Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol.24*

RECENT ADVANCES IN THE CHEMISTRY OF LIGNANS

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Abstract: This chapter describes recent developments in the chemistry of an important group of natural products which have diverse structures and significant biological activity. The emphasis is placed on new methods which have been used for their synthesis and asymmetric synthesis, and on recent advances in our understanding of their biosynthesis. While brief mention is made of the wide range of biological activity which they exhibit, and the use of their derivatives in cancer chemotherapy, the main emphasis is on their organic chemistry, including the unique transformations they undergo which lead to the interconversion of different structural types.

The treatment is not intended to be comprehensive, since this purpose is already served by other review publications, but it seeks to highlight important recent contributions and to identify important themes underlying the chemistry of these compounds.

With these aims in mind the chapter is divided into the following sections:-

1 An introduction, including mention of their diversity of structure and biological activity

2 Biosynthesis, describing recent studies on the biochemical pathways involved

3 Synthesis and asymmetric synthesis, reviewing important synthetic routes to lignans

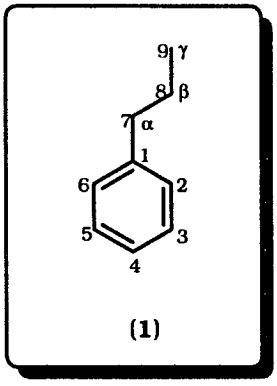
4 Transformations, describing interconversions and specific transformations of particular lignan types

1 INTRODUCTION

Lignans and neolignans are natural products formed by the linking together of two C_6C_3 units (**1**), each of which are derived from the shikimic acid pathway. The term 'lignan' was introduced by Haworth to denote structures which are composed of two C_6C_3 units linked by a β-β (8-8') bond [1]. The term 'neolignan' was introduced later by Gottlieb to distinguish compounds which contain two C_6C_3 units but which are not β-β linked [2]. Several different classes of lignans and neolignans can be identified depending upon the carbon skeletons which they possess [3].

Possibly as a result of their diverse structures, lignans show a wide range of biological activity. For example, there is growing evidence that the consumption of foods rich in lignans can decrease the risk of contracting certain forms of cancer [4-7]. The implication of these findings

is that the lignans ingested, or the compounds into which they are converted by intestinal microflora, can act as cancer-protective agents [8]. Thus the excretion of enterolactone and enterodiol in urine has been correlated with fibre intake, and it has been suggested that these hormone-like substances may be responsible for the cancer-protective effect of a vegetarian diet [9,10]. Certainly the low incidence of breast cancer and prostate cancer in some countries can be correlated with adherence to a largely vegetarian diet[11].

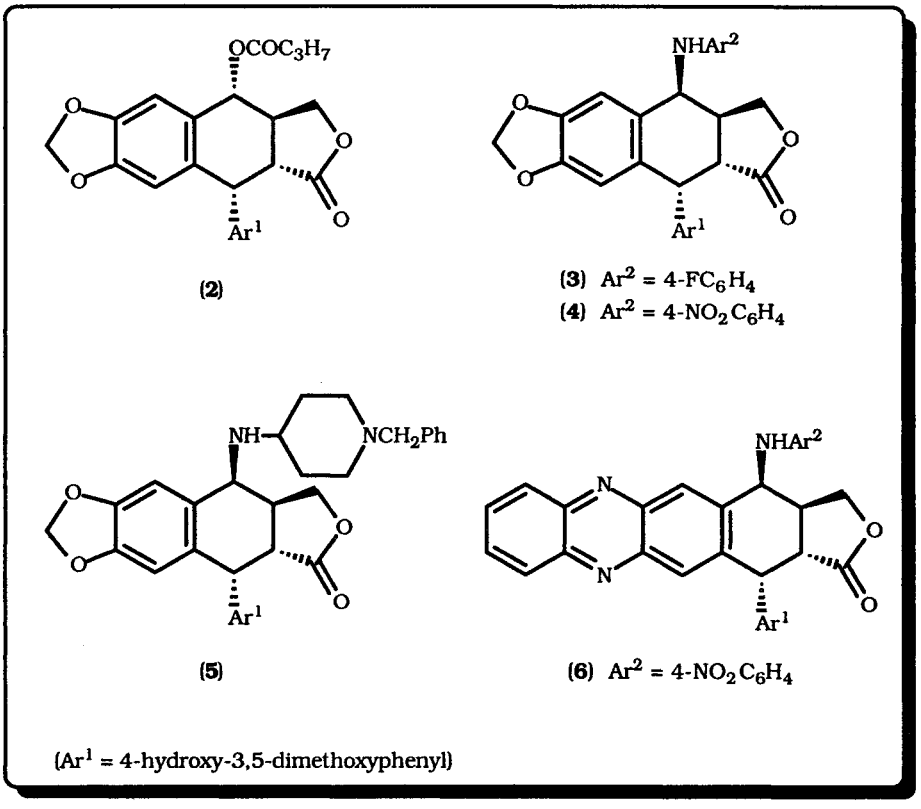


(1)

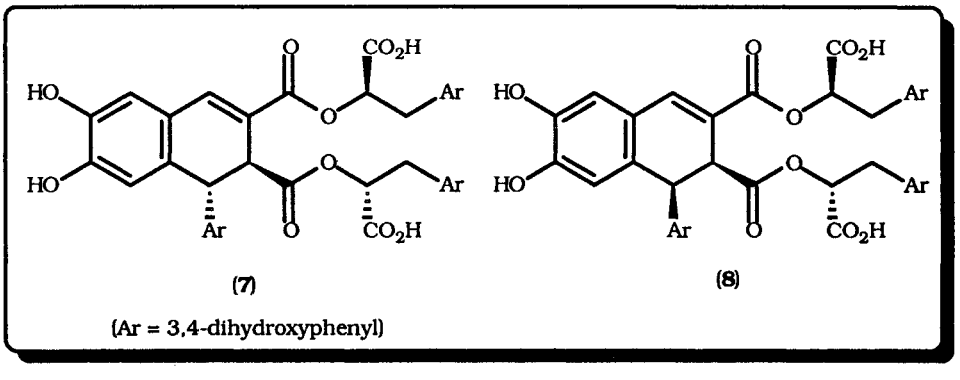
Derivatives of podophyllotoxin play an important role in cancer chemotherapy. As a result there is continuing interest in trying to find an efficient synthesis of podophyllotoxin and in seeking to prepare more active derivatives. Analogues continue to be investigated in an effort to improve upon the antitumour activity of the clinical drug etoposide [12,13]. For example, it has been found that compounds with a $OCH_2CH_2NH_2$ or $NHCH_2CH_2OH$ group in place of the glycosidic moiety of etoposide have a different spectrum of antitumour activity from etoposide itself and therefore may be useful when etoposide resistance occurs. 4-O-Butanoyl-4'-demethylpodophyllotoxin (**2**) is cytotoxic at concentrations 100-1000 times lower than conventional drugs and is active against several drug resistant tumour cell lines [14,15]. Similarly the 4-arylamino derivatives (**3**) and (**4**) are up to 100 times more active than etoposide and show activity against etoposide resistant cells [16,17], while compounds such as (**5**) which can form water soluble salts have increased antitumour activity and improved drug resistance [18], and compounds such as (**6**) exhibit improved activity and are reported to have a novel mechanism of action [19].

Kadsurenone and related lignans are antagonists of the platelet activating factor receptor [20]. They inhibit PAF-induced platelet aggregation by blocking the receptor with which the agonist interacts. Several 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes and dibenzyl-butyrolactones also show high PAF antagonist activity [21]. For example,

syringaresinol and yangambin show antiplatelet aggregation activity [22,23]. Several other lignans inhibit the binding of platelet activating factor to blood platelets [24].



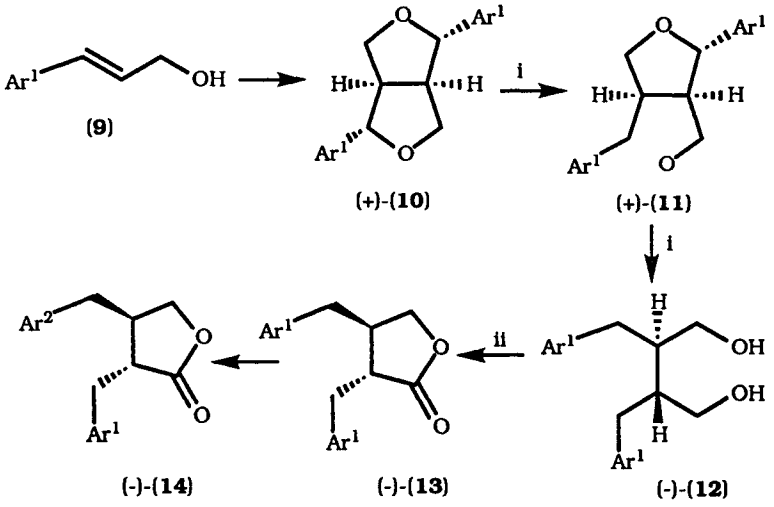
Many other examples of potentially useful biological activity have been reported. Thus, the sodium and potassium salts of (7) and (8), which are



tetramers of caffeic acid, possess significant anti-HIV activity [25]. A number of other lignans, including 3-O-methylnordihydroguaiaretic acid, also display anti-HIV activity [26]. (-)-Arctigenin and (-)-trachelogenin and related compounds strongly inhibit replication of the human immunodeficiency virus (HIV-1) *in vitro* [27,28]. It is thought that these compounds may prevent the increase of topoisomerase II activity involved in virus replication after infection of cells with HIV-1. Some aryltetralins are also potent anti-HIV agents [29].

2 BIOSYNTHESIS

The principle pathways of lignan biosynthesis in *Forsythia* have been elucidated from studies using labelled precursors and cell free extracts. The sequence from coniferyl alcohol (**9**) to (+)-pinoresinol (**10**), (+)-lariciresinol (**11**), (-)-secoisolariciresinol (**12**) and (-)-matairesinol (**13**) is now clearly established (scheme 1) [30-33]. Lewis *et al.* have shown that (+)-pinoresinol (**10**) is formed *via* direct stereoselective coupling of the two coniferyl alcohol molecules, a process which requires the complimentary action of a specific protein and an auxiliary oxidase or peroxidase [34,35]. (+)-Lariciresinol (**11**) and (-)-secoisolariciresinol (**12**) are then formed by consecutive enantiospecific reduction [36], and (-)-secoisolariciresinol is further metabolised into (-)-matairesinol (**13**) *via* enantiospecific dehydrogenation, and into (-)-arctigenin (**14**) *via* regioselective O-methylation [37].

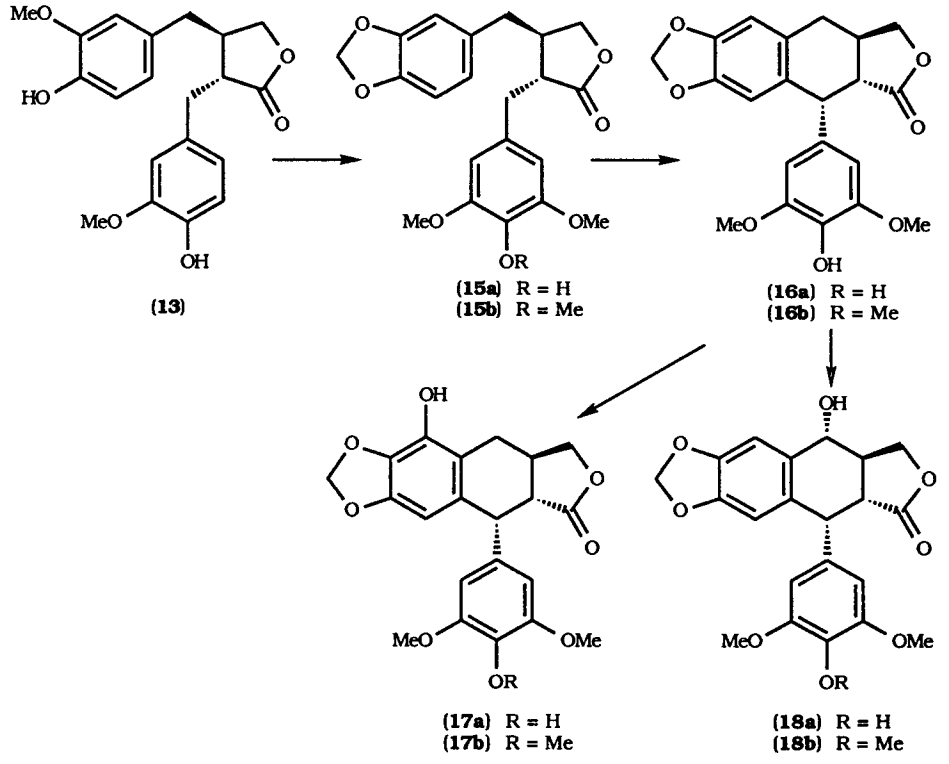


Reagents: i, NADPH; ii $NADP^+$

(Ar^1 = 4-hydroxy-3-methoxyphenyl, Ar^2 = 3,4-dimethoxyphenyl)

Scheme 1.

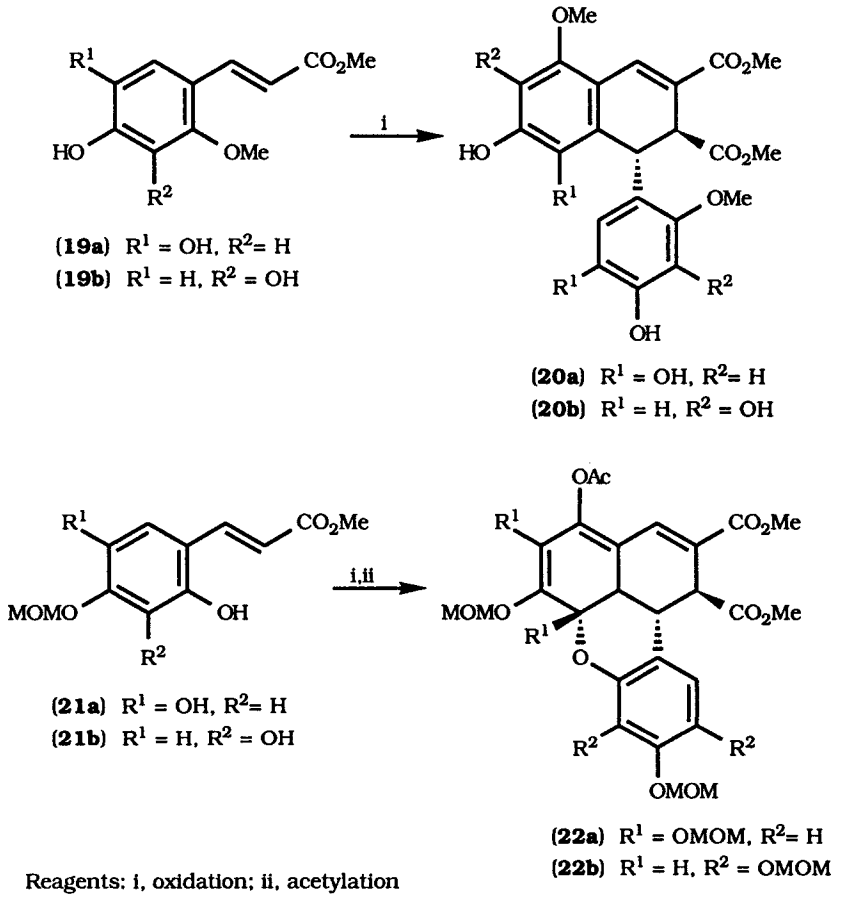
Considerable progress has also been made in elucidating the biosynthetic pathway leading to the podophyllotoxin series (scheme 2) [38,39]. Dewick *et al.* have shown that demethylyatein (**15a**) and yatein (**15b**) are precursors of demethylpodophyllotoxin (**18a**) and podophyllotoxin (**18b**) respectively. Furthermore, 4'-demethyl-deoxypodophyllotoxin (**16a**) and deoxypodophyllotoxin (**16b**) undergo aromatic hydroxylation to yield α-peltatin (**17a**) and β-peltatin (**17b**) respectively. They have also shown that (-)-matairesinol (**13**) is efficiently incorporated into 4'-demethylpodophyllotoxin (**18a**), podophyllotoxin (**18b**), α-peltatin (**17a**) and β-peltatin (**17b**). These facts have been interpreted as indicating that matairesinol is a common precursor of both the 3,4,5-trimethoxyphenyl and 4-hydroxy-3,5-dimethoxyphenyl series.



Scheme 2.

Biomimetic syntheses involving oxidative coupling are a source of constant fascination although they are rarely of synthetic use (cf. section 4.1). Two recent examples are shown in scheme 3. Oxidative coupling of the 4-hydroxycinnamic acid esters (**19a**) and (**19b**) affords the dihydro-naphthalenes (**20a**) and (**20b**) respectively as the major products [40].

The 2-hydroxycinnamic acid esters (**21a**) and (**21b**) in contrast yield the enol acetate derivatives (**22a**) and (**22b**) respectively, after acetylation.



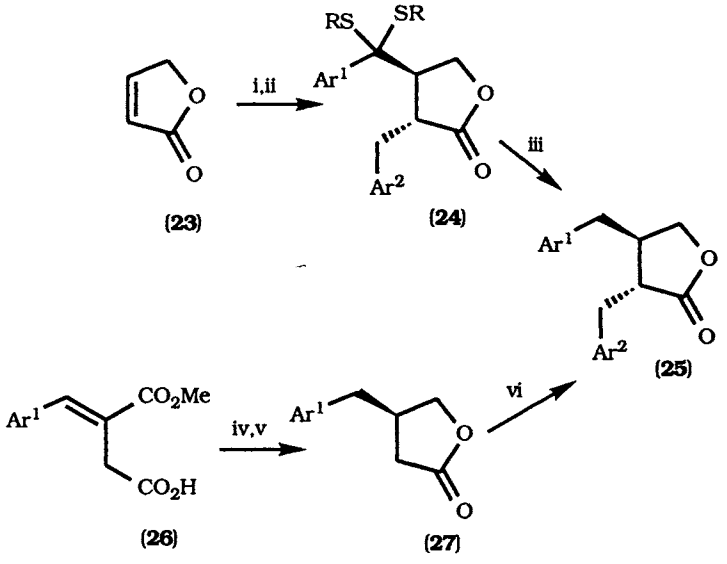
Scheme 3.

3 SYNTHESIS AND ASYMMETRIC SYNTHESIS

3.1 2,3-Dibenzylbutyrolactones

Trans-2,3-dibenzylbutyrolactones constitute a large group of natural products in their own right and are also versatile intermediates for the synthesis of a wide variety of other lignans. The two most common approaches to dibenzylbutyrolactones are illustrated in scheme 4. The first involves conjugate addition by an acyl anion equivalent to butenolide (**23**), followed by alkylation. This route was pioneered by Ziegler [41] and Schlessinger [42] and has subsequently been utilised by other groups

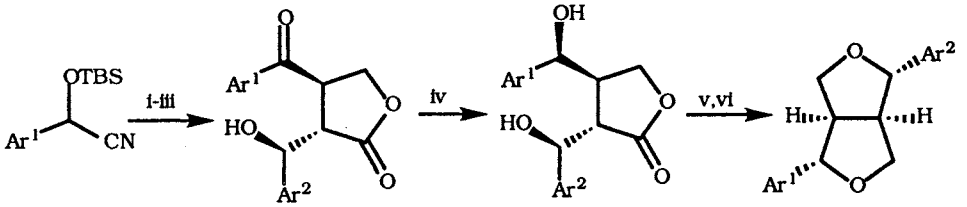
[43,44]. Desulfurisation of the resulting adduct (**24**) gives the required *trans*-dibenzylbutyrolactone (**25**). The second approach utilises a Stobbe condensation to generate the unsaturated ester (**26**), hydrogenation, selective reduction, and alkylation of which leads to the *trans*-dibenzylbutyrolactone (**25**) [45-47].



Reagents: i, $Ar^1C(SR)_2$; ii Ar^2CH_2X; iii Raney nickel: iv H_2/Pd-C; v, $Ca(BH_4)_2$; vi, LDA, Ar^2CH_2X

Scheme 4.

Other acyl anion equivalents and other electrophiles have been employed in the tandem conjugate addition reaction. In particular, the silylated cyanohydrin anion (**28**) represents a useful synthon for further elaboration of the lignan skeleton, and the use of an aromatic aldehyde or acyl derivative as the electrophile opens up further possibilities for subsequent cyclisation reactions. The versatility of this approach is illustrated by the stereoselective reduction of the liberated ketone (**29**) to give the diol (**30**), further reduction of which followed by cyclisation leads to the furofuran skeleton (**31**) (scheme 5) [48]. Similarly, a two-step synthesis of arylnaphthalene lignans (**32**), involving tandem conjugate addition followed by acid-catalysed cyclisation is illustrated in scheme 6 [49]. By using more carefully controlled conditions for the acid-catalysed cyclisation step the aryltetralin intermediates (**33**) can be intercepted and further converted into aryltetralin lignans such as isopodophyllotoxone (**34**) [50].

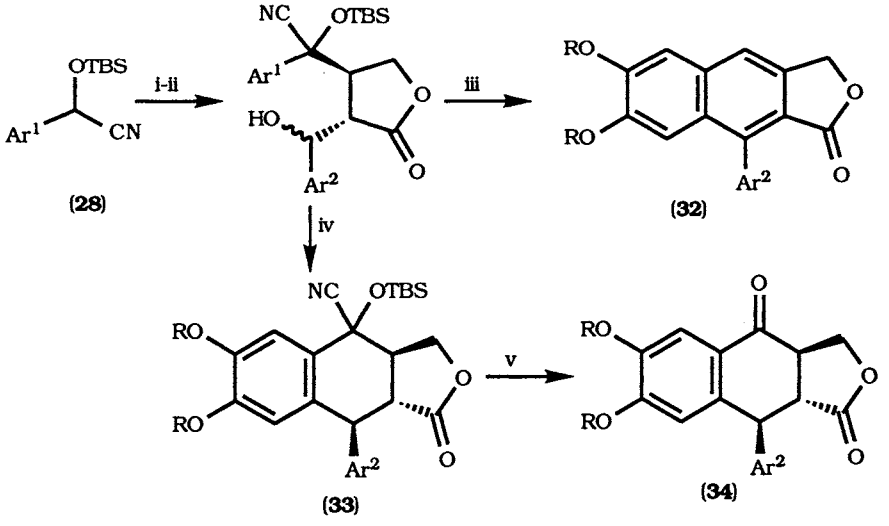


Reagents: i, LDA, butenolide,ii $ZnBr_2$, Ar^2CHO, iii, TBAF; iv L-Selectride; v, $LiAlH_4$; vi, MsCl, pyr

(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4-dimethoxyphenyl

Scheme 5.

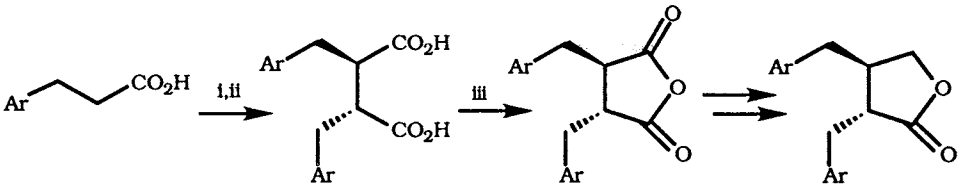
A third route to *trans*-2,3-dibenzylbutyrolactones involves oxidative dimerisation of the dianion of a dihydrocinnamic acid (scheme 7) [51,52]. Reduction of the anhydride to the lactone completes the sequence. This approach, which is ideally suited to the preparation of symmetrically substituted lignans, has also been extended to the preparation of unsymmetrically substituted compounds [53]. This is achieved by reacting an α-iodocarboxylate anion with an appropriate carboxamide dianion or carboxylic acid dianion.



Reagents: i, LDA, butenolide; ii, Ar^2CHO; iii TFA, refl; iv, TFA/CH_2Cl_2 (1 : 1); v, NH_4F

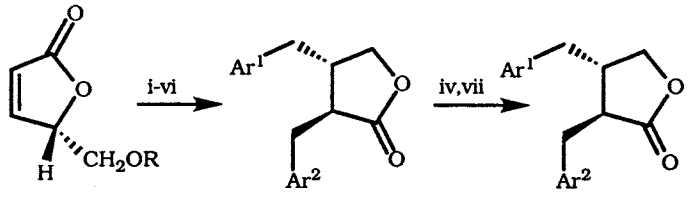
(Ar^1 = 3,4-dimethoxyphenyl or 3,4-methylenedioxyphenyl,
Ar^2 = 3,4-methylenedioxyphenyl or 3,4,5-trimethoxyphenyl)

Scheme 6.



Reagents: i . LDA; ii I_2; iii Ac_2O

Scheme-7.



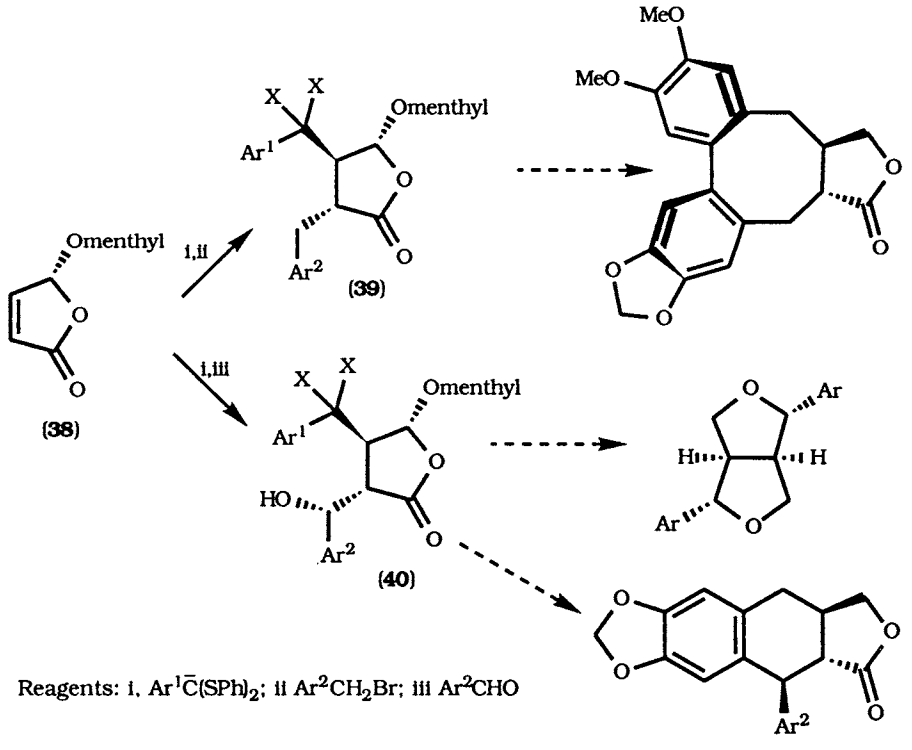
(35) (36) (37)

(R = Bn or CPh_3)

Reagents i, $Ar^2\bar{C}(SR)_2$; ii Ar^1CH_2Br; iii, Raney nickel, iv, $LiAlH_4$; v, IO_4^-; vi, CrO_3; vii, TsCl, pyr.

(Ar^1 = 3,4-methylenedioxyphenyl, Ar^1 = 3,4,5-trimethoxyphenyl)

Scheme 8.

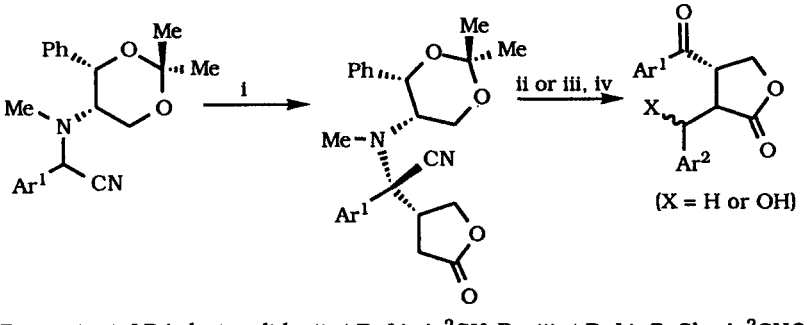


Reagents: i, $Ar^1\bar{C}(SPh)_2$; ii Ar^2CH_2Br; iii Ar^2CHO

Scheme 9.

All of the routes described so far can be readily adapted to provide asymmetric syntheses of lignans. Thus, Koga *et al.* have synthesised (+)-yatein (**36**) and (+)-*trans*-burseran (**37**) by conjugate addition to a chiral butenolide (**35**) (scheme 8) [54,55]. The more readily available menthyloxybutenolide (**38**) has been utilised by other groups [56,57]. The products (**39**) and (**40**) after desulfurisation, serve as precursors for the synthesis of dibenzocyclooctadienes, furofurans and aryltetralins (scheme 9).

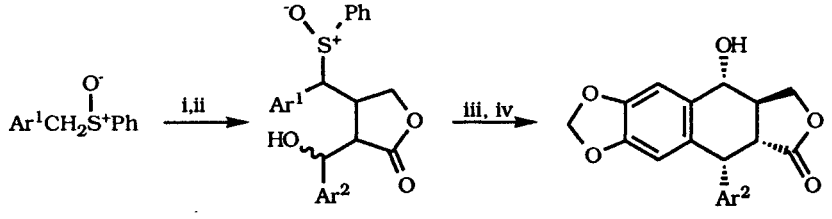
Lithiated α-amino nitriles derived from an enantiomerically pure secondary amine have been used to achieve the asymmetric synthesis of *trans*-dibenzylbutyrolactones (scheme 10) [58]. Enantiomeric excesses of greater than 96% were obtained after removing the chiral auxiliary. When aromatic aldehydes were used as electrophiles the benzylic alcohols were obtained as a mixture of the two epimers with a diastereomeric excess of 60-75%. Addition of a chiral sulfoxide, prepared using a modified Sharpless oxidation, to butenolide has also been utilised as part of an expeditious synthesis of podophyllotoxin (scheme 11) [59].



Reagents: i, LDA, butenolide, ii, *t*-BuLi, Ar^2CH_2Br, iii, *t*-BuLi, $ZnCl_2$, Ar^2CHO; iv $AgNO_3$

(Ar^1 = 3,4-methylenedioxyphenyl)

Scheme 10.

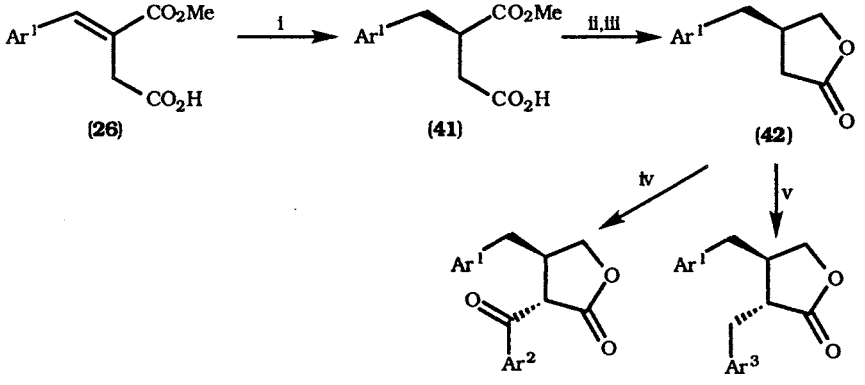


Reagents: i, BuLi, butenolide, ii, Ar^2CHO, iii, TFA; iv, HgO, $BF_3.Et_2O$

(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl)

Scheme 11.

Alternatively, the nonracemic monobenzylbutyrolactones can be prepared by resolution (or asymmetric hydrogenation) of carboxylic acids formed *via* the Stobbe condensation [60-62]. Alkylation of the appropriate monolactones leads to a wide range of lignans including (-)-hinokinin, (-)-yatein, (-)-dimethyl matairesinol, (-)-kusunokinin, (-)-arctigenin and (-)-enterolactone. For example, asymmetric hydrogenation of (**26**) affords *(R)*-(**41**) which can be readily converted to the monobenzylbutyrolactone (**42**) (scheme 12) [63]. Alkylation or acylation then affords the enantiomerically enriched dibenzylbutyrolactone derivatives.



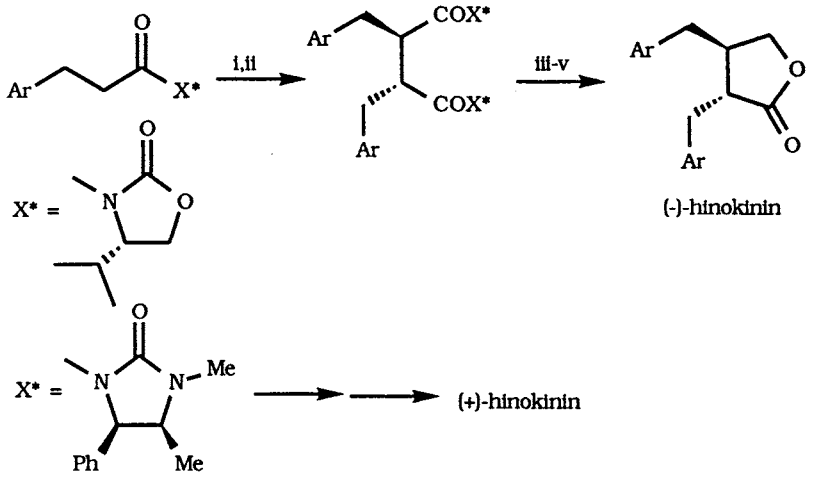
Reagents: i, H_2/(4S,5S)-MOD-DIOP; ii KOH, $Ca(BH_4)_2$; iii, H_3O^+; iv, LDA, Ar^2COX; v, LDA, Ar^3CH_2Br

(Ar^1 = 3,4-dimethoxyphenyl or 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl, Ar^3 = 2,3,4-trimethoxyphenyl)

Scheme 12.

A third approach to asymmetric synthesis involving oxidative dimerisation of dihydrocinnamic acid derivatives is shown in scheme 13 (cf. scheme 7) [64,65]. By choosing an appropriate chiral auxiliary, either (-)- or (+)-hinokinin, for example, can be prepared. In either case removal of the chiral auxiliary leads to an anhydride having C_2 symmetry which can be reduced to the lactone.

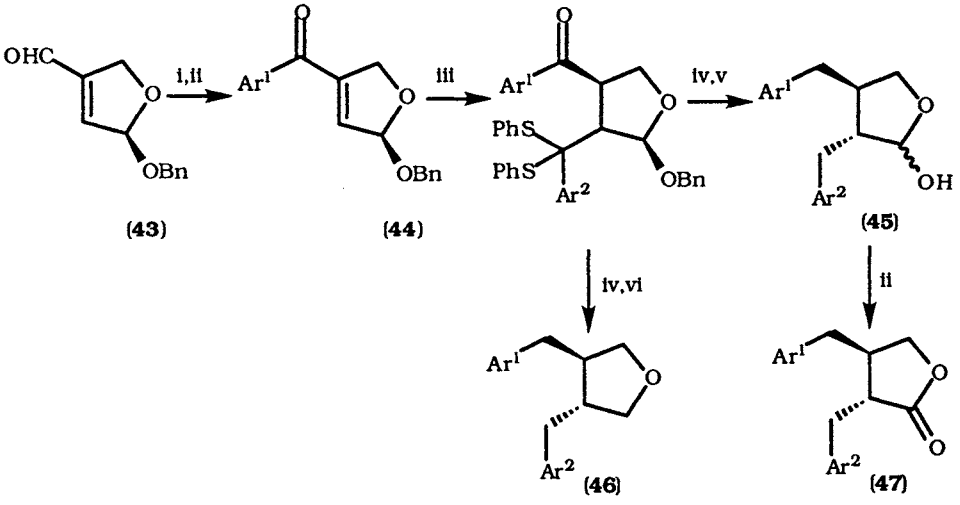
A further versatile approach to enantiomerically enriched 2,3-dibenzylbutyrolactones and 3,4-dibenzyl-tetrahydrofurans is based upon the use of the chiral dihydrofuran (**43**), which is readily available in both *(R)*- and *(S)*- forms by lithium bromide induced ring contraction of benzyl 2,3-anhydro-D- and L-ribopyranoside (scheme 14) [66]. Reaction with an aryl Grignard reagent followed by oxidation gives the corresponding enone (**44**). Conjugate addition of an appropriate sulfur stabilised carbanion to *(R)*-(**44**) followed by treatment with Raney nickel and hydrogenolysis gives (-)-cubebin (**45a**), (-)-deoxycubebin (**46a**), (-)-*trans*-burseran (**46b**), and, after oxidation, (-)-hinokinin (**47a**) and (-)-yatein (**47b**).



Reagents: i, LDA; ii, $TiCl_4$; iii, LiOOH; iv, Ac_2O; v, $NaBH_4$

(Ar = 3,4-methylenedioxyphenyl)

Scheme 13.



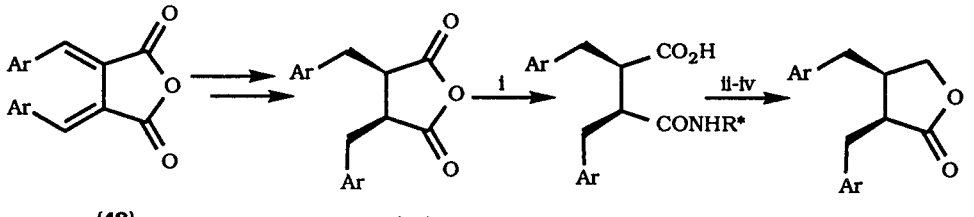
Reagents: i. Ar^1MgBr, ii, CrO_3, pyr; iii, $Ar^2C(SPh)_2^-$; iv, Raney Ni; v, H_2/Pd-C, Pr^i_2NEt; vi H_2/Pd-C, H^+

a, $Ar^1 = Ar^2$ = 3,4-methylenedioxyphenyl

b, Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl

Scheme 14.

Cis-Disubstituted butyrolactones (**50**) have been investigated less extensively than their *trans*-counterparts. One attractive route to such compounds involves the diastereoselective opening of a cyclic *meso*-anhydride (**49**) (scheme 15) [67]. The required anhydride was prepared by a route involving two consecutive Stobbe condensations, leading to the doubly unsaturated anhydride (**48**). Differentiation of the two acyl groups of (**49**) was achieved by reaction with an enantiomerically pure primary amine. The monoacid monoamide was then converted into the required lactone (**50**).

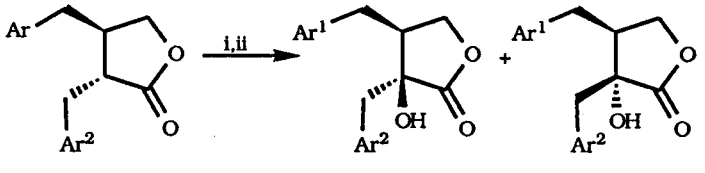


Reagents: i α-phenylethylamine; ii, $ClCO_2Et$, iii, $NaBH_4$; iv, H^+

(Ar=3,4-dimethoxyphenyl, R* = α-phenylethyl)

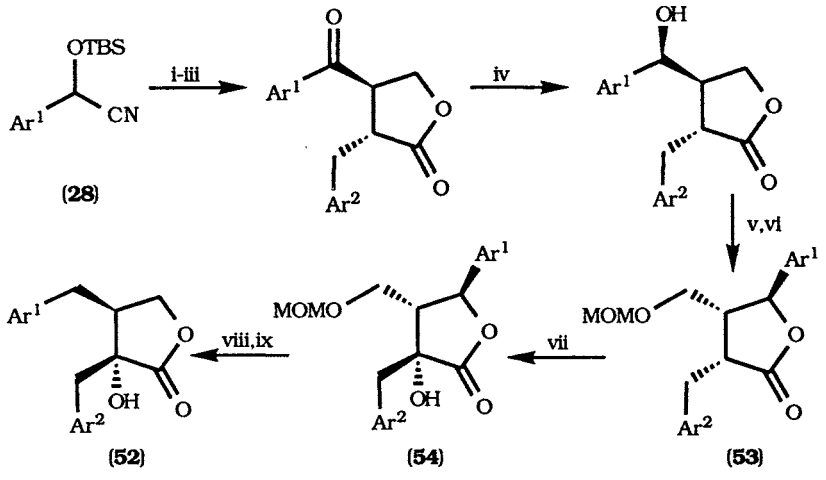
Scheme 15.

2-Hydroxy-2,3-dibenzylbutyrolactones, which are an important group of biologically active lignans, can be synthesised by hydroxylation of the enolates derived from the parent *trans*-2,3-dibenzylbutyrolactones (scheme 16) [68]. Although a mixture of both possible diastereomers is obtained, the 2-hydroxy-*trans*-2,3-dibenzylbutyrolactone (**51**) usually predominates. However, 2-hydroxy-*cis*-2,3-dibenzylbutyrolactones, such as guayadequiol (**52**), can be selectively synthesised by hydroxylation of the enolate derived from the rearranged lactone (**53**), followed by hydrogenolysis of the hydroxylated product (**54**) (scheme 17) [69].



Reagents: i, LHMDS, ii, O_2

Scheme 16.

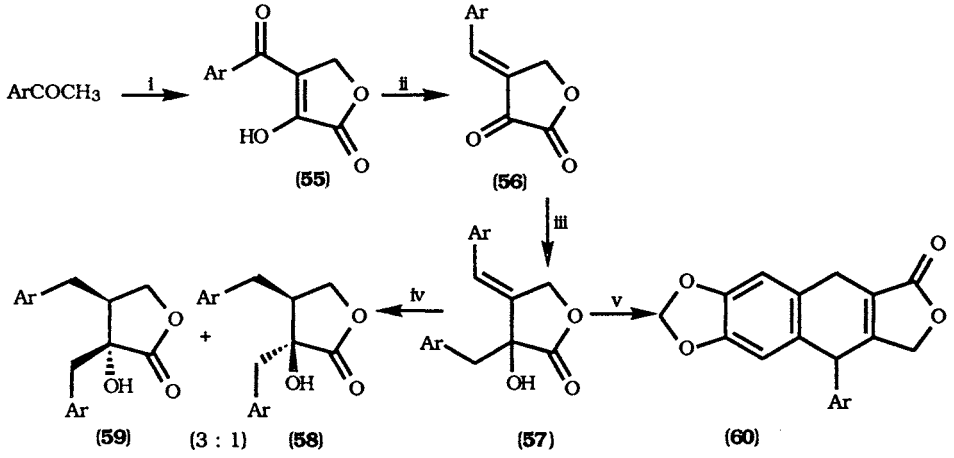


Reagents; i, LDA, butenolide, ii, Ar^2CH_2Br; iii, TBAF; iv, L-Selectride, v, NaH, DMF; vi, MOMCl, Pr^i_2NEt; vii, KHMDS, MoOPH; viii, H_2/Pd-C; ix, H_3O^+

(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4-dimethoxyphenyl)

Scheme 17.

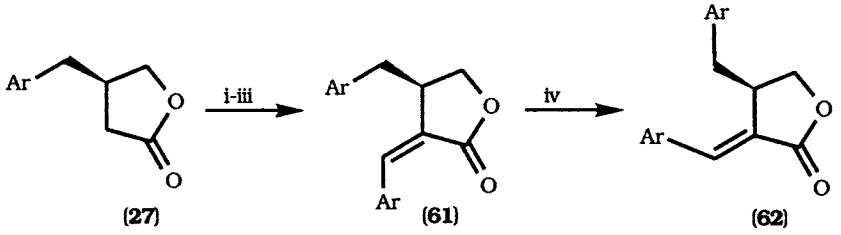
Meridinol (**58**) and epimeridinol (**59**) have been prepared from the unsaturated keto-lactone (**56**) (scheme 18) [70]. Reaction with a benzyl Grignard reagent gave (**57**) which on hydrogenation gave (**58**) and (**59**), while on heating it gave the aryldihydronaphthalene lactone (**60**).



Reagents: i, NaOMe, $(CO_2Et)_2$, CH_2O; ii, $NaBH_4$; iii, $ArCH_2MgCl$; iv, H_2/Pd-C; v, heat (Ar = 3,4-methylenedioxyphenyl)

Scheme 18.

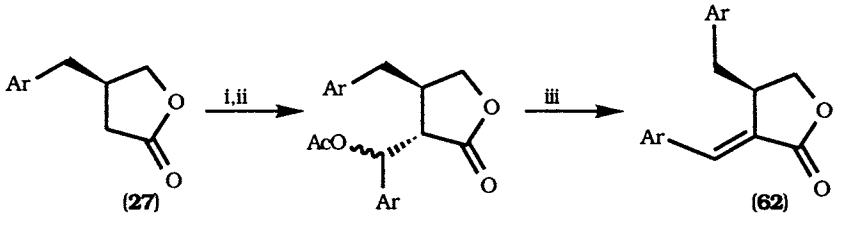
Finally, several recent syntheses involve the preparation of αβ-unsaturated lactones of the savinin or gadain type. Such compounds are readily prepared from the corresponding monobenzyl-butyrolactones by condensation (scheme 19). While elimination of the mesylate leads to the *(Z)*-isomer [71], elimination of the acetate affords the *(E)*-isomer [72]. The (*Z*)-isomer (**61**) can be converted into (-)-savinin (**62**) in high yield by treatment with tributyltin hydride. Hydrogenation of (**61**) or (**62**) affords the *cis*-disubstituted lactones (**63**) (scheme 20) [73].



Reagents: i, LDA, ArCHO; ii, MsCl, Et_3N; iii, DBU; iv, Bu_3SnH, AIBN

(Ar = 3,4-methylenedioxyphenyl)

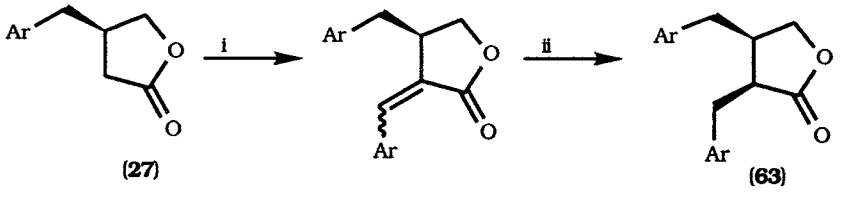
Scheme 19a.



Reagents: i, LDA, ArCHO; ii, Ac_2O, Et_3N, DMAP; iii, NaH

(Ar = 3,4-dimethoxyphenyl or 3,4,5-trimethoxyphenyl)

Scheme 19b.



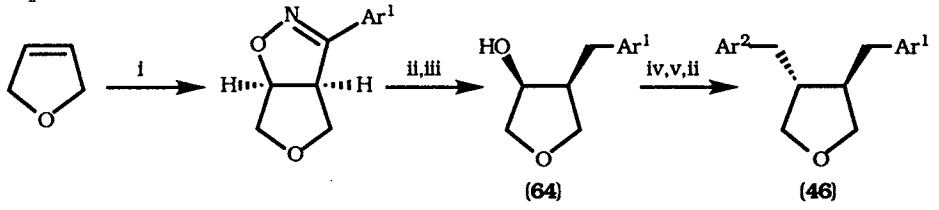
Reagents: i,ArCHO, NaH; ii, H_2/Pd-C

(Ar = 3,4-dimethoxyphenyl or 3,4,5-trimethoxyphenyl)

Scheme 20.

3.2 Tetrahydrofuran derivatives

There are no universally adopted syntheses of lignans in this group but several ingeneous routes have been employed. Thus, deoxycubebin (**46a**) and burseran (**46b**) have been synthesised by a route involving cycloaddition of a nitrile oxide to 2,5-dihydrofuran (scheme 21) [74]. Reductive cleavage of the first formed adduct followed by introduction of the second benzyl substituent gives the *trans*-disubstituted tetrahydrofuran. Kinetic resolution of the intermediate alcohols (**64**) can be used to prepare the nonracemic lignans. Deoxycubebin (**46a**) and burseran (**46b**) have also been synthesised by exploiting a trimethyltin radical mediated cyclisation (scheme 22) [75]. Oxidation of the alkyl tin derivative (**65**) followed by equilibration with base gives the *trans*-3,4-disubstituted tetrahydrofuran (**66**). Chemical resolution of the intermediate alcohols (**67**) in this case permits the nonracemic lignans to be prepared.

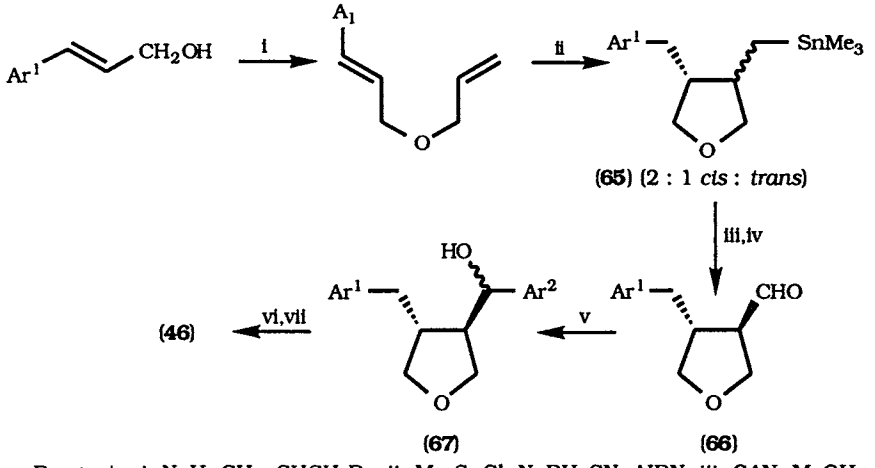


Reagents: 1, $Ar^1\overset{+}{C}N\overset{-}{O}$; ii, Raney Ni; iii, H_2/Pd-C; iv, TsCl v, $Ar^2\overline{C}HSPh$

a, Ar^1 = Ar^2 = 3,4-methylenedioxyphenyl

b, Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl

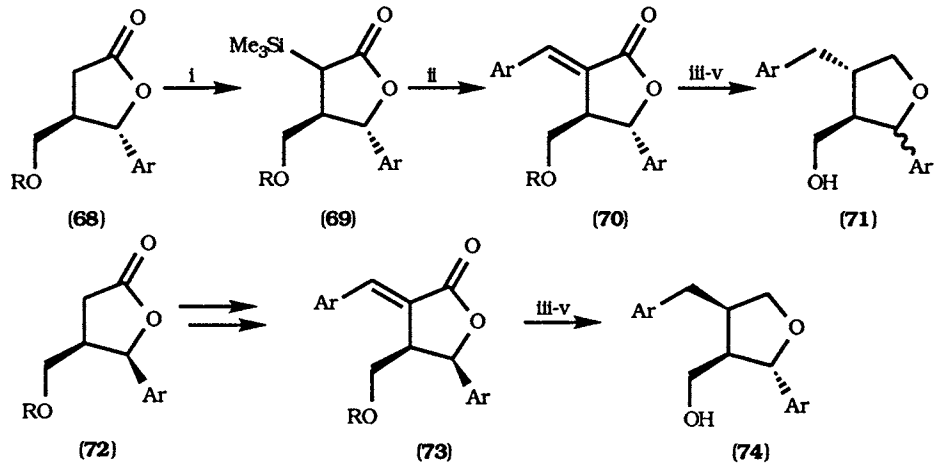
Scheme 21.



Reagents: i, NaH, CH_2=$CHCH_2Br$; ii, Me_3SnCl, $NaBH_3CN$, AIBN; iii, CAN, MeOH; iv, DBU; v, Ar^2Li; vi, Ac_2O/Et_3N; vi, H_2/Pd-C

Scheme 22.

Compounds belonging to the 2-aryl-4-benzyltetrahydrofuran series, including dihydrosesamin (**74**), have been prepared by reduction of the corresponding 2-arylidene lactones (scheme 23) [76]. The starting materials are the *cis* and *trans* paraconic acid derivatives (**68**) and (**72**). These are silylated at C-2 and subjected to a Peterson reaction to give the unsaturated lactones (**70**) and (**73**). The stereochemistry at C-4 in (**70**) and (**73**) determines the outcome of the hydrogenation step leading to (**71**) and (**74**) respectively.



Reagents: i, TMSOTf; ii, LDA, ArCHO; iii, H_2/Pd-C; iv, $LiAlH_4$; v, H_3O^+

(R = TBDMS, Ar, = 3,4-methylenedioxyphenyl)

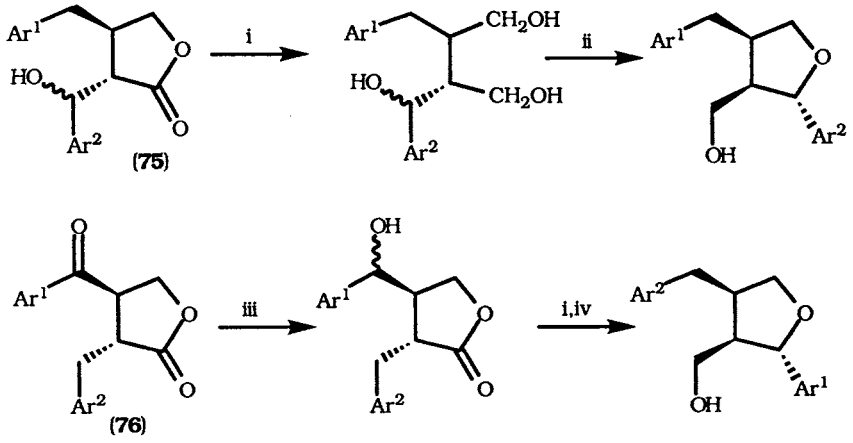
Scheme 23.

Another simple synthesis of lignans of the lariciresinol type (**11**) involves a straightforward reduction of a functionalised dibenzylbutyrolactone such as (**75**) or (**76**) followed by acid-catalysed cyclisation (scheme 24) [77,78]. Cyclisation of the doubly functionalised precursor (**77**) affords access to the furofuran skeleton (**78**) (scheme 25). A second synthesis which has also been extended to the furofuran series involves a radical cyclisation step, which proceeds with high stereoselectivity (scheme 26) [79]. This route has been used to synthesise (**79**) which is a precursor for the synthesis of sesamin and eudesmin [80].

3.3 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes

The classical routes to this group of lignans, which are often referred to as furofurans, involve either oxidative dimerisation of a cinnamic acid or oxidative dimerisation of a β-keto-ester. However a number of other

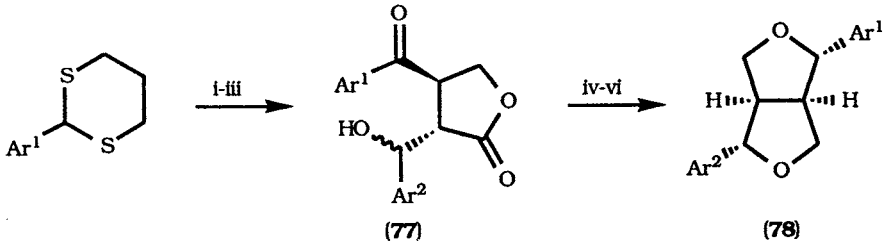
syntheses have been reported, some of which allow two different aryl groups to be introduced. The first such approach to be reported involves trapping the dianion (**80**) with an aromatic aldehyde to give a pair of epimeric lactones (**81**) and (**82**) (scheme 27). One of the epimeric lactones was converted into the dilactone (**83**), which on further transformation gave methyl pluviatilol (**84**) [81]. A second route, which also allows two different aryl groups to be introduced, involves the preparation of the monolactones (**85**) and (**86**) by an intramolecular Mukaiyama cyclisation (scheme 28) [82]. Reduction of the major component, followed by treatment with acid gives pluviatilol (**87**). A third approach involves a Claisen rearrangement on the silyl enol ether derived from one of the lactones (**88**) or (**89**) (scheme 29) [83,84]. Despite the elegance of this approach, the synthesis of the medium ring lactones required for the ring contraction adds a number of steps to the overall synthesis.



Reagents: 1 $LiAlH_4$; ii, $BF_3.Et_2O$, iii, $NaBH_4$; iv, H^+

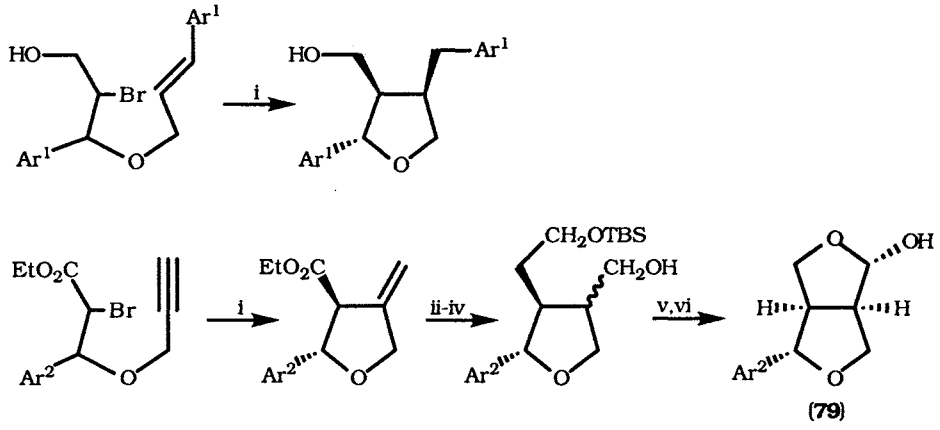
(Ar^1 = Ar^2 = 4-hydroxy-3-methoxyphenyl)

Scheme 24.



Reagents: i, LDA, butenolide, ii, Ar^2CHO; iii, $HgO/BF_3.Et_2O$ iv, $NaBH_4$; v, $LiAlH_4$; vi H^+

Scheme 25.

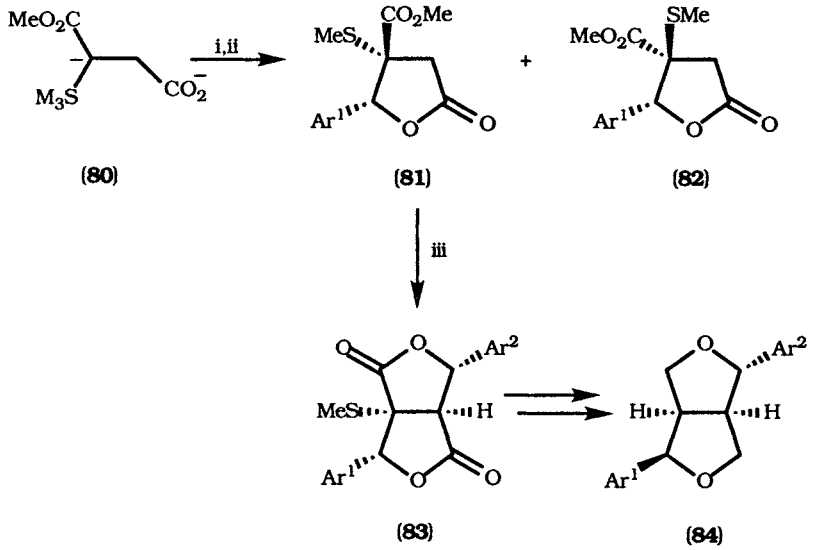


(79)

Reagents: i, Bu_3SnH, AIBN; ii, $LiAlH_4$; iii, TBDMSCl, Et_3N; iv, B_2H_6; v, $(COCl)_2$, DMSO; iv, TBAF

(Ar^1 = 3,4-methylenedioxyphenyl or 4-benzyloxy-3-methoxyphenyl
Ar^2 = 3,4-methylenedioxyphenyl or 3,4-dimethoxyphenyl)

Scheme 26.

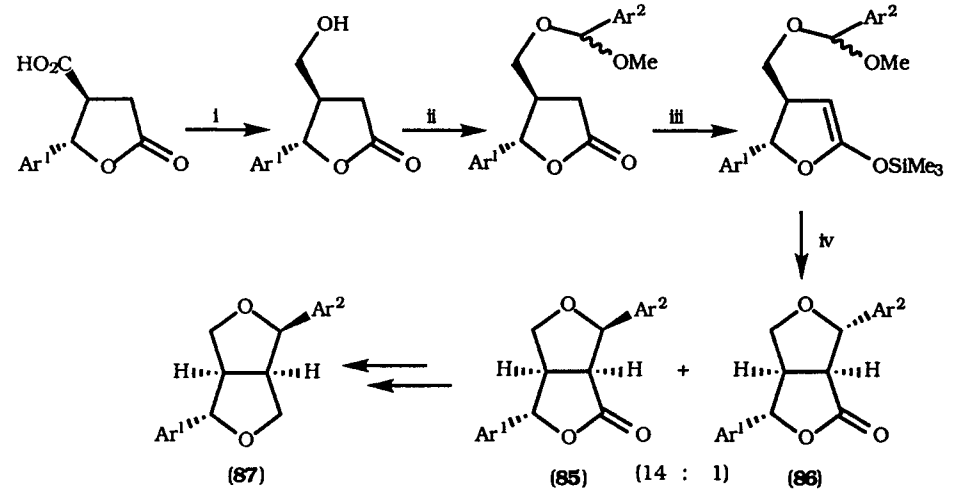


(80) (81) (82)

(83) (84)

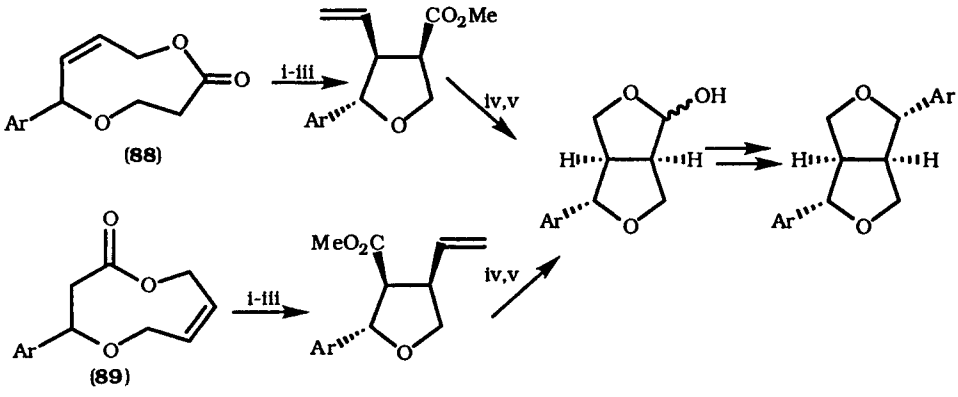
Reagents: i. Ar^1CHO, LDA; ii, TFA, iii, Ar^2CHO, LDA
(Ar^1 = 3,4-dimethoxyphenyl, Ar^2 = 3,4-methylenedioxyphenyl)

Scheme 27.



Reagents: 1, BMS; ii, ArCHClOMe, Et_3N, iii, LDA, TMSOTf, Et_3N; iv, $TiCl_4$
(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 4-hydroxy-3-methoxyphenyl)

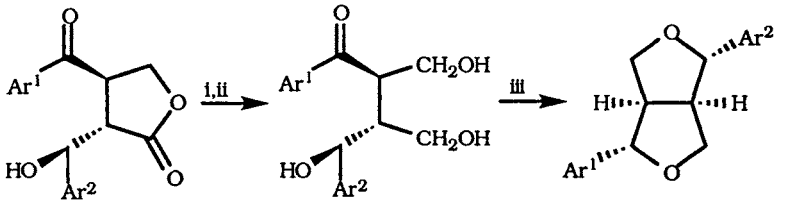
Scheme 28.



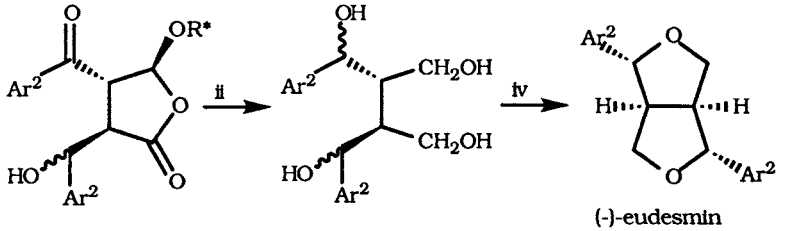
Reagents: i LDA, TMSCl; ii, MeOH, iii, CH_2N_2; iv $LiAlH_4$; v, OsO_4, $NaIO_4$
(Ar = 3,4-methylenedioxyphenyl)

Scheme 29.

As already demonstrated *trans*-dibenzylbutyrolactones are valuable as precursors for the synthesis of a wide range of lignans. For example, the keto-lactones (**90**) and (**91**), which have both been prepared by tandem conjugate addition reactions, provide key intermediates for the synthesis and asymmetric synthesis respectively of lignans of the furofuran type (scheme 30) [85,86].



(90)
(racemic)



(91)
(R* = *d*-menthyl)

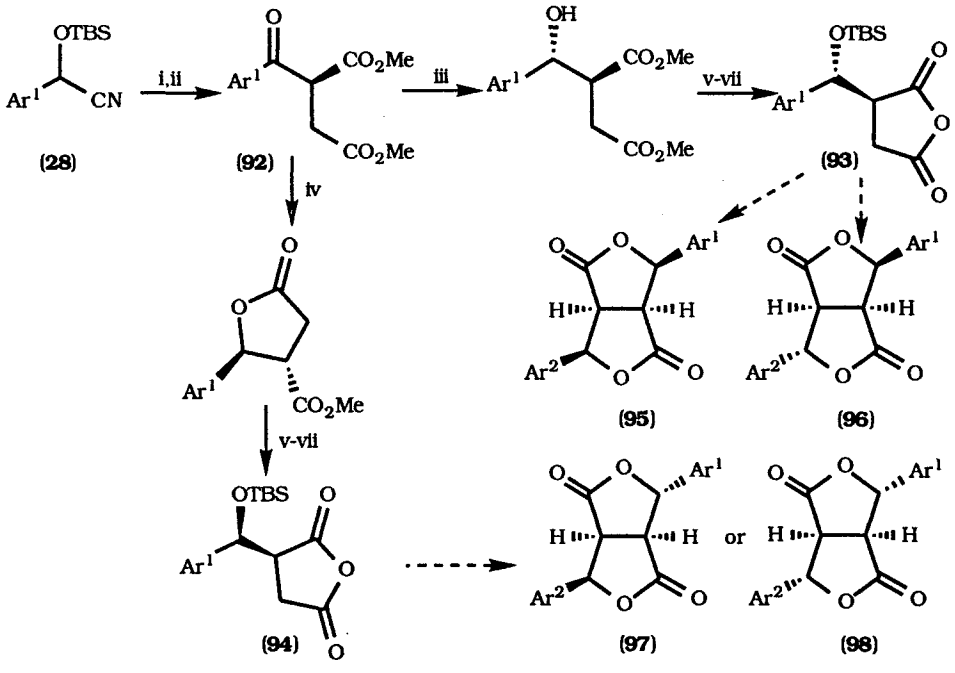
Reagents: i, L-Selectride, ii, $LiAlH_4$; iii, MsCl, pyr., ; $BF_3.Et_2O$

(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4-methoxyphenyl)

Scheme 30.

A versatile divergent route to the four diastereomeric dilactones (**95**)-(**98**) involves stereoselective reduction of the β-keto-ester (**92**) prepared by conjugate addition to dimethyl maleate (scheme 31) [87]. Stereoselective reduction followed by cyclisation to the anhydrides (**93**) and (**94**) sets up the configuration at one of the benzylic chiral centres. The second benzylic centre is defined in the reaction with an aromatic aldehyde leading ultimately to any one of the four possible stereoisomeric dilactones.

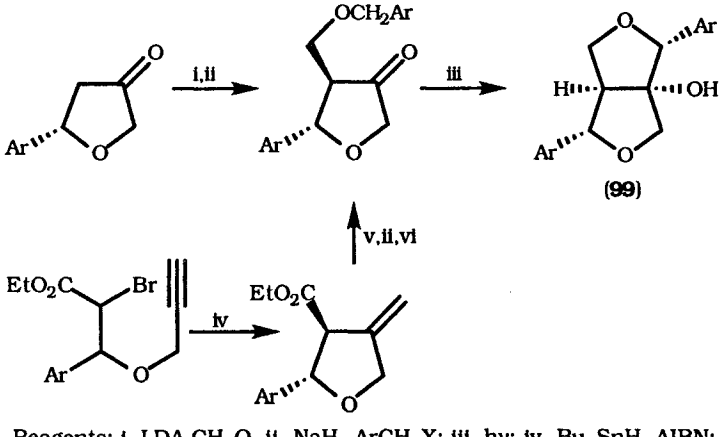
None of the above routes can be directly applied to the synthesis of the 1-hydroxy-2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes such as gmelinol and paulownin, and until recently there were no reported syntheses of this group. However paulownin (**99a**) and isogmelinol (**99b**) have now been synthesised using a novel photocyclisation reaction (scheme 32) [88,89]. Furthermore, neopaulownin (**102**) has been synthesised by a route involving an intramolecular ene reaction (scheme 33) [90]. Epoxidation of the monocyclic product (**100**) followed by ozonolysis and sodium borohydride reduction gave the epoxyalcohol (**101**) which, with PTSA, cyclised stereoselectively to generate (**102**).



Reagents: i, LDA, dimethyl maleate; ii, TBAF; iii, L-Selectride; iv, $Zn(BH_4)_2$; v, TBDMSCl, imidazole; vi, NaOH; vii, Ac_2O

(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4-methoxyphenyl)

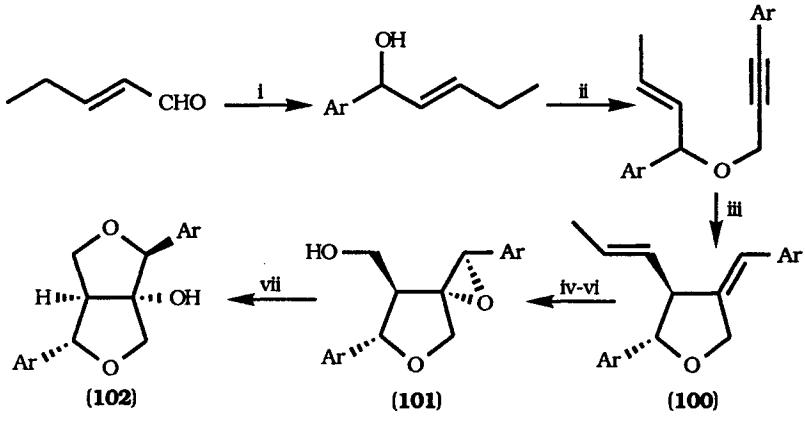
Scheme 31.



Reagents: i, LDA,CH_2O, ii, NaH, $ArCH_2X$; iii, hv; iv, Bu_3SnH, AIBN; v, $LiAlH_4$; vi, O_3

(a, = 3,4-methylenedioxyphenyl; b, = 3,4-methoxyphenyl)

Scheme 32.

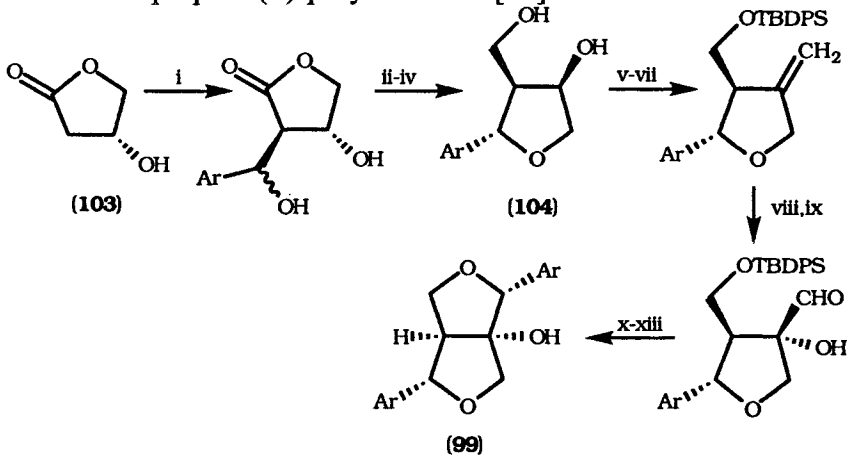


Reagents: i, ArMgBr, ii, $ArC{\equiv}CCH_2Br$; iii,heat, PhMe, Et_3N;
iv, MCPBA, v O_3; vi, $NaBH_4$; vii TsOH

(Ar = 3,4-methylenedioxypehnyl)

Scheme 33.

An asymmetric synthesis of (+)-paulownin (**99a**) starts from the hydroxybutanolide (**103**) which can be readily prepared from (+)-malic acid (scheme 34) [91]. Reaction with an aldehyde introduces the first hydroxybenzyl substituent which is transformed into the tetrahydrofuran derivatives (**104**). This could clearly be further manipulated as shown in Scheme 32 or indeed as shown in Scheme 34. The same approach has also been utilised to prepare (+)-phrymarolin I [92].



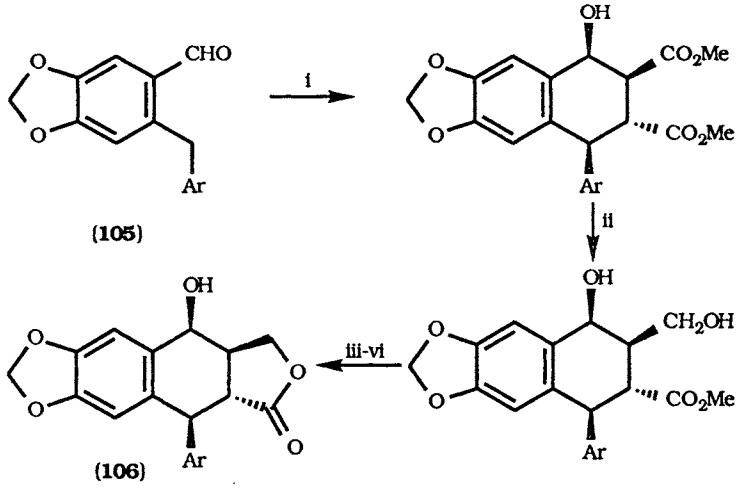
Reagents: i, LDA, Ar^1CHO; ii, DHP, TsOH,iii, $LiAlH_4$; iv, TsOH;
v, TBDPSCl.Et_3N, DMAP, vi, $(COCl)_2$, DMSO, Et_3N;
vii, Tebbe reagent; viii, OsO_4, NMO; ix, DCCl.DMSO, TFA;
x, Ar_2MgBr; xi TBAF; xii, Ac_2O, pyr., DMAP; xiii, PPTS

(Ar = 3,4-methylenedioxyphenyl)

Scheme 34.

3.4 Arylnaphthalene derivatives

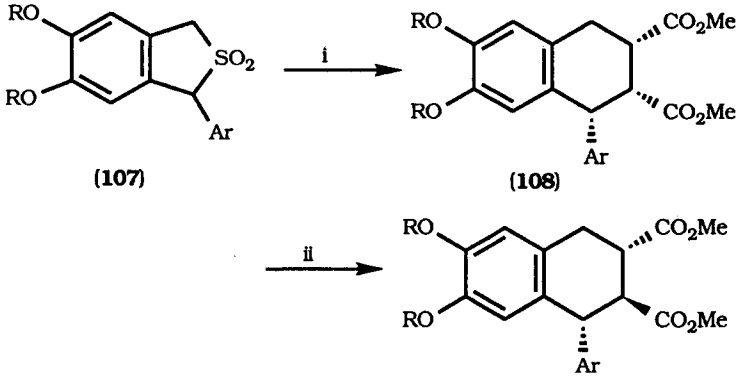
Although several fully aromatic arylnaphthalene lignans display interesting biological activity, the main focus of attention has centred on the tetrahydronaphthalene series, which includes podophyllotoxin. The two most attractive approaches to aryltetralins involve either a Diels Alder reaction or an acid-catalysed cyclisation of a benzylic alcohol derived from a *trans*-2,3-dibenzylbutyrolactone. Thus, epiisopodophyllotoxin (**106**) has been prepared by trapping the photo-enol of aldehyde (**105**) with dimethyl fumarate (scheme 35) [93]. However, the diene component required for the Diels Alder reaction can be generated in many other ways. For example, pyrolysis of the sulfone (**107**) provides ready access to dienes which react with appropriate dienophiles to generate valuable intermediates for lignan synthesis (scheme 36) [94,95]. The reaction with dimethyl maleate is of particular interest in giving an all-*cis* adduct (**108**). In contrast, Charlton and Durst observed a different stereochemical outcome in the addition of dimethyl maleate to the diene generated thermally from the cyclic sulfinate (**109**) (scheme 37) [96]. More recent work by Jones *et al.* has probed the stereochemical aspects of this reaction [97], and provides strong evidence to suggest that the addition of an α-aryl-*o*-quinodimethane to dimethyl maleate normally proceeds with *exo* selectivity [i.e. leading to (**110**)] although, not surprisingly, the stereochemical outcome is very dependent upon the precise reaction conditions.



Reagents: i, hv, dimethyl fumarate; ii $LiBHEt_3$; iii , acetone,H^+; iv KOH; v, H_3O^+ ; vi, DCCI

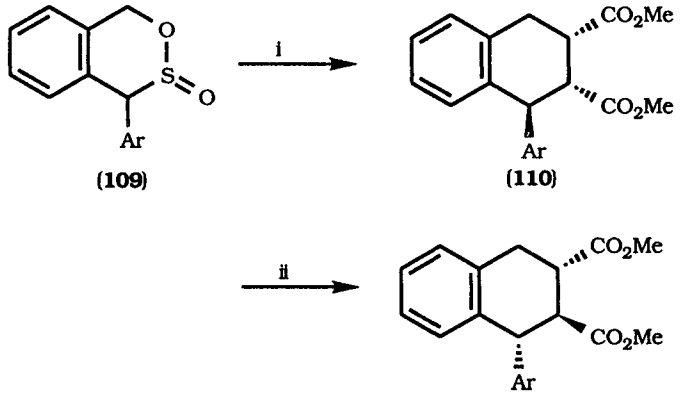
(Ar = 3,4,5-trimethoxyphenyl)

Scheme 35.



Reagents: i, dimethyl maleate, heat; ii, dimethyl fumarate, heat

Scheme 36.

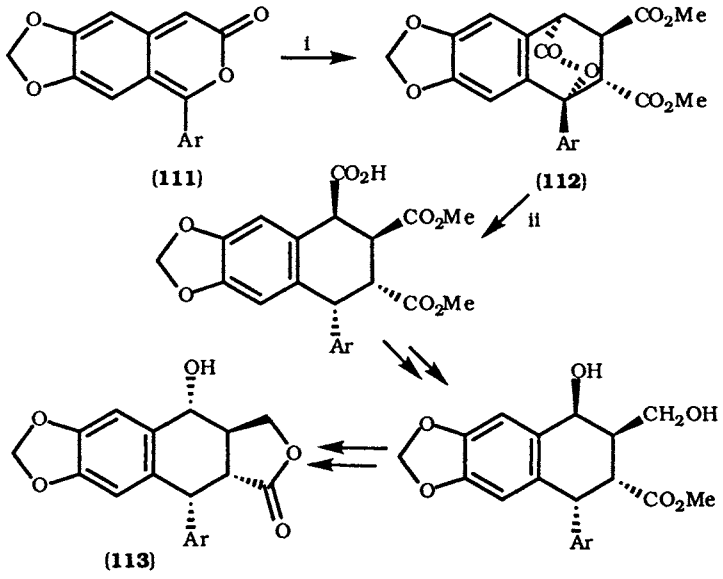


Reagents: i, dimethyl maleate, heat; ii, dimethyl fumarate, heat

Scheme 37.

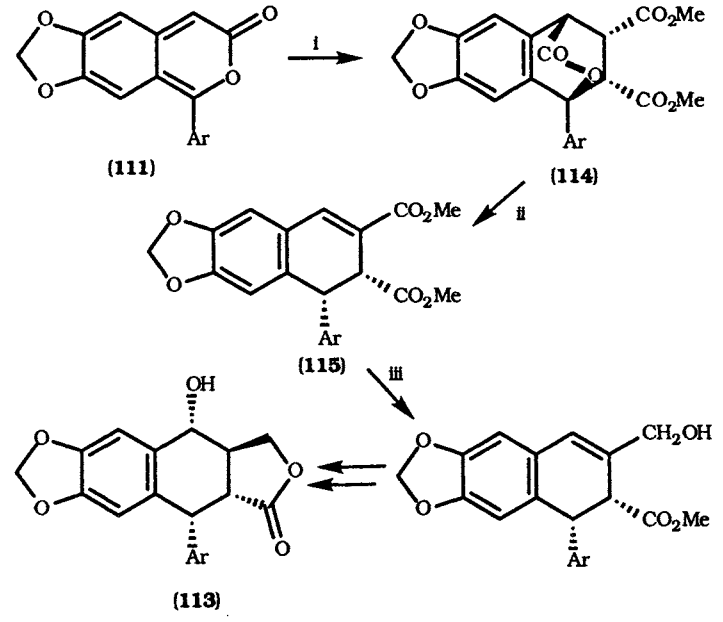
The isolable quinonoid pyrone (**111**) gives two stereoisomeric adducts with dimethyl fumarate, the major one of which (**112**) can be converted into podophyllotoxin (**113**) (scheme 38) [98]. The corresponding adduct from dimethyl maleate (**114**) loses CO_2 on pyrolysis and undergoes a 1,5-sigmatropic shift to yield the 1,2-*cis* product (**115**) which has also been transformed into podophyllotoxin (scheme 39).

In contrast, Rodrigo *et al.* have used the isobenzofuran adduct (**117**) as the key intermediate in their synthesis of podophyllotoxin derivatives (scheme 40) [99]. Stereoselective reduction of the carbon-carbon double bond followed by hydrogenolysis affords access to the isopodophyllotoxin series, whereas C-3 epimerisation prior to



Reagents: i, dimethyl fumarate, heat, ii, H_2, Pt
(Ar = 3,4,5-trimethoxyphenyl)

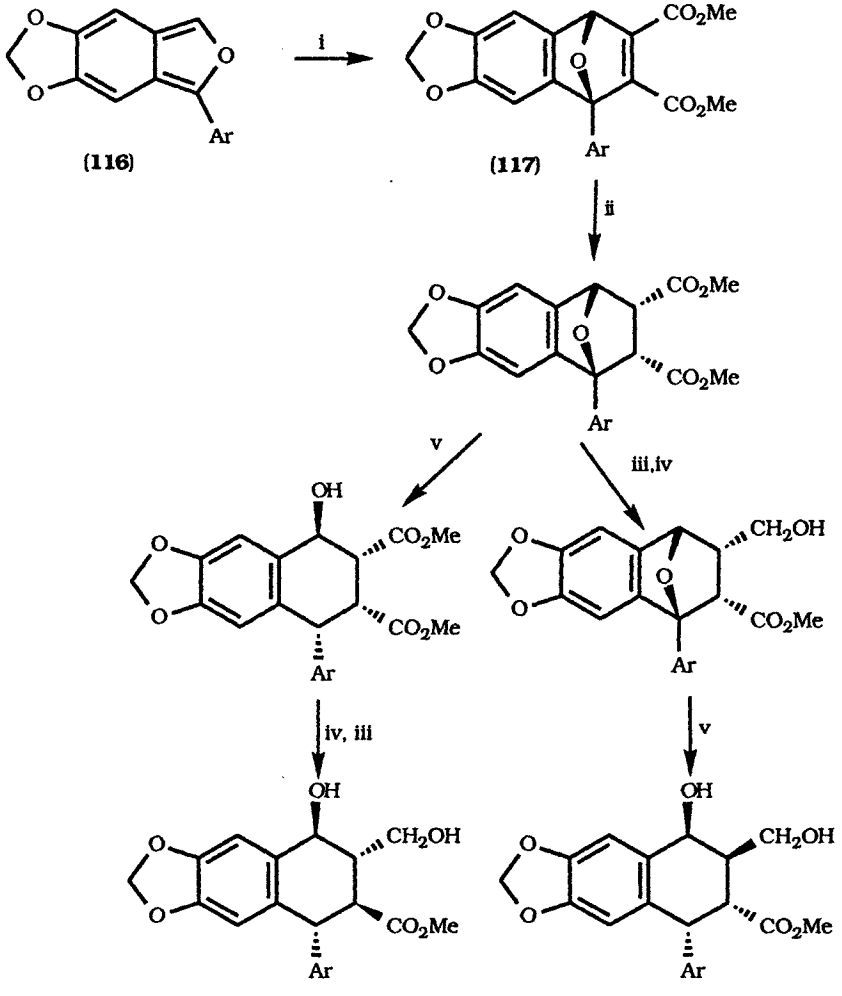
Scheme 38.



Reagents: i, dimethyl maleate; ii heat; iii, $LiBHEt_3$
(Ar = 3,4,5-trimethoxyphenyl)

Scheme 39.

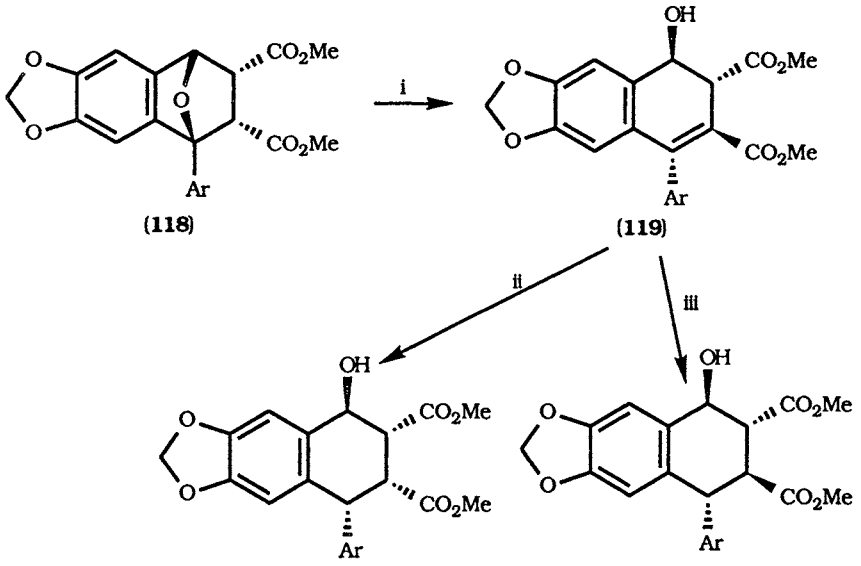
hydrogenolysis leads to the podophyllotoxin series. A more recent variation on this approach involves acid-catalysed cleavage of the oxygen bridge in (**118**), formed in this case by reaction of the isobenzofuran (**116**) with dimethyl maleate, to give the dihydronaphthalene (**119**). Stereoselective reduction of (**119**) affords access to either the isopodophyllotoxin or the isopicropodophyllin series (scheme 41) [100].



Reagents: i, dimethyl acetylenedicarboxylate; ii, H_2/Pd-C; iii, NaOMe; iv, $LiBHEt_3$; v, H_2/Raney Ni

(Ar = 3,4,5-trimethoxyphenyl)

Scheme 40.

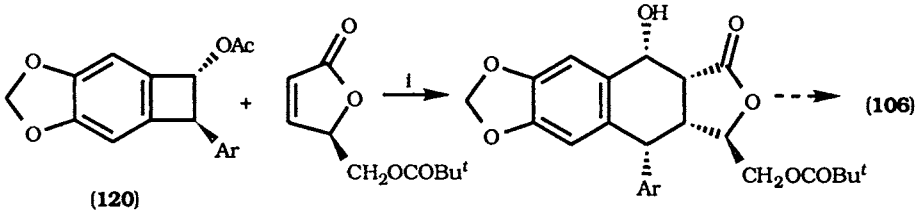


Reagents: i, TFA, ii, [Rh(nbd)(diphos-4)]BF_4; iii, $NiCl_2$, $NaBH_4$

(Ar = 3,4,5-trimethoxyphenyl)

Scheme 41.

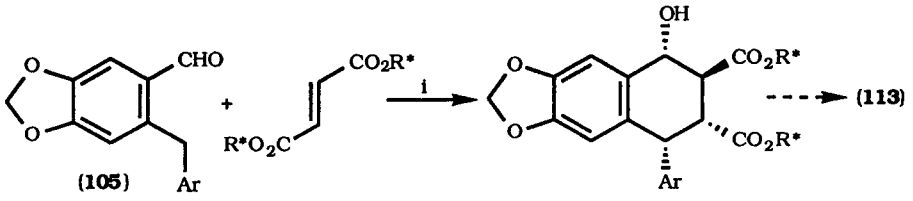
Diels Alder reactions have been used in several asymmetric syntheses of podophyllotoxin and its stereoisomers. Thus, Choy used the benzocyclobutene (**120**) as the diene precursor and a non-racemic butenolide as the dienophile in his synthesis of (-)-epiisopodophyllotoxin (**106**) (scheme 42) [101]. However, the unfortunate regioselectivity of the Diels Alder reaction makes the overall synthesis unnecessarily lengthy. In contrast, Charlton *et al.* used the aldehyde (**105**) as the diene precursor and a non-racemic fumarate as the dienophile in their synthesis of podophyllotoxin (**113**) (scheme 43) [102,103].



Reagents: i, BuLi

(Ar = 3,4,5-trimethoxyphenyl)

Scheme 42.

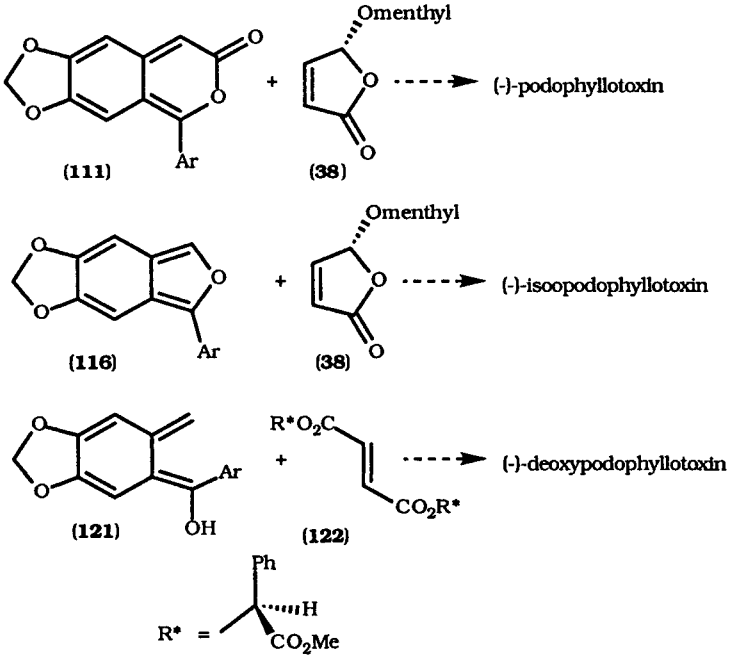


Reagents: i, hv

(R* = (S)-CHMeCO$_2$Me, Ar = 3,4,5-trimethoxyphenyl)

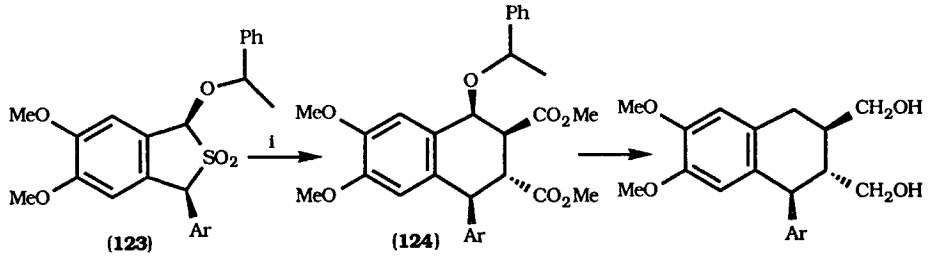
Scheme 43.

An asymmetric synthesis of (-)-podophyllotoxin from the *o*-quinonoid pyrone (**111**) involving *endo* addition to the menthyloxybutenolide (**38**) has been reported (scheme 44a) [104]. An alternative synthesis involving *endo* addition of the isobenzofuran (**116**) to the same dienophile leads to (-)-isopodophyllotoxin (scheme 44b) [105]. Meanwhile Charlton *et al.* have synthesised (-)-deoxypodophyllotoxin by reacting the α-hydroxy-α-aryl-*o*-quinodimethane (**121**) with the fumarate of methyl mandelate (**122**), which proceeds *endo* to the adjacent aryl group (scheme 44c) [106], in contrast to the situation which prevails in the absence of the hydroxyl group (see above). (-)-Isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin have also been synthesised in this way [107].



Scheme 44.

Charlton and Alauddin have also reported an asymmetric synthesis of (+)-isolariciresinol dimethyl ether by using a chiral sulfone in an asymmetric Diels Alder reaction (scheme 45) [108]. The key step here involves elimination of sulfur dioxide from the sulfone (**123**) to yield the *o*-quinonedimethane which undergoes cycloaddition with dimethyl fumarate to give mainly (**124**). They have further extended this work to include the synthesis of a series of retrodendrin derivatives [109].

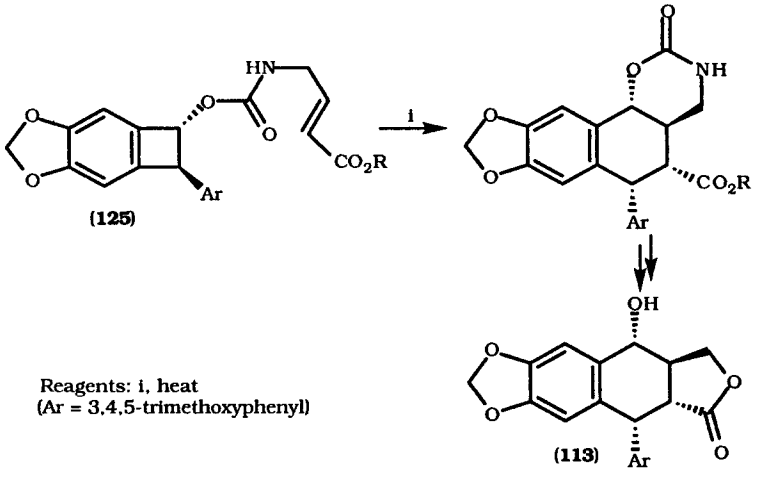


Reagents: i dimethyl fumarate, heat; ii. H_2/Pd-C, iii. $LiAlH_4$

(Ar = 3,4-dimethoxyphenyl)

Scheme 45.

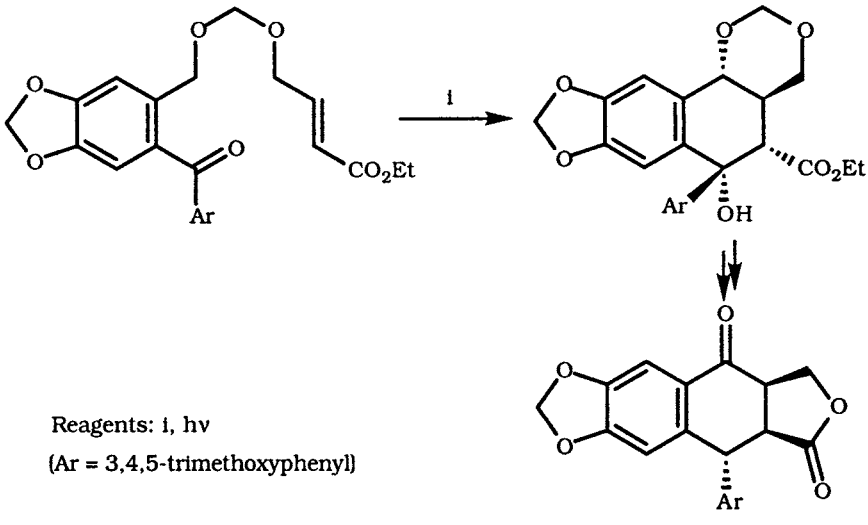
Intramolecular Diels Alder reactions have also been employed. Macdonald and Durst used a urethane linkage to attach the dienophile to a benzocyclobutene in (**125**), leading ultimately to podophyllotoxin (**113**) (scheme 46) [110]. Another synthesis of podophyllotoxin by Kraus and Wu involves a Diels Alder reaction of a photo-enol to which the dienophile is attached by an acetal linkage (scheme 47) [111]. Unfortunately, the later steps proceed in low yield and involve epimerisation at C-2 to give picropodophyllone (**126**).



Reagents: i, heat

(Ar = 3,4,5-trimethoxyphenyl)

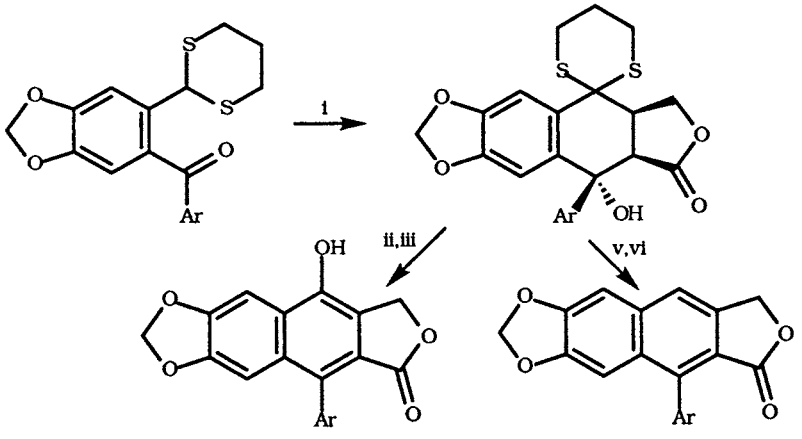
Scheme 46.



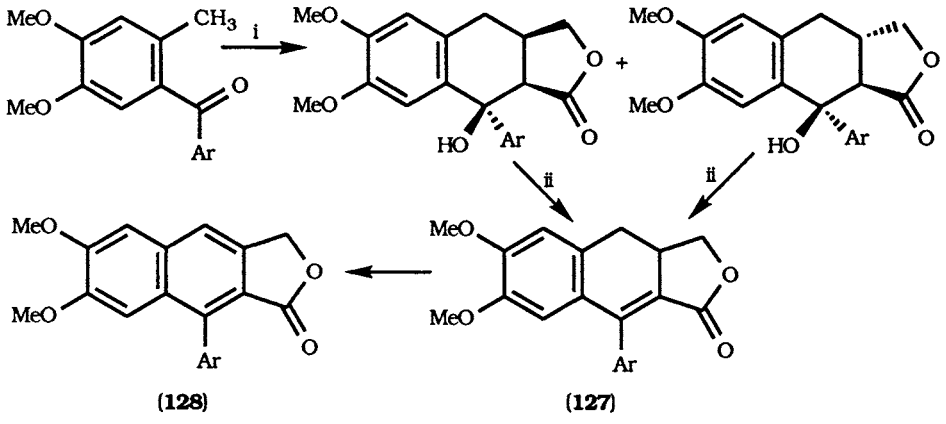
(126)

Scheme 47.

Harrowven has utilised a bimolecular conjugate addition/cyclisation sequence to prepare fully aromatic arylnaphthalene lactones (scheme 48) [112,113]. Similar Michael initiated ring closure reactions have been used to prepare a range of isopicropodophyllone analogues [114], and a similar strategy has been applied to the synthesis of dihydronaphthalene derivatives such as collinusin (**127b**), which on dehydrogenation is converted into justicidin B (**128b**) (scheme 49) [115].



Scheme 48.



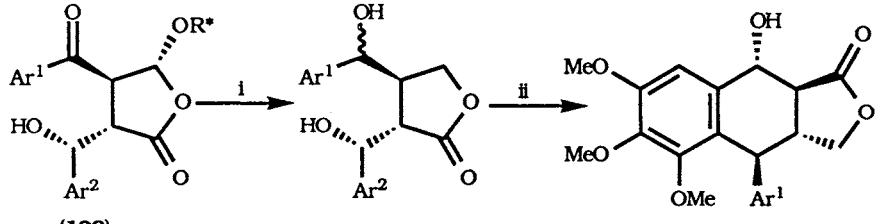
(128) (127)

Reagents: i, LDA, butenolide; ii $SOCl_2$, pyridine

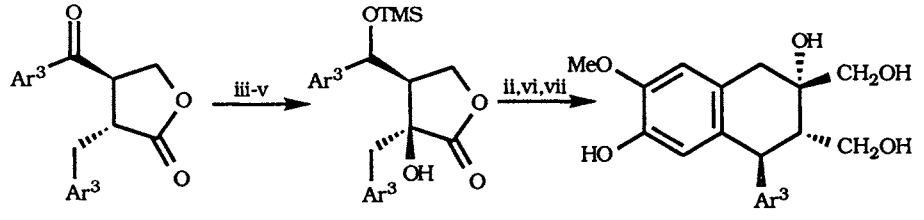
a, Ar = 3,4-dimethoxyphenyl
b, Ar = 3,4-methylenedioxyphenyl

Scheme 49.

Several aryltetralin lignans including isodeoxypodophyllotoxin and isopeltatin have been prepared by the acid-catalysed cyclisation route



(129)
(R* = *l*-menthyl)



(130)
(racemic)

(+/-)-cycloolivil

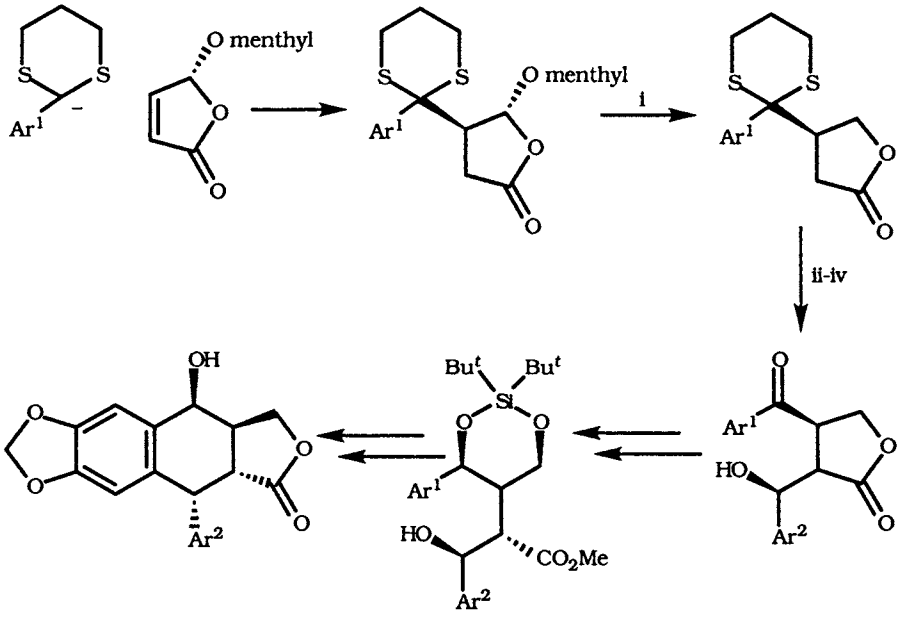
Reagents: i, $NaBH_4$; ii, TFA, iii, L-Selectride, iv, TMSCl, imidazole, v. KHMDS, MoOPH: vi, $LiAlH_4$; vii, H_2, Pd-C

(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl, Ar^3 = 4-hydroxy-3-methoxyphenyl)

Scheme 50.

[116]. For example, the keto-lactones (**129**) and (**130**) which have both been prepared by tandem conjugate addition reactions provide key intermediates for the synthesis of lignans of the aryltetralin type, including cycloolivil (scheme 50) [117,118]. Scheme 51 shows an interesting variation on this theme which gives rise to (-)-epipodophyllotoxin [119]. The outcome of the cyclisation step is controlled by the use of a silylene ether group which plays a crucial role in holding the two reacting centres in the required alignment during the cyclisation step. This device is avoided in the more direct (racemic) synthesis reported by Medarde *et al.* which relies upon the controlled epimerisation of isopodophyllotoxone (**131**) to afford picropodophyllone (**132**) which can then be transformed into podophyllotoxin (**113**) using known methods (scheme 52) [120].

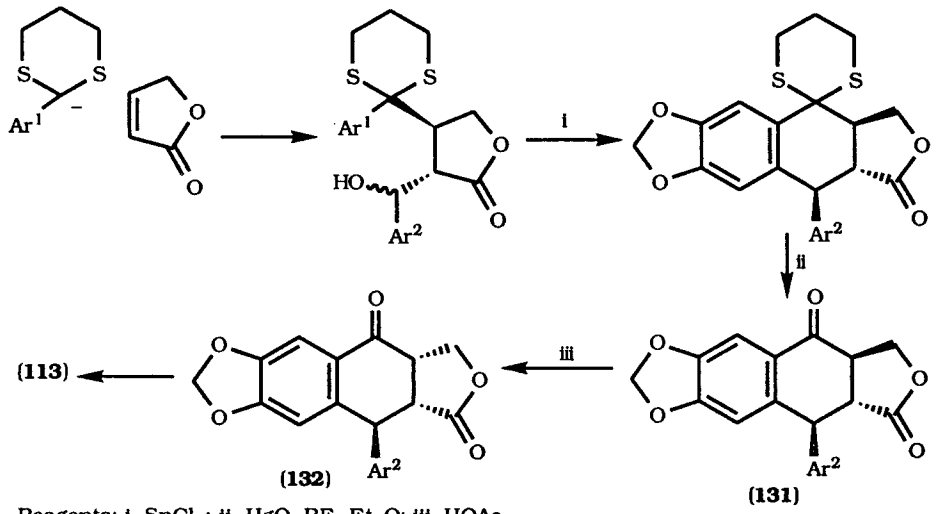
Achiwa *et al.* have prepared the homochiral unsaturated lactone (**134**) by cyclisation of the β-keto lactone (**133**), itself prepared by acylation of the monobenzylbutyrolactone (**27**) (scheme 53) [121]. Reduction of the corresponding hydroxy-acid (**135**), followed by relactonisation, gave (-)-deoxypodophyllotoxin (**136**) as the major product.



Reagents: i, KOH/$NaBH_4$; ii LDA/$Ti(NEt_2)_3Cl$; iii, Ar^2CHO; iv, aq. $HgCl_2/CaCO_3$

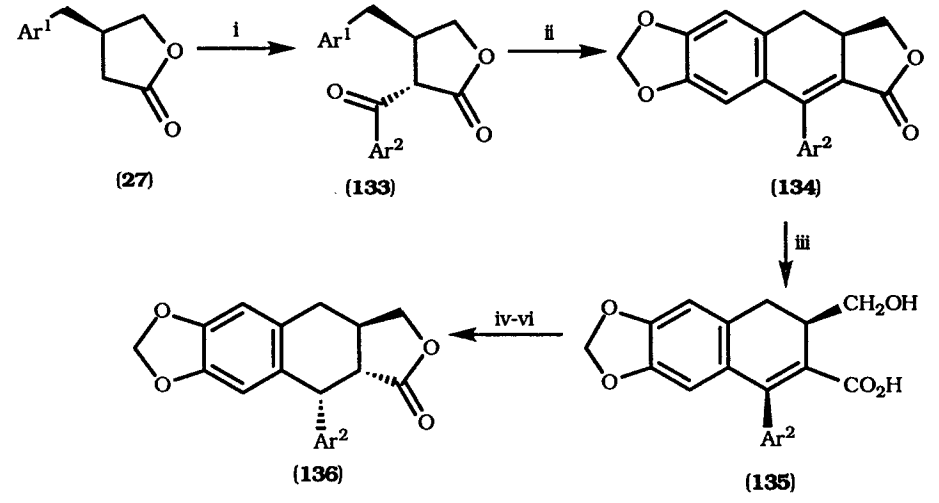
(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl)

Scheme 51.



Reagents: i, $SnCl_4$; ii, HgO, $BF_3.Et_2O$; iii, HOAc
(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl)

Scheme 52.

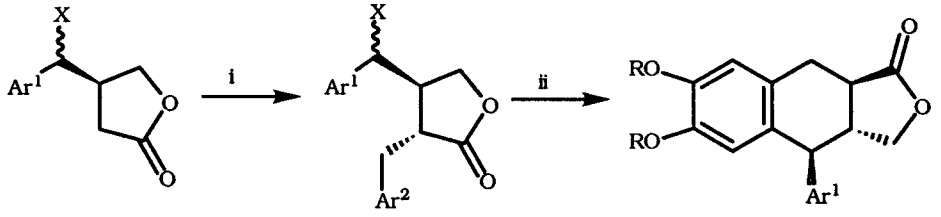


Reagents: i, LDA, Ar^2COCl; ii, HCl/MeOH; iii. KOH; iv, H_2/Pd-C; v, H^+; vi,DCCl
(Ar = 3,4,5-trimethoxyphenyl)

Scheme 53.

Brown *et al.* have carried out asymmetric syntheses of (-)-α-conidendrin and an analogue as shown in scheme 54 [122]. Thus, bromination at the benzylic position of the appropriate monobenzylbutyrolactone (**137**) X=H followed by introduction of a

benzyloxy substituent and alkylation afforded the dibenzylbutyrolactone (**138**) X=OBn. Cyclisation of this compound using a Lewis acid gave the corresponding retro-lactone (**139**).



(**137**) (**138**) (**139**)

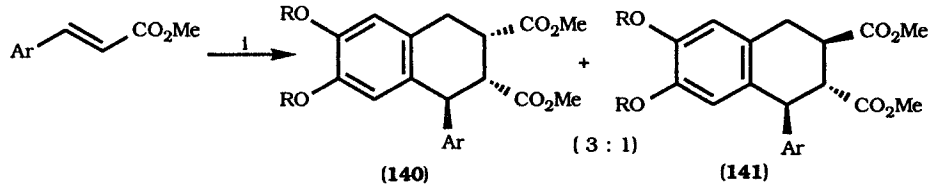
X = H X = OBn

Reagents: i, LHDMS, Ar^2CH_2Br; ii, $BF_3.Et_2O$

(X=OBn, Ar^1 = Ar^2 = 4-hydroxy-3-methoxyphenyl or 3,4-methylenedioxyphenyl)

Scheme 54.

A simple route to symmetrically substituted aryltetralins involves non-oxidative, Lewis acid catalysed dimerisation of cinnamate esters (scheme 55) [123]. Two stereoisomeric products are obtained of which the 2,3-*cis* compound (**140**) predominates.



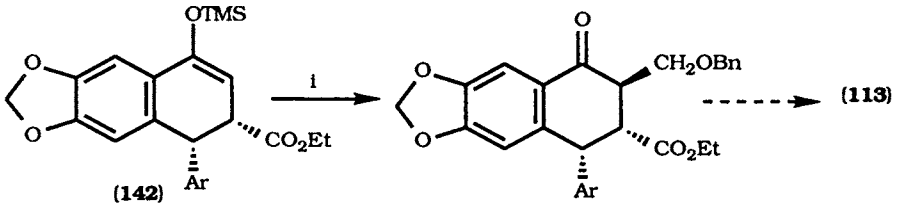
(**140**) (3 : 1) (**141**)

Reagents: i, $BF_3.Et_2O$

(Ar = 3,4-dimethoxyphenyl or 3,4-methylenedioxyphenyl)

Scheme 55.

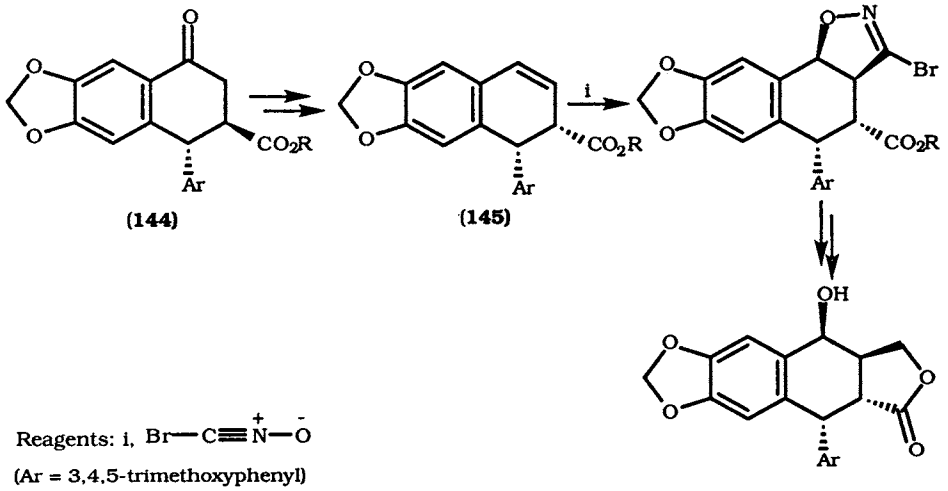
There have been many elegant approaches to podophyllotoxin and its derivatives, some of which have already been highlighted. In the approach of Kaneko and Wong the advanced precursor (**143**) was prepared by a stereoselective Mukaiyama reaction of the key intermediate (**142**). The product (**143**) was then converted into podophyllotoxin (**113**) (scheme 56) [124]. Epipodophyllotoxin has been prepared from the tetralone (**144**) [125]. Functional group transformation and epimerisation at C-2 gave (**145**) and the C-3 and C-4 substituents were then introduced by way of a 1,3-dipolar cycloaddition reaction (scheme 57).



Reagents: i, $CH_2(OBn)_2$, TMSOTf

(Ar = 3,4,5-trimethoxyphenyl)

Scheme 56.

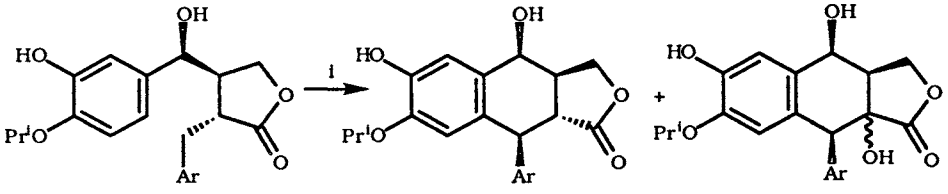


Reagents: i, $Br-C\equiv\overset{+}{N}-\overset{-}{O}$

(Ar = 3,4,5-trimethoxyphenyl)

Scheme 57.

Kutney *et al.* have studied the production of podophyllotoxin derivatives using cultures of *Podophyllum peltatum* and *Catharanthus roseus* [126-128]. In particular they have established procedures for the biotransformation of readily prepared dibenzylbutyrolactones into podophyllotoxin derivatives using a semi-continuous fermentation process (scheme 58). However, even here the major products obtained belong to the 1,2-*trans*- (isopodophyllotoxin) series.

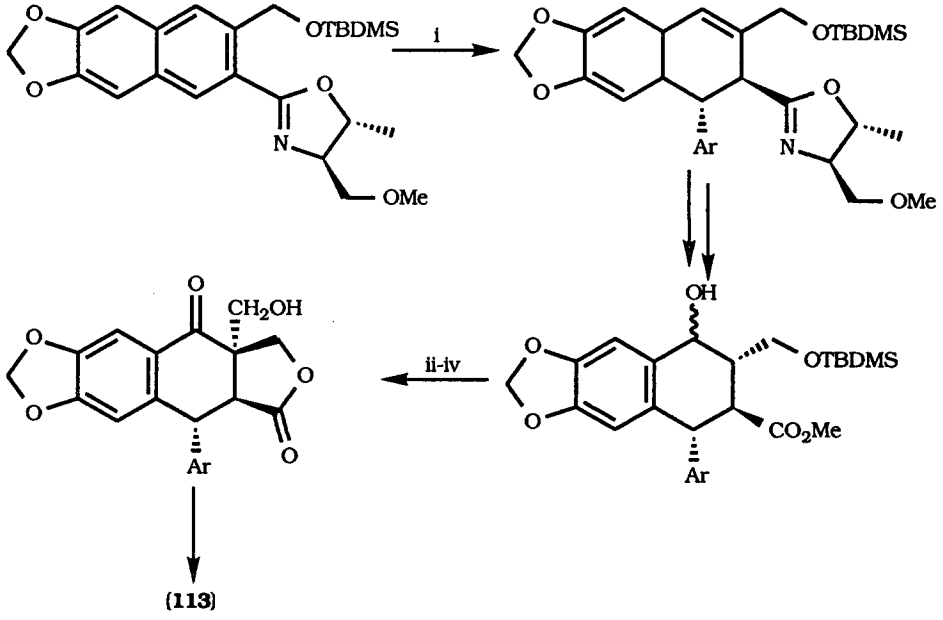


Reagents: i, *Catharanthus roseus or Podophyllum peltatum*

(Ar = 4-hydroxy-3,5-dimethoxyphenyl)

Scheme 58.

Finally, Meyers *et al.* have carried out an asymmetric synthesis of (-)-podophyllotoxin involving conjugate addition to an aryl oxazoline (scheme 59) [129]. The penultimate step involves C-2 epimerisation favouring the *cis*-1,2-geometry.



Reagents: i, ArLi; ii PDC; iii, CH_2O; iv, TsOH

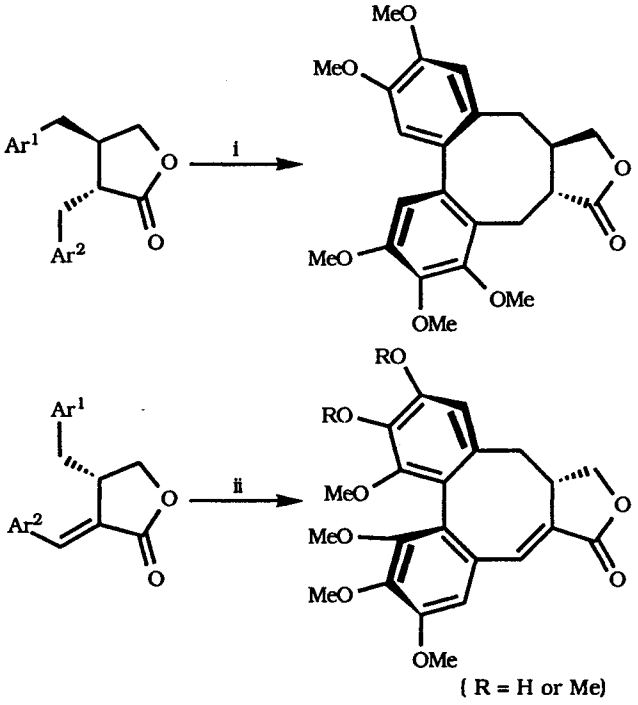
(Ar = 3,4,5-trimethoxyphenyl)

Scheme 59.

3.5 Dibenzocyclooctadiene derivatives

Syntheses of tetrahydrodibenzocyclooctadienes invariably focus on methods for forming the biaryl linkage, usually at a late stage in the synthesis. The use of iron(III)perchlorate [130], ruthenium(IV)dioxide [131], vanadium oxyhalides [132] and thallium(III)trifluoroacetate [133] have all been reported to be the methods of choice for obtaining high yields in this reaction (scheme 60). Such reactions have been used as key steps in the asymmetric synthesis of (+)-schizandrin, (+)-isoschizandrin and (+)-gomisin A [134,135]. The same methodology has also been used for the asymmetric synthesis of (-)-azaisopicrostegane (**149**) by oxidative coupling of the oxazolidinone (**146**) (scheme 61) [136]. In a similar way the racemic azapicrosteganols (**150**) and (**151**) have been prepared starting from (**147**) and (**148**). Oxidation of (**150**) and (**151**) with pyridinium chlorochromate (PCC) gives the ketone (**152**) which undergoes

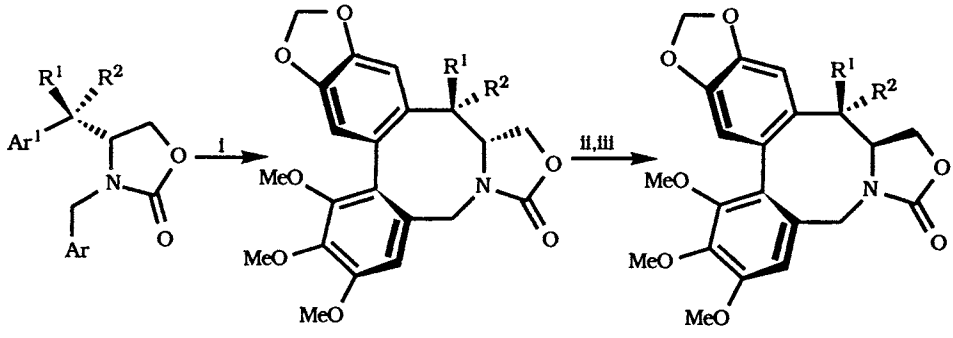
epimerisation with DBU to give (**153**). Reduction of (**153**) with sodium borohydride gives a mixture of the azapicrosteganols (**154**) and (**155**).



Reagents: i, RuO_2, TFA, TFAA, $BF_3.Et_2O$, ii, $Fe(ClO_4)_3$, TFA, CH_2Cl_2

Scheme 60.

Radical-cation coupling with vanadium oxyfluoride has been exploited by Stevenson *et al.* to prepare wuweizisu C (**158**) (scheme 62) [137]. Ruthenium tetra(trifluoroacetate) generated *in situ* (from $RuO_2.2H_2O$ in TFA-TFAA/BF_3-Et_2O) has also been shown to be an extremely effective reagent for non-phenolic oxidative coupling [137-140]. High yields can often be obtained using the ruthenium reagent system, although the reaction fails when methylenedioxy or benzyloxy groups are present [142]. Since many biologically active lignans contain the methylenedioxy group this is a serious limitation and highlights the advantage of having a range of alternative reagents available for this procedure. The ruthenium reagent system gives good yields (80-85%) in some cases when phenolic OH groups are present and can be adapted in all cases to give shorter reaction times by using triflic acid and its anhydride in place of TFA/TFAA or by using ultrasound. Somewhat surprisingly, oxidative coupling of the *cis* lactone (**159**) gave the "normal" stegane atropisomer (**160**) rather than the "iso" series usually obtained from the corresponding *trans*-dibenzylbutyrolactone (scheme 63). This product has been converted into (±)-deoxyschizandrin.



(**146**) $R^1 = R^2 = H$
(**147**) $R^1 = H$, $R^2 = OBn$
(**148**) $R^1 = OBn$, $R^2 = H$

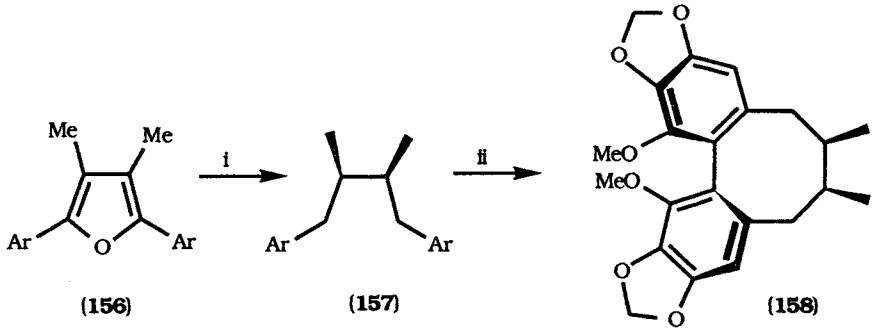
(**149**) $R^1 = R^2 = H$
(**150**) $R^1 = H$, $R^2 = OH$
(**151**) $R^1 = OH$, $R^2 = H$
(**152**) R^1, $R^2 = O$

(**153**) R^1, $R^2 = O$
(**154**) $R^1 = H$, $R^2 = OH$
(**155**) $R^1 = OH$, $R^2 = H$

Reagents: i, VOF_3, TFA, CH_2Cl_2 ; ii, PCC, iii, DBU
(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl)

Scheme 61.

Although the oxidative coupling of phenolic and non-phenolic *trans*-dibenzylbutyrolactones to dibenzocyclooctadiene derivatives can be brought about by a wide variety of reagents, a more detailed mechanistic insight is provided by oxidative phenolic coupling using hypervalent iodine reagents (scheme 64) [143-145] This reaction generates for the first time the spirodienones (**164-167**), previously postulated as intermediates in the synthesis and biosynthesis of stegane and isostegane derivatives. Treatment with acid brings about a stereoselective dienone-phenol rearrangement to give the isostegane compounds (**168-170**). In all cases examined so far an aryl migration has been observed, in contrast to the results on the eupodienones which in the majority of cases rearrange by an alkyl migration (see below). While (**164**), (**166**) and (**167**) give predominantly the isostegane derivatives (**168**), (**169**) and (**170**),

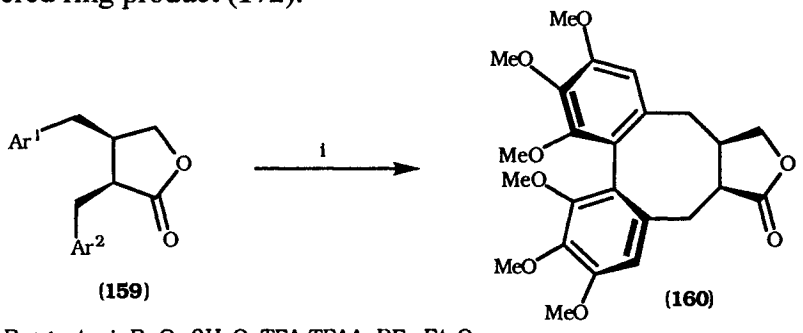


(**156**) (**157**) (**158**)

Reagents: i, Raney nickel; ii, VOF_3

Scheme 62.

rearrangement of (**165**) occurs less readily and leads to the stegane diastereomer of (**169**). Reaction of the *meta*-hydroxy dibenzylbutyrolactone (**171**) under the same conditions leads directly to the eight membered ring product (**172**).

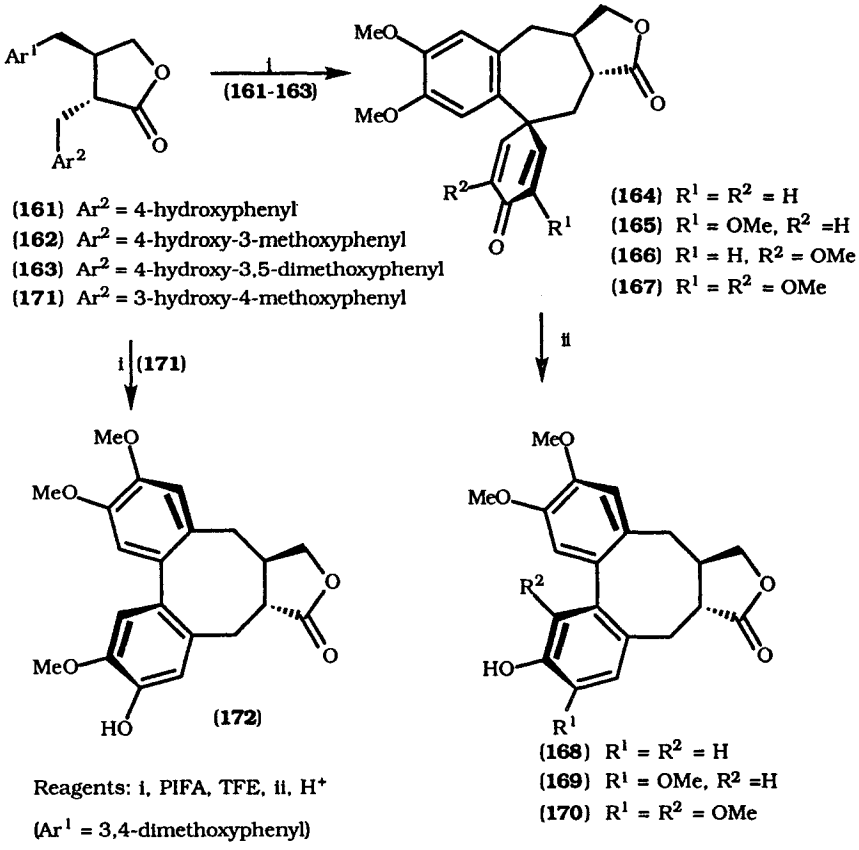


(**159**) (**160**)

Reagents: i, $RuO_2.2H_2O$, TFA-TFAA, $BF_3.Et_2O$

(Ar^1 = Ar^2 = 3,4,5-trimethoxyphenyl)

Scheme 63:



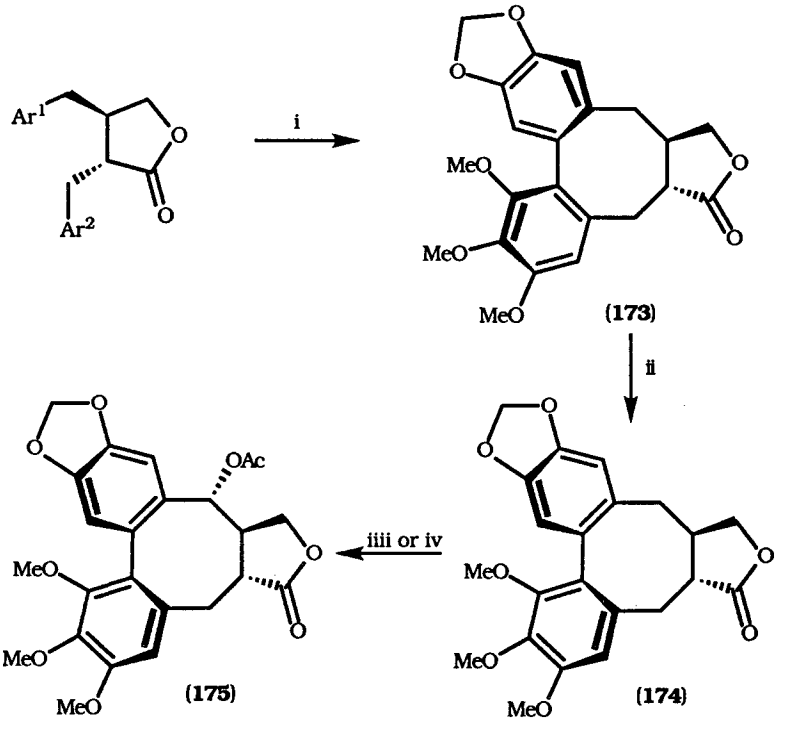
Reagents: i, PIFA, TFE, ii, H^+

(Ar^1 = 3,4-dimethoxyphenyl)

Scheme 64.

Koga and co-workers have synthesised natural (-)-steganacin and (+)-steganacin *via* (+)- and (-)-isostegane (scheme 65) [146]. Thermally induced epimerisation of the biaryl unit of (+)-isostegane (**173**) gave (-)-stegane (**174**) which was acetoxylated to (-)-steganacin (**175**) using either 2,6-dichloro-3,5-dicyano-1,4-benzoquinone (DDQ) in acetic acid or N-bromosuccinimide (NBS) in aqueous tetrahydrofuran, followed by acetylation. Wakamatsu *et al.* have used direct oxidative coupling of the unsaturated lactones (**176**) to give precursors for the asymmetric synthesis of a wide variety of dibenzocyclooctadiene derivatives (scheme 66) [147-152].

A small number of syntheses involve forming the biaryl link before attempting to close the eight membered ring. Thus, Brown *et al.* have designed alternative syntheses of steganone and isostegane involving an Ullmann reaction followed by an intramolecular aldol condensation to form the eight membered ring (scheme 67) [153]. An alternative synthesis of deoxyschizandrin (**178**) involves reductive coupling of the diketone (**177**)



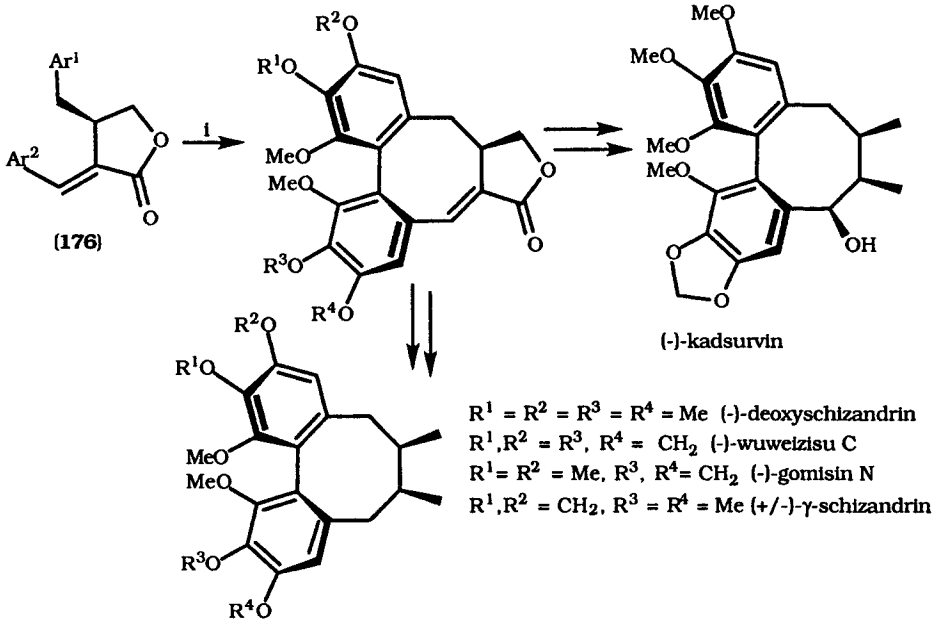
Reagents: i, VOF_3; ii, heat to 200°C, iii, DDQ, HOAc; iv, NBS/H_2O then Ac_2O

(Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4,5-trimethoxyphenyl)

Scheme 65.

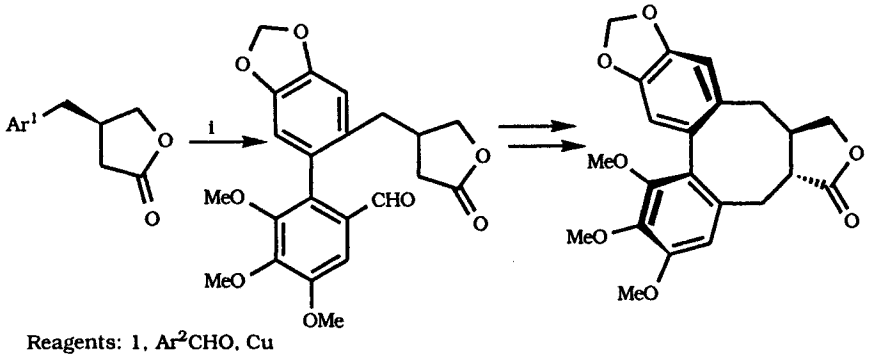
according to the McMurry protocol, followed by hydrogenation of the carbon-carbon double bond produced to give the dibenzocyclooctadiene (scheme 68) [154].

Meyers *et al.* have reported an asymmetric synthesis of (-)-steganone (**179**) in which formation of the biaryl bond represents the first stage in the synthesis of the eight membered ring (scheme 69) [155]. They have also used their oxazoline-mediated coupling approach to carry out asymmetric syntheses of (-)-schizandrin and (-)-isoschizandrin [156].



Reagents: i, $Fe(ClO_4)_3$, TFA, CH_2Cl_2

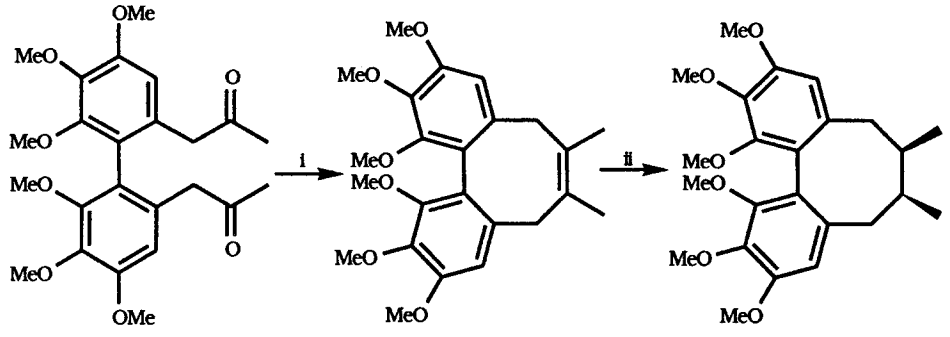
Scheme 66.



Reagents: 1, Ar^2CHO, Cu

(Ar^1 = 2-iodo-4,5-methylenedioxyphenyl, Ar^2 = 2-bromo-3,4,5-trimethoxyphenyl)

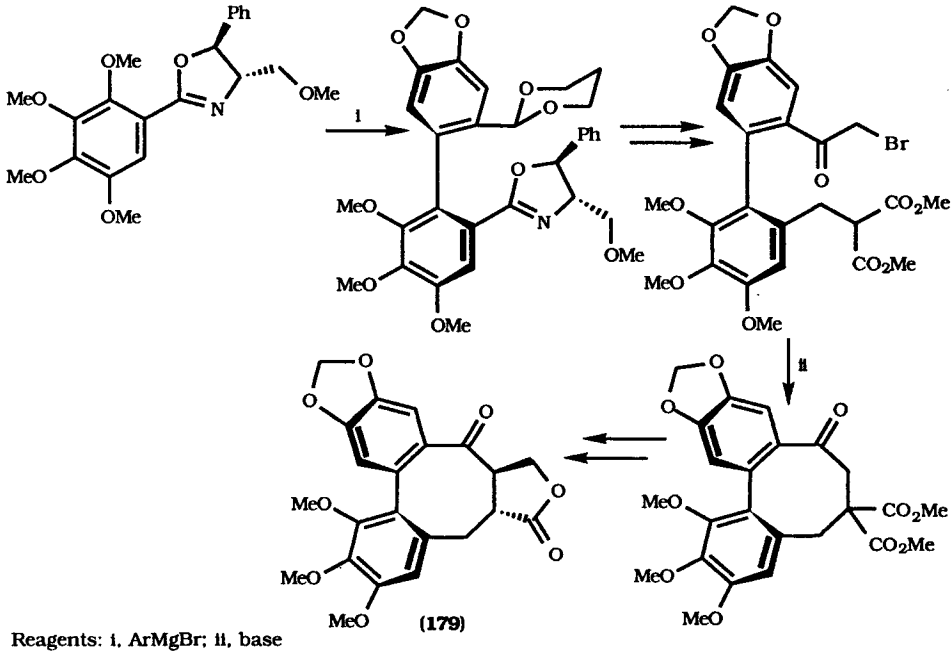
Scheme 67.



(177) (178)

Reagents: i, $TiCl_4$, Mg-Hg; ii H_2/Pd-C

Scheme 68:



(179)

Reagents: i, ArMgBr; ii, base

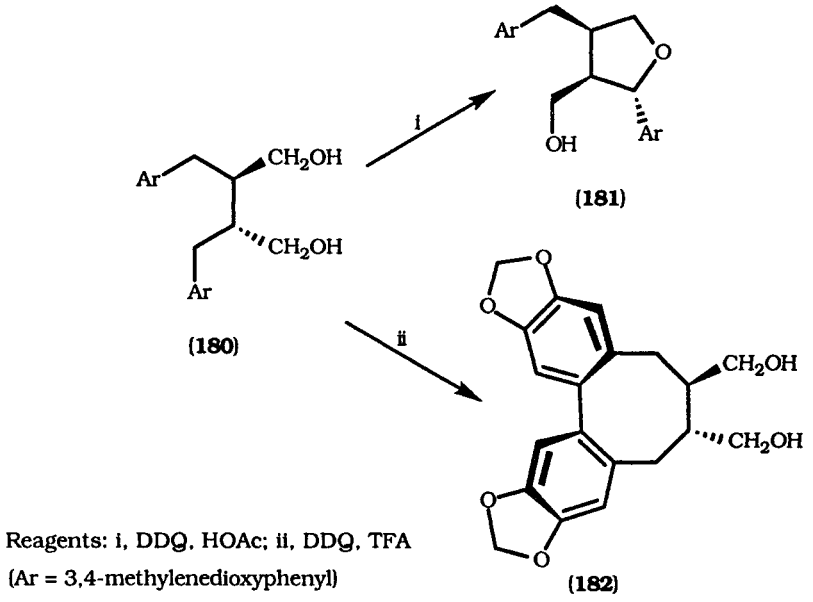
Scheme 69.

4 TRANSFORMATIONS AND INTERCONVERSIONS

4.1 Dibenzylbutane and Dibenzylbutyrolactone Derivatives

Dibenzylbutane derivatives and dibenzylbutyrolactones undergo a wide range of interesting reactions, frequently leading to other lignan types. For

example, when dihydrocubebin (**180**) is treated with DDQ in acetic acid the tetrahydrofuran (**181**) is obtained [157]. However, when DDQ in trifluoroacetic acid is used the dibenzocyclooctadiene (**182**) is produced (scheme 70).

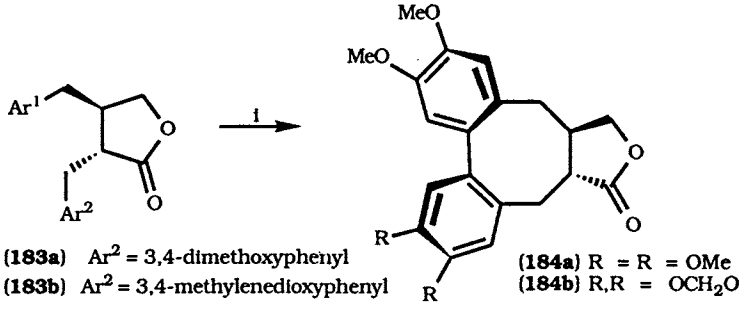


Scheme 70.

DDQ in trifluoroacetic acid (TFA) converts (-)-matairesinol dimethyl ether (**183a**) and (-)-kusunokinin (**183b**) into the dibenzocyclooctadienes (**184a**) and (**184b**) respectively [56]. However, DDQ in dioxane converts (-)-yatein (**185**) into the arylnaphthalene lactone (**186**) and the tetrahydronaphthalene lactone (**187**) [158] (scheme 71).

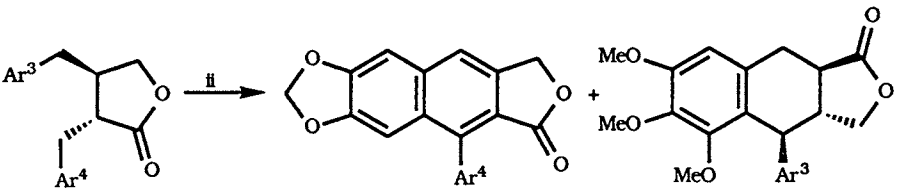
Treatment (**188**) and (**189**) with DDQ in TFA gives (**190**) and deoxyschizandrin (**191**) respectively (scheme 72) [159]. Oxidation with ruthenium dioxide or thallium(III) oxide in a mixture of TFA, TFAA and BF_3 etherate on the other hand gives a mixture of the dibenzocyclooctadienes (**190**) or (**191**) and the aryltetralin (**192**) or (**193**) [160].

Oxidation of the phenolic dibenzylbutane (**194**) using the ruthenium or thallium reagent gives mainly the *para*-coupled product (**195**) with a minor amount of the corresponding *ortho* isomer (**196**) (scheme 73) [161]. Oxidation of (**197a**) and (**197b**) using iron(III) perchlorate affords schizandrin (**198a**) and gomisin A (**198b**) respectively, along with minor amounts (20%) of the corresponding stereoisomer (**199**) (scheme 74) [162]. Similarly (**200a**) affords isoschizandrin (**201a**) along with the stereoisomer (**202a**), while (**200b**) gives (**201b**) and (**202b**) [163].



(183a) Ar^2 = 3,4-dimethoxyphenyl
(183b) Ar^2 = 3,4-methylenedioxyphenyl

(184a) R = R = OMe
(184b) R,R = OCH_2O

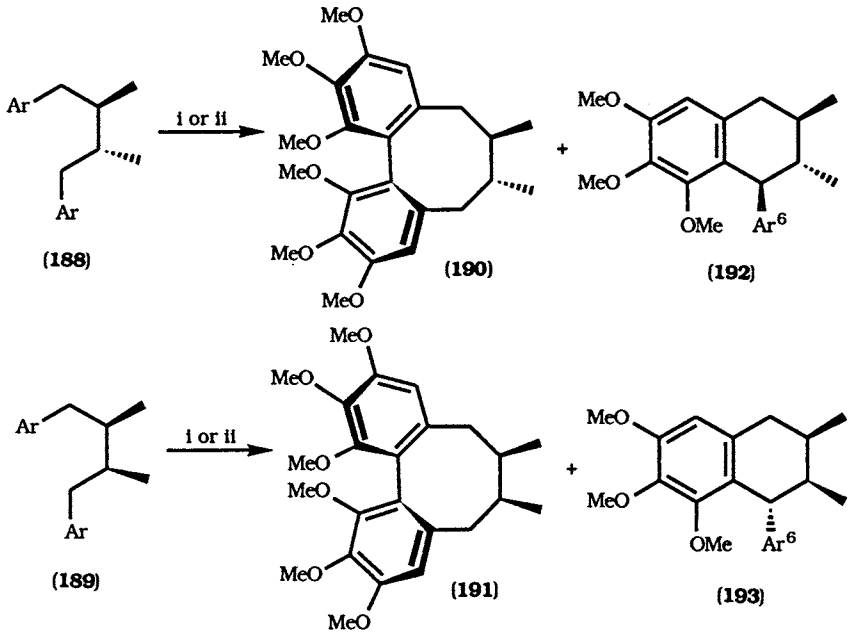


(185) (186) (187)

Reagents: i, DDQ, TFA; ii, DDQ, dioxane

(Ar^1 = 3,4-dimethoxyphenyl, Ar^3 = 3,4-methylenedioxyphenyl, Ar^4 = 3,4,5-trimethoxyphenyl)

Scheme 71.



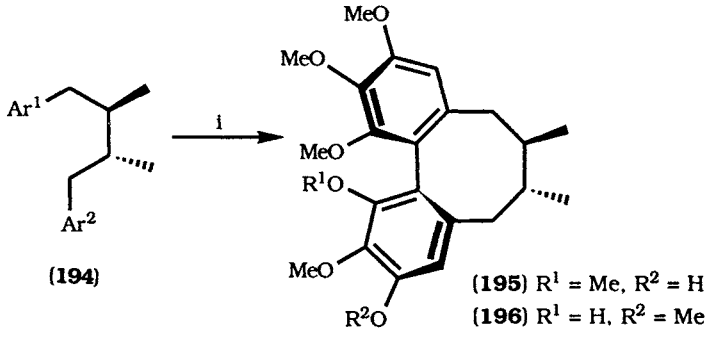
(188) (190) (192)

(189) (191) (193)

Reagents: i, DDQ/TFA; ii RuO_2 or Tl_2O_3 in TFA/TFAA/BF_3.Et_2O

(Ar = 3,4,5-trimethoxyphenyl)

Scheme 72.



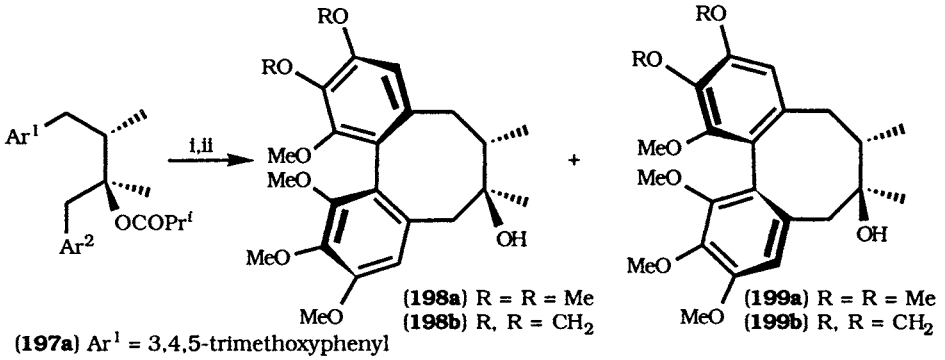
(194)

(195) R^1 = Me, R^2 = H
(196) R^1 = H, R^2 = Me

Reagents: i, Tl_2O_3 or RuO_2, CH_2Cl_2, TFA, TFAA, $BF_3.Et_2O$

(Ar^1 = 3,4,5-trimethoxyphenyl, Ar^2 = 3-hydroxy-4,5-dimethoxyphenyl)

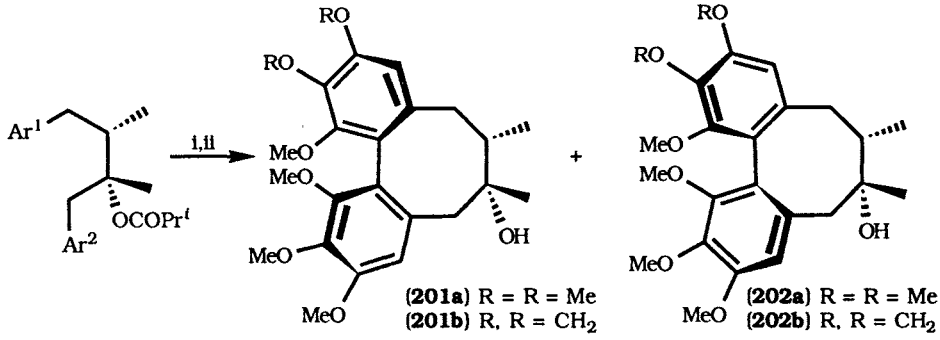
Scheme 73.



(198a) R = R = Me
(198b) R, R = CH_2

(199a) R = R = Me
(199b) R, R = CH_2

(197a) Ar^1 = 3,4,5-trimethoxyphenyl
(197b) Ar^1 = 3-methoxy-4,5-methylenedioxyphenyl



(201a) R = R = Me
(201b) R, R = CH_2

(202a) R = R = Me
(202b) R, R = CH_2

(200a) Ar^1 = 3,4,5-trimethoxyphenyl
(200b) Ar^1 = 3-methoxy-4,5-methylenedioxyphenyl

Reagents: i, $Fe(ClO_4)_3$; ii. KOH

(Ar^2 = 3,4,5-trimethoxyphenyl)

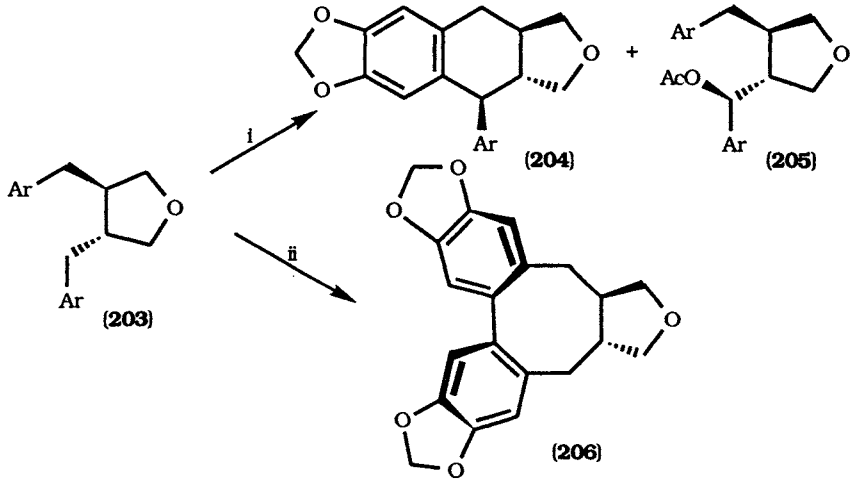
Scheme 74.

4.2 Tetrahydrofurans

Treatment of the 3,4-dibenzyltetrahydrofuran (**203**), derived by cyclisation of dihydrocubebin, with DDQ in acetic acid causes dehydrogenation to the aryltetralin (**204**), presumeably *via* the acetoxy compound (**205**), which is obtained as a second product from the reaction. However the same reaction carried out in TFA affords the dibenzocyclooctadiene (**206**) (scheme 75) [157].

4.3 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes

Some interesting rearrangement reactions are exhibited by lignans in this group. Thus, arboreol (**208**) undergoes an unusual pinacol rearrangement with acid to yield gmelanone (**209**) which represents a biomimetic synthesis of this compound (scheme 76) [164]. Paulownin (**210**) rearranges when oxidised with DDQ in benzene to yield the 4-pyrone (**211**) [165], and the same reagent converts gummadiol (**212**) into the enol lactone (**213**).

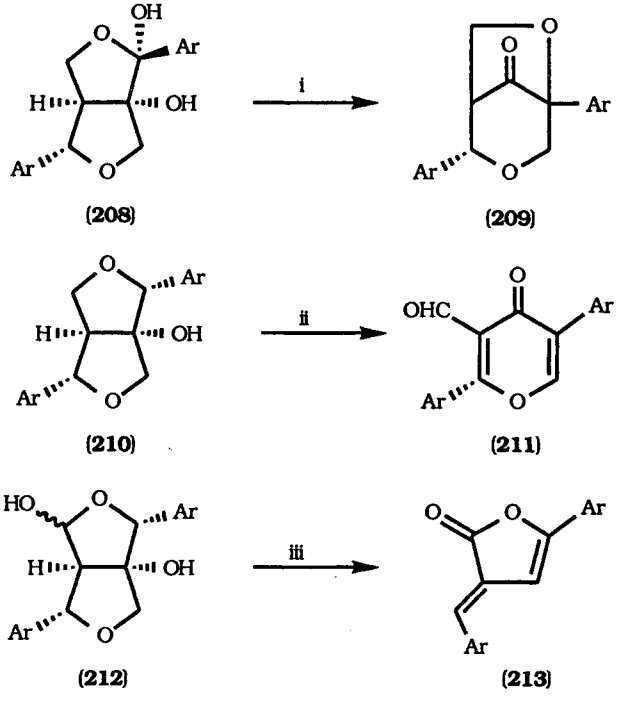


Reagents: i, DDQ, HOAc; ii DDQ, TFA
(Ar = 3,4-methylenedioxyphenyl)

Scheme 75.

The reaction of these compounds with triethylsilane and boron trifluoride-etherate is also of interest. Thus, gmelinol (**214**) gives two products, the major one being (**215**) (scheme 77) [166]. It is formed by reductive rearrangement of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton. The minor product is a 2-aryl-4-benzyltetrahydrofuran (**216**) in

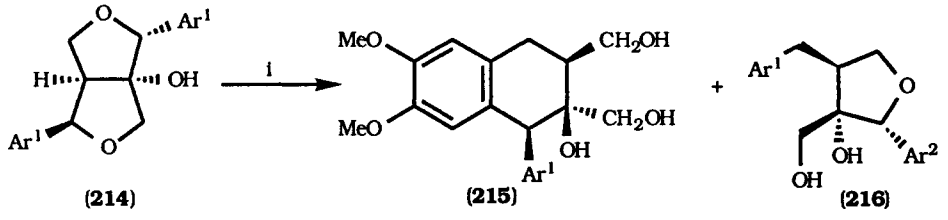
which a methoxy group has been removed from one of the aromatic groups.



Reagents: i, H^+; ii. DDQ

(Ar^1 = 3,4-methylenedioxyphenyl)

Scheme 76.



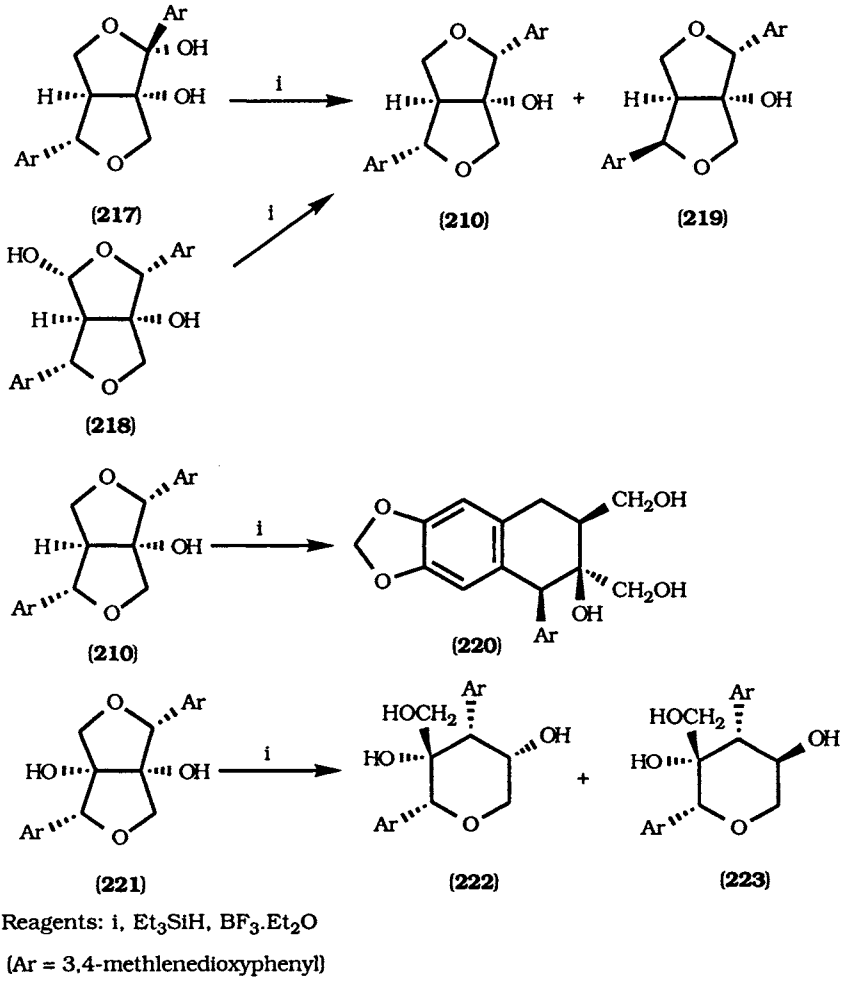
Reagents: i, Et_3SiH, $BF_3.Et_2O$

(Ar^1 = 3,4-dimethoxyphenyl, Ar^2 = 3-methoxyphenyl)

Scheme 77.

Treatment of either arboreol (**217**) or gummadiol (**218**) with triethylsilane and BF_3-etherate yields initially a mixture of paulownin

(**210**) and isopaulownin (**219**). However treatment of paulownin itself (**210**) with the same reagent gives the aryltetralin (**220**), similar to the reaction of gmelinol (see above). Furthermore, wodeshiol (**221**) reacts under the same conditions to give a mixture of two stereoisomeric tetrahydropyran derivatives (**222**) and (**223**) (scheme 78) [167].

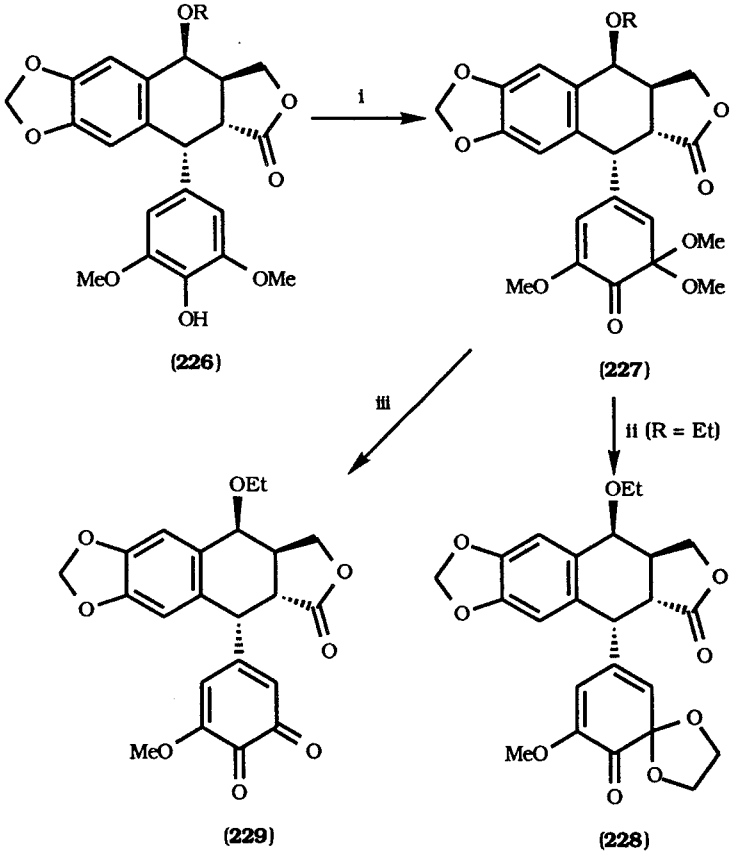


Scheme 78.

Reaction of gmelinol (**214**) with BF_3-etherate and *N,N*-dimethylaniline gives a product (**224**) in which one tetrahydrofuran ring is retained [168]. Reduction of (**224**) with BF_3-etherate and triethylsilane produced (**225**) (scheme 79).

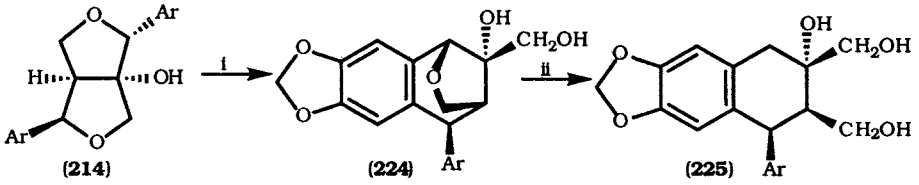
4.4 Arylnaphthalene derivatives

The interest in novel podophyllotoxin derivatives has lead to the preparation of several analogues having structures closely related to the quinonoid intermediates believed to be involved in their mode of action. One of these is the quinone monoketal (**227**) (R = H) obtained by reacting 4'-demethylepipodophyllotoxin (**226**) (R = H) with phenyliodonium diacetate (PIDA) or DDQ in methanol (scheme 80) [169]. The quinone-methide monoketal (**227**) (R = Et), prepared in the same way, undergoes transketalisation by ethylene glycol to give (**228**). Alternatively, hydrolysis of the dimethyl ketal with aqueous acid gives the corresponding *ortho*-quinone (**229**) [170].



Reagents: i, PIDA or DDQ in MeOH, ii, $HOCH_2CH_2OH$, $BF_3.Et_2O$: iii, H_3O^+

Scheme 80.

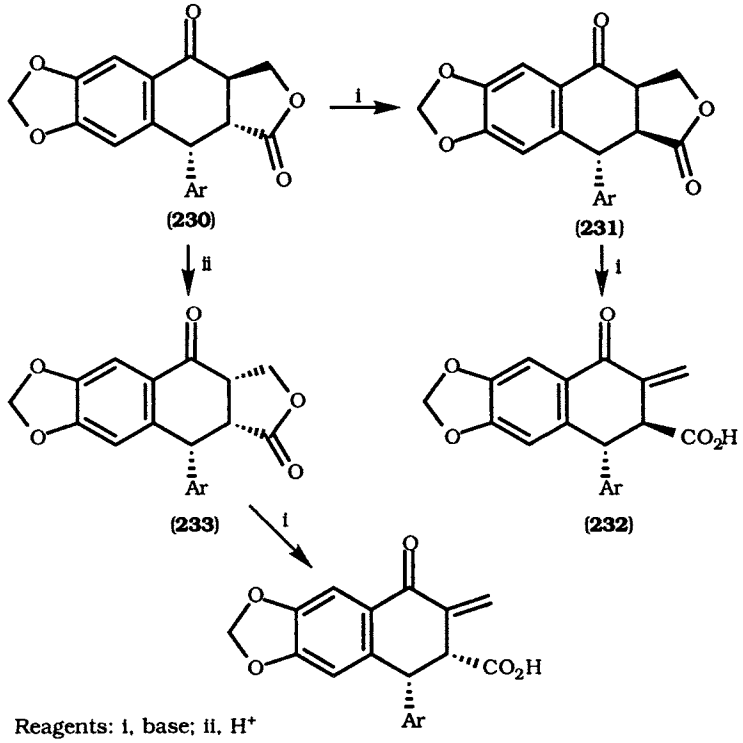


Reagents: i, $BF_3.Et_2O$, $PhNMe_2$; ii $BF_3.Et_2O$, Et_3SiH

(Ar = 3,4-dimethoxyphenyl)

Scheme 79.

Treatment of podophyllotoxone (**230**) with base converts it initially into picropodophyllone (**231**) which on further base treatment yields thuriferic acid (**232**) [171-173]. Indeed it has subsequently been shown that whereas treatment of (**230**) with base gives (**231**) and (**232**), under acidic conditions epimerisation occurs at C-3 to give isopicropodophyllone (**233**) which on treatment with base is converted into epithuriferic acid (**234**) (scheme 81) [174].



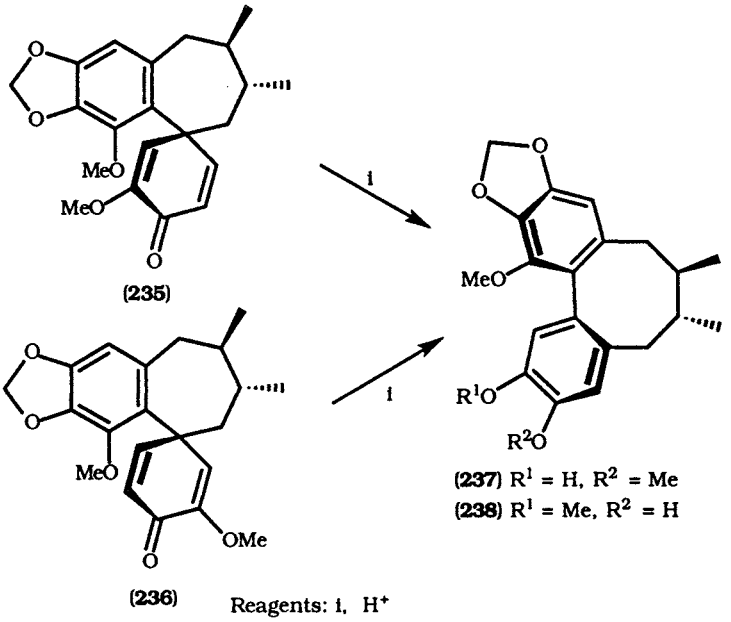
Reagents: i, base; ii, H^+

(Ar = 3,4,5-trimethoxyphenyl)

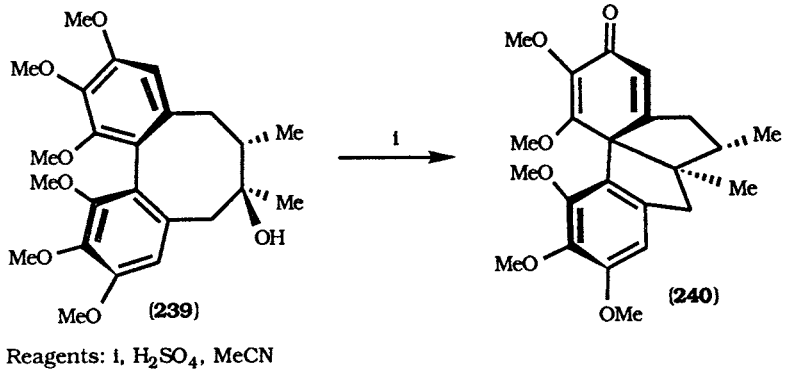
Scheme 81.

4.5 Dibenzocyclooctadiene derivatives

Eupodienones-8 and -9 are representative examples of a series of compounds isolated from the flowers of *Eupomatia laurina* which have been assigned structures (**235**) and (**236**) respectively [175]. They rearrange on exposure to HCl in dioxan to (**237**) and (**238**) respectively, the former involving aryl group migration the latter alkyl group migration (scheme 82). These reactions should be compared with those involved in the biomimetic synthesis of isostegane derivatives described in section 3.5.



Scheme 82.



Scheme 83.

Finally, reaction of schizandrin (**239**) and related compounds under Ritter conditions gives the tetracyclic dienone (**240**) (scheme 83) [176,177].

ABBREVIATIONS

AIBN	=	2,2'-Azobisisobutyronitrile
BMS	=	Borane-dimethyl sulfide
Bn	=	Benzyl
CAN	=	Ceric ammonium nitrate
DBU	=	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCCI	=	*N,N'*-Dicyclohexylcarbodiimide
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	=	3,4-Dihydro-2*H*-pyran
diphos-4	=	1,4-bis(Diphenylphosphino)butane
DMAP	=	4-(*N,N*-Dimethylamino)pyridine
DMF	=	*N,N*-Dimethylformamide
DMSO	=	Dimethylsulfoxide
imid	=	Imidazole
KHMDS	=	Potassium hexamethyldisilazide
LDA	=	Lithium di-*iso*-propylamide
LHDMS	=	Lithium hexamethyldisilazide
L-Selectride	=	Lithium tri-*sec*-butylborohydride
MOD-DIOP	=	4,5-bis[bis(4'-Methoxy-3'5'-dimethylphenyl) phosphinomethyl']-2,2-dimethyl-1,3-dioxolane
MOM	=	Methoxymethyl
MoOPH	=	Oxodiperoxymolybdenum(pyridine) hexamethylphosphoramide
Ms	=	Methanesulfonyl
$NADP^+/NADPH^+$	=	Nicotinamide adenine dinucleotide phosphate
nbd	=	Norbornadiene
NMO	=	N-Methylmorpholine-N-oxide

PCC	=	Pyridinium chlorochromate
PDC	=	Pyridinium dichromate
PIDA	=	Phenyl iodonium diacetate
PIFA	=	Phenyl iodonium bis(trifluoroacetate)
PPTS	=	Pyridinium *p*-toluenesulfonate
pyr	=	Pyridine
refl	=	Reflux
TBAF	=	Tetrabutylammonium fluoride
TBDMS/TBS	=	*tert*-Butyldimethylsilyl
TBDPS	=	*tert*-Butyldiphenylsilyl
Tebbe reagent	=	$Cp_2TiCH_2.Me_2AlCl$
Tf	=	Trifluoromethanesulfonyl
TFA	=	Trifluoroacetic acid
TFAA	=	Trifluoroacetic anhydride
TFE	=	2,2,2-Trifluoroethanol
TMS	=	Trimethylsilyl
Ts	=	*p*-Toluenesulfonyl

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