitrogen atmosphere. Triethylamine (0.34 ml, 250 mg, 2.44 mmol, 1.05 eq) and trimethylsilyl trifluoromethanesulphonate (0.99 ml, 1.14 g, 5.12 mmol, 2.2 eq) were added and the solution was stirred for two hours. Water was added to quench and the organic layer was separated. The aqueous layer was extracted with a further portion of ether and the combined ether extracts were washed with brine and dried ($MgSO_4$). Evaporation of the organic layer and chromatography of the residue gave the title compound (130 mg, 0.63 mmol, 27%) as a 1.1 mixture of diastereoisomers identical by TLC and ^1H NMR to the compound synthesised previously.

α-Chlorobenzylmethyl ether[49] (17).

Freshly distilled benzaldehyde dimethyl acetal (6.08 g, 40.0 mmol) and freshly distilled acetyl chloride (10 ml) were stirred under a nitrogen atmosphere and a catalytic amount of thionyl chloride (0.1 ml) was added. The reaction was stirred overnight before volatile components were removed in vacuo (oil pump) to leave the required ether as an air sensitive, pale yellow oil in an essentially quantitave yield; δ_H(90 MHz, $CDCl_3$) 3.62 (3H, s, OMe), 6.47 (1H, s, CHCl), 7.2-7.7 (5H, m, Ar-H).

Mixed Acetal (18).

Lactone alcohol (15) (1.39 g, 5.88 mmol) was dissolved in dry dichloromethane (50 ml) under nitrogen at 0°C. Triethylamine (5 ml) was added followed by dropwise addition of a solution of α-chlorobenzyl methyl ether (17) (1.38 g, 8.82 mmol, 1.5 eq) in dry dichloromethane (5 ml). The solution was stirred for 15 minutes before washing once with sodium bicarbonate solution and drying ($MgSO_4$). Chromatography [alumina, grade III, ether/petrol (40-60) 1:1 with a few drops of triethylamine] gave the acetal (1.93 g, 92%) as white needles crystallising on elution; m.p. 90°C (Found: C, 67.6; H, 5.8%; M^+ 356.1262. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.7%; M^+ 356.1260); ν_{max}^{KBr} 1770, 1490, 1450, 1250, 1110, 1050 cm^{-1}; δ_H (250 MHz, CD_3COCD_3) 2.60-2.86 (3H, m, 3-H_2, 4-H), 3.28 (3H, 2 x s, OMe), 3.55-3.72 (2H, m, -CH_2O-), 5.25-5.29 (1H, m, 5-H), 5.51-5.53 (1H, 2 x s, OCH(OMe)Ph), 6.00 (2H, s, -OCH_2O-), 6.79 - 6.93 (3H, m, Ar-H), 7.30 - 7.45 (5H, m, Ph-H); δ_c (80 MHz, CD_3COCD_3), 32.5 (CH_2-3), 44.8 - 44.9 (CH-4, x 2), 53.1 (OCH_3), 64.9 - 65.4 (-CH_2O-, x 2), 83.9 - 84.0 (CH-5, x 2), 102.2 (-OCH_2O-), 103.3 - 103.4, 107.3, 108.8, 121.0, 127.5, 128.9 - 129.2 (CH-Ar), 134.2, 139.2 (Ar-C_1', C_1'',), 148.7, 149.0 (Ar-C_3', C_4'), 175.9 (C=O).

2-exo-Phenyl-6-endo-(3,4-methylenedioxyphenyl)-8-oxo-3,7-dioxa bicyclo[3,3,0]octane (23).

Lithium diisopropylamide (2.78mmol) was prepared in dry tetrahydrofuran (20 ml) at 0°C under a nitrogen atmosphere from diispropylamine (0.39 ml, 0.28 g, 2.78 mmol) and n-butyl lithium (1.8 ml of a 1.55M solution in hexane, 2.78 mmol). The resulting solution was cooled to -78°C and a solution of the mixed acetal (18) (0.91 g, 2.53 mmol) in dry tetrahydrofuran (3 ml) was added. After 30 minutes, trimethylsilyl chloride (0.50 ml, 0.43 g, 3.9 mmol) was added to quench and allowed to warm to room temperature. Volatiles were removed in vacuo and the residue was mixed with dry ether (20 ml). Insoluble inorganics were removed by filtration and evaporation of the solvent left a pale yellow oil (1.10 g, 2.57 mmol, 92%). Dry dichloromethane (20 ml) was added and the solution was cooled to -78°C under a nitrogen atmosphere. A solution of titanium tetrachloride (0.30 ml, 0.52 g, 2.74 mmol) in dichloromethane (2 ml) was added and the reaction was stirred for 3 hours at -78°C. Water (20 ml) was added to quench and the mixture was extracted with ethyl acetate (2 x 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica, ether/40-60 petrol, 1:1) to give the title compound (0.22 g, 0.68 mmol, 27%). m.p. 154-155°C (ethyl acetate/hexane) (Found: C, 70.2; H, 5.2%; M^+ 324.0974. $C_{19}H_{16}O_5$ requires C, 70.4; H, 5.0%; M^+ 324.0998); ν_{max}^{KBr} 1780, 1495, 1450, 1260,

1245, 1030, 955, 930, 710 cm^{-1}; δ_H(250 MHz, CD_3COCD_3) 3.29 - 3.37 (1H, m, 5-H), 3.72 (1H, pseudo-t, J 8.9 and 8.9 Hz, 1-H), 3.92 (1H, dd, J 9.5 and 4.9 Hz, 4-H_E), 4.33 (1H, d, J 9.5 Hz, 4-H_A), 5.12 (1H, d, J 8.5 Hz, 2-H), 5.26 (1H, d, J 6.4 Hz, 6-H), 6.01 (2H, s, $-OCH_2O-$), 6.84 - 6.99 (3H, m, Ar-H), 7.22 - 7.43 (5H, m, Ph-H); δ_c(250 MHz, CD_3COCD_3) 51.9, 52.1 (CH-1, CH-5), 76.2 (CH_2-4), 84.4, 86.1 (CH-2, CH-6) 102.3 ($-OCH_2O-$), 107.1, 109.0, 120.7 (CH-Ar), 127.4 128.5, 128.8 (CH-Ar), 135.3, 138.4 (C_1', C_1''-Ar), 148.7, 149.0 (C_3'', C_4''-Ar), 175.9 (C=O); m/z 324 (M^+, 100), 239 (17), 217 (5), 176 (8), 161 (20), 150 (80), 131 (31), 105 (36), 68 (42).

3,4-(Methylenedioxy)benzaldehyde dimethyl acetal (25).

3,4-(Methylenedioxy)benzaldehyde (15.0 g, 100 mmol) was dissolved in trimethylorthoformate (50 ml) and one drop of conc. sulphuric acid was added as catalyst. A deep blue /purple colour forms after ten minutes which disappears on stirring the mixture overnight. Distillation at atmospheric pressure to remove excess solvent was followed by distillation at reduced pressure (142°C/5 mm Hg, Lit[57] 271-272°C/757 mm Hg) to yield the acetal (17.4 g, 89%) as a colourless oil; δ_H(90 MHz, $CDCl_3$), 3.30 (6H, s, -OMe), 5.28 (1H, s, $-CH(OMe)_2$), 5.93 (2H, s, $-OCH_2O-$), 6.72 - 6.95 (3H, m, Ar-H).

∝ -Chloro-3,4-(methylenedioxy)benzyl methyl ether (26).

3,4-(Methylenedioxy)benzaldehyde dimethyl acetal (25) (6.52 g, 33.2 mmol), freshly distilled acetyl chloride (8 ml) and thionyl chloride (0.1 ml) were stirred overnight under a nitrogen atmosphere. The reaction turned a deep purple colour. Volatile components were removed in vacuo (oil pump) to give an essentially quantitative yield of the title ether as a dark oil identified by ^{1}H NMR. δ_H(90 MHz, $CDCl_3$) 3.72 (3H, s, -OMe), 6.07 (2H, s, $-OCH_2O-$), 6.51 (1H, br s, -CH(Cl)OMe), 6.80 - 7.20 (3H, m, Ar-H).

Mixed acetal (27).

Lactone alcohol (15) (1.00 g, 4.24 mmol) was dissolved in dry dichloromethane (30 ml) under nitrogen and cooled to 0°C. Triethylamine (4.0 ml) and then ∝-chloro-3,4-(methylenedioxy) benzyl methyl ether (26) (1.36 g, 1.6 eq) were added and the solution was stirred for 30 minutes. The solution was washed once with sodium bicarbonate solution and dried ($MgSO_4$). Chromatography (alumina, grade III, ether/40-60 petrol 1:1, trace of triethylamine) gave the acetal (1.58 g, 3.94 mmol, 93%) as a pale yellow oil; (Found: M^+, 400.1133. $C_{21}H_{20}O_7$ requires M^+ 400.1158); δ_H(250 MHz, $CDCl_3$) 2.60 - 2.71 (3H, m, 3-H_2, 4-H), 3.32 (3H, 2 x s, -OMe), 3.47 - 3.70 (2H, m, $-OCH_2O-$), 5.23 - 5.27 (1H, m, 5-H), 5.38 - 5.40 (1H, 2 x s, -OCH(OMe)Ar), 5.97 (4H, 2 x s, $-OCH_2O-$ x 2), 6.72 - 6.95 (6H, m, Ar-H).

2-exo-6-exo-bis-3,4-(Methylenedioxy)phenyl-8-oxo-3,7-dioxa bicyclo[3,3,0]octane (1b); (Aptosimon) and 2-endo-6-exo-bis-(3,4-methylenedioxy)phenyl-8-oxo-3,7-dioxa bicyclo[3,3,0]octane (29); (2-epi-Aptosimon).

Mixed acetal (27) (1.58 g, 3.94 mmol) was dissolved in dry THF/ether 1:1 (30 ml) under nitrogen and was cooled to 0°C. Triethylamine (1.21 ml, 0.88 g, 2.2 eq) and trimethylsilyl trifluoromethanesulphonate (1.69 ml, 1.94 g, 2.1 eq) were added and stirred for three hours. Water was added to quench and the solution was extracted with ethyl acetate. The organic layer was washed (2M hydrochloric acid and then brine) and dried ($MgSO_4$). Flash column chromatography (ether/petrol gradient) gave two identifiable fractions; aptosimon (0.28 g, 0.76 mmol, 19%) eluted first as a pale yellow gum followed by 2-epi-aptosimon (0.40 g, 1.09 mmol, 28%) as a white crystalline solid.

Aptosimon; (Found: M^+, 368.0864. $C_{20}H_{16}O_7$ requires 368.0896); δ_H(90 MHz, $CDCl_3$) 3.23 (1H, m, 5-H), 3.42 (1H, dd, J 9.2, 3.5 Hz, 1-H), 4.01 (1H, dd, J 9.5, 4.5 Hz, 4-H), 4.32 (1H, dd, J 9.5, 6.5 Hz, 4-H), 5.28, 5.29 (1H, d, J 3.5 Hz; 1H, d, J 3.5 Hz; 2-H, 6-H), 5.95 (2H, s, $-OCH_2O-$), 5.95 (2H, s, $-OCH_2O-$), 6.79 - 6.98 (6H, m, Ar-H); δ_H(250 MHz, CD_3COCD_3) 3.40 (1H, m, 5-H), 3.67 (1H, m, dd, J 9.8, 3.8 Hz, 1-H), 4.04 (1H, dd, J 8.8, 4.7 Hz, 4-H), 4.33 (1H, dd, J 9.5, 7.4 Hz, 4-H), 5.20 (1H, d, J 3.8 Hz, 2-H), 5.43 (1H, d, J 3.6 Hz, 6-H), 6.00 (2H,

s, $-OCH_2O-$), 6.03 (2H, s, $-OCH_2O-$), 6.82 - 6.98 (6H, m, Ar-H); δ_c(250 MHz, CD_3COCD_3) 50.4, 53.8 (CH-1, CH-5) 73.5 (CH -4), 84.3, 85.3 (CH-2, CH-6), 102.1, 102.3 ($-OCH_2O-$ x 2), 107.1 (2 peaks ?), 108.8, 109.0, 120.0, 120.6, (CH-Ar), 135.0, 135.9 (C_1', C_1''-Ar), 148.8 (x 4 ? v.weak, C_3', C_4', C_3'', C_4''-Ar), 177.4 (C=O); m/z 368 (M^+, 100) 283 (7), 255 (11), 219 (5), 173 (7), 161 (47), 149 (89), 135 (34), 131 (56), 121 (8), 103 (11).

2-epi-Aptosimon; m.p 158 - 159°C (ethyl acetate/hexane) (Found: C, 65.2; H, 4.55%; M^+ 368.0901. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.4%; M 368.0896), ν_{max}^{KBr} 2875, 1765, 1500, 1250, 1170, 1030, 815 cm^{-1}; δ_H(250 MHz, CD_3COCD_3) 3.33 (1H, m, 5-H), 3.68 (1H, pseudo t, J 8.8 and 8.8 Hz, 1-H), 3.90 (1H, dd, J 4.8 and 9.5 Hz, 4-H), 4.31 (1H, d, J 9.5 Hz, 4-H), 5.07 (1H, d, J 8.6 Hz, H-2), 5.27 (1H, d, J 6.5 Hz, 6-H), 5.99 (2H, s, $-OCH_2O-$), 6.03 (2H, s, $-OCH_2O-$), 6.78 - 7.00 (6H, m, Ar-H); δ_c(250 MHz, CD_3COCD_3) 51.8, 52.3 (CH-1, CH-5), 72.4 (CH -4) 84.2, 86.1 (CH-2, CH-6), 101.9, 102.3 ($-OCH_2O-$ x 2), 107.2, 107.7, 108.5, 108.9, 120.7, 120.8 (CH-Ar), 132.3, 135.2 (C_1', C_1''-Ar), 148.1, 148.5, 148.8, 149.1 (C_3', C_4', C_3'', C_4''-Ar), 174.7 (C=O); m/z 368 (M^+, 100%), 283 (10), 255 (11), 189 (6), 173 (7), 161 (42), 149 (98), 135 (36), 131 (46), 121 (8), 103 (8).

4-(tert-Butyldimethylsilyloxy)-3-methoxy benzaldehyde (35).

4-Hydroxy-3-methoxy benzaldehyde (10.05 g, 66.1 mmol) was dissolved in dry dimethylformamide (120 ml) and then imidazole (11.21 g, 165 mmol, 2.5 eq) and tert-butyldimethylsilyl chloride (11.96 g, 79.3 mmol, 1.2 eq) were added and the solution was stirred for 3 hours. 5% sodium bicarbonate solution (100 ml) was added and the mixture was extracted with 40 - 60 petrol (4 x 100 ml). The combined extracts were washed with brine and dried ($MgSO_4$). Concentration of the organic extract in vacuo and distillation gave the title compound (8.87 g, 33.3 mmol, 50%) as a colourless oil. b.p. 143 - 144°C/3 mm Hg (Found; C, 63.3; H, 8.4%; $C_{14}H_{20}O_3Si$ requires C, 63.1; H, 8.3%); δmax 1685, 1595, 1505, 1295, 1160, 905, 845, 790 cm ; δ_H(90 MHz, $CDCl_3$) 0.18 (6H, s, $Si(Me)_2$), 0.96 (9H, s, $SiC(Me)_3$), 3.82 (3H, s, OMe), 6.86 - 6.97 (1H, m, Ar-H), 7.15 - 7.38 (2H, m, Ar-H), 9.92 (1H, s, -CHO); δ_c(90 MHz, $CDCl_3$) - 4.7 ($Si(CH_3)_2$), 18.3 ($Si\,C(CH_3)_3$), 25.4 ($SiC(CH_3)_3$), 55.2 (OCH_3), 110.4, 120.6, 126.6 (CH-Ar), 131.0 (C_1-Ar), 151.2, 151.5 (C_3, C_4-Ar), 190.4 (-CHO); m/z 251 (M^+-CH_3, 6), 209 ($M^+-C(CH_3)_3$, 100), 194 (100), 179 (13), 165 (8), 137 (5), 89 (6), 73 (17), 59 (15).

4-(tert-Butyldimethylsilyloxy)-3-methoxybenzaldehyde dimethyl acetal (36).

Aldehyde (35) (4.13 g, 15.5 mmol), trimethylorthoformate (6 ml) and one drop of conc. sulphuric acid were stirred overnight. The solution became a very deep red colour at the start of the reaction which disappeared as the reaction completed. Distillation (kugelrohr, oven temperature 118 - 125°C/1.0 mm Hg) gave the title compound (2.40 g, 7.99 mmol, 52%) as a colourless oil (Found; M^+, 312.1755. $C_{14}H_{22}O_3Si$ requires 312.1757); δ_H(90 MHz, $CDCl_3$) 0.15 (6H, s, $Si(Me)_2$), 1.00 (9H, s, $SiC(Me)_3$), 3.29 (6H, s, $-CH(\underline{OMe})_2$), 3.79 (3H, s, OMe), 5.30 (1H, s, $-\underline{CH}(OMe)_2$), 6.80 - 7.00 (3H, m, Ar-H); δ_c (90 MHz, $CDCl_3$) - 4.6 ($Si(CH_3)_2$), 18.5 ($Si\underline{C}(CH_3)_3$), 25.8 ($SiC(\underline{CH_3})$), 52.7 ($-CH(OCH_3)_2$), 55.5 ($-OCH_3$), 103.4 ($-CH(OCH_3)_2$), 110.4, 119.4, 120.4 (CH-Ar), 131.7 (C_1-Ar), 145.2, 150.9 (C_3, C_4-Ar); m/z 312 (M^+, 1), 281 (25), 255 (90), 209 (100), 194 (16), 167 (6).

4-Benzyloxy-3-methoxybenzaldehyde (37).

4-Hydroxy-3-methoxybenzaldehyde (20.0 g, 131 mmol) was dissolved in dry acetone (200 ml). Potassium carbonate (36.2 g, 262 mmol), potassium iodide (21.7 g, 1.0 eq) and benzyl bromide (22.4 g, 15.6 ml, 1.0 eq) were added and the mixture refluxed gently overnight under a nitrogen atmosphere. Water and chloroform were added and the solution was extracted with

chloroform. The organic layer was washed (brine) and dried ($MgSO_4$). Evaporation and recrystallisation (ethyl acetate /petrol) gave white crystals (29.1 g, 120 mmol, 92%); m.p 63.5°C (Lit[54] 63 - 64°C); ν_{max}^{KBr} 2840, 1670, 1580, 1260, 1135, 995, 815 cm ; δ_H(90 MHz, $CDCl_3$) 3.93 (3H, s, OMe), 5.24 (2H, s, $-CH_2O-$), 6.95 - 7.52 (8H, m, Ar-H), 9.86 (1H, s, -CHO).

4-Benzyloxy-3-methoxybenzaldehyde dimethyl acetal (38).

4-Benzyloxy-3-methoxybenzaldehyde (37) (4.50 g, 18.5 mmol) was dissolved in trimethylorthoformate (15 ml) and one drop of concentrated sulphuric acid was added as catalyst. The reaction quickly became a very deep purple colour and was stirred overnight, disappearance of the colour indicating completion of the reaction. Distillation gave the title compound (4.89 g, 16.96 mmol, 91%) as a white waxy solid; b.p 164°C/1.0 mm Hg; m.p. 53 - 54°C (Found; H, 7.2; C, 70.8%; M^+, 288.1345. $C_{17}H_{20}O_4$ requires H, 7.0; C, 70.8%; M^+, 288.1362); δ_H (90 MHz, $CDCl_3$) 3.33 (6H, s, $(OMe)_2$), 3.89 (3H, s, OMe), 5.16 (2H, s, $-OCH_2-$), 5.32 (1H, s, $-CH(OMe)_2$), 6.89 - 7.45 (8H, m, Ar-H); δ_c(80 MHz, $CDCl_3$) 52.8 ($-CH(O\underline{C}H_3)_2$), 56.1 ($ArOCH_3$), 71.2 (CH_2), 103.3 ($-\underline{C}H(OMe)_2$), 110.3, 113.8, 119.2 (CH-Ar), 127.3 127.8, 128.5 (CH-Ph), 131.5, 137.2 (C_1-Ar, C_1-Ph), 148.4, 149.7 (C_3, C_4-Ar); m/z 288 (M^+, 13), 257 (16), 166 (5), 151 (4), 113 (3), 91 (100), 65 (5).

α-chloro-(4-benzyloxy-3-methoxybenzyl) methyl ether (39).

Acetal (38) (4.11 g, 14.2 mmol) was dissolved in freshly distilled acetyl chloride (6.0 ml) under nitrogen and thionyl chloride (0.2 ml) was added as catalyst. Overnight stirring and evaporation of the acetyl chloride (oil pump) gave the title compound in an essentially quantitative yield as an air sensitive, pale violet coloured waxy solid, pure by ^{1}H NMR. δ_H (90 MHz, $CDCl_3$) 3.61 (3H, s, OMe), 3.89 (3H, s, OMe), 5.14 (2H, s, CH_2) 6.38 (1H, br s, -CH(Cl)OMe), 6.89 - 7.50 (8H, m, Ar-H).

Mixed acetal (40).

Lactone alcohol (15) (1.00 g, 4.23 mmol) was dissolved in dry dichloromethane (30 ml) at 0°C under nitrogen. Triethylamine (6 ml) was added and then the chloroether (39) (1.5 eq, 1.86 g, 6.3 mmol) in dichloromethane solution (3 ml). This was stirred for 20 minutes before dichloromethane (50 ml) was added and the solution was washed once with sodium bicarbonate solution. Chromatography on a short alumina column (ether/40 - 60 petrol, 2:1) gave the acetal (1.20 g, 2.40 mmol, 59%), a yellow oil as a mixture of diastereoisomers. (Found; M^+ 492.1781. $C_{28}H_{28}O_8$ requires M^+ 492.1784); δ_H(90 MHz, $CDCl_3$) 2.60 - 2.70 (3H, br m, 3-H_2, 4-H), 3.31 (3H, s, OCH(Ar)OCH_3), 3.50 - 3.55 (2H, m, -CH_2O-), 3.86 (3H, s, ArOCH_3), 5.13 (2H, s, OCH_2Ph), 5.15 - 5.28 (1H, m, 5-H), 5.42 (1H, 2 x s,

-OCH(Ar)OMe), 5.92 (2H, s, $-OCH_2O-$), 6.70 - 6.90 (6H, m, Ar-H), 7.25 - 7.48 (5H, m, Ph-H).

2-exo-(4-Benzyloxy-3-methoxyphenyl)-6-exo-(3,4-methylenedioxyphenyl)-8-oxo-3,7-dioxabicyclo[3,3,0]octane (41); (Benzyl Styraxin) and 2-endo-(4-Benzyloxy-3-methoxyphenyl)-6-exo-(3,4-methylenedioxyphenyl)-8-oxo-3,7-dioxabicyclo[3,3,0]octane (42); (Benzyl epi-styraxin).

Mixed acetal (40) (0.70 g, 1.42 mmol) was dissolved in dry ether/tetrahydrofuran (1:1, 40 ml) under nitrogen and cooled to 0°C. Triethylamine (0.45 ml, 0.33 g, 3.2 mmol, 2.3 eq) was added followed by trimethylsilyl trifluoromethanesulphonate (0.60 ml, 0.69 g, 3.1 mmol, 2.2 eq) and was stirred for two hours before quenching with water and extracting with ethyl acetate. The organic layer was washed (brine) and dried ($MgSO_4$). Chromatography on flash column silica (1:2, ethyl acetate/40 - 60 petrol) gave two identifiable compounds, benzyl styraxin (78 mg, 0.169 mmol, 12%) and benzyl epi-styraxin (145.4 mg, 0.316 mmol, 22%). Benzyl styraxin; m.p. 144°C (rhomboids, ethyl acetate/hexane) (Found: C, 70.2; H, 5.5%; M^+, 460.1503. $C_{27}H_{24}O_7$ requires C, 70.4; H, 5.25%; M^+, 460.1522), ν_{max}^{KBr} 2900, 1781, 1601, 1521, 1462, 1271, 1156, 1053, 948, 770 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 3.20 (1H, m, 5-H), 3.46 (1H, dd, J 3.8 and 9.2 Hz, 1-H) 3.90 (3H, s, $-OCH_3$), 4.02 (1H, dd, J 4.7 and 9.2 Hz, $4-H_A$), 4.32 (1H, dd, J 6.8 and 9.4 Hz, $4-H_E$), 5.12 (2H, s, OCH_2Ph), 5.29 (1H, d, J 3.8 Hz, 6-H)

5.34 (1H, d, J 3.7 Hz, 2-H), 5.97 (2H, s, $-OCH_2O-$) 6.74 - 6.93 (6H, m, Ar-H), 7.04 - 7.45 (5H, m, Ph-H); δ_c(80 MHz, $CDCl_3$) 49.9, 53.2 (CH-1, CH-5), 56.1 (OCH_3), 71.2 (OCH_2Ph), 72.7 (CH_2 -4), 83.3, 84.5 (CH-2, CH-6), 101.4 ($-OCH_2O-$), 105.8, 108.5, 109.4, 114.2, 117.4, 119.1 (CH-Ar) 127.3, 127.9, 128.5 (CH-Ph), 133.1, 133.6, 137.1 (C-Ar), 149, 148.0, 148.4, 150.0 (C_3', C_4', C_3'', C_4''-Ar), 176.7 (C=O); m/z 460 (11), 282 (8), 161 (5), 135 (9), 91 (100), 65 (4).

Benzyl epi-styraxin; m.p. 145°C (Found: C, 70.4; H, 5.4%; M^+, 460.1543. $C_{27}H_{24}O_7$ requires C, 70.4; H, 5.3%; M^+, 460.1522); ν_{max}^{KBr} 1770, 1603, 1494, 1447, 1259, 1168, 1038, 1000 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 3.19 (1H, m, 5-H), 3.53 (1H, pseudo-t, J 8.8 and 8.8 Hz, 1-H), 3.88 (1H, dd, J 4.7 and 9.6 Hz, 4-H), 3.89 (3H, s, OMe), 4.27 (1H, d, J 9.7 Hz, 4-H), 5.01 (1H, d, J 8.7 Hz, 2-H), 5.14 (2H, s, OCH_2Ph), 5.20 (1H, d, J 6.6 Hz, 6-H), 5.97 (2H, s, -OCH O-), 6.81 (3H, s, Ar-H), 6.89 - 6.91 (3H, m, Ar-H), 7.26 - 7.45 (5H, m, Ph-H); δ_c(90 MHz, $CDCl_3$) 51.3, 51.5 (CH-1, CH-5), 56.1 ($-OCH_3$), 71.1 (OCH_2Ph), 71.7 (CH_2 -4), 83.9, 85.5 (CH-5, CH-6), 104.4 ($-OCH_2O-$), 106.0, 108.5, 110.4, 114.0, 118.9, 119.4 (CH-Ar) 127.4, 127.8, 128.5 (CH-Ph), 129.2, 133.4, 137.3 (C-Ar), 148.1, 148.4, 149.8 (one peak hidden? C_3', C_4', C_3'', C_4''-Ar), 174.2 (C=O); m/z 460 (M^+, 32), 369 (5), 161 (21), 151 (17), 135 (40), 132 (10), 131 (10), 113 (22), 91 (99), 61 (18), 43 (100).

2-endo-(4-Hydroxy-3-methoxyphenyl)-6-endo-(3,4-methylenedioxyphenyl)-8-oxo-3,7-dioxabicyclo[3,3,0]octane (1c); ((±)styraxin).

Benzyl styraxin (20.0 mg, 4.34 x 10^{-5} mmol) was dissolved in ethyl acetate (10 ml) and hydrogenated over 10% palladium on carbon catalyst (2 mg) until TLC showed that no starting material was present. Filtration (kieselguhr) and evaporation gave the title compound (15.9 mg, 4.29 x 10^{-5} mol, 98%) as a colourless gum. Recrystallisation from chloroform/hexane and then ethanol gave white crystals, identical by ^{1}H NMR to a natural sample. m.p. 108°C (Found: C, 64.5; H 5.3%; M^{+} 370.1053. $C_{20}H_{18}O_{7}$ requires C, 64.9; H, 4.9%; M^{+} 370.1053), ν_{max}^{KBr} 3500, 1750, 1605, 1510, 1490, 1440, 1380, 1040, 940 cm^{-1} ; δ_{H}(400 MHz, $CDCl_3$) 3.22 (1H, m, 5-H), 3.48 (1H, dd, J 3.8 and 9.2 Hz, 1-H), 3.91 (3H, s, OMe), 4.03 (1H, dd, J 4.6 and 9.5 Hz, 4-H), 4.34 (1H, dd, J 6.8 and 9.5 Hz, 4-H), 5.31 (1H, d, J 3.7 Hz, 6-H) 5.35 (1H, d, J 3.5 Hz, 2-H), 5.64 (1H, br s, ArOH) 5.99 (2H, s, $-OCH_2O-$), 6.76 - 6.92 (6H, m, Ar-H), δ_{c}(400 MHz, $CDCl_3$) 49.9, 53.2 (CH-1, CH-5), 56.0 (OCH_3), 72.7 ($-CH_2O-$), 83.4, 84.7 (CH-2, CH-6) 101.5 ($-OCH_2O-$) 105.7, 108.1, 108.5, 114.4, 118.0, 119.0 (CH-Ar), 132.2, 133.1 (C_1', C_1''-Ar), 145.3, 146.7, 148.0, 148.4 (C_3', C_4', C_3'', C_4''-Ar), 176.9 (C=O), m/z 370 (100), 285 (8), 257 (11) 191 (5), 161 (53), 151 (74), 149 (35), 137 (15), 135 (33), 131 (55), 115 (6), 103 (8).

2-exo-(4-Hydroxy-3-methoxyphenyl)-6-endo-(3,4-methylenedioxyphenyl)-8-oxo-3,7-dioxabicyclo[3,3,0]octane (43).

(2-epi-styraxin).

Benzyl-2-epi-styraxin (65.9 mg, 0.143 mmol) was dissolved in ethyl acetate (10 ml) and hydrogenated using a 10% palladium /carbon catalyst until TLC showed no starting material was present. Filtration (kieselguhr) and evaporation gave the title compound (50.6 mg, 0.137 mmol, 96%) as a white crystalline solid; m.p. 165 - 166°C (EtoAc/hexane) (Found: C, 64.7; H, 5.1%; M^+, 370.1056. $C_{20}H_{18}O_7$ requires, C, 64.9; H, 4.9%; M^+, 370.1047); ν_{max}^{KBr} 3462, 2875, 1778, 1502, 1445, 1367, 1240, 1130, 930, 802, 798 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 3.21 (1H, m, 5-H), 3.54 (1H, pseudo t, J 8.8 and 8.8 Hz, 1-H), 3.89 (3H, s, OMe), 3,90 (1H, dd, J 9.7 and 4.7 H , 4-H_E), 4.29 (1H, d, J 9.7 Hz, 4-H_A), 5.02 (1H, d, J 8.7 Hz, 2-H), 5.21 (1H, d, J 6.6 Hz, 6-H), 5.67 (1H, br s, -OH) 5.99 (2H, s, -OCH_2O-), 6.82 - 6.95 (6H, m, Ar-H); δ_c(80 MHz, $CDCl_3$) 51.2, 51.6 (CH-1, CH-5), 56.0 (-OCH_3), 71.7 (CH_2-4), 84.0, 85.6 (CH-2, CH-6), 101.4 (-OCH_2O-), 106.0, 108.5, 109.0, 114.5, 119.4, 119.6 (CH-Ar), 127.9, 133.4 (C_1', C_1'',-Ar), 145.8, 146.7, 148.1, 148.4 (C_3', C_4', C_3'', C_4''-Ar), 174.3 (C=O); m/z 370 (M^+, 100), 257 (24), 173 (14), 161 (53), 151 (73), 149 (44), 135 (36), 131 (54), 103 (17), 68 (14).

2-exo-(4-Benzyloxy-3-methoxyphenyl)-6-endo-(3,4-methylenedioxy phenyl)-3,7-dioxabicyclo[3,3,0]octane (44)

(Benzyl pluviatilol).

Benzyl-2-epi-styraxin (55.5 mg, 0.121 mmol) was dissolved in dry tetrahydrofuran (5 ml) and lithium aluminium hydride (50 mg) was added. The reaction was refluxed for two hours and cooled to 0°C. Methanol/tetrahydrofuran was added dropwise to destroy excess reagent and then 2M hydrochloric acid was added to dissolve inorganics. The solution was extracted with ethyl acetate, washed (hydrochloric acid and brine) and dried ($MgSO_4$). Preparative thin layer chromatography (Silica, ethyl acetate/petrol 1:3) gave the title compound (25.1 mg, 0.0562 mmol, 46%) as a pale yellow oil which refused to recrystallise. (Found: M^+, 446.1710. $C_{27}H_{26}O_6$ requires M^+, 446.1729); δ_H(400 MHz, $CDCl_3$) 2.87 (1H, m, 5-H), 3.26 - 3.33 (2H, m, 8-H_A, 1-H), 3.81 - 3.85 (2H, m, 8-H_E, 4-H_A), 3.91 (3H, s, OMe), 4.10 (1H, d, J 9.0 Hz, 4-H_E), 4.41 (1H, d, J 7.1 Hz, 6-H), 4.84 (1H, d, J 5.2 Hz, 2-H), 5.14 (2H, s, $-OCH_2Ph$), 5.94 (2H, s, $-OCH_2O-$), 6.76 - 6.98 (6H, m, Ar-H), 7.25 (5H, m, Ph-H), δ_c (90 MHz, $CHCl_3$), 50.2, 54.7 (CH-1, CH-5), 56.1 ($-OCH_3$) 69.8, 71.3 (CH_2 -4, CH -8), 71.1 ($-OCH_2Ph$), 82.1 (CH-6), 87.7 (CH-2), 101.0 (-OCH O-), 106.6, 108.1, 109.8, 114.4, 117.8, 119.5 (CH-Ar), 127.4, 127.8, 128.5 (CH-Ph), 131.8, 135.3, 137.3 (C-Ar), 147.2, 147.3, 148.0, 149.8 (C_3', C_4', C_3'', C_4''-Ar); ν_{max}^{KBr} 1589, 1443, 1080, 1040, 930 cm^{-1}; m/z, 446 (M^+, 14%) 203 (5), 161 (5), 149 (14) 135 (30), 113 (6), 91 (100).

2-exo-(4-Hydroxy-3-methoxyphenyl)-6-endo-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3,3,0]octane (45). (Pluviatilol).

Benzyl pluviatilol (20.8 mg, 0.0466 mmol) was dissolved in ethyl acetate (5 ml) and hydrogenated using a 10% palladium /carbon catalyst until TLC showed that no starting material was present. Filtration (kieselguhr) and evaporation gave the title compound (13.5 mg, 0.0379 mmol, 81%). m.p. 142 - 145°C (ethyl acetate, hexane) (Found: M^+, 356.1273. $C_{20}H_{20}O_6$ requires 356.1260); ν_{max}^{KBr} 3470, 1235, 1070, 1030, cm^{-1}; δ_H (400 MHz, $CDCl_3$), 2.88 (1H, m, 5-H), 3.30 - 3.34 (2H, m, 8-H_A, 1-H), 3.80 - 3.86 (2H, m, 8-H_E, 4-H_A), 3.91 (3H, s, -OMe), 4.10 (1H, d, J 9.4 Hz, 4-H_E), 4.42 (1H, d, J 7.0 Hz, 6-H), 4.85 (1H, d, J 5.3 Hz, 2-H), 5.62 (1H, br s, -OH), 5.95 (2H, s, $-OCH_2O-$) 6.73 - 6.94 (6H, m, Ar-H); δ_c(400 MHz, $CDCl_3$) 50.3 (CH-1), 54.8 (CH-5), 56.2 (OCH_3), 69.9 (CH_2-8), 71.2 (CH_2 -4), 82.3 (CH-2), 87.9 (CH-6), 101.2 ($-OCH_2O-$), 106.7 108.3, 108.6, 114.4, 118.6, 119.7 (CH-Ar), 130.5, 135.4 (C_1', C_1'', -Ar), 144.8, 146.8, 147.4, 148.1 (C_3', C_4', C_3'', C_4''-Ar); m/z 356 (M^+, 100), 203 (20), 178 (13), 163 (23), 161 (27), 151 (59) 150 (26) 149 (89), 135 (46), 131 (32).

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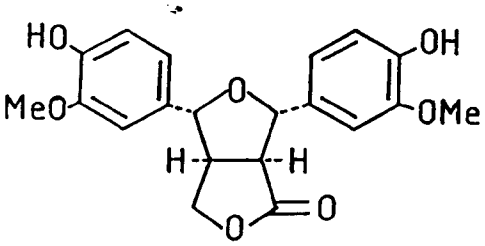
Chapter 3



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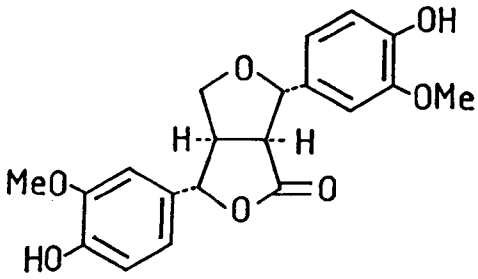

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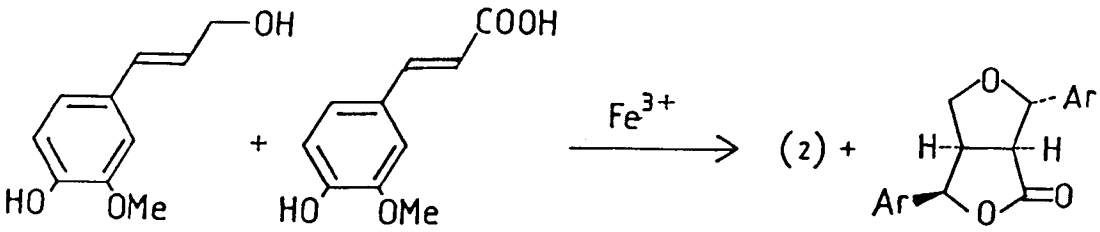

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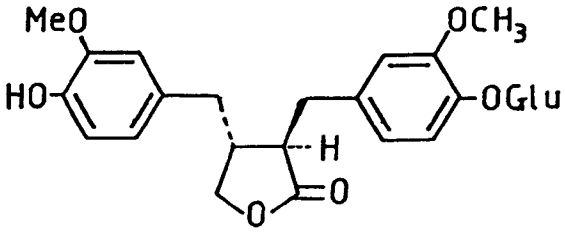
SCHEME 1

The Synthesis of MEL, a Germination Inhibiting Lignan Lactone.

In 1970, Datta, Evenari and Gutterman[1] described an unusual feature of the monocotyledenous plant Aegilops ovata, a possible ancestor of modern cultivated wheat. The grains of this plant were shown to inhibit the germination of lettuce achenes much more in light than in darkness. This unique property led to the isolation of a new lignan[2] reported to be a monoepoxylignanolide (MEL) which was assigned a 2,4-diaryl structure (1). The structure was later reassigned[3] a 2,6-diaryl structure (2) on the basis of arguments presented in the last chapter (page 18) and also by the synthesis of 2,4 and 2,6-diaryl structures (see Chapter 1).

The biological properties of this compound have been studied extensively[4] and the isolation of an "isomeric photoproduct" has been reported as the result of shining "incandescent light" on the isolated lignan. It would appear from the published information that to inhibit the germination of lettuce seedlings efficiently both MEL and its photoproduct are necessary. In this paper[4] however, no spectroscopic data was presented and it is impossible to draw any conclusions about the identity of the photoproduct.

In a later paper[5] from the same laboratories, MEL was synthesised using Fe^{3+} mediated oxidative coupling of coniferyl alcohol (3) and ferulic acid (4) (scheme 1) in very low yields (~7%) along



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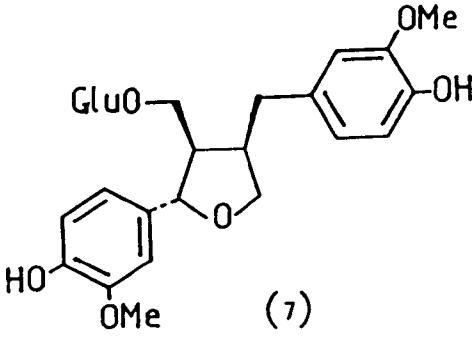


(7)

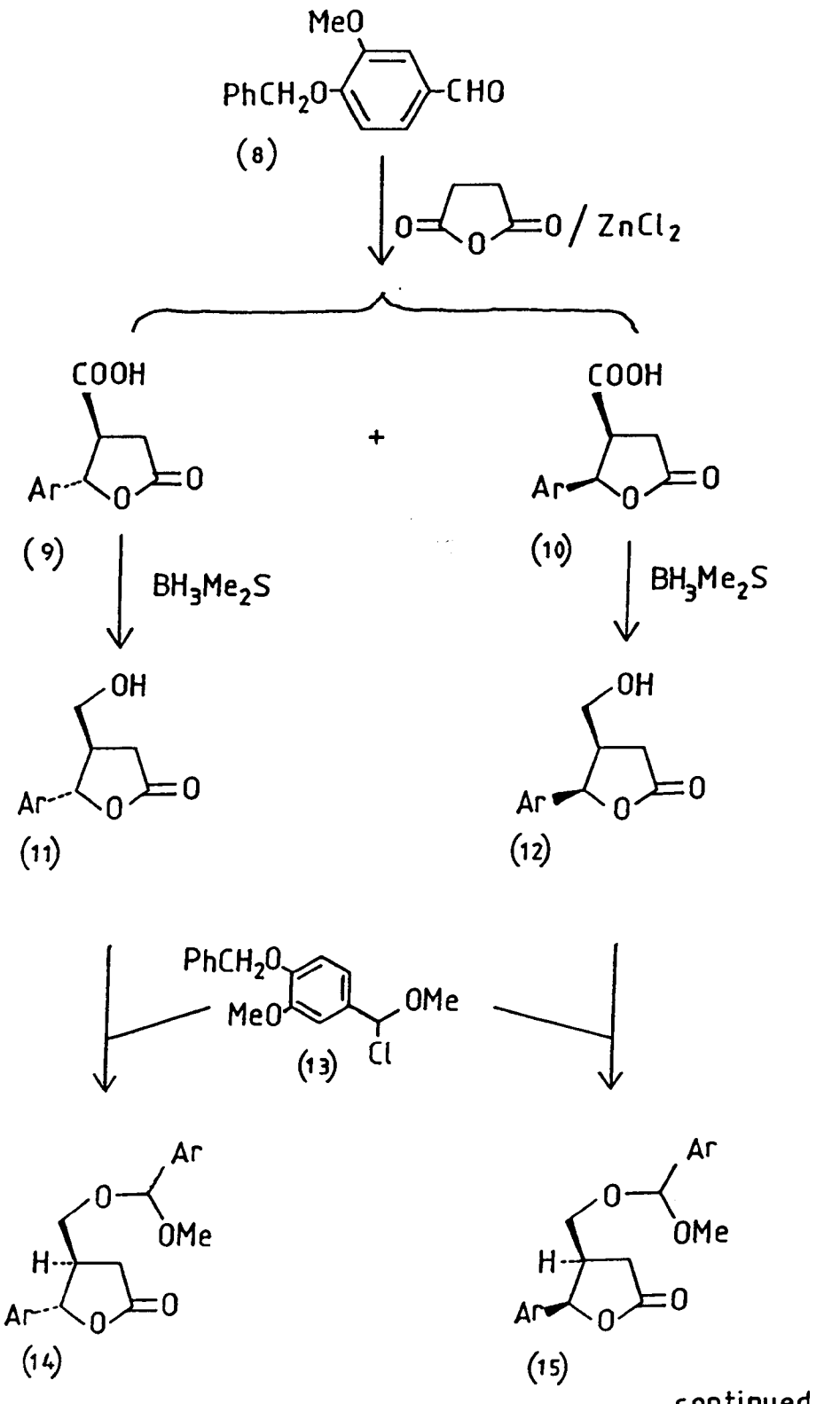
with a host of other coupling products.

One of these was given the name iso-MEL(5) and has a bicyclic structure with one lactone function. There are two aromatic groups in the 2-exo and 6-endo positions. Surprisingly, no reference whatsoever is made in this paper to the earlier published "isomeric photoproduct" and we have no way of knowing if iso-MEL is the photoproduct or not. To the authors' knowledge, there has been no clarification of this point in later literature to the end of 1987.

Other Lignans[6] (6) and [7](7) have been identified as germination inhibitors however neither of these has been shown to be more active in the light than the dark as is the case for MEL.

Given the biological activity of MEL, its interesting and as yet unsolved photochemisty and the synthetic methodology developed for styraxin and aptosimon, we decided that its synthesis would be a worthwhile investigation. If we could isolate and identify the photoproduct from MEL, it would be interesting to compare this with a sample of iso-MEL which might also be prepared using similar chemistry. The chemistry that was envisaged is shown in scheme 2.

Benzyl vanillin (8) reacted as expected with succinic anhydride in the presence of zinc chloride and triethylamine to produce a trans/cis mixture of the 4-aryl paraconic acids (9) and (10) in a



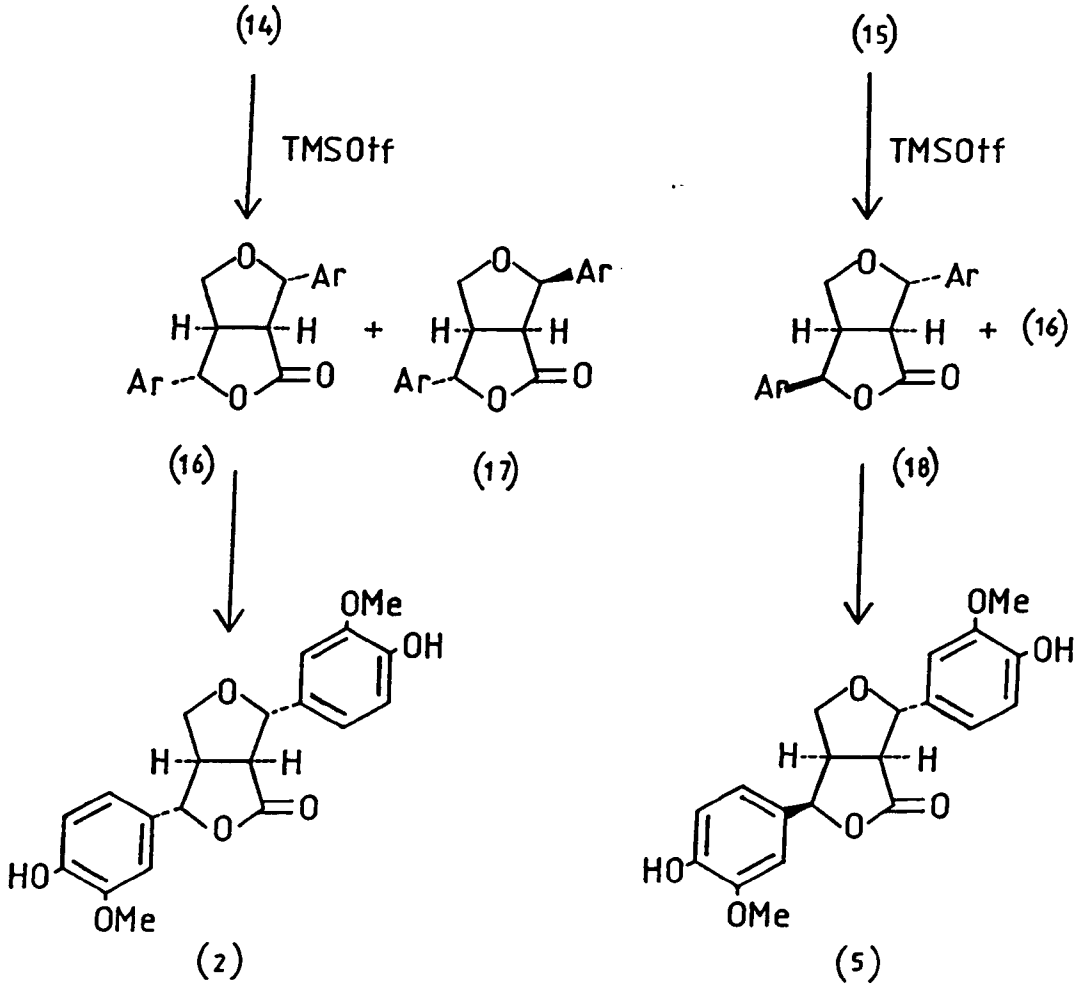
continued

SCHEME 2a

3:2 ratio. The overall yield was 57%. These were reduced using borane/methyl sulphide complex in THF to the corresponding alcohols (11) and (12) in 85% (trans) and 83% (cis) yields as usual.

Taking the trans-alcohol first, this reacted with the α-chloro ether (13) in the presence of triethylamine to produce the mixed acetal (14). Although by TLC examination it was evident that the acetal had been formed in very high yield, chromatographic isolation of this product (alumina, ether/40-60 petrol gradient) gave a somewhat disappointing yield of 34%. Treatment of this acetal with trimethylsilyl trifluoromethanesulphonate and triethylamine gave the 2-exo-6-exo-bisaryl bicyclic lignan type compound (16) in 21% yield and also the corresponding 2-endo-6-exo-isomer (17) in 2% yield after extensive chromatography. It is interesting to note that the natural isomer is the major one isolated in this reaction. As usual, many minor, unidentified by-products were formed in this reaction. The two major compounds could be readily identified by comparing ^{1}H NMR shifts and coupling constants with those for aptosimon and styraxin.

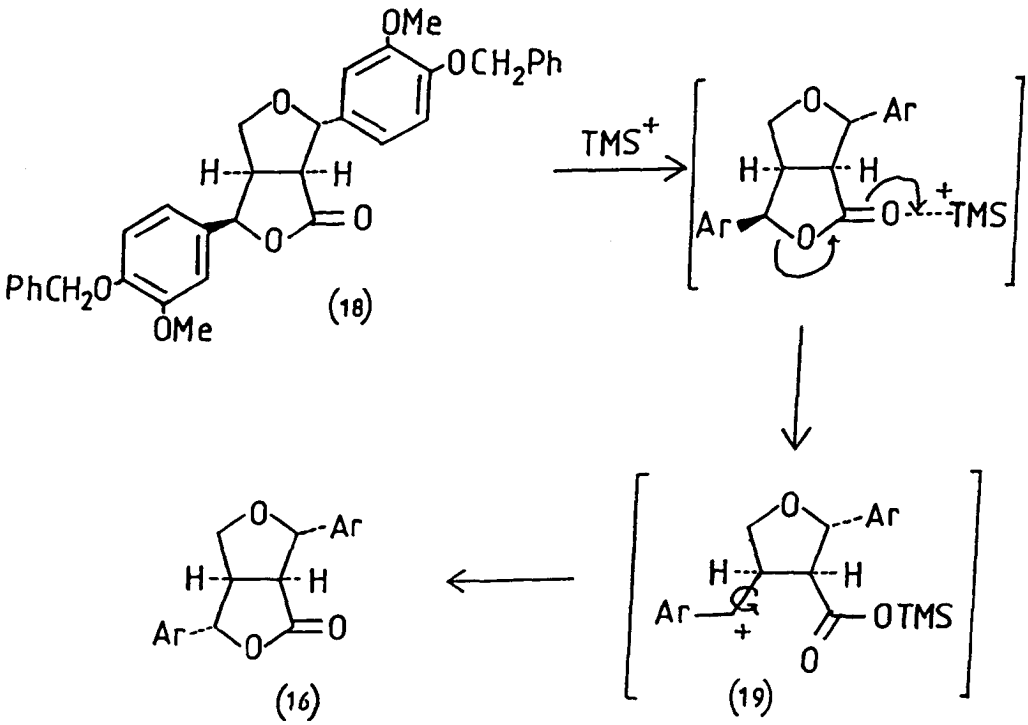
Removal of the benzyl protecting groups from the 2-exo-6-exo isomer (16) using catalytic hydrogenolysis gave a compound that could be identified unambiguously as (±) MEL (2) from its spectroscopic data. The compound however did not recrystallise readily and as such it was not possible to compare melting points with reported literature preparations of (±) MEL made by another



SCHEME 2b

route[4].

The cis-isomer of the lactone alcohol (12) also gave a mixed acetal (15) when reacted with α-chloroether (13) in 42% isolated yield. This in turn cyclised using trimethylsilyl trifluoromethanesulphonate to give two major products. These were identified as the 2-exo-6-endo bicyclic isomer (18) and also the 2-exo-6-exo isomer (16) in 8% and 12% isolated yields respectively. The 2-exo-6-exo isomer from this reaction was initially unexpected but can be explained by the action of the Lewis acid (scheme 3) on the lactone. Here, a planar, benzylic carbocation (19) can be postulated which could recyclise to the more favoured configuration.



SCHEME 3

The 2-exo-6-endo isomer was debenzylated as usual to give a compound which could be recognised as iso-MEL (5) reported by Lavie et al.

A serious problem encountered in this work was the low yields of mixed acetals (14) and (15) that were actually isolated and the subsequent low yields and complex reaction products formed on the cyclisation. In an attempt to overcome losses of mixed acetal during chromotography it was decided to form the acetal and add Lewis acid in a "one pot" process. In THF solution at 0°C, TLC showed that acetal (14) formation was essentially complete after 30 minutes in the presence of excess triethylamine. Addition of trimethylsilyl trifluoromethanesulphonate gave after reaction, work-up and extensive chromatography, the required bicyclic compound (16) in 25% yield based on starting alcohol. The usual complex mixture of products was formed but overall higher yields compensated for this. However, even after extensive column chromatography, brown glasses rather than white crystalline products were formed.

The aim of this work was primarily to study the photochemistry of MEL. A sample of this compound when dissolved in tert- butanol and irradiated with 50 W white light for 20 hours bulb showed no detectable changes by TLC or ^{1}H NMR at 400 MHz. A 100 W bulb with weak UV character on overnight irradiation gave complete decomposition of the starting material producing no detectable iso-MEL whatsoever.

Unfortunately, lack of time prevented further experiments and the research was stopped. Clearly though, there is much more interesting work in this system which is obviously worthy of investigation by future research workers.

Experimental section.

5-(4-Benzyloxy-3-methoxyphenyl)-4-carboxy-dihydro-2(3H) furanone. (trans and cis isomers, (9) and (10)).

Powdered zinc chloride (22.5g, 165mmol) was dried in situ using freshly distilled thionyl chloride. Excess thionyl chloride was removed in vacuo to leave a free flowing white solid. To this solid under nitrogen, was added dry dichloromethane (160ml), succinic anhydride (12.39g, 123.8mmol), and 4-benzyloxy-3-methoxy benzaldehyde. Triethylamine (23.1ml, 16.7g, 165mmol) was added dropwise through a rubber septum using a syringe over half an hour and the resulting solution was stirred overnight. Ethyl acetate (160ml) and 2M hydrochloric acid (160ml) were added, shaken, and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate. The combined organic extracts were washed with hydrochloric acid and brine, and were extracted with saturated sodium bicarbonate solution (3 x 100ml). The combined aqueous extracts were washed with chloroform until no more colour dissolved in the organic layer. Acidification (conc. hydrochloric acid) of the aqueous layer gave the title compound (16.2g, 47.3mmol, 57%; cis:trans(2:3) by ^{1}H NMR) as a mixture of isomers. The isomers could be separated by trituration with ether followed by recrystallisation from ethyl acetate and then aqueous methanol to give analytical samples of the acids as pure white crystalline solids.

trans-Isomer (9) m.p. 125°C (Found: C, 66.4; H, 5.5%; M^+ 342.1109. $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3%; M^+ 342.1103); ν_{max}^{KBr} 3450 (br), 3080 (br), 1760, 1600, 1520, 1465, 1435, 1395, 1275, 1240, 1160, 1045, 970, 825, 675 cm^{-1}; δ_H(400 MHz, CD_3COCD_3) 2.96 (2H, d, J 9.3 Hz, 3-H_2), 3.59 (1H, m, 4-H) 3.84 (3H, s, OMe); 5.13 (2H, s, -OCH_2Ph), 5.57 (1H, d, J 7.7 Hz, 5-H), 6.96-7.14 (3H, m, Ar-H), 7.30-7.50 (5H, m, Ph-H); δ_C(400 MHz, CD_3COCD_3) 33.1 (CH_2-3), 44.8 (CH-4), 56.3 (-OCH_3), 71.3 (-OCH_2Ph), 83.3 (CH-5), 111.2, 114.5, 119.2 (CH-Ar), 128.5, 128.6, 129.2 (CH-Ph), 132.5, 138.4 (C_1'-Ar, C_1''-Ph), 149.8, 151.0 (C_3', C_4'-Ar), 172.6, 174.8 (C=O, COOH); m/z 342 (M^+, 1), 298 (17), 207 (25), 113 (6), 91 (100), 65 (9).

cis-Isomer (10) m.p. 171-2°C (Found: C, 66.6; H, 5.3%; M^+, 342.1116. $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3%; M^+, 342.1103); ν_{max}^{KBr} 2800-3200, 1740, 1710, 1540, 1430, 1340, 1265, 1230, 1200, 1150, 1015, 875, 765, 685 cm^{-1}; δ_H(250 MHz, CD_3COCD_3) 2.91 (2H, d, J 6.4 Hz, 3-H), 3.79 (3H, s, OMe), 3.80 (1H, m, 4-H), 5.09 (2H, s, OCH_2Ph), 5.81 (1H, d, J 7.4Hz, 5-H), 6.87-7.03 (3H, m, Ar-H), 7.32-7.51 (5H, m, Ph-H), δ_C(250 MHz, CD_3COCD_3) 33.3 (CH_2 -3), 47.8 (CH-4), 56.5 (OCH_3), 71.7 (-OCH_2Ph), 82.2 (CH-5), 111.6, 114.9, 119.7 (CH-Ar), 128.2, 129.0, 129.6 (CH-Ph), 130.5, 138.8 (C_1', C_1''-Ar, Ph), 149.9 150.9 (C_3', C_4'-Ar), 172.5, 176.2 (C=O, COOH), m/z 342 (M^+, 16), 298 (39), 207 (50), 165 (7), 131 (7), 103 (7), 91 (100), 77 (7), 65 (25).

trans-5-(4-Benzyloxy-3-methoxyphenyl)-4-hydroxy methyl dihydro-2(3H)furanone (11).

Acid (9) (5.00g, 14.6mmol) was dissolved in dry THF (100ml) under a nitrogen atmosphere and the solution was cooled to 0°C using an ice bath. A solution in tetrahydrofuran of borane-methyl sulphide (11.0ml of a 2M solution, 22mmol, 1.5eq) was added dropwise and the reaction was stirred overnight, the ice bath being allowed to warm to room temperature. Methanol was added dropwise to destroy excess borane and the solution was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer was separated, dried ($MgSO_4$) and evaporated to give the title compound (4.10g, 13.5mmol, 85%) as a colourless gum. This was recrystallised from ethyl acetate/hexane to give a white crystalline solid. m.p. 113°C (Found: C, 69.45; H, 6.2%, M^+, 328.1301. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%; M^+, 328.1311); ν_{max}^{KBr} 3530, 3100-3030, 2990-2900, 1775, 1600, 1515, 1405, 1270, 1230, 1170, 1020, 820, 760, 720; δ_H (400MHz, $CDCl_3$) 2.54-2.70 (4H, m, 3-H_2, 4-H, -OH), 3.64-3.69 (2H, m, -CH_2OH), 3.86 (3H, s, -OCH_3), 5.12 (2H, s, OCH_2Ph), 5.27 (1H, d, J, 6.4 Hz, 5-H), 6.77-6.86 (3H, m, Ar-H), 7.26-7.42 (5H, m, Ph-H); δ_C(400MHz, $CDCl_3$) 31.5 (CH_2-3), 46.0 (CH-4), 56.1 (-OCH_3), 61.2 (-CH_2OH), 71.0 (CH_2Ph), 83.1 (CH-5), 109.4, 113.7, 118.4 (CH-Ar), 127.3, 128.0, 128.6 (CH-Ph), 131.4, 136.8 (C_1'-Ar, C_1''-Ph), 148.4, 149.9 (C_3', C_4'-Ar), 176.7 (C=O); m/z, 328 (M^+, 8), 113 (4), 91 (100), 65 (5), 43 (7).

cis-5-(4-Benzyloxy-3-methoxyphenyl)-4-hydroxymethyl dihydro-2(3H) furanone (12).

Acid (10) (4.38g, 12.8mmol) was dissolved in dry THF (100ml) under a nitrogen atmosphere and the solution was cooled to 0°C. A solution in tetrahydrofuran of borane-methylsulphide complex (9.6ml of a 2M solution, 19.2mmol, 1.5eq) was added dropwise and the reaction was stirred overnight whilst being allowed to warm slowly to room temperature. Methanol was added dropwise to destroy excess reagent and the solution was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with sodium bicarbonate solution and brine.

The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (3.47g, 10.6mmol, 83%) as an oil which solidified on stirring with a small quantity of ether. Recrystallisation (chloroform/hexane) gave an analytical sample. m.p 97-8°C (Found: C, 69.6; H, 6.2%; M^+, 328.1310. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%; M^+, 328.1311); ν_{max}^{KBr} 3450, 3100-2880, 1730, 1510, 1380, 1260, 1200, 1140, 1010, 750, 710 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 1.83 (1H, br s, -OH) 2.57-2.90 (3H, m, 3-H_2, 4-H), 3.29 (2H, m, $-CH_2OH$), 5.12 (2H, s, $-OCH_2Ph$), 5.60 (1H, d, J 6.5 Hz, 5-H), 6.72-6.89 (3H, m, Ar-H), 7.27-7.44 (5H, m, Ph-H); δ_c(250 MHz, $CDCl_3$), 32.2 (CH_2-3), 42.1 (CH-4), 56.2 ($-OCH_3$), 61.3 ($-CH_2OH$), 71.3 (-OCH2Ph), 82.5 (CH-5), 109.5, 114.4, 117.9 (CH-Ar), 127.4, 128.0, 128.6 (CH-Ph), 128.8, 136.9 (C_1', C_1''-Ph, Ar), 148.3, 150.1 (C_3', C_4'-Ar), 176.5 (C=O); m/z 328 (M^+, 25), 243 (7), 123 (3), 113

(2), 91 (100), 65 (18), 55 (5).

Mixed Acetal (14)

Alcohol (11) (1.70g, 5.18mmol) was dissolved in dry dichloromethane (25ml) under a nitrogen atmosphere and was cooled to 0°C. Triethylamine (3.6ml, 2.6g, 5eq) was added followed by a solution in dichloromethane (5ml) of α-chloro ether (13) (2.27g, 7.75mmol, 1.5eq) and the resulting solution was stirred for 15 minutes. The solution was washed once with sodium bicarbonate solution and then dried ($MgSO_4$). Evaporation and rapid chromatography (alumina, ether/petrol 1:1 ----> ether gradient, trace of triethylamine) gave the acetal (1.04g, 1.78mmol, 34%) as a pale yellow oil identified by its ^1H NMR. δ_H(90 MHz, $CDCl_3$) 2.64-2.73 (3H, m, 3-H , 4-H), 3.33 (3H, s, $-CH(OCH_3)$ Ar), 3.52 -3.63 (2H, m, $-CH_2O-$), 3.87 (3H, s, $-OCH_3$), 3.90 (3H, s, $-OCH_3$), 5.19 (4H, s, $-OCH_2Ph$ x 2), 5.27-5.37 (1H, m, 5-H), 5.47 (1H, s, -OCH(OMe)Ar), 6.81-7.07 (6H, m, Ar-H), 7.35-7.55 (5H, m, Ph-H).

2-exo-6-exo-Bis(4-benzyloxy-3-methoxyphenyl)-8-oxo-3,7-dioxa bicyclo [3, 3, 0] octane (16) and 2-endo-6-exo-Bis(4-benzyloxy-3-methoxyphenyl)-8-oxo-3,7-dioxabicyclo[3, 3, 0]octane (17).

Mixed acetal (14) (1.04g, 1.78mmol) was dissolved in dry THF (20ml) under a nitrogen atmosphere and cooled to 0°C. Triethylamine (0.57ml, 0.41g, 4.10mmol, 2.3eq) was added followed by trimethylsilyltrifluoromethanesulphonate (0.87g, 0.76ml, 3.91mmol, 2.2eq) and the solution was stirred for three hours. Water was added to quench and the mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), concentrated and the residue was chromatographed (silica, ethyl acetate/hexane gradient) to give the 2-exo-6-exo-bis-aryl isomer (210mg, 0.380mmol, 21%) and the 2-endo-6-exo-bis-aryl isomer (17mg, 0.03mmol, 2%).

2-exo-6-exo-isomer gave; m.p. 90-91°C (Found: M^+, 552.2150. $C_{34}H_{32}O_7$ requires M^+, 552.2148); ν_{max}^{KBr} 2940, 1780, 1590, 1520, 1270, 1235, 1050, 755 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 3.24 (1H, m, 5-H), 3.45 (1H, dd, J 9.3, 3.8 Hz, 1-H), 3.89, 3.90 (2 x 3H, 2 x s, $-OCH_3$ x 2), 4.02 (1H, dd, J 9.4, 4.6 Hz, 4-H_A), 4.32 (1H, dd, J 9.3, 6.8 Hz, 4-H_E), 5.15 (4H, s, 2 x $-OCH_2Ph$), 5.32 (1H, d, J 3.3 Hz, 6-H), 5.34 (1H, d, J 3.5 Hz, 2-H), 6.74-6.93 (6H, m, Ar-H), 7.25-7.43 (10H, m, Ph-H); δ_C(400 MHz, $CDCl_3$) 49.8, 53.1 (CH-1, -5), 56.05, 56.12 ($-OCH_3$ x 2), 71.0 (-OCH Ph, x 2?), 72.7 (CH_2-4), 83.2, 84.4 (CH-2, CH-6), 108.9, 109.1, 113.88, 113.90, 117.3, 117.6 (CH-Ar), 127.2, 127.3, 127.8, 127.9, 128.53, 128.57

(CH-Ph), 132.1, 133.1, 136.7, 137.0 (C-Ar, Ph), 147.7, 148.4, 149.8, 150.0 (C_3', C_4', C_4'', C'' -Ar) 176.9 (C=O); m/z 552 (M^+, 2), 462 (3), 151 (9), 144 (3), 137 (5), 114 (4), 91 (100), 65 (8).

2-endo-6-exo-<u>isomer</u> gave; m.p. 194°C (Found: C, 73.8; H, 5.9%; M^+ 552.2150. $C_{34}H_{32}O_7$ requires C, 73.9; H, 5.8%; M^+ 552.2148), ν_{max}^{KBr} 2950, 2900, 1780, 1605, 1520, 1265, 1235, 1180, 1140, 1030, 1000, 750 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 3.24 (1H, m, 5-H), 3.55 (1H, t, J 8.9 Hz, 1-H), 3.90 (1H, dd, J 9.5, 4.8 Hz, 4-H_4) 3.897, 3.903 (3H x 2, 2 x s, -OCH_3 x 2), 4.29 (1H, d, J 9.7 Hz, 4-H_A), 5.02 (1H, d, J 8.7 Hz, 2-H), 5.14, 5.17 (2H x 2, 2 x s, -OCH_2Ph x 2), 5.23 (1H, d, J 6.7 Hz, 6-H), 6.80-6.92 (6H, m, Ar-H), 7.25-7.44 (10H, m, Ph-H); δ_c(400 MHz, $CDCl_3$) 51.2, 51.6 (CH-1, CH-5), 56.0, 56.2 (-OCH_3 x 2), 70.9, 71.0 (-OCH_2Ph x 2), 71.6 (CH_2 -4), 83.9, 85.5 (CH-2, CH-6), 109.0, 110.0, 113.6, 113.9, 118.1, 118.9 (CH-Ar), 127.2, 127.3, 127.8, 128.0, 128.5, 128.6 (CH-Ph), 129.0, 132.3 (C_1', C_1''-Ar), 136.8, 137.1 (C-Ph), 148.3, 148.5, 149.6, 150.1 (C_3', C_4', C_3'', C_4''-Ar), 174.5 (C=O); m/z 552 (M^+, 4), 462 (5), 207 (6), 151 (14), 145 (5), 137 (5), 113 (22), 107 (3) 91 (100), 83 (9), 65 (8).

2-exo-6-exo-<u>Bis(4-benzyloxy-3-methoxyphenyl)-8-oxo-3,7-dioxa bicyclo[3, 3, 0]octane (16).</u>

<u>trans</u> - Lactone alcohol (11) (1.00g, 3.05mmol) was dissolved in dry THF (30ml) and cooled to 0°C under a nitrogen atmosphere. Triethylamine (6eq, 18.3mmol, 1.85g, 2.55ml) was added followed

by α-chloro ether (13) (1.1eq, 0.96g) in THF (2ml). The resulting solution was stirred for 30 minutes and TLC showed that no starting alcohol was present. Trimethylsilyl trifluoromethanesulphonate (2.03g, 1.77ml, 9.15mmol, 3.0eq) was added dropwise and the solution was stirred at 0°C for two hours. Usual work-up and chromatography gave the title compound (0.42g, 0.76mmol, 25%) as a brown glass which recrystallised with difficulty from ethyl acetate/hexane. This gave identical spectral and physical data to the compound synthesised previously.

2-exo-6-exo-Bis(4-hydroxy-3-methoxyphenyl)-8-oxo-3,7-dioxa bicyclo[3, 3, 0]octane (2).

Dibenzyl MEL (16) (67.2mg, 0.122mmol) was dissolved in ethyl acetate (10ml) and was hydrogenated over a 10% palladium on carbon catalyst (~10 hours) until TLC showed that both benzyl groups had been cleaved. The catalyst was removed by filtration through kieselguhr and the solvent was evaporated. The residue was chromatographed (flash silica, ether/40-60 petrol 1:1 ----> ether gradient) to give the title compound (35.5mg, 0.095mmol, 78%) as a semi crystalline solid. (Found M^+, 372.1203 $C_{20}H_{20}O_7$ requires M^+ 372.1209); ν_{max}^{KBr} 3400 (br), 1750, 1610, 1505, 1450, 1420, 1270, 1120, 1020 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 3.25 (1H, m, 5-H), 3.48 (1H, dd, J 9.0, 3.9Hz, H-5), 3.88 (6H, s, $-OCH_3$ x 2), 4.04 (1H, dd, J 9.5, 4.5 Hz, 4-H), 4.33 (1H, dd, J 9.4, 6.8 Hz,

4-H), 5.33 (1H, d, J 4 H ,6-H), 5.35 (1H, d, J 3.7 Hz, 2-H), 5.60-5.80 (2H, br s, -OH x 2), 6.77-6.92 (6H, m, Ar-H); δ_C(400 MHz, $CDCl_3$,) 49.9, 53.3 (CH-1, CH-5), 56.02, 56.06 ($-OCH_3$ x 2), 72.7 (CH_2-4), 83.4 , 84.7 (CH-2, 6), 107.9, 108.2, 114.5, 114.8, 118.0, 118.4 (CH-Ar), 131.1, 132.3 (C_1', C_1''-Ar), 145.3, 146.1 146.8, 147.0 (C_3', C_4', C_3'', C_4''-Ar), 177.1 (C=O); m/z 372 (M^+, 27), 287 (3), 259 (7), 233 (9), 167 (70), 163 (86), 151 (100), 137 (65), 131 (91).

Mixed Acetal (15).

cis-Alcohol (12) (1.00g, 3.05mmol) was dissolved in dry dichloromethane (25ml) under a nitrogen atmosphere and cooled to 0°C. Triethylamine (2.13ml, 1.54g, 5eq) was added followed by chloroether (13) (0.96g, 3.65mmol, 1.2eq) and the solution was stirred for fifteen minutes. Sodium bicarbonate solution was added to quench the reaction and the organic layer was separated. The organic layer was washed once with sodium bicarbonate solution and dried ($MgSO_4$). Evaporation and chromatography of the residue (alumina, grade III, ether/40-60 petrol ----> ether gradient) gave the acetal (0.75g, 1.28mmol, 42%) as a colourless oil identified by ^{1}H NMR. δ_H(90 MHz, $CDCl_3$) 2.55-2.80 (3H, m, 3-H_2, 4-H), 3.25-3.37 (2H, m, $-CH_2O$), 3.48 (3H, s, $-CH(OCH_3)Ar$), 3.87, 3.91 (3H x 2, 2xS, OCH_3 x 2), 5.07-5.20 (5H, m, OCH_2Ph x 2, $-OCH(OCH_3)Ar$), 5.61 (1H, d, J 6Hz, 5-H), 6.70-7.00 (6H, m, Ar-H), 7.28-7.48 (10H, m, Ph-H). (Spectrum shows mixture of diastereoisomers).

2-exo-6-exo-bis-(4-Benzyloxy-3-methoxyphenyl)-8-oxo-3,7-dioxa bicyclo[3, 3, 0]octane (16).

Mixed acetal (15) (0.75g, 1.28mmol) was dissolved in dry THF (10ml) under a nitrogen atmosphere and the solution was cooled to 0°C. Triethylamine (0.32g, 0.45ml, 3.21mmol, 2.5eq) was added followed by trimethylsilyl trifluoromethanesulphonate (0.62g, 0.54ml, 2.82mmol) and the solution was stirred for two hours at 0°C. Water was added to quench the reaction and the solution was extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and were evaporated to dryness. The residue was chromatographed repeatedly (silica, ethyl acetate/hexane gradient) and gave a complicated mixture of products.

The title compound (83mg, 0.150mmol, 12%) was identified and gave spectroscopic data identical to that recorded previously.

2-exo-6-endo-bis-(4-Benzyloxy-3-methoxyphenyl)-8-oxo-3, 7-dioxabicyclo[3,3,0]octane (18).

cis-Lactone alcohol (12) (1.07g, 3.26mmol) was dissolved in dry THF (75ml) under a nitrogen atmosphere and was cooled to 0°C. Triethylamine (2.3ml. 1.67g, 16.5mmol, 5eq) was added followed by α-chloroether (13) (1.14g, 3.89mmol, 1.2eq) in THF solution (3ml). The solution was stirred for half an hour

when TLC showed that all the alcohol had reacted. Trimethylsilyl trifluoromethanesulphonate (1.39ml, 1.59g, 2.2eq) was added dropwise and the solution was stirred for one hour. 2M Hydrochloric acid (50ml) was added to the solution at 0°C to destroy excess reagent and the mixture was extracted with ethyl acetate (3 x 50 ml), brine being added to prevent emulsification. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was separated using flash chromatography (silica, ethyl acetate/hexane gradient) to give the title compound (103mg, 0.186mmol, 5.7%) as a white solid. This was recrystallised from ethyl acetate to give a pure sample. m.p. 139-140°C (Found: C, 73.6; H, 6.1%; M+ 552.2148 (V. Weak). $C_{34}H_{32}O_7$ requires C, 73.9; H, 5.8%; M^+ 552.2148); ν_{max}^{KBr} 2940, 1770, 1595, 1520, 1480, 1265, 1240, 1195, 1145, 1020, 775, 715 cm^{-1}; ν_H(400 MHz, $CDCl_3$) 3.46-3.52 (3H, m, 1-H, 4-H_A, 5-H), 3.82 (1H, m, 4-H_E), 3.878, 3.884 (6H, 2 x s, $-OCH_3$ x 2), 5.13, 5.14 (4H, 2 x s, $-OCH_2Ph$ x 2), 5.30 (1H, s, 2-H), 5.68 (1H, d, J 4.7 Hz, 6-H), 6.74-6.91 (6H, m, Ar-H), 7.28-7.43 (10H, m, Ph-H); δ_C(400MHz, $CDCl_3$) 45.3, 54.7 (CH-1, CH-5), 56.1 (CH_3- x 2) 69.7 (CH_2-4), 71.1 ($-OCH_2Ph$ x 2?), 80.2, 83.6 (CH-2, CH-6), 108.6, 109.3, 114.1, 114.2, 117.1, 117.5 (CH-Ar), 127.27, 127.31, 127.9, 128.0, 128.6 (x 2?) (CH-Ph), 129.1, 133.7, 136.7, 137.1 (C_1', C_1'', C_1''', C_1'''', -Ar, Ph), 147.8, 148.0, 149.9, 150.0 (C_3', C_4', C_3'', C_4'' -Ar), 177.0 (C=O).

2-exo-6-endo-Bis-(4-hydroxy-3-methoxyphenyl)-8-oxo-3, 7-dioxabicyclo[3,3,0]octane (6-iso-MEL) (5).

Dibenzyl-6-iso-MEL (18) (57.0mg, 0.103mmol) was dissolved in ethyl acetate (10ml) and was hydrogenated over a 10% paladium on carbon catalyst as usual. The catalyst was removed by filtration through kieselguhr and the solvent was evaporated to leave a crude residue. This was recrystallised from ethyl acetate to give the title compound (34.4mg, 0.0913mmol, 89%) as a white solid. This was clearly impure from its spectroscopic data however by comparison with literature data the title compound could be recognised. m.p. 128-131°C (Lit[4] 131-133°C) (found: M^+, 372.1194. $C_{20}H_{20}O_7$ requires 372.1209), δ_H(400 MHz, $CHCl_3$/trace CD_3OD), 3.54 (3H, m, 1-H, 4-H_A, 5-H), 3.85 (1H, m, 4-H_E), 3.90 (6H, $-OCH_3$ x 2), 5.32, 5.34, 5.35 (3H, 3 x s, 2-H, -OH x 2), 5,75 (1H, d, J 4.4 Hz, 6-H), 6.75-6.92 (6H, m, Ar-H); m/z 372 (M^+, 82), 287 (6), 259 (11), 191 (13), 163 (43), 151 (100), 137 (58), 131 (89).

* Also apparent in the ^1H NMR spectrum are two peaks, δ_H= 4.04 (dd, J 9.5, 4.3 Hz) and 4.34 (dd, J 9.3, 7.1 Hz). These could correspond to 4-H and 4-H in the 2-exo-6-exo-isomer. There was no evidence for this isomer in the dibenzylated material even as an impurity. Possibly this is evidence for the photolability of iso-MEL to MEL. To be certain of this however, pure samples of iso-MEL are required.

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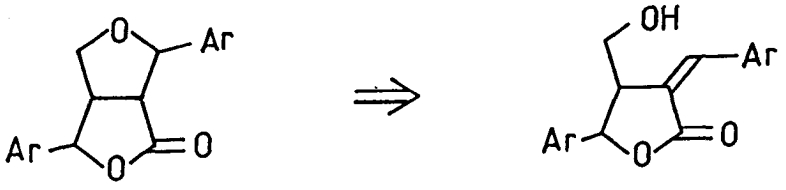
Chapter 4

α-Arylidene Lactones in Lignan Synthesis.

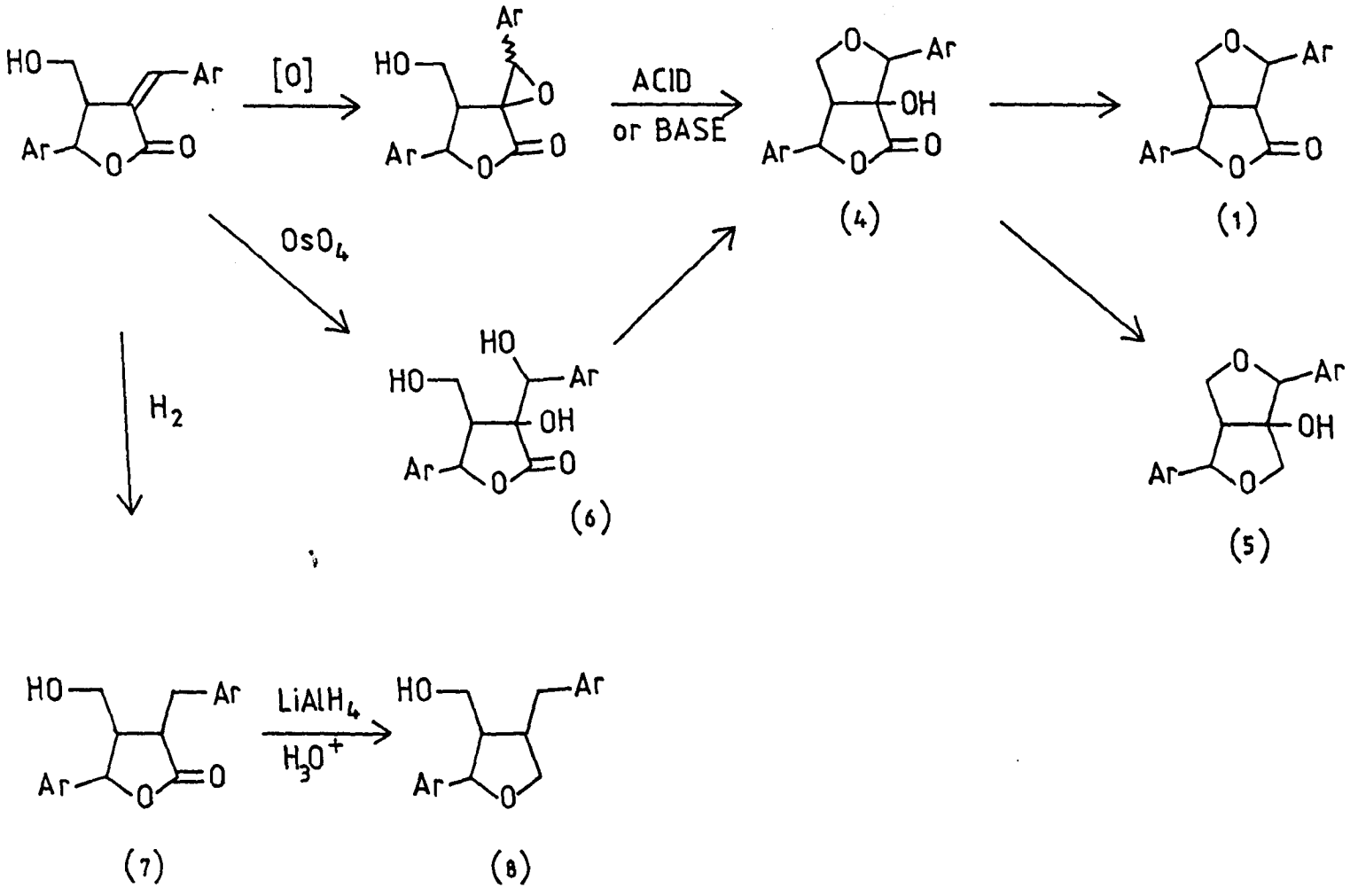
If we consider a 2,6-diaryl-8-oxo-3,7-dioxabicyclo[3, 3, 0]octane lignan (1) we can envisage a number of possible disconnections when trying to devise synthetic routes. One that has not been reported in the literature is the formation of the tetrahydrofuran ring by the intramolecular addition of an alcohol across the double bond of an α-arylidene lactone (2). (scheme 1).



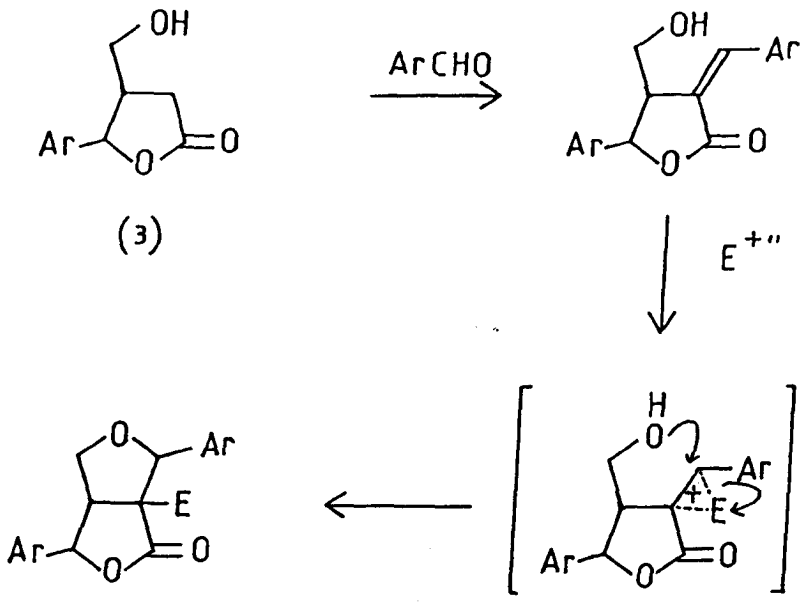
(1) (2)

SCHEME 1

The α-arylidene lactone might be set up by the condensation of a lactone (3) with an aromatic aldehyde and ring closed with a suitable reagent to form a bicyclic system. (scheme 2).

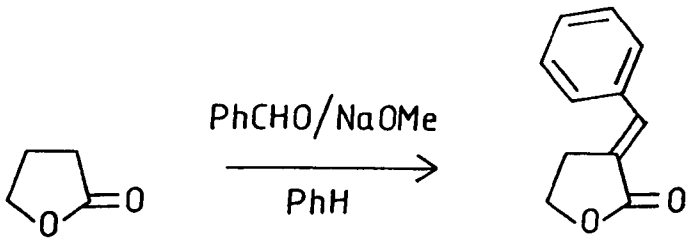

HO
Ar
[O]
Ar
HO
Ar
O
O
ACID
or BASE
O
Ar
OH
Ar
O
O
(4)
O
Ar
Ar
O
O
(1)
OsO4
H2
HO
HO
Ar
OH
Ar
O
O
(6)
O
Ar
OH
Ar
O
(5)
HO
Ar
LiAlH4
H3O+
HO
Ar
Ar
O
Ar
O
(7)
(8)

SCHEME 3



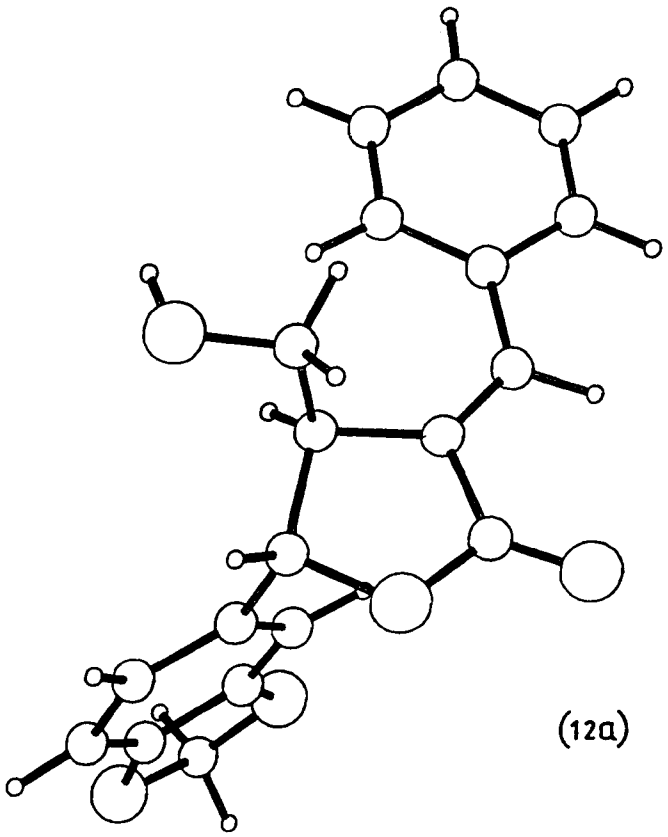
SCHEME 2

Other functionalisations of α-arylidene lactones can also be thought of when considering lignan syntheses. Some of the possibilities are outlined in scheme 3. Epoxidation of the double bond followed by acid or base catalysed ring closure could give the bicyclic skeleton with a hydroxy function α- to the lactone carbonyl (4). This hydroxy function could be removed to give the lignan type structure (1) or alternatively the lactone might be converted to the tetrahydrofuran to give access to the gmelinol type skeleton (5). Treatment of the double bond with osmium tetroxide would give a 1, 3, 4-triol (6) which might also cyclise to the bicyclic hydroxy lactone (4). Another possible route to a lignan family could be hydrogenation of the double bond to give the saturated compound (7) followed by conversion of the lactone group to the corresponding tetrahydrofuran (8) giving entry to the lariciresinol type of natural products.



(9) (10)

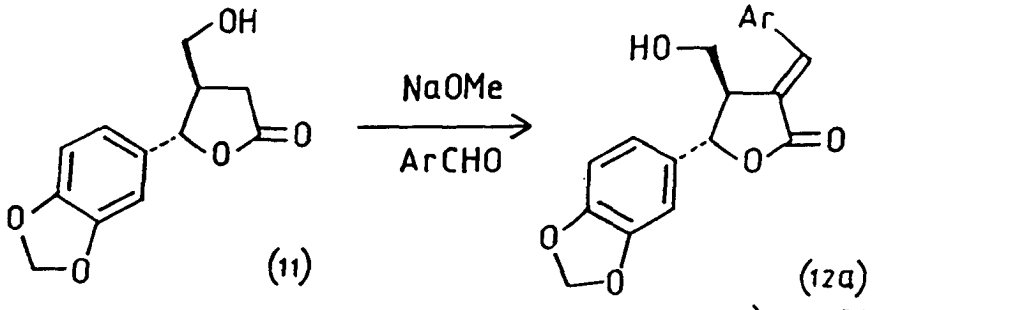
SCHEME 4



(12a)

Sythesis of α-Arylidene Lactones.

The simplest α-arylidene butyrolactone that can be synthesised involves the condensation of butyrolactone (9) itself with benzaldehyde. This has been reported by Zimmer et al[1] using sodium methoxide as base in benzene solvent and decomposing the product with dilute sulphuric acid (scheme 4). An E-configuration was assigned to the product (10) by the authors. This reaction was repeated and after chromatographic isolation gave a 47% yield. Using lactone alcohol (11) (see previous chapters) and benzaldehyde under similar conditions it was possible, after repeated chromatography, to isolate the product (12a) as a viscous oil in 31% yield (scheme 5). This could be recrystallised with difficulty from chloroform/hexane then methanol/trace of water. The structure of the product was confirmed by x-ray crystal-lography and we are indebted to Dr. M.J. Begley for this work.

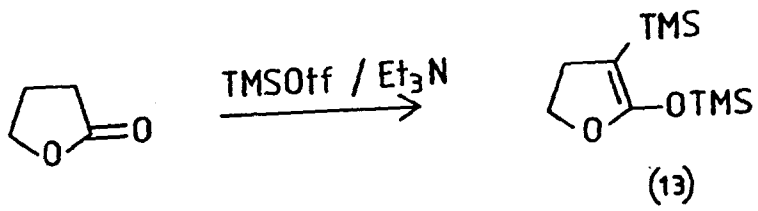


(11) (12a)

a) Ar=Ph

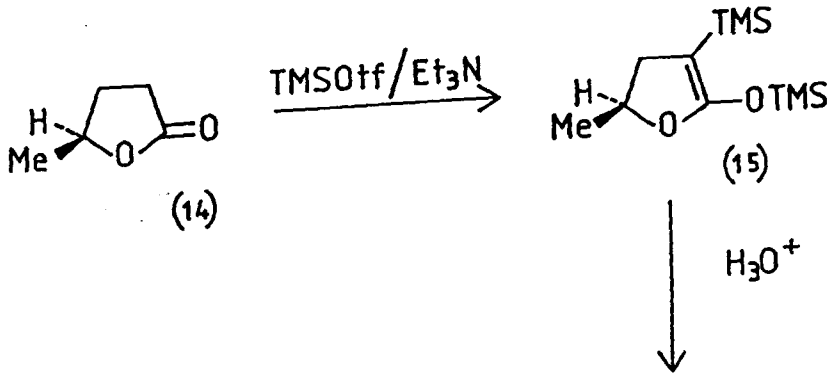
b) Ar =

SCHEME 5



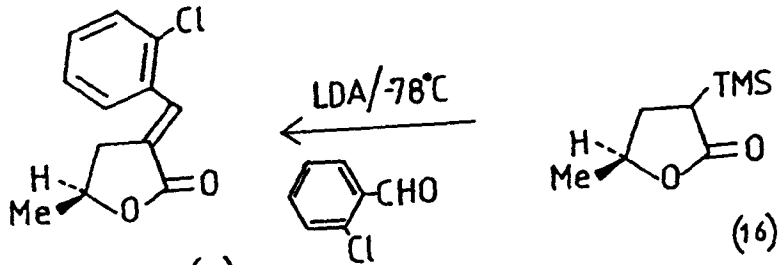
(13)

SCHEME 6



(14)

(15)



(17)

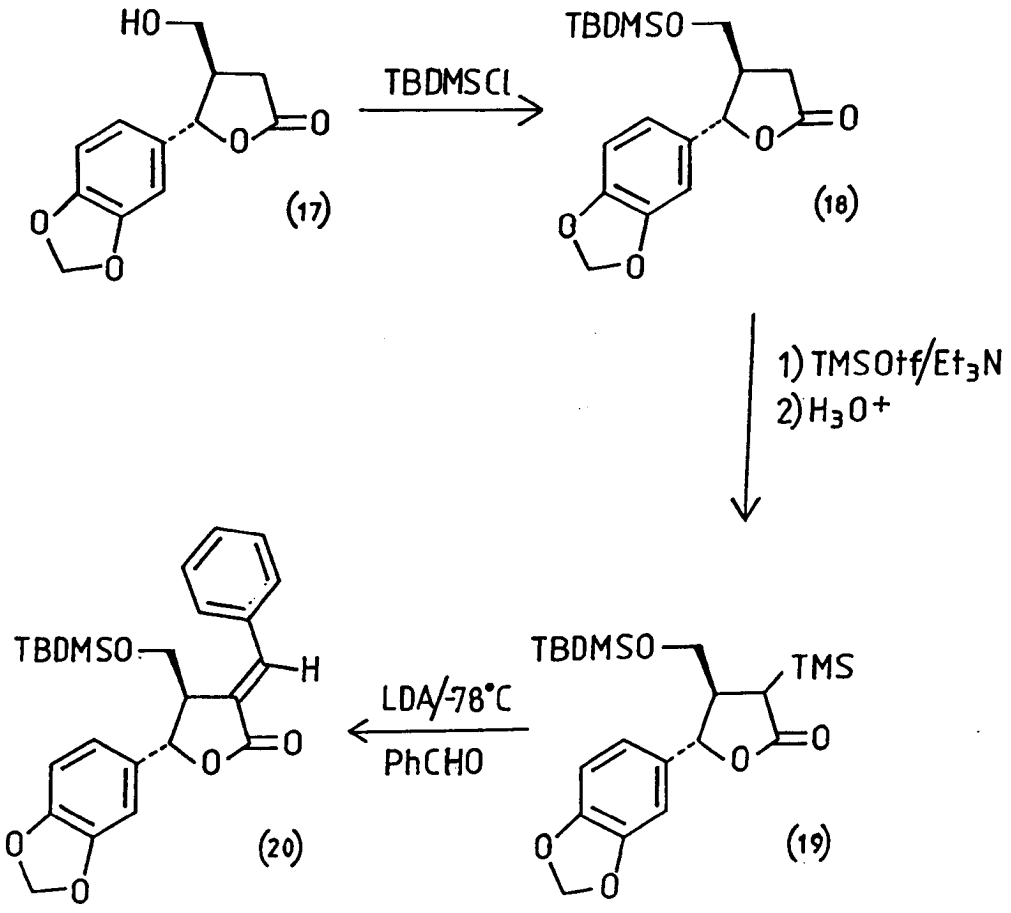
(16)

SCHEME 7

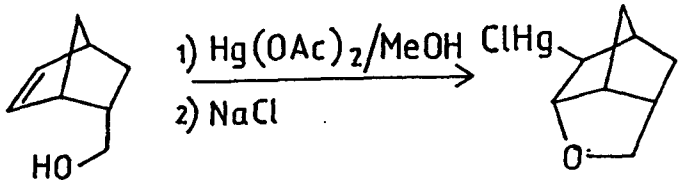
The extensive chromatography required and the poor yields after recrystallisation made this reaction less than satisfactory and other synthetic strategies were sought.

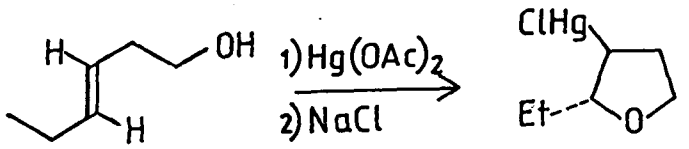
Sanemitsu and co-workers[2] have used a variation of the Peterson reaction for α-arylidene lactone synthesis. Simchen et al[3] (scheme 6) have reported that the reaction between butyrolactone and trimethylsilyltrifluoromethanesulphonate in the presence of triethylamine gave rise to the bis-silylated product (13). This reaction was used by Sanemitsu's group (scheme 7) to introduce a silicon atom into the lactone (14) and the product (15) was in turn hydrolysed to the α-silyl lactone (16). Reaction with LDA and an aromatic aldehyde gave the required product (17).

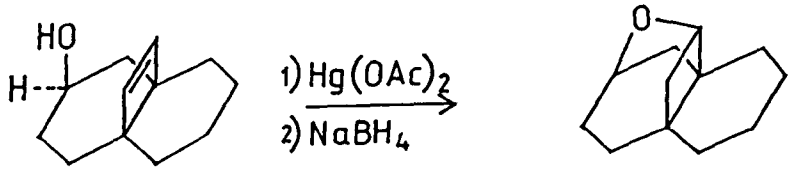
In our work towards lignan systems, the lactone alcohol (11) was protected as the tert-butyldimethylsilyl ether[4] (18) in good yield. This was then reacted with trimethylsilyltrifluoromethanesulphonate/triethylamine followed by an aqueous acid work up. Chromatography afforded the pure α-silyl lactone (19) in 38% yield. Subsequent treatment with LDA and benzaldehyde gave the required compound (20) in 54% yield after purification. The advantage of this procedure over Zimmers' sodium methoxide method is the ease of purification of the final products which recrystallise readily from hexane (scheme 8).

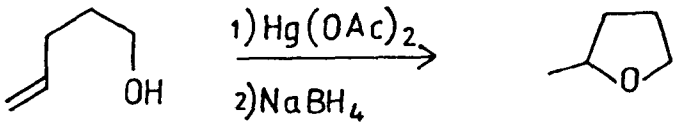

HO
TBDMSCl
TBDMSO
(17)
(18)
1) TMSOtf/Et3N
2) H3O+
TBDMSO
TMS
TBDMSO
H
LDA/-78°C
PhCHO
(19)
(20)

SCHEME 8

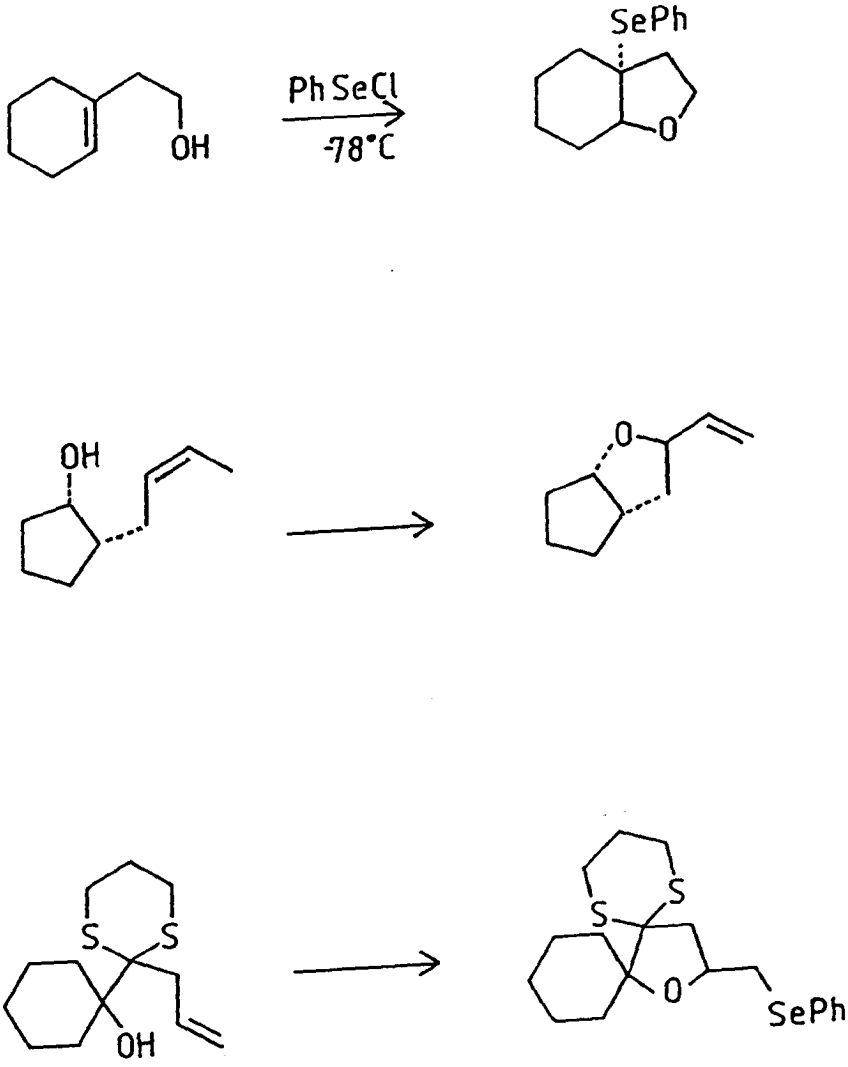

1) Hg(OAc)2/MeOH
2) NaCl
ClHg
HO
O


H
OH
H
1) Hg(OAc)2
2) NaCl
ClHg
Et
O

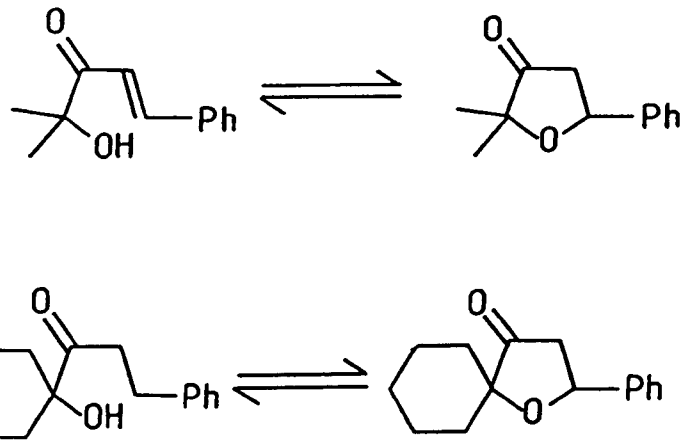

HO
H
1) Hg(OAc)2
2) NaBH4
O


OH
1) Hg(OAc)2
2) NaBH4
O

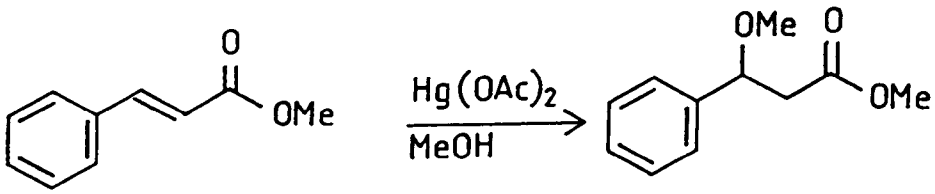
SCHEME 9



SCHEME 10



SCHEME 11



SCHEME 12

Attempted Ring Closure of the Tetrahydrofuran.

Formally, within the nomenclature of Baldwins' rules[5] the ring closure (2) ----> (1) is a 5-endo, trig and disfavoured. There is however literature precedence for the formation of 5-membered rings using both mercury and selenium reagents as well as at least one acid catalysed case (see reactions in schemes 9[6], 10[7] and 11[8]). Traditionally, mercury (II) acetate is the reagent used to add alcohols or water across a double bond, for example methanol has been added to methyl cinnamate[9] (scheme 12).

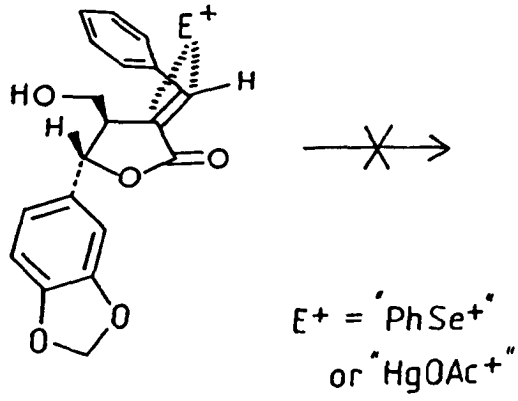
More recently however, the trifluoroacetate[10] has found favour due to its increased solubility in organic solvents. The trifluoroacetate ion is also much less nucleophilic than acetate and is far less likely to attack an intermediate mercurium ion.

The α-arylidene lactone alcohol (12) was treated with mercury (II) acetate in THF and also THF/water solvents however in both cases, no reaction was observed. The reaction also failed with mercury (II) trifluoroacetate, no change being observed after seven days at room temperature or overnight reflux in the absence or presence of water. Sodium borohydride was added to free the mercury and the isolated product was shown by ^{1}H NMR to be unchanged starting material.

Phenyl selenyl chloride is frequently effective in ring closures of this type, typical reaction conditions being dichloromethane

solution at -78°C. No reaction was observed with α-arylidene lactone alcohol (12) at -78°C and even warming to room temperature for a week had no effect on the reaction.

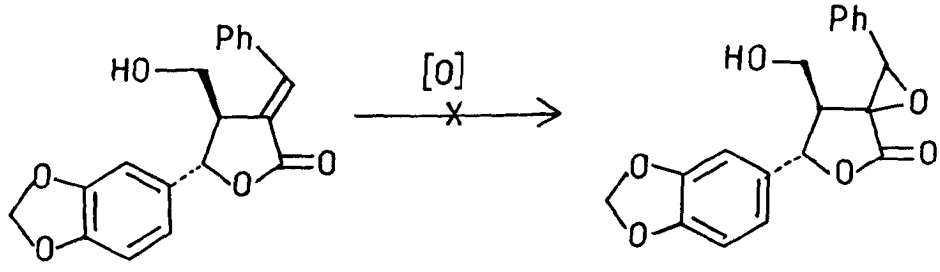
It was very surprising that the double bond in this system should be so completely unreactive. Steric and electronic reasons can be suggested to account for this. The double bond is triply substituted and therefore hindered. If the preferred side of attack for the electrophilic mercury or selenium species is the face opposite the aromatic group on the tetrahydrofuran ring, that is the same face of the molecule as the hydroxymethyl group, then it will not be possible for the alcoholic oxygen function to attack the backside of the intermediate species formed (scheme 13). If the electrophilic species does attack on the correct face for ring closure to occur, it is possible with a five membered ring and a double bond attached to it in the system to



SCHEME 13

keep it rigid and planar, that the oxygen is too remote in space to attack the double bond. Almost certainly of significance is the reduced electron density of the double bond conjugated to the lactone carbonyl group which would thus greatly disfavour electrophilic attack.

Other functionalisations of the double bond need to be tried and one attractive possibility was epoxidation[11]. A wide range of reagents is available and some of these were tried (scheme 14). The most commonly used reagent, m-chloroperbenzoic acid[12] in chloroform proved ineffective even at reflux and for extended

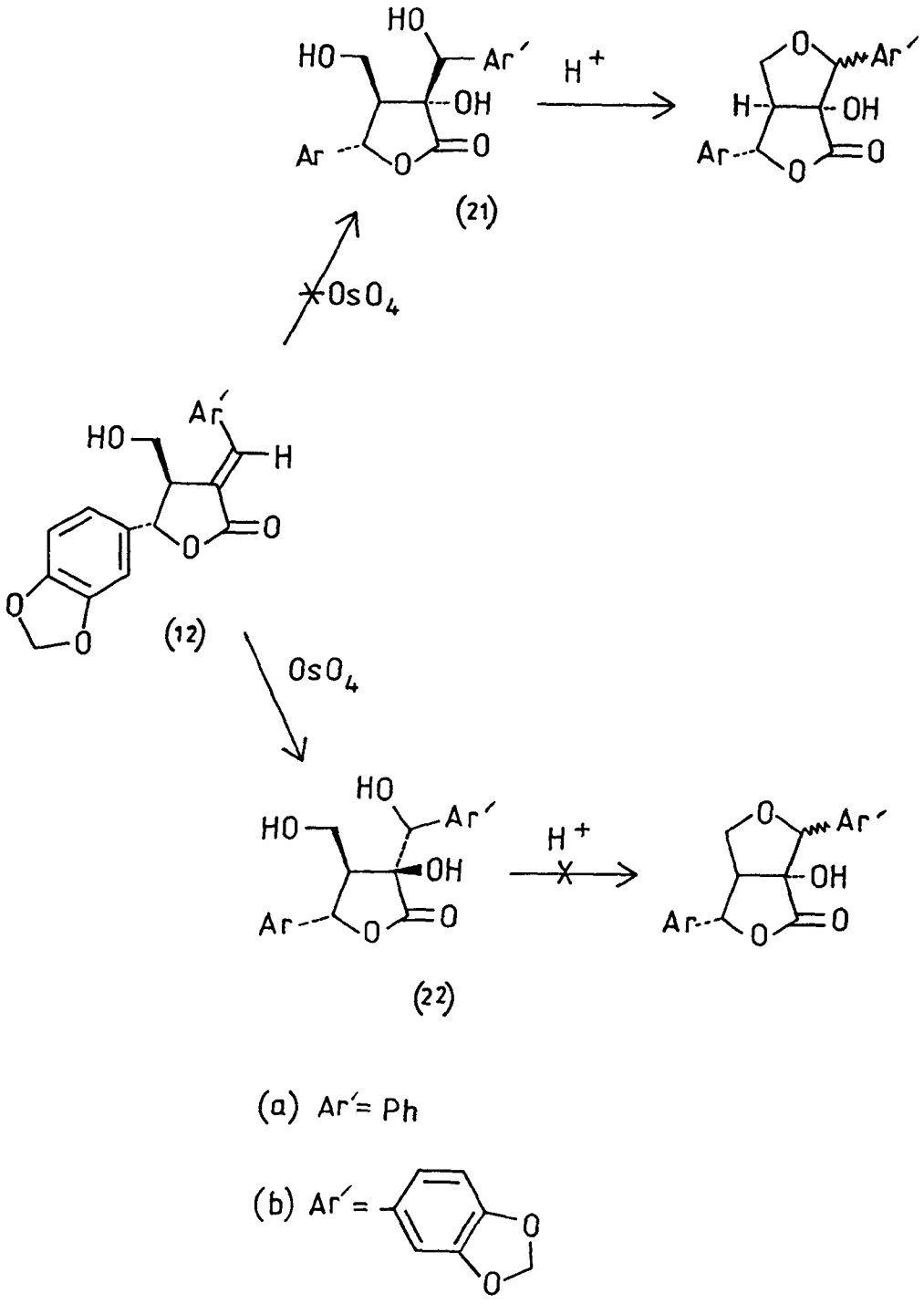


SCHEME 14

periods of time. Similarly, basic hydrogen peroxide (sodium bicarbonate)[13], sodium hypochlorite/pyridine[14] and 3, 5-dinitroper benzoic acid[15] (reported to be as strong as trifluoroperacetic acid) had no effect on the system.

Functionalisation of the double bond was finally achieved by using osmium tetroxide (5 mol%) as a catalyst and regenerating the catalyst in situ with N-methylmorpholine-N-oxide[16]. After 10 days reaction at room temperature in tert-butanol/THF/water (10:3:1) the triol (22a) was isolated in 41% yield as well as unreacted starting material. This reaction served to show just how unreactive the double bond is in this molecule. When acetone was used as solvent and the reaction was left for two weeks, complete decomposition occurred. Spectroscopic and analytical data clearly showed that a triol had been formed but on exposure to acid (methanol, 1 drop conc. hydrochloric acid) no ring closure occurred.

Despite the failure to ring close the last molecule the result was none the less encouraging. With a (3, 4-methylenedioxy) phenyl substituent to replace the phenyl we could expect ring closure to be far more rapid. The appropriate α-arylidene lactone (12b) was prepared from the lactone alcohol (9) and 3, 4-methylenedioxy benzaldehyde in 34% yield using sodium methoxide in benzene (scheme 5). On reaction with osmium tetroxide and N-methylmorpholine-N-oxide for 10 days, a triol (22b) was found in 28% isolated yield. Also recovered was unreacted starting



(a) Ar'= Ph

(b) Ar'=

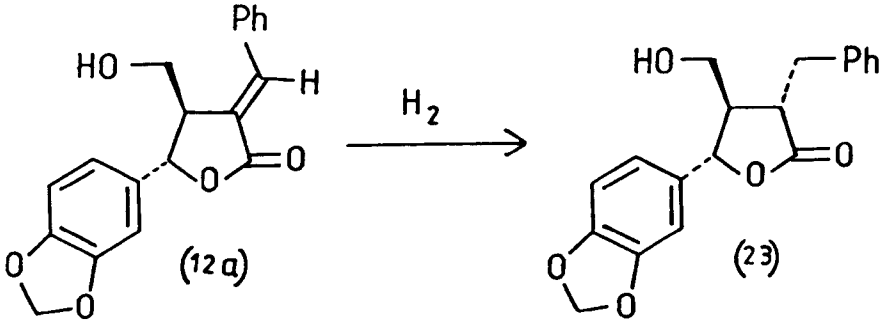
SCHEME 15

material (40%). Again on exposure to acid (hydrochloric acid in methanol) no ring closure was observed.

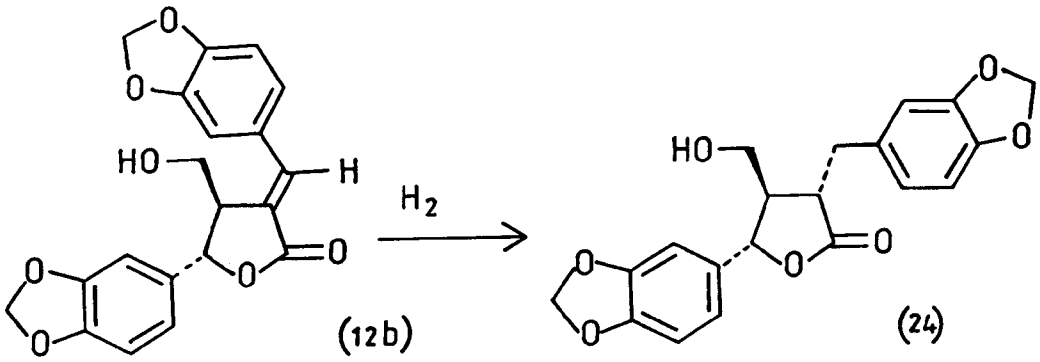
The only explanation possible for this failure to ring close must be the stereochemistry of the triol. Depending on the face of attack of the osmium tetroxide, two possible products (21) and (22) can be formed. Only one of these (22) can cyclise and it would be reasonable to assume that the subtituents at the 3 and 4 positions on the lactone ring of the triol we have synthesised exist in a trans configuration (scheme 15).

The other obvious functionalisation of a double bond to try is hydrogenation. The double bond in the α-benzylidene lactone (12a) reduced cleanly and smoothly to one compound (23a) only (scheme 16). The stereochemistry of this compound, an oil, was difficult to assign from spectroscopic data and was finally decided upon using an indirect method involving a known natural product.

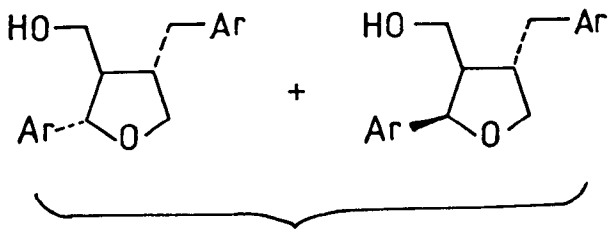
The 3,4-(methylenedioxy)benzylidene lactone (12b) was hydrogenated cleanly to one compound (24) (scheme 17). This was presumably of the same stereochemistry as compound (23) above. Lithium aluminium hydride reduction of this compound followed by acid catalysed ring closure gave two tetrahydrofurans (25a) and (25b). These compounds were both clearly similar to the known lignan, dihydrosesamin[17] (27) by ^{1}H NMR yet were obviously different. Had the original hydrogenation taken place so that hydrogen was



SCHEME 16



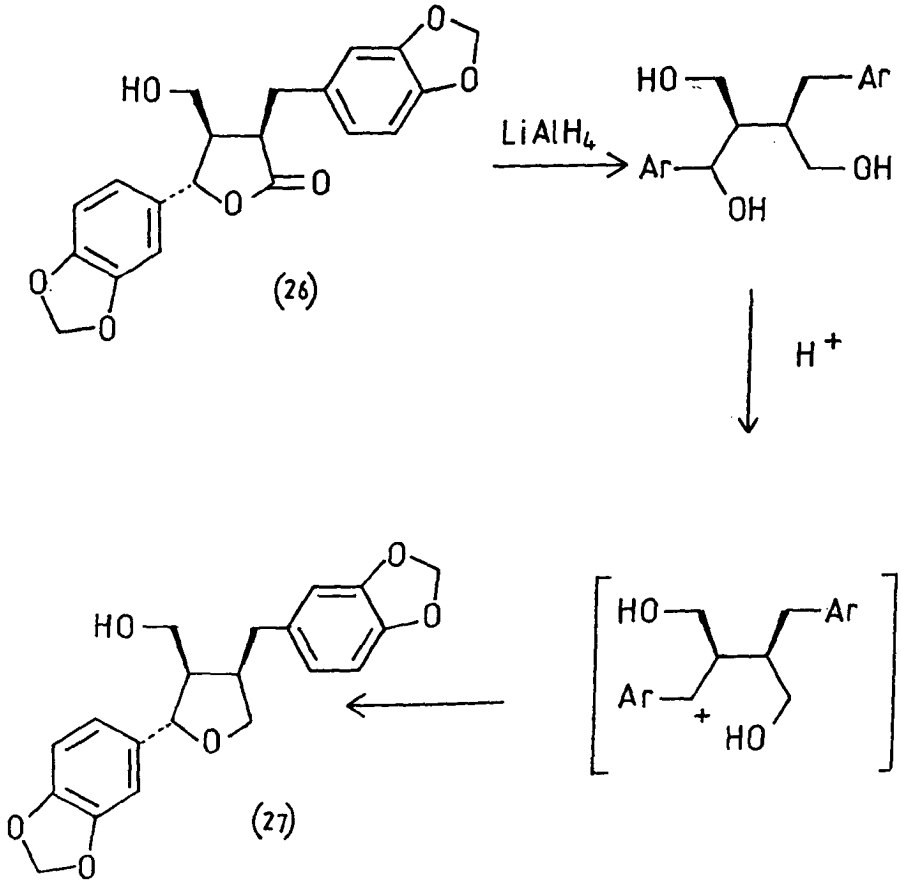
1) $LiAlH_4$
2) H_3O^+



(25a)+ (25b)

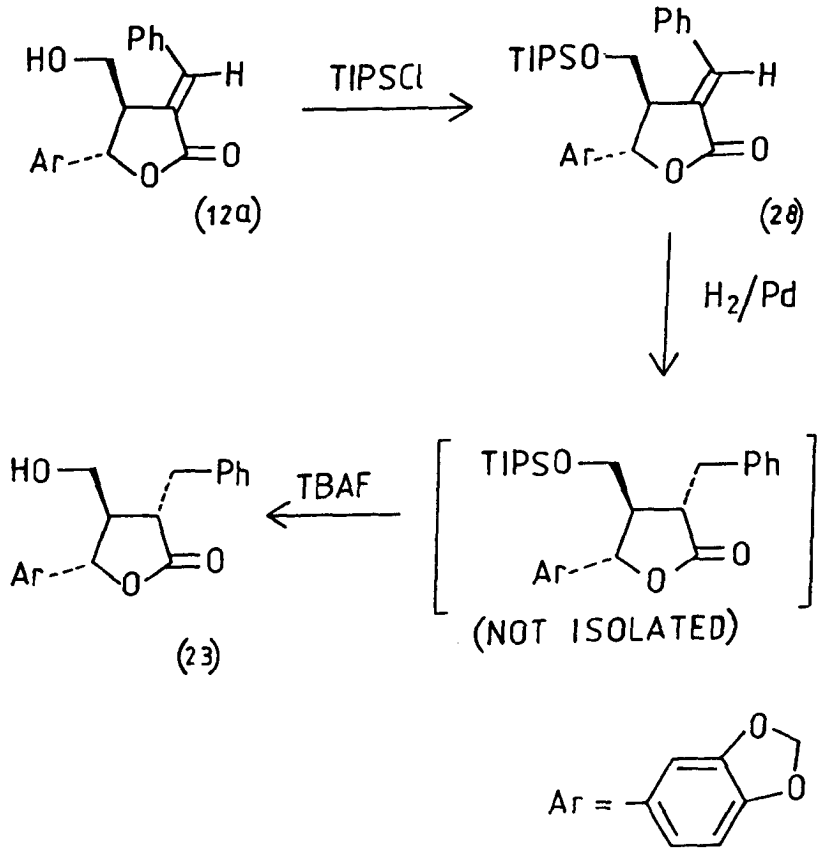
SCHEME 17

added to the same face of the molecule as the aromatic group attached to the lactone ring then the compound (26) would have been formed (scheme 18). It is very likely that lithium aluminium hydride reduction and acid catalysed cyclisation of this compound would have produced dihydrosesamin. This however was not the case and we are forced to conclude that hydrogenation of (12b) has occured on the face opposite to the ring aromatic group and that this compound (24) in turn, on reduction and cyclisation, gave rise to the two isomers (25a) and (25b).

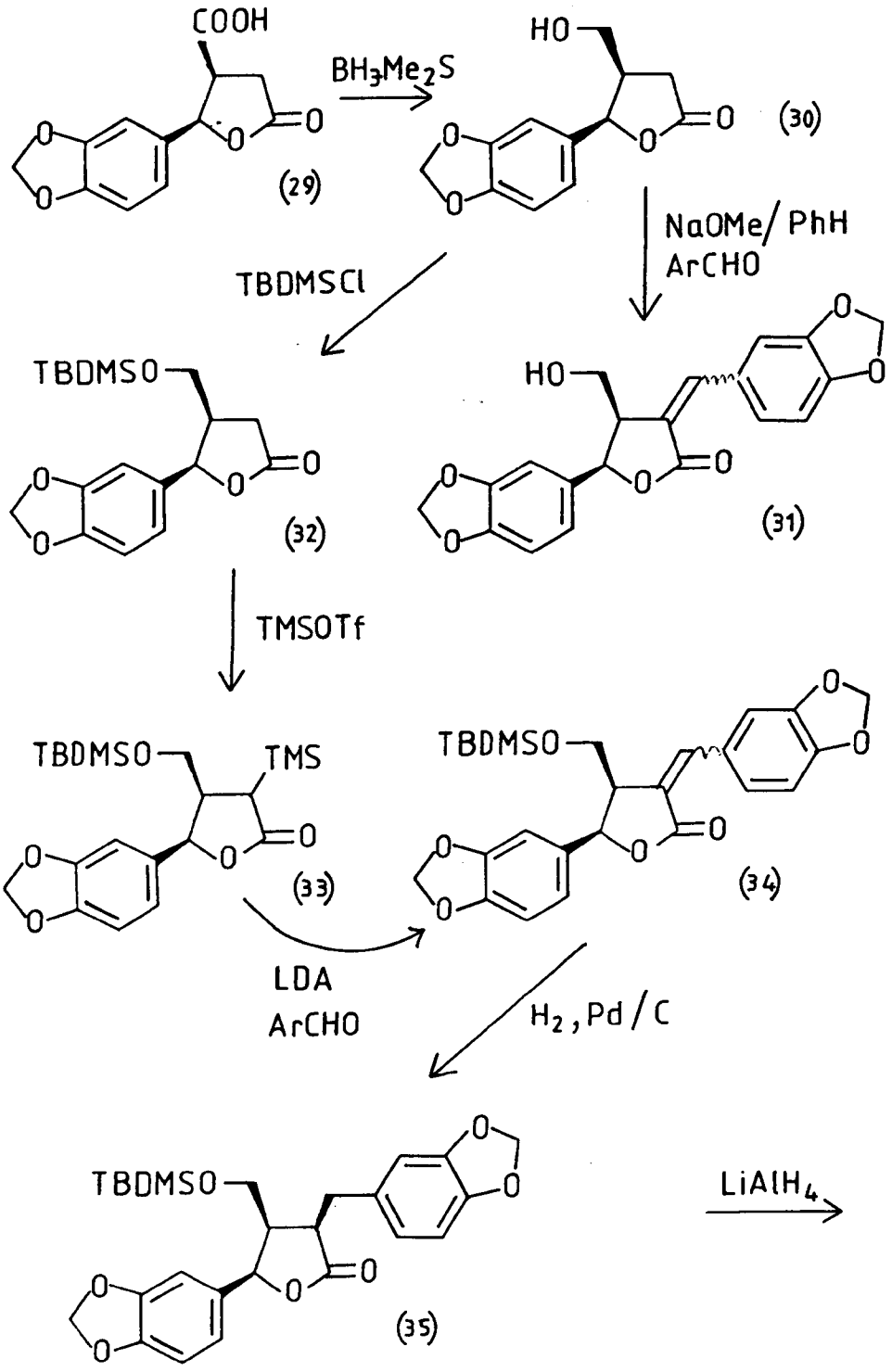


SCHEME 18

A possible way to reverse the face on which hydrogenation occurs might be to block the hydroxymethyl function with a bulky protecting group. A triisopropylsilyl group[18] was chosen as silicon protecting groups are generally easy to introduce and remove. The silyl ether (28) was formed in 43% isolated yield using standard conditions (imidazole, DMF solvent) and the double bond reduced cleanly as expected. This product was not isolated pure or characterised but was treated with tetrabutylammonium fluoride in THF solvent to deprotect. Only one isomer (23) was evident and this proved to be identical (400 MHz ^{1}H NMR) to that synthesised from the free alcohol (scheme 19).

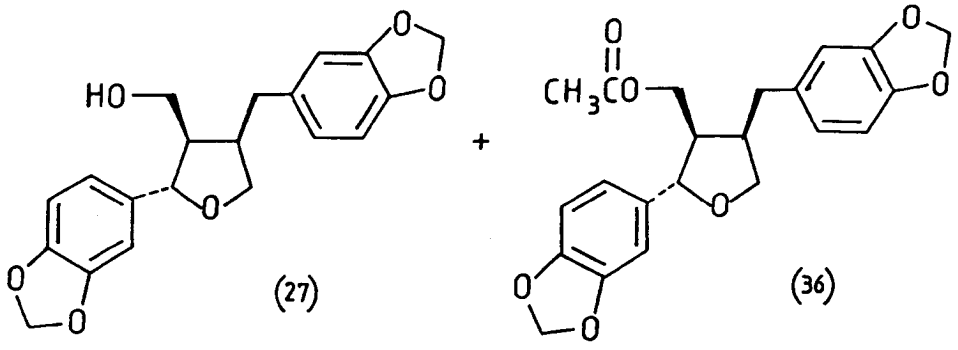


SCHEME 19

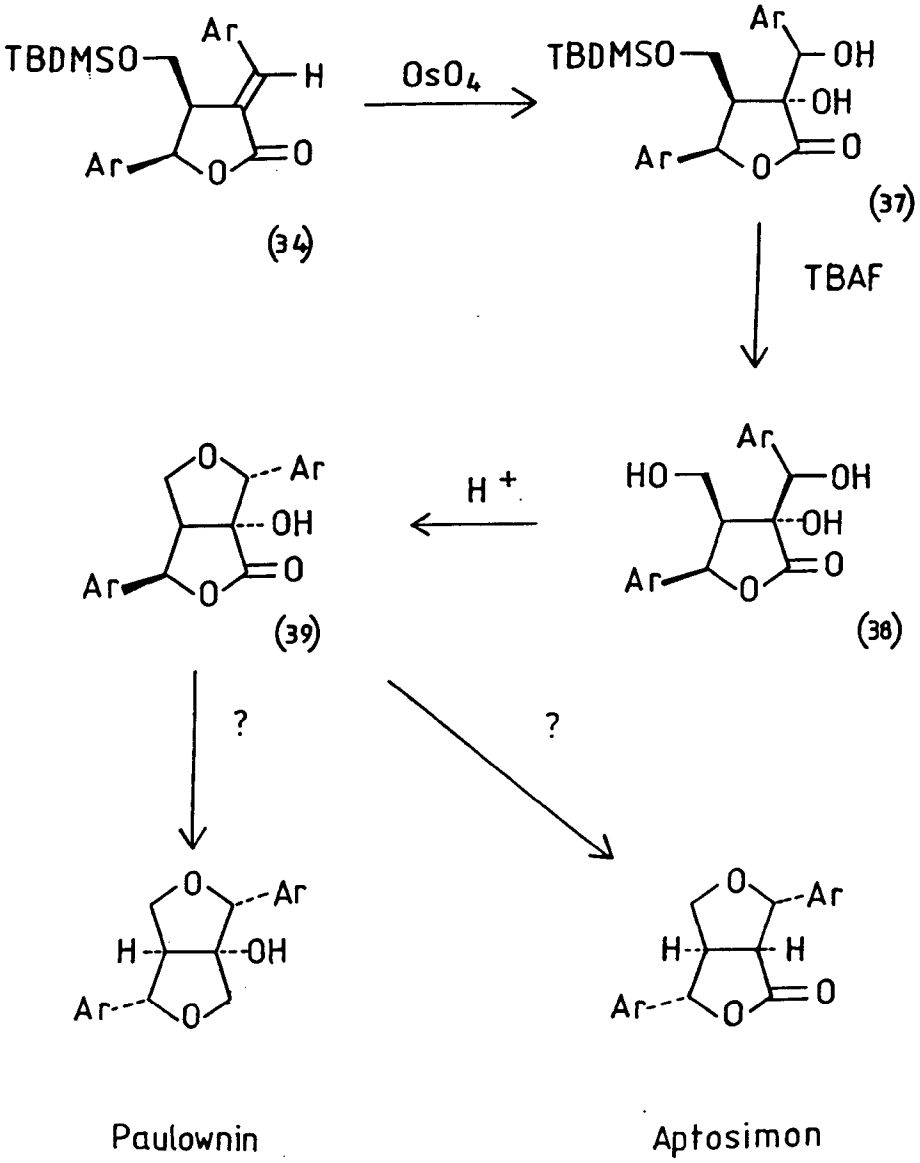

COOH
BH3Me2S
HO
(29)
(30)
NaOMe/ PhH
ArCHO
TBDMSCl
TBDMSO
HO
(32)
(31)
TMSOTf
TBDMSO
TMS
TBDMSO
(33)
(34)
LDA
ArCHO
H2, Pd / C
TBDMSO
LiAlH4
(35)

The lithium aluminium hydride reduction and subsequent cyclistion of the lactone (24) to the two tetrahydrofuran isomers (25a) and (25b) was interesting, showing that the aryl substituent at the 5-position on the ring would assume the thermodynamically most favourable stereochemistry. Remembering that the Lawlor-McNamee paraconic acid synthesis[19] produced both a cis and a trans isomer we decided to use this to advantage. The cis-isomer of the acid (29), (scheme 20) was reduced to the alcohol (30) using borane -methyl sulphide complex in 81% yield. This was in turn reacted with 3,4-methylenedioxybenzaldehyde and sodium methoxide in benzene to give the α-arylidene lactone (31). This compound proved very insoluble in the usual solvents for hydrogenation however and was abandoned.

The alcohol (30) was protected as the tert-butyldimethylsilyl ether (32, 98%) and subjected to trimethylsilyl trifluoromethane -



SCHEME 20

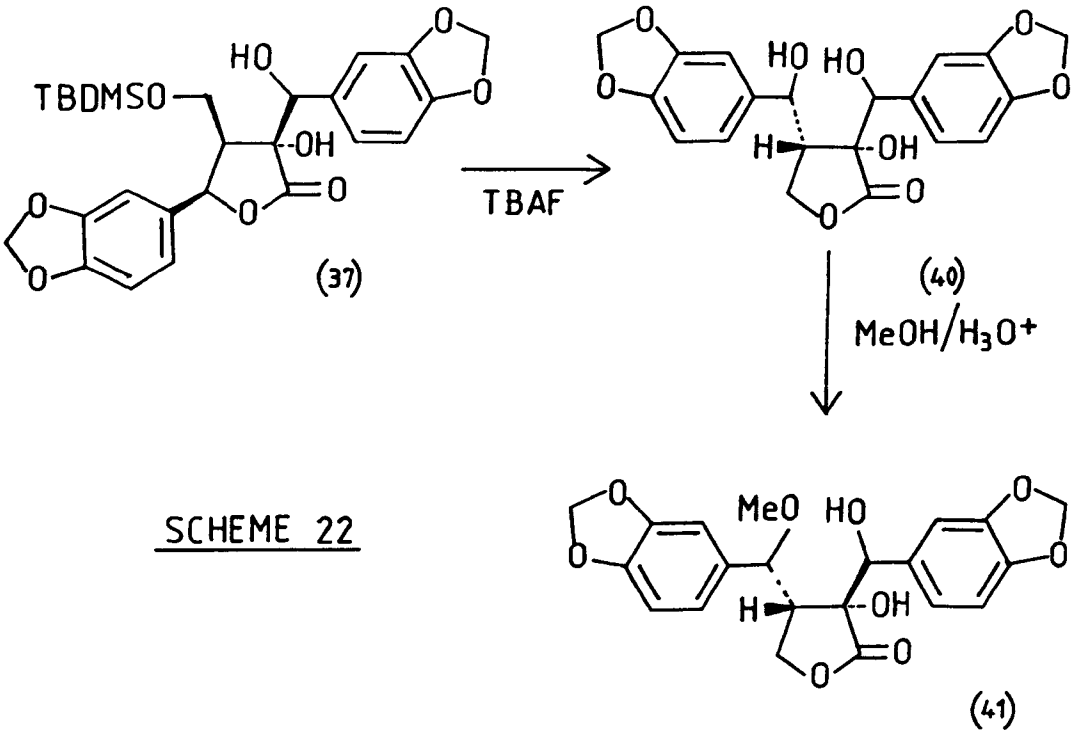

TBDMSO
Ar
H
Ar
O
O
(34)
OsO4
TBDMSO
Ar
OH
OH
Ar
O
O
(37)
TBAF
HO
Ar
OH
OH
Ar
O
O
(38)
H +
O
Ar
OH
Ar
O
O
(39)
?
?
O
Ar
H
OH
Ar
O
Paulownin
O
Ar
H
H
Ar
O
O
Aptosimon

SCHEME 21

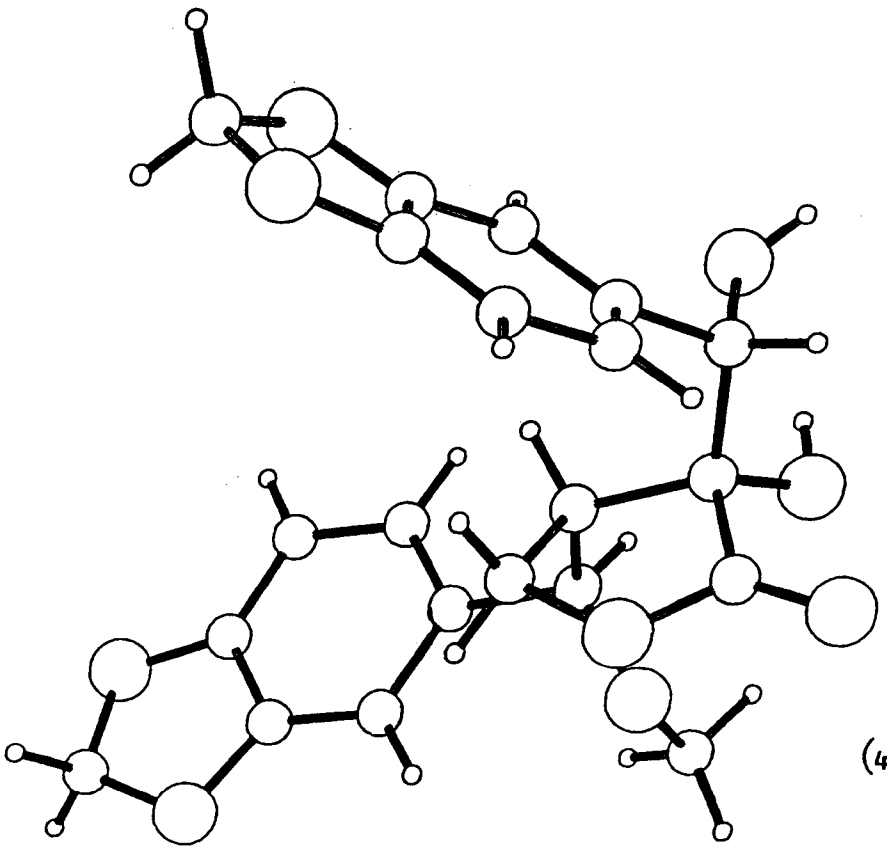
sulphonate silylation (33, 27%) and then Peterson reaction with 3,4-methylenedioxybenzaldehyde to the expected olefin (34, 60%). Hydrogenation gave a single isomer (35) which was treated with lithium aluminium hydride. Ethyl acetate quench and acid work up gave a mixture of two compounds, (±)-dihydrosesamin (27, 26% yield) and its acetate (36, 8% yield). This serendipitous reaction avoided a deprotection step and also provided a known and characterised derivative of the natural product[17]. (±)-Dihydrosesamin is a constituent of Daphne tangutica, a herb used in chinese folk medicine as a remedy for rheumatism and toothache. (No evidence was presented in this paper however to suggest that (-)-dihydrosesamin is an active component of the plant).

This success in stereochemical control offered hope for the bicyclic lignan system. Possibly a 1,4-diol could be set up with the correct stereochemistry for ring closure. The resulting bicyclic system might then be converted to any of a series of natural products (scheme 21).

Diol formation took place as expected and this product (37) was subjected to tetrabutylammonium fluoride desilylation. The product from this reaction was not the expected triol (38) but was instead a different lactone (40) (scheme 22). The identity of this new compound was revealed when attempts to ring close in methanolic hydrochloric acid produced only a new methylated compound (41) which was identified by x-ray crystallography. We thank Dr M.J. Begley for this identification.

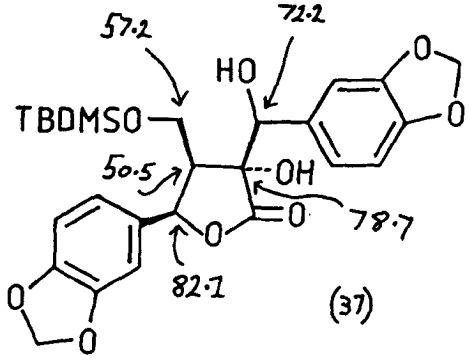

TBDMSO
HO
OH
O
O
O
O
O
O
(37)
TBAF
HO
HO
H
OH
O
O
O
O
O
O
(40)
MeOH/H3O+
MeO
HO
H
OH
O
O
O
O
O
O
(41)

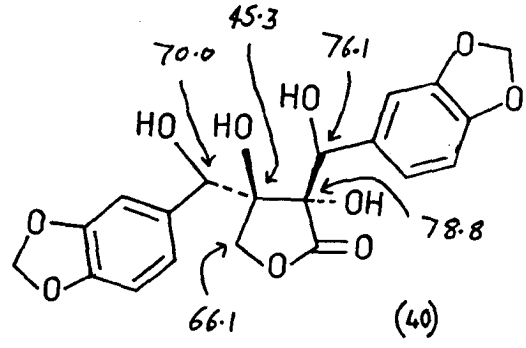
SCHEME 22

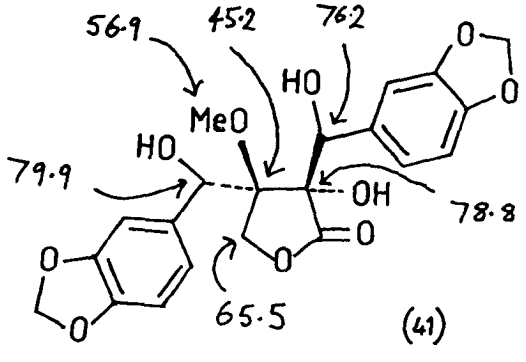


(41)

^{13}C NMR Spectroscopy clearly showed that the lactones (40) and (41) were very similar, differing only by the presence of a methoxy group, whereas the lactone (37) was noticeably different (scheme 23). A shift of +9.9 ppm was observed for the carbon atom at the site of methoxylation as would be expected[20]. The crucial reaction seems to occur on desilylation. The lactone (37) is a strained molecule with three bulky substituents competing for space on the same face of a five membered ring. If the silicon protecting group is removed to leave an alkoxide anion, models show that this is close enough in space to attack the lactone ring causing rearrangement to the new lactone (40), (scheme 24). This would be accompanied by release of a large amount of strain. The incorporation of just one methoxy group in the lactone (41) could be explained by an assisted solvolysis mechanism. Models again

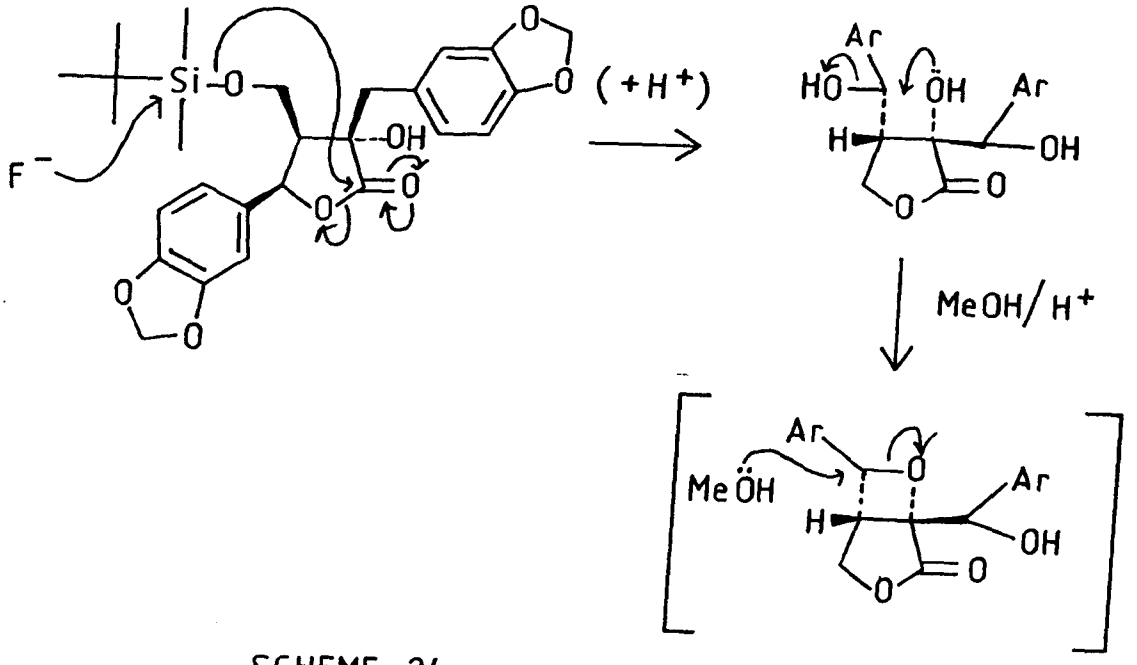






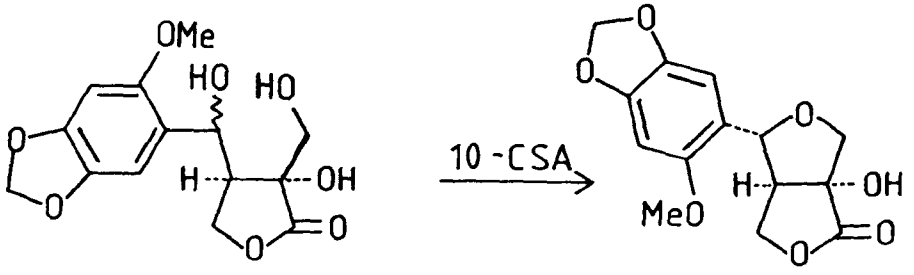
^{13}C NMR

SCHEME 23



SCHEME 24

(41)



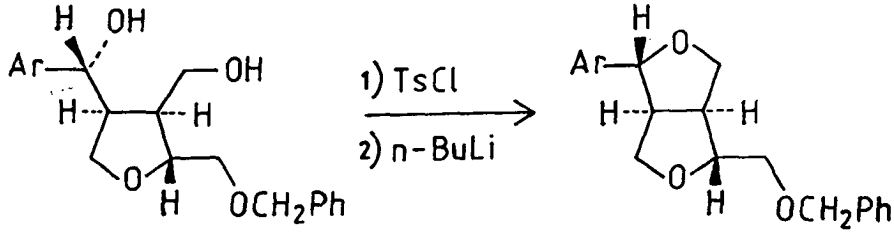
SCHEME 25

show that the 3-hydroxy function is suitably positioned to assist in this. To the authors knowledge, there are no known naturally occurring lignans of this general structure.

Time prevented other attemps at ring closures however this area would be worthy of further investigation.

Other similar ring closures in lignan structures have appeared in the recent literature. Ishibashi and Taniguchi[21] have used catalytic 10 - camphor sulphonic acid in their synthesis of phrymarolin (scheme 25). Takano and co-workers have used a base catalysed S_N2 type reaction in their work. Here, a tosyl group was introduced as a suitably positioned leaving group (scheme 26).

In our work on α-arylidene lactones we have produced a novel synthesis of (±)-dihydrosesamin and it is possibly that an approach of this type may yet prove to be an entry into the 3,7 -dioxabicyclo[3,3,0]octane skeleton.



SCHEME 26

Experimental Section.

3-E-(Phenylmethylene) dihydro-2-furanone (10).

γ-Butyrolactone (2.84g, 2.53ml, 33.0mmol) was dissolved in dry benzene (30ml). Benzaldehyde (3.50g, 3.35ml, 33.0mmol) and sodium methoxide (2.00g, 37.0mmol) were added and the mixture was stirred for two hours. 10% sulphuric acid was added to dissolve inorganics and to acidify and the resulting mixture was stirred overnight. The organic layer was separated and was washed with brine before drying ($MgSO_4$). Evaporation and chromatography of the residue (silica, ether/40-60 petrol) gave the title compound (2.74g, 15.5mol, 47%) as a white solid. Recrystallisation (40-60 petrol) gave short white needles. m.p. 117-118°C (Lit[1] 116-117°C).

trans-4-Hydroxymethyl-5-(3,4-methylenedioxyphenyl)-E-phenyl methylene dihydro-2-furanone (12a).

Lactone alcohol (11) (4.00g, 1.95mmol) was dissolved in dry benzene (80ml) and benzaldehyde (2.60ml, 2.70g, 25.6mmol, 1.5eq) and sodium methoxide (2.01g, 37.2mmol, 2.2eq) were added and the suspension was stirred overnight. The solution was acidified with 10% sulphuric acid and stirred for four hours. Work-up and extensive chromatography (silica, ethyl acetate/hexane) gave the title compound (1.70g, 5.24mmol, 31%) as a solid.

Recrystallisation from chloroform (trace of hexane) gave the pure compound. m.p. 146°C (Found: C, 70.4; H, 5.1%, M^+, 324.1003. $C_{19}H_{16}O_5$ requires C, 70.4; H, 5.1%, M^+, 324.0998); ν_{max}^{KBr} 3460, 2930, 1725, 1645, 1500, 1460, 1315, 1260, 1190, 1045, 975, 830, 780, 700 cm^{-1} , δ_H(400 MHz, $CDCl_3$) 2.17 (1H, br s, -OH), 3.69-3.78 (2H, m, $-CH_2OH$), 3.96 (1H, dd, J 10.2, 3.6 Hz, 4-H), 5.62 (1H, d, J 1.6 Hz, 5-H), 5.96 (2H, s, $-OCH_2O-$), 6.77-6.79 (3H, m, Ar-H), 7.36-7.54 (5H, m, Ph-H), 7.67 (1H, d, J 2.0 Hz, C=CHPh); δ_C(400 MHz, $CDCl_3$) 49.8 (CH-4), 61.8 (CH_2), 81.4 (CH-5), 101.2 ($-OCH_2O-$), 105.8, 108.4, 118.9 (CH-Ar), 124.3 (C-3), 129.1 130.2, 131.4 (CH-Ph), 133.4, 134.2 (C_1', C_1'', -Ar, Ph), 139.7 (C=CHPh), 147.6, 148.1 (C_3', C_4'-Ar), 172.5 (C=O); m/z 324 (M^+, 33), 236 (6), 205 (5), 174 (14), 162 (6), 151 (100), 149 (65), 145 (16), 129 (85), 115 (34), 105 (35), 93 (19), 65 (23).

trans-(4-tert-Butyldimethylsilyloxymethyl)-5-(3,4-methylene dioxyphenyl) dihydro-2(3H)-furanone (18).

trans-Lactone alcohol (11) (3.24g, 13.7mmol), imidazole (2.33g, 34.2mmol, 2.5eq) and tert-butyldimethylsilyl chloride were dissolved in dry dimethylformamide (50ml) and stirred overnight. 5% sodium bicarbonate solution was added to the solution and the mixture was extracted with 40-60 petrol (4x50ml). The combined extracts were dried ($MgSO_4$), evaporated and the residue was chromatographed (silica, ether/40-60 petrol) to give the title compound (3.50g, 9.99mmol, 73%) as a colourless oil which

solidified on standing. An analytical sample was recrystallised from hexane. m.p. 57°C (Found: C, 61.7; H, 7.8%; $M^+-{}^tBu$, 293.0865. $C_{18}H_{26}O_5Si$ requires C, 61.7; H, 7.5%; $M^+-{}^tBu$, 293.0846); ν_{max}^{KBr} 2950, 2860, 1770, 1500, 1310, 1275, 1200, 1105, 1005, 950, 840, 785 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.07, 0.08 (3H x 2, 2 x s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 2.56 (1H, m, 4-H), 2.62-2.67 (2H, (m), 3-H_2), 3.66 (2H, d, J 4.0 Hz, $-CH_2O-$), 5.27 (1H, d, J 6.6 Hz, 5-H), 5.97 (2H, s, $-OCH_2O-$), 6.78-6.82 (3H, m, Ar-H); δ_C(250 MHz, $CDCl_3$) - 5.4 ($Si-CH_3$), 18.3 (Si-C), 25.9 ($-C(CH_3)_3$), 31.2 (CH_2-3), 46.5 (CH-4), 61.6 ($-CH_2O-$), 82.9 (CH-5), 101.4 ($-OCH_2O$), 106.3, 108.4, 119.6 (CH-Ar), 132.9 (C_1 -Ar), 148.0, 148.3 (C_3', C_4'-Ar), 176.0 (C=O); m/z 293 ($M^+-C(CH_3)$, 16), 263 (100), 245 (8), 207 (6), 161 (7), 149 (10), 135 (15), 131 (9), 75 (37), 73 (21), 59 (11).

trans-4-(tert-Butyldimethylsilyloxymethyl)-5-(3,4-methylene dioxyphenyl)-3-trimethylsilyl-dihydro-2(3H)-furanone (19).

Lactone (18) (1.06g, 3.02mmol) was dissolved in dry tetrahydro furan (25ml) under a nitrogen atmosphere and the solution was cooled to 0°C. Triethylamine (1.26ml, 0.92g, 3eq) was added followed by trimethylsilyl trifluoromethane sulphonate (1.46ml, 1.68g, 7.55mmol, 2.5eq) and the solution was stirred for two hours. Ether (50ml) was added and the solution was washed with 2M hydrochloric acid. The aqueous extracts were washed with ether and the ether extracts were combined, dried ($MgSO_4$) and

were evaporated. The residue was chromatographed (silica, ether /40-60 petrol) to give the title compound (0.47g, 1.14mmol, 38%) as a colourless oil identified by ^1H NMR and M.S. (Found: M^+, 422.1954. $C_{21}H_{34}O_5Si$ requires M^+, 422.1945); δ_H(90 MHz, $CDCl_3$) 0.04 (15H, m, $SiCH_3$) 0.84 (9H, S, $-C(CH_3)_3$).

trans-4-(tert-Butyldimethylsilyloxymethyl-5-(3,4-methylene dioxyphenyl)-E-phenylmethylene-dihydro-2-furanone (20).

Lithium diisopropylamide was prepared from diisopropylamine (0.18ml, 0.13g, 1.28mmol) and n-butyl lithium (0.90ml of a 1.4M solution in hexane, 1.26mmol) in dry tetrahydrofuran (25ml) solution at 0°C under a nitrogen atmosphere. This was cooled to -78°C (dry ice/acetone bath) and a solution of α-silyllactone (19) (0.47g, 1.14mmol) in dry tetrahydrofuran (2ml) was added and the resulting solution stirred for 15 minutes. Freshly distilled benzaldehyde (0.21g, 2.0mmol) in dry tetrahydrofuran (1ml) was added and the solution was stirred for 2 hours before being allowed to warm to room temperature over one hour. Water was added to quench and the solution was extracted with ether (3x 20ml). The combined ether extracts were washed (brine) and dried ($MgSO_4$). Evaporation and chromatography of the residue (silica, ether/40-60 petrol) gave the title compound (0.27g, 0.62mmol, 59%) as a viscous oil which recrystallised from hexane. m.p. 97-98°C (Found: C,68.85; H, 7.25%; M^+, 438.1852. $C_{25}H_{30}O_5Si$ requires C, 68.5; H, 6.9%; M^+, 438.1863), ν_{max}^{KBr} 2925, 2895, 2855, 1740, 1645,

1495, 1235, 1185, 1035, 850, 785, 695 cm^{-1}; δ_H(400MHz, $CDCl_3$) 0.03, 0.05 (3H x 2, 2 x S, $Si(CH_3)_2$), 0.91 (9H, s, $-C(CH_3)_3$), 3.78 (2H, m, $-CH_2O-$), 3.92 (1H, m, 4-H), 5.59 (1H, s, 5-H), 4.94 (2H, s, $-OCH_2O-$), 6.78-6.79 (3H, m, Ar-H), 7.39-7.53 (5H, m, Ph-H), 7.65 (1H, s, C=CHPh); δ_C(400MHz, $CDCl_3$) -5.44, -5.49 ($Si(CH_3)_2$), 18.2 (Si-C), 25.8 ($C(CH_3)_3$), 50.4 (CH-4), 62.4 ($-CH_2O-$), 81.0 (CH-5), 101.2 ($-OCH_2O-$), 105.6, 108.4, 118.6 (CH-Ar), 124.5 (C-3), 129.0, 130.0, 130.2 (CH-Ph), 133.7, 134.7 (C_1',C_1''-Ar, Ph), 139.2 (C=CHPh), 147.5, 148.1 (C_3',C_4'-Ar), 172.0 (C=O); m/z 438 (M^+,1), 381 (25), 351 (100), 277 (6), 229 (8), 219 (9), 191 (9), 149 (17), 135 (22), 113 (8), 89 (19), 73 (58).

3-α-Benzyl-4-β-hydroxymethyl-5-α-(3,4-methylenedioxyphenyl)-dihydro-2(3H)-furanone (23).

α-Benzylidene lactone (12a) (72.9mg, 0.225mmol) was dissolved in ethyl acetate (5ml) and hydrogenated using a 10% palladium on carbon catalyst. The solution was filtered through kieselguhr and evaporated to give the title compound (71.8mg, 0.220mmol, 98%) as a colourless gum. This was purified using preprative thin layer chromatography (ethyl acetate/hexane). (Found: M^+, 326.1163. $C_{19}H_{18}O_5$ requires M^+, 326.1154); ν_{max}^{KBr} 3460, 2905, 1760, 1490, 1450,

1250, 1260, 1180, 1040, 995, 810, 705 cm^{-1}; δ_H(400MHz, $CDCl_3$) 2.10 (1H, br s, -OH), 2.21 (1H, m, 4-H), 3.02 (1H, m, CH_AH_BPh), 3.12-3.22 (2H, m, 3-H, CH_AH_BPh), 3.32 (1H, dd, J 11.3, 4.0 Hz, $-CH_AH_BOH$), 3.46 (1H, dd, J 11.2, 3.3 Hz, $-CH_AH_BOH$), 5.13 (1H, d, J 9.2 Hz, 5-H), 5.91 (2H, s, $-OCH_2O-$), 6.53-6.77 (3H, m, Ar-H), 7.17 -7.36 (5H, m, Ph-H); δ_C(400MHz, $CDCl_3$) 35.0 ($-CH_2Ph$), 43.2 (CH-3), 50.7 (CH-4), 59.0 ($-CH_2OH$), 81.1 (CH-5), 101.3 ($-OCH_2O-$), 106.6, 108.2, 120.4 (CH-Ar), 127.0, 128.8, 129.3 (CH-Ph), 132.0, 137.8 (C_1',C_1''-Ar, Ph), 148.0, 148.1 (C_3', C_4'-Ar), 177.9 (C=O); m/z 326 (M^+, 64), 178 (20), 151 (74), 150 (53), 149 (30), 135 (11), 91 (31), 65 (10), 61 (16), 43 (100).

3-β-Hydroxy-4-β-hydroxymethyl-3-α-hydroxyphenylmethyl-5--(3,4-methylenedioxyphenyl)dihydro-2-furanone (22a).

α-Benzylidene lactone (12a) (87mg, 0.268mmol) was dissolved in tert-butanol/tetrahydrofuran/water 10:3:1 (5ml) and N-methyl morpholine-N-oxide (120mg, 4eq) and osmium tetroxide solution (3.5mg, in 0.35ml tert-butanol, 5mol%) was added. The solution was stirred for 10 days before solid sodium metabisulphite (1g) and water (2ml) were added. Stirring was continued for an hour to ensure that all osmium tetroxide was destroyed. The mixture was partitioned between ethyl acetate (20ml) and brine (20ml). The organic layer was separated and the aqueous layer was re-extracted

with a further portion of ethyl acetate. The combined organic extracts were washed with sodium metabisulphite solution before drying ($MgSO_4$) and evaporation of the solvent. Purification of the residue on preparative thin layer chromatography (silica, ethyl acetate/hexane 1:2) gave the title compound (39.0mg, 0.109 mmol, 41%) and unreacted starting material. The product was recrystallised from chloroform to give white crystals. m.p. 151 -154°C (Found; C, 63.4; H, 5.1%; M^+, 358.1067. $C_{19}H_{18}O_7$ requires C, 63.7; H, 5.1%; M^+, 358.1053); ν_{max}^{KBr} 3520-3340, 2900, 1740, 1490, 1450, 1260, 1195, 1115, 1040, 980, 940, 825; δ_H(250MHz, CD_3COCD_3) 2.78 (1H, m, 4-H), 4.08-4.11 (2H, m, CH_2OH), 4.21 (1H, br s, -OH), 4.56 (1H, br s, -OH), 5.19 (1H, s, -CHOH(Ph)), 5.39 (1H, br s, -OH), 5.42 (1H, d, J 10.3 Hz, 5-H), 6.03 (2H, s, $-OCH_2O-$), 6.85-6.97 (3H, m, Ar-H), 7.23-7.45 (5H, m, Ph-H); δ_C(250MHz, CD_3COCD_3) 57.7 ($-CH_2OH$), 58.6 (CH-4), 76.1 (-CH(OH)Ph), 79.8 (C-3), 80.7 (CH-5), 102.3 ($-OCH_2O-$), 107.7, 108.9, 121.8 (CH-Ar), 127.9, 128.3, 129.2 (CH-Ph), 134.0, 140.4 (C_1', C_1''-Ar, Ph), 148.9 (x2?, C_3', C_4'-Ar), 176.1 (C=O); m/z 358 (M^+,14), 252 (71), 221 (56), 203 (11), 175 (65), 151 (52), 135 (63), 107 (73), 93 (28), 77 (100).

4-β-Hydroxymethyl-5-α-(3,4-methylenedioxyphenyl)-3-E-(3,4-methylenedioxybenzylidene)dihydro-2(3H)-furanone (12b).

Lactone alcohol (11) (4.0g, 16.95mmol), piperonal (3.80g, 25mmol, 1.5eq) and sodium methoxide (2.01g, 2.2eq) were stirred together in dry benzene (80ml) overnight. 2M sulphuric acid was added to acidify and stirred for four hours. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica, ethyl acetate/hexane) to give a yellow gum, which on standing in a little ethyl acetate gave crystals of the title compound. (2.1g, 5.70mmol, 34%). This was recrystallised from ethyl acetate/hexane to give white crystals. m.p. 150°C (Found; C, 64.9; H, 4.4%; M^+, 368.0876. $C_{20}H_{16}O_7$ requires C, 65.2, H, 4.4%, M^+, 368.0896); ν_{max}^{KBr} 3420, 2960-2900, 1715, 1640, 1610, 1500, 1455, 1270, 1220, 1045, 935, 825 cm^{-1}; δ_H(400MHz, CD_3COCD_3) 3.72 (2H, m, 4-H, $-CH_AH_BOH$), 3.99 (1H, m, $-CH_{A-B}OH$), 5.64 (1H, d, J 0.9 Hz, 5-H), 5.99 (2H, 2 x d, J 0.9 Hz, $-OCH_2O-$), 6.08 (2H, 2 x d, J 0.9 Hz, $-OCH_2O-$), 6.81-6.83, 6.91-6.94, 7.22-7.24 (6H, m, Ar-H), 7.49 (1H, d, J 1.2 Hz, C=CHAr), δ_C(400MHz, CD_3COCD_3) 51.0 (CH-4), 62.4 ($-CH_2OH$), 81.4 (CH-5), 102.3, 102.8 ($-OCH_2O-$, x2), 106.5, 109.0, 109.5, 109.6, 119.6, 127.4 (CH-Ar), 123.9 (C-3), 129.0, 136.2 (C_1', C_1''-Ar), 138.8 (C=CHAr), 148.4, 149.0, 149.4, 150.3 (C_3', C_4', C_3'', C_4''-Ar), 172.3 (C=O); m/z 368 (M^+ 64), 337 (22), 271 (9), 260 (7), 237 (11), 218 (17), 200 (16), 190 (73), 173 (36), 159 (57), 149 (85), 122 (10), 85 (100), 59 (35).

4-β-Hydroxymethyl-3-α-(3,4-methylenedioxybenzyl)-5-α-(3,4-methylenedioxyphenyl)dihydro-2(3H)-furanone (24).

Lactone alcohol (12b) (103.1mg, 0.280mmol) was dissolved in ethyl acetate (5ml) and hydrogenated using a 10% palladium on carbon catalyst until TLC showed that all the olefin had reacted. Filtration through kieselguhr and evaporation to dryness gave an oil which after purification on preparative thin layer chromatography (silica, ethyl acetate/hexane 1:1) afforded the title compound (68.0mg, 0.184mmol, 66%) as a colourless gum. (Found; M^+, 370.1050. $C_{20}H_{18}O_7$ requires 370.1053), ν_{max}^{KBr} 3440, 2900, 1765, 1490, 1445, 1250, 1040, 935, 815, 735 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 2.17 (1H, br s, -OH), 2.23 (1H, m, 4-H), 2.95 (1H, dd, J 15.4, 8.4 Hz, $-CH_AH_BAr$), 3.06-3.12 (2H, m, 3-H, $-CH_AH_BAr$), 3.42 (1H, dd, J 11.4, 4.1 Hz, $-CH_AH_BOH$), 3.53 (1H, dd, J 11.2, 3.4 Hz, $-CH_AH_BOH$), 5.14 (1H, d, J 9.0 Hz, 5-H), 5.92, 5.93 (2 x 2H, 2 x s, $-OCH_2O-$ x 2), 6.56-6.73 (6H, m, Ar-H); δ_C(400MHz, $CDCl_3$) 34.6 ($-CH_2Ar$), 43.4 (CH-3), 50.5 (CH-4), 59.1 ($-CH_2OH$), 81.1 (CH-5), 101.0, 101.3 ($-OCH_2O-$ x 2), 106.5, 108.1, 108.4, 109.6, 120.3, 122.3 (CH-Ar), 131.3, 132.1, (C_1', C_1''-Ar), 146.5, 147.87, 147.94, 148.1 (C_3', C_4', C_3'', C_4''-Ar), 178.0 (C=O); m/z 370 (M^+, 21), 178 (100), 150 (10), 149 (6), 135 (76), 122 (18), 77 (12), 51 (25).

3-β-Hydroxy-4-α-(3,4-methylenedioxybenzyl)-2-α-(3,4-methylenedioxyphenyl)tetrahydrofuran and 3-β-hydroxy-4-α-(3,4-methylenedioxybenzyl)-2-β-(3,4-methylenedioxyphenyl)tetrahydrofuran (25a and 25b).

Lactone (24) (38.6mg, 0.104mmol) was dissolved in dry tetrahydro furan (5ml) and fresh lithium aluminium hydride (20mg) was added and the mixture was refluxed for two hours. The mixture was poured into ethyl acetate (20ml) and inorganic salts were removed by washing with 2M hydrochloric acid. The organic layer was separated and dried ($MgSO_4$). Evaporation and purification of the residue on preparative thin layer chromatography (silica, ethyl acetate/hexane) gave two products, isomer A (3.0mg, $8.4x10^{-6}$mol, 8%) first off plate and isomer B (2.9mg, 8.1x10 mol, 8%) having lower Rf value.

Isomer A. (M^+ not observed); δ_H(400 MHz, $CDCl_3$) 1.59 (-OH), 1.95 (1H, m, 4-H), 2.45 (1H, m, 3-H), 2.66 (1H, dd, J 13.7, 8.4 Hz, $-CH_AH_BAr$), 2,76 (1H, dd, J 13.7, 6.9 Hz, CH_AH_BAr), 3.62 (2H, d, J 5.5 Hz, $5\text{-}H_2$), 3.82 (1H, dd, J 8.8, 6.0 Hz, $-CH_AH_BOH$), 3.94 (1H, dd, J 8.8, 7.3 Hz, $-CH_AH_BOH$), 4.59 (1H, d, J 8.0 Hz, 2-H), 5.93, 5.96 (2 x 2H, 2 x s, $-OCH_2O-$ x 2), 6.61-6.91 (6H, m, Ar-H).

Isomer B. (Found; M^+ 356.1234. $C_{20}H_{20}O_6$ requires 356.1260); δ_H (400 MHz, $CDCl_3$) 1.59 (-OH) 2.08 (1H, m, 4-H), 2.41 (1H, m, 3-H), 2.63 (1H, dd, J 13.8, 8.7 Hz, $-CH_AH_BAr$), 2.79 (1H, dd, J 13.7, 6.4 Hz, $-CH_AH_BAr$), 3.83 (1H, dd, J 8.9, 6.0 Hz, $-CH_AH_BOH$), 3.93

(1H, dd, J 8.8, 7.3 Hz, $-CH_AH_BAr$), 4.07 (2H, m, 5-H_2), 4.52 (1H, d, J 8.1 Hz, 2-H), 5.93, 5.96 (2H x 2, 2 x s, $-OCH_2O-$ x 2), 6.58-6.87 (6H, m, Ar-H).

3-β-Hydroxy-4-β-hydroxymethyl-3-α-hydroxy (3,4-methylenedioxybenzyl)-5-α-(3,4-methylenedioxyphenyl) dihydro-2(3H)-furanone (22b).

α-Arylidene lactone (12b) (200.1mg, 0.543mmol) was dissolved in tert-butanol/tetrahydrofuran/water 10:3:1 (10ml) and osmium tetroxide (6.9mg in 0.69ml tert-butanol) and N-methyl morpholine -N-oxide (127mg, 1.08mmol, 2.0eq) were added. The solution was stirred for ten days before solid sodium metabisulphite (1g) and water (2ml) were added to destroy excess reagent. After stirring for a further hour the mixture was added to ethyl acetate (20ml) and washed with brine. The organic layer was separated and the aqueous layer was re-extracted with a further portion of ethyl acetate. The combined organic extracts were washed with aqueous metabisulphite solution and dried ($MgSO_4$). Evaporation of the solvent and separation of the residue on preparative thin layer chromatography gave the title compound (60.3mg, 0.150mmol, 28%) and unchanged starting material (80mg, 2.16×10^{-4}mol, 40%). Recrystallisation from chloroform gave the triol as white crystals. m.p. 185°C (Found; C, 59.9; H, 4.4%; M^+, 402.0934. C_{20}

$H_{18}O_9$ requires C, 59.7; H, 4.5%; M^+, 402.0951); ν_{max}^{KBr} 3510-3340, 2900, 1735, 1490, 1445, 1335, 1255, 1195, 1115, 1035, 930, 820 cm^{-1}; δ_H(250 MHz, CD_3COCD_3) 2.76 (1H, m, 4-H), 4.06-4.08 (2H, m, $-CH_2OH$), 4.17 (1H, s, -OH) 4.53 (1H, m, -OH), 5.12 (1H, s, -CH(OH)Ar) 5.37 (1H, d, J 4.0 Hz, -CH(OH)Ar), 5.41 (1H, d, J 10.4 Hz, 5-H), 5.97, 6.03 (2H x 2, 2 x s, $-OCH_2O-$ x 2), 6.73-6.96 (6H, m, Ar-H); δ_C(400 MHz, CD_3COCD_3) 57.6 ($-CH_2OH$), 58.5 (CH-4), 75.7 (-CH(OH)Ar), 79.6 (C-3), 80.7 (CH-5), 101.8, 102.3 ($-OCH_2O-$ x2), 107.69, 107.72,108.8, 109.7, 121.8, 122.7 (CH-Ar), 134.0, 134.4 (C_1', C_1'', -Ar), 147.7, 148.0, 148.9, 149.0 (C_3', C_4', C_3'', C_4'', -Ar), 176.2 (C=O); m/z 402 (M^+, 2) 384 (15), 252 (80), 234 (17) 221 (66), 203 (13), 175 (47), 161 (21), 151 (100), 150 (31), 149 (55) 135 (65), 131 (20), 93 (26), 65 (25).

5-α-(3,4-Methylenedioxyphenyl)-3-E-phenylmethylene -4-triisopropylsiloxymethyldihydro-2-furanone (28).

α-Benzylidene lactone alcohol (12a) (0.74g, 2.28mmol) was dissolved in dry dimethylformamide (20ml) and then triisopropyl silylchloride (0.53g, 2.74mmol, 0.59ml, 1.2eq) and imidazole (0.39g, 5.73mmol, 2.5eq) were added. The solution was stirred overnight and poured into sodium carbonate solution. The mixture was extracted with ethyl acetate (3 x 20ml) and the combined extracts were washed with water and brine to remove extracted

dimethylformamide. The organic layer was separated, dried ($MgSO_4$), and evaporated to dryness before purification of the residue by chromatography (silica, ether/40-60 petrol) to afford the title compound (0.47g, 0.98mmol, 43%) as a colourless oil. (Found; M^+, 480.2328. $C_{28}H_{36}O_5Si$ requires 480.2332); δ_H(250 MHz, $CDCl_3$) 0.96 (21 H, s, $[CH(CH_3)_2]_3$), 3.60 (1H, m, 4-H), 3.64 (1H, dd, J 18.4, 9.1 Hz, $-CH_AH_BOSi$), 3.91 (1H, dd, J 9.3, 3.5 Hz, $-CH_AH_BOSi$), 5.57 (1H, s, 5-H), 5.83 (2H, s, $-OCH_2O-$), 6.65-6.73 (3H, m, Ar-H), 7.27-7.30 (3H, m, Ph-H), 7.41-7.44 (2H, m, Ph-H), 7.56 (1H, d, J 1.7 Hz, C=CH Ph); δ_C(250 MHz, $CDCl_3$) 11.9 (Si-CH), 18.0 ($-(CH_3)_6$), 50.6 (CH-4), 62.9 (CH_2), 81.0 (101.2), 105.7, 108.4, 118.7 (CH-Ar), 124.8 (C-3), 129.0, 129.9, 130.2 (CH-Ph), 133.9, 134.9 (C_1', C_1'', -Ar), 139.2 (C=CHAr), 147.6, 148.2 (C_3', C_4', -Ar), 171.9 (C=O); m/z 480 (M^+, 3), 437 (11), 423 (17), 407 (100), 306 (7), 219 (8), 191 (8), 149 (24), 135 (15), 121 (11), 91 (8), 75 (12).

Hydrogenation and deprotection of TIPS protected compound.

α-Benzylidene lactone (28) (0.179g, 0.372mmol) was dissolved in ethyl acetate (10ml) and hydrogenated using a 10% palladium on carbon catalyst. The crude product was filtered through kiesel guhr and was evaported to dryness. The residue was dissolved in tetrahydrofuran (5ml) and a solution of tetrabutylammonium fluoride (1.1ml of a 1.0M solution, 1.1mmol, 3eq) was added.

The resulting solution was stirred overnight and examination by TLC showed that only one isomer was present. Purification using preparative thin layer chromatography (silica, ethyl acetate/hexane) produced only one compound (85.2mg, 0.261mmol, 70%) identical to that synthesised before (28) by 400 MHz ^{1}H NMR and TLC.

cis-4-Hydroxymethyl-5-(3,4-methylenedioxyphenyl)dihydro-2(3H)-furanone (30).

cis-Lactone acid (29) (4.00g, 16.0mmol) was dissolved in dry tetrahydrofuran (50ml) under a nitrogen atmosphere and was cooled to 0°C. A solution in tetrahydrofuran of borane-methyl sulphide complex (12.0ml of a 2M solution, 24.0mmol, 1.5eq) was added over ten minutes using a syringe via a rubber septum. The reaction was stirred overnight and allowed to warm slowly to room temperature. Excess reagent was destroyed by adding methanol dropwise and then the resulting solution was evaporated to dryness in vacuo. Ethyl acetate (50ml) and 5% sodium bicarbonate solution (50ml) were added to dissolve the residue and the organic layer was separated. The organic layer was washed (sodium bicarbonate solution and brine) and then dried ($MgSO_4$) before evaporation of the organic solvent gave the title compound (3.06g, 12.95mmol, 81%) as a viscous oil. This was purified using chromatography (silica, ethyl acetate/petrol) but the compound still refused to recrystallise

from the usual solvents. (Found; M^+, 236.0668. $C_{12}H_{12}O_5$ requires 236.0685); ν max 3460 (br), 2920, 1790, 1511, 1462, 1260, 1180, 1050, 945, 815 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 1.86 (1H, br, -OH), 2.63 (1H, dd, J 17.5, 4.9 Hz, 3-H), 2.76 (1H, dd, J 17.5, 8.3 Hz, 3-H), 2.86-2.93 (1H, m, 4-H), 3.31-3.36 (2H, m, $-CH_2OH$), 5.60 (1H, d, J 6.8 Hz, 5-H), 5.98 (2H, s, $-OCH_2O-$), 6.74-6.82 (3H, m, Ar-H); δ_C(400 MHz, $CDCl_3$) 32.2 (CH_2-3), 42.1 (CH-4), 61.2 ($-CH_2$ OH), 82.6 (CH-5), 101.4 ($-OCH_2O-$), 106.0, 108.4, 118.3 (CH-Ar), 129.4 (C_1-Ar), 147.8, 148.1 (C_3, C_4-Ar), 176.7 (C=O); m/z, 236 (M^+, 18), 151 (100), 150 (8), 149 (9), 123 (5), 121 (3), 93 (45), 65 (14).

cis-4-tert-Butyldimethylsilyloxymethyl-5-(3,4-methylene dioxyphenyl)dihydro-2(3H)-furanone (32).

cis-Lactone alcohol (30) (2.00g, 8.47mmol) was dissolved in dry dimethylformamide (25ml). Imidazole (1.44g, 21.2mmol, 2.5eq) and tert-butyldimethylsilyl chloride (1.53g, 10.15mmol, 1.2eq) were added and the solution was stirred overnight. The reaction mixture was poured into 5% sodium bicarbonate solution (50ml) and extracted with ether (4x50ml). The combined ether extracts were washed (water and brine) and dried ($MgSO_4$) before being evaporated to dryness to give the title compound (2.91g, 8.30mmol, 98%) as a colourless, viscous oil. Column chromatography (silica, ether/40-60 petrol) gave the pure silyl ether which recrystallised from hexane to give white needles. m.p. 69°C (Found: C, 61.75; H, 7.7%; M^+, 350.1535 $C_{18}H_{26}O_5Si$ requires C, 61.7; H, 7.5%; M^+, 350.1550); ν_{max}^{KBr} 2915, 2860, 1755, 1510, 1445, 1240, 1120, 1050, 850, 785 cm^{-1}; δ_H(250 MHz, $CDCl_3$) -0.09, -0.07 (6H, 2 x s, $Si(CH_3)_2$), 0.85 (9H, s, $SiC(CH_3)_3$), 2.54-2.82 (3H, m, 3-H_2, 4-H), 3.28-3.30 (2H, m, $-CH_2OSi$), 5.56 (1H, d, J 6.3 Hz, 5-H), 5.96, 5.97 (2H, 2 x d, J 1.3 Hz, $-OCH_2O-$), 6.72-6.84 (3H, m, Ar-H); δ_C(250 MHz, $CDCl_3$) -5.7 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(\underline{CH}_3)_3$), 32.5 (CH_2-3), 42.5 (CH-4), 61.6 ($-CH_2OSi$), 82.9 (CH-5), 101.2 ($-OCH_2O-$), 106.7 108.2, 119.2 (CH-Ar), 129.7 (C_1'-Ar), 147.5, 147.9 (C_3', C_4' -Ar), 176.1 (C=O); m/z 350 (M^+, 1%), 293 (14), 263 (100), 245 (6), 219 (6), 205 (5), 161 (5), 149 (6), 135 (14), 131 (9), 113 (6), 75 (47).

4-β-tert-Butyldimethylsilyloxymethyl-5-β-(3,4-methylene dioxyphenyl)-3-α-trimethylsilyl dihydro-2(3H)-furanone (33).

cis-Lactone (32) (1.79g, 5.11mmol) was dissolved in dry ether (25ml) under a nitrogen atmosphere and was cooled to 0°C. Triethylamine (1.64ml, 1.19g, 11.75mmol, 2.3eq) and trimethylsilyl trifluoromethanesulphonate (2.07ml, 2.39g, 2.1eq) were added and the solution was stirred for one hour. 2M Hydrochloric acid (50ml) and ether (50ml) were added, shaken and the organic layer separated. The ether extract was washed with 5% sodium bicarbonate solution, dried ($MgSO_4$) and was evaporated to dryness. The resulting crude solid was columned (silica, ether/40-60 petrol 1:2) to yield the title compound (0.59g, 1.40mmol, 27%) as a white solid. This was characterised and used without further purification. (Found: $M^+ - C_4H_9$, 365.1209. $C_{21}H_{34}Si_2O_5 - C_4H_9$($C_{17}H_{25}Si_2O_5$) requires 365.1240); δ_H(90 MHz, $CDCl_3$) -0.09 (6H, s, $Si(CH_3)_2$), 0.26 (9H, s, $Si(CH_3)_3$), 0.83 (9H, s, $SiC(CH_3)_3$), 2.36 (1H, d, J 2.2 Hz, 3-H), 2.71 (1H, m, 4-H), 3.15-3.24 (2H, AB X m, $-CH_2OSi$), 5.42 (1H, d, J 7.0 Hz, 5-H), 5.97 (2H, s, $-OCH_2O-$), 6.77-6.83 (3H, m, Ar-H); m/z 365 ($M^+ - C_9H_9$, 24), 335 (365 - 2 x CH_3, 19), 263 (9), 201 (6), 173 (6), 147 (64), 135 (35), 73 (100).

4-β-tert-Butyldimethylsilyloxy-5-β-(3,4-methylenedioxyphenyl)-3-E-(3,4-methylenedioxyphenylmethylene)dihydro-2(3H)-furanone (34).

Lithium diisopropylamide was prepared in dry tetrahydrofuran (20ml) under a nitrogen atmosphere at 0°C from diisopropylamine (0.22ml, 0.156g, 1.54mmol) and a solution in hexane of n-butyl lithium (1.28ml of a 1.20 M solution, 1.54mmol). The solution was cooled to -78°C (dry ice/acetone bath) and a solution of the α-silyl lactone (33) (0.59g, 1.40mmol in 2ml tetrahydrofuran) was added. The reaction was stirred for fifteen minutes to allow the anion to form and then a solution of piperonal (0.23g, 1.54mmol, 1.1eq in 2ml tetrahydrofuran) was added. The solution was stirred for one hour at -78°C and was then allowed to warm to 0°C over an hour. Water was added to quench and the reaction mixture was diluted with ether (50ml) and brine (50ml). The ether layer was separated and the aqueous phase was re-extracted with more ether. The combined ether phases were washed (2M hydrochloric acid) and dried ($MgSO_4$). The organic solvent was evaporated and the residue was chromatographed (silica, ether/40-60 petrol 1:3) to give the title compound (0.447g, 0.926mmol, 60%) which was recrystallised from hexane to give white crystals. m.p. 167-8°C (Found: C, 64.6; H, 6.4%; M^+, 482.1768. $C_{26}H_{30}O_7$ Si requires C, 64.7; H, 6.3%; M^+ 482.1761); ν_{max}^{KBr} 2945, 2900, 2870, 1745, 1650, 1490, 1445, 1265, 1180, 1040, 940, 815, 780 cm^{-1}; δ_H(400 MHz, $CDCl_3$) -0.24 (6H, 2 x s, $Si(CH_3)_2$), 0.73 (9H, s, $SiC(CH_3)_3$), 3.41 (1H, dd, J 10.3, 4.0 Hz, $-CH_AH_BOSi$), 3.60 (1H, dd, J 10.3, 5.2

Hz, $-CH_A\underline{H_B}OSi$), 3.74-3.79 (1H, m, 4-H), 5.53 (1H, d, J 6.4 Hz, 5-H), 5.96-5.97 (2H, 2 x s, J 1.4 H , $-OCH_2O-$), 6.01-6.02 (2H, 2 x d, J 1.3 Hz, $-OCH_2O-$), 6.77-7.15 (6H, m, Ar-H), 7.54 (1H, d, J 1.5 Hz, C=C$\underline{H}$Ar); δ_C (400 MHz, CDCl) -5.9 ($Si(CH_3)_2$), 18.1 ($Si\underline{C}(CH_3)_3$), 25.7 (Si $C(\underline{CH_3})_3$), 46.4 (CH-4), 60.7 (CH_2), 80.9 (CH-5), 101.2, 101.7 ($-OCH_2O-$ x 2) 107.1, 108.1, 108.8, 109.1, 119.5, 126.6 (CH-Ar) 125.7 (C-3), 128.4, 129.3 (C_1', C_1'' -Ar), 137.6 (C=CHAr), 147.4, 147.7, 148.4, 149.3 (C_3', C_4', C_3'', C_4'' -Ar), 172.2 (C=O); m/z 482 (M^+, 19), 425 (65), 395 (92), 321 (13), 305 (6), 273 (32), 149 (14), 135 (45), 89 (41), 73 (100).

4-β-tert-Butyldimethylsilyloxymethyl-3-β-(3,4-methylene dioxybenzyl)-5-β-(3,4-methylenedioxyphenyl)dihydro-2(3H)-furanone (35).

α-Arylidene lactone (34) (151.4mg, 0.314mmol) was dissolved in ethyl acetate (10ml) and hydrogenated using a 10% palladium on carbon catalyst. The catalyst was filtered off through kieselguhr and the solution was evaporated to dryness. The residue was chromatographed (silica, ether/40-60 petrol 1:4 ----> 1:3 gradient) to give the title compound (112.8mg, 0.233mmol, 74%) as a white crystalline solid which was recrystallised from hexane. m.p. 107°C (Found: C, 64.4; H, 6.9%; M^+, 484.1902. $C_{26}H_{32}O_7Si$ requires C, 64.4; H, 6.7%; M^+, 484.1918); ν_{max}^{KBr} 2950, 2930, 2900, 1760, 1500, 1450, 1245, 1165, 1075, 1045, 925, 840, 785 cm^{-1}; δ_H (400 MHz, $CDCl_3$) -0.18, -0.01 (3H x 2, 2 x s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 2.52 (1H, m, 3-H), 2.84 (1H, dd, J 15.0, 10.5 Hz, $-CH_AH_BAr$), 3.10 (1H, m, 4-H), 3.28 (1H, d, J 10.8 Hz, $-CH_AH_B$ OSi), 3.35 (1H, dd, J 15.0, 3.35 Hz, $-CH_AH_BAr$), 3.57 (1H, dd, J 10.8, 2.6 Hz, $-CH_AH_BOSi$), 5.43 (1H, d, J 5.4 Hz, 5-H), 5.94 (4H, s, $-OCH_2O-$ x 2), 6.71-6.79 (5H, m, Ar-H), 6.93 (1H, s, Ar-H); δ_H (400 MHz, $CDCl_3$) -6.0 ($Si(CH_3)_2$), 17.8 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 30.8 ($-CH_2Ar$), 45.0 (CH-3), 45.3 (CH-4), 57.8 ($-CH_2O-$), 81.7 (CH-5), 101.0, 101.1 ($-OCH_2O-$ x 2), 106.7 108.0, 108.4, 108.6, 119.0, 121.2 (CH-Ar), 129.7, 133.3 (C_1', C_1'' ,-Ar), 146.1, 147.0, 147.6, 147.9 (C_3', C_4', C_3'', C_4''), 177.0 (C=O); m/z 484 (M^+, 14), 427 (33), 397 (72), 305 (17), 275 (19), 262 (62), 231 (15), 185 (30), 161 (26), 149 (12), 135 (100), 89 (45), 73 (64).

3-β-Hydroxymethyl-4-β-(3,4-methylenedioxybenzyl)-2-α-(3,4-methylenedioxyphenyl)tetrahydrofuran (27) (Dihydrosesamin) and 3-β-Acetoxymethyl-4-β-(3,4-methylenedioxybenzyl)-2-α-(3,4-methylenedioxyphenyl)tetrahydrofuran (36) (Dihydrosesamin acetate).

Lactone (35) (91.0mg, 0.188mmol) was dissolved in dry tetrahydro furan (5ml). Lithium aluminium hydride (60mg) was added and the mixture was refluxed for one hour. The reaction was allowed to cool and ethyl acetate was added dropwise with stirring to destroy excess reagent. 2M Hydrochloric acid (50ml) and ethyl acetate (50ml) were added and shaken until all inorganic salts had dissolved. The inorganic layer was separated and re-extracted with more ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica, ether/40-60 petrol gradient) to give as colourless oils, dihydrosesamin (17.2mg, 0.0483mmol, 26%) and its acetate (6.2mg, 0.0151mmol, 8%). The spectral data from these compounds could be compared to literature data.

Dihydrosesamin; (Found: M^+, 356.1268, $C_{20}H_{20}O_6$ requires M^+, 356.1260); $\nu_{max}^{CHCl_3}$ 3380, 2880, 2780, 1610, 1500, 1440, 1110, 1030, 950 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 1.67 (1H, br s, -OH), 2.35 (1H, m, 3-H), 2.52 (1H, dd, J 13.5, 10.4 Hz, $-CH_2Ar$), 2.69 (1H, m, 4-H), 2.87 (1H, dd J 13.4, 5.2 Hz, $-CH_2Ar$), 3.71 (1H, dd, J 8.6, 6.5 Hz, 5-H), 3.74 (1H, dd, J 12.6, 6.5 Hz, $-CH_2OH$) 3.88 (1H, dd, J 10.8, 6.9 Hz, $-CH_2OH$), 4.04 (1H, dd, J 8.5, 6.6 Hz,

5-H), 4.79 (1H, d, J 6.2 Hz, 2-H), 5.93, 5.94 2H x 2, 2 x s, $-OCH_2O-$ x 2), 6.62-6.83 (6H, m, Ar-H); δ_C(400 MHz, $CDCl_3$) 33.3 ($-CH_2Ar$), 42.3 (CH-4), 52.6 (CH-3) 60.9 ($-CH_2OH$), 72.9 (CH_2-5), 82.9 (CH-2), 100.9, 101.0 ($-OCH_2O-$ x 2), 106.3, 108.1, 108.3, 108.9, 119.1, 121.4 (CH-Ar), 134.2, 137.1 (C_1', C_1'' -Ar), 146.0, 147.7, 147.8, 147.9 (C_3', C_4', C_3'', C_4'' -Ar); m/z 356 (M^+, 50), 234 (6), 217 (5), 203 (6), 192 (15), 178 (13), 173 (10), 151 (24), 149 (37), 135 (100), 122 (9), 93 (11), 77 (20).

Acetate; (Found: M^+, 398.1338. $C_{22}H_{22}O_7$ requires 398.1366); $\nu_{max}^{CHCl_3}$ 1725, 1480, 1430, 1120, 930 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 2.04 (3H, s, $-CH_3$), 2.47-2.54 (2H, m, $-CH_2Ar$), 2.69 (1H, m, 3-H), 2.80 (1H, dd, J 13.4, 5.0 Hz, $-\underline{CH}_2$ Ar), 3.71 (1H, dd, J 8.6, 6.9 Hz, 5-H_A), 4.05 (1H, dd, J 8.6, 6.6 Hz, 5-H_B), 4.15 (1H, dd, J 11.2, 7.5 Hz, $-\underline{CH_A}H_BOAc$), 4.31 (1H, dd, J 11.2, 4.3 Hz, $-CH_A\underline{H_B}OAc$), 4.76 (1H, d, J 6.1 Hz, 2-H), 5.93, 5.94 (2H x 2, 2 x s, $-OCH_2O-$ x 2), 6.60-6.81 (6H, m, Ar-H); δ_C(400 MHz, CDCl), 21.0 (CH_3), 33.3 ($-CH_2Ar$), 42.4 (CH-4),49.2 (CH-3), 62.7 ($-OCH_2OH$), 72.8 (CH_2-5), 83.1 (CH-2), 101.0, 101.1 ($-OCH_2O-$ x 2), 106.3, 108.1, 108.4, 108.9, 119.2, 121.5 (CH-Ar), 133.8, 136.6 (C_1', C_1'', -Ar), 146.1, 147.1, 147.9 (x2?) (C_3', C_4', C_3'', C_4'' -Ar), 171.0 (C=O); m/z 398 (M^+, 56), 338 (12), 217 (10), 203 (31), 188 (16), 173 (15), 162 (13), 149 (52), 135 (100), 113 (10), 77 (18).

4-β-tert-Butyldimethylsilyloxymethyl-3-α-hydroxy-3-β-(α-hydroxy-3,4-methylenedioxybenzyl)-5-β-(3,4-methylenedioxyphenyl)dihydro-2(3H)-furanone (37).

α-Arylidene lactone (34) (106.9mg, 0.222mmol) was dissolved in tert-butanol/tetrahydrofuran/water, 10:3:1 (10ml). N-Methyl morpholine-N-oxide (52mg, 0.44mmol, 2eq) and osmium tetroxide (2.8mg in 0.28ml tert-butanol solution, 0.011mmol, 5mol%) were added and the sealed solution was stirred for 17 days. Excess osmium tetroxide was destroyed by adding solid sodium metabisulphite (1g) and water (2ml). After one hour further stirring, the reaction mixture was partitioned between ethyl acetate (50ml) and brine (30ml) and the organic layer was separated. The aqueous phase was re-extracted with ethyl acetate and the combined oganic extracts were washed with saturated sodium metabisulphite solution. The organic solution was dried ($MgSO_4$), evaporated to dryness and the residue was chromatographed (silica, ether/40-60- petrol 1:3 ----> 1:1 gradient) to give the title compound (70.8mg, 0.137mmol, 62%) as a white crystalline solid. This was recrystallised from hexane /trace of chloroform; m.p. 188-90°C (Found: C, 60.05; H, 6.4%. $C_{26}H_{32}O_9Si$ requires C, 60.45; H, 6.2%); ν_{max}^{KBr} 3500, 3445, 2940, 2860, 1770, 1490, 1450, 1270, 1185, 1040, 940, 815, 775, 705 cm^{-1}. δ_H(400 MHz, $CDCl_3$) -0.25, -0.05 (3H x 2, 2 x s, $Si(CH_3)_2$), 0.95 (9H, s, Si $C(CH_3)_3$), 2.39 (1H, m, 4-H), 3.16 (1H, d, J 11.0 Hz, $-CH_AH_BOSi$), 3.33 (1H, dd, J 10.8, 2.4 Hz, $-CH_AH_BOSi$), 4.14 (1H, d, J 2.7 Hz, -CH(OH)Ar), 4.25 (1H, s, 3-OH), 5.23 (1H, d, J 2.3

Hz, -CH(OH)Ar), 5.96-5.99 (4H, m, $-OCH_2O-$ x 2), 6.03 (1H, d, J 5.2 Hz, 5-H), 6.75-7.06 (6H, m, Ar-H); δ_C(400 MHz, $CDCl_3$) -6.4, -5.9 ($Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 50.5 (CH-4), 57.2 (CH_2), 72.2 (-CH(OH)Ar), 78.7 (C-3), 82.1 (CH-5), 101.2, 101.3 ($-OCH_2O-$ x 2, 106.7, 108.3 (x2?), 108.9, 118.9, 122.9 (CH-Ar), 129.0, 131.5 (C_1', C_1'', -Ar), 147.3, 147.8, 148.00, 148.03 (C_3', C_4', C_3'', C_4'' -Ar), 177.3 (C=O).

3-α-Hydroxy-3-β-(α-hydroxy-3,4-methylenedioxybenzyl)-4-α-(α-hydroxy-3,4-methylenedioxybenzyl)-dihydro-2(3H)-furanone (40).

Diol (37) (58.0mg, 0.112mmol) was dissolved in tetrahydrofuran (10ml) and tetrabutylammonium fluoride (0.34ml of a 1.0M solution in tetrahydrofuran, 3eq) was added. The solution was stirred overnight and TLC showed that the reaction was complete. The solvent was evaporated in vacuo and the residue was dissolved in methanol (10ml) and two drops of conc. hydrochloric acid were added. The solution was stirred for an hour and the solvent was again removed in vacuo. The residue was purified using column chromatography (flash silica, ether/40-60 petrol gradient) to give the title compound (25.6mg, 0.0667mmol, 59%) as a white semi-crystalline solid which could not be recrystallised. (Found: C, 60.0; H, 4.9%. $C_{20}H_{18}O_9$ requires C, 59.7; H, 4.5%); δ_H(400 MHz, $CDCl_3$) 2.26 (1H, br s, -OH), 2.66 (1H, m, 4-H), 3.33 (1H, dd, J 8.2, 9.3 Hz, 5-H_A), 3.70 (1H, br s, -OH), 4.24 (1H, br s, -OH), 4.26 (1H, dd, J 9.4, 5.1 Hz, 5-H_B), 4.91 (1H, s, ArCH(OH)-), 4.93 (1H, s, Ar'CH(OH)-), 5.03 (1H, br s, -OH), 5.92, 5.93 (2H x 2, 2 x s, $-OCH_2O-$ x 2), 6.65-6.97 (6H, m, Ar-H); δ_C (400 MHz, $CDCl_3$) 45.3 (CH-4), 66.1 (CH_2-5), 70.0 (ArCH(OH)C-4), 76.1 (ArCH(OH)C-3), 78.8 (C-3), 101.2, 101.3 ($-CH_2O-$ x 2), 106.1, 107.1, 108.30, 108.35, 118.5, 120.7 (CH-Ar), 130.3, 135.0 (C_1', C_1'', -Ar), 146.9, 147.9, 148.0, (one peak hidden ? C_3', C_4', C_3'', C_4'', -Ar), 178.3 (C=O); m/z (M^+ not seen on EI), 252 ($C_{12}H_{12}O_6$, 32) 151 (100), 150 (63), 149 (67), 135 (6), 121 (12), 93 (30).

3-α-Hydroxy-3-β-(α-hydroxy-3,4-methylenedioxybenzyl)-4-α-(α-methoxy-3,4-methylenedioxybenzyl)-dihydro-2(3H)-furanone (41).

α-Arylidene lactone (32) (165.4mg, 0.3427mmol) was reacted as described previously with osmium tetroxide/N-methyl morpholine -N-oxide and worked up to give the crude product. This was then treated with tetrabutylammonium fluoride as explained before to remove the silicon protecting group. The crude product from this reaction was then dissolved in methanol (15ml) and two drops of conc. hydrochloric acid were added. The solution was refluxed gently for an hour and allowed to cool. TLC showed that essentially only one compound was present. The solvent was removed in vacuo to reveal a yellowish gum which was purified by flash chromatography (silica, ether/40-60 petrol gradient) to give the title compound (55.5mg, 0.133mmol, 39%) as a white crystalline solid. Recrystallisation from chloroform/hexane gave white needles of the pure compound which were identified by x-ray crystallography and gave the following data: m.p. 172-3°C (Found: C, 60.0; H, 4.9. M^+, 384.0831. $C_{21}H_{20}O_9$ requires C, 60.6; H, 4.8%, M^+, 384.0845); ν_{max}^{KBr} 3470, 3000, 2940, 1750, 1490, 1445, 1260, 1150, 1040, 930, 815 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 1.68 (1H, br s, -OH), 2.58 (1H, m, 4-H), 3.25 (3H, s, -OCH), 3.36 (1H, dd, J 9.4, 7.9 Hz, 5-H_A), 4.30 (1H, dd, J 9.4, 5.1 Hz, 5-H_B), 4.33 (1H, br s, -OH), 4.52 (1H, d, J 2.8 Hz, ArCH(OMe)-), 4.90 (1H, s, ArCH(OH)-), 5.95 (2H, 2 x d, J 1.5 Hz, $-OCH_2O-$), 5.97 (2H, 2 x d, J 1.4 Hz, $-OCH_2O-$), 6.65-6.98 (6H, m, Ar-H); δ_C(400 MHz, $CDCl_3$),

45.2 (CH-4), 56.9 ($-OCH_3$), 65.5 (CH -5), 76.2 (Ar<u>CH</u>(OH)-), 78.3 (C-3), 79.9 (Ar<u>CH</u>(OMe)-), 101.2 (two peaks here ?, $-OCH_2O-$), 106.4, 107.3, 108.3, 108.6, 119.5, 120.4 (CH-Ar), 130.5, 132.0 (C_1', C_1'', -Ar), 147.4, 147.8, 147.9, 148.3 (C_3', C_4', C_3'', C_4''-Ar), 177.1 (C=O); m/z 384 (M^+, very weak), 266 (7), 165 (100), 151 (11), 121 (11).

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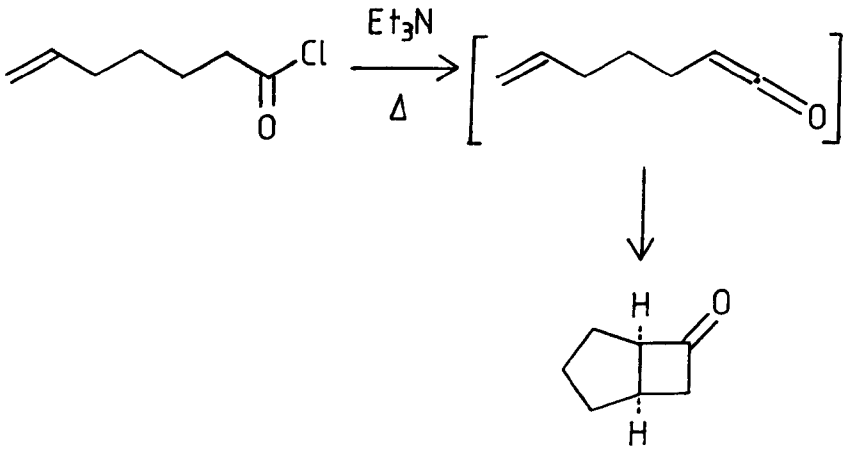
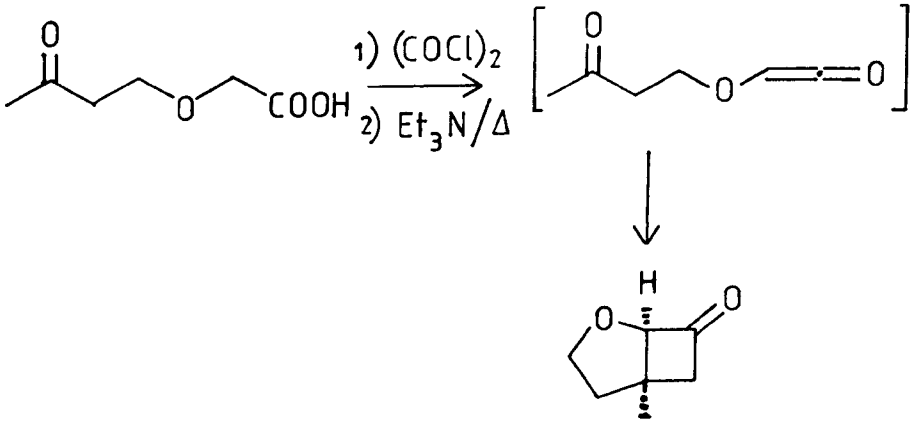
Chapter 5



SCHEME 1

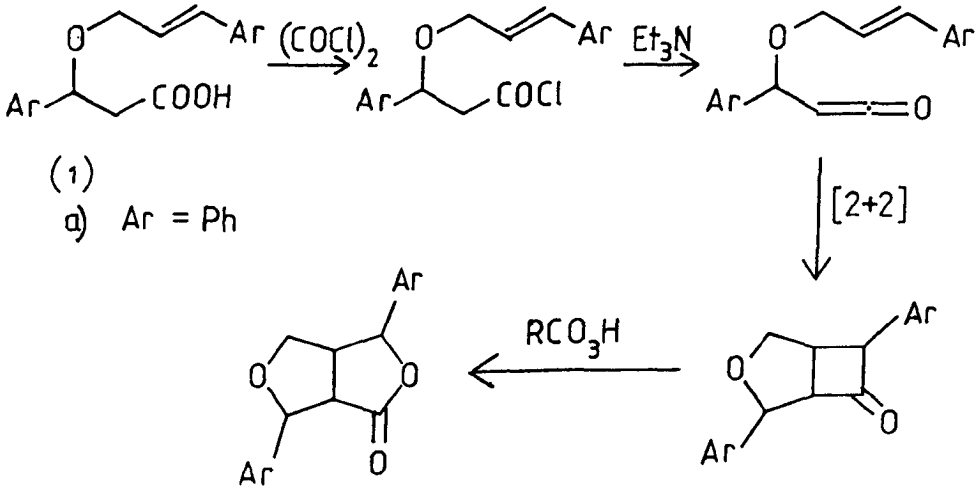


SCHEME 2

Intramolecular [2+2] Cyclisation Approach to Lignans.

A known reaction is the addition of ketenes to double bonds to form cyclobutanones. In recent years it has been shown that a suitably set up system can undergo an intramolecular [2+2] cyclo addition to create bicyclic compounds containing cyclobutanone rings[1]. A number of examples have been cited in the literature and two examples are shown in schemes 1 and 2. Moderate to high yields have been achieved.

Considering 2,6-diaryl-3,7-dioxabicyclo [3,3,0]octane lignans (2) as synthetic targets, an intramolecular [2+2] cyclisation followed by a Baeyer-Villiger oxidation can be envisaged as a route to these compounds (scheme 3).



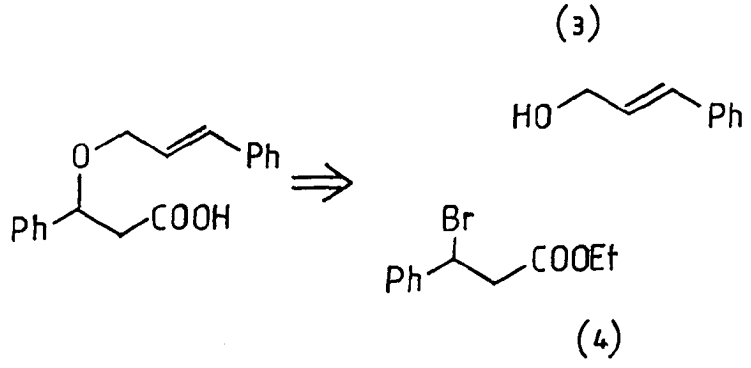
(1)

a) Ar = Ph

(2)

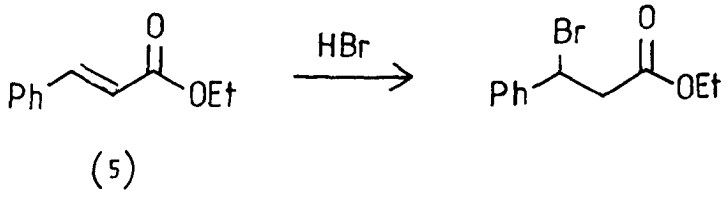
SCHEME 3

The first synthetic target became the acid (1a, Ar = Ph) and a number of approaches were tried. One possibility that was investigated was a Williamson type ether synthesis as shown in scheme 4.



SCHEME 4

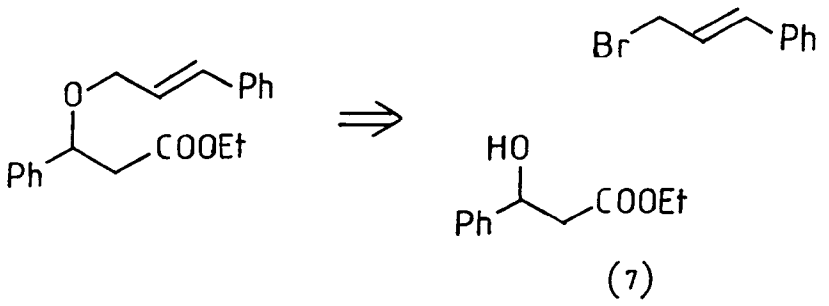
Hydrobromination of ethyl cinnamate (5) was attempted. 48% Hydrobromic acid proved ineffective as was passing hydrogen bromide gas through a dichloromethane solution of the compound. 45% Hydrobromic acid in acetic acid gave the required product (4) in approximately 30% yield as judged by ^{1}H NMR spectroscopy. Complete addition was achieved by cooling a solution of ethyl cinnamate in 45% hydrobromic acid in acetic acid to 0°C.



(5)

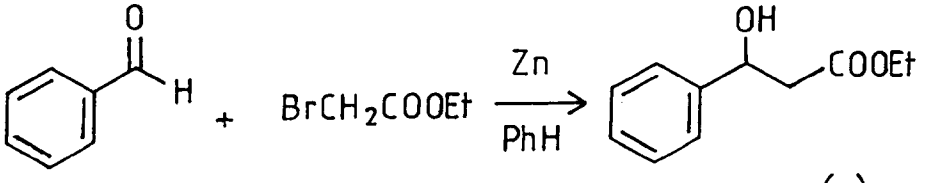
SCHEME 5

(8)



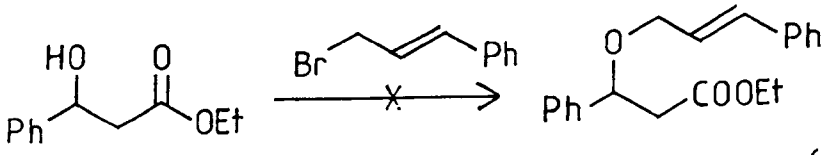
(7)

SCHEME 6



(7)

SCHEME 7



(6)

(a) NaH/ THF

(b) Ag_2O/DMF or Et_2O

(c) NaH/DMSO

(d) BuLi / Et_2N NEt_2 /THF

SCHEME 8

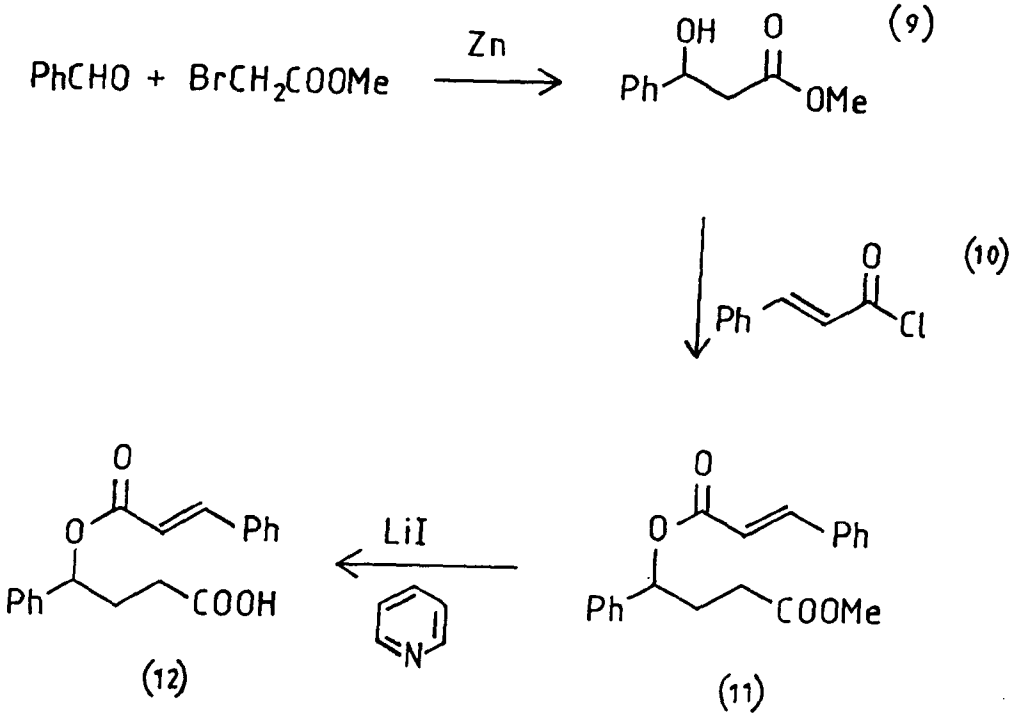
Hydrogen bromide gas was then passed through the solution. The isolated product showed no trace of double bond present. All attempts at distillation under high vacuum or atmospheric pressure gave rapid loss of hydrogen bromide despite reported literature conditions[2].

The alkoxide of cinnamyl alcohol was generated in THF solution using sodium hydride. When this solution was added to a solution of ethyl-3-phenyl-3-bromo propionate, immediate loss of hydrogen bromide was observed.

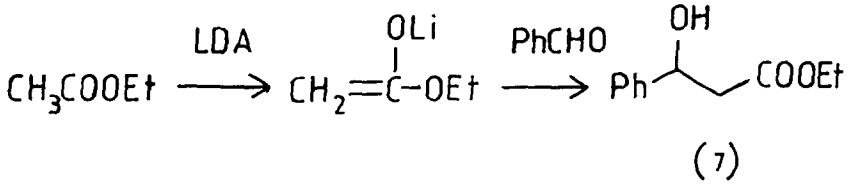
An alternative to this type of reaction is to exchange the bromo and hydroxy functions to give the alcohol (7) and cinnamyl bromide (8) as starting materials (scheme 6). The hydroxy ester (7) was prepared in good yields using the Reformatski reaction between ethyl bromoacetate and benzaldehyde[3] (scheme 7).

Reaction of this compound with cinnamyl bromide in refluxing acetone using potassium carbonate as base (with or without potassium iodide present) gave complicated and unidentifiable mixtures. This and other attempted ether formations are shown in scheme 8. The reaction was unsuccessful in all cases, complicated by the ease of elimination to form ethyl cinnamate.

A similar model that would be easier to form is the corresponding ester (11) that could be synthesised from the reaction between hydroxy ester (9) and cinnamoyl chloride (10). The hydroxy



SCHEME 9



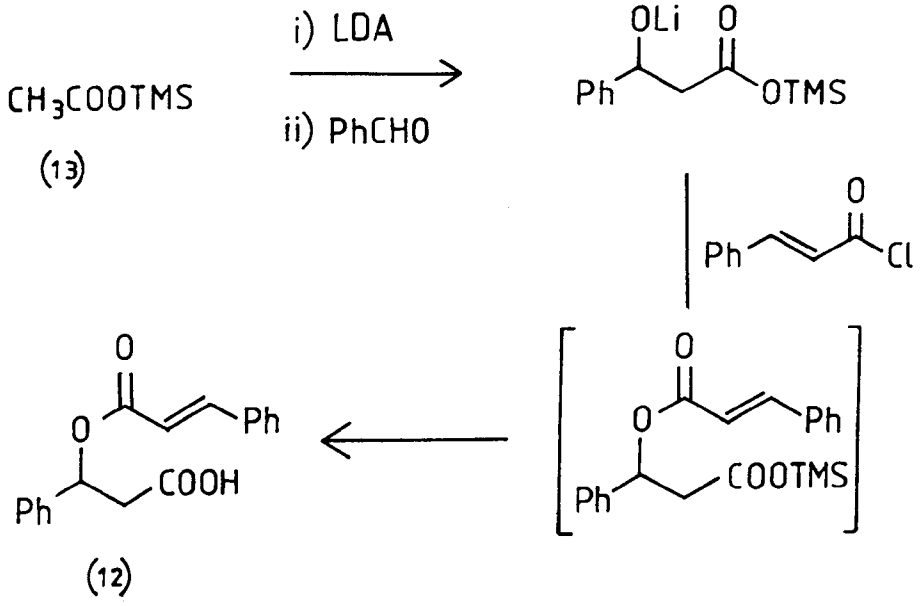
SCHEME 10

methyl ester (9) was prepared using methyl bromoacetate as a starting material in the Reformatski reaction (scheme 9) in high yields. Subsequent esterification with cinnamoyl chloride (10) in pyridine gave the expected product (11) in good yield. The problem of methyl ester cleavage to form the free acid (12) was complicated by the presence of a second ester function in the molecule.

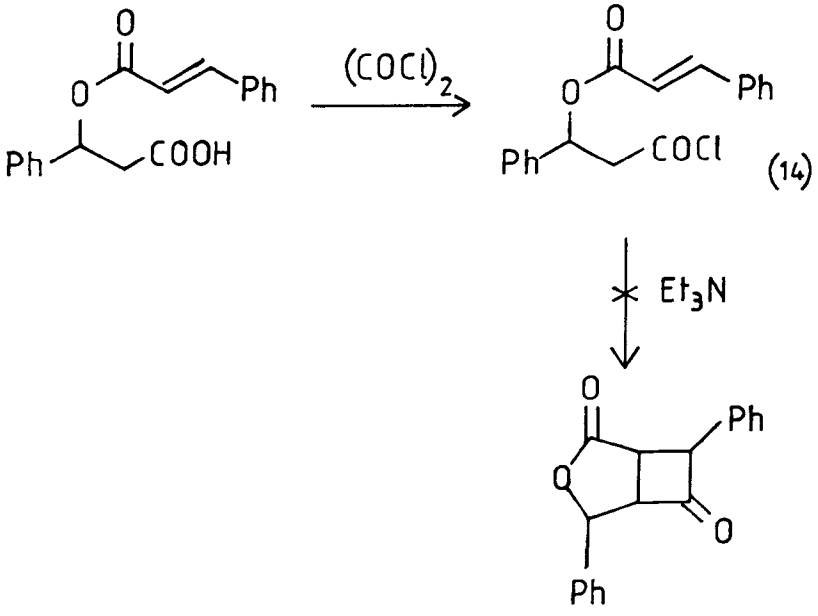
In an attempt to selectively cleave only the methyl ester, lithium iodide was used in refluxing pyridine[4]. A 24 hour reflux gave the desired compound (12) in 7% yield. Also isolated from the reaction mixture was cinnamic acid in 20% yield. The very low yield in this reaction led to other strategies being investigated.

A known reaction is the formation of the enolate of an ester using a strong base and trapping this with an aldehyde[5]. The enolate of ethyl acetate was generated at -78°C using LDA in solvent. This was trapped with benzaldehyde and gave the expected hydroxy ester (7) in 95% crude yield (scheme 10).

An extension of this reaction would be to use an acetate ester with an easily cleaved group which could reveal the carboxylic acid function. Trimethylsilyl acetate (13) was treated with LDA at -78°C and the enolate was reacted with benzaldehyde[6]. The reaction was quenched by adding cinnamoyl chloride (10) and the product isolated after aqueous acid work-up was the expected acid



SCHEME 11

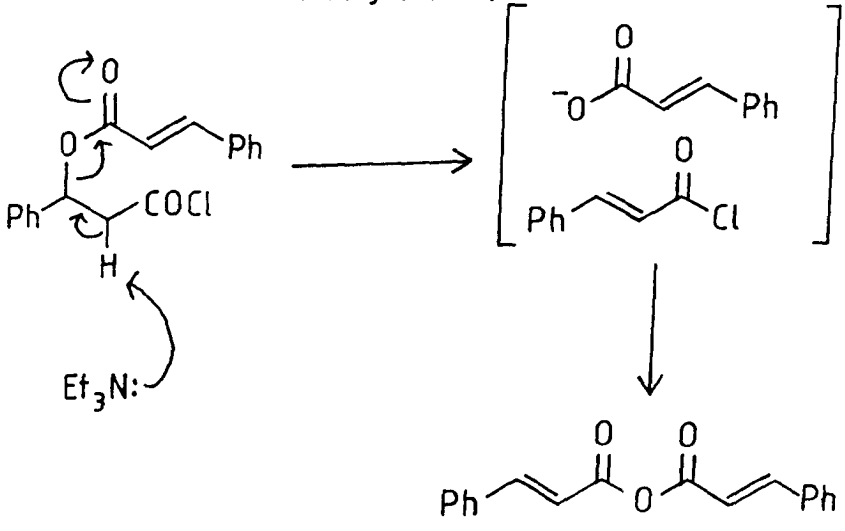


SCHEME 12

(12) albeit in very low yield (9%) after isolation (scheme 11). This reaction did however generate sufficient product to investigate the [2+2] cyclisation (scheme 12).

The acid chloride (14) was formed in THF solution using oxalyl chloride at room temperature. The solvent was removed under high vacuum and the residue was dissolved in toluene. Triethylamine was added and the solution was refluxed for 20 minutes which gave a single product by TLC. This product was isolated as an oil and although by TLC was much less polar than cinnamic acid, its ^{1}H NMR spectrum was virtually superimposable on that of cinnamic acid. A possible identity for the product was cinnamic anhydride (15), although this was not confirmed conclusively. A possible mechanism for its formation is shown in scheme 13.

This type of system would appear to be too labile to undergo the required [2+2] cyclisation - it is very likely that the required ketene was never actually formed.



SCHEME 13

(15)

Experimental.

Ethyl-3-bromo-3-phenyl propionate (4).

Ethyl cinnamate (10.0 g, 56.8 mmol) was dissolved in 45% W/W hydrobromic acid in acetic acid (15 ml). The solution was cooled to 0°C a slow stream of hydrogen bromide gas was passed through for two hours. Ethyl acetate (100 ml) was added and the mixture was washed repeatedly with brine, water and finally sodium bicarbonate solution to remove all traces of acetic acid. Drying ($MgSO_4$) and evaporation gave a colourless oil (10.8 g, 74%). δ_H ($CDCl_3$, 90 MHz) 1.17 (3H, t, J 7 Hz, $-CH_3$), 3.18-3.33 (2H, m, $-CHBrC\underline{H}_2$), 4.15 (2H, q, J 7 Hz, $-CH_2$), 5.36-5.51 (1H, m, $C\underline{H}BrCH_2-$), 7.28-7.53 (5H, m, Ph-H).

Ethyl 3-hydroxy-3-phenyl propionate[3] (7).

Activated zinc dust (10.44 g, 164 mmol) was charged to a 3-necked round bottom flask. A solution of ethyl bromoacetate (16.0 ml, 24.1 g, 144 mmol) and benzaldehyde (16.0 ml, 16.7 g, 157 mmol, 1.1 eq) in sodium dried benzene (80 ml) and dry ether (20 ml) was added dropwise at a rate so that gentle reflux was maintained. The solution was then refluxed for one hour to complete the reaction. 2M Hydrochloric acid was added to dissolve inorganics and the organic layer was separated. Drying ($MgSO_4$), evaporation and distillation gave the title compound (17.8 g, 91.6 mmol, 64%) as a colourless oil; b.p. 160°C, 13-14 mm Hg (Lit[3] 151-154°C,

11-12mm); δ_H($CDCl_3$, 90 MHz) 1.17 (3H, t, J 7 Hz, $-CH_3$), 2.51-2.70 (2H, m, CH_2CO) 3.62 (1H, s, -OH), 4.08 (2H, q, J 7 Hz, $-\underline{CH}_2\,CH_3$), 7.27 (5H, s, Ph-H).

Methyl 3-hydroxy-3-phenyl propionate[7] (9).

Methyl bromoacetate (8.0 ml, 12.9 g, 85.4 mmol) and benzaldehyde (9.45 ml, 9.9 g, 93.0 mmol, 1.1 eq) in dry benzene (40 ml) and dry ether (10 ml) solution was added dropwise to activated zinc dust (6.20 g, 95 mmol) to maintain a steady reflux. The reaction was refluxed for a further hour when the initial addition was complete. 2M Hydrochloric was added to dissolve inorganics and the organic layer was separated and dried ($MgSO_4$). Evaporation and distillation gave the title compound (6.38 g, 43.0 mmol, 51%) as a colourless oil; b.p. 160-164°C/18 mm Hg Lit[7]; δ_H($CDCl_3$, 90 MHz) 2.64-2.72 (2H, m, CH_2), 3.62 (3H, s, OMe), 4.16 (1H, s, OH), 5.00-5.17 (1H, m, CHBr), 7.30 (5H, s, Ph-H).

Cinnamoyl chloride[8] (10).

Cinnamic acid (10.0 g, 67.5 mmol) was dissolved in thionyl chloride and the solution was stirred for one hour. Evaporation and distillation gave the acid chloride (9.76 g, 58.6 mmol, 87%) as a pale yellow oil; b.p. 82-85°C/1 mm Hg.

Methyl-3-cinnamoyloxy-3-phenyl propionate (11).

Methyl-3-hydroxy-3-phenyl propionate (9), (4.0 g, 27 mmol) and cinnamoyl chloride (10) (4.49 g, 27 mmol) were dissolved together in pyridine (20 ml) and stirred overnight. The reaction was poured into ethyl acetate (100 ml) and the solution was extracted with 2M hydrochloric acid to remove pyridine. The organic solution was dried ($MgSO_4$) and evaporated. The crude residue was purified by column chromatography (silica, ethyl acetate/ 60-80 petrol 1:6) to give the title compound (6.15 g, 19.8 mmol, 73%) as a colourless oil. (Found: C, 73.5; H, 6.0%. $C_{19}H_{18}O_4$ requires C, 73.5; H, 5.85%); max 1725, 1705, 1630, 1495, 1450, 1440, 1420, 1365, 1305, 1255, 1220, 1205, 1175, 1075, 1010, 775, 700 cm^{-1}, δ_H ($CDCl_3$, 90 MHz) 2.70-3.23 (2H, ABX multiplet, CH_2) 3.67 (3H, s, OMe), 6.30-6.43 (1H, m, $C\underline{H}$ CH_2), 6.48 (1H, J 17 Hz, $C\underline{H}COO$), 7.33-7.63 (10H, m, Ph-H), 7.80 (1H, J 17 Hz, $C\underline{H}Ph$); δ_c($CDCl_3$, 400 MHz), 41.4 (CH_2), 51.9 (OCH_3), 72.3 ($C\underline{H}CH_2$), 117.8, 126.5, 128.1, 128.4, 128.7, 128.9, 130.4 (CH), 134.3, 139.3 (C_1', C_1'' - Ph), 145.4 (CH), 165.7, 170.2 (C=O x 2).

3-Cinnamoyloxy-3-phenyl propionic acid (12).

Methyl ester (11) (1.25 g, 4.03 mmol) and lithium iodide (0.54 g, 4.03 mmol) were refluxed in pyridine (10 ml) overnight. Extraction into ethyl acetate and washing with 2M hydrochloric acid, gave a solution containing mostly unchanged starting material. The organic phase was extracted with sodium bicarbonate

solution which on acidification gave a white precipitate. Purification by preparative TLC (silica, ethyl acetate/ hexane) gave cinnamic acid (20 mg) and the title compound (80 mg, 0.27 mmol, 7%). Recrystallisation from ethyl acetate and DMSO/ water gave the pure compound as white crystals; mp 184-185°C; (Found: C, 72.6; H, 5.7%, M+1 (FAB) 297. $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.4%; M+1, 297), $\delta_H(CD_3SOCD_3$ 250 MHz) 2.82-3.01 (2H, AB mult, CH_2), 6.18 (1H, dd, J 8.7, 5.3 Hz), 6.65 (1H, d, J 16.0 Hz, CHCOO), 7.31-7.46 (8H, m, Ph-H), 7.67 (1H, d, J 16.2 Hz, CHPh), 7.69-7.13 (2H, m, Ph-H), $\delta_c(CD_3SOCD_3$, 250 MHz) 41.3 (CH_2), 72.5 ($CHCH_2$), 118.3 126.8, 128.9, 128.95, 129.4, 131.0, 134.4, 140.2, 145.5 (CH=CH, CH=Ph) 165.7, 171.5 (C=O), m/z (FAB) 297 (M+1), 277, 257, 201, 185, 149, 131, 110, 100, 93, 75, 57, 45.

Ethyl-3-hydroxy-3-phenyl propionate[5] (7).

Lithium diisopropylamide was prepared from diisopropylamine (1.58 ml, 11.3 mmol) in *tetrahydrofuran* (30 ml) at 0°C by adding a solution n-butyl lithium in *hexane* (7.6 ml of a 1.45 M solution, 11.3 mmol) under a nitrogen atmosphere. The solution was cooled to -78°C and ethyl acetate (1.00 ml, 10.24 mmol) was added. After five minutes stirring, benzaldehyde (0.95 ml, 0.99 g, 9.31 mmol) was added and the solution was stirred for one hour. Aqueous quench and ether extraction gave after drying ($MgSO_4$) and evaporation, the title compound (1.72 g, 8.85 mmol, 95%) as a colourless oil. Spectral data was identical to the compound prepared from the Reformatski reaction.

3-Cinnamoyloxy-3-phenyl propionic acid (12).

Lithium diisopropylamine (18.6 mmol) was prepared as usual from diisopropylamine and n-butyul lithium in tetrahydrofuran (100 ml) at 0°C. This was cooled to -78°C and trimethylsilyl acetate (13) (2.00 ml, 1.64 g, 12.4 mmol) was added. The solution was stirred for 20 minutes to complete enolate formation. Benzaldehyde (2.63 g, 24.8 mmol) was added and the reaction mixture was allowed to warm to room temperature over 1 hour. Cinnamoyl chloride (10) (2.07 g, 12.4 mmol) in dry THF (2 ml) solution was added and the reaction was stirred for 1 hour at room temperature. Acid work-up and bicarbonate extraction gave after re-acidification, a mixture of cinnamic acid and the required product. Trituration with chloroform dissolved the cinnamic acid and left crude product. Recrystallisation (ethyl acetate) gave the title compound (0.33 g, 1.11 mmol, 9%) with physical data identical to that prepared before.

Attempted [2+2] cyclisation.

Acid (12) (0.100 g, 0.34 mmol) was dissolved in THF (10 ml) and oxalyl chloride (0.09 ml, 3 eq) was added. The solution was stirred under a nitrogen atmosphere for one hour. The solvent was removed under high vacuum and dry toluene (10 ml) was added. Triethylamine (0.24 ml, 5 eq) was added and the solution was refluxed for 20 minutes. The solution was washed with 2M hydrochloric acid and brine then dried ($MgSO_4$). Evaporation gave

an oil (30 mg) which although much more mobile than cinnamic acid on TLC, resembles cinnamic acid closely by ^{1}H NMR.

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