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Some Aspects of the Chemistry of Lignans

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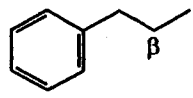
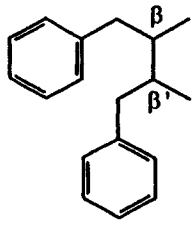
1. INTRODUCTION

The term *lignan(e)* was introduced by R.D. Haworth in 1936 in a review article dealing with natural resins (1). He noted the widespread natural occurrence of "propylbenzene derivatives" (e.g., safrole, eugenol, caffeic acid), designated as C_6-C_3 units, and recognized the existence of a group of phenolic resinols whose structures might be formally derived from two such C_6C_3 units. For the latter, of which all known at that time possessed a bond between the β-carbon atoms of the C_3 chain, the general name lignan has become established.



C_6-C_3 Unit



Lignan Carbon Framework

Many related natural products have subsequently been identified with the significant structural difference of having the C_6-C_3 units bonded at sites other than $\beta\beta'$. For these, the useful designation "*neolignan*" was introduced (2). Ambiguity has since arisen however from use of the same term with a conflicting definition, based upon possible biogenetic rather than structure considerations (3). Most workers in this field, nevertheless, express a preference for the original Haworth definition of lignan, and this article is restricted to that understanding. The first significant reviews of lignans appeared in 1955, with that of Erdtman (4) having particular significance in

laying the foundation of consideration of the biogenesis of these products, and that of Hearon and MacGregor (5) offering comprehensive coverage (314 references) of the chemistry of the 33 members known at that time. Later reviews emphasizing systematics and nomenclature followed (6,7). The first extensive multi-authored monograph was published in 1978 (8) and a volume surveying the chemical, biological and clinical properties has recently become available (9). Recognition of the increasing significance of biological properties and potential pharmacological applications (10-13) has further stimulated interest in this field, with timely literature reviews by Whiting (14). A review devoted to the synthesis of lignans (15) has additionally been up-dated with emphasis on asymmetric methodology (16).

An accurate accounting of the total number of natural lignans of well-defined structure takes on an element of a Sisyphean task since scarcely a month passes without reports of newly isolated products, particularly in the pages of *Phytochemistry* and *The Journal of Natural Products*. Useful compilations, although inevitably out-dated, do however exist (13,17,18). Suffice it to say that, within the Haworth lignan definition and excluding natural glycoside and ester variants, about 500 natural compounds are known. With few exceptions, these can be conveniently and unambiguously sub-classified within the structural sub-classes [A-J, Scheme 1] corresponding to

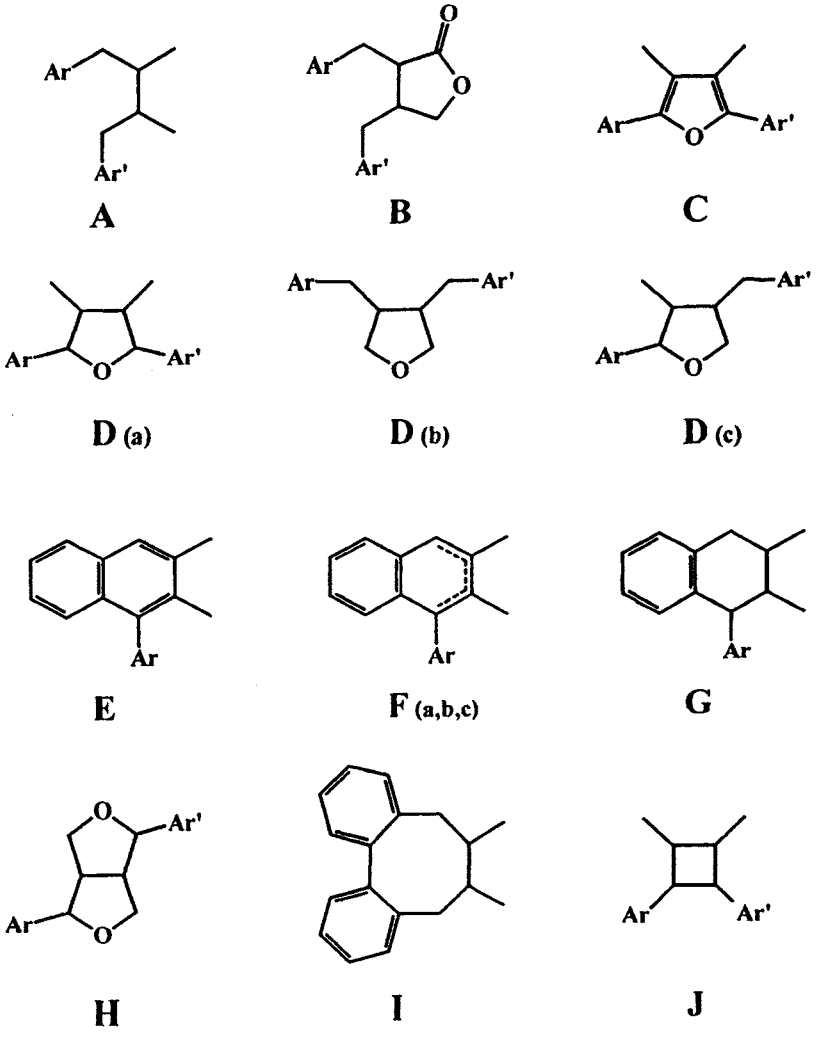
A Dibenzylbutanes
B Dibenzylbutyrolactones
C Furans
D Tetrahydrofurans (in three sub-groups, D(a), D(b), and D(c))
E Arylnaphthalenes
F Aryldihydronaphthalenes
G Aryltetralins
H Tetrahydrofurofurans
I Dibenzocyclo-octadienes
J Diarylcyclobutanes

The aryl group substitution patterns found in lignans are delineated in Scheme 2. The rings may be mono-, di-, tri-, or tetrasubstituted by the common phenolic hydroxyl, methyl ether and methylenedioxy groups. With a few exceptions (isolated notably from mammalian sources), all lignans have an oxygenated substituent *para*

to the C_3 sidechain precursor unit.

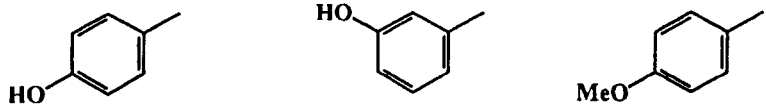
This survey is organized to provide a balanced overview of the above ten structural sub-classes (A-J). The choice of topics is of necessity both subjective and selective, but includes within each group representative members which have been of significance in the development of the field or isolated from natural sources with demonstrated biological activity. Emphasis is also given to synthetic methods

Scheme 1. Lignan Structure Sub-Classification

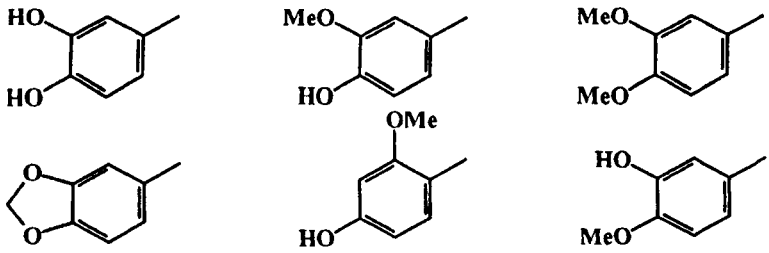


Scheme 2. Substitution on C_6-C_3 Unit

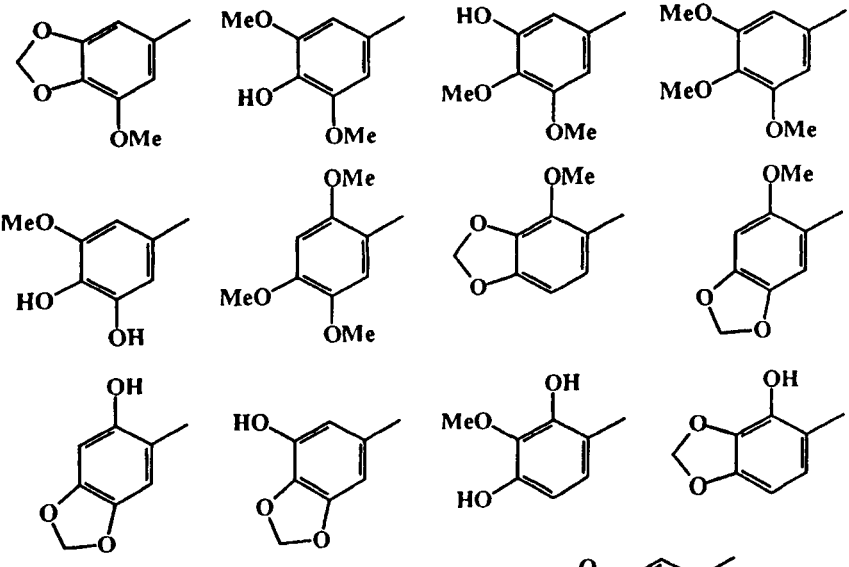
Mono-



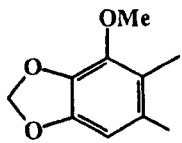
Di-



Tri-



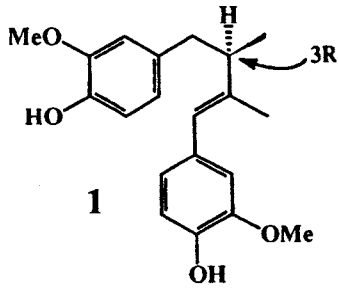
Tetra-



which appear to have general applicability, unless they have been extensively and recently reviewed elsewhere. Since this article is directed to the non-specialist, questions of systematic nomenclature are avoided, in the interest of simplicity and clarity within each group, and since no comprehensive system yet appears to have gained general approval (19).

A. DIBENZYLBUTANES

When last reviewed as a lignan group fifteen years ago (20), there were 17 members of reasonably well-established structure; that number has now more than tripled. The most venerable is (-)-guaiaretic acid (1), isolated from the gum and heartwood of "lignum vitae." Of particular significance was the establishment of the configuration of the sole chiral centre (3R), initially by chemical correlation with (-)-3,4-dihydroxyphenylalanine of known absolute configuration (21). It has also served as a useful standard for chemical correlation of natural members of other lignan structural sub-classes.



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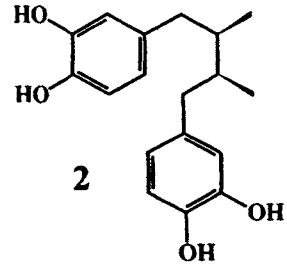


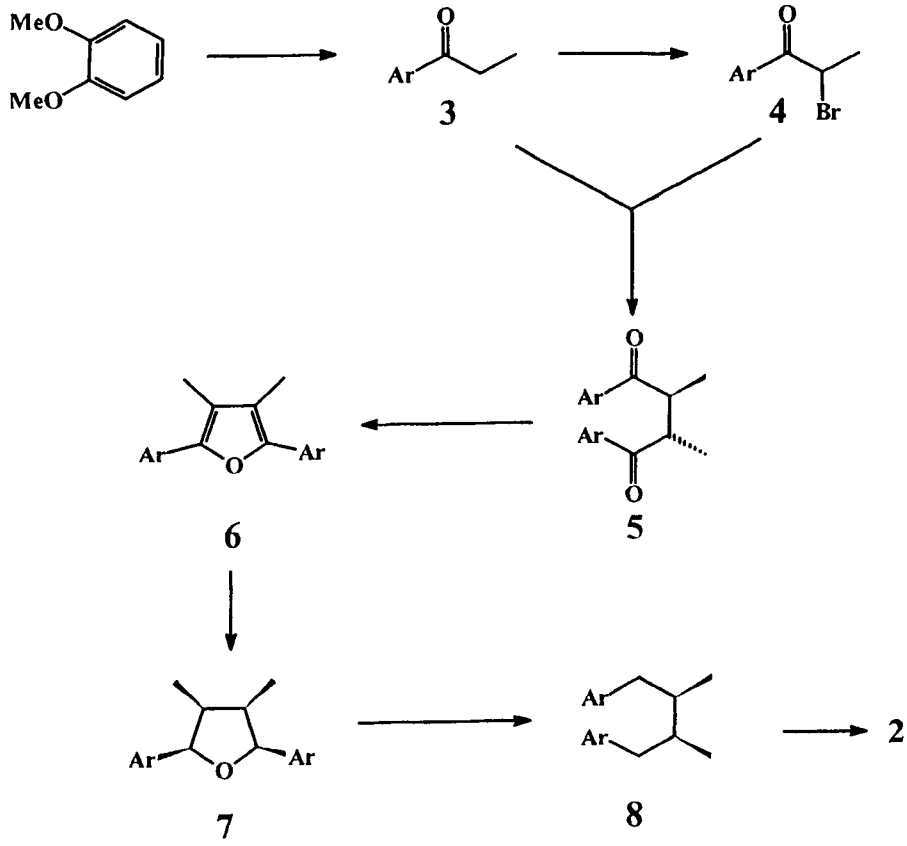
2

Meso-nordihydroguaiaretic acid (2) occurs in high concentrations in the resinous exudate of *Larrea divaricata* (the creosote bush of south-western U.S.A. and Mexico). Recognized about 50 years ago as an excellent natural fat anti-oxidant, numerous other pharmacological applications and industrial (non-food) uses have been discovered and were interestingly and succinctly reviewed in 1972 (22). Effectiveness against a variety of oxidative-reductive and other enzymes has been demonstrated and it is used extensively as a standard for comparison of other lipoxygenase inhibitors now being widely developed (23).

A synthesis of NDGA aimed to be economically competitive with natural

extraction has been developed in the Hoffmann-LaRoche laboratories and outlined in Scheme 3 (24). Friedel-Crafts propionylation of veratrole in chloroform gave the ketone (3), which on bromination yielded the α-bromoketone (4). An improved procedure for alkylation of (4) with the sodium enolate of (3), by conducting the reaction in liquid ammonia at -33°, produced the racemic diketone (5). The yield in each of these steps surpassed 90%, as did the acid-catalyzed dehydration of (5) to the furan (6). A survey of catalytic hydrogenation conditions provided reliable conversion to the *cis*-tetrahydrofuran (7) or the tetramethyl ether hydrogenolysis

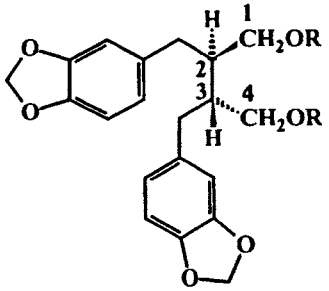
Scheme 3. Synthesis of NDGA



Ar = 3,4-Dimethoxyphenyl.

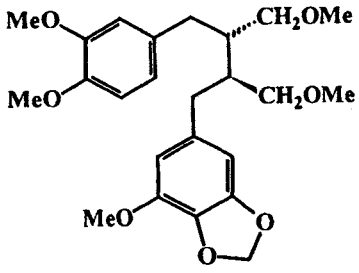
product (8) which on demethylation yielded NDGA (2).

The principal functional group variations found in this family are hydroxyl groups (at C-1 and -4) or the corresponding ethers or esters. These are exemplified by (-)-dihydrocubebin (9), a constituent of *Piper guineense* (West African Black Pepper) used in treatment of coughs, intestinal disease, venereal disease, and rheumatism (25), ariensin (10) occurring in the exudate of the bark of *Bursera ariensis* and reportedly used as a cicatrizing agent (26), and (+)-niranthin (11), one of many lignans isolated from *Phyllanthus niruri* (27).



9 (-)-Dihydrocubebin, R=H

10 Ariensin, R=$COCH_3$

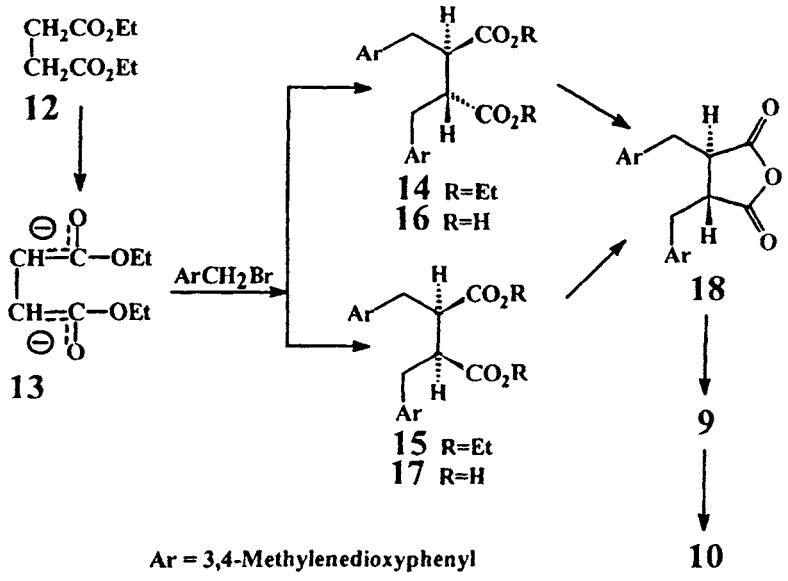


11 (+)-Niranthin

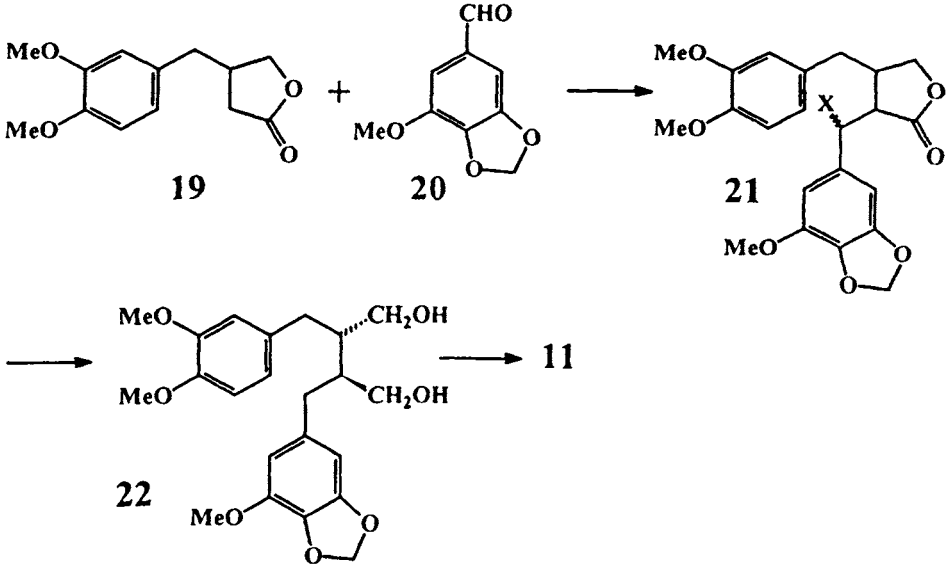
Syntheses of (9) and (10) were conveniently effected (Scheme 4) starting from diethyl succinate (12) (28). The resultant dienolate (13), obtained by the action of two equivalent of lithium di-isopropylamide (29) gave on alkylation with methylenedioxybenzyl bromide in excellent yield a mixture of the (±)-ester (14) and *meso*-ester (15) which by alkaline hydrolysis yielded the dicarboxylic acid mixture (16) and (17). Without separation, this mixture on heating wih acetic anhydride gave the known *trans*-dipiperonylsuccinic anhydride (18) (30). Reduction of (18) with lithium aluminium hydride gave (±)-dihydrocubebin (9), acetylation of which yielded (±)-ariensin (10).

A synthesis of (±)-niranthin (11) (31) (Scheme 5) addresses the issue of the two aryl rings having different substituents. β-Benzylbutyrolactones of type (19) are now readily available in racemic and enantiomeric forms (see next section) via classical Stobbe reaction procedures. The lithium enolate of (19) (32) reacted

Scheme 4. Synthesis of (±) - Dihydrocubebin (9) and (±)- Ariensin (10)



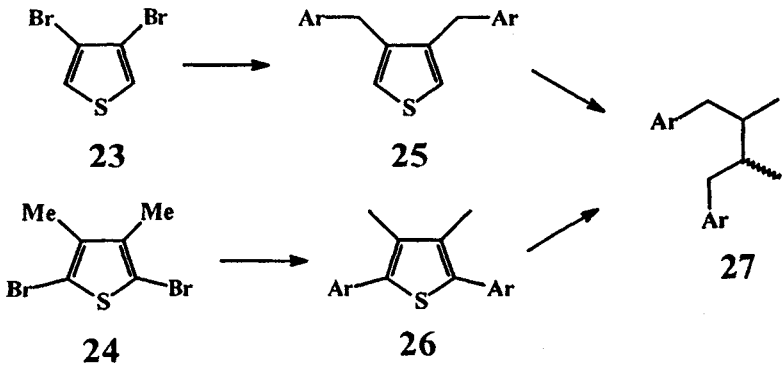
Scheme 5. Synthesis of (±)- Niranthin



readily with the aldehyde (20) (33) to give a mixture of epimeric alcohols (21, X = OH) which on catalytic hydrogenolysis gave the dibenzylbutyrolactone (21, X = H). Standard lithium aluminium hydride reduction to the diol (22) and methylation yielded (±)-niranthin (11).

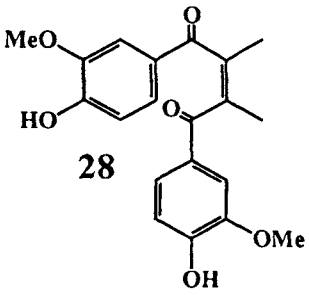
An interesting approach in which the thiophenes (23) and (24) are used as the C_4-butane building block has been communicated (Scheme 6) (34). Cross-coupling of (23) with benzylmagnesium halides or (24) with arylmagnesium halides gave the respective dibenzylthiophenes (25) and dimethyldiarylthiophenes (26). These transformations were effected by use of a nickel phosphine complex, and transformation to the dibenzylbutanes (27) accomplished by Raney nickel desulfurisation. The overall pathway has also been modified for the synthesis of unsymmetrically substituted lignans. A disadvantage appears to be lack of stereospecificity in the terminal reduction step.

Scheme 6. **Thiophene Based Synthesis of Dibenzylbutanes**



Additional structural features found among members of this lignan group include benzylic hydroxyl and carbonyl groups, carboxylate ester functions and alkene unsaturation. Examples of such members (Scheme 7) include furoguaiaoxidin (28, from *Guiacum officinale* (35)), saururinone (29, from *Saururus cernuus* (36)), hydroxybuphthalmin (30, from *Heliopsis buphthalmoides* (37)) and the veratrylpiperonylbutanol (31), from *Virola elongata* (38)).

Scheme 7.



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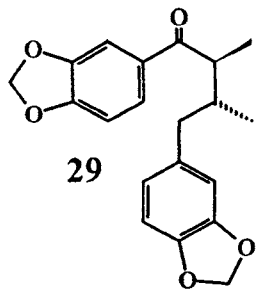

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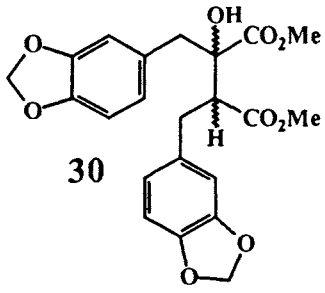

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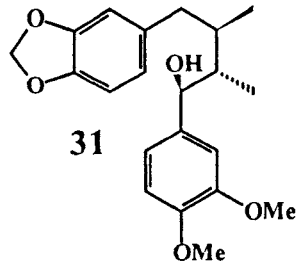

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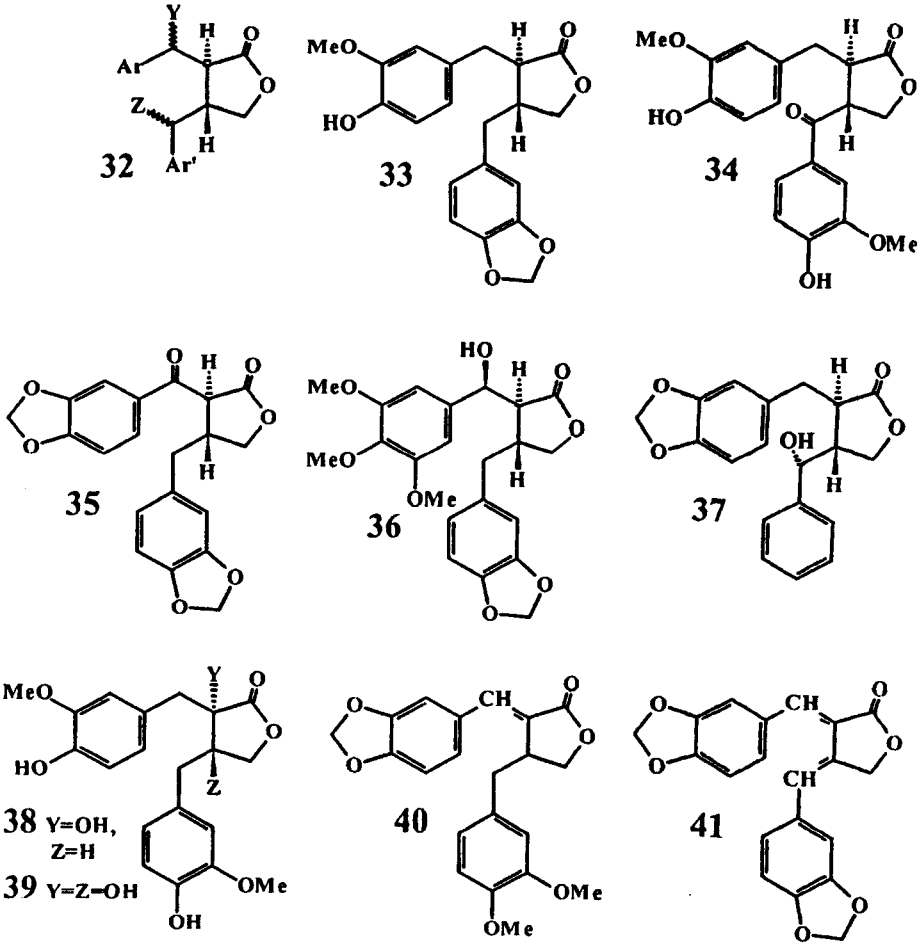
B. DIBENZYLBUTYROLACTONES

Over sixty natural dibenzylbutyrolactone lignans are known; about two thirds can be incorporated by the general formula (**32**); Y,Z may be -H, -OH or =O (Scheme 8). Representative examples are pluviatolide (**33**), oxomatairesinol (**34**), oxohinokinin (**35**), podorhizol (**36**) and parabenzlactone (**37**). Others, such as wikstromol (**38**) and thujastandin (**39**) are α-hydroxy or $\alpha\beta$-dihydroxybutyrolactones. Benzylidene and dibenzylidebutyrolactones such as suchilactone (**40**) and taiwanin A (**41**) are also known.

β-Benzyl-γ-butyrolactones (**44**) for which convenient preparative procedures are available, and improved techniques for their α-alkylation and α-hydroxyalkylation, provide the most common synthetic route for these lignan sub-classes (39). The Stobbe condensation (40) of aryl aldehyde with dimethyl succinate (Scheme 9) leads to the half-ester (**42**) which can be catalytically hydrogenated at atmospheric pressure to give the dihydro half-ester (**43**). Selective reduction of the potassium salt of the latter can be effectively achieved by calcium borohydride (41)

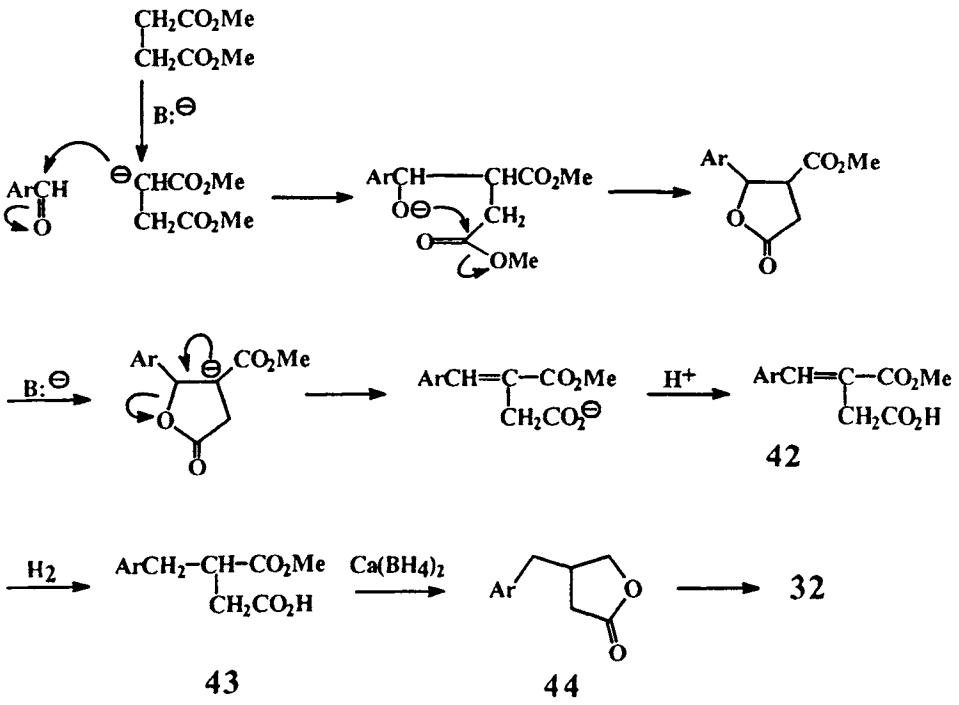
Scheme 8. Dibenzylbutyrolactone Lignan Structures



to yield the lactone (44). Treatment of the lithium enolate with the necessary aldehyde (ArCHO) leads to the epimeric alcohols (32, Y = H, Z = OH) or with the benzyl bromide ($Ar'CH_2Br$) gives the lactone (32, Y = Z = H). More detailed discussions of application of the Stobbe reaction and useful variations pertinent to lignan synthesis have been provided (42,43).

The occurrence and identification of enterolactone (45) in human pregnancy urine and other mammalian sources (44,45) attracted immediate interest in

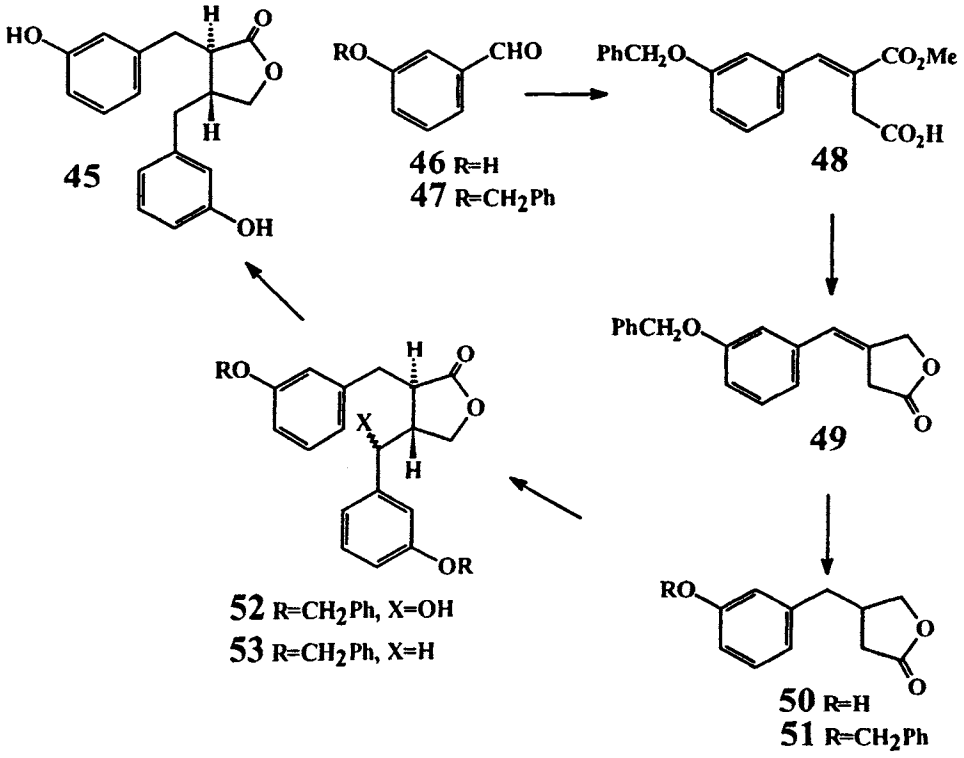
Scheme 9.



biological function and potential medical use. These aspects have recently been summarized (46). From a chemical viewpoint, this compound presented unusual features, e.g., occurring from other than a plant source, in a racemic form and lacking *p*-phenolic (or ether) sub-unit functionality. Several syntheses were reported shortly thereafter, including two based on Stobbe procedures (47,48). As based on the Scheme 9 outline, a straightforward synthesis (48) is available. The benzyl ether (**47**) obtained from *m*-hydroxybenzaldehyde (**46**) was condensed with dimethyl succinate to give the half-ester (**48**) which was converted to the benzylidene lactone (**49**) and thence the benzyl lactone (**50**) by catalytic hydrogenation. Alkylation of the derived benzyl ether (**51**) with (**47**) gave the mixture of epimeric alcohols (**52**); alternatively, alkylation with *m*-benzyloxybenzyl bromide yielded (**53**). Both (**52**) and (**53**) produced enterolactone (**45**) on hydrogenolysis (Scheme 10).

A second dibenzylbutyrolactone synthesis procedure which has found wide application utilizes a "tandem conjugate addition" to butenolide (49,50,51) and has

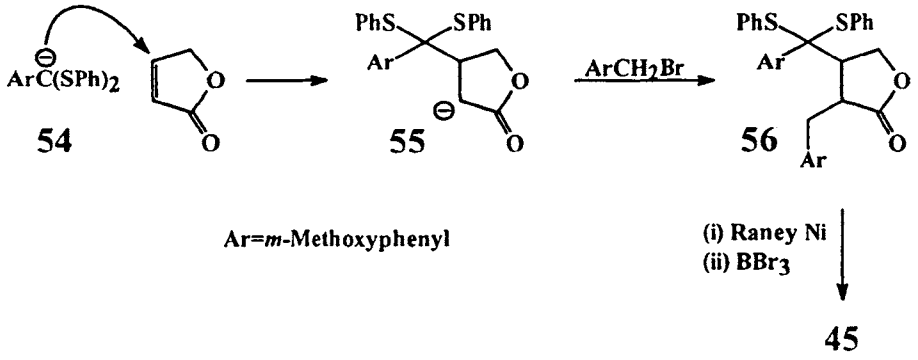
Scheme 10.



been applied to a preparation of enterolactone (45) (52) (Scheme 11). Thus the anion of *m*-methoxybenzaldehyde phenylthioacetal (54) added in Michael fashion to butenolide and the product (55) trapped by *m*-methoxybenzyl bromide to produce enterolactone dimethyl ether (56), which on Raney nickel desulfurisation and demethylation with boron tribromide (53) yielded (45).

A measure of the interest in the biological activity of these dibenzylbutyrolactone lignans is evinced in the recent spate of publications dealing with the total synthesis of the natural optically active products. Again, the Stobbe condensation pathway (Scheme 9) has been usefully exploited for this purpose. In a series of papers, resolution of the intermediate hemisuccinate esters (43) by chiral bases has been described (54), as has asymmetric hydrogenation (55), and the optically active lignan products synthesized in the usual way (43 → 44 → 45).

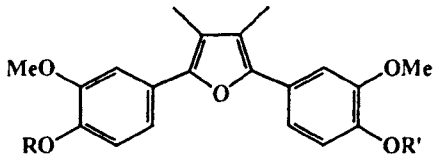
Scheme 11. Tandem Conjugate Addition Route to Enterolactone



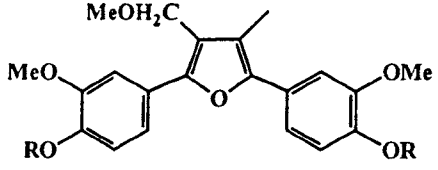
Other methods of preparation and diastereoselective alkylation of chiral butyrolactones (44) are summarized in the recent review of asymmetric synthesis of lignans (16).

C. FURANS

Numerically, this lignan class is presently the least significant, and all known members have been isolated from tne same source, the heartwood of *Guaiacum officinale*. Originally (56) furoguaiacin (57) (also known as α-guaiaconic acid) (57) was isolated as the dimethyl ether derivative (58) and methylfuroguaiacin (59) was isolated as the ethyl ether (60). Later (58), from a more polar extract, furoguaiacidin



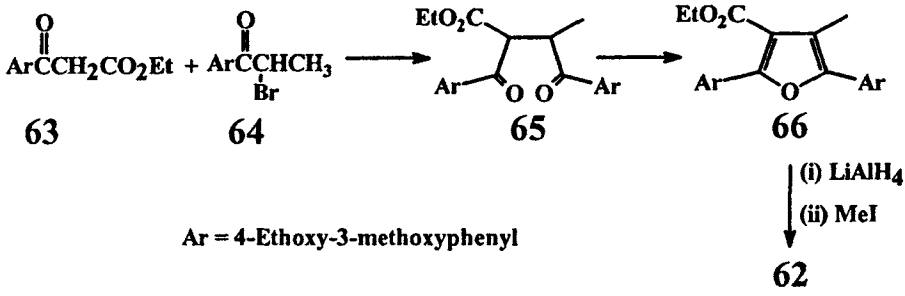
57 R=R'=H
58 R=R'=Me
59 R=Me, R'=H
60 R=Me, R'=Et



61 R=H
62 R=Et

(61) was isolated as the diethyl ether (62). These compounds are clearly amenable to synthesis by the standard furan heterocycle construction procedures. A synthesis of furoguaiacidin diethyl ether (62) is outlined in Scheme 12 (59). Alkylation of the β-keto ester (63) with the α-bromopropiophenone (64) yielded the diketo ester (65) which was converted to the furan (66) by acid-catalyzed dehydration. Reduction of (66) with lithium aluminium hydride, and methylation of the resultant alcohol yielded (62).

Scheme 12. Synthesis of Furoguaiacidin Diethyl Ether (62)



63 64 65 66 62

Ar = 4-Ethoxy-3-methoxyphenyl

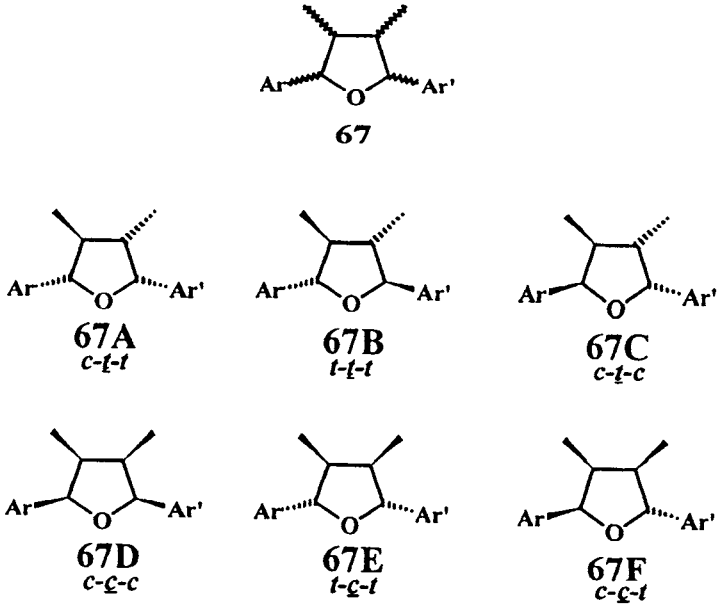
D. TETRAHYDROFURANS

a. 2,5-Bisaryltetrahydrofurans

When a review of this class appeared in 1987, there were 24 natural members listed (60). Well over double this number of compounds of reasonably established constitution are now known.

As represented by the generic formula (67), with the exception of a few members which bear hydroxymethyl groups at C-3 or C-3 and -4, R = R′ = CH_3 in all natural products of this group. This allows for six diastereomers, represented here as three 3,4-*trans*-dimethyl (68 A,B,C) and three 3,4-*cis*-dimethyl (68 D,E,F) tetrahydrofurans. In the common situation in which R = R′ = CH_3 and Ar = Ar′, ten stereoisomers may exist, consisting of diastereomeric pairs (A,B,C,F and their enantiomers) and two meso forms (D,E) (Scheme 13). Where Ar = Ar′ = 3,4-dimethoxyphenyl, all are now known and the trivial names, veraguensin (67A), galbelgin (67B), saucernetin (67C), tetrahydrofuroguaiacin B (67D), galgavin (67E) and ganschisandrin (67F) assigned.

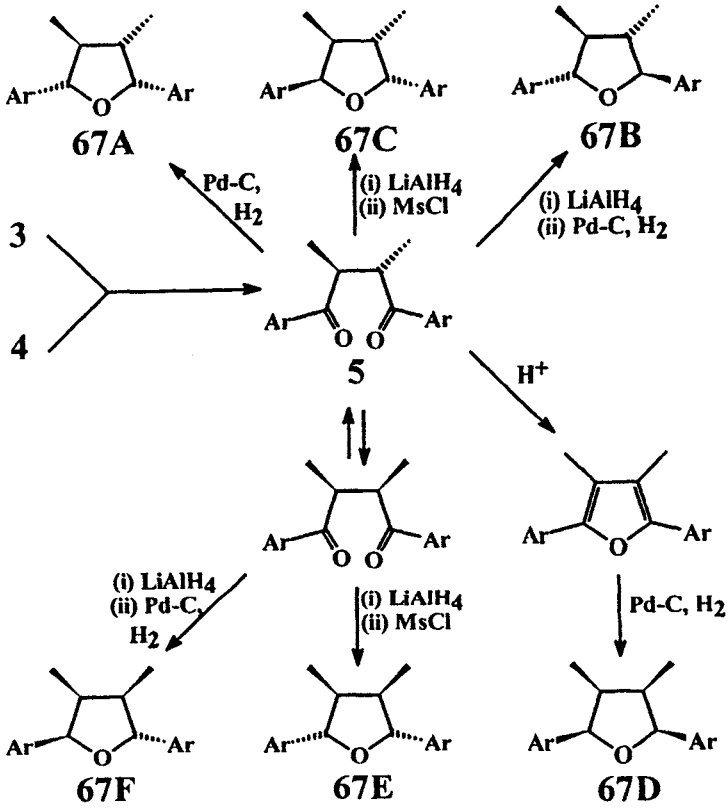
Scheme 13.



This lignan group gained significance in providing a lead in the development of potent platelet-activating factor antagonists. Platelet-activating factor (PAF) is a highly potent phospholipid found in a variety of cells (platelets, basophils, neutrophils, eosinophils, mast cells, endothelial cells, macrophages) implicated in inflammatory processes and eliciting biological response by interaction with specific receptors. It has become increasingly likely that PAF has multiple effects which may be relevant in many human diseases, and enormous recent activity in studying these effects has been an anticipated consequence. Much diverse information on these topics is now available in multi-author books or lengthy reviews (e.g., 61-65). To gauge the effect of PAF in a wide range of pathophysiological states and to develop drugs for use in human disease, an extensive search has ensued, particularly in major pharmaceutical company laboratories, to identify PAF antagonists. A screening programme initiated by the Merck Research Laboratory based upon an assay measuring the inhibition of binding of [^{3}H] PAF to rabbit platelet membrane preparations (66) revealed in 1982 that (±)-veraguensin (67A) (67) was a potent PAF antagonist. The natural product (+)-veraguensin was first isolated from the Mexican

tree *Ocotea veraguensis* Mez. (Lauraceae) (68). This discovery led to the preparation (67,69-73) and inhibitor assay of all veraguensin stereoisomers. It was concluded that the all-*cis* isomer (67D) was in fact the most potent antagonist of this group (72). The six isomers required for assay were prepared (72) as summarized in Scheme 14.

Scheme 14.

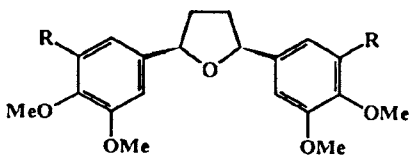


Ar=3,4-Dimethoxyphenyl

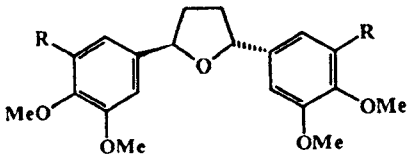
In assay of the four 3,4-*bisnor* analogues (68-71) of these lignan tetrahydrofurans, it emerged that *trans*-2,5-bis(3,4,5-trimethoxyphenyl) tetrahydrofuran (L-652,731) (71) was the most potent of all ten compounds tested (Scheme 15).

Further chemical elaboration led to (±)-*trans*-2-(3-methoxy-5-methylsulfonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl) tetrahydrofuran (L-659,989) (72) (74), which was biochemically and pharmacologically characterized (75), and also obtained

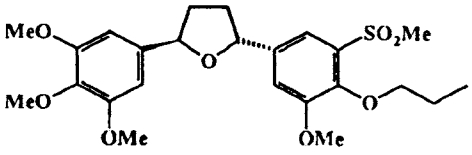
Scheme 15. Tetrahydrofuran PAF Antagonists



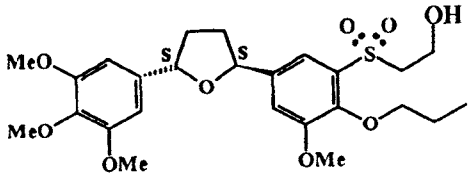
68, R=H
69, R=OMe



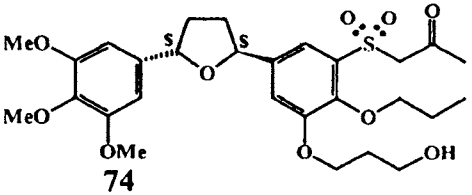
70, R=H
71, R=OMe (L-652,731)



72 (L-659,989)



73 (MK 287)

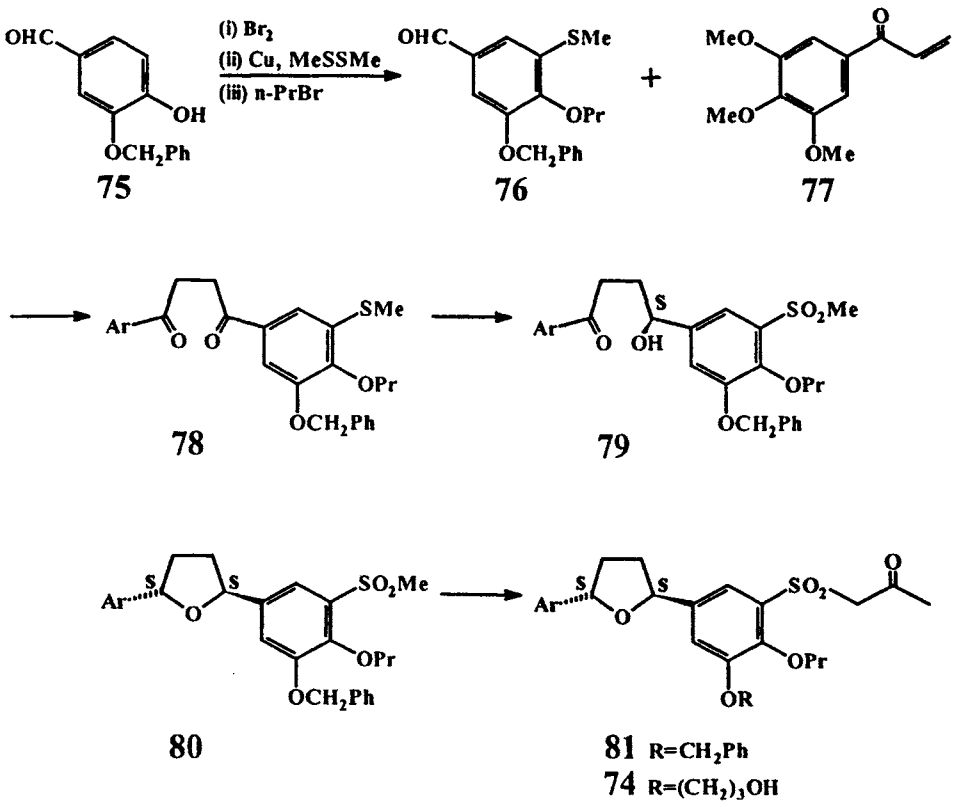


74

in both optically active forms (76,77). In order to achieve improved metabolic stability and pharmacokinetic profile, polar group modifications were investigated, from which the (-)-2S,5S-*trans*-isomer of MK287 (73) emerged as a potent, specific and orally active PAF receptor antagonist, and chosen for clinical trial for asthma (78). Most recently, the development of (-)-*trans*-(2S,5S)-2-[3-(2-oxopropyl)sulfonyl]-4-*n*-propoxy-5-(3-hydroxypropoxy) phenyl-5-(3,4,5-trimethoxy-phenyl) tetrahydrofuran (74) with further improvement of *in vivo* potency and drug characteristics has been described (79). The synthesis of this "third generation tetrahydrofuran derivative" is outlined in Scheme 16.

In each of these diaryltetrahydrofuran syntheses, the significant starting material was a diarylbutane-1,4-dione, conveniently prepared by the Stetter reaction involving catalyzed addition of an aldehyde to an activated alkene (80). 3-Benzyloxy-4-hydroxybenzaldehyde (75) was converted to 3-(methylthio)-4-*n*-propoxy-5-(benzyloxy)benzaldehyde (76) by three standard steps and reacted with 3,4,5-

Scheme 16. Synthesis of 74

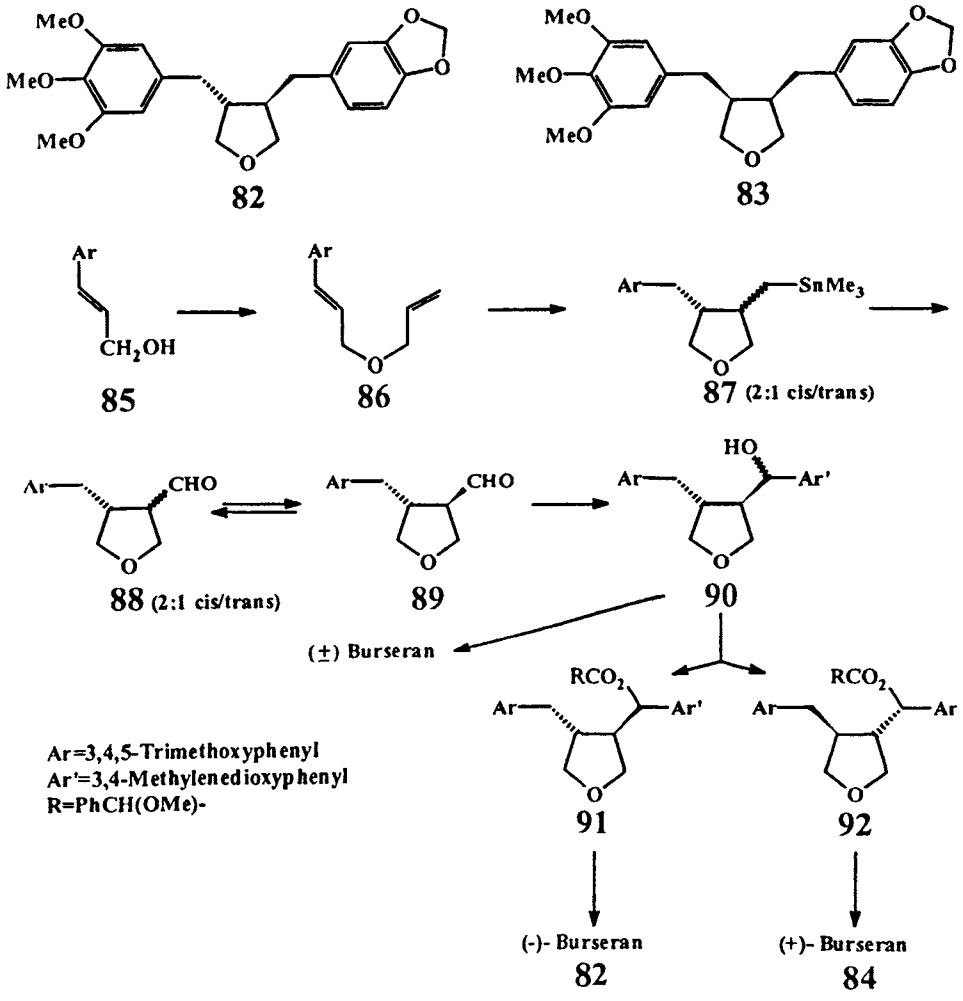


trimethoxyphenyl vinyl ketone (77) under Stetter conditions to yield the diketone (78). Oxidation of (78) with *m*-chloroperbenzoic acid and reduction with the chiral reducing agent S-BINAL-H (81) in a regio- and enantioselective manner yielded the S-alcohol (79). Reduction of (79) with sodium borohydride andcyclization with trifluoroacetic acid gave chirally pure *trans*-(80) and the *cis*-isomer, which could be equilibrated under acid conditions to increase the yield of (80). A three step sequence completed the synthesis of 74. The methylsulfone anion of (80) with ethyl acetate gave the ketosulfone (81) which on hydrogenolytic debenzylation and re-alkylation with 3-bromopropanol yielded (74). The preparation of a water-soluble phosphate ester pro-drug derivative equipotent to (74) *in vivo* was also disclosed.

b. 3,4-Bisbenzyltetrahydrofurans

This is the smallest group of lignan tetrahydrofurans with fewer than ten members. All of reasonably well defined constitution are 3,4-*trans*-disubstituted. Of these, most attention has been directed towards burseran, a constituent of *Bursera microphylla* with tumour-inhibiting properties (82). Optically pure (-)-*trans*-burseran (**82**) and (+)-*cis*-burseran (**83**) were stereoselectively synthesized from chiral butyrolactones and gas chromatographic comparison indicated that the natural

Scheme 17. Synthesis of (+)- and (-)- Burseran



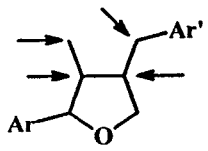
anti-tumour lignan is the *trans* isomer (83,84). An interesting coupling reaction pathway to (±)-burseran has been devised (85) and routes to both (-)-burseran (82) and (+)-burseran (84) have recently been described (86,87). The latter, in which a radical-mediated carbocyclization is the key step, is outlined in Scheme 17.

Allylation of 3,4,5-trimethoxycinnamyl alcohol (85) gave the diene (86), which underwent cyclization on radical stannylation (88) to yield (87). A selective oxidative cleavage of the trimethylstannyl group of (87) with ceric ammonium nitrate gave the aldehyde mixture (88) with same stereochemical ratio. The *trans*-isomer (89), obtained in high excess (>23:1) after equilibration was treated with 3,4-methylenedioxyphenyllithium to give the separable epimeric adducts (90). Resolution of (90) with (S)-O-methylmandelic acid gave the diastereomeric esters (91) and (92), which were separately hydrogenolyzed to give (-)-burseran (82) and (+)-burseran (84) respectively.

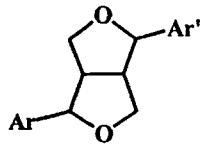
c. 2-Aryl-3-methyl-4-benzyltetrahydrofurans

At this time, there are known about 30 members of this sub-class (93) which

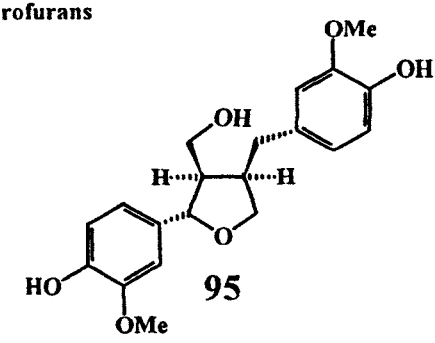
Scheme 18. 2-Aryl-3-methyl-4-benzyltetrahydrofurans



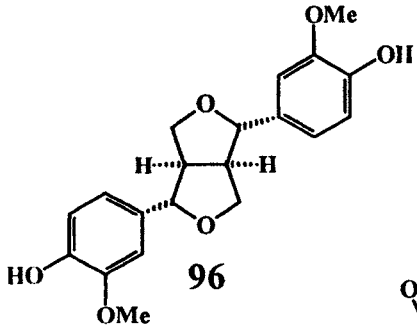
93



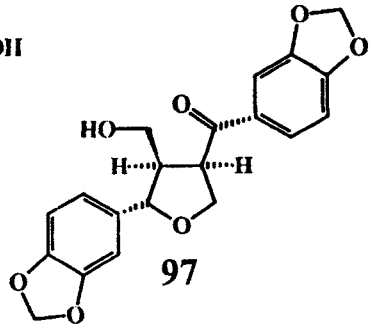
94



95



96



97

bears a close structural resemblance to the furofuran group (**94**) (Scheme 18). A close biogenetic correspondence may also be presumed from the observations that in the natural tetrahydrofurans the C-3 substituent is almost invariably a hydroxymethyl group and that the C-3 and C-4 substituents have a *cis*-relationship. As a comparison, (+)-lariciresinol (**95**), an extract of the resinous exudate of the European larch (*Larix decidua*) is seen as a dihydro-derivative of (+)-pinoresinol (**96**) which displays inhibitory activity against cyclic adenosine monophosphate phosphodiesterase (89). Little attention has been devoted to syntheses of this class *per se* but preparations by benzylic hydrogenolysis (Pd/H_2 or $NaNH_3$) of suitable furofurans (e.g., (**96**) → (**95**)) are well known (90-91).

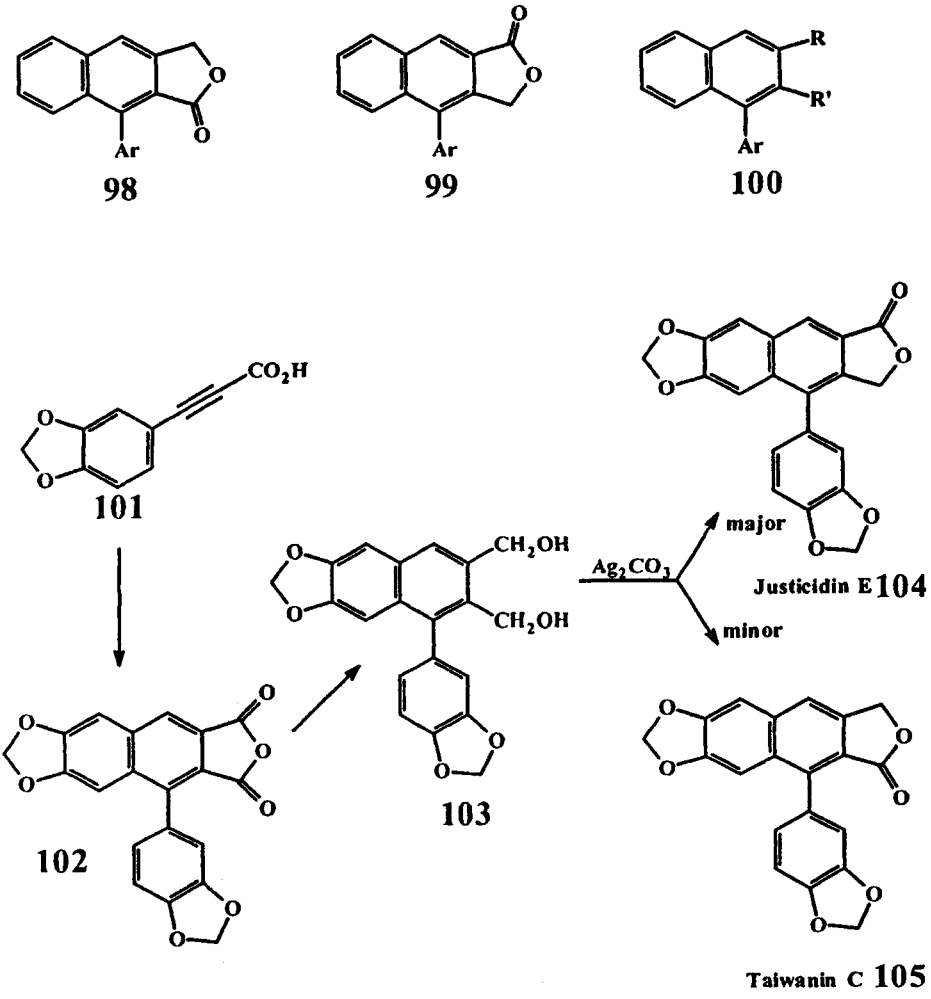
The principal substituent variations found naturally are hydroxyl functions (at locations denoted by arrows in (**93**)) or benzylic ketone groups as in (+)-arborone (**97**), isolated from the heartwood of *Gmelina arborea* (92).

E. ARYLNAPHTHALENES

This group of over 40 known natural members can be conveniently subdivided on a structure basis into naphthalene-2-carboxylic acid lactones ("down" lactones) (**98**), naphthalene-3-carboxylic acid lactones ("up" lactones) (**99**) and non-lactonic naphthalenes (**100**). In this last group, in the most common situation, R = R′ = Me, but examples are known in which R and R′ are hydroxymethyl groups or amide groups. Additionally R′ may be -CHO, $-CO_2H$ or H. Although there were numerous structure mis-assignments made in the early literature and ultimately corrected by unambiguous synthesis, proton magnetic resonance spectra determination has enormously simplified constitution assignment (93).

A convenient route to lignans of this class is apparent from the known transformation of the phenylpropiolic acid to the anhydride of phenylnaphthalene-2,3-dicarboxylic acid by the action of acetic anhydride (Scheme 19). This reaction was discovered about a century ago (94); the interesting early history has been briefly reviewed (95) and a wide generality of the reaction demonstrated (96). It is particularly useful for products bearing identical substituents in rings A and C. Thus, it has been long known that 3,4-methylenedioxyphenylpropiolic acid (**101**) on

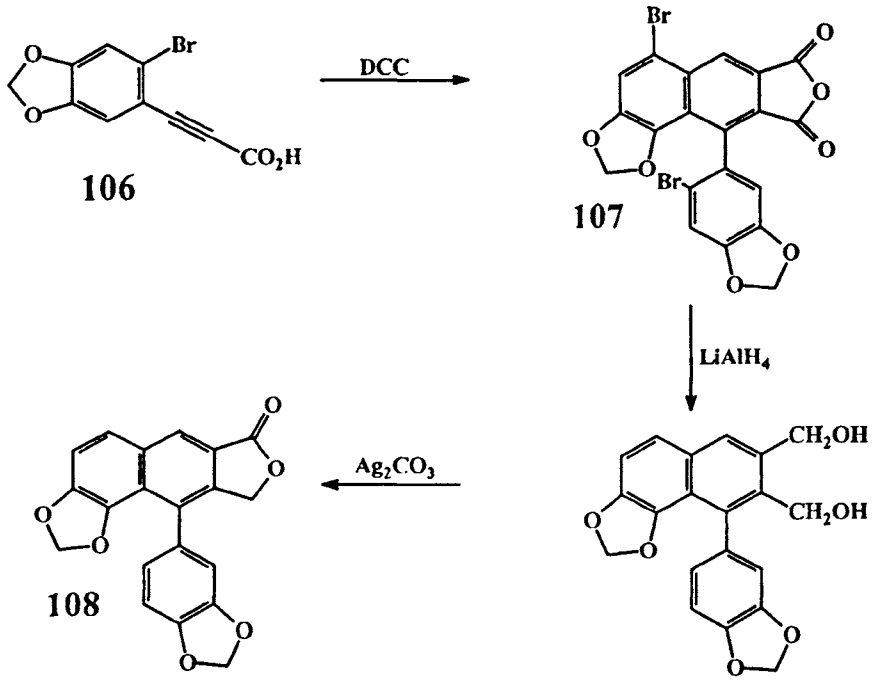
Scheme 19. Arylnaphthalene Lignans : Lactone Synthesis



heating with acetic anhydride yields the anhydride (**102**) (97). Reduction with lithium aluminium hydride and oxidation of the resultant diol (**103**) with Fétizon's reagent yielded both lactones, justicidin E (**104**), a piscicidal constituent of *Justicia procumbens*, and taiwanin C (**105**) which had been isolated from *Taiwania cryptomeroides* (93). As anticipated, oxidation occurred with high stereoselectivity of the less hindered hydroxymethyl group (**104**:**105**, *ca* 4:1). A shorter procedure, which yields both lactone products with the opposite stereoselective outcome consists of direct reduction of anhydride with sodium borohydride (98).

When 2-bromo-4,5-methylenedioxyphenylpropiolic acid (106) failed, on heating with acetic anhydride, to yield the desired intramolecular cyclized anhydride (107), the problem was overcome by the use of dicyclohexylcarbodiimide in dimethoxyethane solution below 0° (99,100). The product (107) was subsequently used (101,102) as an intermediate for the synthesis of helioxanthin (108) (Scheme 20) which had been isolated and identified as a constituent of *Heliopsis helianthoides* (103,104).

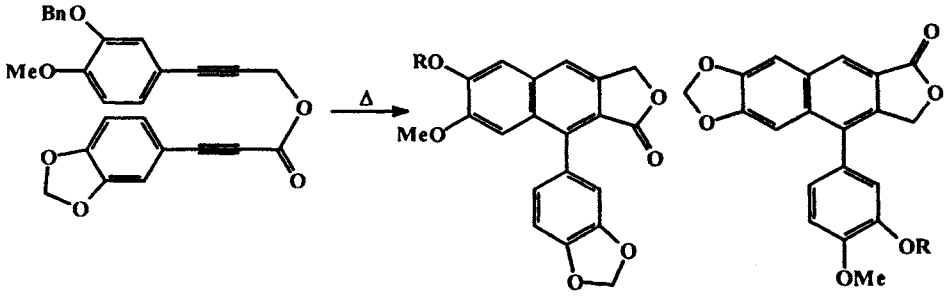
Scheme 20. Synthesis of Helioxanthin



In a series of papers under the rubric of Intramolecular Diels-Alder Reactions during 1963-1976, the cyclization *inter alia* of phenylpropargyl phenylpropiolate esters, i.e., functionality designed to produce arylnaphthalene lactones essentially in one step, was extensively examined (105). With the aryl rings differently substituted by the common substituents, there is little regioselectivity in the cyclization step. A

useful application is the recently reported synthesis (106) (Scheme 21) of the natural lactones, daurinol (**112**) and retrochinensin (**113**). The former, a constituent of *Haplophyllum dauricum* (107-109), bears in ring A the isovanillyl fragment; this is extremely rare among lignans and in some cases is based on equivocal evidence. The latter was first isolated as a constituent from an anti-depressant extract from *Justicia prostata* (110). By heating the di-ynic ester (**109**) in xylenes, the lactones (**110**) and (**111**) were obtained and separated. Debenzylation of (**110**) by a catalytic hydrogenation procedure (111) gave daurinol (**112**). Similar debenzylation of (**111**) followed by methylation of the resultant phenol yielded retrochinensin (**113**).

Scheme 21. Synthesis of Daurinol and Retrochinensin



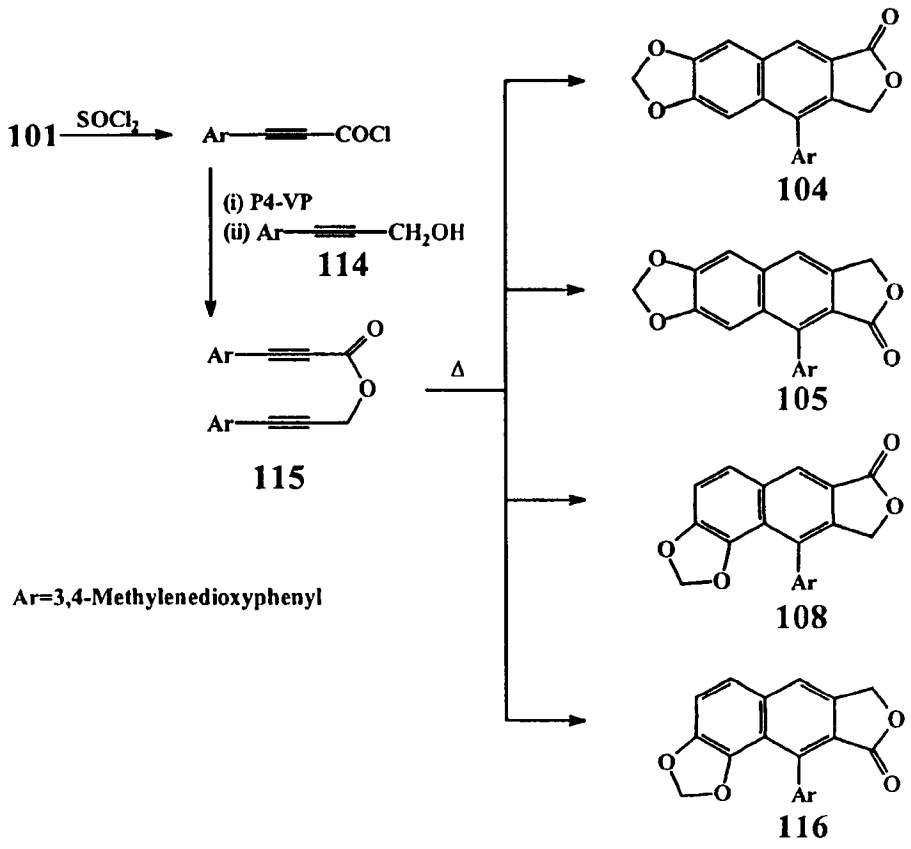
109

110 R=Bn
112 R=H

111 R=Bn
113 R=Me

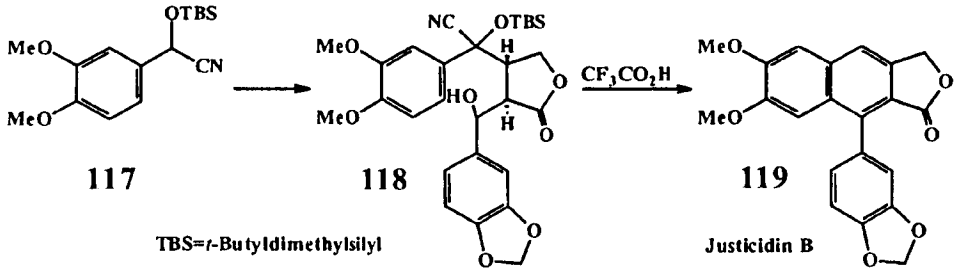
The overall modest yields achieved in these syntheses have recently been markedly improved by the use of the solid-phase copolymer of 4-vinylpyridine (P4-VP) (112) in the formation of the starting di-ynic esters. For example, when a suspension of P4-VP polymer in dichloromethane was stirred with the acid chloride from (**101**) and then the propargyl alcohol (**114**), the ester (**115**) was obtained excellent yield. By heating in xylene, (**115**) underwent intramolecular cyclization to yield justicidin E(**104**) and taiwanin C(**105**) as the major products; in addition, the isomers helioxanthin (**108**) and retrohelioxanthin (**116**) could also be isolated (Scheme 22) (113). Increased interest in these four lactone products has resulted from an assay which indicates 5-lipoxygenase inhibitory activity (114).

Scheme 22. Intramolecular Cyclization of Arylpropargyl Arylpropiolate Esters



A general two-step synthesis of arylnaphthalenes from O-*t*-butyldimethylsilylcyanohydrins involving a tandem conjugate addition-aldol reaction, followed by

Scheme 23.

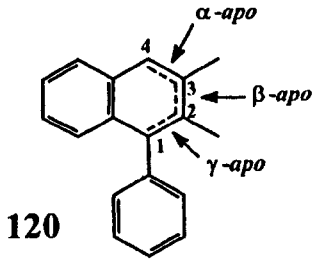


acid-catalyzed construction of the naphthalene ring has recently been described (115) and an example shown in Scheme 23. The known *t*-butyldimethylsilylcyanohydrin (117) derived from veratraldehyde gave on successive treatment with lithium diisopropylamide, 2-butenolide and piperonal the butyrolactone(118), which on refluxing with trifluoracetic acid gave the natural lactone, justicidin B (119).

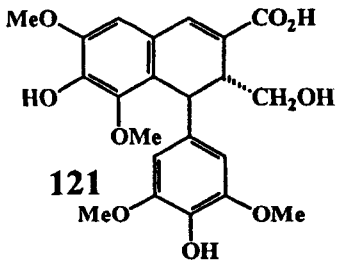
F. ARYLDIHYDRONAPHTHALENES

About 14 natural compounds of this lignan sub-class are known, among which are examples of 1,2-dihydro, 1,4-dihydro and 3,4-dihydro-1-arylnaphthalenes. The double bond locations are also designated as *α-apo*, *β-apo* and *γ-apo* respectively

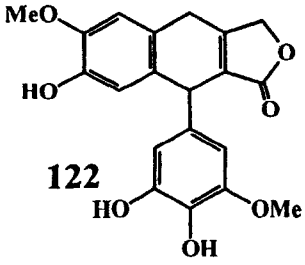
Scheme 24. Aryldihydronaphthalene Lignans



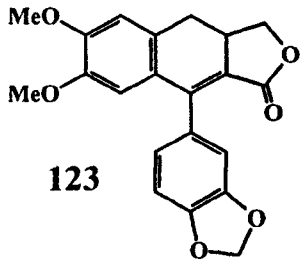
120



121



122



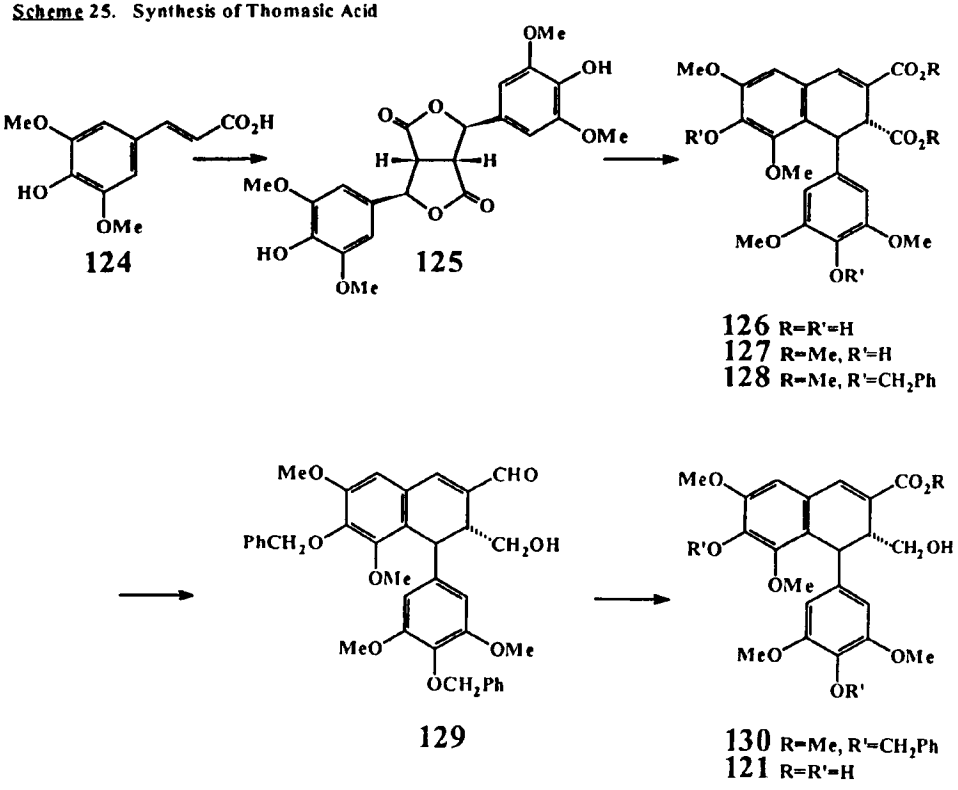
123

(120) (Scheme 24). A representative of each group is thomasic acid (121), an extractive of the heartwood of *Ulmus thomasii* Sarg. ("rock elm") (116), β-*apo*plicatitoxin (122) from *Thuja plicata Donn.* (Western Red Cedar) (117), and collinusin (123) from the leaves of *Cleistanthus collinus* (118).

a. 1,2-Dihydro-1-arylnaphthalene Lignans

The structure (121) of thomasic acid was established by extensive spectroscopic and chemical degradation studies (116,119,120) and presents several interesting features. It is one of the few lignans occurring naturally in racemic form and in possessing a free carboxyl group. In addition, the *trans* vicinal substituents (at C-1,2) adopt a diaxial conformation. The synthesis of this product (Scheme 25) was

Scheme 25. Synthesis of Thomasic Acid



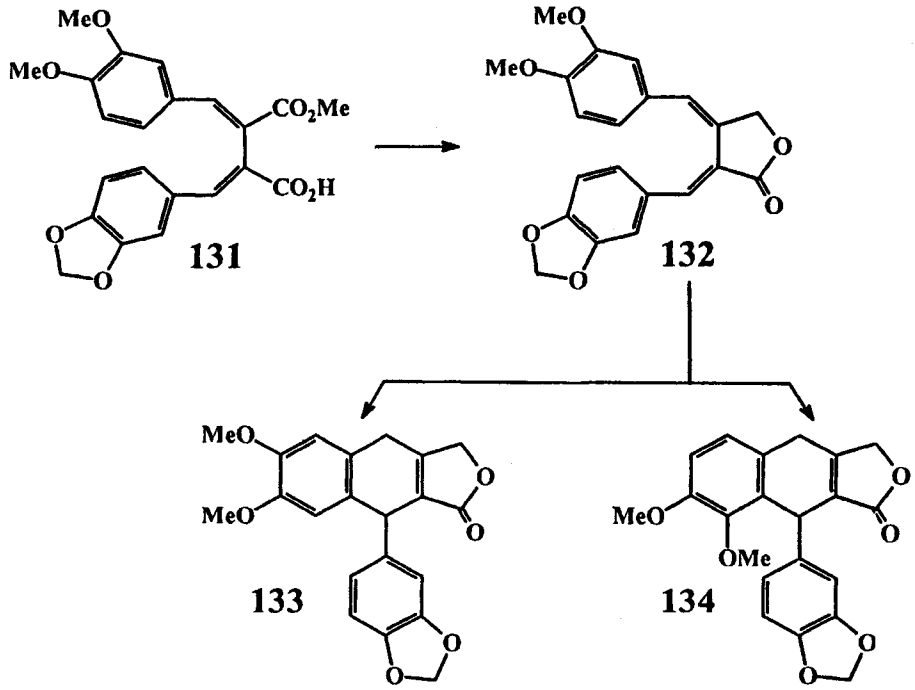
based on biomimetic speculation (121). Phenolic oxidation of sinapic acid (124) gave the dilactone (125) (122), which with hydrochloric acid in aqueous dioxan gave the

congener, thomasidioic acid (126); similar treatment in methanol gave the dimethyl ester (127). Reduction of the dibenzyl ether (128) with lithium aluminium hydride followed by selective allylic oxidation with manganese dioxide yielded the aldehyde (129). The aldehyde function was selectively oxidized in the presence of the primary alcohol function (123) to give the methyl ester (130) which on standard debenzylation and hydrolysis produced thomasic acid (121).

b. β-Apolignans

A significant synthesis pathway for such products (Scheme 26) involves specific photoconversion of 2,3-dibenzylidene-butyrolactones, usually prepared by Stobbe

Scheme 26. β-Apolignans



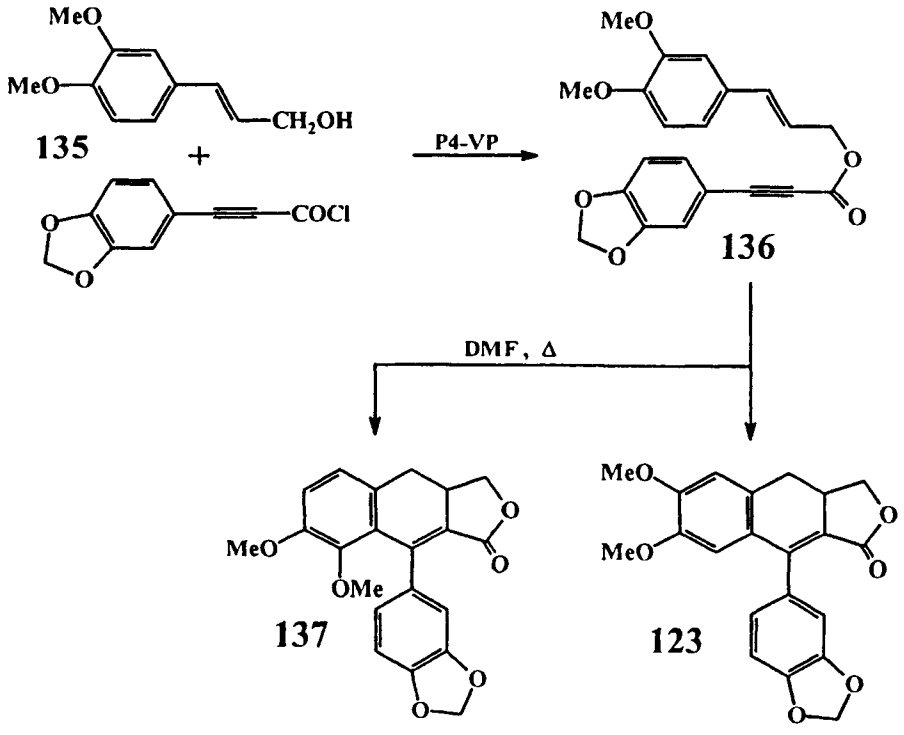
condensation methods (124). For example, condensation of dimethyl piperonylidenesuccinate with veratraldehyde gave the half ester (131), which on selective reduction ($LiAlH_4$ at -25°) followed by acidification yielded the lactone (132). Photoirradiation (light filtered through borosilicate glass) of (132) gave a

mixture from which the β-*apo*lignans (**133**, 56% yield) and (**134**, 28% yield) were isolated. Of further interest, air oxidation of β-*apo*lignans provides an additional pathway to the corresponding arylnaphthalene and 4-hydroxyarylnaphthalene lactones.

c. γ-*Apo*lignans

The γ-*apo*lignan, collinusin (**123**) was isolated from *Cleistanthus collinus*, a highly poisonous plant reportedly used for insecticidal, piscicidal and suicidal purposes (125). Unlike the cyclization of arylpropargyl arylpropiolates which proceeds with little regioselectivity, cinnamyl arylpropiolates give aryldihydronaphthalene-2-carboxylic acid lactones with excellent regioselectivity (105). A synthesis of collinusin (**123**) using this method (126) has recently been markedly improved (127) (Scheme 27). Polymer (P4-VP)-mediated esterification

Scheme 27.



of 3,4-methylenedioxypropiolyl chloride with 3,4-dimethoxycinnamyl alcohol (**135**) gave the ester (**136**) in 89% yield, which on heating in dimethylformamide gave collinusin (**123**) in 84% yield and the isomer (**137**) in 5% yield. Excellent agreement in the spectroscopic data indicates that the latter is one of the lignans isolated from the tumor-inhibiting extract of *Polygala polygama* (128,129) which had previously been considered to have the *β-apo*polygamatin structure (**134**).

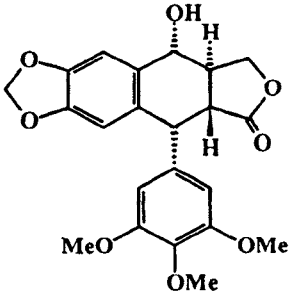
G. ARYLTETRALINS

About 90 aryltetralin lignans are presently known of which one, podophyllotoxin (**138**), may be claimed to have generated most interest within the entire lignan field. Podophyllum is the name given to the dried roots and rhizomes derived commercially from *Podophyllum peltatum* L. (a North American plant known variously as "May apple," "American mandrake," "Indian apple," "wild lemon," "duck's foot" and vegetable calomel) and *Podophyllum emodi* Wall. (a related Indian species). The water-insoluble alcohol-soluble fraction of podophyllum possesses most of the recognized biological activity of the original root and is referred to as podophyllum resin or podophyllin. The early history incorporating medicinal attributes is available in intriguing reviews (130,131). The isolation of podophyllotoxin from the resin is usually dated to 1880 (132) with structure elucidation being completed in 1951, after particularly notable contributions from Borsche, Späth, Hartwell and their coworkers (for comprehensive review coverage, see references (5) and (131)). The first pioneering classical total synthesis of (±)-podophyllotoxin was communicated in 1962 (133) with experimental details being provided in 1966 (134).

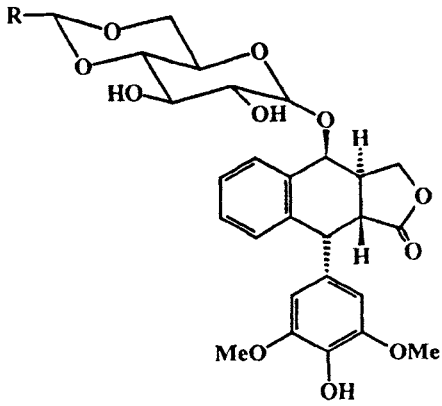
The anti-neoplastic activity of podophyllotoxin and derivatives has prompted continuous development into clinical agents for treatment of human neoplasia. The semi-synthetic 4′-demethylepipodophyllotoxin derivatives, Etoposide (**139**) and Teniposide (**140**), developed by a Sandoz (Basel) group have attracted considerable attention (135-137) (Scheme 28). They have established antitumour activity with lesser toxicity and mechanism of action differing from podophylloxin itself.

Enormous activity has been exerted dealing with syntheses of podophyllotoxin and the related diastereomeric forms (Scheme 29) and a masterly summarizing review

Scheme 28.



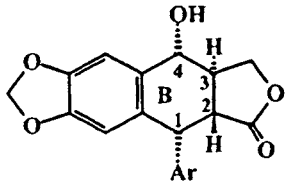
138



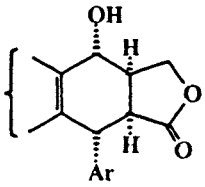
139 R=CH_3 Etoposide (VP-16-213)

140 R=  Teniposide (VM-26)

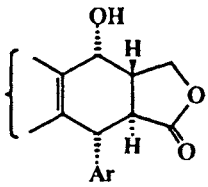
Scheme 29. Podophyllotoxin and Diastereomers



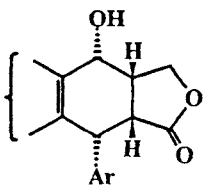
Podophyllotoxin



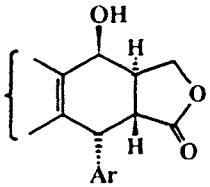
Picropodophyllin



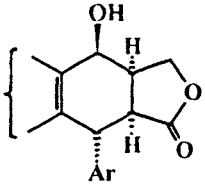
Epiiso-podophyllotoxin



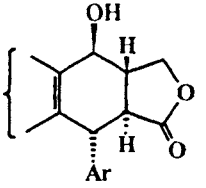
Epiiso-picropodophyllin



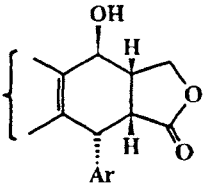
Epipodophyllotoxin



Epipicropodophyllin



Isopodophyllotoxin



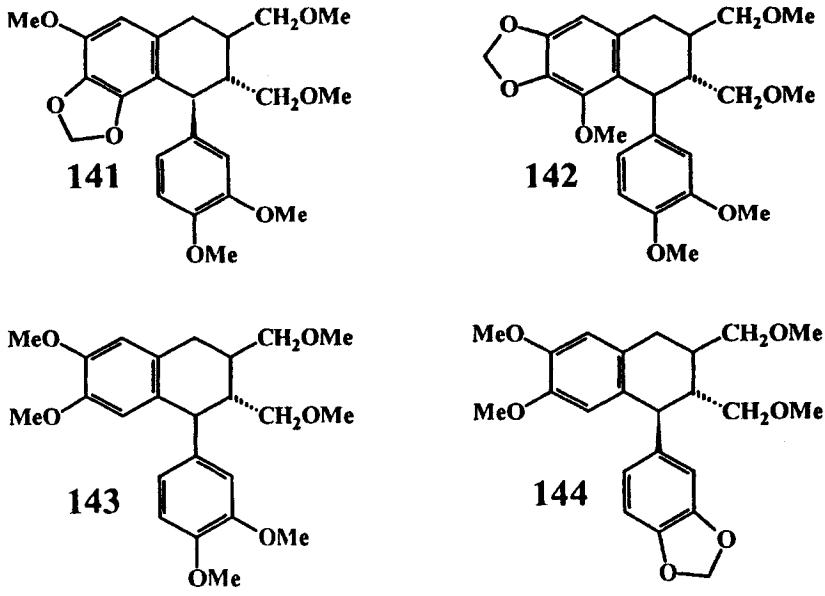
Isopicropodophyllin

Ar = 3,4,5-Trimethoxyphenyl

has just appeared (138). A paper encompassing a comprehensive route to all eight diastereomeric *Podophyllum* lignans is particularly worthy of attention (139).

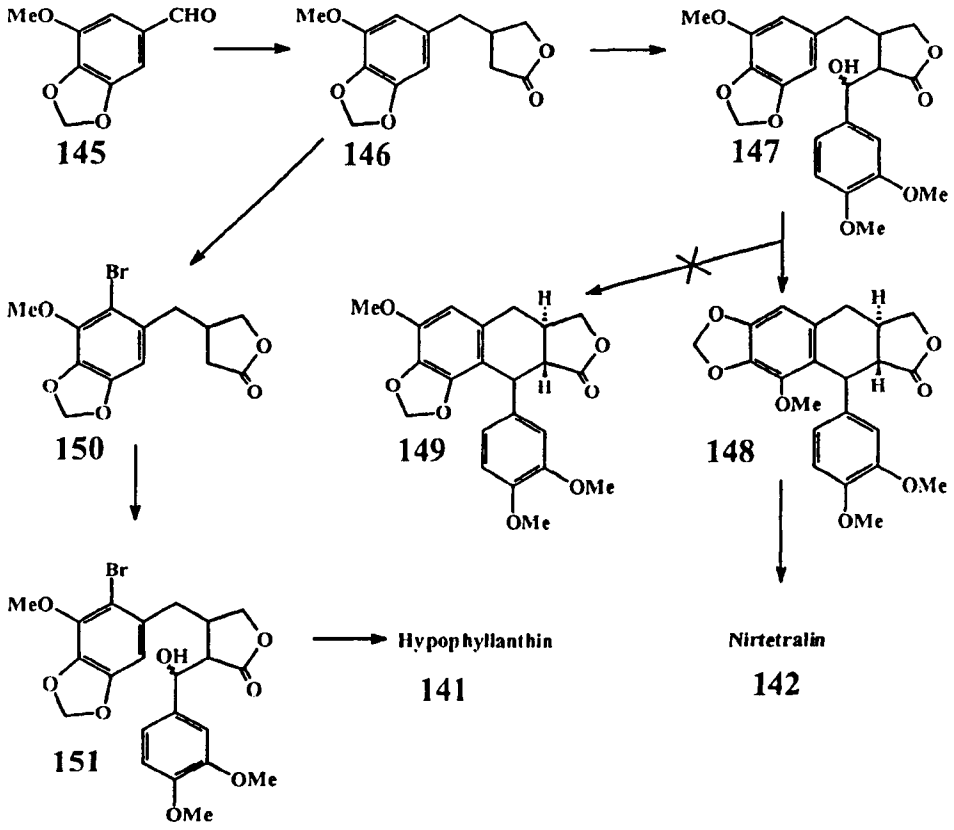
In certain cases, structure elucidation of aryltetralin lignans has only been established by total synthesis of the (±)-compounds. Noteworthy in this respect have been the constituents of *Phyllanthus niruri* Linn. (Euphorbiaceae), extracts of which have been used medicinally (in treatment of asthma, jaundice and bronchial infections) (140). Considerable confusion resulted mainly from differing interpretations of spectroscopic data, and at least five different structures were proposed for the major constituent, hypophyllanthin. The structure of the aryltetralin constituents established by unequivocal synthesis (141) are shown in Scheme 30: they were given the names hypophyllanthin (**141**), nirtetralin (**142**), phyltetralin (**143**) and lintetralin (**144**).

Scheme 30. Aryltetralin Lignans of *Phyllanthus niruri*



Related syntheses of (**141**) and (**142**) are outlined in Scheme 31. The starting aldehyde (**145**) (142) was converted by now standard procedures to the benzylic butyrolactone (**146**) and thence to the mixture of epimeric alcohols (**147**). Acid-

Scheme 31. Synthesis of Hypophyllanthin and Nirtetralin



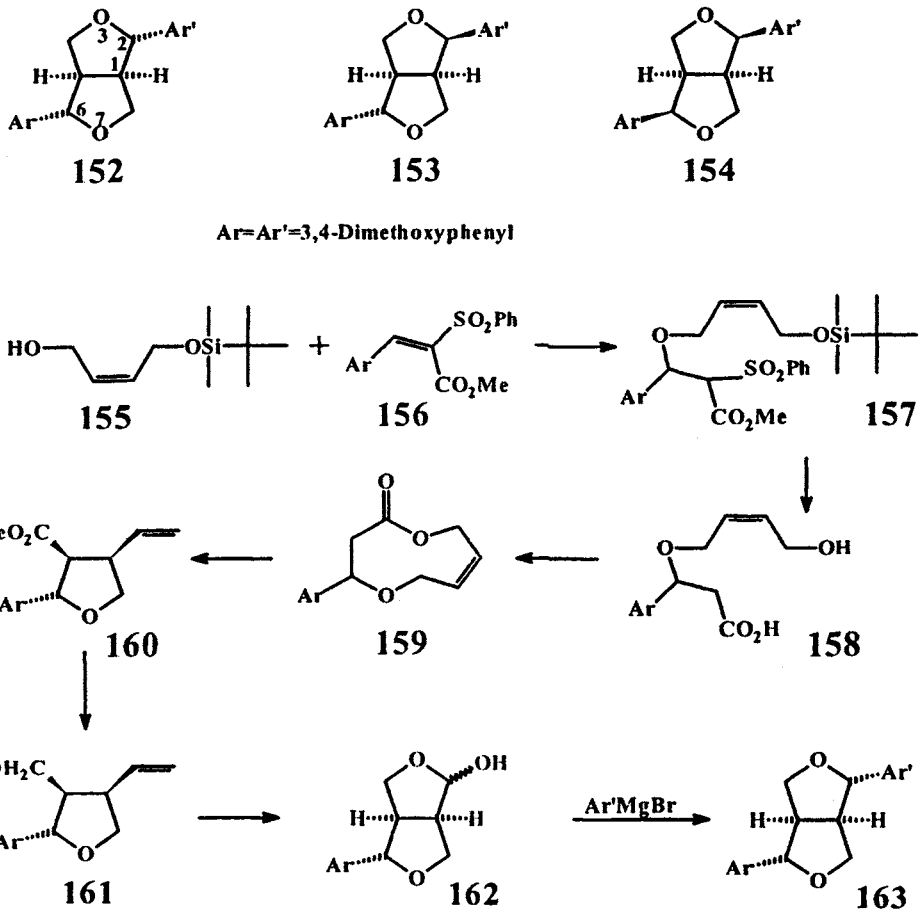
aluminium hydride reduction of (**148**) and methylation of the resultant diol gave (±)-nirtetralin (**142**). Bromination of (**146**) proceeded as expected (electrophilic substitution *ortho-* to the methoxyl substituent) to produce (**150**) which by the same procedures *via* (**151**) gave (±)-hypophyllanthin (**141**) (143). The same general pathway provided (±)-phyltetralin (**143**) and (±)-lintetralin (**144**) (144).

H. TETRAHYDROFUROFURANS

This lignan sub-class of 2,6-diaryl-3,7-dioxabicyclo[3,3,0]octanes, is one of the largest and most widely distributed groups. About 100 members are known, if natural glycoside derivatives are included. As expected, the five-membered heterocyclic rings are constrained in *cis* fusion. When the aryl groups are identically

substituted, three distinct stereochemical series are possible and well established. Representatives are eudesmin (**152**) (most stable with "equatorial" aryl groups), *epi*eudesmin (**153**) (of lesser stability with one "equatorial" and one "axial" aryl group) and *dia*eudesmin (**154**) (of least stability with two "axial" aryl groups). They may undergo epimerisation under acidic conditions (145). Principal structural group variation within the standard structures are additional hydroxyl groups at one or more of positions 1, 2 and 4.

Scheme 32. Tetrahydrofurofurans



Structure elucidation of the natural tetrahydrofurofurans by chemical methods, particularly hydrogenolytic cleavage of the heterocyclic ring to simpler identifiable moieties has been well reviewed (146,147). Reliable consignment of configuration has now been considerably aided by PMR, CMR and NOE experiments and significant data has been usefully tabulated (148).

The monographs (8,9) also present clear expositions of methods of synthesis. A recent communication addressing a short approach to both symmetrical and unsymmetrical tetrahydrofurofuran lignans is outlined in Scheme 32 (149). Michael addition of the sodium salt of the silyl monoprotected diol (**155**) to the α-sulfonylcinnamate (**156**) gave the ether (**157**) which on desulfurization and hydrolysis gave the hydroxy acid (**158**). Lactonization of (**158**) by the Mukaiyama method (150) to (**159**) was followed by a Claisen rearrangement under specific conditions (151) leading to the tetrahydrofuran (**160**) following esterification. Reduction to the tetrahydrofuranmethanol (**161**) followed by oxidative cleavage of the vinyl group yielded the known (±)-samin (**162**) which with arylmagnesium halide and dehydration gave the lignan structure (**163**). The latter stages of this synthesis scheme had previously been reported (152). An alternative approach to that outlined in Scheme 32, with the aim of ready adaptation to asymmetric synthesis, has been recently reported (153).

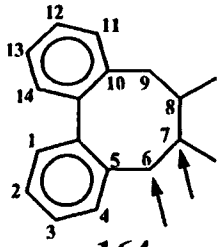
I. DIBENZOCYCLO-OCTADIENES

About 50 members of this class (including esters of natural alcohols) are known; most have been isolated from the fruit, leaves and seeds of *Schizandra* species, extracts of which have long been used in Asia for medicinal purposes. These extracts are the basis of drugs known in China as Wu-Wei-Zi and in Japan as Kita-gomisi. The isolated products are usually denoted by names or variants (including alphabetical letter attachments) of schizandrin, gomisin and wuweizisu. Two other significant sources are *Kadsura* species (with typical product names as kadsurin and kadsuranin) and *Steganotaenia araliaceae* (giving rise to steganes).

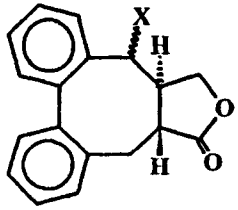
The structurally simplest natural members have phenol, phenolic ether and/or phenolic ester functional groups at C-1,2,3,12,13,14 and methyl groups at C-7 and

8. In addition, alcohol or derived ester functional groups (benzoates, angelates, tiglates) may be located at C-6 and/or C-7 (164) (Scheme 33). The *Steganotaenia* products are modifications with a *trans*-lactone group at C-7 and 8 and alcohol, ester or carbonyl group at C-9 (165).

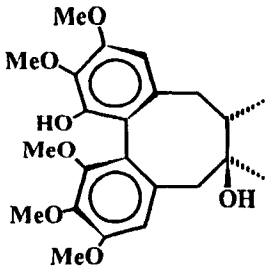
Scheme 33. Dibenzocyclo-octadienes



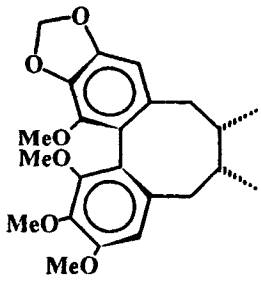
164



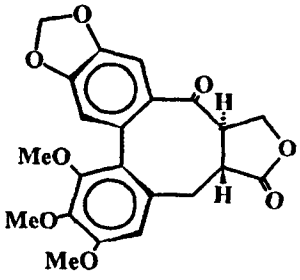
X=-OH, -O-CR, =O 165



166 R-(+)-Gomisin H



167 S-(-)-Gomisin N



168 S-(-)-Steganone

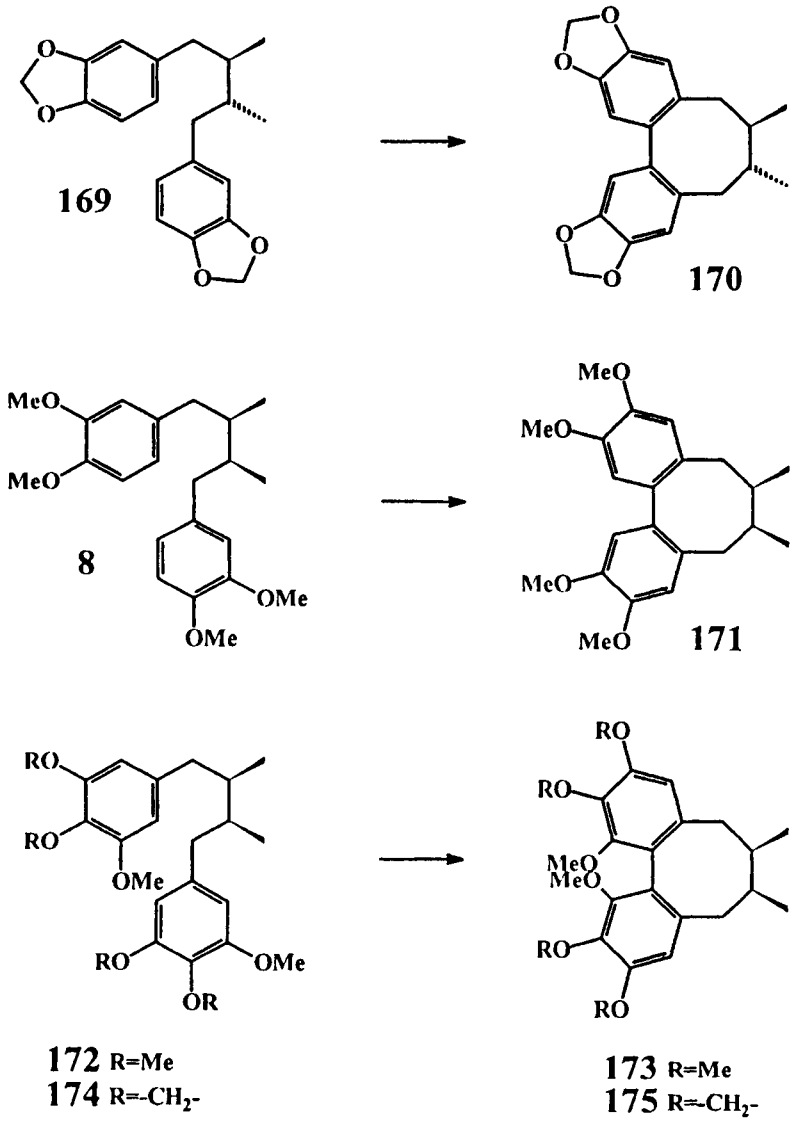
A particularly interesting feature of this lignan sub-class is that the aryl groups, with rotation restricted by locking within the cyclo-octane ring, confer dissymmetry to the molecule. Both R- and S- configurations are well represented in the natural products, e.g., R-(+)-gomisin H (166), S-(-)-gomisin N (167) and S-(-)-steganone (168).

The earliest work on the isolation and structure elucidation was performed by Kochetkov and co-workers (154,155). Particularly noteworthy have been the continuing efforts of Ikeya and Taguchi and their co-workers on the isolation, structure elucidation and absolute configuration determination of the schizandrins and gomisins beginning in 1979 (156). Application of a wide range of techniques (UV,

MS, CD, X-ray crystal analysis, PMR, CMR and NOE difference spectroscopy) used significantly by these workers has been usefully summarized (157).

The use of vanadium oxyfluoride as a reagent for the intramolecular oxidation of non-phenolic substrates (158) provided a convenient synthesis pathway to dibenzocyclo-octadienes (Scheme 34). It was shown that the racemic diarylbutane

Scheme 34.



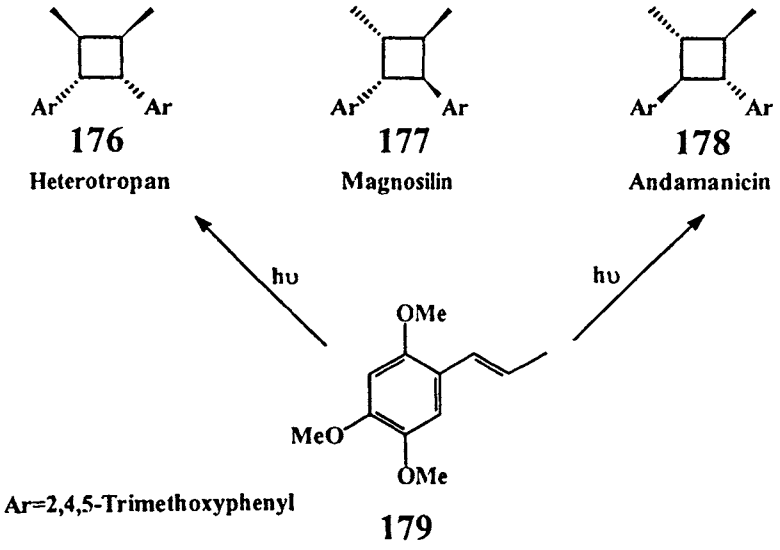
(169) with this reagent gave the *trans*-dimethyl product (170) and the *meso*-analogue (8) give the *cis*-dimethyl analogue (171) (159). With this established, oxidation of the hexamethoxydiaryl-butane (172) with vanadium oxyfluoride in trifluoroacetic acid gave (±)-deoxyschizandrin (173) (159) and similar treatment of (174) gave (±)-wuweizusin C (175) (142). This intramolecular oxidation route is also applicable to the natural lactones from dibenzylbutyrolactones. A variety of alternative oxidants used for the same purpose and including thallium tris(trifluoroacetate) (160), ruthenium tetrakis(trifluoroacetate) (161), bis(trifluoroacetoxy)iodobenzene (162) and ferric perchlorate (163) have subsequently been introduced.

The discovery of antileukemic activity possessed by the lactones isolated from *Steganotaenia araliaceae* (164) has prompted considerable efforts directed towards their synthesis. These have recently been admirably reviewed (165).

J. DIARYLCYCLOBUTANES

All known members of this group have the comparatively rare 2,4,5-trimethoxyphenyl group as the aryl component. Heterotropan (176) was isolated from *Heterotropa takaoi* with the assigned configuration supported by NOE measurements, and was synthesized by photo-dimerization of (E)-asarone (179) (166). A stereoisomer isolated from *Magnolia salicifolia* was named magnosilin and assigned structure (177) (167). Both products were subsequently isolated from the same source, *Piper cubeba* (168). A third stereoisomer, isolated from *Piper sumatranum* var. *andamanica* with the all-*trans* structure (178) was named andamanicin, and also obtained from the complex mixture obtained from irradiation of (179) (169) (Scheme 35). Acoradin (from *Acorus calamus*) (170) and bisasaricin (from *Acorus gramineus*) (171) have been reported as diarylcyclobutanes, but with unassigned configurations. Although this subclass has structures in accordance with our definition of *lignan*, it seems probable that a distinctly different mode of biogenesis is involved. The acid-catalyzed dimerization of (179) yields an arylindane neo-lignan product (180) (172,173).

Scheme 35. Diarylbutanes



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