ABSTRACT

A Dissertation Presented to the Faculty of the Graduate School of Arts and Sciences of Braitdeis University, Waltham, Massachusetts,

by Tesfaye Biftu

PART I

SYNTHETIC ROUTES TO LIGNANS

2,3-Diaroylbutanes were selectively converted with high stereospecificity to 2,5-diaryl-3,4-dimethylfurans or 2,3-diarylbutanes. The racemic forms of the dibenzylbutane lignans, dihydroguaiaretic acid dimethyl ether 26a, austrobilignan-5 26b and austrobilignan-6 26e and the diaryltetrahydrofuran lignans, veraguensin 27a and its piperonyl analogue 27b have been readily synthesized. The synthesis of the dissimilar substituted 2,5-diaryltetrahydrofuran austrobilignan-7 27er was limited by isomer formation and separation difficulty. A short convenient synthesis of the aryltetralin lignan, galbulin 37a and the all-trans tetrahydrofuran lignan, galbelgiri 31a are also reported. 1,4-Diarylbutanes undergo

intramolecular oxidation with vanadium oxytrifluoroide to yield dibenzo [a,c] cyclooctenes. Short synthetic routes to the lignan, (±)-deoxyschizandrin 43d have been developed from 3,4,5-trimethoxypropiophenone.

PART II

ISOLATION AND STRUCTURE ELUCIDATION OF CONSTITUENTS OF ELAEGIA UTILIS

By neutral solvent extraction of Elaegia utilis resin, there have been isolated the flavone apigenin 12 and the tetracyclic triterpenoid, isofouquierol 10 whose structure has been confirmed. By saponification of the insoluble residue, dammarenediol-II 1 (in dimorphic form) and a new triterpenoid, 30, 20S,26-trihydroxydammar-24-ene 6 were obtained from the neutral fraction.

PART I. SYNTHETIC ROUTES TO LIGNANS

PART II. ISOLATION AND STRUCTURE ELUCIDATION OF CONSTITUENTS OF *ELAEGIA UTILIS*

A Dissertation

Presented to

The Faculty of the Graduate School of Arts and Sciences

Brandeis University

Department of Chemistry

In Partial Fulfillment
of the Requirements of the Degree
Doctor of Philosophy

By

Tesfaye Biftu

August 1978

To Aba Fira Biftu Diko
for understanding my deepest desire for
education and making it possible

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I gratefully acknowledge the expert guidance, patience, and keen interest of Prof, Robert Stevenson. I would also like to thank Mr. Paul H. Todd Jr. and Mr. Karl R. Sandelin of KALSEC Inc. for their constant encouragement. Dr. Alvaro Femádez - Pérez of the Institute de Ciencias Naturales, Universidad Nacional de Colombia is thanked for providing the Elaegia utilis resih. I would also like to extend my greastest appreciation to my wife Senait Teffera for typing this thesis, and Michael Biftu (age 4) for keeping me felicitous.

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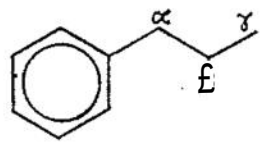
SYNTHETIC ROUTES TO LIGNANS

INTRODUCTION

Lignans constitute a class of natural products characterized by the bonding of two phenylpropyl groups at the β-carbon atoms. Haworth[1] originated the term "lignane" to denote their frequent occurrence in wood. Ritchie[2] proposed that the definition of lignan be expanded to include all natural products that arise primarily from the oxidative coupling of p-hydroxyphenylpropane units.

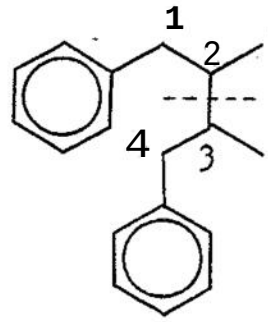


The lignans are found widely distributed throughout the coniferae and other plant families and have been isolated from the heartwood of exogenous trees, oils, resins, rhizomes, seeds, and leaves.

Lignan Sub-classification

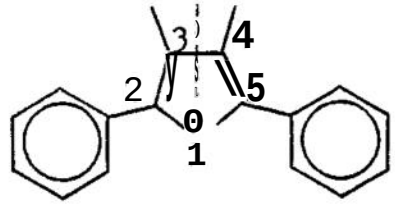
The lignans, of which over 200 naturally occurring compounds are currently known, can be subdivided into ten structural groups. Their formal derivation by β-bonding of two phenylpropyl moieties is readily discerned. These are shown and listed below:

1,4-Diarylbutane



1

2,5-Diarylfurane



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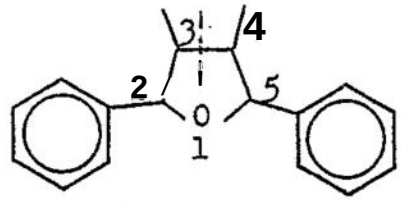
2,5-Diaryltetrahydrofuran



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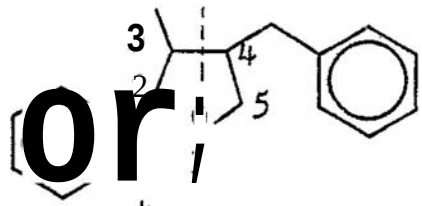
2-Aryl-4-benzyltetrahydrofuran



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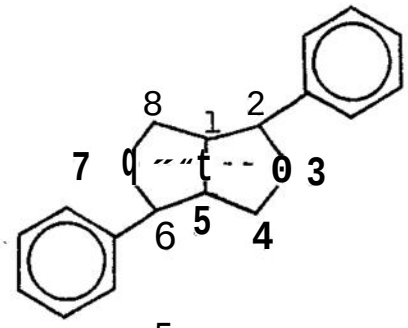
2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane



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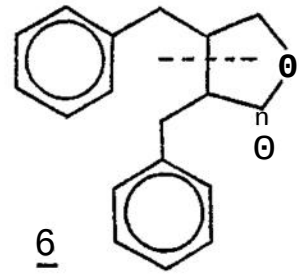
2,3-Dibenzylbutyrolactone



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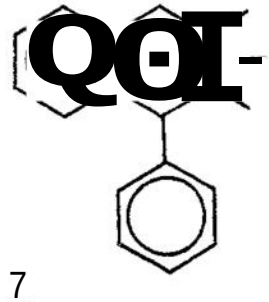
1-Arylnapthalene



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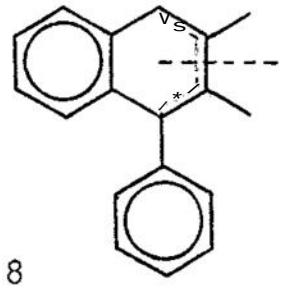
1-Aryldihydronaphthalene



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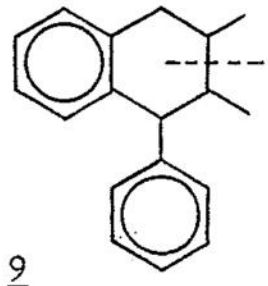
1-Aryltetrahydronaphthalene



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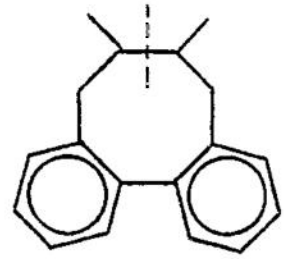
Dibenzocyclooctene



10

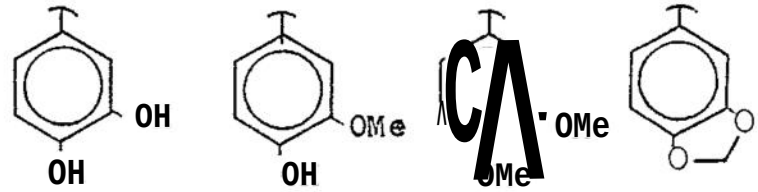
The three classes ?,8, and 9 are sometimes consolidated into one group as the cyclolignans.

All the presently known naturally occurring lignans contain oxygen functions on both aromatic rings*, These groups are either methoxyl, methylenedioxy or hydroxyl, and one is always para to the precursory C_3 side chain.

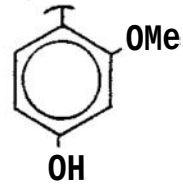
The substitution patterns most commonly found in the aryl ring of lignans are shown below.

4-Mono-

3,4-Di-



2,4-Di-



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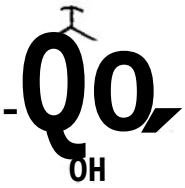
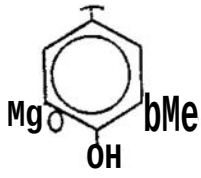
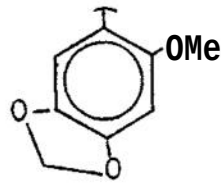
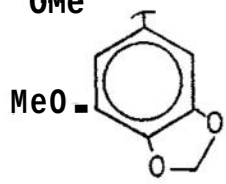
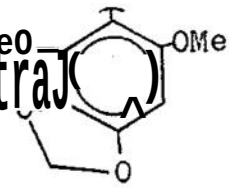
*Freudenberg[3] and Weinges[4] show in their reviews of lignans a compound lacking ring A substitution. However, this is due to a Chem, Abstr. mistake in abstracting a Japanese article. [5] The compound is in fact identical with (-)-desoxypodophyllotoxin.[5,6]

3,4,5-Tri-no-   

2,4,5-Tri-  

2,3,4,6-Tetraj 

In the non-aryl region, the following functionality has been found

Alcohol (1^{o}, 2^{o}, 3^{o}), ester and glycoside

Methyl ether (1^{o},3^{o}) and ethyl ether

Y-Lactone

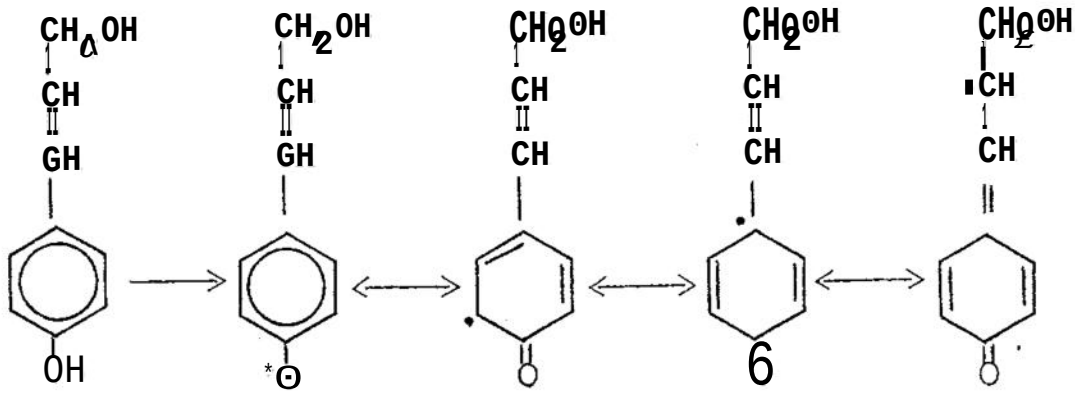
Ketone

Biosynthesis of Lignans

The phenylpropanoids are one of the most widely occurring groups of natural products within the plant kingdom. They are found as monomers (coniferaldehyde, cinnamic acid, etc.), dimers (lignans), and polymers (lignin). Naturally, the biogenesis of all three categories is intimately related. Both the lignans and lignins are apparently derived from the monomers.

Therefore, the biosynthesis of lignans can be logically considered as, firstly, the formation of phenylpropane monomers, then bonding of two such C_6-C_3 units and subsequent modification.[4] An initial dehydrogenation at the phenolic hydroxyl group yields the phenoxy radical A stabilized by resonance (B-D). Of the several possible canonical forms, the free radical appears to react mainly as the quinonemethide radical (D) to yield lignans /Scheme 1-1/.

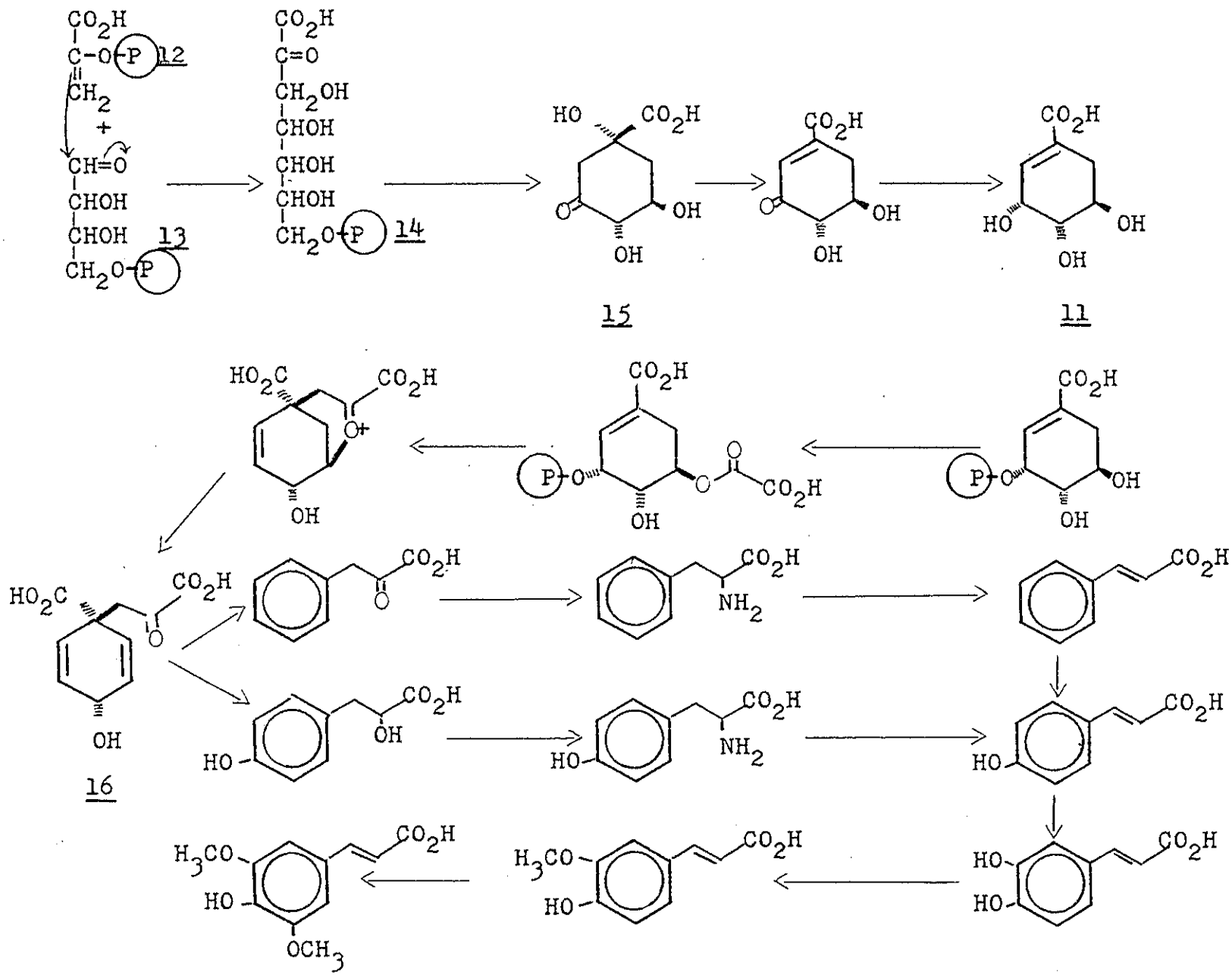
Scheme 1-1



A B C D

The formation of natural products containing aromatic rings from nonaromatic precursors has been of considerable interest for many years. Davis[7,8] suggested shikimic

acid, 11, as a biochemical precursor of aromatic compounds, Hendrickson[R] points out that of 117 benzene rings contained in a number of simple phenylpropane compounds and lignans 92% contain oxidation patterns typical of those derived from shikimic acid. The proposed biosynthetic scheme[A] for the production of phenylpropanbid compounds via shikimic acid is shown on the next page, Phosphoenolpyruvic acid, 12, and erythrose 4-phosphate, 1A, condense to yield 2-keto-3-deoxy-7-phosphoglucoheptonic acid, 14, which after cyclization yields the next known intermediate, 5-dehydroquinic acid, ljj. Dehydration of ljj followed by reduction of the ketone group leads to shikimic acid, 11, Shikimic acid is converted into prephenic acid, 16, by the addition of 12 and rearrangement. The C-l decarboxylation of prephenic acid followed by modification of the side chain and aromatic ring leads to the aromatic compounds shown. Shikimic acid could also give rise to phenylpropanbid compounds via benzoic acid precursors which could condense with a malonyl unit as shown below.


12
13
14
15
11
16

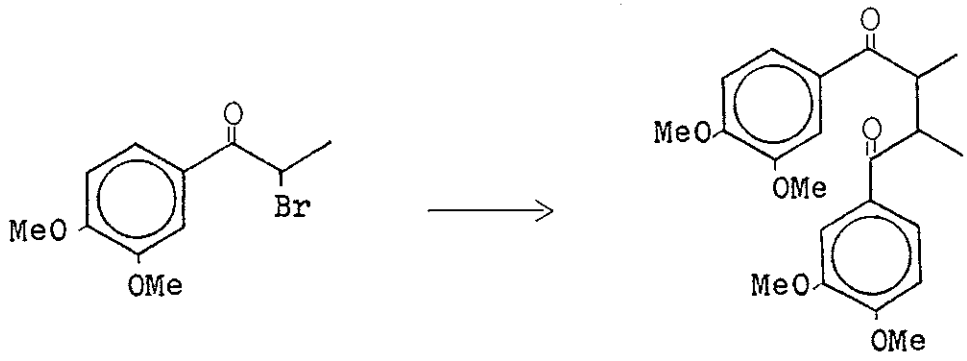
Several reviews covering the chemistry and biosynthesis of lignans have appeared.[10-16]

The first part of this dissertation describes several short and convenient synthesis of lignans of various classes (furans, tetrahydrofurans, diarylbutanes, cyclolignans and bisbenzocyclooctenes) from 2,3-diaroylbutanes.

Formation of 2,3-Diaroylbutanes

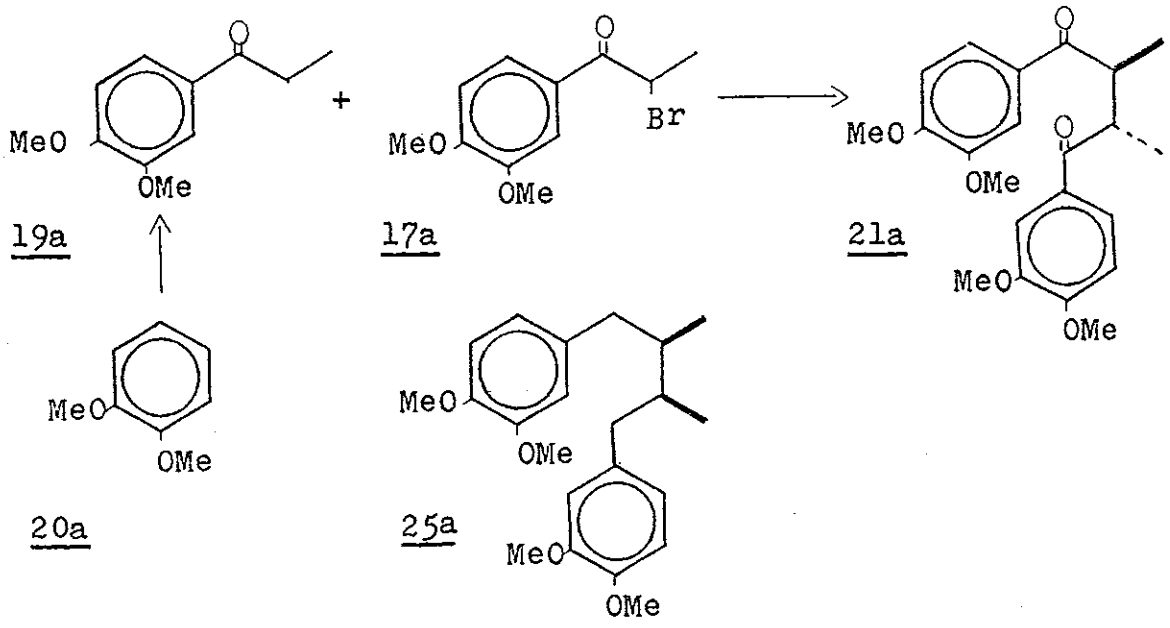
a. By α-Bromoketone Alkylation

Heating α-bromo-3,4-dimethoxypropiophenone 17a with copper powder in refluxing xylene has been reported[17] to give 2,3-diveratroylbutane 18a in 28% yield, but in attempts to repeat this using a variety of copper powders and solvents, Perry and co-workers[18] could not obtain this product in more than 7% yield.



17a 18a

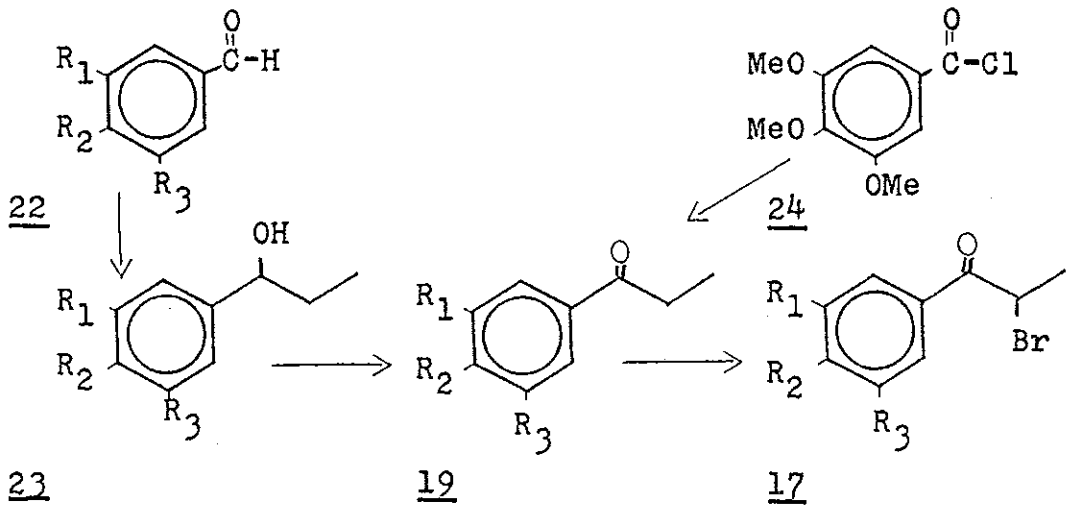
During the development of a commercial scale synthesis of the food anti-oxidant nordihydroguiaretic acid 25a, these latter workers developed a stereoselective, high yield alkylation reaction to form the 2,3-diaroylbutane skeleton.[18] Thus, when 3,4-dimethoxypropiophenone 19a, prepared by acylation of veratrole 20a with propionyl chloride, was



alkylated with the corresponding α-bromoketone 17a in liquid ammonia with sodamide as the base, a 90% yield of the racemic diketone 21a was isolated.[18] In view of the ease and high yield reported for this reaction, the generality and extension of this reaction toward the synthesis of other lignans is here studied. More specifically, it was sought to determine if this reaction could be adapted to yield diketones in which the aryl groups are not identical, and if these diketones could be converted to lignans of various classes (e.g. furans, tetrahydrofurans, diarybutanes, cyclolignans, bisbenzocyclo-octenes) and if other aryl substituents (methylenedioxy, benzyloxy) were stable to the reaction condition.

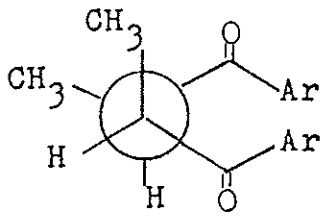
For this purpose, the starting ketones 19a-d were required. Two methods of synthesis were employed. The first involved Grignard addition of ethylmagnesium bromide to the substituted benzaldehydes 22a-d followed by Jones' oxidation of the intermediate alcohols 23a-d. We found that this procedure gave the required ketones in over 90% yield. The bromoketones 17a-d were also subsequently prepared in excellent yield by treating the ketones 19a-d with bromine in chloroform.

By a second procedure, the ketone 19d was also prepared from diethylcadmium and 3,4,5-trimethoxbenzoyl chloride 24 as previously described.[19]

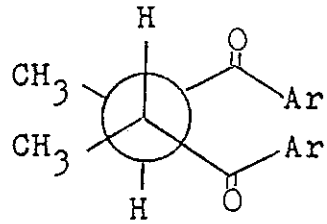


	R_1	R_2	R_3
a	OMe	OMe	H
b	$-OCH_2O-$		H
c	OMe	OBz	H
d	OMe	OMe	OMe

Next,the alkylation of the sodium enolates of 19a-d, prepared by sodium amide in liquid anhydrous ammonia, with the α-bromo derivatives 17a-d was studied, and the diaroylbutanes 21a-d were obtained in over 90% yields. The expected racemic configuration of these diketones, in analogy with the earlier work,[18] was confirmed by the characteristic methyl group chemical shifts. On the average, the methyl groups of the meso diketone conformer are closer to, and therefore more shielded by, the aroyl groups than are the methyl groups of the racemic diketone conformer shown below.



Meso

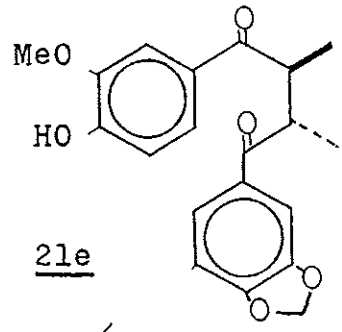


Racemic

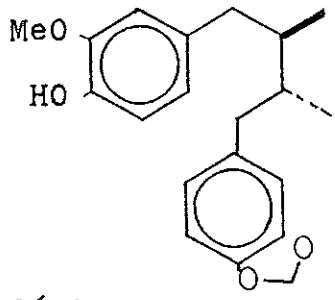
Thus, the chemical shifts of the secondary methyl groups in the racemic configuration are found in the range (δ 1.30-1.35) and of the meso configuration in the range (δ 1.15-1.20).

The diaroylbutanes, 21a-d all have identical aryl ring substitution. We next examined the formation of a diaroylbutanes of dissimilar aryl substitution. For this purpose, a synthesis of the diaroylbutane 21e was sought, since this should be an important intermediate for the synthesis of the diarylbutane, austrobilignan-6 26e' and the tetrahydrofurane,

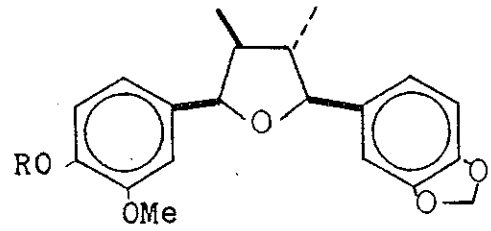
austrobilignan-7 27e' whose structure had been established[20] by conversion to calopiptin 27e''', a constituent of Piptocalyx moorei Oliv.[21,22] Accordingly the reaction of the methyl-



21e



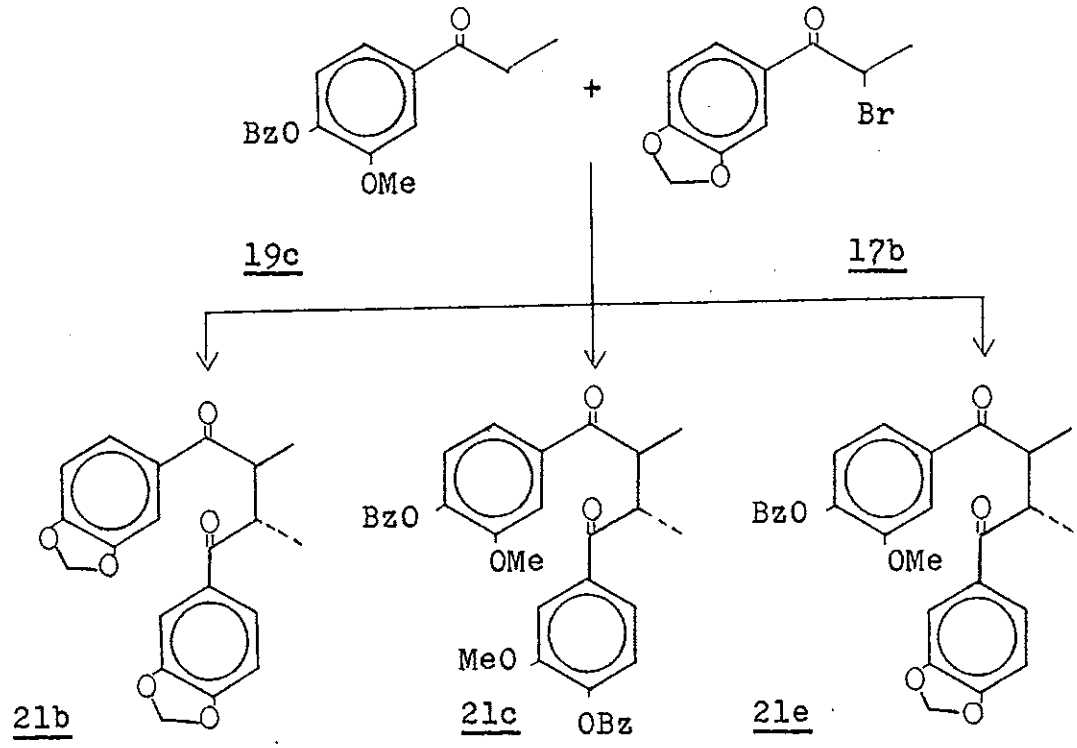
26e'



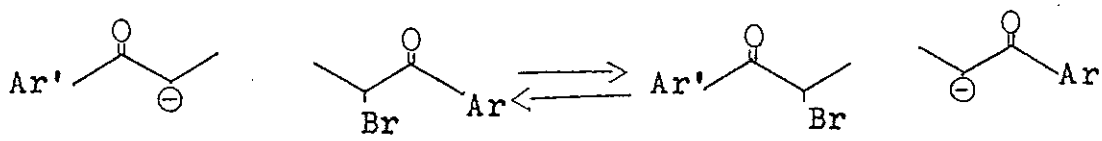
27e' R=H

27e''' R=Me

enedioxyphenyl bromoketone 17b with the anion derived from 4-benzyloxy-3-methoxypropiophenone 19c[23] was examined. When 19c was added rapidly to 17b there was obtained a mixture of all three diketones 21b, 21c and 21e. It was presumed that the symmetrical diketones had been formed as



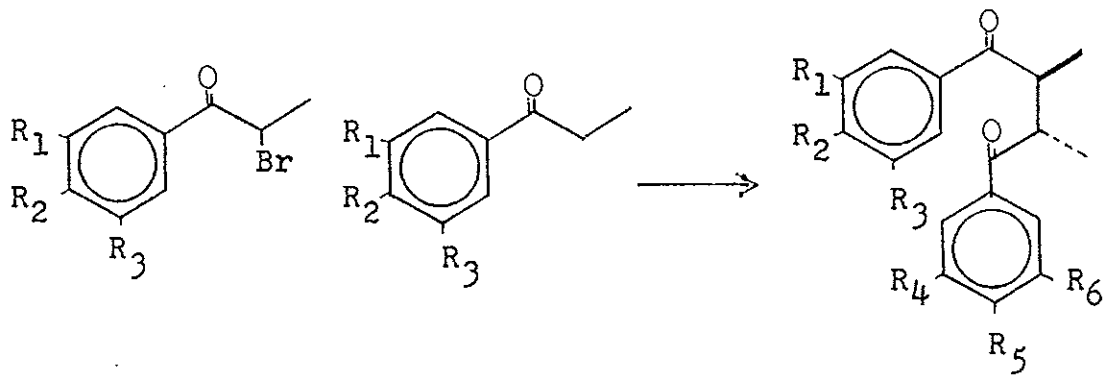
a consequence of competitive displacement on bromine versus carbon,[24] viz.



Consequently, in the hope of minimizing the formation of the symmetrical diketones, a slow addition of the bromoketone to the enolate was studied. This change in experimental condition in fact improved the yield of the desired unsymmetrical diketone 21e to 77%.

The above reactions establish the compatibility of sodium amide alkylation with the synthesis of methylenedioxy, methoxy and protected phenolic compounds. Also, it is demonstrated that unsymmetrical diketones could be synthesised in high yield.

The racemic diketones prepared by alkylation of aryl ketones with aryl α-bromoketones in this study are listed in the following table.



17 19 21

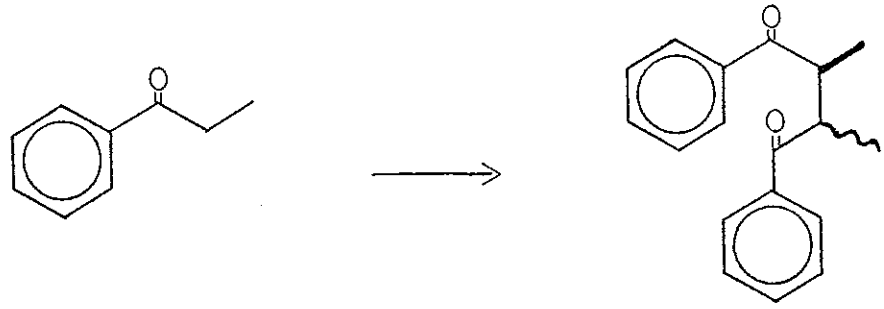
	R_1	R_2	R_3	R_4	R_5	R_6
a	OMe	OMe	H	OMe	OMe	H
b	$-OCH_2O-$		H	$-OCH_2O-$		H
c	OMe	OBz	H	OMe	OBz	H
d	OMe	OMe	OMe	OMe	OMe	OMe
e	OMe	OBz	H	$-OCH_2O-$		H

b. By Enolate Oxidation

Recently reported methods for the synthesis of 1,4-diketones involve oxidative coupling of a ketone enolate with cupric chloride[25] or cupric trifluoromethanesulphonate.[26]

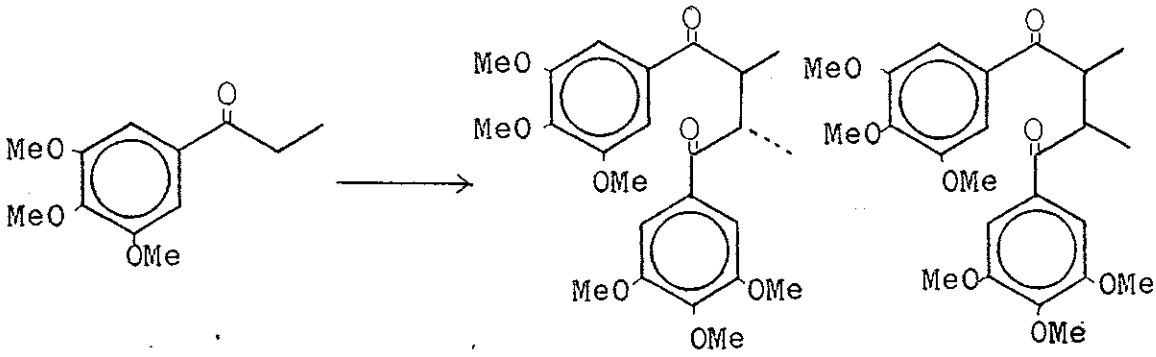
$$2RC(OLi)=CR'R'' + 2Cu(OTf)_2 \longrightarrow RC(=O)-C(R')-C(R')-C(=O)R + 2CuOTf + 2LiOTf$$

For example a solution of lithium enolate of propiophenone 19f in THF, generated from propiophenone and lithium diisopropylamide, when treated with cupric trifuoromethanesulphonate[27] prepared from cupric carbonate and triflic acid, gave 1,4-diphenyl-2,3-dimethylbutan-1,4-dione in 80% yield.[26] The configuration of this diketone and its n.m.r. data were not provided in the paper.



19f

To test the utility of this method as a general route for the synthesis of symmetrical diketones, the lithium enolate of 3,4,5-trimethoxypropiophenone 19d was oxidized with cupric trifluoromethanesulphonate. This ketone was chosen, since it was hoped to use the diketone product for a synthesis of (±)-deoxyschizandrin (see later). Two products were obtained in this reaction. The first, which seprated at the ether-water interface on work up, proved to be the meso diketone 18d (δ 1.3). The second product obtained from the ether-soluble layer was the racemic diketone 21d (δ 1.17). This isomers were in ca. 2:3 ratio.



19d 18d 21d

The observed insolubility of the meso diketone in the ether layer indicated that base-catalyzed isomerization of the (±)-diketone in ether should result in precipitation of the desired meso diketone, and such conversion was in fact effected in over 90% yield.

Synthesis of Lignans from 2,3-Diaroylbutanes

The availability of 2,3-diaroylbutanes has permitted the synthesis of six lignan sub-classes. These are :

a. 2,5-Diarylfurans

b. 2,5-Diaryltetrahydrofurans

c. 1-Aryldihydronaphthalenes

d. 1-Aryltetrahydronaphthalenes

e. 1,4-Diarylbutanes

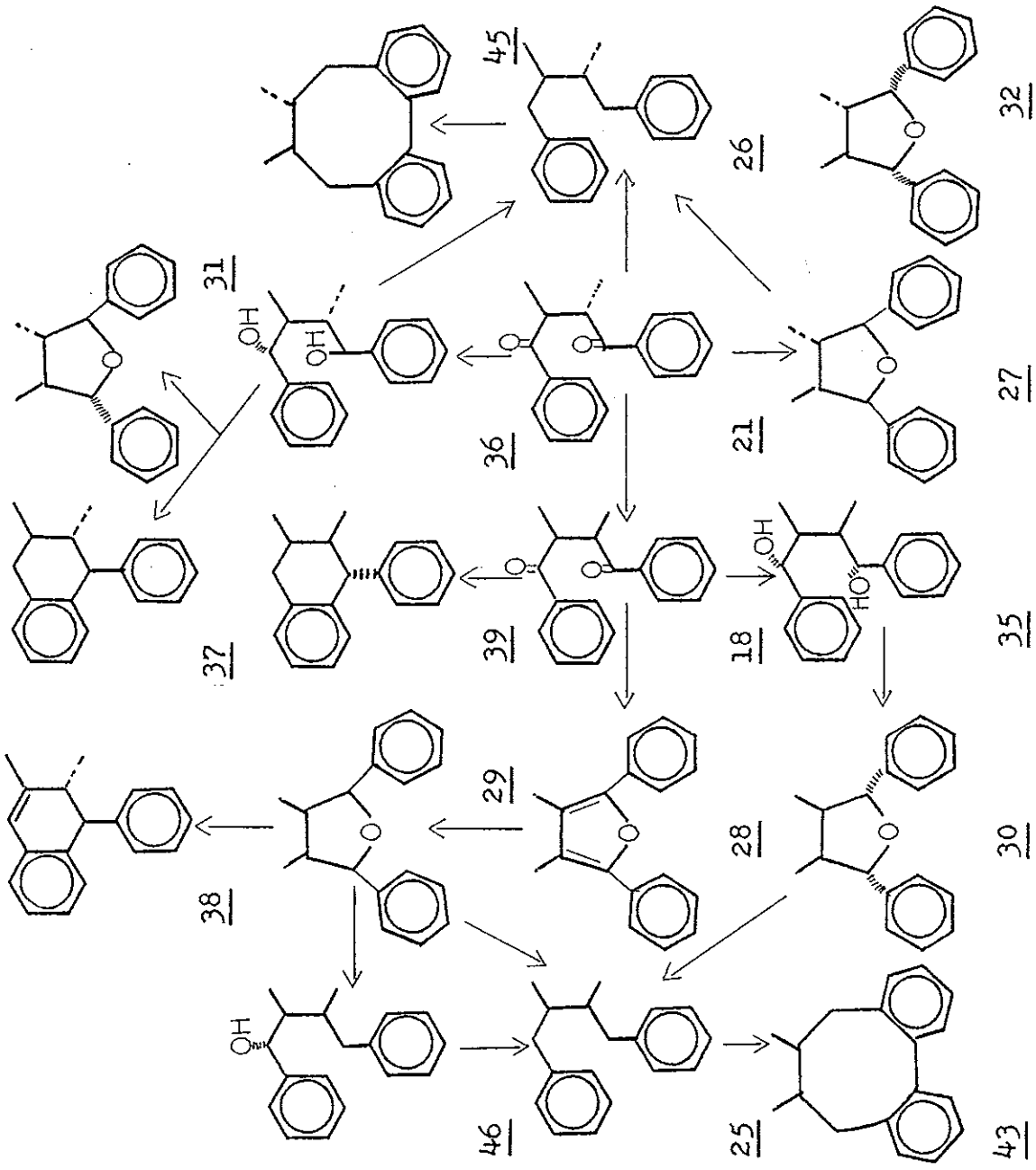
f. Bisbenzocyclo-octenes

A graphic outline of these transformations is given on the next page.

a. 2,5-Diarylfurans

The natural occurrence of this class of lignan is comparatively rare.

It is well known that, 1,4-diketones are converted to furans on acid treatment. In connection with the synthesis of (±)-deoxyschizandrin (see later) the hexamethoxydiaryl furan 28d was required. This was readily accomplished by acid catalyzed dehydration of either the meso diketone 18d or the racemic diketone 21d. This particular furan has not yet been reported as a natural product.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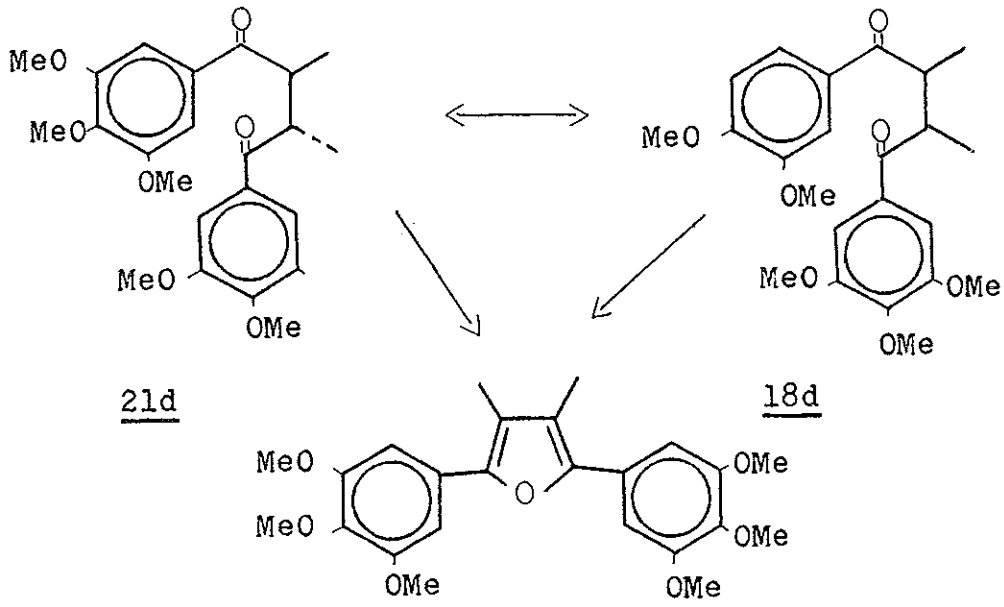
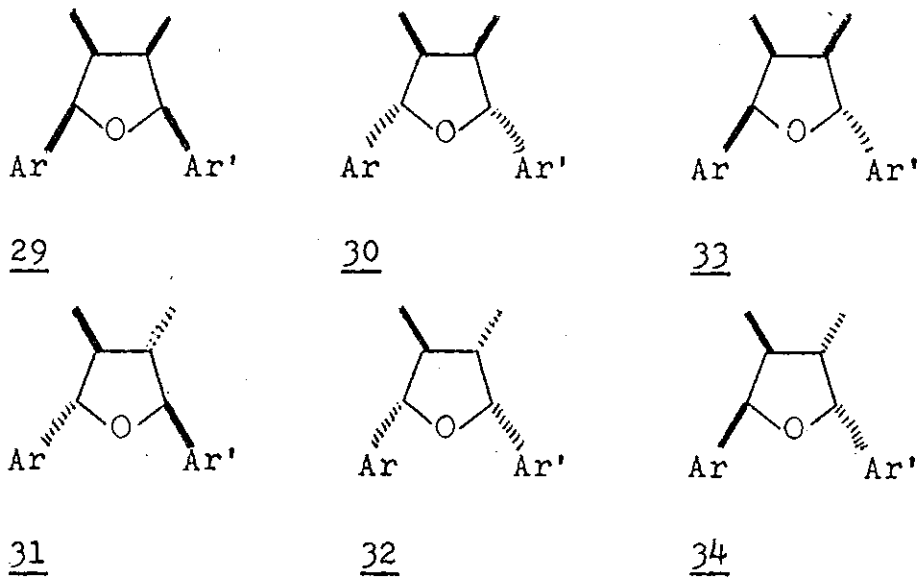


21d 18d

28d

b. 2,5-Diaryltetrahydrofuran Lignans

Of the six possible stereoisomeric forms of αα'-diaryl-ββ'-dimethyltetrahydrofurans (29-34) that can exist, four have

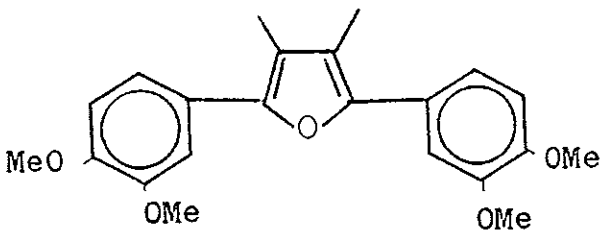


29 30 33

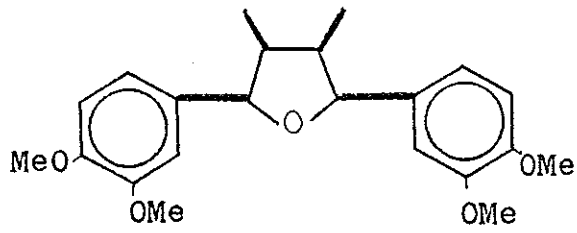
31 32 34

been found naturally occurring. These are the cis-meso 29, the trans-meso 30, the all-trans r-2H, 3c, 4t, 5c 31, and the r-2H, 3t, 4c, 5t 32 forms. The synthesis of each of these four naturally occurring types is now discussed.

The synthesis of the cis-meso tetrahydrofurane 29a, by catalytic hydrogenation of diaryldimethyl furan 28a has been reported by Haworth.[28] In an analogous manner, catalytic

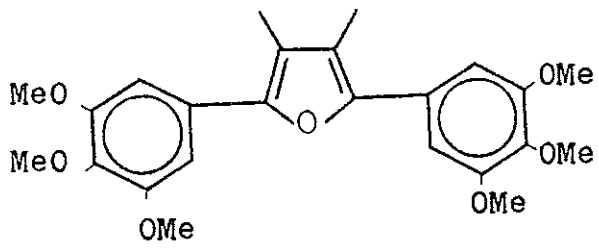


28a

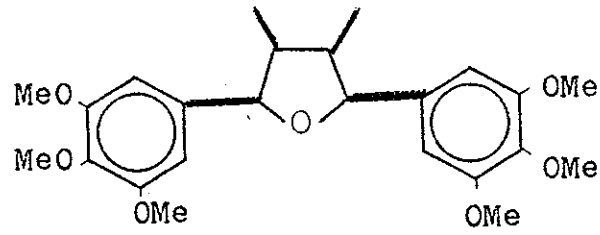


29a

hydrogenation of the furan 28d in acetic acid gave the cis-meso form 29d. The methyl groups, being highly shielded by



28d

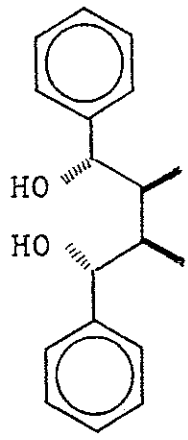


29d

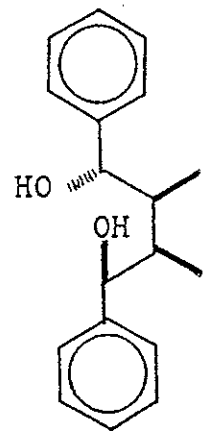
the aryl rings, appear at high field (δ 0.67). The two benzylic protons are equivalent as expected. These p.m.r. data readily establish the symmetry of the hydrogenation product.

Trans-meso tetrahydrofurane 30a was prepared by acid catalyzed equilibration of the cis-meso form 29a.[28] This method gives mixtures of products and the yield of the desired production was low.

It has now been found that meso diketones could be converted in excellent yield to trans-meso tetrahydrofurans, by the following procedure. For example, reduction of the meso diketone 18d with lithium aluminium hydride gave a diol whose n.m.r. spectrum indicates non-equivalence of the methyl groups. Of the two possible configurational isomers, the symmetrical (meso) or the unsymmetrical (racemic) structure, the former is excluded by the n.m.r. evidence. This diol,



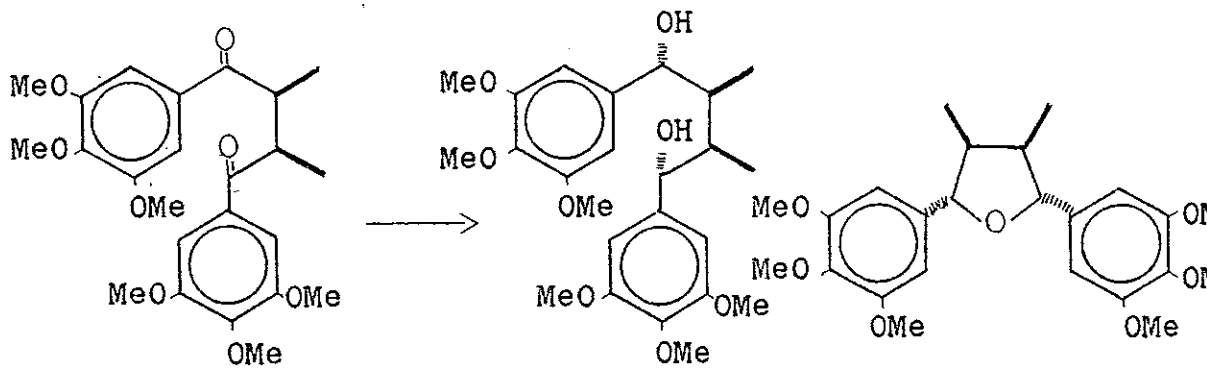
Meso



Racemic

which could have been formed by an intramolecular hydride transfer from the intermediate alkoxymetal hydride is accordingly formulated as 35d.

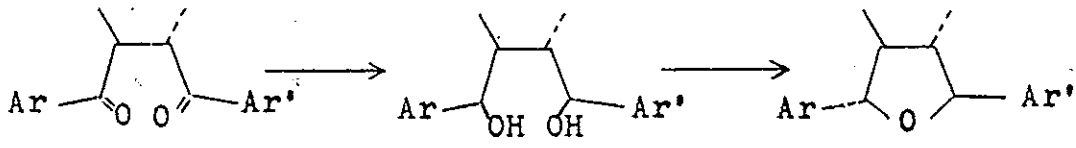
This diol underwent dehydration with great ease. Attempts to form the corresponding dimesyl or dibromo derivative by treatment with methanesulphonyl chloride or triphenylphosphine dibromide resulted in formation of the known[29] trans-meso tetrahydrofurane 30d in good yield. The formation of this product could be explained in terms of an initial formation of methanesulphonyl (or bromide) derivative of one of the hydroxyl groups. This derivative, being a good leaving group, will then be intramolecularly



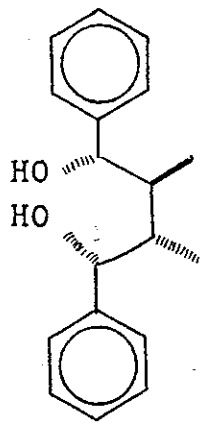
18d 35d 30d

displaced by the second hydroxyl oxygen yielding the trans-meso tetrahydrofuran. The trans-meso form has, of course, equivalent sec-methyl groups, which are less shielded by the aryl rings and, hence, appear at a relatively lower field (δ 0.85).

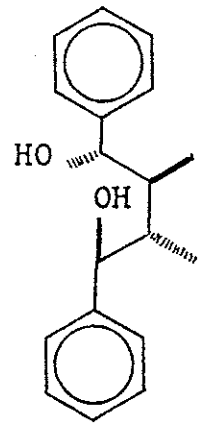
We have now developed a short synthesis path from (±)-diaroylbutanes for formation of all-trans tetrahydrofurans. This involves reduction of the (±)-diketone with lithium aluminium hydride followed by exposure of the resulting diol to catalytic hydrogenation conditions in acetic acid.



Reduction of the racemic diketone 21a with lithium aluminium hydride yielded a diol whose n.m.r. spectrum exhibited non-equivalent secondary methyl groups. Of the two possible diol products, a racemic unsymmetrical diol and a racemic symmetrical diol, the former was accepted and is

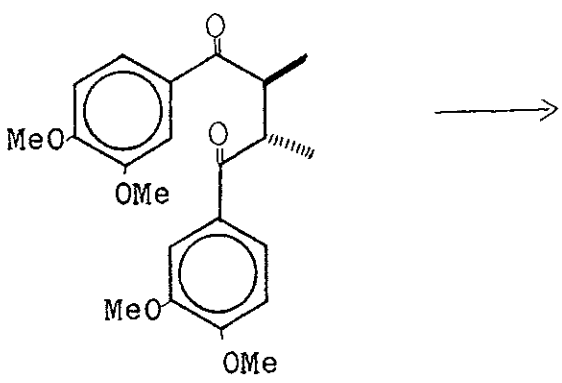


Racemic Unsymmetrical

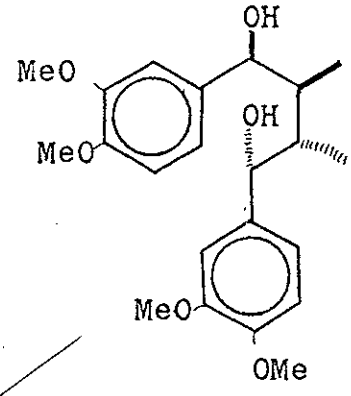


Racemic Symmetrical

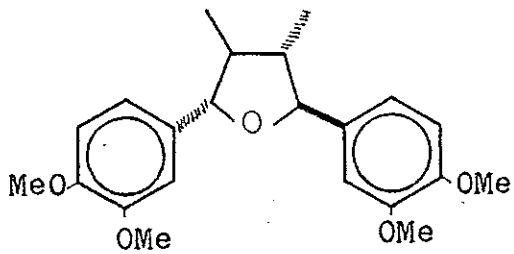
accordingly formulated as 36a. The n.m.r. spectrum of the non-crystalline diacetate derivative also revealed non-equivalent methyl and acetoxyl groups. On hydrogenation of this diol in acetic acid, two products were readily isolated by fractional crystallization. The first, obtained in 22% yield, and identified as the aryltetralin (±)-galbulin 37a had been first synthesized[30] in 1952, prior to the isolation of the (-)-form, as a constituent of the bark of Himantandara baccata.[31] Several other syntheses of this product or inter-conversions from other lignans of known structure have been reported.[32-36] The second, a dehydration product obtained in ca. 50% yield identified as (±)-galbelgin[33] 31a, the all-trans substituted tetrahydrofuran isomer of veraguensin, which has also been obtained previously in low yield[37] or by a more circuitous route.[38]



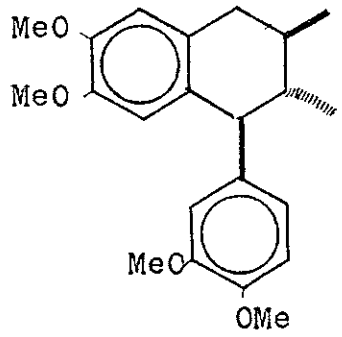
21a



36a

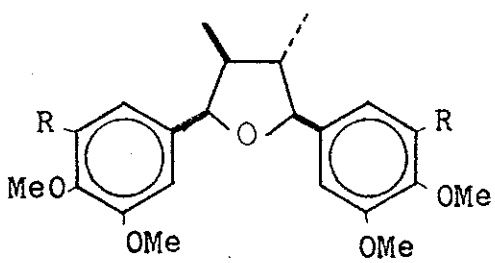


31a



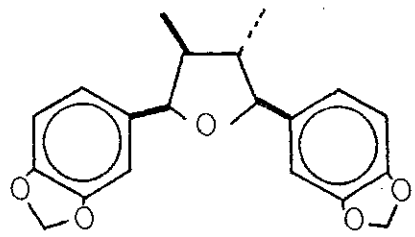
37a

Representatives of an r-2H, 3c, 4t, 5c form symmetrical tetrahydrofuranes are 27a, 27b and 27d. (+) Veraguensin 27a was first isolated[21] from the wood Ocotea veraguensis and



27a-R=H

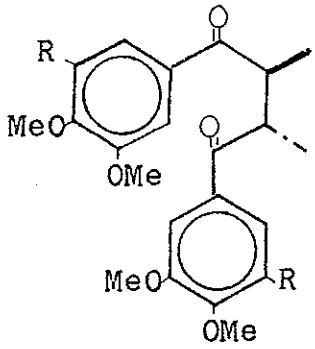
27d-R=OMe



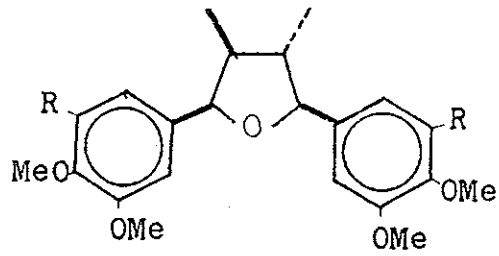
27b

subsequently[39] from the leaves of Trimenia papuana. Veraguensin was isolated previously in racemic form in low yield as one of the products isolated by enzyme-catalyzed oxidation of (E)-and (Z)-iso-eugenol, followed by diazomethane methylation.[37] Recently it was synthesised by an oxidative phenolic coupling of a bromo-ferulic acid derivative.[40]

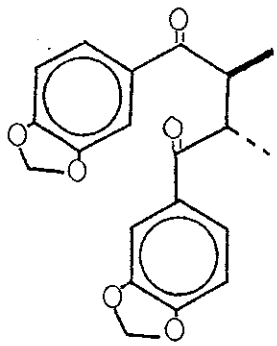
We have now found that a convenient and short synthesis of veraguensin 27a and analogous compounds could be effected by catalytic (Pd-C) hydrogenation of the racemic diketones with catalyst/substrate ratio of ca. 0.5. Thus, when the racemic diketone 21a was reduced under this condition, (±)-veraguensin 27a, was isolated in good yield. Similarly, reduction of 21b and 21d gave 27b and 27d respectively. The



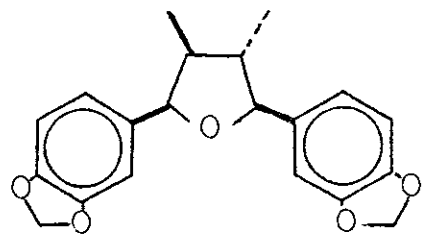
21a-R=H, 21d-R=OMe



27a-R=H, 27d-R=OMe



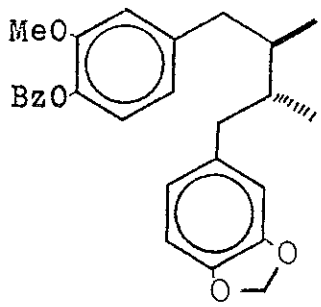
21b



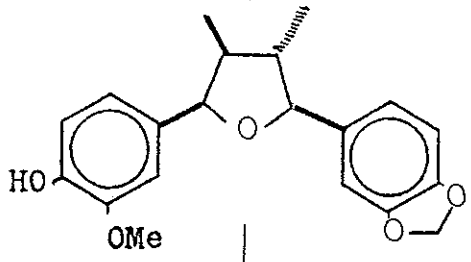
27b

magnetic non-equivalence of the α and α' benzylic protons and the β and β'-methyl protons of these compounds is a clear indication of one of the four substituents of the tetrahydrofuran ring being trans to the other three.

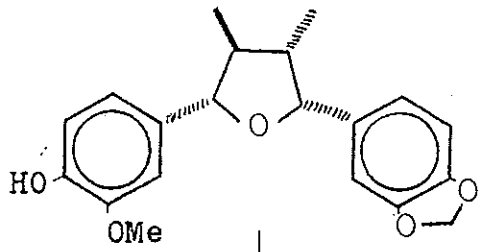
Attention was next turned to configurational analogues with dissimilar aryl ring substituents. An example of such a natural product is austrobilignan-7 27e'.[20,21,22] In an attempted synthesis of this compound, the reduction of the unsymmetrical diketone 21e was performed under the same conditions, i.e. conditions conducive to tetrahydrofuran formation. The crude product had a n.m.r. spectrum in excellent agreement with that reported for austrobilignan-7 27e', except for the appearance of two methoxyl signals in a 1:1 ratio. It was concluded that the formation of 27e' was accompanied, as would be expected, by the closely related structural analogue 32e' with identical configuration. Attempts at chromatographic separation of these isomers (silica, alumina, polyamide) were unsuccessful. A partial separation of the acetate derivatives 27e" and 32e" was effected on silica gel, but neither was obtained crystalline or pure. It appears that this methodology of synthesis of dissimilar substituted 2,5-diaryltetrahydrofurans will be limited by the isomer formation and separation difficulty.



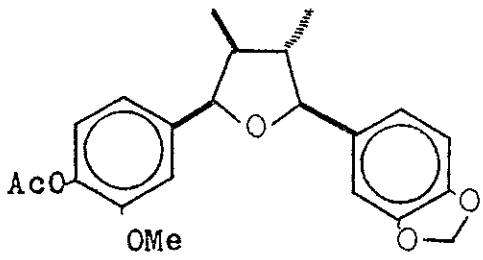
21e



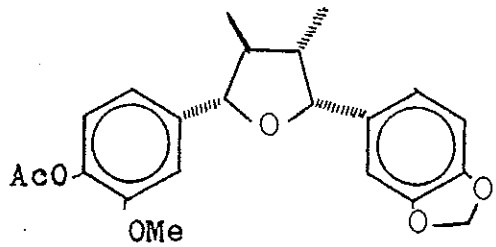
27e'



32e'



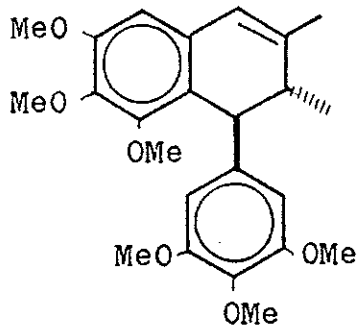
27e"



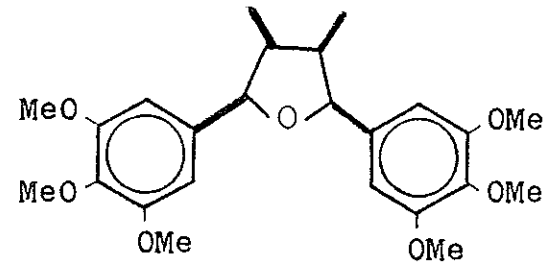
32e"

c. 1-Aryldihydronaphthalenes

A route to 1-aryldihydronaphthalenes was uncovered. Thus, when the previously prepared cis-meso tetrahydrofuran 29d was treated with perchloric acid-acetic acid at room temperature the aryldihydronaphthalenes 38d was obtained. This particular compound has not been reported as a natural product.



38d

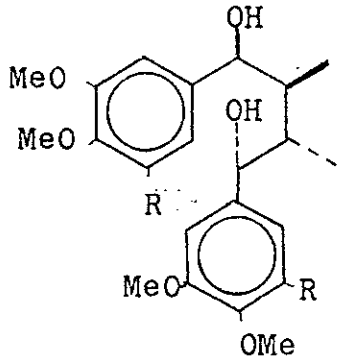


29d

d. 1-Aryltetrahydronaphthalenes

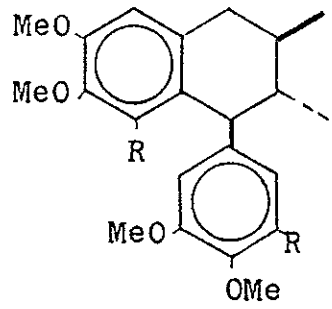
The 1-aryltetrahydronapthalenes are the largest and longest known of cyclolignans and they have been studied extensively.[15,16] They contain at least three asymmetric centers.

As noted earlier one of these, the all trans (±)-galbulin 37a was prepared by catalytic reduction of the diol 36a in acetic acid. A similar reduction of the unsymmetrical racemic diol 36d in ethanol gave the all-trans aryltetralin 37d.



36a-R=H

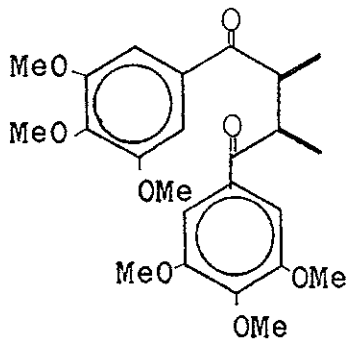
36d-R=OMe



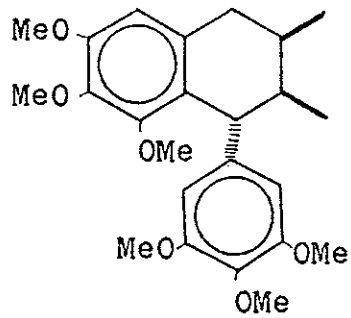
37a-R=H

37d-R=OMe

We have now developed a pathway to aryltetralins of r-1H, 2c, 3c configuration (e.g. compound 39d). We found that hydrogenation of the meso diketone 18d in tetrahydrofuran gave a crystalline product with an empirical formula $C_{24}H_{32}O_4$. On the basis of the n.m.r. spectrum it was formulated as the aryltetralin 39d in which the 1-aryl group adopts the more stable axial conformation (trans to the C-3 equatorial methyl group.



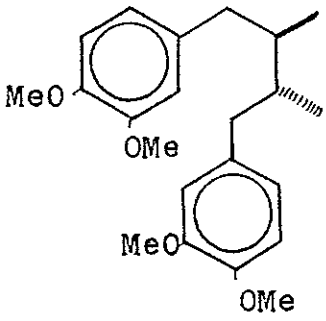
18d



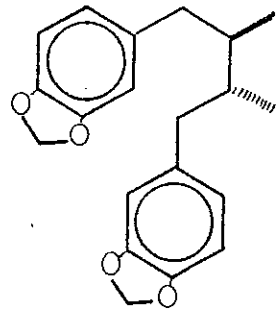
39d

e. 1,4-Diarylbutanes

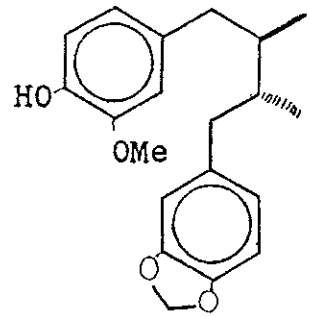
Examples of naturally occurring 1,4-diarylbutanes are (±)-dihydroguaiaretic acid 26a,[43] austrobilignan-5 26b[20] and austrobilignan-6 26e',[20].



26a



26b

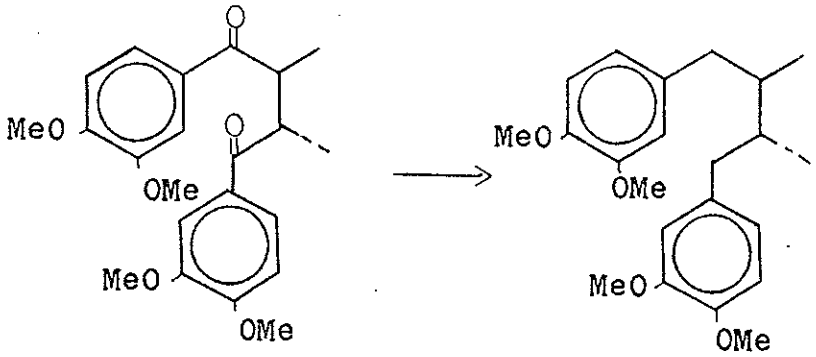


26e'

The meso and racemic forms of these lignans were conveniently synthesized from the meso or racemic diketones respectively.

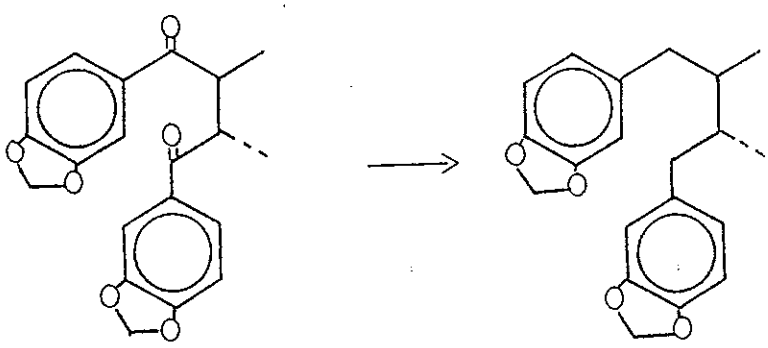
We have thus, found that in several instances, direct catalytic hydrogenation of the starting diketones with high catalyst/substrate ratio (>1.0) provides an excellent pathway to the required diarylbutane.

Catalytic hydrogenation of 21a with palladium-carbon, gave on direct crystallization from the reaction mixture (±)-dihydroguaiaretic acid dimethyl ether 26a, previously synthesized by a less direct Stobbe synthesis pathway.[43]



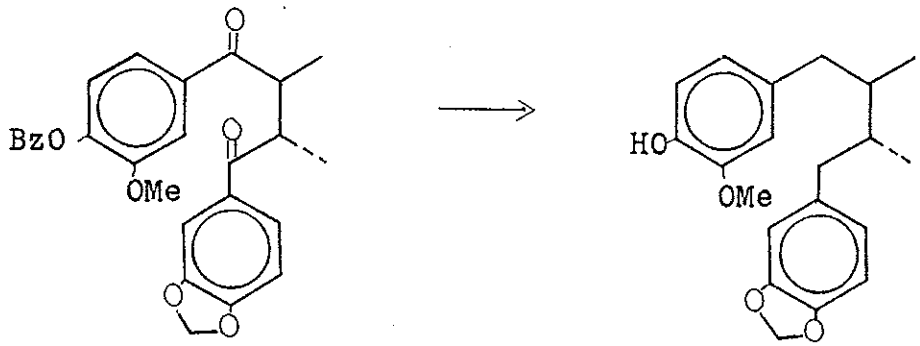
21a 26a

The diketone (±)-2,3-bis(3,4-methylenedioxybenzoyl) butane, 21b under the same conditions gave the butane 26b, the (-)-enantiomer of which has recently been isolated from Austrobaileya scandens and designated as austrobilignan-5[20] The hydrogenolysis product 26b is accordingly formulated as (±)-austrobilignan-5. Like the natural product, it was isolated as an oil, but was readily characterized as a crystalline dibromo derivative.



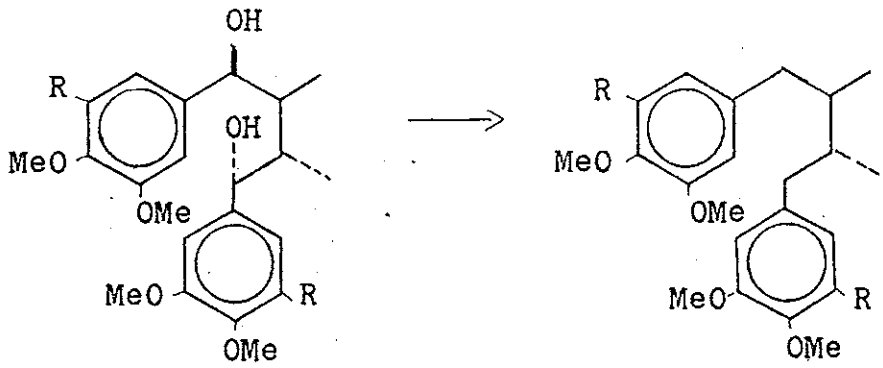
21b 26b

Similarly, hydrogenation of the mixed diketone 21e in acetic acid readily gave the vanillylpiperonylbutane with n.m.r. spectrum identical to that reported for austrobilignan-6 26e'.



21e 26e'

An alternative route to diarylbutanes synthesis is by the reduction of the diol obtained from lithium aluminium hydride reduction of diaroylbutane. As earlier discussed, the diols 36a, and 36d on hydrogenolysis in acetic acid yielded 26a, and 26d respectively.

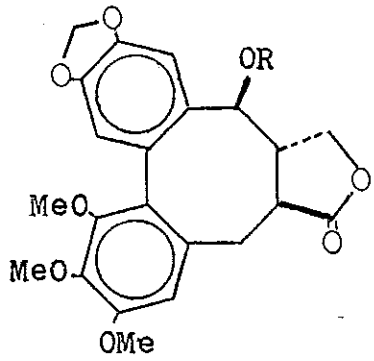


36a-R=H
36d-R=OMe

26a-R=H
26d-R=OMe

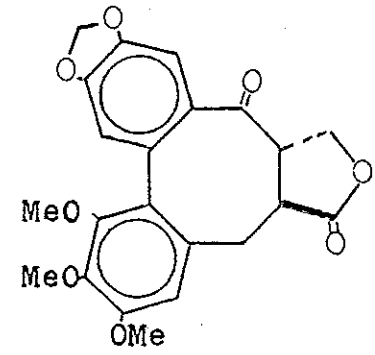
f. Bisbenzocyclo-octenes

Over twenty naturally occurring bisbenzocyclo-octenes have been isolated and are now recognized as a sub-group of lignans. They include the schizandrins,[44,45] the gomisins,[46] the steganes[47] and kadsurins.[48] The significant therapeutic activity already reported for several of these products has promoted much recent activity in both synthesis and structure elucidation, and synthesis of (±)-steganacin 40[49,50] (±)-steganol 41,[49,50] (±)-steganone 42,[49-51] (±)-deoxyschiz-

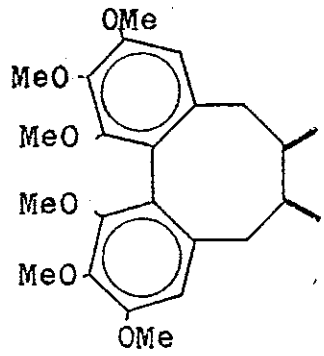


40-R=CH_3CO

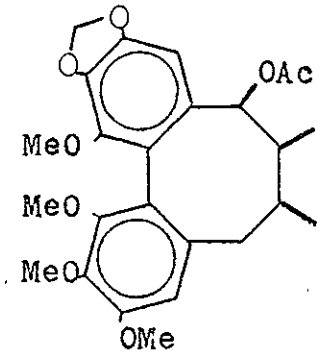
41-R= CO



42



43



44

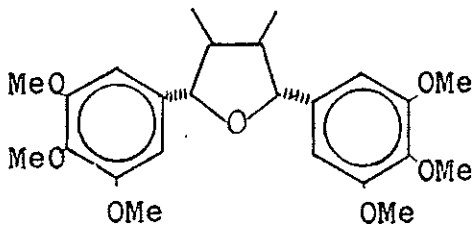
andrin 43d[52,57] and (±)-kadsurin 44[53] have been reported within the last two years. Other significant approaches to the bisbenzocyclo-octene skeleton have also been described recently.[54-56]

A short synthesis of (±)-deoxyschizandrin 43d, a constituent of the seed oil of Schizandra chinensis Baill, (Magnoliaceae), developed from the earlier work in this dissertation, but involving additionally an intramolecular cyclization of a hexamethoxydiarylbutane, is now described.

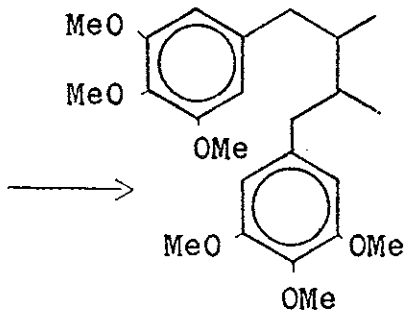
The introduction of vanadium oxytrifluoride as a reagent for the intramolecular oxidation of non-phenolic substrates[58] prompted preliminary experiments to ascertain if the lignan bisbenzocyclo-octene skeleton might be simply assembled from a 1,4-diarylbutane. Accordingly, the bis-methylenedioxyphenylbutane 26b, previously prepared[59] in confirmation of the structure of (±)-austrobilignan-5,[20] was treated with vanadium oxytrifluoride and yielded in 60% yield a high-melting product whose p.m.r. spectrum was in complete agreement with the dibenzo [a,c] cyclo-octene structure 45b. Similar oxidation of meso-dihydroguaiaretic acid dimethyl ether 25a, of well established configuration,[18] yielded the tetramethoxy analogue 43a. In an analogous manner, the racemic form 26a was also converted to 45a.

Attempted preparation of the immediate synthetic precursor meso-1,4-bis-(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane 25d by direct hydrogenolysis of the meso diketone 18d was unsuccessful.

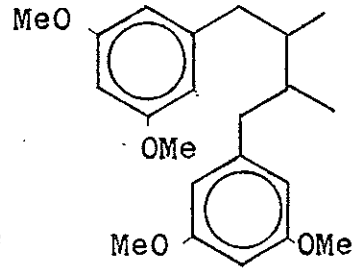
It had been hoped that catalytic hydrogenolysis of the tetrahydrofuran 29d would yield the meso-butane 25d directly, since such a reduction had been reported for the veratryl analogue.[18] However, all attempts to accomplish this under a variety of hydrogenation conditions, were unsuccessful. Again, the tetrahydrofuran 30d was resistant to catalytic hydrogenolysis, but was successfully cleaved by reduction with sodium in liquid ammonia to yield the required meso-diaryldimethylbutane 25d. A minor by-product, readily separated by thin-layer chromatography was the analogue 45 in which reductive de-alkoxylation of the p-methoxyl function had occurred. Ample precedent for this behaviour exists.[25] The meso-cis-tetrahydrofuran 29d was also subjected to sodium-ammonia reduction under the same conditions. The crude product could most reasonably be formulated, by consideration of the p.m.r. spectrum as the alcohol 46d, and as expected on hydrogenation in acetic acid yielded the same required meso diarylbutane 25d. Sodium-ammonia reduction of the tetrahydrofuran 32d in acetic acid yielded the racemic diarylbutane 26d.



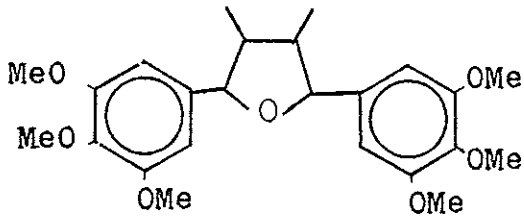
30d



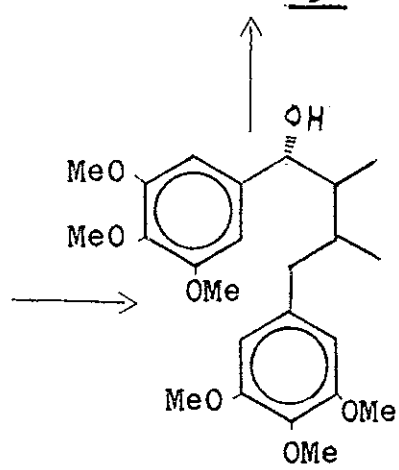
25d



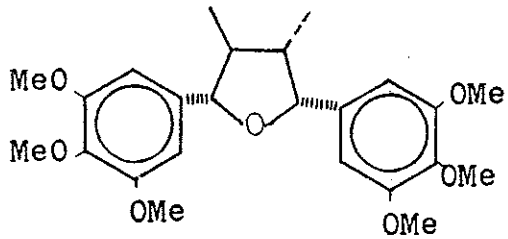
45



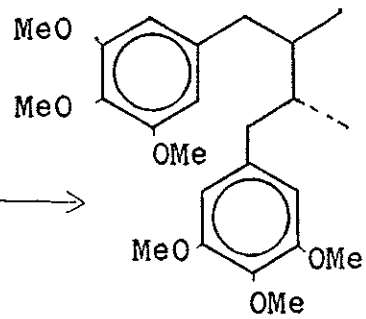
29d



46d

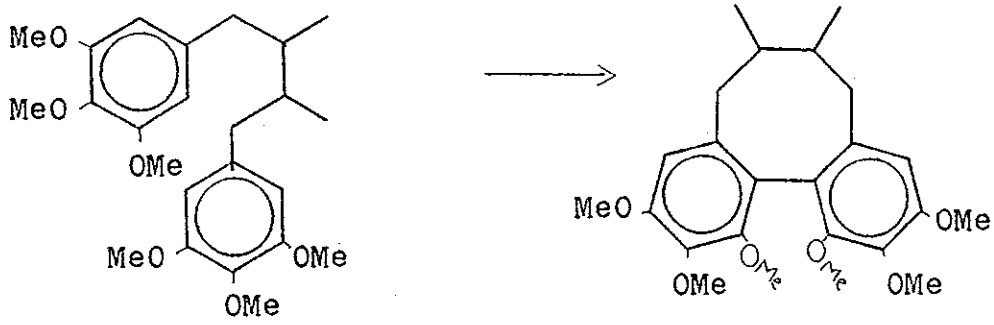


32d



26d

Oxidation of 25d with vanadium oxytrifluoride gave the dibenzo [a,c] -cyclo-octene 43d with m.p. and p.m.r. spectrum in excellent agreement with the racemic product, reported by Ghera, Ben-David and Becker in a fifteen step synthesis, and which had been identified with the natural product by comparison of i.r., u.v. and p.m.r. spectra.[52] This short synthesis should be of general applicability and affords considerable economy of effort. Since considerable uncertainty exists regarding the configurations at C-6,&7 of other Schizandra products, this should also open the way for proof by synthesis.



25d 43d

Summary

From diaroylbutanes, the following racemic form of natural products have been synthesized.

2,5-Diaryltetrahydrofurans

galbelgin

veraguensin

austrobilignan-7

1,4-Diarylbutanes

dihydroguaiaretic acid

austrobilignan-5

austrobilignan-6

1-Aryltetrahydronaphthalenes

galbulin

Bisbenzocyclo-octenes

deoxyschizandrin

EXPERIMENTAL

Melting points were determined on either a Fisher-Johns or a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra, unless otherwise stated, were determined in KBr pellets using a Perkin-Elmer model 137 spectrophotometer. Ultraviolet absorption spectra were measured in 95% ethanol solution, unless otherwise specified, on a Cary 14 spectrophotometer (purchased on NSF Grant GP-1745). Nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer (purchased on NIH Grant GM-13183). The solvent was deuteriochloroform, unless otherwise specified, with tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in ppm relative to the TMS internal standard. Low and high resolution mass spectra were recorded on LKB MS and Atlas mass spectrometer respectively through the courtesy of the Upjohn Company. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee, and by Chemalytics Laboratories, Temple, Arizona.

Analytical thin layer chromatography (tlc) were run on a 0.25 mm thick layer of silica gel GF_{254} (Merck). Products were detected by their ultraviolet fluorescence or by absorption of iodine vapor. Preparative thin layer chromatography

were run on either 1.00 or 1.75 mm thick layer of silica gel $PF_{254+366}$ (Merck). Products were detected by their ultraviolet fluorescence and eluted by extraction in a soxhlet extractor.

3,4-Methylenedioxypropiophenone 19b. —A solution of piperonal (40 g) in ether (100 ml) was added over 15 min. to a solution of ethylmagnesium bromide, prepared from magnesium (7.6 g), and ethyl iodide (31 ml) in ether (100 ml). The mixture was stirred for an additional 15 min., worked up in the usual way and the ethylpiperonylcarbinol product (45.9 g) dissolved in acetone (200 ml) and oxidized with excess Jones reagent (1.4 M). The dark oil product (35.5 g) was distilled at 120°/25 mm. Hg to give the ketone 19b as a white solid (31 g), m.p. 38-39° (lit.[41] m.p. 38-39°). δ 1.20 (t, J 7 Hz, Me) 2.91 (q, J 7 Hz, CH_2), 6.03 (s, $-OCH_2O-$) and 6.73-7.65 (m, three ArH).

4-Benzyloxy-3-methoxypropiophenone 19c.—A solution of O-benzylvanillin (20g) in benzene was added over 15 min. to ethylmagnesium bromide, prepared from magnesium (2.2g), Vitride (0.5 ml), ethyl bromide (7.4 ml) and ether (100 ml), the mixture stirred for an additional 15 min. and worked up in the usual way. Removal of solvent gave a solid alcohol δ 0.87 (t, 3H, CH_3), 1.50-1.98 (m, 2H, CH_2), 2.33 (s, 1H, OH), (s, 3H, OMe), 4.45 (t, 1H, ArCH-), 5.08 (s, 2H, $PhCH_2$), 6.80-7.50 (m, 8H, aryl H) which was dissolved in acetone (150 ml) and oxidized with excess Jones' reagent (1.4 M, 60 ml) at 0-10°. Work up gave the crude product as a solid (21.5g)

which crystallized from methylene chloride-isopropyl ether as prisms (18.0g), m.p. 99-101° (lit.[60] m.p. 98-101°), δ 1.20 (t, 3H, CH_3), 2.93 (g, 2H, CH_2), 3.92 (s, 3H, OCH_3), 5.22 (s,2H, $PhCH_2$), 6.83-7.65 (m, 8H, aryl H).

3,4,5-Trimethoxypropiophenone 19d. — A solution of 3,4,5-trimethoxybenzaldehyde (15 g) in ether (100 ml) was added to a solution of ethylmagnesium bromide, prepared from magnesium (2.75 g), Vitride (1 ml), ethyl bromide (10 ml) and ether (100 ml). The mixture was stirred for 15 min, then worked up in the usual way to give the intermediate arylethylcarbinol as a colourless oil (17 g), δ 0.95 (t, 3H, J 7 Hz, Me), 1.6-1.9 (m, 2H, CH_2), 2.03 (s, 1H, OH), 3.87 (s, 3H,4-OMe), 3.89 (s, 6H, 3- and 5-OMe), 4.45 (t, 1H, J 7 Hz, ArCH) and 6.62 (s, 3H, ArH). To a solution of this alcohol in acetone (100 ml) at 0° was added Jones' reagent (1.4 M, 60 ml), the mixture stirred at room temp. for 1 hr, then worked up by aqueous dilution and ether extraction to yield the ketone 19d as long needles (14.2 g), m.p. 52-53° from light petroleum. δ 1.22 (t,3H, J 7 Hz, Me), 2.97 (q, 2H, J 7 Hz, CH_2), 3.92 (s, 9H, ArOMe) and 7.27 (s, 2H, ArH). The ketone with same m.p. prepared less conveniently from diethylcadmium and 3,4,5-trimethoxybenzoyl chloride as previously described.[19]

α -Bromo-3,4-methylenedioxypropiophenone 17b prepared in quantitative yield by bromine addition in chloroform solution, crystallized from methanol as needles, m.p. 54-55° (lit.[42] m.p. 52-53°). δ 1.89 (d, J 7 Hz, Me), 5.56 (q, J 7 Hz, COCHBr), 6.07 (s, $-OCH_2O-$) and 6.82-7.78 (m, three ArH).

α -Bromo-4-benzyloxy-3-methoxypropiophenone 17c, prepared in quantitative yield in chloroform solution,[61] crystallized from methanol as clusters of needles, m.p. 89-91° (lit m.p. 86-87°,[61] 87-90° [60]), δ 1.69 (d, 3H, CH_3), 3.90 (s, 3H, OMe), 5.20 (s, 2H, $PhCH_2$), 5.24 (q, 1H, CHBr), 6.83-7.70 (m, 8H, aryl H).

α -Bromo-3,4,5-trimethoxypropiophenone 17d. — Bromination of the ketone 19d, (4.48 g) in chloroform solution as previously described[15] gave the bromoketone 17d as needles (5.3 g), m.p. 84-85° from methanol (lit.[15] m.p. 83-84°). δ 1.87 (d, 3H, J 7 Hz, Me), 3.93 (s, 9H, ArOMe), 5.15 (q, 1H, J 7 Hz, CHBr) and 7.35 (s, 2H, ArH).

(±)-2,3-Bis(3,4-methylenedioxybenzoyl) butane 21b.— To liquid ammonia (ca. 100 ml), ferric chloride (a few mg) was added, followed by sodium (430 mg) and the mixture stirred until disappearance of the blue colour. The ketone 19b, (3.0 g)

in tetrahydrofuran (100 ml) was then added and stirred for 15 min., followed by the solid bromoketone 17b, (4.35 g). Stirring was continued for 1 hr., solid ammonium chloride then added, and the ammonia allowed to evaporate. The mixture was filtered, washed with chloroform and the solvents removed. Crystallization of the gum from methylene chloride-methanol gave the diketone 21b as fine needles, (3.0 g), m.p. 206-207° (Found: C, 67.8; H, 5.2. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%). δ 1.26 (d, J 7 Hz, two sec. Me), 3.67-4.03 (m, two -COCH-), 6.05 (s, two $-OCH_2O-$) and 6.82-7.77 (m, six ArH).

(±)-2,3-Bis-(3,4,5-trimethoxybenzoyl)butane 21d. — To liquid ammonia (50 ml) was added ferric chloride (25 mg) followed by sodium (400 mg), and the mixture stirred until disappearance of the blue colour. The ketone 19d (2.6 g) was added with continued stirring for 15 min, followed by the bromoketone 17d (3.5 g). After a further hour, ammonium chloride (3 g) and dichloromethane (50 ml) were added, the ammonia allowed to evaporate and the mixture filtered and washed with dichloromethane (25 ml). The combined filtrate was diluted with methanol and concentrated to yield the racemic diketone 21d as long needles (4.8 g), m.p. 165-166°, ν (KBr) 1660 cm^{-1}. (Found: C, 64.47; H, 6.84. $C_{24}H_{30}O_8$ req. C, 64.56; H, 6.77%). δ 1.32 (d, 6H, J 7 Hz, sec. Me), 3.92 (s, 18 H, ArOMe) and 7.28 (s, 4H, ArH).

(±)-2(4'-Benzyloxy-3'-methoxybenzoyl)-3(3',4'-methylenedioxy) butane 21e. — To liquid ammonia (250 ml), ferric chloride (20 mg) was added, followed by sodium (880 mg) and the mixture stirred until the blue colour disappeared. A solution of 4-benzyloxy-3-methoxypropiophenone (9.3 g) in tetrahydrofuran (150 ml) was then added and stirred for 15 min. A solution of the bromoketone 17b (9.8 g) in tetrahydrofuran (100 ml) was added dropwise over 90 min and stirred for a further 30 min. before ammonium chloride (4 g) was added, and the ammonia allowed to evaporate. The mixture was filtered, washed with tetrahydrofuran (50 ml) and the combined filtrate evaporated under reduced pressure to give a residual light brown solid (16.3 g), a portion of which (10.5 g) was dissolved in benzene (ca. 50 ml) and chromatographed on a column (12" x 1½" dia.) of silica gel (Merck 60). After elution with benzene (100 ml) gave no product and benzene-chloroform (25:2, 500 ml) gave a gum (2.04 g, not further examined), benzene-ethyl acetate (1:1, 500 ml) gave a solid (7.6 g) which on crystallization from methanol gave the butane 21e as spiked prisms (7.1 g), m.p. 113-116°. (Found: C, 72.4; H, 5.9. $C_{27}H_{26}O_6$ requires C, 72.6; H, 5.9%) δ 1.25 (d, J 6 Hz, two sec. Me), 3.67-4.17 (m, two -COCH-), 3.88 (s, ArOMe), 5.22 (s, two $-OCH_2O-$), 6.78-7.77 (m, eleven ArH).

In an experiment in which the bromoketone was added in one portion, all three diketones 21b, 21c and 21e were detected

in the residual product. On chromatography on alumina, elution with benzene-chloroform (10:1 to 4:1) gave the dipiperonylbutane 21c and with chloroform a mixture of 21b and 21e, readily separated by fractional crystallization from methanol, 21e being the more soluble constituent.

Preparation of Cupric Triflate.—Cupric carbonate, 5g (0.0405 mol), was slurried with 200 ml of acetonitrile and 12 g of trifluoro-methanesulfonic acid (0.080 mol) was added slowly, as vigorous evolution of carbon dioxide took place. The solution was stirred for 30 min and filtered; the resulting blue filtrate was concentrated to dryness. The crude salt was rinsed several times with light petroleum ether and then redissolved in acetonitrile. Diethyl ether was added until the solution was cloudy and the solution was allowed to cool to -20° in a freezer. A light blue precipitate was obtained which was dried in a vacuum for 28 hr. The yield of pale blue salt obtained was 8 g.

Meso-2,3-Bis-(3,4,5-trimethoxybenzoyl) butane 18d-(a) n-Butyl lithium (9.1 ml, 2.2 molar in hexane) was added to a solution of di-isopropylamine (2.94 ml) in tetrahydrofuran (18.6 ml) under nitrogen, stirred at 0° for 15 min, then cooled to -78°. A solution of the propiophenone 19d (4 g) in tetrahydrofuran (30 ml) was added with stirring for 1 hour

followed by a solution of copper (I) trifluoromethanesulphonate (7.18 g) in acetonitrile (20 ml). After stirring for a further hour at -78° and 30 min at room temp., ammonium chloride (6 g) was added and the mixture poured into ice-water and extracted with ether. The solid which precipitated at the interfacial layer was collected and recrystallized from dichloromethane-methanol to give the meso-diketone 18d as long needles (1.3 g) m.p. 194-196°. (Found: C, 64.40; H, 6.80. $C_{24}H_{38}O_8$ req. C, 64.56; H, 6.77%). δ 1.17 (d, 6H, J 7 Hz, sec. Me), 3.97 (s, 18H, ArOMe) and 7.33 (s, 4H, ArH).

Evaporation of the washed and dried ether layer yielded the (±)-diketone 21d, (2.1 g) identical to that prepared by alkylation of ketone 19d with bromoketone 17d.

(b) A solution of sodium methoxide (90 mg) in methanol (10 ml) was added to a solution of the (±)-diketone 21d in tetrahydrofuran (20 ml)-diethyl ether (50 ml) and the mixture stirred at room temp. overnight, the precipitated meso-diketone (302 mg, m.p. 196-197°) was collected. Concentration of the filtrate gave, after one day, a further 72 mg of the same product. The meso-diketone was also rather soluble in methanol, cyclohexane, and acetic acid.

3,4-Dimethyl-2,5-bis(3',4',5'-trimethoxyphenyl) furan 28d. — To a solution of the racemic diketone 21d, (700 mg)

in dichloromethane (4 ml) was added 4 ml of an aqueous methanolic hydrogen chloride solution (made by diluting 5 ml of conc. hydrochloric acid to 100 ml with methanol). The mixture was heated under reflux for 10 min, and cooled, to yield the furan 28d as prisms (653 mg), m.p. 155-157°. (Found: C, 67.34; H, 6.41. $C_{24}H_{28}O_7$ req. C, 67.27; H, 6.59%). δ 2.23(s, 6H, Me), 3.91 (s, 6H, Ar 4'-OMe), 3.95 (s, 12H, 3' and 5'-ArOMe) and 6.91 (s, 4H, ArH).

Treatment of the meso-diketone 18d (500 mg, as prepared below) under the same conditions yielded the same furan (460 mg

r-2, c-5-Bis-(3',4',5'-trimethoxyphenyl)-c-3, c-4-dimethyl tetrahydrofuran 29d. — A solution of the furan 28d, (1.5 g) in acetic acid (20 ml) was stirred with palladium-carbon (10%, 3.5 g) under hydrogen for 16 hr. After filtration and evaporation, the residual oil (1.26 g) was crystallized from ether to yield the meso-cis-tetrahydrofuran 29d as prisms, m.p. 109-110°. (Found: C, 66-83; H, 7.50. $C_{24}H_{32}O_7$ req. C, 66.65; H, 7.46%). δ 0.67 (d, 6H, J 7 Hz, C-3 and -4 Me), 3.88 (s, 18H, ArOMe), 5.15 (d, 2H, J 7 Hz, H-2 and -5) and 6.70 (s, 4H, ArH).

Under a variety of catalytic hydrogenation conditions in tetrahydrofuran solution at pressures up to 2000 lb/in^2, 29d was recovered unchanged.

Dehydration of Racemic Unsymmetric Diol 35d. — a) With methanesulphonyl chloride. Methanesulphonyl chloride (1 ml) was added to a solution of the diol 35d, (650 mg) in pyridine (20 ml) at room temperature. The mixture was stirred for 20 hr., then worked up via ether to yield a light brown oil (475 mg) which crystallized from ether-light petroleum the meso-trans-tetrahydrofuran, t-3, t-4-dimethyl-r-2, C-5-bis-(3,4,5-trimethoxyphenyl) tetrahydrofuran 30d, as m.p. 90-92° (308 mg) (lit.[37], m.p. 90-90.5°). δ 1.07 (d, 6H, J 7 Hz, C-3 and 4 Me), 2.1-2.6 (m, 2H, H-3 and 4), 3.85 (s, 18H, six OMe), 4.52 (d, 2H, J 6 Hz), and 6.70 (s, 4H, ArH). Inspection of the p.m.r. spectrum of the crude reaction product indicated it was a mixture of the meso-trans 30d and meso-cis 29d isomers in a 7:1 ratio. The same result was obtained by carrying out the reaction for 15 min. at 0° with dichloromethane-tri-n-butylamine as solvent. The meso-trans-tetrahydrofuran was recovered unchanged from attempted catalytic hydrogenolysis with palladium-carbon in tetrahydrofuran.

b) With triphenylphosphine dibromide. A solution of the diol 35d (500 mg) in acetonitrile (5 ml) was added dropwise at room temperature to a solution of triphenylphosphine dibromide, prepared at 0° by addition of bromine (360 mg) to triphenylphosphine (620 mg) in acetonitrile (10 ml). The mixture was stirred for 10 min., then filtered and evaporated.

The residue was dissolved in benzene-ether (4:1) and filtered through a silica column (4" x ½" dia). Elution with the same solvent (80 ml) gave a colourless oil (62 mg) followed by the meso-trans-tetrahydrofuran 30d (367 mg) eluted by the next 200 ml of solvent.

2,3-Dimethyl-1,4-diveratrylbutane-1,4-diol 36a. — Lithium aluminium hydride (0.5 g) in tetrahydrofuran (10 ml) was added to a solution of the diketone 21a, (500 mg) in the same solvent the mixture stirred at room temp. for 1 hr., then worked up in the usual way. Crystallization of the product (500 mg), once from ethanol, then from chloroform-light petroleum yielded the diol 36a as flakes, m.p. 125-126° (Found: C, 67.6; H, 7.7. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.7%). δ 0.59 (d, J 7 Hz, sec. Me), 1.05 (d, J 7 Hz, sec. Me), 1.80-2.45 (m, two CHMe), 3.88 (s, four OMe), 4.2-4.7 (m,two ArCHOH-), and 6.65-6.95 (m, six ArH).

Acetylation with acetic anhydride-pyridine in the usual way gave a non-crystalline diacetate, δ 0.66 (d, J 7 Hz, sec. Me), 1.03 (d, J 7 Hz, sec. Me), 2.03 (s, OAc), 2.07 (s, OAc), 3.78, 3.82, and 3.88 (all s, 1,1 and 2 OMe resp.), 5.51 (d, J 3.5 Hz ArCH) 5.67 (d, J 3.5 Hz, ArCH) and 6.58-6.86 (m, six ArH

2,3-Dimethyl-1,4-dipiperonylbutane-1,4-diol 36b, — A suspension of the diketone 21b, (1.0 g) in tetrahydrofuran

(20 ml) was added to lithium aluminium hydride (1.0 g) in the same solvent (20 ml), the mixture stirred for 1 hr. and worked up in the usual way. Crystallization of the product from chloroform-hexane afforded the diol 36b as rosette clusters (650 mg), m.p. 141-142°. (Found: C, 67.0; H, 6.25. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%), δ 0.54 (d, J 7 Hz, sec. Me), 1.02 (d, J 7 Hz, sec. Me), 2.00-2.57 (m, two CHMe), 4.32 (d, J 9 Hz, ArCHOH), 4.53 (d, J 8 Hz, ArCHOH), 5.93 and 5.97 (both s, two $-OCH_2O-$) and 6.67-6.95 (m, six ArH).

2,3-Dimethyl-1,4-Bis-(3',4',5'-trimethoxybenzoyl) butane -1,4-diol 36d. — A solution of the racemic diketone 21d, (0.5 g) in tetrahydrofuran (30 ml) was added to lithium aluminium hydride (0.5 g) in the same solvent (10 ml), the mixture stirred at room temp. for 1 hr, then worked up in the usual way. Trituration of the product with chloroform-light petroleum gave the racemic unsymmetrical diol 36d, as a solid of indefinite m.p. (softening ca. 135-140° with cleaving ca. 165-176°). Found: C, 63.89; H, 7.70. $C_{24}H_{34}O_8$ req. C, 63.98; H, 7.61%). δ 0.72 (d, 3H, J 7 Hz, sec. Me), 1.08 (d, 3H, J 7 Hz, sec. Me), 2.0-2.25 (m, 2H, H-2 and H), 3.82 and 3.85 (each s, 18H, six ArOMe), 4.2-4.7 (m, 2H, ArCHOH-), 6.48 (s, 2H, ArH) and 6.62 (s, 4H, ArH).

and crystallized from hexane to give 1,2,3,4-tetrahydro-6, 7,8-trimethoxy-t-2, t-3-dimethyl-r-1-(3',4',5'-trimethoxyphenyl) naphthalene 39d as prisms (98 mg), m.p. 105-107°. (Found: C, 69.41; H, 7.80. $C_{24}H_{32}O_6$ req. C, 69.21; H, 7.74%). δ 0.90 (d, 3H, J 6 Hz C-3 or 3 Me), 0.93 (d, 3H, J 7 Hz, C-3 or 2 Me), 1.6-2.1 (m, 2H, H-2 and 3), 2.2-2.8 (m, 2H, $ArCH_2$), 3.40 (s, 3H, 8-OMe), 3.75 (s, 6H, two ArOMe), 3.81 (s, 6H, two ArOMe), 3.87 (s, 3H, ArOMe), 4.02 (d, 1H, J = 2.5 Hz, H-1), 6.22 (s, 2H, H-2' and 55') and 6.47 (s, 1H, H-5).

b) By lithium aluminium hydride. Lithium aluminium hydride (0.5 g) was added to a solution of the meso-diketone (410 mg) in tetrahydrofuran, stirred at room temperature for 1 hr., then worked up in the usual way to give the racemic unsymmerica diol, (I RS, 2 SR, 3 RS, 4 RS)-1,4-bis-(3',4',5'-trimethoxyphenyl)-2,3-dimethylbutane-1,4-diol 35d as an amorphous solid, (Found: C, 64.00; H, 7.61. $C_{24}H_{34}O_8$ req. C, 63.98; H, 7.61%). δ 0.66 (d, 3H, J 7 Hz, sec. Me), 0.92 (d, 3H, J 7 Hz, sec. Me), 1.8-2.2 (m, 2H, H-2 and 3), 3.83 (s, 18H, six ArOMe), 4.2-4.4 (m, 1H, ArCHOH-), 4.6.4.9 (m, 1H, ArCHOH-) and 6.52 (s, 4H, ArH).

(±)-Dihydroguaiaretic Acid Dimethyl Ether 26a. — Palladium-charcoal (10%, 500 mg) was added to a solution of the diketone 21a (500 mg) in ethanol (50 ml) and stirred under hydrogen for

20 hr. One crystallization of the residue, obtained by removal of catalyst and solvent, from methanol gave the (±)-dimethyl ether 26a as prisms (260 mg) m.p. 71° (lit[43] m.p. 70.4-71.2°), δ 0.84 (d, J 6.5 Hz, two sec. Me), 1.5-1.95 (m, two CHMe), 2.3-2.65 (m, four $ArCH_2$), 3.80 (s, two OMe), 3.82 (s, two OMe) and 6.55-6.85 (m, six ArH).

(±)-1,4-Bis(3',4'-methylenedioxyphenyl)-2,3-dimethylbutane (±)-Austrobilignan-5 26b.—(a) A solution of the diol 36b, (300 mg) in acetic acid (50 ml) was stirred under hydrogen with palladium-charcoal (10%, 200 mg) overnight, and worked up in the usual way to yield (±)-austrobilignan-5 26b as an oil, with n.m.r. spectrum in excellent agreement with that reported for (-)-austrobilignan.

A solution of bromine (two equiv.) in chloroform was added to 26b (260 mg) in the same solvent, the mixture heated under reflux for 5 min., treated with charcoal, filtered and evaporated. Crystallization of the product from methanol gave (±)-1,4-bis (2'-bromo-4',5'-methylenedioxyphenyl)-2,3-dimethylbutane as prisms (150 mg), m.p. 135-136°. (Found: C, 49.6; H, 4.2. $C_{20}H_{20}Br_2O_4$ requires C, 49.6; H, 4.2. δ 0.88 (d, J 7 Hz, two sec. Me), 1.50-2.25 (m, two CHMe), 2.33-3.00 (m, two $ArCH_2$), 5.93 (s, two $-OCH_2O-$), 6.60 (s, two H-6') and 6.97 (s, two H-3') (b) Hydrogenation of the diketone 21b

(201 mg) in acetic acid (50 ml) with palladium-carbon (10%, 460 mg) gave 26b, identical to that prepared in (a).

(±)-1,4-Bis-(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane 26d. — (a) A solution of the (±)-unsymmetrical diol 36d, (350 mg) in acetic acid (20 ml) was stirred with palladium-carbon (10%, 0.3 g) under hydrogen for 72 hr. After filtration and evaporation, the residue was crystallized from methanol to give the (±)-dimethylbutane 26d as prisms, m.p. 126-128° (lit.[37] m.p. 129-130°. (Found: C, 68.97; H, 8.23. Calc. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19%). δ 0.86 (d, 6H, J 6 Hz, C-2 and 3 Me), 1.5-2.0 (m, 2H, H-2 and 3), 2.35-2.65 (m, 4H, $ArCH_2$), 3.76 (s, 12H, four ArOMe), 3.79 (s, 6H, two ArOMe) and 6.30 (s, 4H, ArH).

(b) To liquid ammonia (100 ml), sodium (ca. 70 mg) was added, followed by a solution of the tetrahydrofuran 27d, (700 mg) in 1,2-dimethoxyethane (30 ml). More sodium (240 ml) was then added and the mixture stirred for 10 min. After addition of water (6 ml), the ammonia was allowed to evaporate and the dimethoxyethane removed under reduced pressure. The residue was dissolved in dichloromethane, washed with water, dried and evaporated to yield a product mixture (580 mg) which was chromatographed on alumina (Grade 3). Elution with ether-light petroleum (1:5) gave after one crystallization the same (±)-dimethylbutane (100 mg), m.p. 125-127° as obtained in (a).

(±)-1(3',4'-Dimethoxyphenyl)-4(3',4'-methylenedioxyphenyl)-2,3-dimethylbutane (±)-Austrobilignan-6 26e'. — A solution of the diketone 21e (510 mg) in acetic acid (100 ml) was stirred with palladium-carbon (10%, 2g) under hydrogen for 3½ hr. Filtration and solvent removal gave (±)-austrobilignan-6 26e' as a gum (390 mg), PMR spectrum, same as lit.[17]

Sodium-Ammonia Reduction of meso-trans-Tetrahydrofuran 30d. — To a liquid ammonia (100 ml), sodium (0.1 g) was added followed by a solution of the meso-trans-tetrahydrofuran 30d, (720 mg), in 1,2-dimethoxyethane. More sodium (0.3 g) was then added and the mixture stirred for 15 min. After addition of water (8 ml), the ammonia was allowed to evaporate, and dichloromethane (65 ml) was added to the residue, which was filtered and evaporated. The product was subjected to preparative t.l.c. (benzene (85)-ether (15)). The front-running zone (R_f 0.75) gave meso-1,4-bis-(3,5-dimethoxyphenyl)-2,3-dimethylbutane 45 (51 mg) as a colourless oil, which did not crystallize from the common solvents, δ 0.87 (d, 6H, J Hz, C-2 and 3 Me)1.5-2.0 (m, 2H, H-2 and 3), 2.2-2.9 (m, 4H, $ArCH_2$), 3.77 (s, 12H, four ArOMe) and 6.33 (s, 6H, six ArH). An intermediate zone (R_f 0.55) yielded 173 mg of an unidentified mixture. The third zone (R_f 0.33) gave meso-1,

4-bis-(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane 25d as short prisms (394 mg) from methanol, m.p. 87-89°. (Found: C, 68.82; H, 8.23%. $C_{24}H_{34}O_6$ reg. C, 68.87; H, 8.19%). δ 0.88 (d, 6H, J 6 Hz, C-2 and 3 Me), 1.5-2.0 (m,2H, H-2 and 3), 2.2-2.9 (m, 4H, $ArCH_2$), 3.85 (s, 18H, six ArOMe), and 6.38 (s, 4H, four ArH).

Hydrogenolysis of meso-cis-Tetrahydrofuran 29d. — The meso-cis tetrahydrofuran (740 mg) was treated with sodium and ammonia in the same manner as the meso-trans isomer, and gave an oil (602 mg) which t.l.c. purfication (ether-light petroleum (1:1) gave an oil (310 mg) considered to be 46d. δ 0.66 (d, 3H, J 7 Hz, sec. Me), 0.91 (d, 3H, J H Hz, sec. Me), 1.7-2.3 (m, 2H), 3.95 (s, 18H, six ArOMe), 4.40 (d, 1H, ArCHO-), 6.47 (s, 2H, two ArH), and 6.57 (s, 2H, two ArH). A solution of this product (250 mg) in acetic acid (50 ml) was stirred under hydrogen with palladium-carbon (10%, 250 mg) for 20 hr. Work-up in the usual way gave the meso-diaryl butane 25d, (166 mg).

(±)-Deoxyschizandrin 43d. — Trifluoracetic acid methylene chloride (1:4, 10 ml) was added to a solution of the hexamethoxy-diarylbutane 25d, (54 mg) in methylene chloride (15 ml) at -78° and the mixture stirred for 10 min. Vanadium oxytrifluoride (100 mg) was then added with stirring at the same temperature

for 30 min and at room temperature for a further 30 min. After solvent removal, concentrated ammonium hydroxide solution (3 ml) was added and the mixture extracted with ether. Evaporation of the washed and dried extract gave a solid (49 mg) which on t.l.c. (ether-light petroleum (1:1) gave a front running zone, which on elution and crystallization from methanol gave 5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-trans-6,7-dimethyldibenzo a,c cyclo-octene (deoxyschizandrin 43d as short prisms (20 mg) from methanol, m.p. 114-115° (lit[52] m.p. 112-113°), δ 0.73 (d, 3H, J 7 Hz, sec. Me), 1.00 (d, 3H, J 7 Hz, sec. Me), 1.9-2.1 (m, 2H, H-6 and 7), 2.2-2.7 (m, 4H, two $ArCH_2$), 3.60 (s, 6H, two ArOMe), 3.90 (s, 12H, four ArOMe) and 6.55 (s, 2H, two ArH).

Action of Vanadium Oxyfluoride on meso-Dihydroguaiaretic Acid Dimethyl Ether 25a. — To a solution of the ether 25a, (180 mg, 0.5 mmole) in dichloromethane (10 ml) containing (372 mg, 3 mmole) in dichloromethane (10 ml) containing trifluoroacetic acid (1 ml) over 10 min. at 5°. The mixture was stirred at room temp. for 2 hr., poured on to ice, and the separated organic layer washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. The residue was chromatographed on a column of alumina (Grade III), elution with ether-light petroleum (1:4) giving a fraction

(80 mg) which crystallized from the same solvents to give cis-6,7-dimethyl-5,6,7,8-tetrahydro-2,3,10,11-tetramethoxydibenzo a,c cyclo-octene 43a as needles, m.p. 175-177°. (Found: C, 74.31; H, 7.58. $C_{22}H_{28}O_4$ req. C, 74.13; H, 7.92%). δ 0.80 (d, 3H, J 6 Hz, sec. CH_3), 1.05 (d, 3H, J 6 Hz, sec. CH_3), 1.04-2.0 (m, 2H, MeCH), 2.05-2.66 (m, 4H, $ArCH_2$), 3.88 (s, 6H, ArOMe), 3.93 (s, 6H, ArOMe) and 6.75 (s, 4H, ArH).

Treatment of diaryl butane 26a with VOF_3.— 280 mg of product 26a dissolved in 50 ml of methylene chloride was treated with 5 ml of 14% trifloroacetic anhydride trifloroacetic acid and stirred at -78°C for 10 min. Then 286 mg of VOF_3 was added and stirred for 1 hr after which the temp. was raised to 0°C and stirred for 2 hrs. at that temperature. 12 g of citric acid was added and stirred at room temp. for ½ hr, 50 ml water added and methylene chloride layer washed two more times with ca. 50 ml of water and then dried over Na_2SO_4 and evaporated to give 242 mg light brown residue. Passing the product through florasil with benzene gave colorless oily product 211 mg which could not be crystallized from common solvents. Nmr corresponds well to structure 45a.

Action of Vanadium Oxyfluoride on (±)-1,4-Bis(3',4'-methylenedioxyphenyl)-2,3-dimethylbutane 26b. — Vandium

oxyfluoride (0.5 g) was added to a solution of the butane 26b, (220 mg) and trifluoroacetic acid (6 ml) in dichloromethane (55 ml) at 0°. The mixture was stirred at 0° for 1 hr. and at room temperature for a further 3 hr. Citric acid (3 g) was then added, followed by water, and the separated organic layer washed with water and 10% sodium carbonate solution. Evaporation of the dried (Na_2SO_4) extract gave a residual brown solid (210 mg) which was dissolved in benzene and filtered through Florisil (F-101) to yield a colourless solid (129 mg) which crystallized from methanol to give trans-6,7-dimethyl-5,6,7,8-tetrahydro-2,3,10,11-bismethylenedioxy-dibenzo- a,c cyclo-octene 45b as long prisms, m.p. 251-252°. (Found: C, 74.10; H, 6.40. $C_{20}H_{20}O_4$ req. C, 74.05; H, 6.22%). δ (measured at 200 MHz) 1.03 (d, 6H, J 6 Hz, sec. CH_3), 1.25 (br,s, 2H, MeCh), 2.23 and 2.31 (6-line m, 4H, J_{gem} 14 Hz, J_{vic} 9.5 and 1 Hz, $ArCH_2$), 5.94 (s, 4H, OCH_2O), 6.70 (s, 2H, ArH) and 6.74 (s, 2H, ArH).

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PART II

ISOLATION AND STRUCTURE ELUCIDATION OF CONSTITUENTS OF *ELAEGIA UTILIS*

FLAVONE AND TRITERPENES CONSTITUENTS FROM ELAEGIA UTILIS

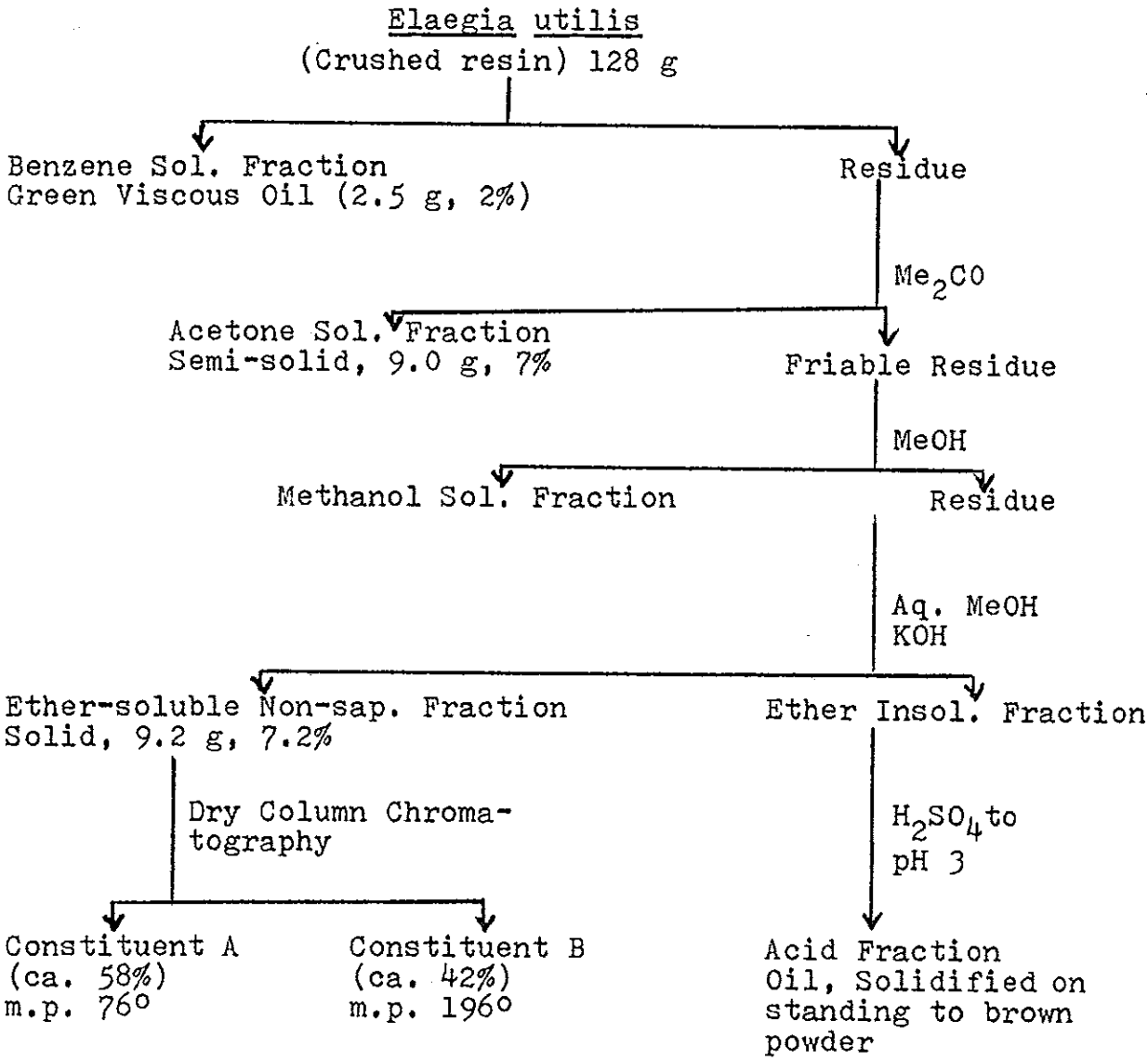
Elaegia utilis is found in the Departamento of Narino, Colombia in cold soil regions (2500-3000 metres altitude). The buds yield a resin, known locally as Barniz de Pasto. It was Provided by Dr. Alvano Fernádez-Pérez of the Instituto de Ciencias Naturales, Universidad National de Colombia.

Barniz de Pasto is used both as an adhesive and as a fine translucent wood finish. It has also found use as a protective coating for paintings.[1] The isolation and identification of constituents isolated by neutral solvent extraction and from the non-saponifiable fraction was carried out (Scheme 2-1).

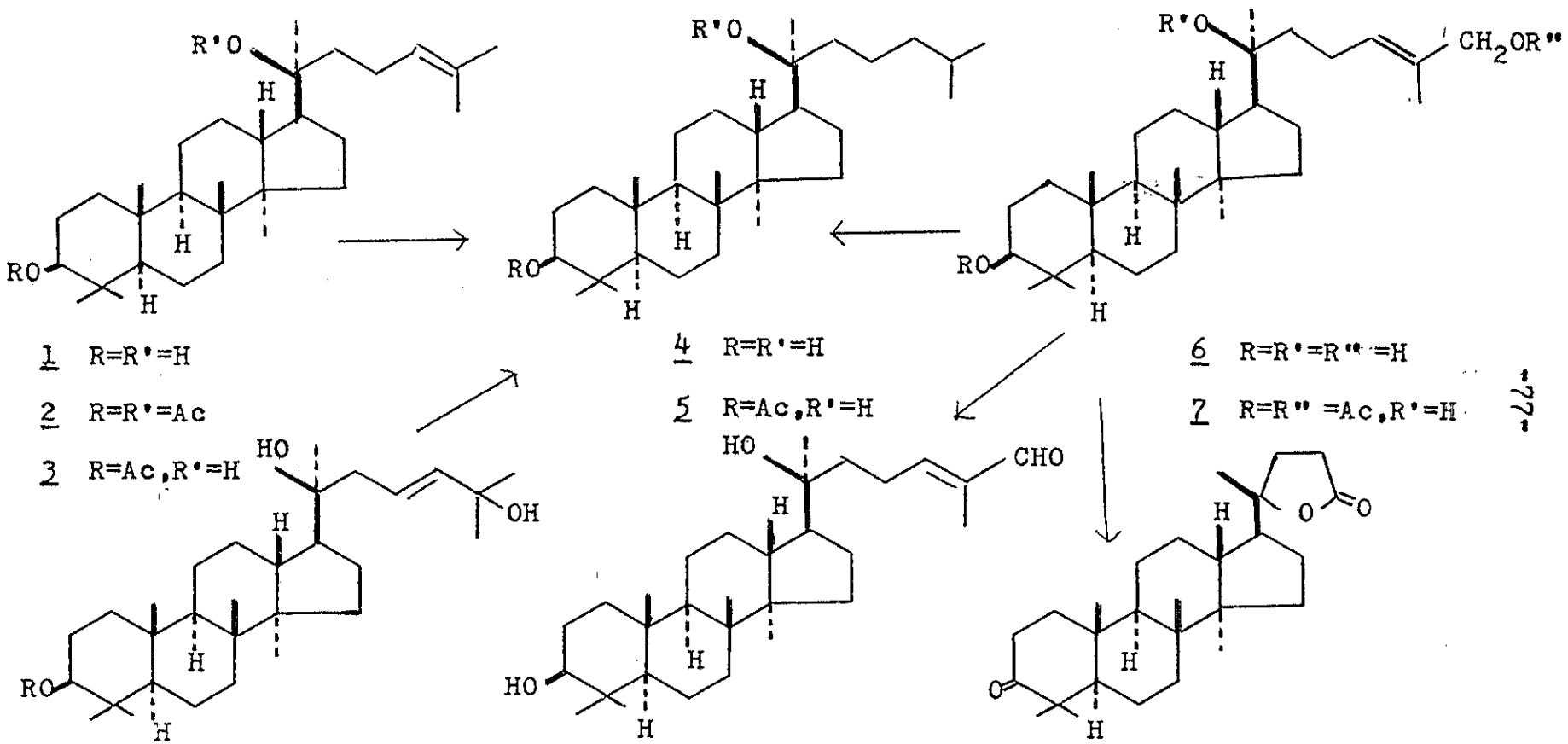
The resin was successively extracted with benzene, acetone and methanol and the insoluble residue saponified. From the neutral non-saponifiable fraction, there were obtained two products (designated constituents A and B) readily separated by silica gel thin layer or dry column chromatography.[2]

Constituent A was identified as a low-melting modification of 3β ,20S-dihydroxydammar-24-ene (dammarenediol-II), 1 a tetracyclic triterpene diol previously isolated from

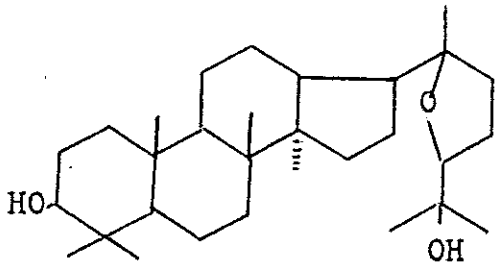
Scheme 2-1


Elaegia utilis
(Crushed resin) 128 g
Benzene Sol. Fraction
Green Viscous Oil (2.5 g, 2%)
Residue
Me2CO
Acetone Sol. Fraction
Semi-solid, 9.0 g, 7%
Friable Residue
MeOH
Methanol Sol. Fraction
Residue
Aq. MeOH
KOH
Ether-soluble Non-sap. Fraction
Solid, 9.2 g, 7.2%
Ether Insol. Fraction
Dry Column Chroma-
tography
H2SO4 to
pH 3
Constituent A
(ca. 58%)
m.p. 76°
Constituent B
(ca. 42%)
m.p. 196°
Acid Fraction
Oil, Solidified on
standing to brown
powder

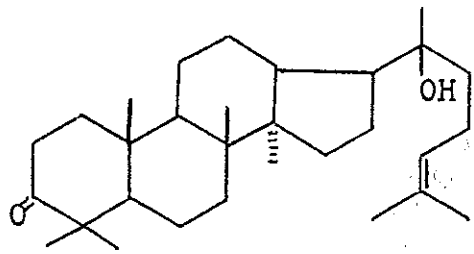
dammar resin.[3,4] Although it was obtained beautifully crystalline from aqueous ethanol and with empirical analysis in agreement for molecular formula $C_{30}H_{50}O_2$, immediate identification of this product as 1 was precluded by several apparent discrepancies. The melting point (range 75-79°) was incompatible with that reported (range 130-134°) by several groups.[3,5,6] The mass spectrum did not reveal the corresponding molecular ion, but instead the $M-H_2O^+$ parent peak apparently customary for tertiary alcohols of this type.[7] Characterization by acetylation, furthermore, yielded in addition to a monoacetate (with constants in excellent agreement with those reported for dammerenediol-II monoacetate 3), a diacetate $C_{34}H_{56}O_4$ hitherto unreported. The n.m.r. spectra of constituent A and the two acetate derivatives, for which excellent comparison data exist,[8-10] were consistent with their formulation as 1-3. In addition, catalytic hydrogenation of the diol 1 and monoacetate 3 yielded respectively the known dihydro products, 4 and 5. The possibility that the low melting point of 1 might be attributable to mixed crystal formation with an unidentified impurity was considered unlikely, since the isolated diol yielded the monoacetate derivative in ca. 98% isolated yield when the acetylation was conducted at room temperature. The dimorphic nature of dammarenediol-II was finally established by crystallization interchangeably


R'O
RO
H
CH_2OR''
HO
OH
CHO
O
1 R=R'=H
2 R=R'=Ac
3 R=Ac,R'=H
4 R=R'=H
5 R=Ac,R'=H
6 R=R'=R''=H
7 R=R''=Ac,R'=H
10 R=H
11 R=Ac
9
8

from aqueous ethanol or nitromethane to yield the respective lower and higher melting forms. Of relevance, work on the structure elucidation of ocotillol 15 required dammarenediol-II monoacetate which was obtained by sodium borohydride reduction of the ketone, dipterocarpol 16 followed by acetylation.[11]



15

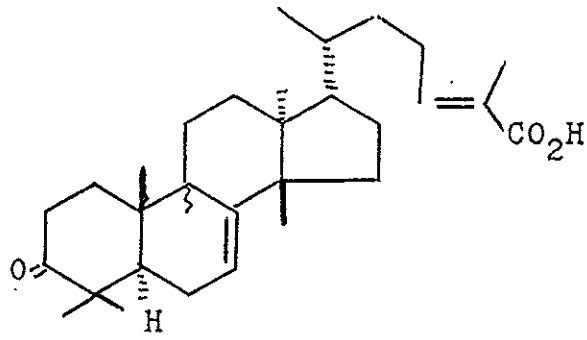


16

The intermediate alcohol (flakes, m.p. 78.5-82° from methanol) was presumbly the same form of dammarenediol-II as here reported.

Constituent B had a molecular formula, $C_{30}H_{52}O_3$, and gave a negative tetranitromethane unsaturation test although the n.m.r. spectrum indicated one vinyl proton. On acetylation at room temperature, it yielded a diacetate derivative which gave a positive yellow colour with tetranitromethane. From this it was concluded that constituent B possessed an allylic alcohol function. Of more import, on catalytic

hydrogenation, it gave in excellent yield dammarane-3β, 20S-diol 4. This greatly simplified the structure elucidation, since it now necessitated only the appropriate locating of the double bond and allylic hydroxyl group. On oxidation with Jones reagent, constituent B yielded the known[3,4,12] keto-trisnorlactone 8, thus restricting placement of the allylic alcohol functionality to the terminus of the dammarane sidechain. Of the remaining structure possibilities, we favour formulation of constituent B as 3β, 20S, 26-trihydroxydammar-24-ene 6. Since the hydrogenation evidence established the presence of secondary and tertiary alcohol functions, a two proton multiplet shown by the triol at δ 4.20 in the n.m.r. spectrum (shifted to δ 4.47 in the derived diacetate) supports the conclusion that the remaining hydroxyl function is primary. In additional support, oxidation of the triol with manganese dioxide in tetrahydrofuran yielded a conjugated aldehyde 9. An assignment of configuration to the double bond is not totally unequivocal. We favour the trans (E)-configuration for the parent triol (as in formula 6), since the low field chemical shift value of the olefinic proton in the derived aldehyde 9 suggests strong deshielding by the carbonyl function. The aldehyde does, however, have a rather low ultraviolet molecular extinction coefficient; a similar situation pertains with masticadienonic acid.[13,14]

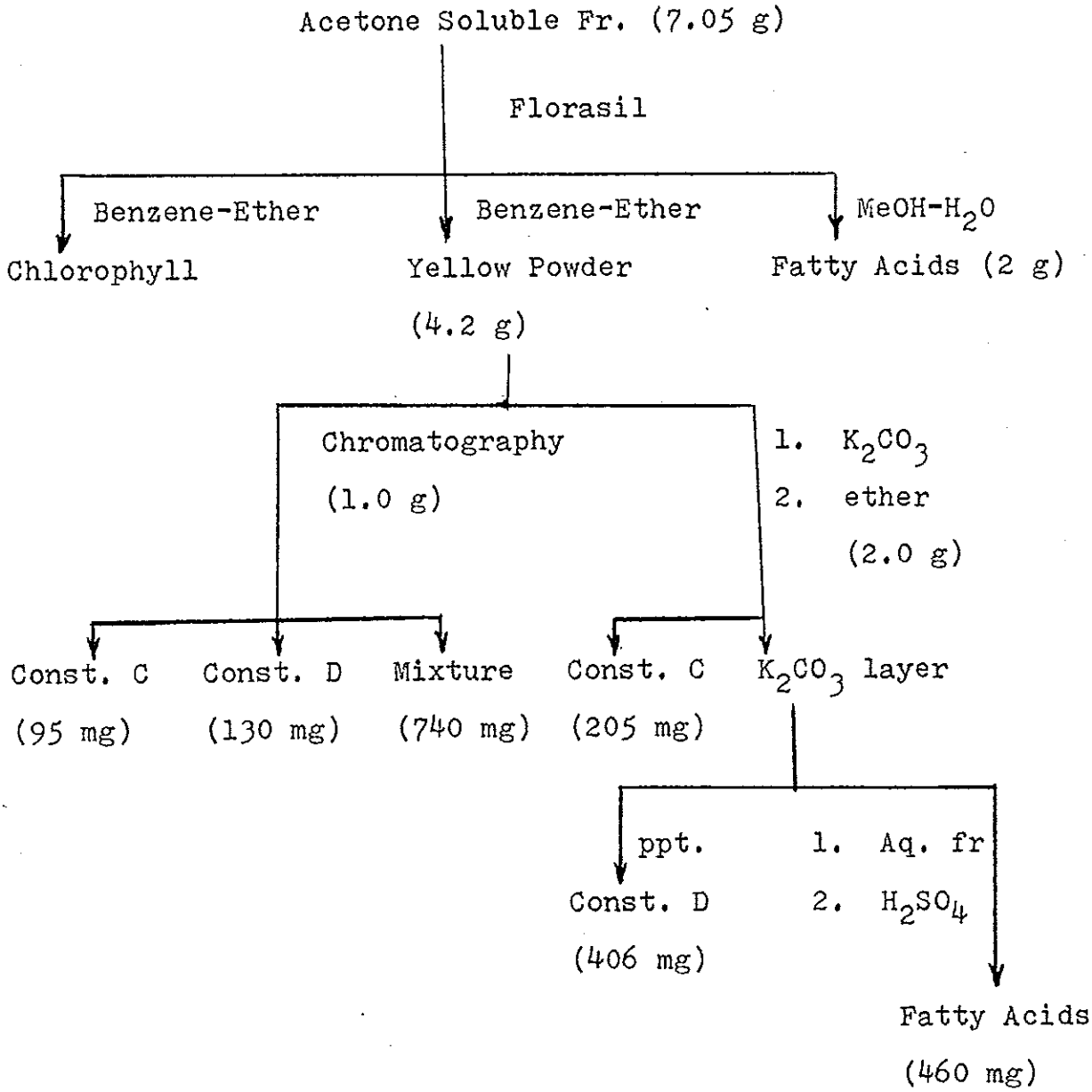


Masticadienonic Acid

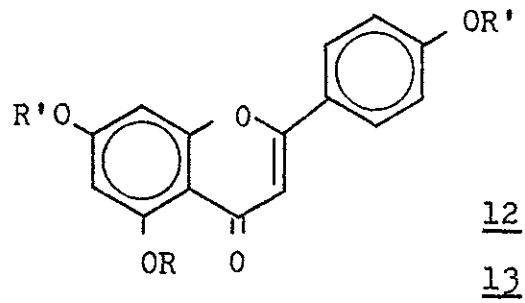
From the acetone-soluble fraction, two products (constituents C and D) were readily separated and identified [scheme 2-2]. The empirical constants and n.m.r. spectrum of constituent C corresponded closely to those reported for isofouquierol, a dammarane triterpenoid recently isolated from Fouquiera splendens Engelm and for which the structure 10, on the basis of the n.m.r. spectrum and without configuration assignment was suggested.[15] This identification was confirmed by formation of the monoacetate derivative 11 with concordant data. Since we have also converted 10 by catalytic hydrogenation to dammarane-3β, 20S-diol 4, this establishes the constitution of isofouquierol as 3β,20S,25-trihydroxy-dammar-23-ene.

Constituent D, which was separated from 10 either by dry column chromatography or extraction by aqueous potassium

Scheme 2-2


Acetone Soluble Fr. (7.05 g)
Florasil
Benzene-Ether
Chlorophyll
Benzene-Ether
Yellow Powder
(4.2 g)
MeOH-H2O
Fatty Acids (2 g)
Chromatography
(1.0 g)
1. K2CO3
2. ether
(2.0 g)
Const. C
(95 mg)
Const. D
(130 mg)
Mixture
(740 mg)
Const. C
(205 mg)
K2CO3 layer
ppt.
Const. D
(406 mg)
1. Aq. fr
2. H2SO4
Fatty Acids
(460 mg)

carbonate, was obtained as a yellow solid whose mass spectrum (M^+ 270) indicated a molecular formula $C_{15}H_{10}O_5$. With diazomethane, it yielded a dimethyl ether derivative (M^+ 298) and with pyridine-acetic anhydride treatment a tri-acetate derivative (M^+ 396). The n.m.r. spectra of constituent D and derivatives were consistent with formulation of the former as the flavone, 4',5,7-trihydroxyflavone (apigenin) 12 and this was confirmed by direct comparison



12 R=R'=H

13 R=R'=Ac

14 R=H,R'=Me

with an authentic specimen and derivatives. The n.m.r. and mass spectra of apigenin and derivatives are readily interpreted from the existing data available from general reviews of flavonoid compounds.[16]

From the benzene-soluble fraction, dammarenediol-II 1 was obtained by thin layer chromatographic separation.

EXPERIMENTAL

N.m.r. spectra were determined for solutions in [^{2}H]-chloroform (unless otherwise stated) with tetramethylsilane as internal standard. Analytical and preparative thin layer chromatography procedures were carried out on Silica Gel 60PF-254+366 (Merck) and Silica Gel 60(70-230 mesh)(Merck) respectively. M.p. 's were determined with either a Gallenkamp or Fisher-Johns apparatus and are uncorrected.

Fractionation of Elaegia utilis Resin. — The hard resin (128 g, crushed by hammering) was placed in a Soxhlet thimble and extracted with benzene for two days to yield a green viscous oil (2.5 g, 2%), then with acetone for the same time to give a greenish gummy solid (9.0 g, 7%). The insoluble fraction, then in a friable state, was ground to a fine powder and re-extracted wiht methanol to give a thick brown oil (2.5 g, 2%).

The residue was heated under reflux with 50% aqueous methanol (600 ml) containing potassium hydroxide (30 g) for 2 hr, cooled, diluted with water (600 ml) and extracted with ether (3 x 250 ml). Evaporation of the washed and dried (Na_2SO_4) extract yielded the neutral non-saponifiable fraction

as a white solid (9.2 g, m.p. ca. 100-150°). Acidification of the aqueous phase precipitated a less dense oil, which on separation and standing 2-3 days solidified to a brown powder (ca. 70%).

Isolation of Constituents A and B from Neutral Non-Saponifiable Fraction.

(a) Thin layer chromatography. A solution of the solid (100 mg) in tetrahydrofuran (ca. 1 ml) was applied as a band to a silica gel G plate (1 mm; 20 x 20 cm) and developed with benzene-ether (3:1). Visualization with iodine revealed two zones (R_f 0.3-0.5 and 0.0-0.2), each of which was extracted with ether. Solvent removal from higher R_f zone gave constituent A (52 mg, m.p. 75° after one crystallization from aqueous ethanol) and from lower R_f zone constituent B (40 mg, m.p. 196° from ethanol).

(b) Dry column chromatography. Silica gel (100 g) was dried at 110° for 24 hr, then deactivated by addition of 12 ml water. To a solution of the neutral fraction (20 g) in tetrahydrofuran (50 ml), silica gel (20-30 g) was added, and the solvent removed under pressure in a rotary evaporator. The resultant free-flowing solid was added to the top of a column of silica gel (25 x 2" dia.) which was then percolated with benzene-ether (85:15). The first 150 ml of eluate contained

no product, and the subsequent 2500 ml was evaporated to give constituent A (11.5 g, homogeneous by t.l.c., R_f 0.60, benzene-acetonitrile (4:1)). Elution with methanol (2000 ml) then yielded constituent B (8.1 g, homogeneous by t.l.c., R_f 0.30, same solvent system).

Identification of Constituent A as Dammarenediol-II (3β, 20S-Dihydroxydammar-24-ene) 1-(a) Crystallization of constituent A from aqueous ethanol gave beautiful long needles, m.p. 75-76°, $[\alpha]_D$ + 34° (c, 0.9), ν 3350 cm^{-1}, yellow colour with tetranitromethane. (Found: C, 81.1; H, 11.8. Calc. for $C_{30}H_{52}O_2$: C, 81.0; H, 11.8%). (Found 426.3875. $C_{30}H_{50}O(M-H_2O)^+$ requires M^+ 426.3862. δ 0.77, 0.84, 0.87, 0.97(2), 1.14 (six tert. Me groups), 3.19 (m, 3α-H) and 5.07 (m, H-24).
(b) Acetylation at 100°. A mixture of constituent A (2.01 g), pyridine (50 ml) and acetic anhydride (50 ml) was heated on the steam-bath for 24 hr, then worked up in the usual way to give a solid product (2.21 g, R_f 0.26, 0.47, benzene-ether (2:1)). A solution of the product (850 mg) in light petroleum (100 ml) was chromatographed on alumina (25 x 2.5 cm) and eluted successively with light petroleum (400 ml), light petroleum-benzene (1:1, 200 ml), benzene (300 ml), benzene-ether (9:1, 200 ml) and benzene-ether (4:1, 500 ml). After the first 860 ml eluted nothing, the next 170 ml gave 3β, 20S-diacetoxy-

dammar-24-ene 2 as prisms (410 mg), m.p. 148-150°, $[\alpha]_D$ + 42° (c, 0.5), (Found: C, 77.2; H, 10.7. $C_{34}H_{56}O_4$ requires C, 77.4; H, 10.5%). δ 0.86 (s, 4α and 4β Me), 0.88 (s, 10β and 14α Me), 0.98 (s, 8β Me), 1.38 (s, 20 Me), 1.62 (m, 26 and 27 Me), 1.95 (s, 20-OAc), 2.03 (s, 3β-OAc), 4.15 (m, 3α-H) and 5.08 (m, H-24). The last 130 ml yielded 3β-acetoxy-20S-hydroxydammar-24-ene 3 (440 mg), m.p. 136-137°, $[\alpha]_D$ + 38° (c, 0.5) as flakes from methanol. (lit.[3] for dammarenediol-II monoacetate, m.p. 135-137° $[\alpha]_D$ + 37°). δ 0.86 (s, 4α and 4β Me), 0.88 (s, 10β and 14α Me), 0.98 (s, 8β Me), 1.14 (s, 20 Me), 1.62 (m, 26 and 27 Me), 2.03 (s, 3β-OAc), 4.49 (m, 3α-H) and 5.09 m (H-24).

(c) Acetylation at Room Temp. A mixture of constituent A (1.1 g) in pyridine-acetic anhydride was allowed to stand overnight at room temp. and the product worked up as in (b) to give dammarenediol-II monoacetate 3 as flakes (1.1 g), m.p. 136-137°. A solution of 3 (151 mg) in methanol (15 ml) was stirred overnight with 20% aqueous potassium hydroxide (20 ml), worked up and crystallized from methanol and nitromethane to give dammarenediol-II 1 as short prisms, m.p. 132-133° $[\alpha]_D$ + 33° (c, 0.2) (lit.[4] m.p. 131-133°, $[\alpha]_D$ + 33°. When recrystallized from aqueous ethanol, the m.p. was 77-79°.

(d) Catalytic Hydrogenation. To a solution of constituent A (430 mg) in ethanol (25 ml) was added palladium-carbon (10%,

100 mg), and the mixture stirred under hydrogen at room temp. for 1 hr. Removal of catalyst and solvent and crystallization of the solid residue from nitromethane gave dammarane-3β, 20S-diol 4 as small prisms, m.p. 131-133°, $[\alpha]_D$ + 36° (c, 0.5). (lit.[4] for dammaranediol-II, m.p. 133-135°, $[\alpha]_D$ + 35°. Similar hydrogenation of constituent A monoacetate yielded 3β-acetoxy-20S-hydroxydammarane 5 as needles, m.p. 106-108°, $[\alpha]_D$ + 40° (c, 0.62). (lit.[4] for dammaranediol-II monoacetate, m.p. 106-108°, $[\alpha]_D$ + 41°),

Conversion of 3β,20S-Diacetoxydammar-24-ene 2 to Dammarenediol-II 1. — Lithium aluminium hydride (250 mg) was added to a solution of the diacetate (42 mg) in ether (10 ml), the mixture refluxed for 4 hr, then worked up in the usual way to give dammarenediol-II (31 mg), m.p. 132-133°, from nitromethane.

Identification of Constituent B as 3β,20S,26-Trihydroxydammar-24-ene 6.—Recrystallization of constituent B from ethanol gave 3β, 20S,26-trihydroxydammar-24-ene as glistening plates, m.p. 198-199°, $[\alpha]_D$ ± 0° (c, 0.26), ν 3350 cm^{-1}, with a negative tetranitromethane test. (Found: C, 78.5; H, 11.6. $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.4%). Mass spectrum: found

442.3797. $C_{30}H_{50}O_2$ $(M-H_2O)^+$ requires M^+ 442.3811). δ (in pyridine-d_5) 0.87, 0.95, 1.00(2), 1.18 and 1.35 (six tert. Me groups) 1.80 (s, 27 Me), 3.30 (m, H-3α), 4.20 (m, (2H), H-26) and 5.75 (m, H-24).

3β,26-Diacetoxydammar-24-en-20-ol 7.—Acetylation of the triol 5 (100 mg) in pyridine-acetic anhydride at room temp. overnight gave the triol diacetate 7, m.p. 110-112°, $[\alpha]_D$ + 16° (c, 0.9) as short needles from methanol. It gave a yellow colour with tetranitromethane (Found: C, 75.15; H, 10.45. $C_{34}H_{56}O_5$ requires C, 74.95; H, 10.4%). δ 0.86 (s, 4α and 4β Me), 0.88 (s, 10β and 14α Me), 0.98 (s, 8β Me), 1.15 (s, 20 Me), 1.71 (s, 27 Me), 2.03 (s, OAc), 2.06 (s, OAc), 4.47 (m, 3α-H) 4.47 (m, (2H), H-26), 5.48 (m, H-24).

Catalytic Hydrogenation of Constituent B.—A solution of the triol 6 (195 mg) in ethanol (40 ml) was stirred with palladium-carbon (5%, 40 mg) under hydrogen at room temp. Crystallization of the solid residue (196 mg), obtained by filtration and evaporation, gave dammarane-3β,20S-diol 4 (100 mg), m.p. 132-133°, $[\alpha]_D$ + 32° (c, 0.4) (identical by t.l.c., i.r. and n.m.r.).

Oxidation of Constituent B to Keto-trisnorlactone 8. - To a solution of the triol 6 (200 mg) in acetone (50 ml) was added Jones' reagent (2 ml, 1.4 M) and the mixture allowed to stand for 2 hr, filtered, diluted with water (50 ml) and the product extracted with ether (3 x 40 ml). Evaporation of the washed and dried extract gave a solid (192 mg, m.p. 52-56°, showing 2 principal spots on t.l.c., R_f 0.27, 0.75, $CHCl_3$). Preparative t.l.c. and isolation of the product with lower R_f gave the keto-trisnorlactone 8, m.p. 182-184°, $[\alpha]_D$ + 69° (c, 0.93), ν 1775 and 1705 cm^{-1}, (M^+ 414.3146. $C_{22}H_{42}O_3$ requires M^+ 414.3134). N.m.r. spectrum same as previously reported.[11]

3β, 20S-Dihydroxydammar-24-en-26-al 9. — Manganese dioxide (2.0 g) was added to a solution of the triol 6 (206 mg) in dry tetrahydrofuran (30 ml), the mixture stirred at room temp. overnight, then filtered and evaporated to give the aldehyde 9 as a solid foam, homogeneous by t.l.c., but not obtained crystalline from the common solvents. (Found: C, 78.2; H, 10.8. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%). δ 0.77 (s, 4α Me), 0.85 (s, 4β Me), 0.88 (s, 14α Me), 0.97 (8β and 10β Me), 1.15 (s, 20 Me), 2.20 (s, 27 Me), 3.18 (m, 3α H), 6.52 (m, H-24), 9.45 (s, H-26), ν 1680 and 1600 cm^{-1}; λ 228 nm (ε 5600).

Isolation of Constituents C and D from Acetone-Soluble Fraction. — The greenish gummy solid (7.05 g) was dissolved in ether-benzene (1:1) and filtered through a column (4 x 1.5" dia.) of Florisil (Fisher, 100-200 mesh) to remove pigments. Elution with the same solvent (2 li) and evaporation gave a residual yellow powder (4.2 g), and with methanol-water (4:1) an acid fraction as a brown viscous oil (1.95 g).

(a) Dry column chromatography. A solid suspension of the yellow powder (1.0 g) on silica gel (10 g) was added to the top of a dry column (7 x 1.5" dia.) of silica gel, which was then percolated with benzene-ether (3:2). The first 100 ml of eluate yielded constituent C (95 mg), the next 140 ml yielded no residue and the subsequent 150 ml yielded constituent D (130 mg).

(b) Without chromatography. The yellow powder (2.0 g) was added to a solution of potassium carbonate (1.2 g) in water (30 ml), the mixture stirred at room temp. for 3 hr, then diluted with water (100 ml) and extracted with ether (3 x 50 ml). Evaporation of the dried extract yielded constituent C (205 mg). Addition of acetic acid (4 ml) to the aqueous fraction precipitated constituent D as a yellow solid (406 mg) collected by filtration. Further acidification to pH 3 gave a precipitate (460 mg) of an acid mixture.

Identification of Constituent C as 3β,20S,25-Trihydroxydammar-23-ene (Isofouquierol) 10.—After isolation as above, constituent C was crystallized once from nitromethane and methanol to give isofouquierol 10 as prisms, m.p. 101-103°, $[\alpha]_D$ + 22° (c, 1.1) (lit.[15] m.p. 108, $[\alpha]_D$ + 24°), with n.m.r. spectrum identical to that reported. On acetylation, it yielded a monoacetate 11, m.p. 134-136°, $[\alpha]_D$ + 34° (c, 0.67). (lit.[15] m.p. 137-140°, $[\alpha]_D$ + 37°).

The triol 10 (12 mg) was stirred in ethanol (20 ml) under hydrogen with palladium-carbon (5%, 20 mg) for 4 hr. Filtration, evaporation and crystallization of the residue from nitromethane gave dammarane-3β,20S-diol 4 (6 mg), m.p. and mixed m.p. 130-132°.

Identification of Constituent D as 4',5,7-Trihydroxyflavone (Apigenin) 12.—Crystallization of constituent D from acetone gave apigenin 12 as yellow needles, m.p. 351-354° dec. (lit.[17] m.p. 348-350°). δ [$(CD_3)_2SO$] 6.30 (d, J 2 Hz, H-6), 6.51 (d, J 2 Hz, H-8), 6.71 (s, H-3), 7.02 (d, J 9 Hz, H-3' and 5'), 7.91 (d, J 9 Hz, H-2' and 6') and 13.08 (s, C-5 OH); cf.[18] m/e 270 (M^+, 100), 2.42 (38), 152 (34), 151 (38), 124 (25), 121 (50) and 118 (31); cf.[19] ν (KBr) ca. 3000, 1655, 1610, 1505, 1360 and 837 cm^{-1}.

Apigenin Triacetate 13, obtained from 12 by pyridine-acetic anhydride treatment overnight and crystallization from methanol had m.p. 179-181° (lit.[17] 181-182°). δ 2.33 (s, 4' and 7-OAc), 2.42 (s, 5-OAc), 6.62 (s, H-3), 6.86 (d, J 2 Hz, H-6), 7.24 (d, J 9 Hz, H-3' and 5'), 7.35 (d, J 2 Hz, H-8), 7.87 (d, J 9 Hz, H-2' and 6'); cf.[18] m/e 396 (M^+, 4), 355 (75), 354 (80), 270 (100), 241 (38), 213 (13), 153 (23), 152 (19), 124 (23), 123 (25) and 118 (28). ν (KBr) 1780, 1655 and 1210 cm^{-1}.

Apigenin 4',7-Dimethyl Ether 14 obtained from 12 by treatment with diazomethane in ether-methanol and crystallization from chloroform-methanol had m.p. 170-173°. (lit.[20] m.p. 170-171°). δ 3.87 (s, 4' and 7-OMe), 6.35 (d, J 2 Hz, H-3), 6.47 (d, J 2 Hz, H-8), 6.53 (s, H-3), 7.02 (d, J 9 Hz, H-3' and 5'), 7.83 (d, J 9 Hz, H-2' and 6'); cf.[21]. m/e 298 (M^+, 100), 269 (16), 255 (10), 166 (12), 162 (3), 138 (10), 135 (17), 132 (17) and 95 (14). ν (KBr) 3230, 1670, 1505 and 845 cm^{-1}.

Examination of Benzene-Soluble Fraction. — Thin layer chromatographic separation (silica gel G, benzene-ether) of the benzene-soluble fraction (200 mg) gave a zone (R_f 0.55), which on elution and crystallization yielded dammarenediol-II 4 (29.4 mg), m.p. 132-133°.

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