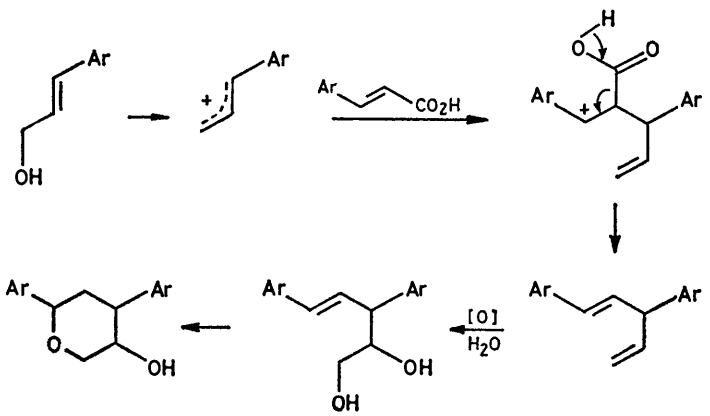
Stereoselective Total Syntheses of the (±)-Di-*O*-methyl Ethers of Agatharesinol, Sesquirin-A, and Hinokiresinol, and of (±)-Tri-*O*-methylsequirin-E, Characteristic Norlignans of Coniferae

By **Angel Paez Beracierta** and **Donald A. Whiting,*** Department of Chemistry, The University, Nottingham NG7 2RD

Total syntheses of the (±)-di-*O*-methyl ethers of the norlignans sequirin-A, agatharesinol, and hinokiresinol, and of (±)-tri-*O*-methyl sequirin-E are described. *p*-Methoxyacetophenone was converted into *p*-methoxybenzoylethylene and thence into 4-(*p*-methoxybenzoyl)-2,2-dimethyl-1,3-dioxolan (13). The glycidic acid (15) was obtained from (13) by Darzens condensation with benzyl chloroacetate and hydrogenolysis of the resulting ester. Decarboxylation–rearrangement in hot acetone of the glycidic acid was stereoselective providing the desired diastereoisomer (17) (>80%) of 2,2-dimethyl-1,3-dioxolan-4-yl-(*p*-methoxyphenyl)acetaldehyde. Reaction of (17) with *p*-methoxybenzylidenetriphenylphosphorane gave *trans*- and *cis*-(±)-dimethylagatharesinol acetonides The *trans*-acetonide (19) was hydrolysed to (±)-dimethylagatharesinol (21); pyrolysis of the mixed orthoformate of the latter provided (±)-dimethylhinokiresinol. The *cis*-isomer (18) was hydrolysed and cyclised to yield (±)-dimethylsequirin-A. Reaction of the aldehyde (17) with 3,4-dimethoxybenzylidenetriphenylphosphorane, followed by acid-catalysed cyclisation, afforded (±)-trimethylsequirin-E, *via* the acetonide (20). An alternative approach to dimethylagatharesinol is discussed.

THE heartwood constituents of some members of the Coniferae include a small group of phenols apparently related biogenetically to lignans but with a C_{17} skeleton, *i.e.*, norlignans. All but one of the known examples are based on a 1,3-diarylpentane structure; these are the *trans*-1,3-diaryltetrahydropyrans sequirin-A (1),[1] -B [2] (2), -E [3] (3), -F [3] (4), and -G [3] (5), the 1,3-diarylpentenediols sequirin-C [2] (6) and agatharesinol [4] (7), the 1,3-diarylpentadiene hinokiresinol [5] (8), and the further oxidised example athrotaxin [6] (9). Sequirin-D [7] (10) also has a C_{17} skeleton but appears to have a different biosynthesis.

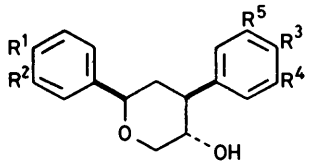


Hypothetical biogenesis of norlignans

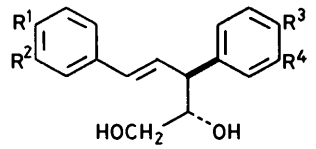
[1] R. Riffer and A. B. Anderson, *Phytochemistry*, 1967, **6**, 1557; Y. Kai, *J. Japan Wood Res. Soc.*, 1967, **11**, 23.
[2] N. A. R. Hatam and D. A. Whiting, *J. Chem. Soc.* (*C*), 1968, 1921.
[3] P. Henley-Smith and D. A. Whiting, *Phytochemistry*, 1976, **15**, 1285.
[4] B. R. Thomas and C. R. Enzell, *Acta Chem. Scand.*, 1965, **19**, 913; *Tetrahedron Letters*, 1966, 2395.
[5] Y. Hirose, N. Oishi, H. Nagaki, and T. Nakatsuka, *Tetrahedron Letters*, 1965, 3665.
[6] P. Daniels, H. Erdtman, K. Nishimura, T. Norin, P. Kierkegaard, and M. Pilotti, *J.C.S. Chem. Comm.*, 1972, 246.

Such compounds are reported to occur [1-7,8] in a few genera (*Agathis*, *Chamaecyparis*, *Sequoia*, *Sequoiadendron*, *Athrotaxis*, *Cryptomeria*) belonging to Coniferae.

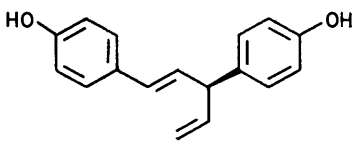
We have previously described methods for the total synthesis [9] of (±)-trimethylsequirin-B and (±)-trimethylsequirin-C and now report on the use of these approaches for syntheses of the (±)-dimethyl ethers of agatharesinol, sequirin-A, and hinokiresinol, which although not yet reported to occur together in one species, may share a common origin from coumaric acid and coumaryl alcohol as indicated in the Scheme.



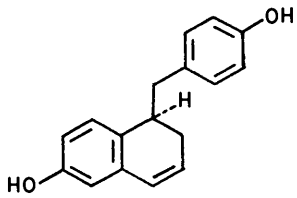
(1) $R^1 = R^3 = OH, R^2 = R^4 = R^5 = H$
(2) $R^1 = R^3 = R^4 = OH, R^2 = R^5 = H$
(3) $R^1 = R^2 = R^3 = OH, R^4 = R^5 = H$
(4) $R^1 = R^2 = R^3 = R^4 = OH, R^5 = H$
(5) $R^1 = R^2 = R^3 = R^4 = R^5 = OH$



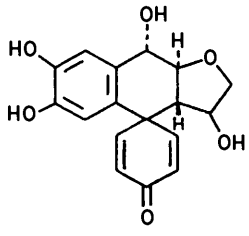
(6) $R^1 = R^3 = R^4 = OH, R^2 = H$
(7) $R^1 = R^3 = OH, R^2 = R^4 = H$



(8)



(10)



(9)

The key synthetic intermediate was the arylacetaldehyde (17), which was constructed from *p*-methoxyacetophenone. The latter was subjected to a Mannich reaction to provide 3-dimethylamino-*p*-methoxypropiophenone; the methiodide of this base decomposed smoothly when shaken with aqueous sodium hydrogen carbonate to yield *p*-methoxyphenyl vinyl ketone. Alkaline hydrogen peroxide converted the vinyl ketone into the αβ-epoxyketone (11), which was hydrolysed in dilute acid to the diol (12). The diol (12) readily formed the acetonide (13) by acid-catalysed reaction with acetone. The acetonide (13) was then treated with benzyl chloroacetate and potassium t-butoxide in a Darzens condensation; the benzylglycidic ester (14) thus prepared was hydrogenolysed over palladium to provide the free glycidic acid (15), obtained as a crystalline solid, very prone to decomposition in solution. Since the further reactions, with decarboxylation, of an analogue of this acid were followed in our earlier work, they were not repeated for (15). All steps so far proceeded with yields in the range 60—90%.

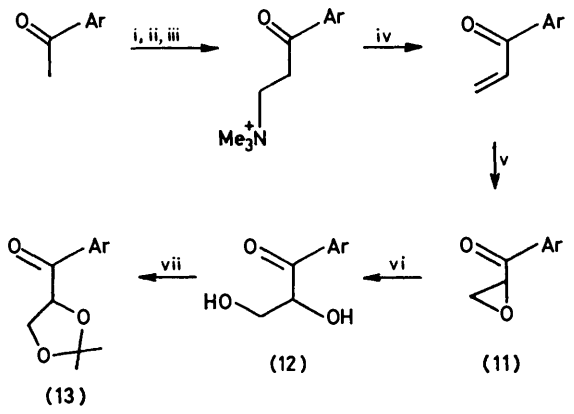
Stereoselective rearrangement and decarboxylation of the glycidic acid was effected by heating acetone solutions at 100° in a sealed tube to give the aldehydes (16) and (17); the desired stereoisomer (17) predominated (*ca.* 5 : 1, by ^{1}H n.m.r. analysis). Product control in this reaction is not likely to reflect the diastereoisomeric composition of the glycidic acids (15); the stereochemistry of this acid is not known but is inconsequential since decarboxylation yields a racemic enol intermediate whose ketonisation controls product stereochemistry. The relative thermodynamic stabilities of (16) and (17) therefore probably determine the stereochemical course of the reaction; molecular models of the staggered conformations (16a) and (17a) indicate destabilisation of the former by gauche aryl–methylene repulsions. Assignment of stereochemistry depends on the conversion of (17) into the natural products, now to be discussed.

[7] M. J. Begley, R. V. Davies, P. Henley-Smith, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1973, 649.

[8] K. Funoaka, Y. Kuroda, Y. Kai, and T. Kondo, *J. Japan Wood. Res. Soc.*, 1963, **9**, 139; C. R. Enzell, Y. Hirose, and B. R. Thomas, *Tetrahedron Letters*, 1967, 793.

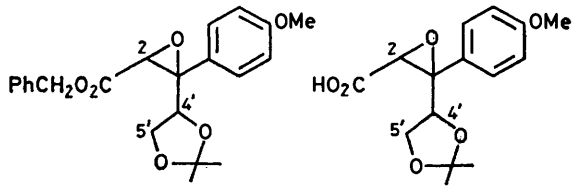
[9] R. V. Davies, N. A. R. Hatam, and D. A. Whiting, *J.C.S. Perkin I*, 1973, 2359.

The mixture of (16) and (17) (without purification) was treated with *p*-methoxybenzylidenephosphorane to

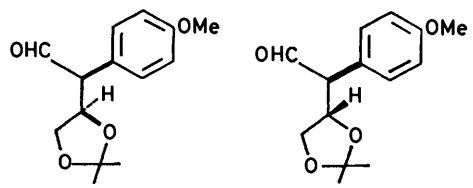


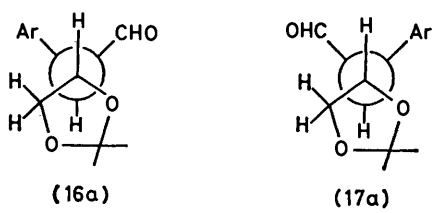
Reagents: i, $Me_2NH{\cdot}HCl$, CH_2O; ii, aq. Na_2CO_3; iii, MeI; iv, aq. $NaHCO_3$–Et_2O; v, H_2O_2, NaOH, −20 °C; vi, H_3O^+; vii, Me_2CO, HCl

yield the *cis*- and *trans*-acetonides (18) and (19) (overall yield from glycidic acid, *ca.* 40%). Traces of minor



stereoisomers were removed at this stage by chromatography, when the *cis*- and *trans*-isomers were separated. The *trans*-acetonide (19) was spectroscopically and

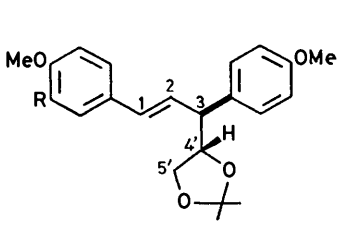




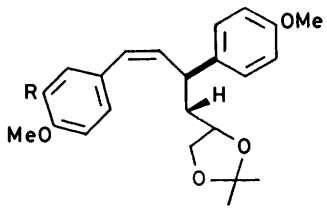
chromatographically identical with *trans*-di-*O*-methylagatharesinol acetonide prepared from natural agatharesinol.[3] Brief treatment with acid gave (±)-*trans*-di-*O*-methylagatharesinol (21), m.p. 124—126°, also with solution spectra parallel to those of an authentic optically active specimen.

[10] J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734, 736.

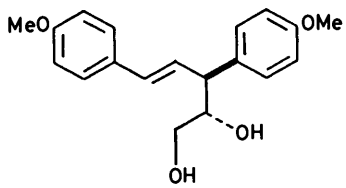
The *cis*-acetonide (18) (which isomerised slowly, when set aside, to the *trans*-form) was refluxed with methanolic acid, when removal of acetone was followed by cyclisation, essentially quantitatively and stereospecifically to afford (±)-*O*-dimethylsequirin-A (23), m.p. 108—110°, spectroscopically and chromatographically identical with the ether of natural sequirin-A. Cyclisation of the diol (22) involves protonation at C-2 and intramolecular trapping of the C-1 carbocation by the C-5 hydroxy-group. Trapping by the C-4 hydroxy-group was not observed, possibly an instance of the preference for 6-



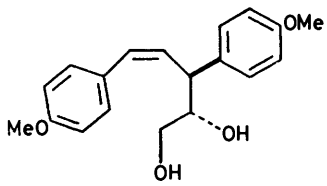
(19) R = H
(20a) R = OMe



(18) R = H
(20b) R = OMe



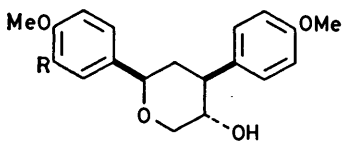
(21)



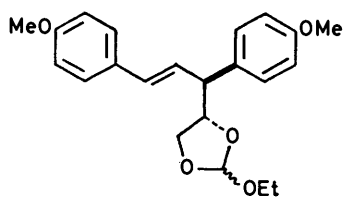
(22)

endo-trig over 5-*endo-trig* cyclisation.[10] The high stereospecificity is presumably a result of a transition state reflecting the all-equatorial product geometry.

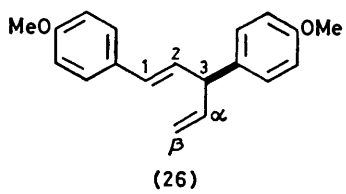
(±)-Tri-*O*-methylsequirin-E (24) was prepared in a similar fashion; the mixture of the aldehydes (16) and



(23) R = H
(24) R = OMe



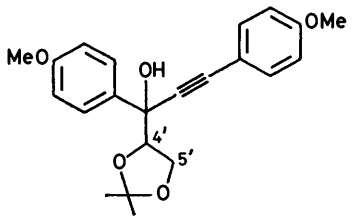
(25)



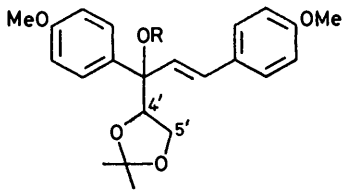
(26)

(17) was treated with 3,4-dimethoxybenzylidenetriphenylphosphorane in benzene, and the intermediate acetonides (20) both cyclised, without separation, on prolonged refluxing with aqueous acidified methanol.

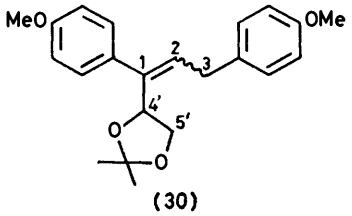
(±)-Tri-*O*-methylsequirin-E was obtained, m.p. 125—126°, authenticated by the usual comparisons with the ether of natural sequirin-E.



(27)



(28); R = H
(29); R = SO_2Me



(30)

The *trans*-diol (21) was heated with triethyl orthoformate and a trace of benzoic acid to yield the mixed orthoformate (25); pyrolysis at 150—160° of this orthoformate proceeded cleanly to yield (±)-di-*O*-methylhinokiresinol (26). Similar treatment of the *cis*-diol (20) also gave (26), with stereomutation of the disubstituted double bond. Limited spectroscopic data are presented for natural hinokiresinol, and no natural sample was available to us. However our product was authenticated by detailed ^1H n.m.r. analysis. The salient features are the *trans* 1-H,2-H (τ 3.4, 4.2; $J_{1,2}$ 12 Hz), the methine 3-H (τ 5.4; $J_{2,3}$ 10, $J_{3,\alpha}$ 6 Hz), and terminyl vinyl α-H and β-H_2 (τ 3.9 and 4.8; $J_{\beta,\beta'}$, 5, $J_{\alpha,\beta}$ 10, $J_{\alpha,\beta'}$ 18 Hz). Electron-impact fragmentation followed the pattern described for the natural phenol.[11] Since dimethylhinokiresinol (26) is clearly the more stable isomer, its status as 1,2-*trans* is hardly in doubt, and is supported by the magnitude (12 Hz) of $J_{1,2}$. This coupling is at the low end of the range for *trans*–*vic* ethylene protons, and markedly lower than $J_{1,2}$ for (19) or (21) (16 Hz), but the origins of this difference are not apparent to us. It is notable that $J_{2,3}$ is larger in (26) than in (19) (10 and 7 Hz), but conformational differences may be involved. The natural 1,4-diene displays [5] $\nu_{max.}$ 967 cm^{-1}, interpreted as *trans*-disubstituted ethylene C–H deformation. However the *cis*–*trans* pairs (18) and (19), (21) and (22) cannot be clearly differentiated by such a band, all of the compounds showing i.r. absorptions in this region.

In an alternative approach to dimethyl agatharesinol, the ketone (13) was condensed with *p*-methoxyphenylacetylene in sodamide–liquid ammonia giving the diastereoisomers of the acetylenic alcohol (27). Lithium aluminium hydride reduction provided the corresponding *trans*-olefinic alcohol (28). The methanesulphonate (29) of this alcohol was formed at −78°, and reduced with lithium aluminium hydride. A little of the desired *trans*-acetonide (19) was isolated, but the major product was the isomeric acetonide (30). Allylic rearrangement thus intervenes in the reduction. The geometry of (30) was not investigated.

EXPERIMENTAL

The following generalisations apply. Samples for i.r. spectroscopy were prepared as potassium bromide discs. ^1H N.m.r. spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as internal standard; s = singlet, d = doublet, t = triplet, and m = multiplet. O*H* Resonances were detected by D_2O exchange. Analytical t.l.c. used silica gel G (Merck/Stahl), with iodine vapour or u.v. visualisation; 1 mm layers were employed in preparative work. Organic solutions were dried over anhydrous magnesium sulphate and evaporated under reduced pressure.

3-Dimethylamino-4′-methoxypropiophenone Methiodide.—*p*-Methoxyacetophenone (60 g), paraformaldehyde (16 g), and dimethylammonium hydrochloride (44 g) were dissolved in isopentyl alcohol (100 cm^3) with hydrochloric acid (0.8 cm^3), and the solution was heated under reflux for 1 h. The solution was filtered hot, diluted with acetone (250 cm^3), and set aside at 0°. 3-Dimethylamino-4′-methoxypropiophenone hydrochloride was filtered off and recrystallised from ethanol, m.p. 180—182° (lit.,[12] m.p. 187°) (78 g, 81%). The free base was obtained by basification (sodium carbonate) of an aqueous solution of the salt, and was collected in ether. After evaporation of the ethereal solution, the crude base (49 g) was heated under reflux with methyl iodide (45 g) in ethanol (100 cm^3) for 2 h. On cooling the desired methiodide was recrystallised from methanol as yellow needles, m.p. 190—192°[13] (76 g, 78%).

p-Methoxybenzoylethylene Oxide (11).—A slurry of the

[11] C. R. Enzell, B. R. Thomas, and I. Wahlberg, *Tetrahedron Letters*, 1967, 2211.
[12] Beilstein, ' Handbuch der Organischen Chemie,' Band XIV, S.11, p. 142.
[13] N. V. Sidgwick, ' The Organic Chemistry of Nitrogen,' Clarendon, Oxford, 1966, p. 117.

foregoing methiodide (40 g) with water (1.2 dm³) containing sodium hydrogen carbonate (40 g) was shaken with ether (1.6 dm³) for 4 h. The aqueous layer was separated off and extracted with ether. The combined ethereal solutions were washed (0.1M-hydrochloric acid, water) and evaporated to yield *p*-methoxybenzoylethylene (16 g, 84%) as a pale yellow oil, very prone to polymerisation. It had $\nu_{max.}$ (liq. film) 2 950, 2 750, 1 680 (C=O), 1 600, 1 520, 840, and 800 cm⁻¹; τ 2.1 (2 H, d, *J* 9 Hz, *o*-ArH), 2.8 (1 H, dd, *J* 10 and 18 Hz, =C*H*=), 3.1 (2 H, d, *J* 9 Hz, *m*-ArH), 3.6 (1 H, dd, *J* 2 and 18 Hz, =CH*H*), 4.2 (1 H, dd, *J* 2 and 10 Hz, =C*H*H), and 6.2 (3 H, s, OMe). The vinyl ketone (13 g, used without further purification) was dissolved in methanol (150 cm³) and treated dropwise with stirring with 30% hydrogen peroxide (40 cm³) containing 6M-sodium hydroxide (12 cm³). The temperature of the mixture was maintained at −20°. After 2 h, saturated aqueous ammonium chloride (100 cm³) was added, and the methanol evaporated off under reduced pressure at −10°. The residue was extracted with dichloromethane. The organic extracts with washed (aq. ammonium chloride, sat. aq. sodium chloride), dried, and evaporated. The residual oil was chromatographed on a silica column, with chloroform elution. The desired p-*methoxybenzoylethylene oxide* (11) (10 g, 80%) was eluted first, and crystallised from methanol, m.p. 41—42° (Found: C, 67.05; H, 5.3. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.65%); $\nu_{max.}$ 1 685 (C=O), 1 600, 1 520 (Ar), 860, and 760 cm⁻¹; τ 2.1 (2 H, d, *J* 9 Hz, *o*-ArH), 3.1 (2 H, d, *J* 9 Hz, *m*-ArH), 5.9 (1 H, dd, *J* 2 and 4 Hz, C*H*), 6.2 (3 H, s, OMe), 6.95 (1 H, dd, *J* 5 and 6 Hz, C*H*H), and 7.15 (1 H, dd, *J* 2 and 6 Hz, CH*H*); *m/e* 178.063 ($C_{10}H_{10}O_3$ requires 178.064).

p-*Methoxybenzoylethylene Glycol*.—*p*-Methoxybenzoylethylene oxide (11) (9 g), acetone (450 cm³), water (150 cm³), and 2M-sulphuric acid (12 cm³) were heated under reflux together for 48 h. After evaporation of most of the acetone, the mixture was diluted with water and extracted with chloroform. The combined organic extracts were washed (aq. sodium hydrogen carbonate, water), dried, and evaporated. Crystallisation of the residue from benzene gave the *glycol* (12) (6.2 g, 62%), m.p. 108—110° (Found: C, 60.8; H, 6.45. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.15%); $\nu_{max.}$ 3 400 (OH), 1 680 (C=O), 1 600, 1 580, 840, and 800 cm⁻¹; τ 2.1 (2 H, d, *J* 9 Hz, *o*-ArH), 3.0 (2 H, d, *J* 9 Hz, *m*-ArH), 4.9 (1 H, dd, *J* 2, and 3 Hz, *CH*OH), 5.8—6.4 (2 H, m, C*H*₂OH), 6.1 (3 H, s, OMe), 7.8 (1 H, s, OH), and 8.3 (1 H, s, OH); *m/e* 196.074 ($C_{10}H_{12}O_4$ requires 196.074).

4-(p-*Methoxybenzoyl*)-2,2-*dimethyl*-1,3-*dioxolan* (13).—The foregoing glycol (12) (6 g) was dissolved in dry acetone (600 cm³) and hydrochloric acid (0.3 cm³), and anhydrous sodium sulphate (6 g) was added; the mixture was stirred for 3 days at ambient temperature. Anhydrous sodium hydrogen carbonate (6 g) was added, and after a further 4 h the mixture was filtered. After evaporation the residue was crystallised from methanol to provide the *dioxolan* (13) (5.3 g, 72%), m.p. 59—61° (Found: C, 66.35; H, 6.65. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.85%); $\nu_{max.}$ 1 685, 1 600, 1 575, 860, and 820 cm⁻¹; τ 2.1 (2 H, d, *J* 9 Hz, *o*-ArH), 3.1 (2 H, d, *J* 9 Hz, *m*-ArH), 4.8 (1 H, t, *J* 7 Hz, 4-H), 5.6 (2 H, d, *J* 7 Hz, 5-H), 6.2 (3 H, s, O*CH*₃), and 8.6 (6 H, s, 2 × C*H*₃); *m/e* 236.015 ($C_{13}H_{16}O_4$ requires 236.012).

Benzyl 3-(2,2-*Dimethyl*-1,3-*dioxolan*-4-*yl*)-3-(4-*methoxyphenyl*)-2,3-*epoxypropionate* (14).—The foregoing dioxolan (13) (6.5 g) was added, under nitrogen and at 0°, to a stirred suspension of potassium t-butoxide (6 g) in benzene (60 cm³). Benzyl chloroacetate [14] (7.3 g) was added dropwise, and the mixture was stirred for 24 h at ambient temperature under nitrogen. Water was then added and the organic layer was separated off. The aqueous part was extracted with ether, and the bulked organic extracts washed, dried, and evaporated. The residue was chromatographed on a silica column; the fraction eluted with light petroleum (b.p. 40—60°)–ethyl acetate (5 : 1) crystallised from ether (5.2 g, 54%) to yield the *ester* (14), m.p. 78—79° (from methanol) (Found: C, 68.75; H, 6.35. $C_{22}H_{24}O_6$ requires C, 68.75; H, 6.3%); $\nu_{max.}$ (KBr) 1 730, 1 610, 1 520, and 850 cm⁻¹; $\nu_{max.}$ (CCl_4) 1 760, 1 730,[15] 1 610, 1 520, and 850 cm⁻¹; τ 2.7—3.5 (9 H, ArH), 5.2 (2 H, s, PhCH_2), 5.6 (1 H, t, *J* Hz, 4′-H), 6.1 (2 H, d *J* 7 Hz, 5′-H_2), 6.2 (1 H, s, 2-H), 6.3 (3 H, s, OMe), and 8.7 (6 H, s, 2 × Me); *m/e* 384.157 ($C_{22}H_{24}O_6$ requires 384.155).

3-(2,2-*Dimethyl*-1,3-*dioxolan*-4-*yl*)-3-(4-*methoxyphenyl*)-2,3-*epoxypropionic Acid* (15).—The foregoing benzyl ester (14) (0.5 g) in ethanol (20 cm³) was hydrogenated over 5% palladium–carbon, using a Brown hydrogenator (1 mol. equiv. of hydrogen taken up). Filtration, evaporation, and crystallisation gave the *epoxy-acid* (15), m.p. 59—64° (decomp.) (from ether) (Found: C, 61.1; H, 6.4. $C_{15}H_{18}O_6$ requires C, 61.3; H, 6.15%); $\nu_{max.}$ 3 500br, 1 730br, 1 610, 1 520, and 820 cm⁻¹; τ 2.4 (1 H, s, CO_2H), 2.7 (2 H, d, *J* 9 Hz, *o*-ArH), 3.2 (2 H, d, *J* 9 Hz, *m*-ArH), 5.5 (1 H, t, *J* 7 Hz, 4′-H), 6.0 (2 H, d, *J* 7 Hz, 5′-H_2), 6.2 (1 H, s, 2-H), 6.4 (3 H, s, OMe), and 8.7 (6 H, s, 2 × Me).

cis- *and* trans-(±)-*Di*-O-*methylagatharesinol Acetonide* (18) *and* (19).—The foregoing epoxy-acid (15) (1.5 g) in acetone (20 cm³) was heated at 100° in a sealed Pyrex tube for 3 h. The product was evaporated to dryness and the residue dissolved in dry benzene (20 cm³). To this solution under argon was slowly added *p*-methoxybenzylidenetriphenylphosphorane in benzene [from *p*-methoxybenzyltriphenylphosphonium chloride in benzene (20 cm³) and 2M-butyllithium in n-hexane (2.7 cm³)] until the red colour of the ylide persisted. The mixture was stirred for 30 min, and then water (100 cm³) was added. The benzene layer was separated off and the aqueous layer extracted with ether. The combined organic extracts were washed, dried, and evaporated to a gum. This residue was chromatographed on a silica column, with light petroleum (b.p. 40—60°)–ethyl acetate (4 : 1) as eluant and monitoring by t.l.c. The major product (an oil, 0.6 g) was separated into two components by preparative layer chromatography (p.l.c.) using multiple elution with the same solvent mixture. The compound of lower R_F crystallised from methanol (120 mg), m.p. 78—79°, and proved to be (±)-trans-*di*-O-*methylagatharesinol acetonide* (19) (Found: M^+ 354.184. $C_{22}H_{26}O_4$ requires 354.183); this product was chromatographically indistinguishable from *trans*-dimethylagatharesinol acetonide prepared from the natural norlignan [3] and had parallel solution i.r. and ^{1}H n.m.r. spectra: τ 2.7—3.4 (8 H, m, ArH), 3.6 (1 H, d, *J* 16 Hz, 1-H), 4.0 (1 H, dd, *J* 7 and 16 Hz, 2-H), 5.4—5.7 (1 H, m, 4′-H), 5.9—6.2 (2 H, m, 5′-H), 6.3 (6 H, s, OMe), 6.5 (1 H, t, *J* 7 Hz, 3-H), 8.7 (3 H, s, Me), and 8.8 (3 H, s, Me). The isomeric cis-*acetonide* (18) (Found: M^+ 354.184) was isolated (180 mg) as a gum; ^{1}H.m.r. data were similar to those for the *trans*-isomer, but displayed $J_{1,2}$ 9 Hz.

[14] H. Dahn and H. Hauth, *Helv. Chim. Acta*, 1959, **42**, 1214.

[15] H. H. Morris and R. H. Young, *J. Amer. Chem. Soc.*, 1957, **79**, 3408.

(±)-trans-*Di*-O-*methylagatharesinol* (21).—The *trans*-acetonide (19) (100 mg) was heated under reflux for 30 min in methanol (25 cm³) containing conc. hydrochloric acid (0.5 cm³). After removal of methanol by evaporation the residue was partitioned between water and ether. The combined ether extracts were washed, dried, and evaporated. The residual gum was subjected to p.l.c., using benzene–acetonitrile (3 : 1) as eluant; the major band afforded an oil, which was crystallised from chloroform and from methanol to yield (±)-trans-*di*-O-*methylagatharesinol* (21) (60 mg, 75%), m.p. 124—126° (Found: M^+ 314.151. $C_{19}H_{22}O_4$ requires 314.152); $\nu_{max.}$ 3 400, 1 610, 1 520, 1 250, and 840 cm^{-1}, τ[$(CD_3)_2SO$] 2.6—3.1 (8 H, m, ArH), 3.6 (1 H, dd, *J* 8 and 16 Hz, 2-H), 3.8 (1 H, d, *J* 16 Hz, 1-H), 5.3 (1 H, d, *J* 5 Hz, CHO*H*), 5.5 (1 H, t, *J* 10 Hz, CH_2OH), 6.3 (6 H, s, OMe), and 6.5—7.0 (4 H, β-H_2, α- and 3-H).

(±)-*Di*-O-*methylsequirin-A* (23).—The *cis*-acetonide (18) (120 mg) was heated under reflux in methanol (25 cm³) with conc. hydrochloric acid (1 cm³) for 4 days. Isolation of product as in the previous experiment, gave, after p.l.c. [benzene–acetonitrile (3 : 1)] an oil which was crystallised twice from ether and then from methanol to yield (±)-*di*-O-*methylsequirin-A* (23) (90 mg, 75%), m.p. 108—110°, (Found: M^+ 314.152. $C_{19}H_{22}O_4$ requires 314.152); $\nu_{max.}$ 3 500, 1 610, 1 520, 1 250, 1 030, and 840 cm^{-1}; the n.m.r. spectrum was indistinguishable from that of the authentic natural material.[3]

(±)-*Di*-O-*methylhinokiresinol* (26).—*trans*-Di-O-methylagatharesinol (21) (60 mg), ethyl orthoformate (3 cm³), and benzoic acid (1 mg) were heated together from 95 to 110° over 1 h. Excess of ethyl orthoformate was distilled off and the residue heated at 150—160° for 1 h. The product was diluted with water and extracted with ether. Combined ether extracts were washed, dried, and evaporated; p.l.c. of the residue [benzene–acetonitrile (3 : 1)] gave as the major product a clear gum which failed to crystallise (15 mg), and which was identified as (±)-*di*-O-*methylhinokiresonol* (26) (Found: M^+ 280.146 7. $C_{19}H_{20}O_2$ requires 280.146 3); τ 2.6—3.2 (8 H, m, ArH), 3.4 (1 H, d, *J* 12 Hz, 1-H), 3.6—4.1 (1 H, m, *J* 6, 10, and 18 Hz, α-H), 4.2 (1 H, dd, *J* 10 and 12 Hz, 2-H), 4.8 (2 H, m, β-H_2), 5.4 (1 H, dd, *J* 6 and 10 Hz, 3-H), and 6.1 (6 H, s, OMe).

(±)-*Tri*-O-*methylsequirin-E* (24).—The aldehyde (17) was prepared as described above (for dimethylagatharesinol acetonides) from the glycidic acid (15) (1.3 g); to the acid (15), in dry benzene (20 cm³), and under dry argon, was added 3,4-dimethoxybenzyltriphenylphosphorane [from 3,4-dimethoxybenzyltriphenylphosphonium chloride (1.96 g), benzene (20 cm³), and 15% butyl-lithium in hexane (2 cm³)], dropwise, until the red ylide colour persisted. The mixture was stirred for 30 min before dilution with water. The benzene layer was removed, and the aqueous solution extracted with ether. Combined organic extracts were washed, dried, and evaporated. The residual gum was separated by p.l.c. [light petroleum–ethyl acetate (4 : 1)], and the major component (0.3 g), a mixture of the *cis*- and *trans*-isomers (20), was isolated. This mixture was not purified but treated in methanol (25 cm³) with conc. hydrochloric acid (1 cm³) at reflux for 4 days. The product was isolated as described for dimethylsequirin-A (23), and crystallised from methanol to yield (±)-*tri*-O-*methylsequirin-E* (24), (30 mg), m.p. 125—126° (Found: M^+ 344.164. $C_{20}H_{24}O_5$ requires 344.162). It was identical in t.l.c. (3 different solvent systems) with an authentic sample[3] derived from natural sources, and had closely similar solution i.r. and n.m.r. spectra to those of the authentic material.

1-(2,2-*Dimethyl*-1,3-*dioxolan*-4-*yl*)-1,3-*bis*-(p-*methoxyphenyl*)*prop*-2-*yn*-1-*ol* (27).—Anisylacetylene (1.7 g) in dry tetrahydrofuran (5 cm³) was added dropwise with stirring to a mixture of dry tetrahydrofuran (5 cm³) and 1.5M-butyl-lithium in hexane (8 cm³). After 5 min 4-(*p*-methoxybenzoyl-2,2-dimethyl-1,3-dioxolan (13) (3 g) in dry tetrahydrofuran (5 cm³) was added dropwise over 10 min, the reaction mixture being maintained at −15°. After a further 2 h at this temperature, saturated aq. ammonium chloride (100 cm³) was added and the mixture stirred for 30 min and then extracted with ether. The ether extracts were washed (aq. ammonium chloride, water), dried, and evaporated. The product was chromatographed using a dry silica column technique (t.l.c. monitoring). The major fraction (4.2 g) crystallised from ether–hexane (1 : 1). Recrystallisation from methanol gave the *propynol* (27) (2.4 g), m.p. 113—114° (Found: C, 71.95; H, 6.9. $C_{22}H_{24}O_5$ requires C, 71.7; H, 6.6%); $\nu_{max.}$ 3 500, 2 250, 1 610, 1 520, and 840 cm^{-1}; τ 2.4 (2 H, d, *J* 9 Hz, *o*-ArH), 2.6 (2 H, d, *J* 9 Hz, *o*-ArH), 3.1 (2 H, d, *J* 9 Hz, *m*-ArH), 3.2 (2 H, d, *J* 9 Hz, *m*-ArH), 5.7 (1 H, q, *J* 7 Hz, 4′-H), 5.9 (2 H, d, *J* 7 Hz, 5′-H_2), 6.2 (6 H, s, OMe), 6.5 (1 H, s, OH), and 8.4 and 8.6 (both 3 H, s, Me); M^+ 368.162 ($C_{22}H_{24}O_5$ requires 368.163).

1-(2,2-*Dimethyl*-1,3-*dioxolan*-4-*yl*)-1,3-*bis*-(p-*methoxyphenyl*)*prop*-2-*en*-1-*ol* (28).—The foregoing propynol (27) (1.8 g) in dry tetrahydrofuran (5 cm³) was added to a stirred slurry, at 0°, of lithium aluminium hydride (0.8 g) in dry tetrahydrofuran (10 cm³). This mixture was stirred for 24 h at ambient temperature, ether was then added, and the excess of hydride was decomposed with water. The mixture was filtered and the filtrate evaporated to afford a solid which was recrystallised from methanol to provide the *propenol* (28) (1.6 g, 87%), m.p. 96—98° (Found: C, 71.75; H, 7.3. $C_{22}H_{26}O_5$ requires C, 71.35; H, 7.1%); $\nu_{max.}$ 3 500, 1 620, 1 520, and 840 cm^{-1}; τ 2.5 (2 H, d, *J* 9 Hz, *o*-ArH), 2.7 (2 H, d, *J* 9 Hz, *o*-ArH), 3.2 (2H, d, *J* 9 Hz, *m*-ArH), 3.3 (2 H, d, *J* 9 Hz, *m*-ArH), 3.4 (1 H, d, *J* 16 Hz, 3-H), 3.8 (1 H, d, *J* 16 Hz, 2-H), 5.4 (1 H, t, *J* 7 Hz, 4′-H), 6.1 (2 H, d, *J* 7 Hz, 5′-H_2), 6.3 (6 H, s, OMe), 7.1 (1 H, s, OH), and 8.6 (6 H, s, 2 × Me); M^+ 370.175 ($C_{22}H_{26}O_5$ requires 370.178).

Reduction of the Methanesulphonate (29) *of the Propenol* (28).—The foregoing propenol (28) (1 g), in dry ether (50 cm³), was added dropwise to a mixture, maintained at −20°, of dry ether (20 cm³) and 1.5M-butyl-lithium (1.3 cm³). This mixture was stirred for 10 min, methanesulphonyl chloride (0.3 g) was added, and a white precipitate formed. After 5 min more, lithium aluminium hydride (0.1 g) in dry ether (20 cm³) was added dropwise and the stirring was continued for 3 h, while keeping the temperature at −20°. Isolation of product as in the previous preparation gave an oil; t.l.c. analysis [benzene–ethyl acetate (4 : 1)] indicated a major product with R_F close to that of *trans*-di-*O*-methylagatharesinol (21). This product (0.3 g), containing two close-running components, was collected from a silica column [benzene–ethyl acetate (4 : 1)] and further separated by p.l.c. using triple elution with light petroleum–ethyl acetate (4 : 1). The minor component, of lower R_F, proved to be *trans*-di-*O*-methylagatharesinol acetonide (19) (15 mg), m.p. 77—79° from methanol, by t.l.c. comparison (3 solvent systems) and mixed m.p. (±)-

trans-Di-*O*-methylagatharesinol (21) was obtained on hydrolysis as already described. The major fraction yielded a clear gum, which did not crystallise, which was identified as 1-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)-1,3-*bis*-(p-*methoxyphenyl*)*prop*-1-*ene* (30) (Found: M^+, 354.181. $C_{22}H_{26}O_4$ requires 354.183); $\nu_{max.}$ (liq. film) 1 610, 1 520, and 840 cm^{-1}, τ 2.5—3.2 (8 H, m, ArH), 4.0 (1 H, t, *J* 8 Hz, 2-H), 5.4 (1 H, t, *J* 7 Hz, 4′-H), 5.8 (2 H, d, *J* 7 Hz, 5′-H_2), 6.2 (6 H, s, OMe), 6.6 (2 H, d, *J* 8 Hz, 3-H_2), and 8.4 and 8.5 (both 3 H, s, Me).

[7/2167 *Received*, 12*th December*, 1977]