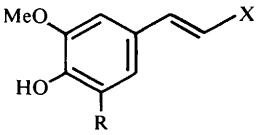
The Synthesis of Lignans and Neolignans

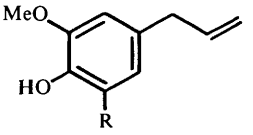
By R. S. Ward
CHEMISTRY DEPARTMENT, UNIVERSITY COLLEGE OF SWANSEA, SINGLETON PARK, SWANSEA, SA2 8PP

1 Introduction

Lignans and neolignans are formed in nature by the oxidative dimerization of various C_6C_3 phenols [*e.g.* (1)—(4)].[1] Indeed some lignans and neolignans can be prepared from cinnamyl alcohols and propenyl phenols, either by enzymic oxidation or by using conventional oxidizing agents such as $FeCl_3$ and Ag_2O.



(1; X = CH_2OH)
(2; X = CO_2H)
(3; X = Me)

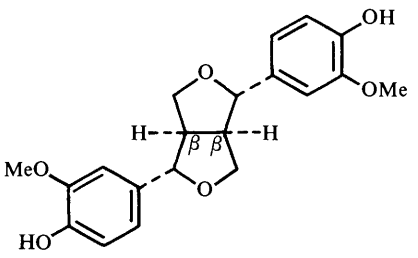


(4)

(*a*; R = H)
(*b*; R = OMe)

The distinction between the terms lignan and neolignan has led to much confusion over the years, since at least two conflicting definitions have been proposed. Traditionally the term *lignan* was reserved for compounds such as (5) and (6) in which the two C_6C_3 units are linked by a bond connecting the central (β) carbon atoms of each side chain.[2] The term *neolignan* was introduced to designate compounds such as (7) and (8) in which the two C_6C_3 units are not linked by a β—β bond.[3,4] According to the most recent definition, however, lignans [*e.g.* (5) and (7)] are formed by oxidative coupling of cinnamyl alcohols and/or cinnamic acids, whereas neolignans [*e.g.* (6) and (8)] are formed by oxidative coupling of propenylphenols and/or allyl phenols.[5,6] Since the latter definition does not identify any fundamental chemical difference between the two series of compounds so defined, the former definition is to be preferred and is adopted in this review.

[1] 'Chemistry of Lignans', ed. C. B. S. Rao, Andhra University Press, 1978.
[2] R. D. Haworth, *J. Chem. Soc.*, 1942, 448.
[3] O. R. Gottlieb, *Phytochemistry*, 1972, **11**, 1537.
[4] O. R. Gottlieb, *Rev. Latinoamer. Quim.*, 1974, **5**, 1.
[5] O. R. Gottlieb, in 'New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity', Springer-Verlag, Berlin-Heidelberg, 1977, p. 227—248.
[6] O. R. Gottlieb, *Fortsch. Chem. Org. Naturst.*, 1978, **35**, 1.



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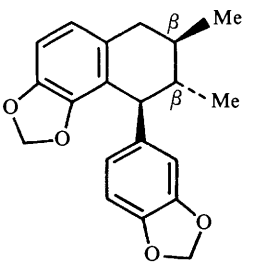

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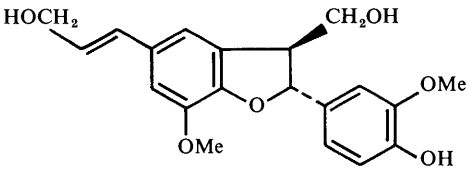

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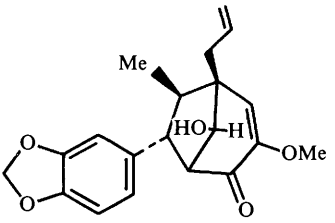
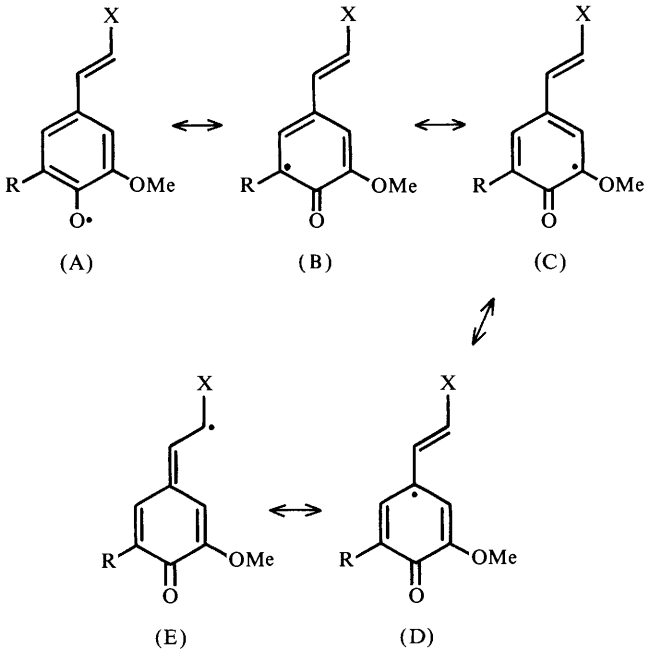


(8)

The many varied structures which lignans and neolignans possess can be accounted for by the different possible modes of coupling of the phenoxy-radicals generated by oxidation of (1)—(4). Thus, lignans are formed by further modification (*e.g.* reduction, cyclization, hydration) of the intermediate obtained by coupling together two canonical forms of type E, whereas neolignans (as defined above) are formed from other combinations of the canonical forms A—E. It is also of interest to note that different modes of coupling do indeed occur in oxidative coupling reactions depending upon the method of oxidation or the oxidizing agent employed (see Sections 1 and 2).

Lignans and neolignans have attracted much interest over the years on account of their widespread ocurrence in nature,[7] and on account of their broad range of biological activity.[5] Thus, several lignans and neolignans are known to exhibit anti-tumour activity,[8–12] while others function as growth inhibitors and anti-fungal agents.[13,14] Of possibly even greater importance is the recent isolation

[7] J. R. Cole and R. M. Wiedkopf, ref. 1, Chap. 2.
[8] C. Keller-Juslen, M. Kuhn, A. von Wartburg, and H. Stähelin, *J. Med. Chem.*, 1971, **14**, 936.
[9] S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, and R. F. Bryan, *J. Am. Chem. Soc.*, 1973, **95**, 1335.
[10] S. G. Weiss, M. Tin-Wa, R. E. Perdue, and N. R. Farnsworth, *J. Pharm. Sci.*, 1975, **64**, 95.
[11] J. L. Hartwell, *Cancer Treat. Rep.*, 1976, **60**, 1031.
[12] S. K. Carter and R. B. Livingston, *Cancer Treat. Rep.*, 1976, **60**, 1141.
[13] T. Kamikado, C. F. Chang, S. Murakoshi, A. Sakurai, and S. Tamura, *Agric. Biol. Chem. (Jpn.)*, 1975, **39**, 833.
[14] G. B. Russell, P. Singh, and P. G. Fenemore, *Aust. J. Biol. Sci.*, 1976, **29**, 99.



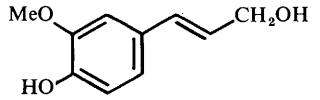
of lignans from animals, including human beings,[15-18] which has led to the suggestion that such compounds may be examples of a new type of hormone controlling cell growth.

The many varied types of structure that lignans and neolignans can possess have presented a considerable challenge to organic chemists over the years and indeed many elegant syntheses have been reported. In the present review the methods that have been used to prepare lignans and neolignans are classified according to the types of reaction employed rather than according to the types of compound prepared. Thus, it can be seen that most of the syntheses that have been carried out depend in fact upon a limited number of key reactions, which have been used to construct the basic 18-carbon skeleton. Particular emphasis has been placed on new methods of synthesis involving, for example, non-phenolic oxidative coupling, cycloaddition to quinone monoketals, and conjugate addition by acyl anion equivalents. However, due prominence is also accorded to classical routes involving phenolic oxidative coupling, Diels Alder reactions, and Stobbe condensations, which are, in many ways, still unsurpassed as versatile routes to a whole range of lignans and neolignans.

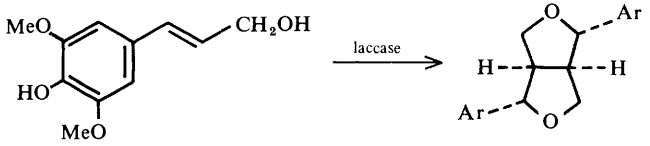
[15] S. R. Stitch, P. D. Smith, D. Illingworth, and K. Toumba, *J. Endocrinol.*, 1980, **85**, 23P.
[16] S. R. Stitch, J. K. Toumba, M. B. Groen, C. W. Funke, J. Leemhuis, J. Vink, and G. F. Woods, *Nature*, 1980, **287**, 738.
[17] K. D. R. Setchell, R. Bull, and H. Adlercreutz, *J. Steroid Biochem.*, 1980, **12**, 375.
[18] K. D. R. Setchell, A. M. Lawson, F. L. Mitchell, H. Adlercreutz, D. N. Kirk, and M. Axelson. *Nature*, 1980, **287**, 740.

2 Phenolic Oxidative Coupling

The oxidative coupling reactions of coniferyl alcohol and sinapyl alcohol constitute biomimetic syntheses of lignans and neolignans. Thus, enzyme catalysed oxidation of coniferyl alcohol (1*a*) yields a mixture of products including pinoresinol (5) and dehydrodiconiferyl alcohol (7),[19] while oxidative coupling of sinapyl alcohol (1*b*) affords a high yield of syringaresinol (9).[20]



(1) (1*a*)



(2) (1*b*) (9)

(Ar = 3,5–dimethoxy-4-hydroxyphenyl)

The oxidative coupling reactions of ferulic acid and sinapic acid are much more useful from a synthetic point of view, however, since the dilactones produced have unambiguous structures and are amenable to a wide range of structural modifications (Schemes 1 and 2). The dilactone (10), for example, is produced in 30% yield by oxidation of ferulic acid (2*a*).[21] Treatment with methanolic HCl causes rearrangement to the aryldihydronaphthalene (11), which can be further converted into a mixture of the arylnaphthalene lactones (12) and (13).[22] Alternatively, hydrogenation followed by dehydration affords the anhydride (14), which is converted by reduction into matairesinol (15).[22] Reduction of the acetylated dilactone (16) with lithium aluminium hydride (LAH) yields the tetrol (17), which can be cyclized to give pinoresinol (5), and the methylated dilactone (18) can be similarly converted into eudesmin (19).[23] Partial reduction of the dilactones (10) and (18) can be achieved using di-isobutyl aluminium hydride (DIBAL), which affords the dilactols (20) and (21).

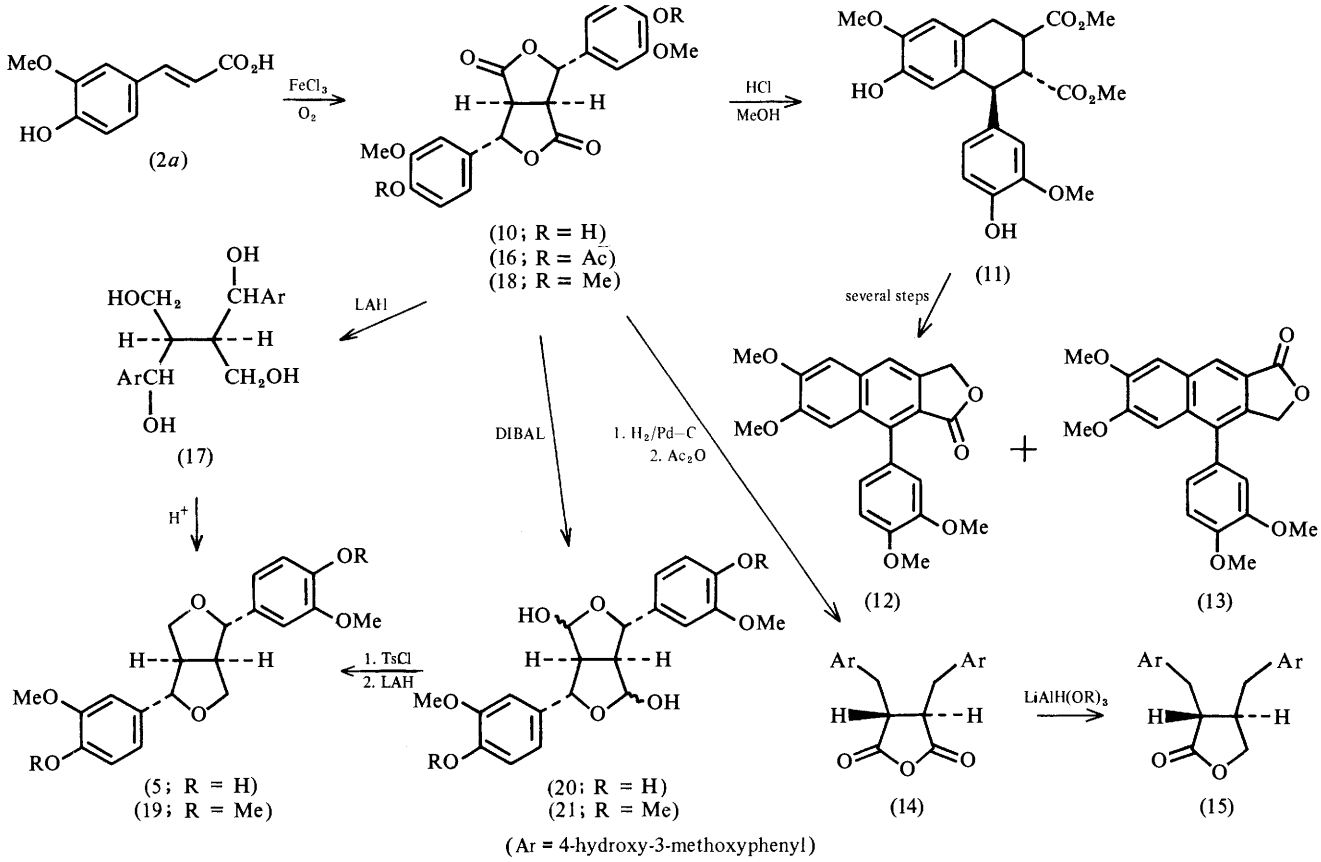
[19] (*a*) K. Freudenberg and H. H. Hubner, *Chem. Ber.*, 1952, **85**, 1181. (*b*) C. J. Sih, P. R. Ravikumar, F.-C. Huang, C. Buckner, and H. Whitlock, *J. Am. Chem. Soc.*, 1976, **98**, 5412.

[20] (*a*) K. Freudenberg and G. Grion, *Chem. Ber.*, 1959, **92**, 1355. (*b*) E. E. Dickey, *J. Org. Chem.*, 1958, **23**, 179.

[21] (*a*) H. Erdtman, *Svensk. Kem. Tidskr.*, 1935, **47**, 223. (*b*) N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 1944, 535.

[22] Y. Takei, K. Mori, and M. Matsui, *Agric. Biol. Chem. (Jpn.)*, 1973, **37**, 637.

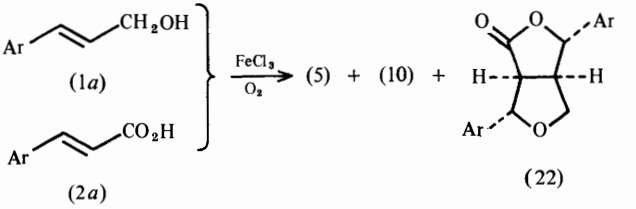
[23] A. Pelter, R. S. Ward, D. J. Watson, P. Collins, and I. T. Kay, *J. Chem. Soc., Perkin Trans. 1*, 1982, 175.


MeO
CO2H
HO
(2a)
FeCl3
O2
OR
OMe
MeO
RO
(10; R = H)
(16; R = Ac)
(18; R = Me)
HCl
MeOH
CO2Me
CO2Me
OMe
OH
(11)
several steps
LAH
OH
CHAr
HOCH2
CH2OH
ArCH
OH
(17)
DIBAL
1. H2/Pd–C
2. Ac2O
(12)
(13)
H+
1. TsCl
2. LAH
(5; R = H)
(19; R = Me)
(20; R = H)
(21; R = Me)
Ar
(14)
LiAlH(OR)3
(15)
(Ar = 4-hydroxy-3-methoxyphenyl)

Scheme 1

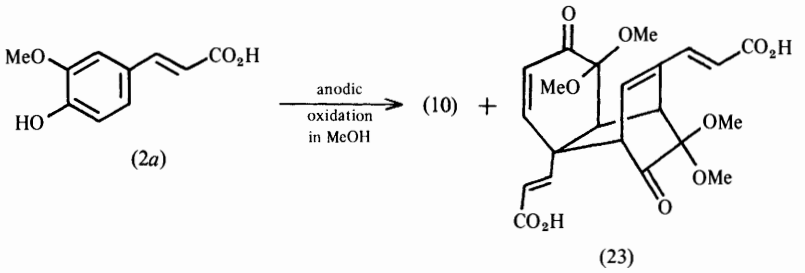
These can be further converted by tosylation followed by LAH reduction into the parent 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes.[23] Furthermore, since this last sequence does not involve ring-opened intermediates it constitutes an unambiguous synthesis of this class of lignans.[23]

As would be expected, oxidation of a mixture of coniferyl alcohol (1*a*) and ferulic acid (2*a*) affords a mixture of pinoresinol (5) and the dilactone (10), along with the monolactone (22) which is a potent germination inhibitor.[24] Anodic oxidation of ferulic acid gives only a 6% yield of the dilactone (10) but gives a high yield (70%) of the asatone-type compound (23),[25] formed by cyclodimerization of a dienone intermediate corresponding to canonical form C of the phenoxy-radical.



(3)

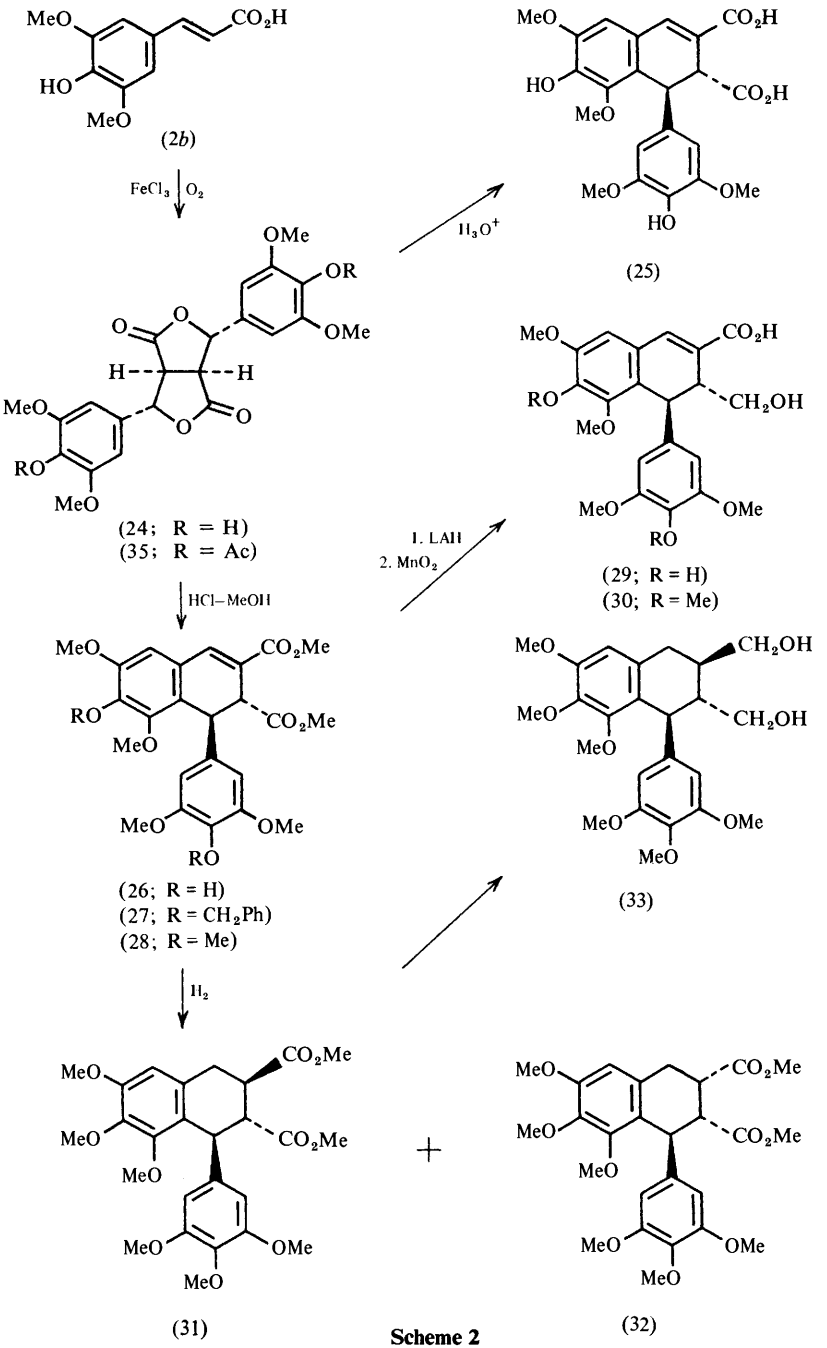
(Ar = 4-hydroxy-3-methoxyphenyl)



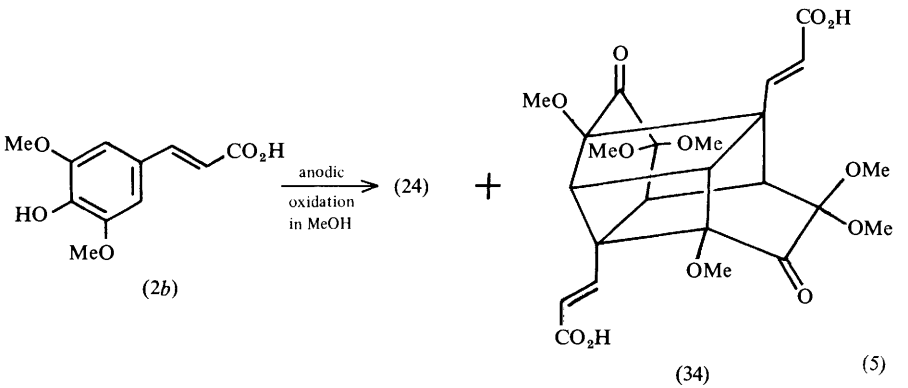
(4)

The dilactone (24) is produced in 80% yield by phenolic oxidation of sinapic acid (2*b*).[26] Treatment with aqueous acid yields thomasadioic acid (25), whereas treatment with methanolic HCl gives the dimethyl ester (26). Further modification of the benzyl ether (27) or the methyl ether (28) affords thomasic acid (29) and its dimethyl ether (30). Hydrogenation of (28) affords a mixture of the isomeric aryltetralins (31) and (32) of which the former has been converted into lyoniresinol dimethyl ether (33).[27] Anodic oxidation of sinapic acid (2*b*) gives a low yield (9%) of an isoasatone derivative (34) in addition to the dilactone (24).[25]

[24] R. Cooper, H. E. Gottlieb, D. Lavie, and E. C. Levy, *Tetrahedron*, 1979, **35**, 861.
[25] M. Iguchi, A. Nishiyama, H. Eto, Y. Terada, and S. Yamamura, *Chem. Lett.*, 1979, 1397.
[26] (*a*) K. Freudenberg and H. Schraube, *Chem. Ber.*, 1955, **88**, 16. (*b*) R. Ahmed, M. Lehrer, and R. Stevenson, *Tetrahedron Lett.*, 1973, 747; *Chem. Ind.* (*London*), 1973, 1001; *Tetrahedron*, 1973, **29**, 3753.
[27] A. F. A. Wallis, *Aust. J. Chem.*, 1973, **26**, 585 and 1571.

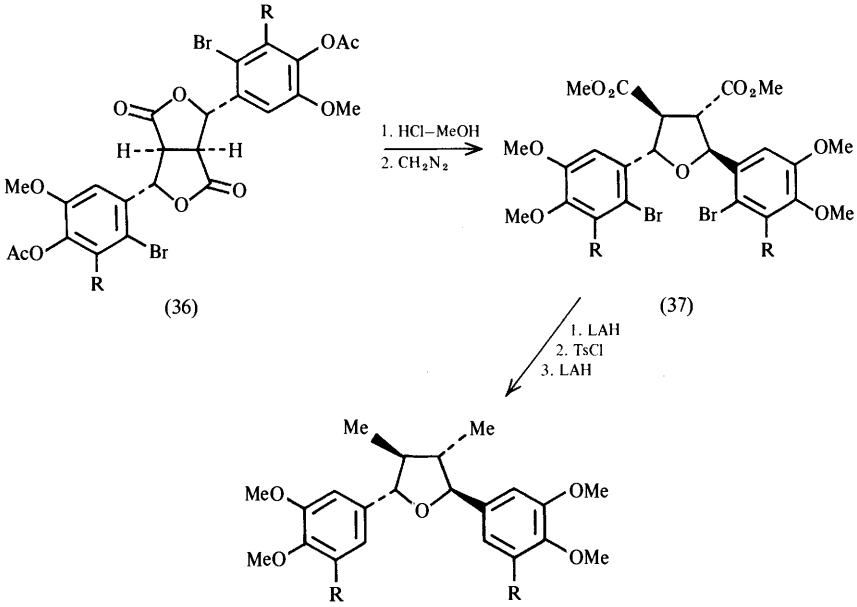

(2b)
FeCl3 | O2
(24; R = H)
(35; R = Ac)
HCl–MeOH
(26; R = H)
(27; R = CH2Ph)
(28; R = Me)
H2
(31)
H3O+
(25)
1. LAH
2. MnO2
(29; R = H)
(30; R = Me)
(33)
+
(32)

Scheme 2



(2*b*) (34) (5)

Several substituted dilactones have been prepared by oxidative coupling of appropriately substituted cinnamic acids.[28,29] Some of the dilactones so produced or indeed produced by direct halogenation of the parent dilactones [(16) and (35)] are useful for preparing other lignan types, as for example by acid catalysed rearrangement to tetrahydrofuran derivatives (Scheme 3).[30] In this instance, the



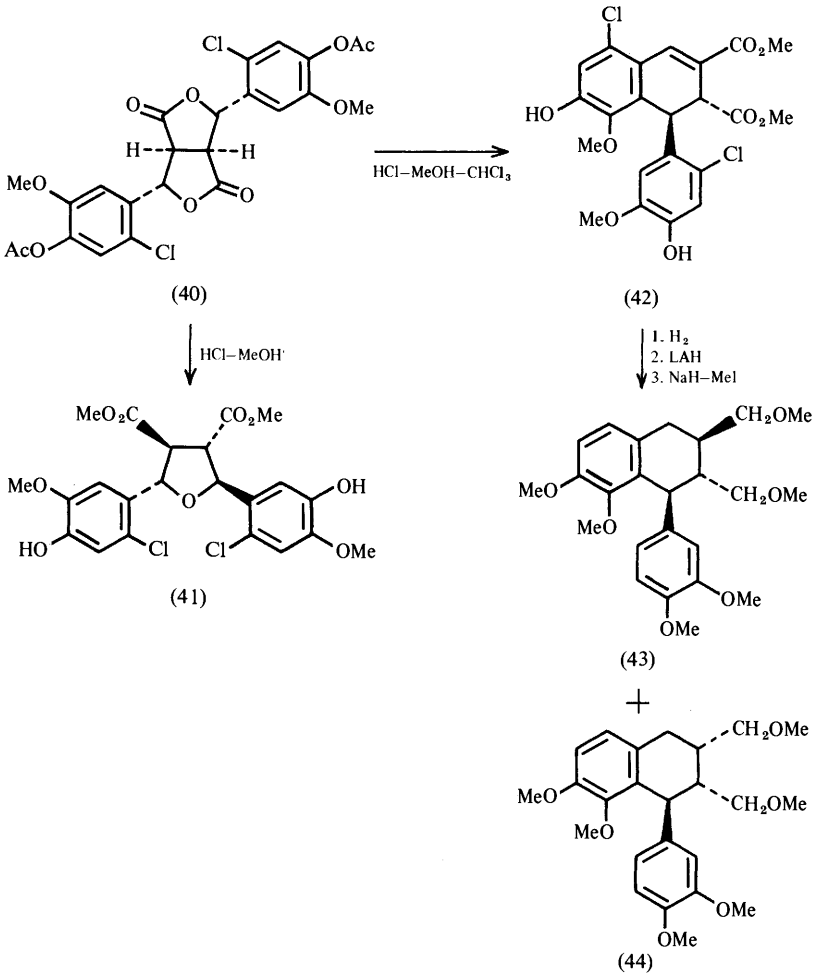
(36) (37)

(38; R = H) galbelgin
(39; R = OMe) grandisin

Scheme 3

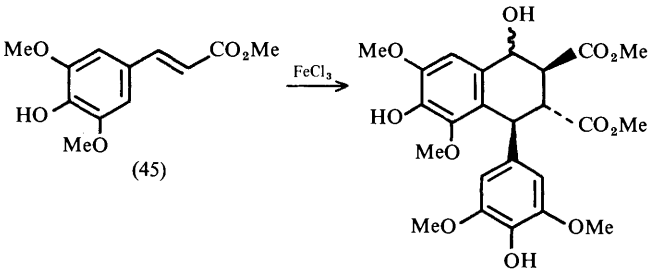
[28] Y. Kumada, H. Naganawa, T. Takeuchi, H. Umezawa, K. Yamashita, and K. Watanabe, *J. Antibiotics*, 1978, **31**, 105.
[29] R. Ahmed, F. G. Schreiber, R. Stevenson, J. R. Williams, and H. M. Yeo, *Tetrahedron*, 1976, **32**, 1339.
[30] R. Stevenson and J. R. Williams, *Tetrahedron*, 1977, **33**, 285.

presence of the halogen atom serves to divert the normal course of the cyclization reaction. In other instances, and depending on the reaction conditions (Scheme 4), the presence of the halogen atom can be used to produce a different oxygenation pattern in the aryldihydronaphthalene (42), and hence in the aryltetralins (43) and (44), by blocking the normal position of ring closure.[30]



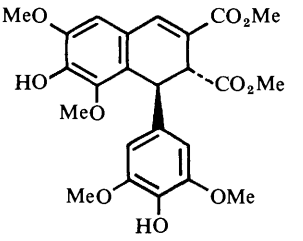
Scheme 4

Phenolic oxidation of methyl sinapate (45) yields a mixture of compounds of which the major component (61%) is the 4-hydroxyaryltetralin (46).[27] Acid catalysed dehydration affords the dimethyl ester of thomasadioic acid (26).[27]



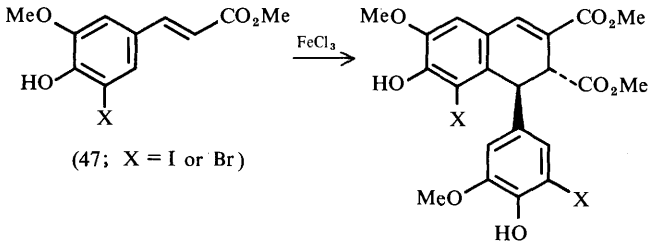
(45) (46)

(6)

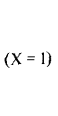


(26)

The dihalogenated aryldihydronaphthalenes (48) can be directly prepared from the corresponding cinnamate esters and the iodo-derivative (48; X = I) forms the starting point for a synthesis of isolariciresinol dimethyl ether (49).[29]



(47; X = I or Br) (48)



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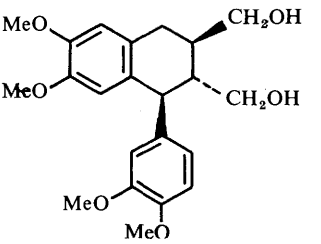
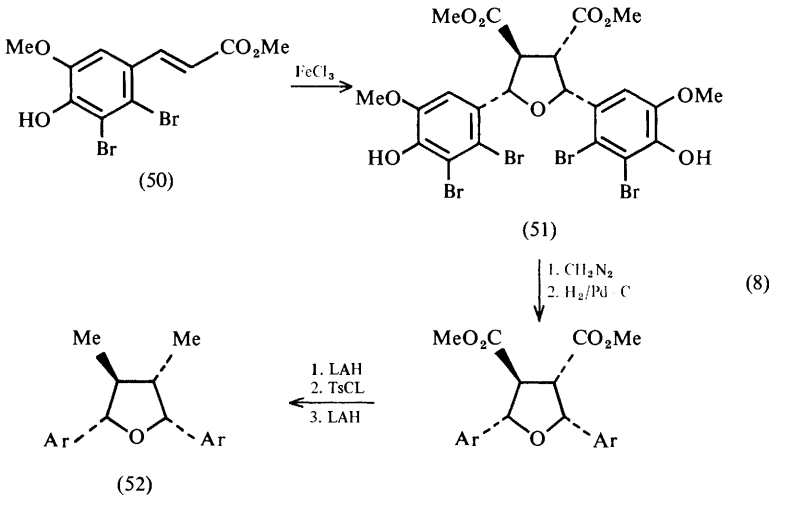




(50) (51) (52) (8)

(Ar = 3,4-dimethoxyphenyl)

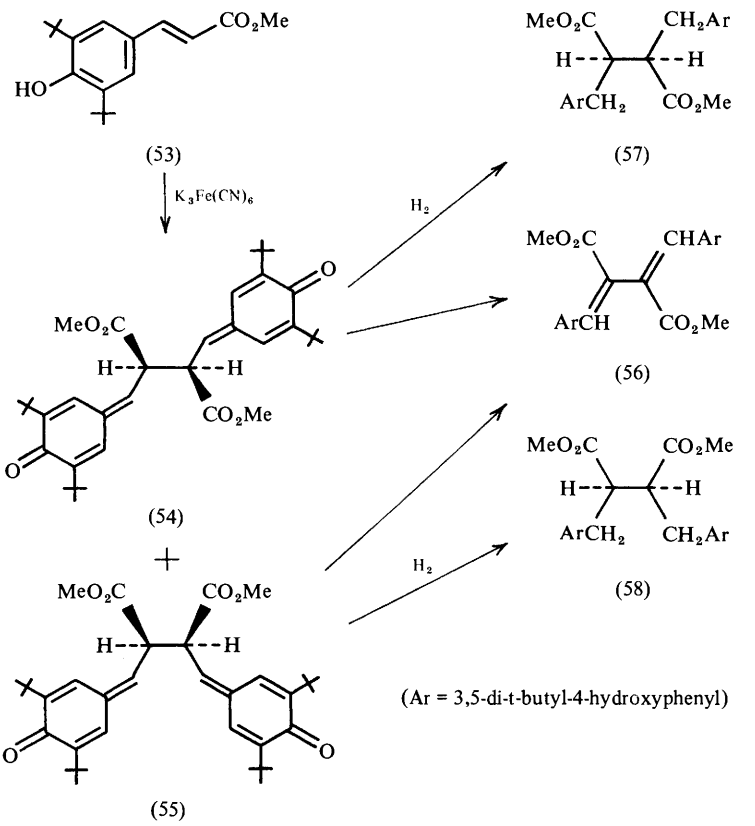
In contrast, phenolic oxidation of the dibromoferulate (50) affords the tetrahydrofuran derivative (51) directly, leading eventually to veraguensin (52).[29]

Phenolic oxidation of the cinnamate ester (53) yields the bisquinonemethides (54) and (55), which both undergo tautomerization to afford the diarylbutadiene (56), but on hydrogenation yield the diarylbutanes (57) and (58) respectively (Scheme 5).[31]

The oxidative coupling of various allyl and propenyl phenols is involved in the biosynthesis of several lignans and neolignans and affords a convenient route to a number of such compounds. Thus, (*E*)-isoeugenol (3*a*) is converted by oxidation into a mixture of compounds of which dehydrodi-isoeugenol (59) is the major component.[32-36] (*Z*)-Isoeugenol gives a similar range of products.[32]

In contrast, chemical or enzymic oxidation of the (*E*)-2,6-dimethoxypropenylphenol (3*b*) yields a mixture of two tetrahydrofuran derivatives (60) and (61) as major products (Scheme 6).[32] Their methyl ethers rearrange in acid to give the aryldihydronaphthalene (62), illustrating once again the ready interconversion of the various lignan types under acid conditions. Oxidation of the (*Z*)-isomer of the same phenol yields four diastereoisomeric tetrahydrofuran derivatives.[32]

[31] K. V. Sarkanen and A. F. A. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1878.
[32] K. V. Sarkanen and A. F. A. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1869.
[33] H. Cousin and H. Herissey, *Compt. rend.*, 1908, **147**, 247; *Bull. Soc. Chim. Fr.*, 1908, **3**, 1070; *J. Pharm. Chim.*, 1908, **28**, 93.
[34] K. Eskins, C. Glass, W. Rohwedder, R. Kleiman, and J. Slonekar, *Tetrahedron Lett.*, 1972, 861.
[35] I. J. Miller, *Tetrahedron Lett.*, 1972, 4955.
[36] M. Iguchi, A. Nishiyama, M. Hara, Y. Terada, and S. Yamamura, *Chem. Lett.*, 1978, 1015.



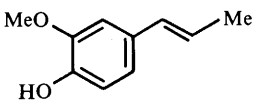
Scheme 5

Oxidation of (3*b*) with ferric chloride yields (64) as the major product along with a number of other minor products as indicated.[27] Oxidation of the (*Z*)-isomer with ferric chloride also gives a similar range of products.

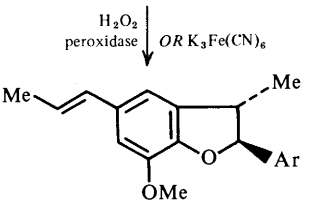
Anodic oxidation of eugenol (4*a*) and the allylphenol (4*b*) gives various dimeric products, including the asatone derivatives (66) and (67).[37,38] Oxidation of (4*a*) with thallium nitrate in methanol also yields asatone derivatives.[39]

Finally, a mixed phenolic oxidation is involved in the synthesis of eusiderin (68),[40] and a remarkable reaction involving the generation of five contiguous

[37] M. Iguchi, A. Nishiyama, Y. Terada, and S. Yamamura, *Chem. Lett.*, 1978, 451.
[38] M. Iguchi, A. Nishiyama, Y. Terada, and S. Yamamura, *Tetrahedron Lett.*, 1977, 4511.
[39] M. Niwa, H. Noda, H. Kobayashi, and S. Yamamura, *Chem. Lett.*, 1980, 85.
[40] L. Merlini and A. Zanarotti, *Tetrahedron Lett.*, 1975, 3621; L. Merlini, A. Zanarotti, A. Pelter, M. P. Rochefort, and R. Hänsel, *J. Chem. Soc., Perkin Trans. 1*, 1980, 775.



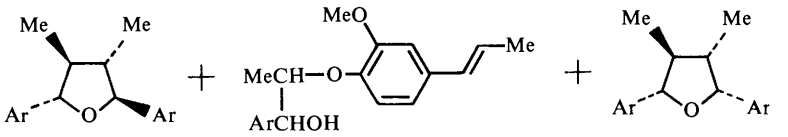
(3*a*)



(59) (65%)

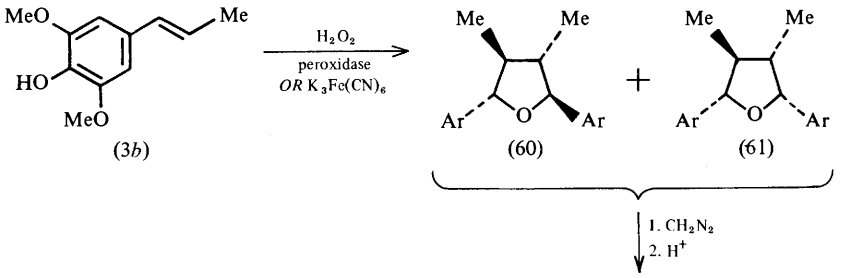
(9)

+

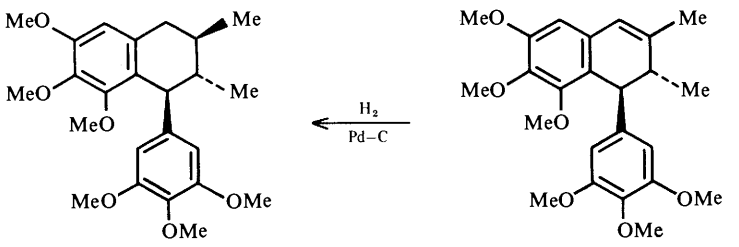


(4%) (17%) (9%)

(Ar = 4-hydroxy-3-methoxyphenyl)



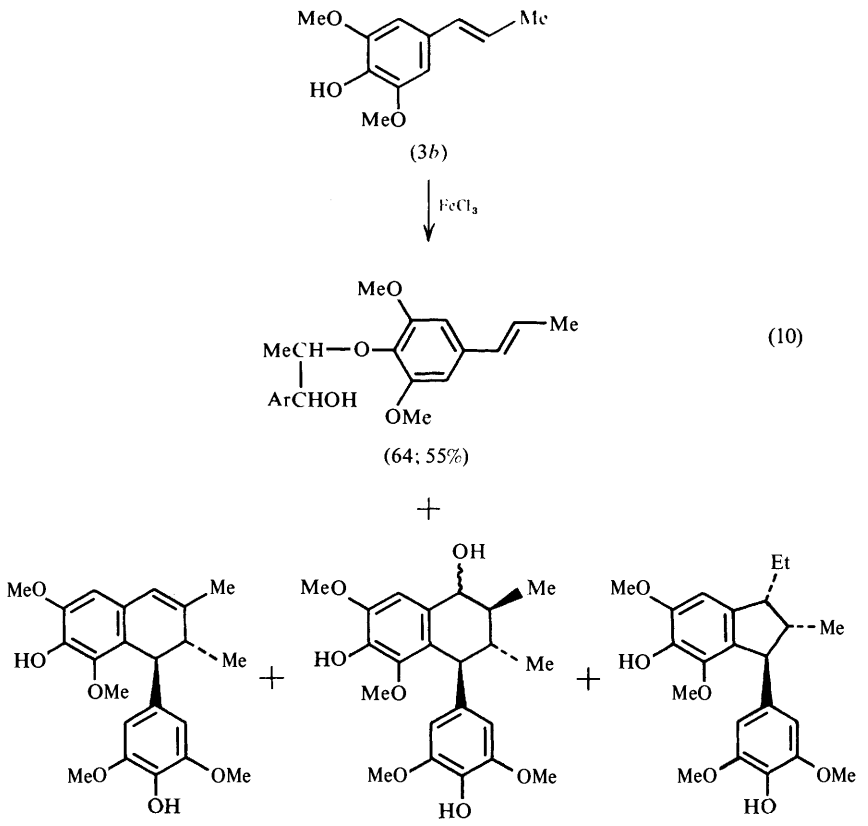
(3*b*) (60) (61)



(63) (62)

(Ar = 3,5-dimethoxy-4-hydroxyphenyl)

Scheme 6



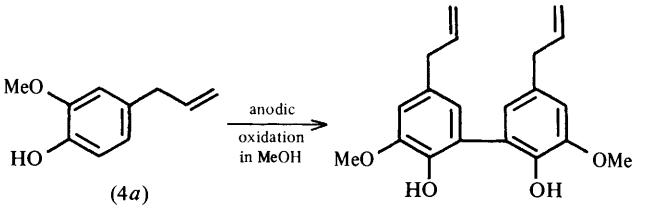
(Ar = 3,5-dimethoxy-4-hydroxyphenyl)

asymmetric centres with the correct relative stereochemistry is involved in the synthesis of carpanone (70) by phenolic oxidation of the propenylphenol (69). Intramolecular cycloaddition of the intermediate bis-quinonemethide is held to be responsible for the high stereoselectivity of this reaction.[41,42]

3 Non-phenolic Oxidative Coupling

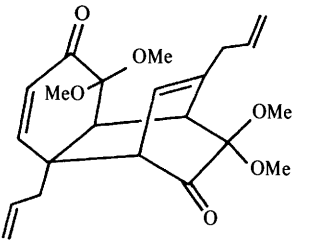
Several lignan syntheses are based on the recently developed technique of non-phenolic oxidative coupling using reagents such as thallium(III) trifluoroacetate and vanadium oxyfluoride. For example, treatment of the diarylbutane (71) with either of these reagents generates the dibenzocyclo-octadiene (72), which

[41] M. Matsumoto and K. Kuroda, *Tetrahedron Lett.*, 1981, 4437.
[42] O. L. Chapman, M. R. Engel. J. P. Springer. and J. C. Clardy, *J. Am. Chem. Soc.*, 1971, **93**, 6696.

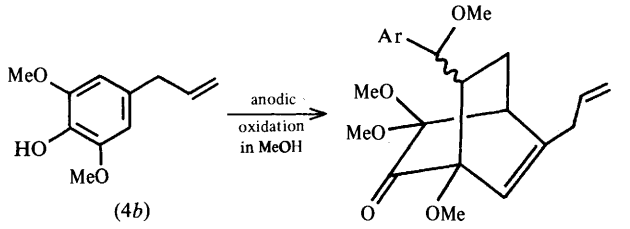


(4*a*) (65)

+

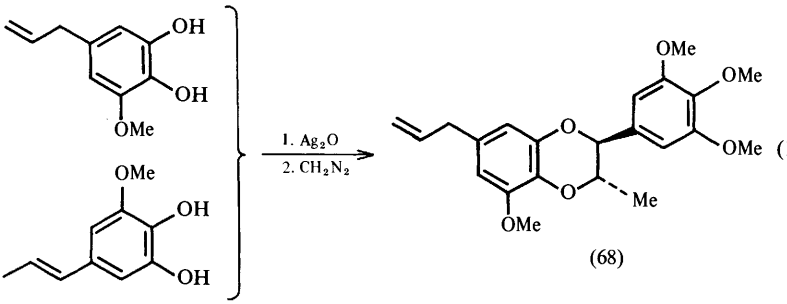


(66) (11)

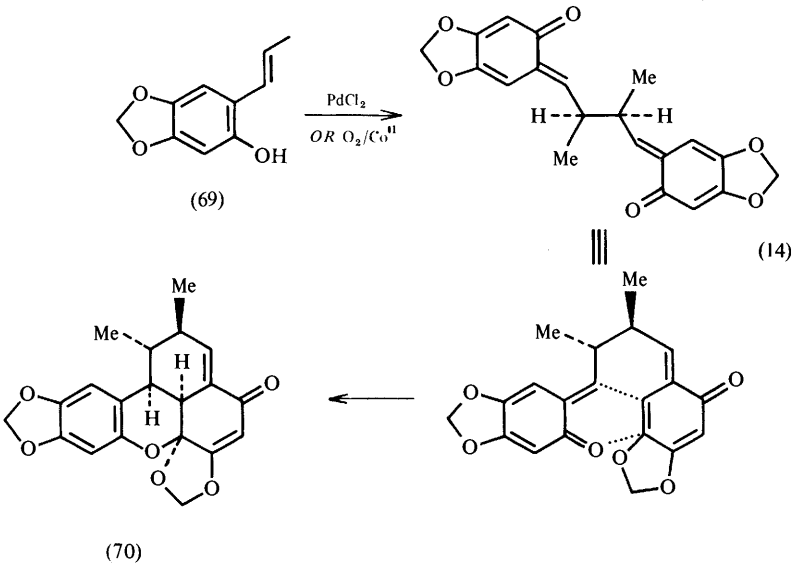


(4*b*) (67) (12)

(Ar = 3,5-dimethoxy-4-hydroxyphenyl)



(68) (13)

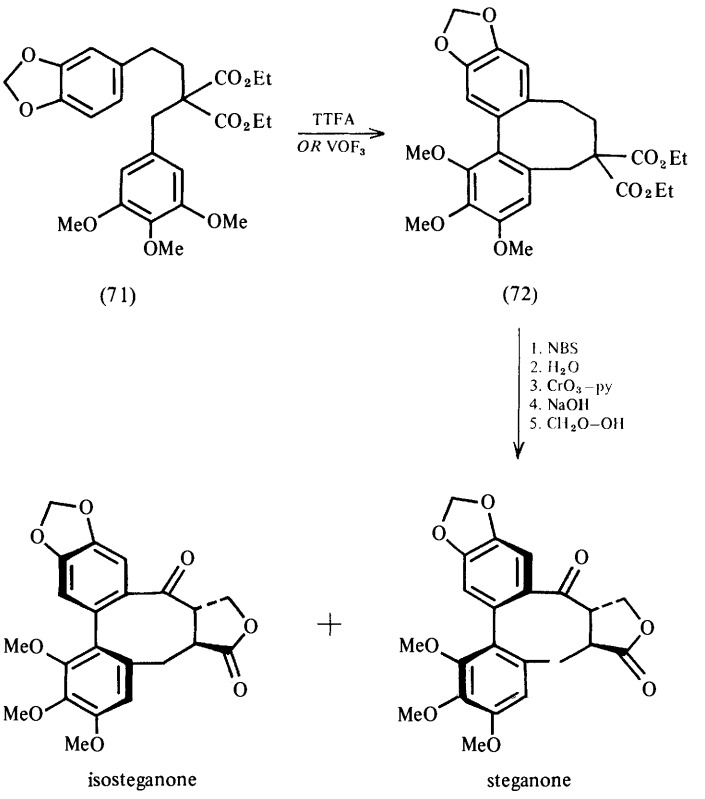


has been used by Kende *et al.* for the synthesis of steganone and isosteganone (Scheme 7).[43,44] The formation of a biaryl link by non-phenolic oxidative coupling is also a key step in Schlessinger's synthesis of isostegane (see section 6),[45] and Stevenson's synthesis of deoxyschizandrin (see section 10).[46] Indeed Stevenson has demonstrated the general applicability of this reaction for the synthesis of dibenzocyclo-octadienes.[46]

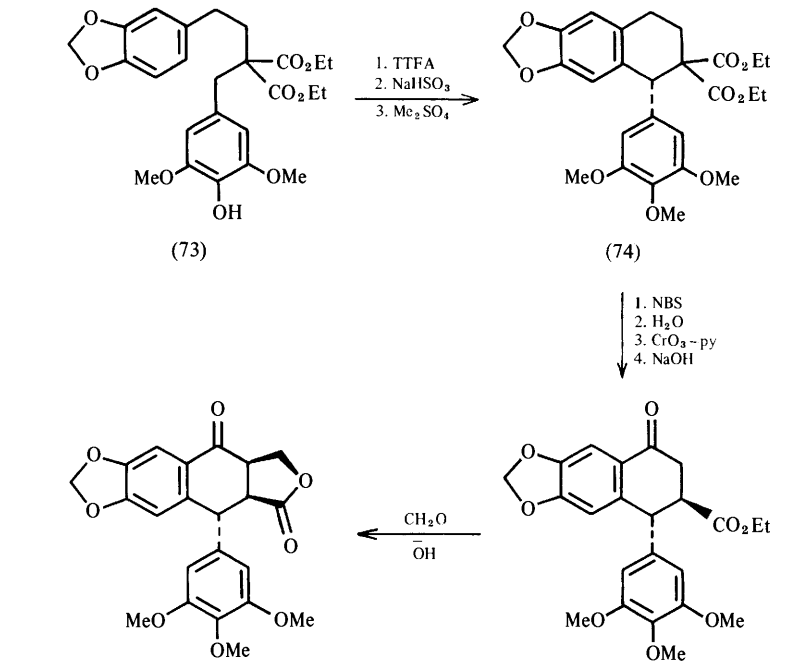
In contrast, oxidation of the monophenol (73) affords the aryltetralin (74), which has been converted by means of a similar series of reactions into picropodophyllone (Scheme 8).[47] Clearly the presence of one phenolic group represents a useful control element that may be of general use in dictating the size of ring produced.

Another non-phenolic oxidative coupling reaction, which has strong similarities to many of the reactions discussed in the previous section, is the oxidative dimerization of cinnamic acids using thallium(III) trifluoroacetate.[48]

[43] A. S. Kende and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1976, **98**, 267.
[44] A. S. Kende, L. S. Liebeskind, C. Kubiak, and R. Eisenberg, *J. Am. Chem. Soc.*, 1976, **98**, 6389 and R. C. Cambie, M. G. Dunlop, P. S. Rutledge, and P. D. Woodgate, *Synth. Commun.*, 1980, **10**, 827.
[45] R. E. Damon, R. H. Schlessinger, and J. P. Blount, *J. Org. Chem.*, 1976, **41**, 3772.
[46] T. Biftu, B. G. Hazra, and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2276.
[47] A. S. Kende, L. S. Liebeskind, J. E. Mills, P. S. Rutledge, and D. P. Curran, *J. Am. Chem. Soc.*, 1977, **99**, 7082 and A. S. Kende and P. S. Rutledge, *Synth. Commun.*, 1978, **8**, 245.
[48] E. C. Taylor, J. G. Andrade, G. J. H. Rall, and A. McKillop, *Tetrahedron Lett.*, 1978, 3623 and E. C. Taylor, J. G. Andrade, G. J. H. Rall, K. Steliou, G. E. Jagdamann, and A. McKillop, *J. Org. Chem.*, 1981, **46**, 3078.

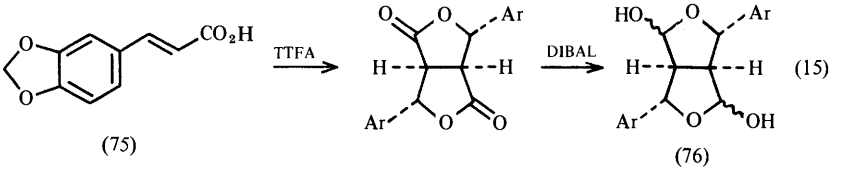

CO2Et
CO2Et
TTFA
OR VOF3
MeO
OMe
OMe
(71)
(72)
1. NBS
2. H2O
3. CrO3–py
4. NaOH
5. CH2O–OH
isosteganone
steganone

Scheme 7



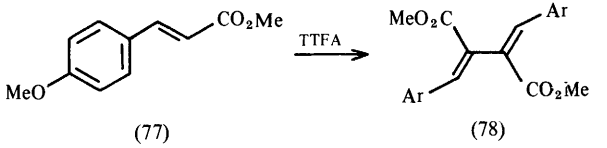
Scheme 8

This reaction has been used to prepare 4,8-dihydroxysesamin (76), which is at the present time the only naturally occurring example of a 4,8-dihydroxy-furofuran.[23] Oxidation of the cinnamate ester (77) affords a high yield of the diarylbutadiene (78).[48]



(15)

(Ar = 3,4-methylenedioxyphenyl)

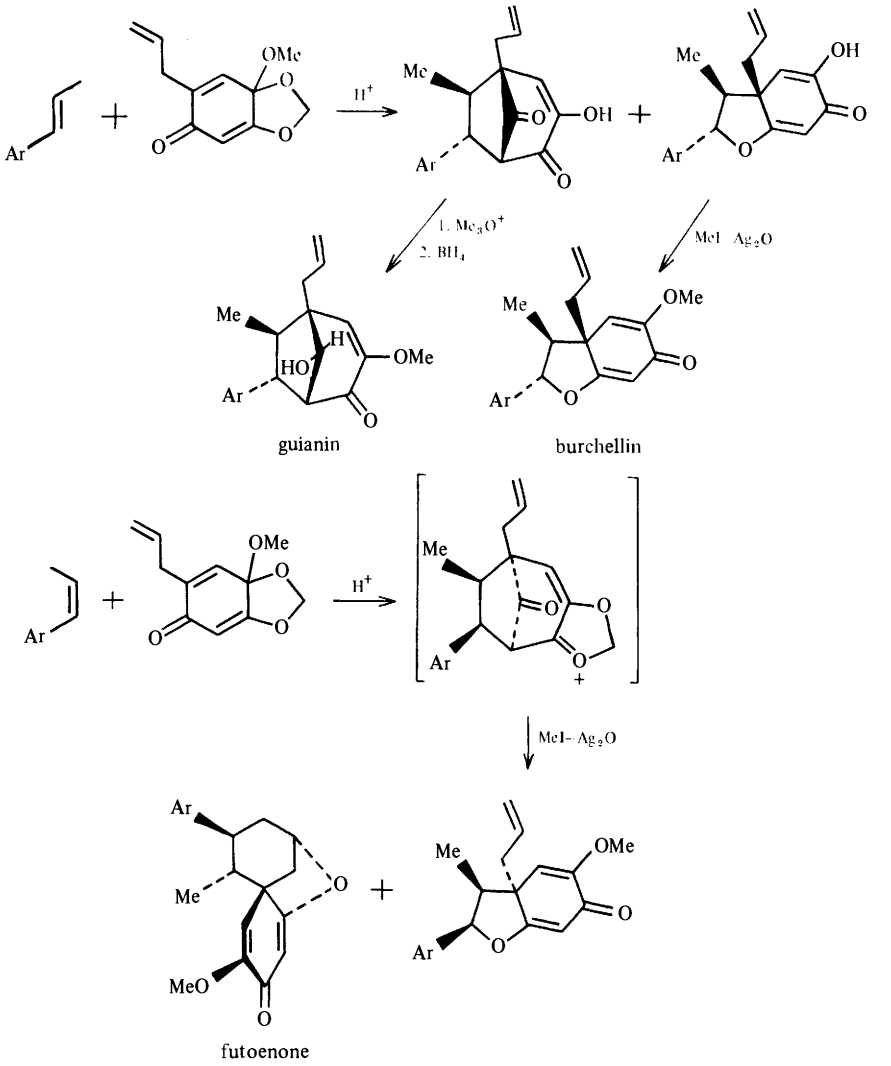


(16)

(Ar = 4-methoxyphenyl)

4 The Use of Quinone Ketals

Büchi has shown that various neolignans can be prepared by the reaction of electron-rich alkenes with appropriately substituted quinone monoketals under acidic conditions. By varying the reaction conditions, and in particular the acid catalyst employed, the reaction can be directed to give predominantly either the burchellin, guianin, or futoenone series (Scheme 9).[49,50] It has been suggested



futoenone

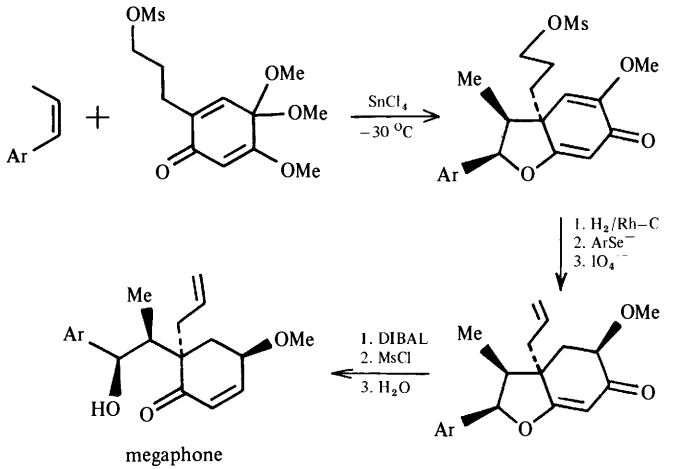
(Ar = 3,4-methylenedioxyphenyl)

Scheme 9

[49] G. Büchi and C.-P. Mak, *J. Am. Chem. Soc.*, 1977, **99**, 8073.
[50] G. Büchi and P.-S. Chu, *J. Org. Chem.*, 1978, **43**, 3717.

that the formation of the bicyclo[3.2.1]octane series involves a concerted [4+2] cycloaddition of a cyclohexadienyl cation to the alkene and that the dihydrobenzofuran and futoeone series result from subsequent isomerization of these products. The close relationship between the dihydrobenzofurans and the bicyclo[3.2.1]octanes is further emphasized by their ready interconversion under acidic conditions.[51] Gottlieb has suggested that the preferred direction of these rearrangements is determined by steric interactions in the vicinity of the tetra-substituted sp^3 hybridized C atom.[51] The bicyclo[3.2.1]octane derivatives can also be further converted into tropolone derivatives.[52]

A similar scheme to that outlined above has been utilized by Büchi *et al.* to synthesize megaphone,[53] a compound known to exhibit anti-tumour activity. Eventual ring opening of the tetrahydrobenzofuran derivative affords the required cyclohexenone (Scheme 10).



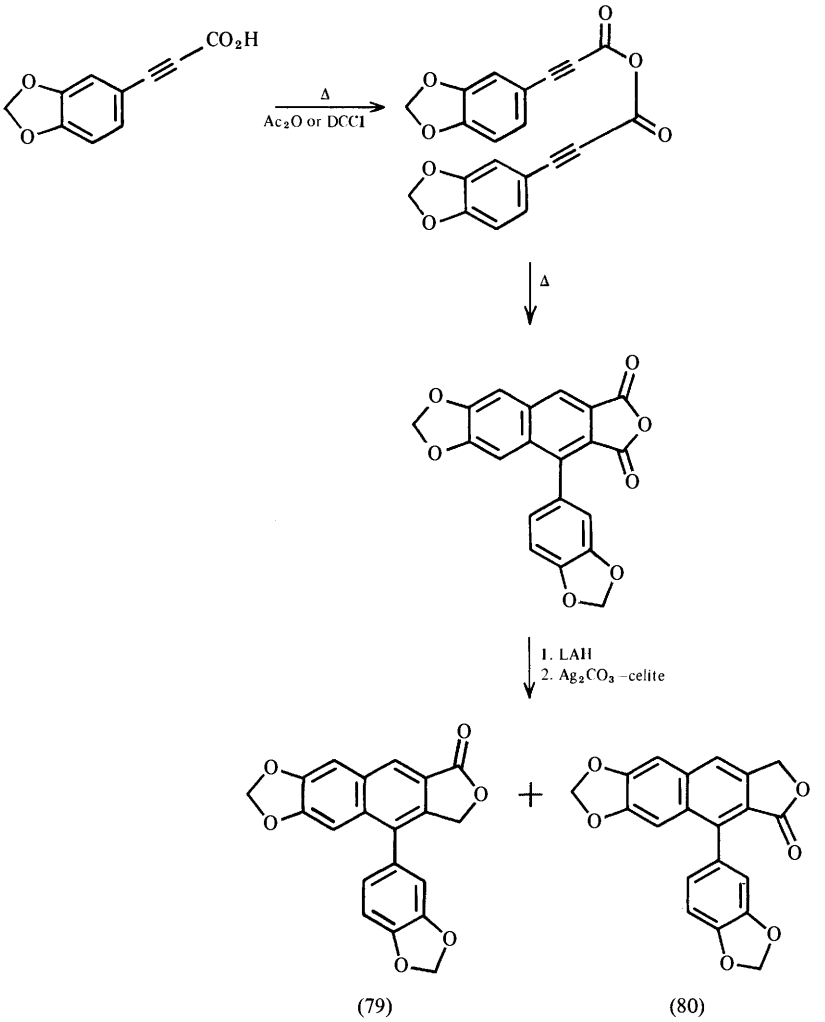
(Ar=3,4,5-trimethoxyphenyl)

Scheme 10

5 Diels Alder and Related Reactions

Diels Alder reactions have been widely used to synthesize lignans of the aryl-naphthalene and aryltetralin series. The first approach, involving cyclization of an acetylenic acid anhydride (Scheme 11), is illustrated by the synthesis of justicidin E (79) and taiwanin C (80).[54,55]

[51] M. A. de Alvarenya, U. Brocksom, O. R. Gottlieb, M. Yoshida, R. Filho, and R. Figliuolo, *J. Chem. Soc., Chem. Commun.*, 1978, 831.
[52] C.-P. Mak and G. Büchi, *J. Org. Chem.*, 1981, **46**, 1.
[53] G. Büchi and P.-S. Chu, *J. Am. Chem. Soc.*, 1981, **103**, 2718.
[54] T. L. Holmes and R. Stevenson, *J. Org. Chem.*, 1971, **36**, 3450.
[55] D. Brown and R. Stevenson, *Tetrahedron Lett.*, 1964, 3213, and *J. Org. Chem.*, 1965, **30**, 1759.



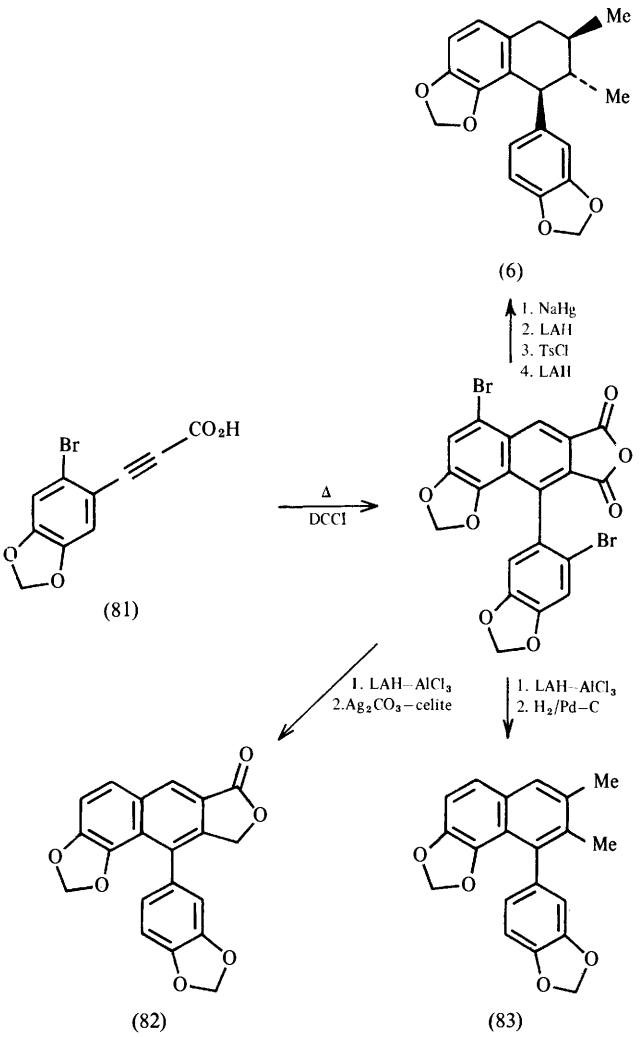
(79) (80)

Scheme 11

By using the 2-bromophenylpropiolic acid (81) the direction of cyclization can be controlled in such a way as to yield the 7,8-dioxygenated system as found in helioxanthin (82), otobain (6), and dehydro-otobain (83) (Scheme 12).[56,57]

[56] T. L. Holmes and R. Stevenson, *Tetrahedron Lett.*, 1970, 199 and *J. Chem. Soc.* (*C*), 1971, 2091.

[57] I. Maclean and R. Stevenson, *Chem. Ind.* (*London*), 1965, 1379 and *J. Chem. Soc.* (*C*), 1966, 1717.

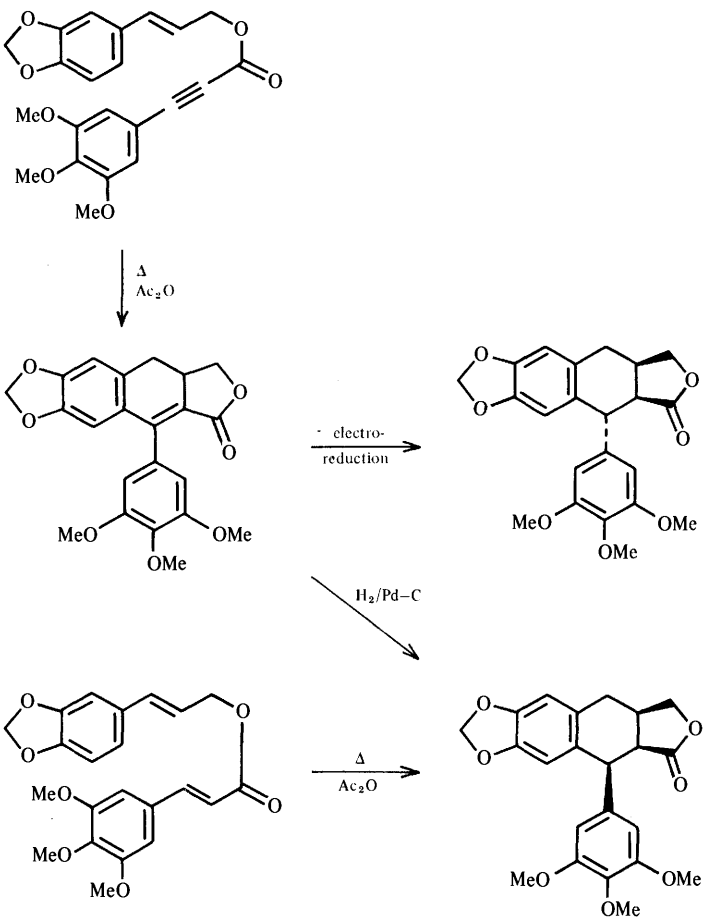


Scheme 12

A second approach, involving the cyclization of a doubly unsaturated ester was used extensively by Klemm and co-workers for the synthesis of several aryltetralin lactones (Scheme 13).[58–61] The same approach has also been used by

[58] L. H. Klemm and K. W. Gopinath, *Tetrahedron Lett.*, 1963, 1243.
[59] L. H. Klemm, K. E. Gopinath, D. Hsu-Lee, F. W. Kelly, E. Trod, and T. M. McGuire, *Tetrahedron*, 1966, **22**, 1797.
[60] L. H. Klemm and P. S. Santhanam, *J. Org. Chem.*, 1968, **33**, 1268.
[61] L. H. Klemm, D. R. Olson, and D. V. White, *J. Org. Chem.*, 1971, **36**, 3740.

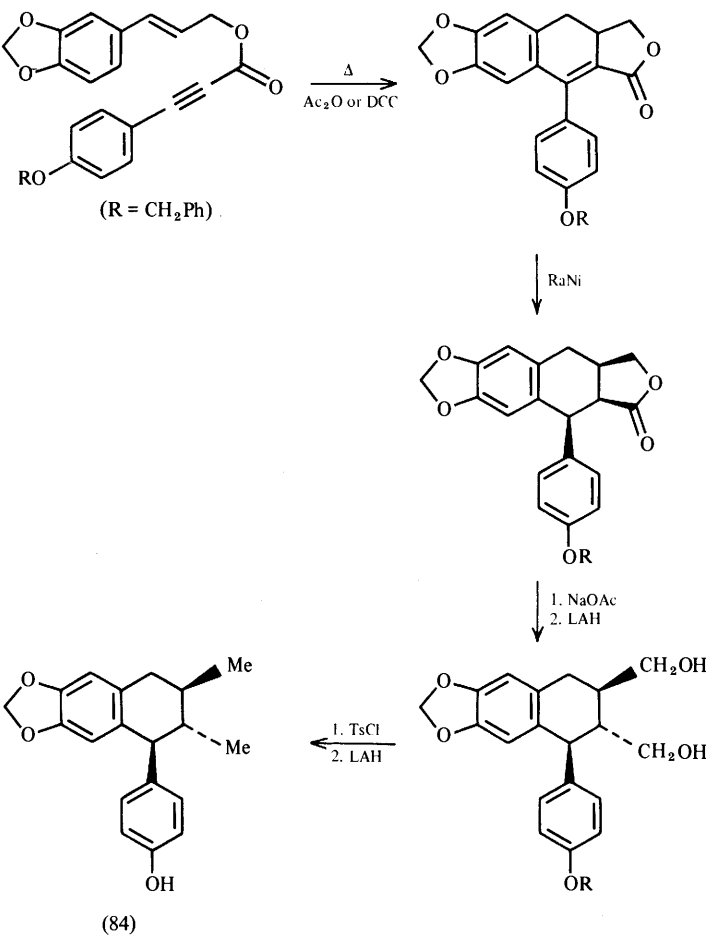
Stevenson *et al.* for the synthesis of collinusin and justicidin B,[62,63] and by Joshi *et al.* for the synthesis of attenuol (84) (Scheme 14).[64]



Scheme 13

Not surprisingly it is the multiple bond adjacent to the carbonyl group which acts as the dienophile in most cases, although in the case of the doubly acetylenic ester (85) both possible lactones are obtained.[58,59] Thus, whereas the *trans*-

[62] E. Block and R. Stevenson, *Chem. Ind. (London)*, 1970, 894 and *J. Org. Chem.*, 1971, **36**, 3453.
[63] F. Kohen, I. Maclean, and R. Stevenson, *J. Chem. Soc. (C)*, 1966, 1775.
[64] B. S. Joshi, N. Viswanathan, V. Balakrishnan, D. H. Gawad, and K. R. Ravindranath, *Tetrahedron*, 1979, **35**, 1665.

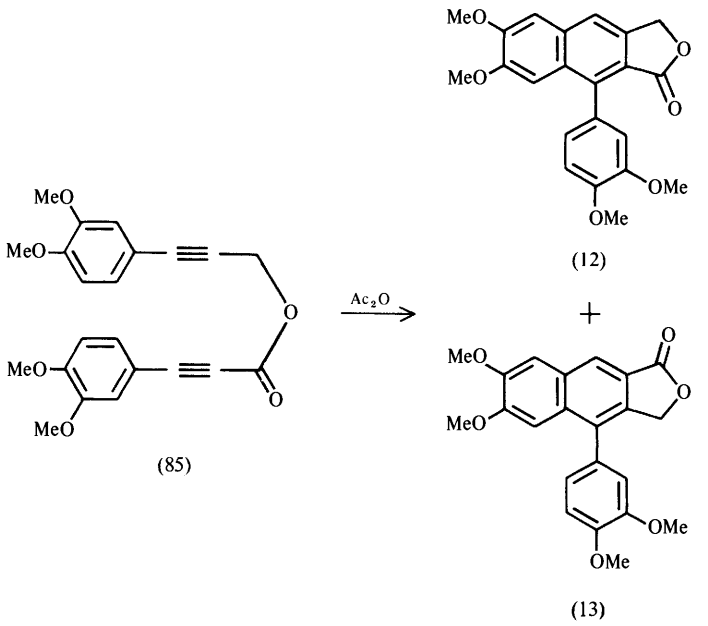


Scheme 14

cinnamyl moiety functions only as a diene, the phenylpropargyl group may serve as either diene or dienophile.

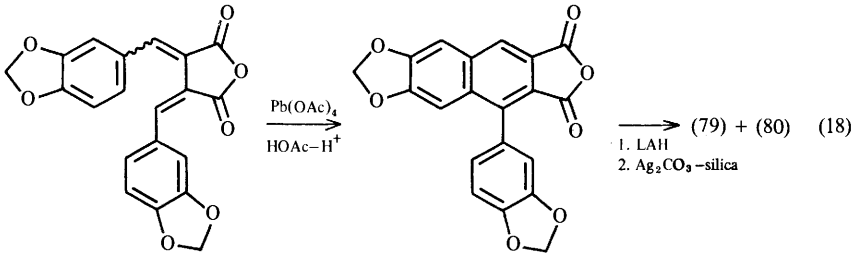
The oxidative cyclization of a doubly unsaturated succinic anhydride can also be used, as illustrated by the synthesis of justicidin E (79), taiwanin C (80), and helioxanthin (82).[65] This process formally involves an electrocyclic ring-closure followed by dehydrogenation. Indeed, cyclization of the di(arylmethylene)-succinic anhydrides and the corresponding lactones can also be achieved photo-

[65] A. S. R. Anjaneyulu, V. Kameswara Rao, P. Satyanarayana, and L. R. Row, *Indian J. Chem.*, 1973, **11**, 203 and A. S. R. Anjaneyulu, V. Kameswara Rao, A. Madhusudhana Rao, and L. R. Row, *Curr. Sci.*, 1974, **43**, 542.



(85) (12) (13) (17)

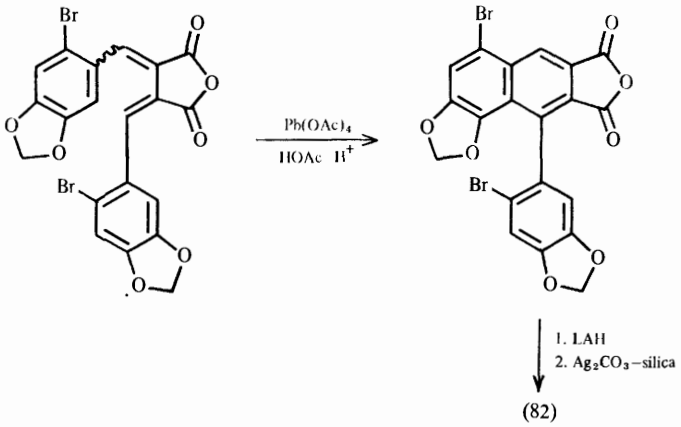
chemically,[66,67] and in the case of the lactones at least, the initial products obtained are the expected 1,4-dihydroarylnaphthalenes [*e.g.* (86)].[67] Photosensitized oxygenation of the doubly unsaturated lactones gives a low yield of the corresponding 4-hydroxyarylnaphthalene lactones.[68]



(18)

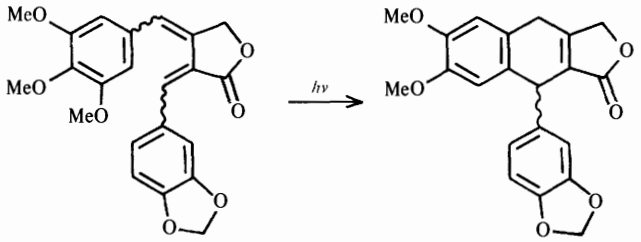
An elegant recent application of the Diels Alder reaction for the synthesis of lignans involves the generation *in situ* of an isobenzofuran such as (87) and its reaction with dimethyl acetylenedicarboxylate (DMAD), leading for example to dehydropodophyllotoxin (88) (Scheme 15).[69] The same general approach has

[66] D. C. Ayres, B. G. Carpenter, and R. C. Denney, *J. Chem. Soc.*, 1965, 3578.
[67] H. G. Heller and P. J. Strydom, *J. Chem. Soc., Chem. Commun.*, 1976, 50.
[68] Z.-I. Horii, K. Ohkawa, and C. Iwata, *Chem. Pharm. Bull.*, 1972, **20**, 624.
[69] H. P. Plaumann, J. G. Smith, and R. Rodrigo, *J. Chem. Soc., Chem. Commun.*, 1980, 354, and S. O. de Silva, C. St. Denis, and R. Rodrigo, *J. Chem. Soc., Chem. Commun.*, 1980, 995.



(19)

(82)



(20)

(86)

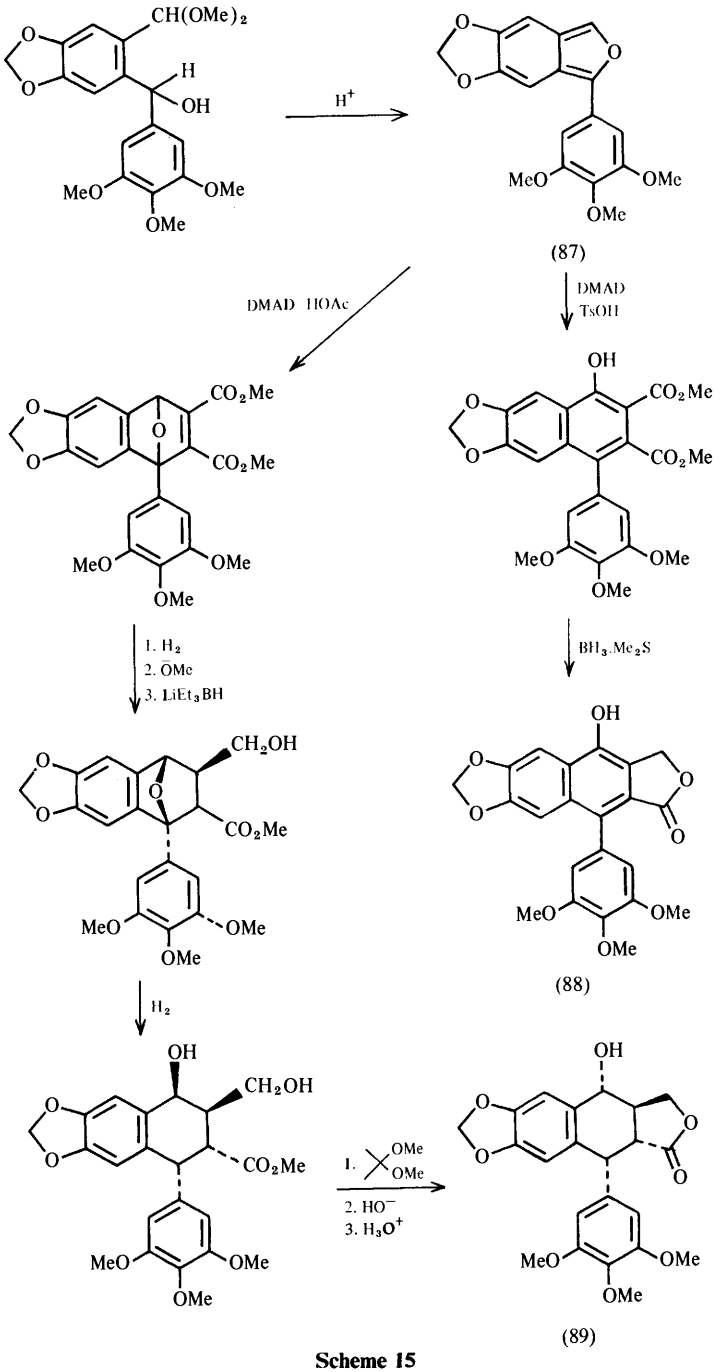
also been used to prepare taiwanin E, chinensinaphthol and diphyllin. In the absence of a strong acid the initial adduct can be isolated and selectively reduced leading eventually, in the case illustrated, to podophyllotoxin (89).[70]

Photoenolization provides an alternative way of generating a quinone-dimethane intermediate suitable for cycloaddition to a dienophile, and two distinctly different approaches have been developed using this reaction. The first starts from an appropriate benzophenone derivative (90)[71] whereas the second involves a formyldiphenylmethane [*e.g.* (92)].[72] The latter route has the added attraction that it automatically generates a 4-hydroxy-substituent, leading

[70] R. Rodrigo, *J. Org. Chem.*, 1980, **45**, 4538 and D. Rajapaksa and R. Rodrigo, *J. Am. Chem. Soc.*, 1981, **103**, 6208.

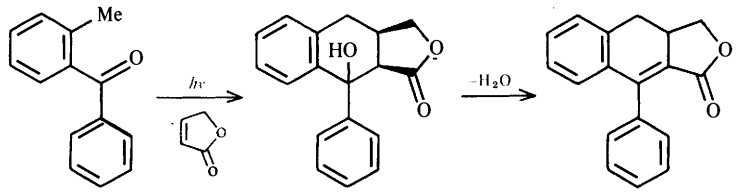
[71] E. Block and R. Stevenson, *J. Chem. Soc., Chem. Commun.*, 1971, 711 and *J. Chem. Soc., Perkin Trans. 1*, 1973, 308.

[72] B. J. Arnold, S. M. Mellows, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1266.

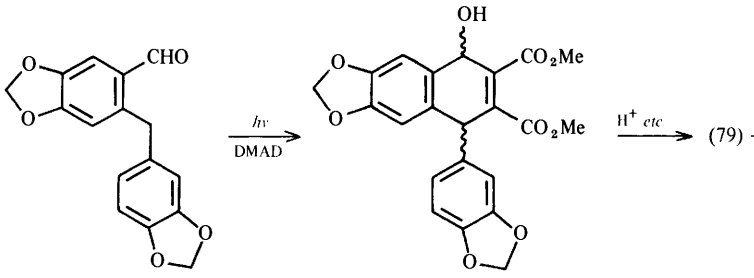

CH(OMe)2
H
OH
MeO
OMe
OMe
H+
(87)
DMAD HOAc
DMAD
TsOH
CO2Me
CO2Me
1. H2
2. OMe
3. LiEt3BH
BH3.Me2S
CH2OH
(88)
H2
1.
2. HO−
3. H3O+
(89)

Scheme 15

for example to taiwanin E (93), whereas the former offers a potentially useful route to various dihydroarylnaphthalenes [*e.g.* (91)].

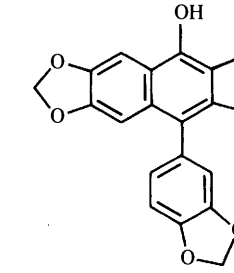


(90) (91) (21)



(92)

(22)



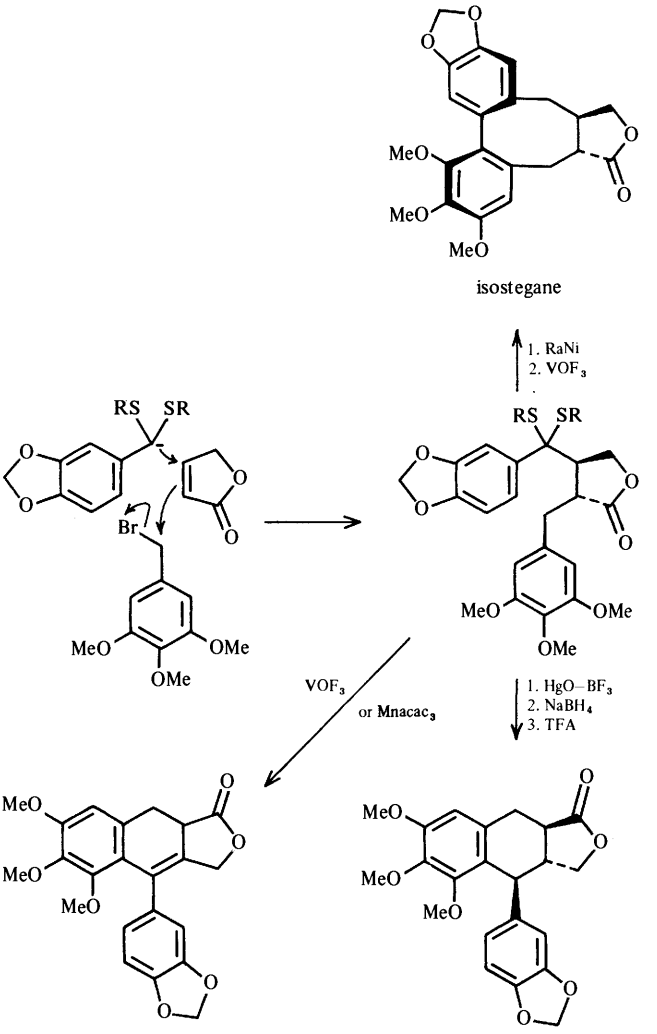
(93)

6 Conjugate Addition Reactions

The conjugate addition of a thioacetal carbanion to butenolide followed by trapping of the enolate anion so generated with a suitable electrophile provides a short, efficient approach to the construction of the basic lignan skeleton. Thus Ziegler *et al.*[73] have used benzyl halides and aromatic aldehydes to trap the enolate anions and have studied various cyclization reactions of the dibenzylbutyrolactones produced (Schemes 16 and 17). The synthesis of isostegane by

[73] F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.*, 1978, **43**, 985.

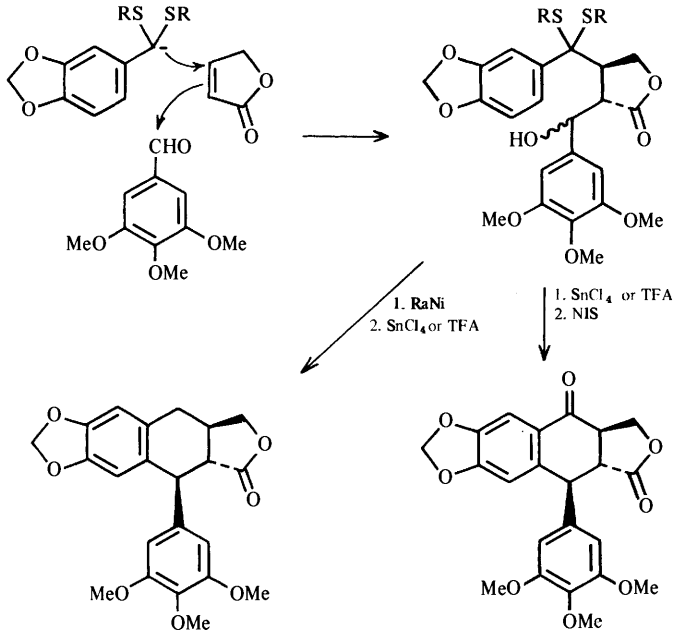
this route was first accomplished by Schlessinger *et al.*,[45] who suggested the possible involvement of a spirodienone intermediate in the cyclization step.



Scheme 16

Pelter *et al.*[74] have utilized a similar scheme to provide a general route to dibenzylbutyrolactones, including 'Factor X' (94), which is the first lignan to be isolated from animal sources.[15–18] It has also been shown that treatment of the

[74] A. Pelter, R. S. Ward, and P. Satyanarayana, *Tetrahedron Lett.*, 1981, 1549.



deoxyisopodophyllotoxin isopodophyllotoxone

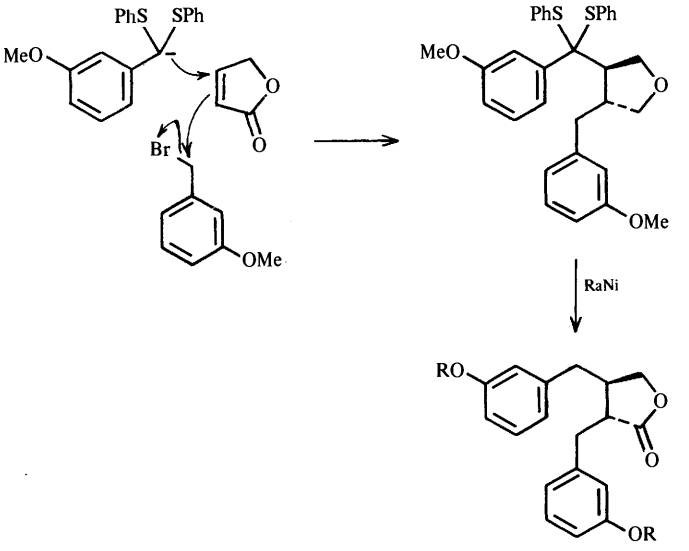
Scheme 17

bis(thiophenyl) derivatives of the dibenzylbutyrolactones with mercury(II) trifluoroacetate affords the corresponding arylnaphthalenes (95) in good yield.[75] No trace of the intermediate dihydroarylnaphthalenes was detected.

Gonzalez *et al.*[76] have utilized a similar sequence to synthesize isodiphyllin, and Mpango and Snieckus have carried out similar conjugate addition reactions on an *N,N*-dimethyl α,β-unsaturated amide.[77] Of possibly greater importance is the use of a chiral butenolide to carry out asymmetric syntheses of the lignans (+)-burseran (96), (−)-isostegane (97), and (+)-steganacin (98).[78]

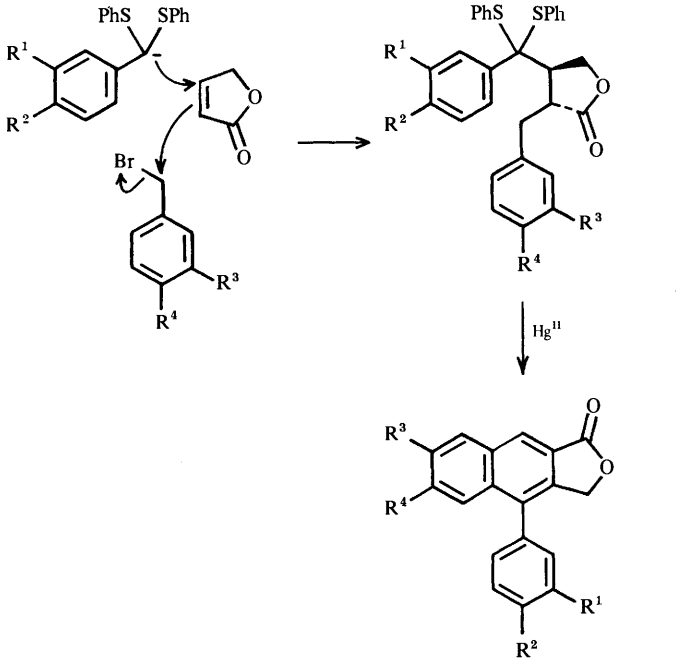
In what can be regarded as a logical extension of this approach Kende *et al.*[79] have employed conjugate addition of an aryl-lithium reagent and intramolecular trapping by a benzyl bromide to prepare the aryltetralin system directly, as shown in Scheme 18.

[75] A. Pelter, R. S. Ward, P. Satyanarayana, and P. Collins, *Tetrahedron Lett.*, 1982, 571.
[76] A. G. Gonzalez, J. P. Perez, and J. M. Trujillo, *Tetrahedron*, 1978, **34**, 1011.
[77] G. B. Mpango and V. Snieckus, *Tetrahedron Lett.*, 1980, 4827.
[78] K. Tomioka, T. Ishiguro, and K. Koga, *Tetrahedron Lett.*, 1980, 2973, and *J. Chem. Soc. Chem. Commun.*, 1979, 652.
[79] A. S. Kende. M. L. King, and D. P. Curran, *J. Org. Chem.*, 1981, **46**, 2826.


PhS
SPh
MeO
O
O
Br
OMe
PhS
SPh
MeO
O
OMe
RaNi
RO
O
O
OR

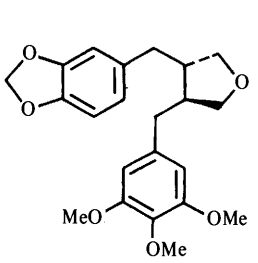
(23)

(94; R = H)

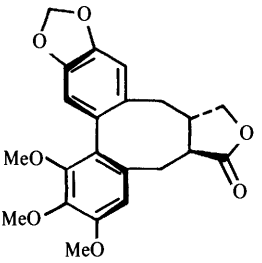

PhS
SPh
R1
R2
O
O
Br
R3
R4
PhS
SPh
R1
R2
O
O
R3
R4
Hg11
O
O
R3
R4
R1
R2

(24)

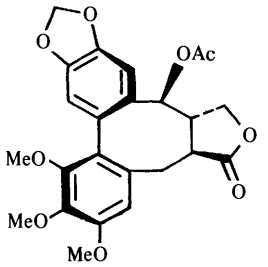
(95)



(96)



(97)



(98)

7 Alkylation and Acylation of Monolactones

Several syntheses of lignans are closely related to the conjugate addition reactions described in the last section in that they involve treating an enolate anion of a benzylbutyrolactone with an alkylating or acylating agent. Thus, the reaction of the anion derived from 4-(3′,4′-methylenedioxybenzyl)butyrolactone (99) with an aromatic aldehyde furnishes an α-hydroxybenzylbutyrolactone derivative (100), which can be cyclized under acidic conditions to give an aryltetralin [*e.g.* (84)].[80] The same reaction can also be carried out in an intramolecular fashion starting from a biaryl derivative and leading, as indicated, to picrostegane (102) and isopicrostegane (103).[81] Two other examples of the condensation of an aromatic aldehyde with a benzylbutyrolactone are included in the next section (see Scheme 24).

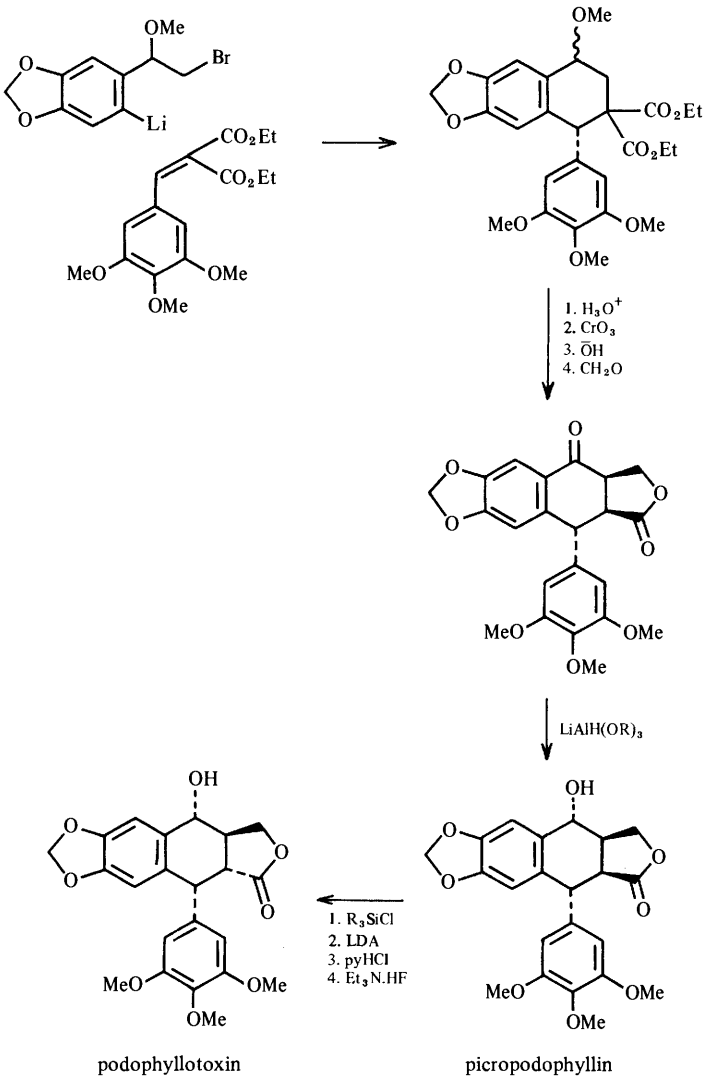
The chiral monolactones (104) and (105) have been used as a starting point for asymmetric syntheses of several lignans including (+)-podorhizon, (−)-podorhizol, (−)-isodeoxypodophyllotoxin, (+)-isosteganone, and (−)-steganone (Schemes 19 and 20).[82,83]

[80] E. Brown, M. Loriot, and J.-P. Robin, *Tetrahedron Lett.*, 1979, 1389: *cf.* E. Brown, J.-P. Robin and R. Dhal, *J. Chem. Soc., Chem. Commun.*, 1978, 556.

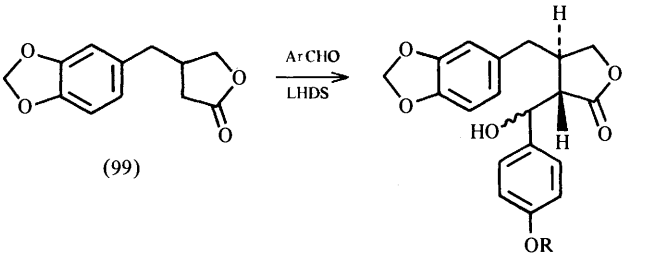
[81] E. Brown and J.-P. Robin, *Tetrahedron Lett.*, 1978, 3612:*cf.* E. Brown, R. Dhal, and J.-P. Robin, *ibid.*, 1979, 733.

[82] K. Tomioka, H. Mizuguchi, and K. Koga, *Tetrahedron Lett.*, 1978, 4687 and K. Tomioka and K. Koga, *ibid.*, 1979, 3315.

[83] J.-P. Robin, O. Gringore, and E. Brown, *Tetrahedron Lett.*, 1980, 2709.


OMe
Br
Li
O
O
CO2Et
CO2Et
MeO
OMe
OMe
OMe
CO2Et
CO2Et
MeO
OMe
OMe
1. H3O+
2. CrO3
3. OH
4. CH2O
O
O
O
O
MeO
OMe
OMe
LiAlH(OR)3
OH
O
O
O
O
MeO
OMe
OMe
1. R3SiCl
2. LDA
3. pyHCl
4. Et3N.HF
OH
O
O
O
O
MeO
OMe
OMe
podophyllotoxin
picropodophyllin

Scheme 18

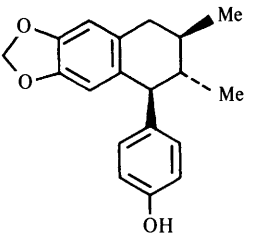


(99)

(100)

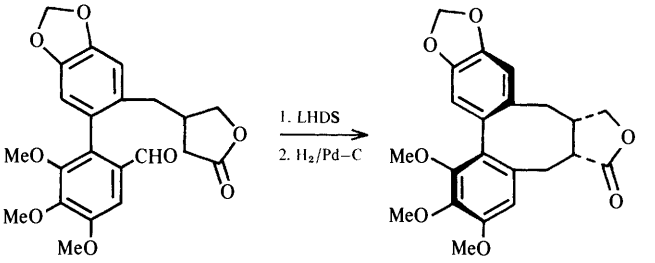
H^+ *etc*

(25)



(Ar = 4-benzyloxyphenyl)

(84)

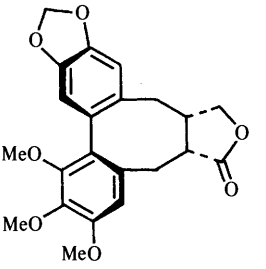


(101)

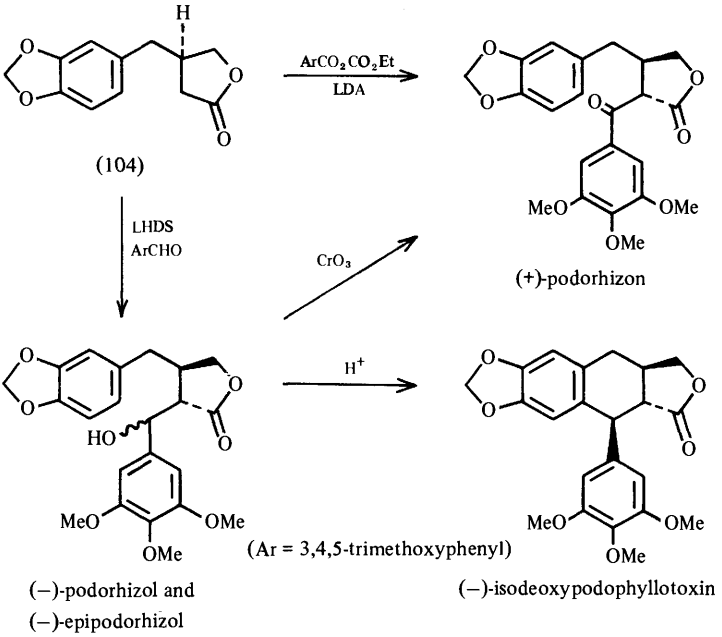
(102)

+

(26)



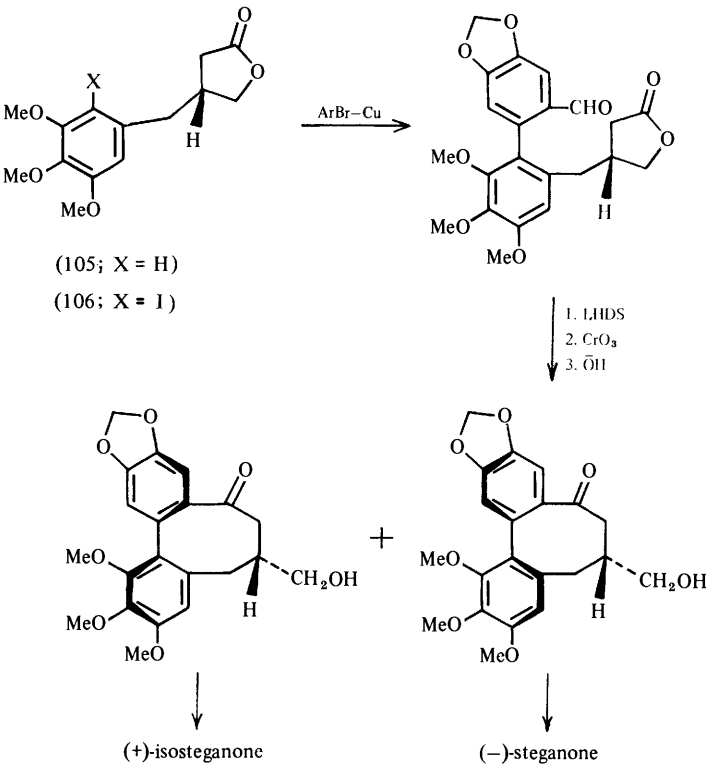
(103)



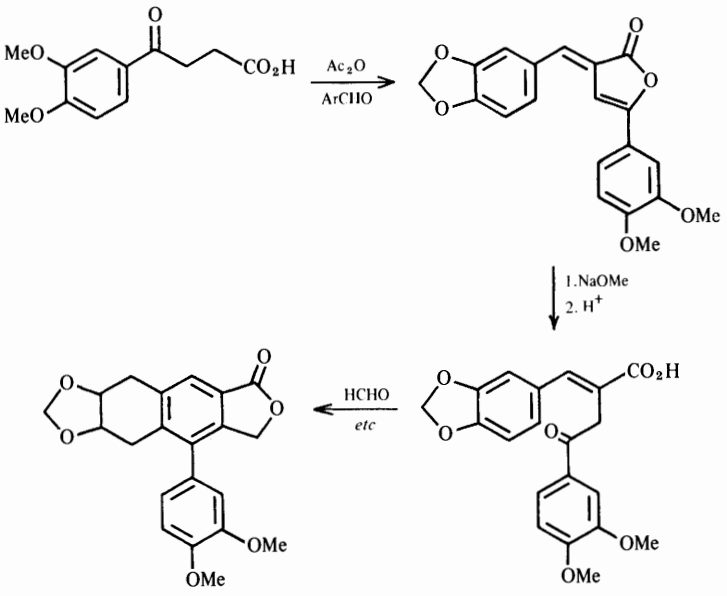
Scheme 19

Condensation reactions involving γ-lactones of a rather different type are involved in Munakata *et al.*'s syntheses of arylnaphthalene lactones, which are shown in Schemes 21 and 22.[84] The scope and mechanism of the latter reaction sequence, involving as it does a most unusual rearrangement process, has been further studied by Ayres *et al.*[85]

[84] K. Munakata, S. Marumo, K. Ohta, and Y.-L. Chen, *Tetrahedron Lett.*, 1967, 3821 and *Agric. Biol. Chem. (Jpn.)*, 1971, **35**, 431.
[85] D. C. Ayres and J. W. Mundy, *J. Chem. Soc. (C)*, 1969, 637.


X
MeO
MeO
MeO
H
O
O
O
ArBr–Cu
CHO
O
O
O
O
MeO
MeO
MeO
H
(105; X = H)
(106; X = I)
1. LHDS
2. CrO_3
3. $\bar{O}H$
CH_2OH
H
+
(+)-isosteganone
(–)-steganone

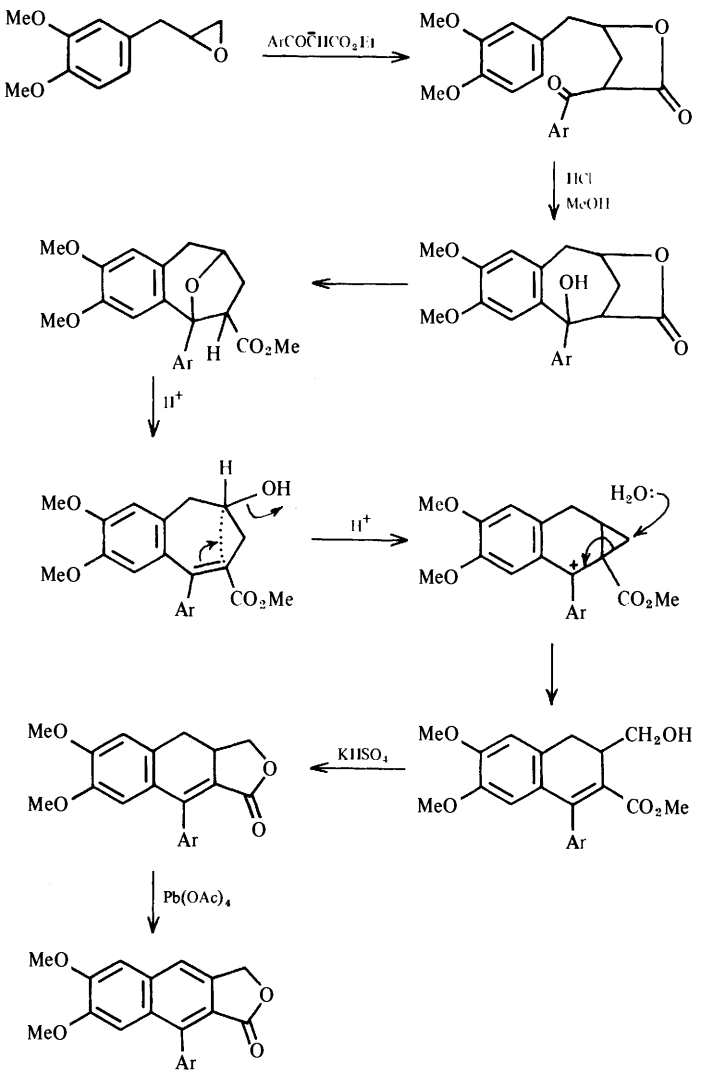
Scheme 20



retrochinensin

(Ar = 3,4-methylenedioxyphenyl)

Scheme 21



(Ar = 3,4-methylenedioxyphenyl)

Scheme 22

8 Stobbe Condensation

The Stobbe condensation has been frequently used to construct the basic lignan skeleton,[65–68] and can be illustrated by Crombie's syntheses of (−)-cubebin and

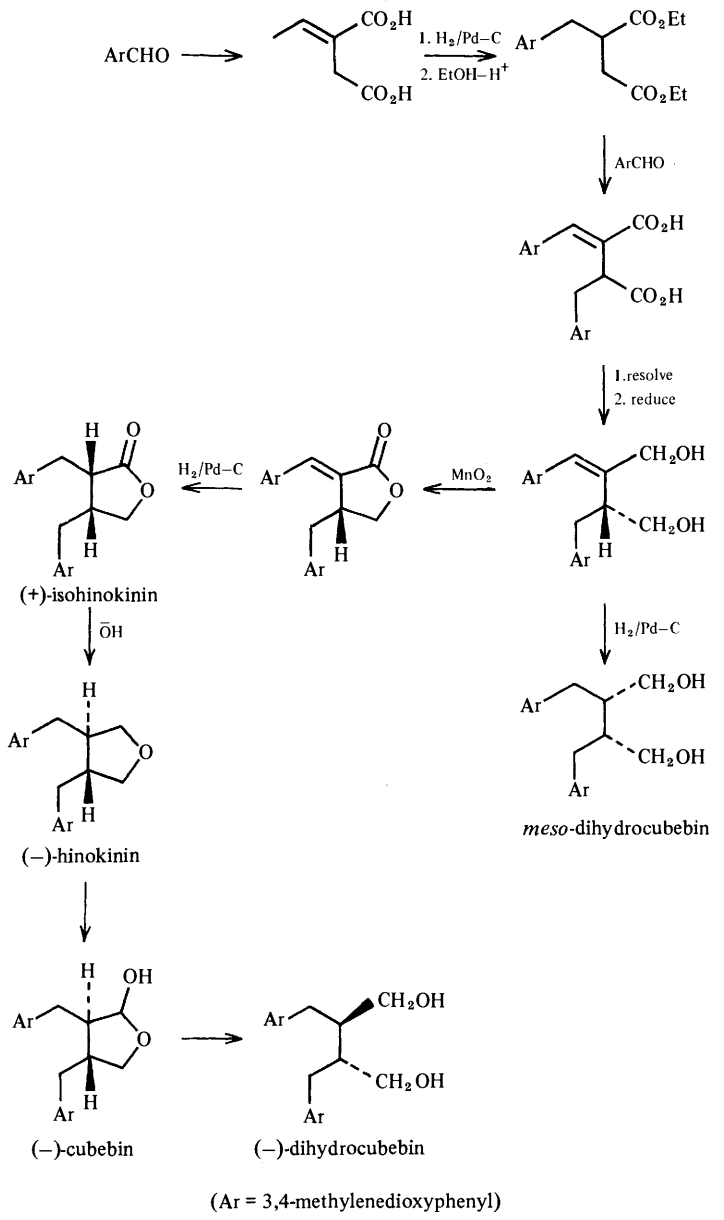
related compounds (Scheme 23).[86] A similar approach was also used to prepare the various isomers of dihydroguiaretic acid dimethyl ether,[87] and has been used more recently by Stevenson *et al.*[88] to prepare the aryltetralins nirtetralin and hypophyllanthin (Scheme 24). The structures of the last compounds, which occur together in *Phyllanthus niruri*, have been the subject of much controversy over the years. Further elaboration of the benzylbutyrolactones is achieved by reaction with an aromatic aldehyde as outlined in the last section, and final reduction followed by methylation affords the isomeric lignans, having spectral characteristics identical to the naturally occurring materials.

In contrast, the Japanese group of Horii *et al.*[89,90] have used the Stobbe condensation of a benzophenone derivative, an approach pioneered by Gensler *et al.*,[91] to prepare arylnaphthalene lactones as shown in Scheme 25 and 26. In this case the isomeric arylnaphthalene lactones can be prepared from a common precursor by protecting the formyl group at C-3 as an isoxazole derivative, while reducing the ester group at C-2.

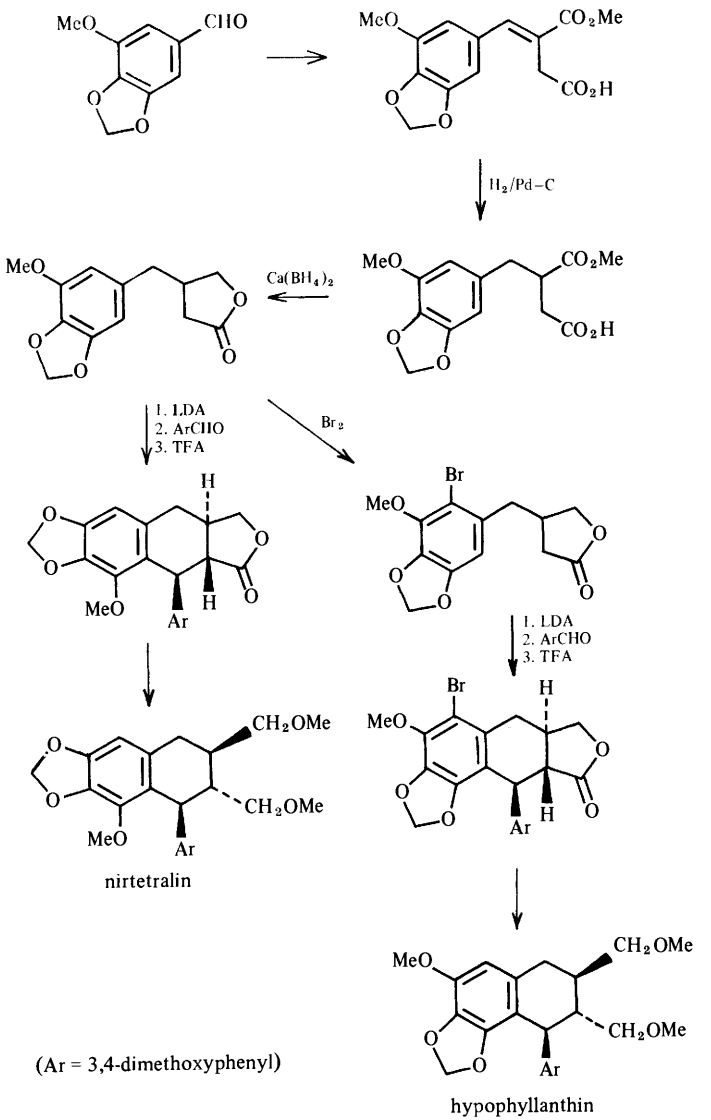
9 From Chalcones

Chalcones contain a basic 15-carbon skeleton and require the addition of an extra three carbon atoms to afford the lignan framework. They are, however, conveniently prepared by condensation of aromatic aldehydes with acetophenones and hence represent useful precursors for the preparation of natural products containing two aromatic rings linked by an aliphatic chain. It has been shown that the basic aryltetralin framework can be constructed by the addition of a two-carbon unit in the form of a sulphonium ylide as shown in Scheme 27.[92] Rearrangement of the intermediate cyclopropane, which proceeds in a stepwise manner, affords an aryltetralin directly, requiring only the addition of a final one-carbon unit to complete the synthesis of the full carbon skeleton of the aryltetralin lactones, and providing yet another elegant approach to this medicinally important series of compounds.

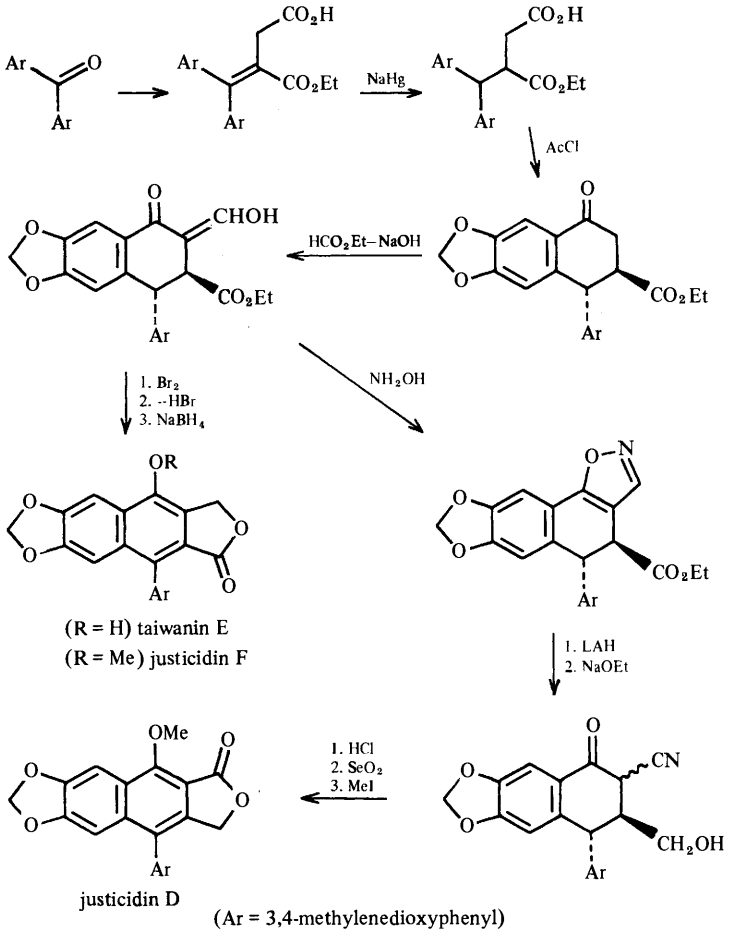
[86] J. E. Batterbee, R. S. Burden, L. Crombie, and D. A. Whiting, *J. Chem. Soc. (C)*, 1969, 2470.
[87] A. W. Strecker, *J. Am. Chem. Soc.*, 1951, **79**, 3823.
[88] P. A. Ganeshpure and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1681 and G. E. Schneiders and R. Stevenson, *ibid.*, 1982, 999.
[89] Z.-I. Horii, M. Tsujiuchi, and T. Momose, *Tetrahedron Lett.*, 1969, 1079 and Z.-I. Horii, M. Tsujiuchi, K.-I. Kanai, and T. Momose, *Chem. Pharm. Bull.*, 1977, **25**, 1803.
[90] Z.-I. Horii, K. Ohkawa, S.-W. Kim, and T. Momose, *Chem. Pharm. Bull.*, 1968, **16**, 2404; 1969, **17**, 1878; 1971, **19**, 535.
[91] W. J. Gensler, C. M. Samour, S. Y. Wang, and F. Johnson, *J. Am. Chem. Soc.*, 1960, **82**, 1714.
[92] W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2920; 1982, 271 and 1029.


ArCHO
CO2H
CO2H
1. H2/Pd–C
2. EtOH–H+
Ar
CO2Et
CO2Et
ArCHO
CO2H
CO2H
Ar
1.resolve
2. reduce
CH2OH
CH2OH
MnO2
H2/Pd–C
(+)-isohinokinin
OH
(–)-hinokinin
meso-dihydrocubebin
OH
(–)-cubebin
(–)-dihydrocubebin
(Ar = 3,4-methylenedioxyphenyl)

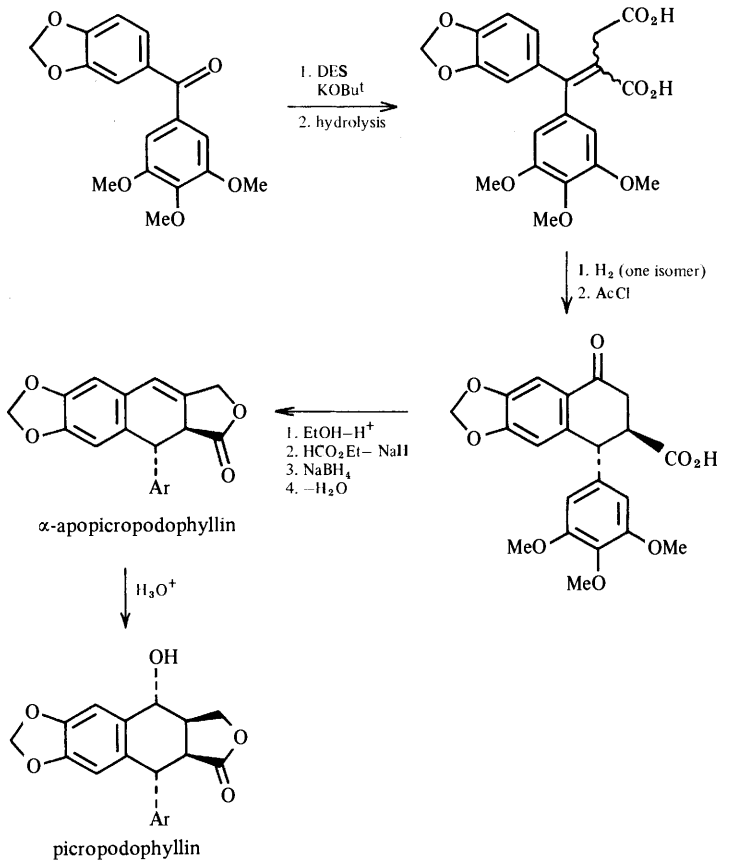
Scheme 23


MeO
CHO
MeO
CO2Me
CO2H
H2/Pd-C
MeO
CO2Me
CO2H
Ca(BH4)2
MeO
1. LDA
2. ArCHO
3. TFA
Br2
H
MeO
Ar
H
Br
MeO
1. LDA
2. ArCHO
3. TFA
Br
H
MeO
Ar
H
CH2OMe
CH2OMe
MeO
Ar
nirtetralin
CH2OMe
CH2OMe
MeO
Ar
hypophyllanthin
(Ar = 3,4-dimethoxyphenyl)

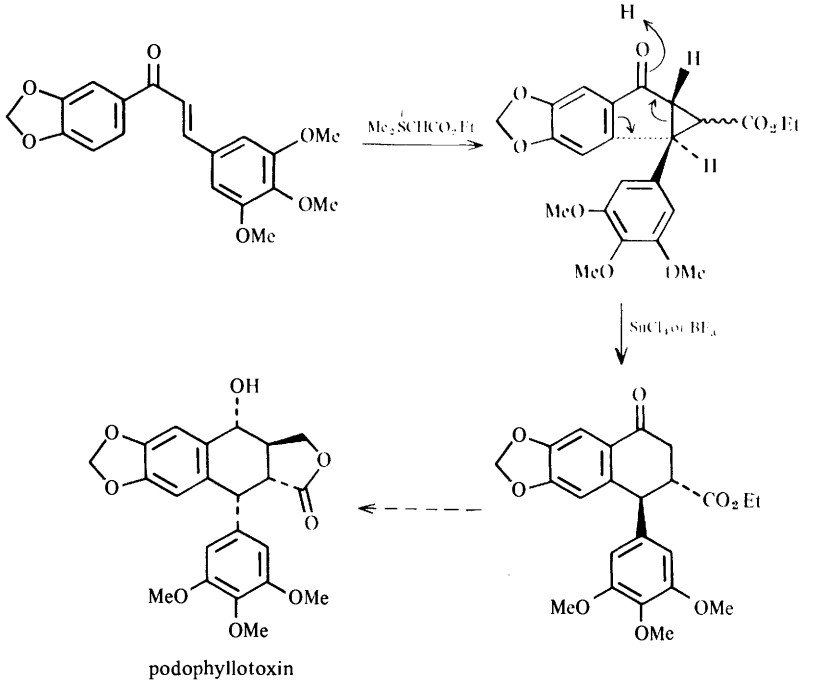
Scheme 24


Ar
O
Ar
CO2H
Ar
CO2Et
Ar
NaHg
CO2H
Ar
CO2Et
Ar
AcCl
O
O
O
CO2Et
Ar
HCO2Et–NaOH
O
CHOH
O
O
CO2Et
Ar
1. Br2
2. –HBr
3. NaBH4
NH2OH
OR
O
O
O
O
Ar
(R = H) taiwanin E
(R = Me) justicidin F
O–N
O
O
CO2Et
Ar
1. LAH
2. NaOEt
OMe
O
O
O
O
Ar
justicidin D
1. HCl
2. SeO2
3. MeI
O
CN
O
O
CH2OH
Ar
(Ar = 3,4-methylenedioxyphenyl)

Scheme 25


1. DES
KOBu^t
2. hydrolysis
1. H_2 (one isomer)
2. AcCl
1. EtOH–H^+
2. HCO_2Et– NaH
3. $NaBH_4$
4. $-H_2O$
H_3O^+
α-apopicropodophyllin
picropodophyllin

Scheme 26



podophyllotoxin

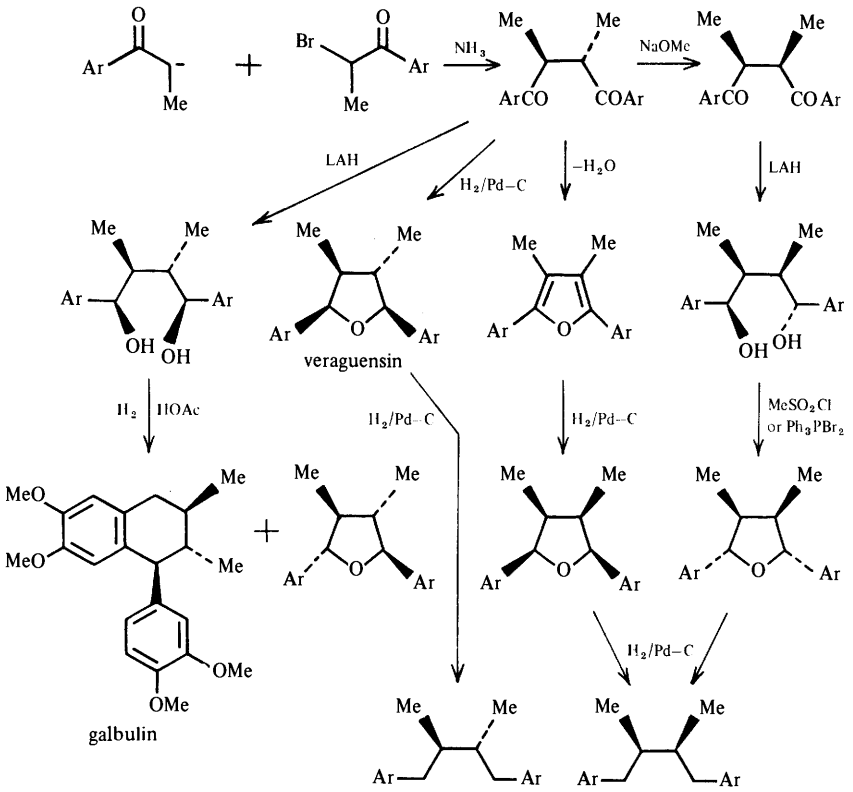
Scheme 27

10 From Furans and 1,4-Diketones

1,4-Diketones are readily converted into a number of lignan types (Scheme 28). Thus, partial reduction followed by cyclization affords tetrahydrofuran or aryltetralin derivatives, whereas complete reduction affords dibenzylbutanes, the stereochemistry of which in general depend upon the configuration of the original diketone.[46,93,94] The dibenzylbutanes can also be subjected to non-phenolic oxidative coupling (section 3) to afford dibenzocyclo-octadienes of the deoxyschizandrin type.

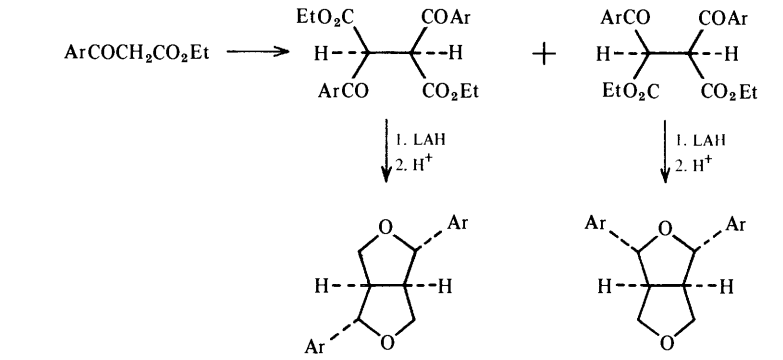
1,4-Diketones can also be prepared by the coupling together of β-keto-esters (Scheme 29). This method, which is based on the early work of Knorr, yields a mixture of the *threo* and *erythro* isomers of the diketo-diesters that can in most cases be separated by fractional crystallization. Reduction followed by cyclization then affords either the naturally occurring 2,6- or the unnatural 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes.[95] Cyclization to a furan followed by

[93] C. W. Perry, M. V. Kalnins, and K. H. Deitcher, *J. Org. Chem.*, 1972, **37**, 4371.
[94] T. Biftu, B. G. Hazra, R. Stevenson, and J. R. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1147.
[95] A. Pelter, R. S. Ward, D. J. Watson, and I. R. Jack, *J. Chem. Soc., Perkin Trans. 1*, 1982, 183.

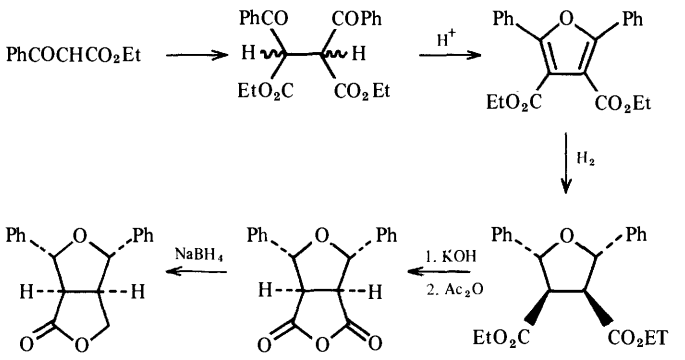


Scheme 28

reduction has also been used in one case to prepare a 2,4-diarylmonolactone (Scheme 30).[24]

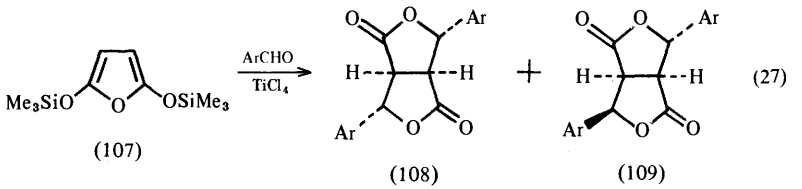


Scheme 29



Scheme 30

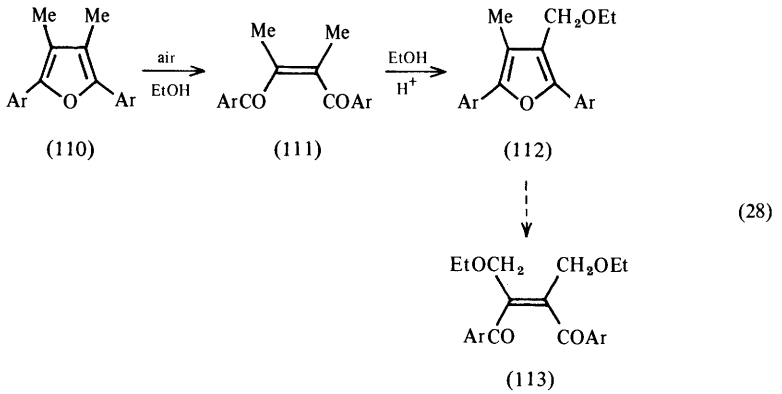
Brownbridge and Chan[96] have used the disiloxyfuran (107) to prepare dilactones of type (108) and (109) having diequatorial and equatorial–axial configurations respectively. The proportions of the two isomers obtained depend upon the number of moles of $TiCl_4$ used and the nature of the aryl group.



(107) (108) (109) (27)

The unusual enedione, diethyl furoguaioxidin (113), has been prepared by sequential introduction of alkoxy-functions into the methyl groups of a 2,5-diaryl-3,4-dimethylfuran (110).[97] Aerial oxidation of the furan affords an enolizable enedione (111) which reacts with ethanol to give the ethoxy-substituted compound (112). Repetition of the sequence then affords (113).

[96] P. Brownbridge and T.-H. Chan, *Tetrahedron Lett.*, 1980, 3427.
[97] P. Majumbar and M. Bhattacharyya, *J. Chem. Soc., Chem. Commun.*, 1975, 702.



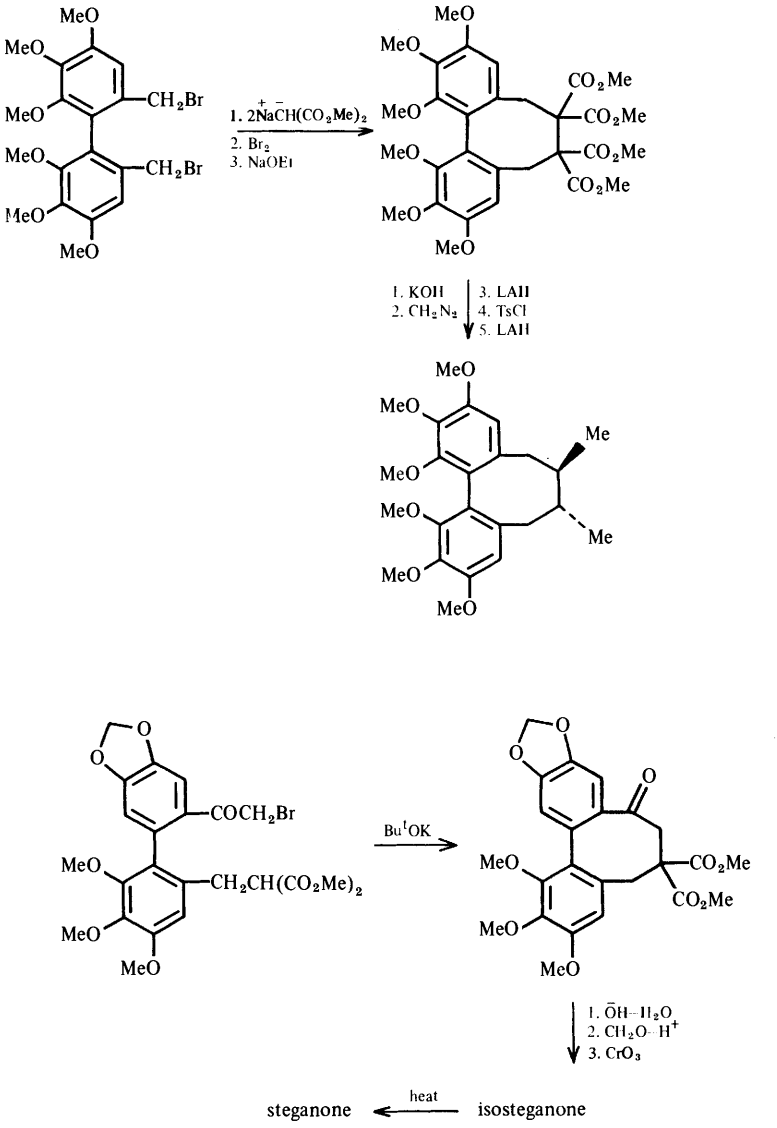
(28)

11 From Biphenyl and Phenanthrene Derivatives

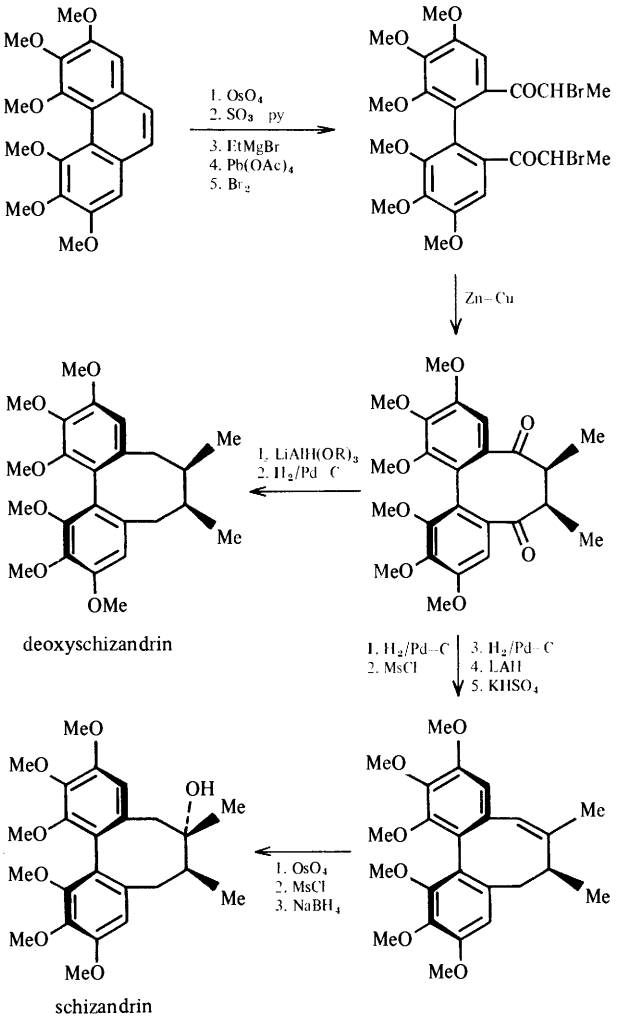
The main group of lignans containing a biaryl linkage is the dibenzocyclo-octadiene group of which steganone, schizandrin, and kadsurin are members. One approach to the synthesis of such compounds, which has already been dealt with in section 2, involves the formation of the biaryl linkage at a late stage in the synthesis by oxidative coupling. An alternative approach is to start from a simple biphenyl derivative and proceed to form the eight-membered ring and the remainder of the molecule at a later stage in the synthesis (*cf.* section 6). Further examples of this approach are illustrated in Schemes 31 and 32.[98–102] Two main methods have been used to complete the synthesis of the cyclo-octadiene ring, using either malonic esters (Scheme 31) or Wurtz coupling (Scheme 32). The biphenyl derivatives can be obtained either by the standard Ullmann coupling methods,[80,81,83,98,99] or by the oxidative cleavage of phenanthrene derivatives (see Scheme 32).[100–102]

Another elegant way of proceeding from a phenanthrene derivative to the dibenzocyclo-octadiene series involves the ring expansion of an enamine by cycloaddition to dimethyl acetylenedicarboxylate (Scheme 33).[103] Subsequent conversion of the enamine into a ketone and of the diester into a lactone produces steganone and isosteganone.

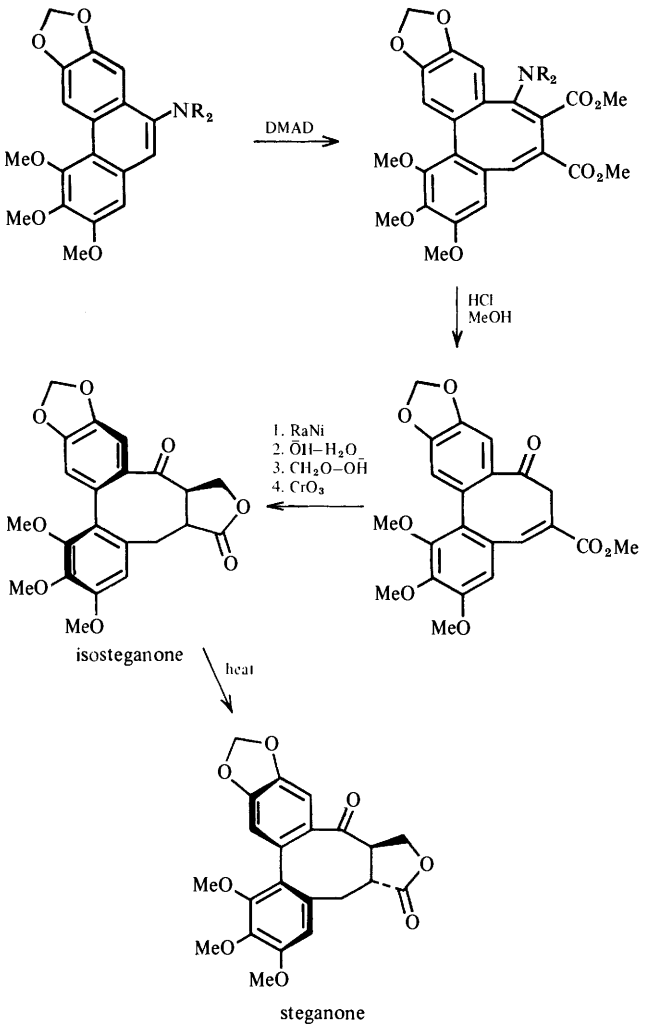
[98] N. K. Kochetkov, A. Ya. Khorlin, and O. S. Chizhov, *Izv. Akad. Nauk SSSR, Otd. Khim.*, 1962, 856 and *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1964, 1036.
[99] F. E. Ziegler, K. W. Fowler, and N. D. Sinha, *Tetrahedron Lett.*, 1978, 2767.
[100] M. Mervic and E. Ghera, *J. Am. Chem. Soc.*, 1977, **99**, 7673.
[101] E. Ghera, Y. Ben-David, and D. Becker, *Tetrahedron Lett.*, 1977, 463 and M. Mervic, Y. Ben-David, and E. Ghera, *ibid.*, 1981, 5091.
[102] E. Ghera and Y. Ben-David, *J. Chem. Soc., Chem. Commun.*, 1978, 480.
[103] D. Becker, L. R. Hughes, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1674; *cf.* E. R. Larson and R. A. Raphael, *ibid.*, 1982, 521.


MeO
MeO
MeO
MeO
MeO
CH2Br
CH2Br
1. 2NaCH(CO2Me)2
2. Br2
3. NaOEt
CO2Me
CO2Me
CO2Me
CO2Me
1. KOH
2. CH2N2
3. LAH
4. TsCl
5. LAH
Me
Me
COCH2Br
CH2CH(CO2Me)2
BuᵗOK
O
1. ⁻OH–H2O
2. CH2O–H+
3. CrO3
steganone
heat
isosteganone

Scheme 31


MeO
MeO
MeO
MeO
MeO
MeO
1. OsO_4
2. SO_3 py
3. EtMgBr
4. $Pb(OAc)_4$
5. Br_2
COCHBrMe
COCHBrMe
Zn–Cu
Me
OMe
deoxyschizandrin
1. $LiAlH(OR)_3$
2. H_2/Pd C
O
1. H_2/Pd–C
2. MsCl
3. H_2/Pd–C
4. LAH
5. $KHSO_4$
OH
1. OsO_4
2. MsCl
3. $NaBH_4$
schizandrin

Scheme 32

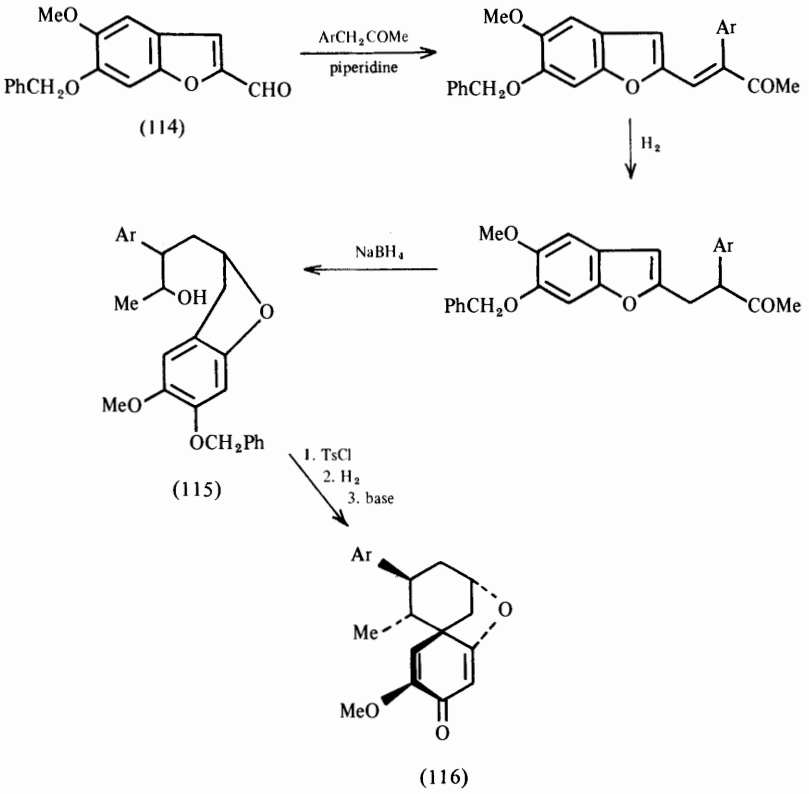


Scheme 33

12 Miscellaneous

An alternative approach to futoenone (116) starts from a benzofuran derivative (114).[104] Cyclization of the dihydrobenzofuran (115) with expulsion of a *p*-toluenesulphonate group supplies the third ring of the tricyclic framework (Scheme 34).

[104] A. Ogiso, M. Kurabayashi, A. Takashi, H. Mishima, and M. C. Woods, *Chem. Pharm. Bull.*, 1970, **18**, 105.


MeO
PhCH2O
CHO
(114)
ArCH2COMe
piperidine
MeO
Ar
PhCH2O
COMe
H2
MeO
Ar
PhCH2O
COMe
NaBH4
Ar
Me
OH
MeO
OCH2Ph
(115)
1. TsCl
2. H2
3. base
Ar
Me
MeO
(116)

Scheme 34