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CONCERNING PHYLTETRALIN

SYNTHESIS OF *LIGNAN ARYLTETRALIN* ISOMERS

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Abstract—The acid-catalyzed rearrangement of diaryl-dilactones, readily obtained by oxidation of ferulic acid derivatives, is examined as a synthesis route to aryltetralins. Two structures which have been proposed for the lignan, phyltetralin, are shown by synthesis of the two diastereomeric 1-veratryltetralins (**3A**) and (**3B**), to be untenable. Conidendrin has been converted to isolariciresinol tetramethyl ether (**21**) and comparison of empirical constants and spectra with those reported for phyltetralin strongly suggest that the lignan has the enantiomeric constitution (**26**).

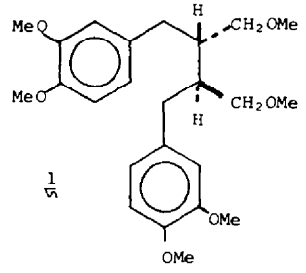
The plant *Phyllanthus niruri* Linn. (Euphorbiaceae) has reportedly been used in the treatment of jaundice, asthma and bronchial infections.[1] From the leaves, there have been isolated[1-3] by Ramachandra Row and his colleagues five lignans of which two (phyllanthin and niranthin) are members of the diarylbutane class and three (hypophyllanthin, nirtetralin and phyltetralin) belong to the aryltetralin group. The constitution[2] of phyllanthin (**1**), the major constituent of the mixture has been rigorously established, by synthesis[4] from (−)-eudesmin and (+)-veratrylsuccinic acid, as 2*S*,3*S* - bis(3',4' - dimethoxybenzyl) butanediol dimethyl ether and an analogous structure (**2**) has been proposed for niranthin.[3,5]

The structures of the aryltetralin constituents must still be regarded as uncertain. For hypophyllanthin, $C_{24}H_{30}O_7$, at least three isomeric structures have been proposed.[1,6,7,3] Nirtetralin is an isomer of hypophyllanthin, and one of the stereoisomeric structures (**3A**,**3B**) has been tentatively assigned to phyltetralin.[3]

For phyltetralin, the molecular formula $C_{24}H_{32}O_6$ is well established and the principal structural features (four aryl methoxyl groups, two methoxymethyl groups, two benzyl protons, one dibenzyl proton and five aryl protons) are readily discerned in the PMR spectrum. The additional alicyclic and methoxymethylene protons incorporated in formulae **3A-B** were also assigned.[3] Since the interpretation of the PMR spectrum is not unequivocal, (see later), we sought to test the validity of the structure proposals for phyltetralin by synthesis of both stereoisomers (**3A** and **3B**).

The key intermediate target for synthesis is an appropriately substituted aryl *trans* - 1,2 - dihydronaphthalene dicarboxylic acid derivative, which would yield both required C-3 epimers on suitable reduction of the C-3-double bond. A convenient pathway to such aryldihydronaphthalenes was apparent from the prior synthesis of the lignan structural analogue,[8] thomasidioic acid, but two unsuccessful attempts to adapt it for the synthesis of *Phyllanthus* lignans have been reported.[9,10]

The starting compound for this project was the dehydroferulic acid dilactone diacetate (**4**), readily available from ferulic acid by oxidation followed by acetylation. Treatment with iodobenzene dichloride gave the dichloride (**5**) whose PMR spectrum, confirmed the expected substitution site. In our earlier work, it was established that the dibromo analogue (**6**) was converted to the all-*trans* tetrahydrofuran (**7**) on treatment with hydrogen chloride in methanol-dioxan at room tem-



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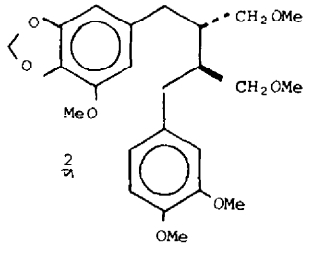

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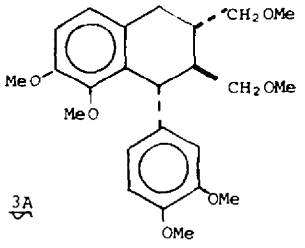
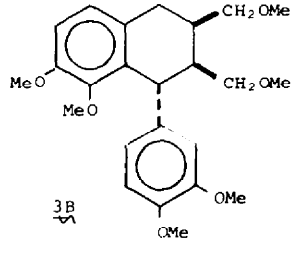


3A



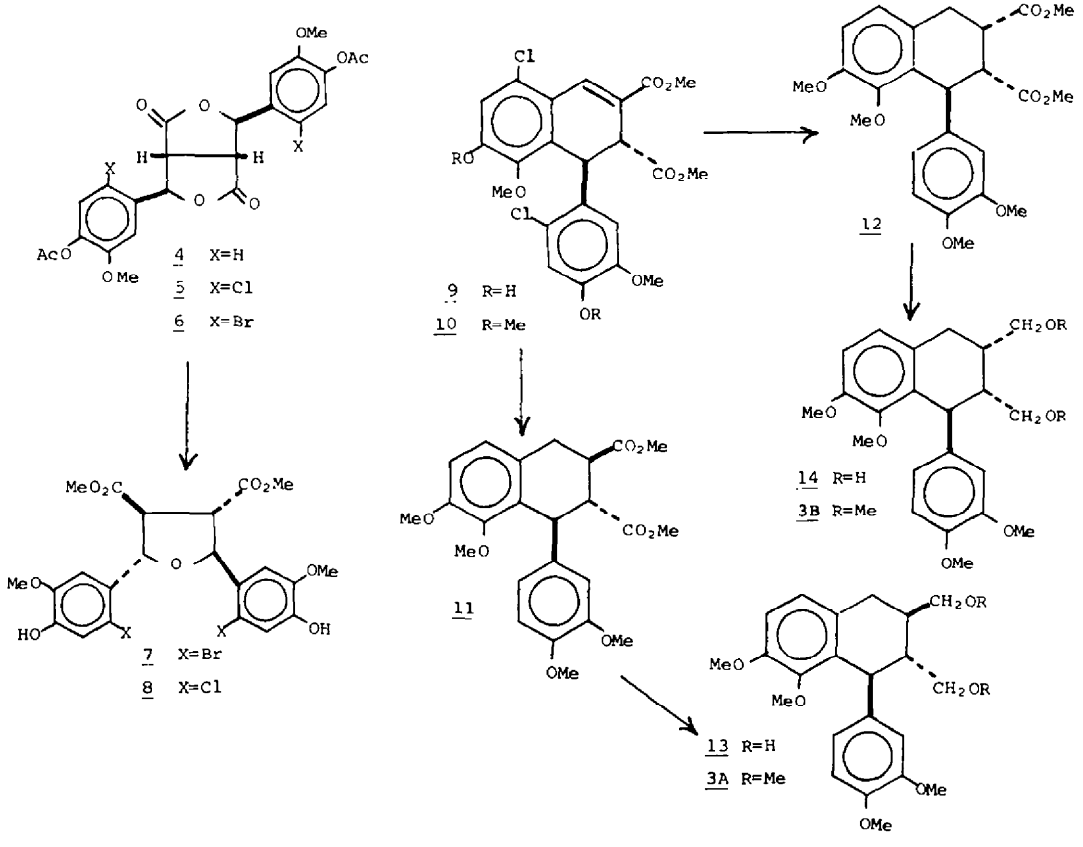
3B

perature. The dichloride (**5**) under the same conditions gave, as expected, the dichloro analogue (**8**). We have now found that saturation of a solution of **5** in chloroform–methanol with hydrogen chloride yields the required aryldihydronaphthalene (**9**) in reasonable yield. The PMR spectrum of this product, $C_{22}H_{20}Cl_2O_8$, for which excellent analogues exist,[8,9,11] confirms the presence of the two carbomethoxyl groups, two aryl methoxyl groups, three aryl protons, one vinyl proton and the *trans*-configuration of the substituents at C-1 and 2. Treatment of **9** with diazomethane yielded the tetramethyl ether (**10**).

It has been established by Wallis[11] that catalytic hydrogenation of an analogous dihydronaphthalene (with 6,7,8,3',4',5'-hexamethoxyl substitution) yielded both C-3 epimers with a 2,3-*trans*:2,3 *cis* ratio of approximately 2:1. When subjected to similar hydrogenation, the dichlorotetramethyl ether (**10**) underwent reductive dechlorination in addition to the double bond reduction to yield a product mixture, which was separated by multiple development tlc to yield both the major 2,3-*trans* diester (**11**) and 2,3-*cis* diester (**12**). The configurational assignments to **11** and **12** are both self-consistent and in good agreement with the earlier comparison data.[11] Thus, the 1-aryl ring of **11**, having a *cis* relationship with the C-3 carbomethoxyl group adopts an equatorial conformation and the 8-methoxyl group (δ 3.27) experiences more shielding than in the isomer **12**, in which the *trans*-relationship of 1-aryl and C-3 substituents permits the aryl ring to adopt an *axial* conformation with lesser deshielding (δ 3.43) of its proximate 8-methoxyl group. In further corrobation, the coupling constant (J 7 Hz) of the H-1 proton of **11** (expected of J ax-ax) is larger than that of **12** (J 2 Hz), expected of J eq-eq.

To complete the synthesis of each isomer (**3A** and **3B**) proposed for the structure of phyltetralin, each of the di-esters, (**11** and **12**), was reduced by LAH to the corresponding diols (**13** and **14**) which were converted to the methoxymethyl derivatives by treatment with methyl iodide and sodium hydride in dimethylsulphoxide.[12] We find that the PMR spectra of the synthetic compounds (**3A** and **3B**) are markedly different from that reported for phyltetralin. *Inter alia*, neither has an aryl proton signal at as high field as δ 6.23, nor methoxymethyl signals with the *same* chemical shift (δ 3.26) and each has a methoxyl group (attributable to C-8 OMe) at higher field than the highest field aryl methoxyl signal (δ 3.58) reported for phyltetralin. We consequently conclude that the structures **3A/B** which have been tentatively proposed for phyltetralin are untenable.

The interpretation[3] of the PMR spectrum of phyltetralin from which structure **3A/B** followed raises some questions. In particular, the highest field aryl methoxyl group (δ 3.58), considered to be shielded by the pendant aryl ring, was placed at C-8 which in turn, on biogenetic grounds, would imply a second methoxyl group at C-7. In support of this, a doublet signal at δ 6.23 (J 8 Hz) indicated an *ortho*-coupled aryl proton and was attributed to H-5 in agreement. This latter attribution, however, is weakened by the absence of specific assignment of the H-6 proton to which it should be coupled. More questionable however is the conclusion of "ring C in α-equatorial conformation which alone permits the shielding effect experienced by 8-OMe." A survey of data relevant to this question, to which Wallis had early drawn attention,[13] suggests that an 8-methoxyl group should be much more shielded (typically in the range δ 3.20–3.35). If, in fact, phyltetralin possesses such a function, it would suggest an *axial* conformation of



ring C. In agreement with this, compounds **11** and **13** have the most shielded (C-8) aryl methoxyl signal at δ 3.27, 3.25 respectively, with the *cis*-1,3-functions equatorially disposed. In comparison, in compounds **12** and **14** in which the *trans*-1,3-functions permit the aryl ring to adopt a more stable axial conformation, the corresponding signals are at somewhat lower field (δ 3.43 and 3.30). By themselves, the aryl methoxyl chemical shifts of phyltetralin (δ 3.88, 3.84, 3.80 and 3.58) are well accommodated by a ring C veratryl system with the remaining methoxyl groups at C-6 and C-7. Excellent comparison data are provided in the reported spectra of (−)-conidendrin dimethyl ether[14] (**15**) (δ 3.88, 3.86, 3.80 and 3.59), galbulin[15] (**16**) (δ 3.80, 3.76, 3.73 and 3.50), galcatin[16] (**17**) (δ 3.85 and 3.80) and otobaphenol methyl ether[16,17] (**18**) (δ 3.80 and 3.58). With this information, we were encouraged to prepare the veratryltetralin analogues of **3A/B** with a ring A methoxyl groups located at C-6,7 instead of C-7,8.

The availability of α-conidendrin (**19**) provided an excellent starting material for each desired product, (**21** and **25**). Methylation of **19** yielded α-dimethylconidendrin (**15**)[19] which on reduction with LAH gave the diol **20**,[20] generally known as isolariciresinol dimethyl ether. Methylation of **20** (MeI–NaH–DMSO) gave 1β - (3',4' - dimethoxyphenyl) - 2α,3β - bismethoxymethyl - 6,7 - dimethoxy - 1,2,3,4 - tetrahydronaphthalene (**21**).

Treatment of α-conidendrin with sodium methoxide as previously described[21] yielded β-conidendrin (**22**) which was converted successively (as in the α-series) to β-dimethylconidendrin (**23**),[21] β-conidendryl alcohol dimethyl ether (**24**)[22] and 1β - (3',4' - dimethoxyphenyl) - 2α,3α - bismethoxymethyl - 6,7 - dimethoxy - 1,2,3,4 - tetrahydronaphthalene (**25**).

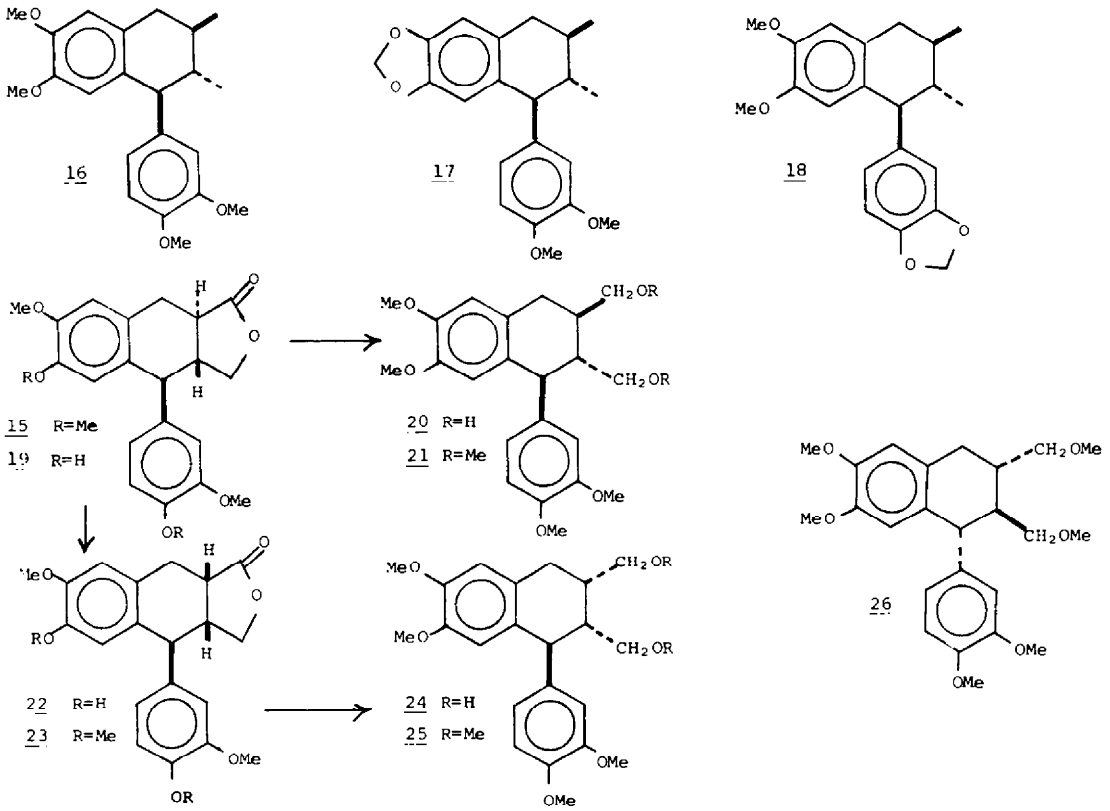
The empirical constants (m.p. 110–111°, $[\alpha]_D$ − 13°) and excellent correspondence of the aryl methoxyl group chemical shift values (δ 3.88, 3.83, 3.80 and 3.58) found for "isolariciresinol tetramethyl ether" (**21**) lend credence to the possibility that it is in fact the enantiomer of phyltetralin (m.p. 110°, $[\alpha]_D$ + 17.5°, δ (OMe) 3.88, 3.84, 3.80 and 3.58). In addition the PMR spectrum of **21** exhibits a high field aryl proton signal (δ 6.25 s.) attributable to the shielded H-8 proton (compare the δ 6.23 d. signal reported for phyltetralin). The major discrepancy casting doubt on this conclusion is that the methoxymethyl protons found in **21** are singlets at δ 3.35 and 3.27 as opposed to the same chemical shift values (δ 3.26) reported for these protons in phyltetralin. Until a direct comparison of specimens can be made with PMR and solution IR spectra determined under the same conditions—which unfortunately has not been possible to date*—the structure **26** should be regarded as a viable constitution of phyltetralin.

Addendum*—In a letter dated 5 Feb. 1977, Prof. Ramachandra Row states, after having reviewed this manuscript and copies of the pertinent spectra that "the structure of phyltetralin is settled finally." Accordingly, phyltetralin should now be formulated as 1α - (3',4' - dimethoxyphenyl) - 2β,3α - bis - methoxymethyl - 6,7 - dimethoxy - 1,2,3,4 - tetrahydronaphthalene (26**).

EXPERIMENTAL

M.ps were determined with either a Gallenkamp or Fisher–Johns apparatus and are uncorrected. PMR spectra were determined for solutions with TMS as internal reference on a Varian A60 spectrometer.

r - 1H,2*c*,6*c* - *Bis* - (4' - *acetoxy* - 2' - *chloro* - 5' - *methoxyphenyl*) - 3,7 - *dioxabicyclo* - [3.3.0] - *octane* - 4,8 - *dione* (**5**). Compound[10] **4** (5.65 g) was dissolved in boiling AcOH



(110 ml) containing NaOAc (2.5 g) Iodobenzene dichloride (8.5 g) was then added, the mixture stirred for 15 min, poured into ice-water (*ca.* 100 ml) and extracted with CH_2Cl_2 (3 × 40 ml). The extract was washed with 1% $Na_2S_2O_3$ (100 ml) and water and the solvents removed. The residual solid was extracted by trituration with light petroleum to remove most of the iodobenzene, then recrystallized from CH_2Cl_2–MeOH to give the *dichloro dilactone diacetate* (**5**) as soft cotton-like needles (5.0 g), m.p. 237–238°. (Found: C, 53.43; H, 3.73. $C_{24}H_{20}Cl_2O_{10}$ requires: C, 53.45; H, 3.74%). PMR spectrum: δ ($CDCl_3$) 2.28 s (6, OAc), 3.60 s (2, H-1 and 5), 3.83 s (6, OMe), 6.10 s (2, H-2 and 6), 6.87 s (2, H-2') and 7.17 s (2, H-5').

Product of lower quality and yield were obtained by:

(a) Addition of a soln of chlorine in AcOH to the dilactone diacetate in the same solvent, in the absence or presence of NaOAc.

(b) Passage of Cl_2 gas into a soln of the dilactone diacetate until excess visible by colour and

(c) The thallation-halogenation technique used successfully for the dibromo analogue.[10]

r - 2,*t* - 5 - *Bis*(2' - *chloro* - 4' - *hydroxy* - 5' - *methoxyphenyl*) - *tetrahydrofuran* - *t* - 3,*c* - 4 - *dicarboxylic acid dimethyl ester* (**8**). A soln of HCl in MeOH (3%, 100 ml) was added to a soln of **5** (5.35 g) in dioxane (75 ml). The mixture was allowed to stand at room temp. for 48 hr under N_2, poured into ice-water (150 ml), extracted with CH_2Cl_2 (3 × 50 ml), washed with water (3 × 100 ml) and the dried (Na_2SO_4) extract evaporated. Crystallization of the residue from CH_2Cl_2-isopropyl ether gave the *dichloro bisphenol* (**8**) as prisms (1.4 g, m.p. 188–191°), raised to m.p. 194–195° for analysis. (Found: C, 52.44; H, 4.40. $C_{22}H_{22}Cl_2O_9$ requires: C, 52.71; H, 4.42%.) PMR spectrum δ ($CDCl_3$) 3.48–3.63 m (2, H-3 and 4), 3.70 s (6, CO_2Me), 3.95 s (6, OMe), 5.77–5.96 m (2, H-2 and 5), 6.93 s (H-3') and 7.15 s (H-6').

Dimethyl 5 - *chloro* - 7 - *hydroxy* - 8 - *methoxy* - 1(2' - *chloro* - 4' - *hydroxy* - 5' - *methoxyphenyl*) - trans - 1,2 - *dihydronaphthalene* - 2,3 - *dicarboxylate* (**9**). A soln of **5** (4.6 g) in a mixture of $CHCl_3$ (90 ml) and MeOH (60 ml) cooled in an ice bath was saturated with HCl gas at such a rate that the temp. was kept below 30°, then stirred overnight at room temp. The soln was concentrated under reduced presure (to *ca.* 25 ml) and the resultant ppt (1.17 g, m.p. 263–270°) collected, washed with CH_2Cl_2-light petroleum (2:1, 90 ml) and crystallized from THF–aqueous MeOH to give the *dihydronaphthalene* (**9**) as hard needles (960 mg), m.p. 268–271°. (Found: C, 54.57; H, 4.18. $C_{22}H_{20}Cl_2O_8$ requires: C, 54.67; H, 4.17%). PMR spectrum: δ [$(CD_3)_2CO$ with $(CD_3)_2SO$] δ 3.52 s (3, C-8 OMe), 3.57 s and 3.65 s (6, two CO_2Me), 3.73 s (3, C-5' OMe), 4.02 d (J 1.5 Hz, 1, H-2), 5.55 d (J 1.5 Hz, 1, H-1), 6.07 s (1, H-6'), 6.82 s (1, ArH), 7.10 s (1, ArH) and 8.03 s (1, H-4).

Dimethyl - 5 - *chloro* - 7,8 - *dimethoxy* - 1(2' - *chloro* - 4',5' - *dimethoxyphenyl*) - trans - 1,2 - *dihydroaphthalene* - 2,3 - *dicarboxylate* (**10**). A soln of **9** (960 mg) in THF (50 ml) was treated with excess diazomethane, the solvents removed and the solid residue recrystallized from CH_2Cl_2–MeOH to give the *tetramethyl ether* (**10**) as rosettes of stout needles (800 mg), m.p. 172–174°. (Found: C, 56.14; H, 4.90. $C_{24}H_{24}Cl_2O_8$ requires: C, 56.37; H, 4.73%). PMR spectrum: δ ($CDCl_3$) 3.55 s (3, C-8 OMe), 3.62 s and 3.67 s (6, two (CO_2Me)) 3.78 s, 3.82 s and 3.87 s (9, C-7, 4' and 5' OMe), 4.06 d (J 1 Hz, 1, H-2), 5.61 d (J 1 Hz, 1, H-1), 6.05 s (1, H-6'), 6.93 s (1, ArH), 6.97 s (1, ArH) and 8.12 s (1, H-4).

Catalytic hydrogenation of aryl dihydronaphthalene (**10**). A soln of **10** (800 mg) in EtOH (125 ml) was stirred with Pd-C (10%, 2.5 g) under H_2 for 3 days (negligible uptake after first day). After filtration and solvent evaporation, PMR examination of the residual product indicated incomplete dechlorination. The hydrogenation was repeated twice more with fresh catalyst for 1 day, and the mixture (560 mg) subjected to multiple development tlc using 2% isopropyl alcohol in benzene as developing solvent on four plates (20 × 20 cm, 1 mm thick) of Merck silica (PF 254 + 366). The slower-running (and major) constituent was eluted from the lower half of the plate with Me_3OH–CH_2Cl_2 (1:9) and recrystallized from ether-hexane to give *dimethyl* 1,2,3,4 - *tetrahydro* - 7,8 - *dimethoxy* - r - 1 - (3',4' - *dimethoxyphenyl*)*naphthalene* - t - 2,c - 3 - *dicarboxylate* (**11**) as clusters of needles (200 mg), m.p. 100–101°. (Found: C, 64.90; H, 6.28. $C_{24}H_{28}O_8$ requires: C, 64.85; H, 6.35%). PMR spectrum: δ ($CDCl_3$) 2.87–3.22 m (4, H-2, 3, 4), 3.27 s (3, C-8 OMe), 3.60 s and 3.65 s (each 3, C-2 and 3 CO_2Me), 3.80 s (3, OMe) and 3.82 s (6, two OMe), 4.68 d (1, J 7 Hz, H-1), 6.57–6.93 m (5, ArH).

The faster-running (minor) constituent was similarly extracted from the upper half of the plate, crystallized once from ether-hexane then from aqueous MeOH to give *dimethyl* 1,2,3,4 - *tetrahydro* - 7,8 - *dimethoxy* - r - 1 - (3',4' - *dimethoxyphenyl*)*naphthalene* - t - 2,t - 3 - *dicarboxylate* (**12**) as fine needles, m.p. 78–80°. (Found: C, 65.05; H, 6.46. $C_{24}H_{28}O_8$ requires: C, 64.85; H, 6.35%). PMR spectrum: δ ($CDCl_3$) 2.95–3.33 (4, H-2, 3, 4), 3.43 s (3, C-8 OMe), 3.63 and 3.70 (each 3, C-2 and 3 CO_2Me), 3.83 s (6, two OMe) and 3.85 s (3, OMe), 5.07 d (1, J 2 Hz, H-1), 6.40 dd (1, J 2, 8 Hz, H-6') and 6.67–6.97 m (4, ArH).

The integrated PMR spectrum of the hyrogenated mixture indicated a 2,3-*trans* (**11**):2,3 *cis* (**12**) ratio of *ca.* 2:1.

r - 1 - (3',4' - *Dimethoxyphenyl*) - t - 2,c - 3 - *bismethoxymethyl* - 7,8 - *dimethoxy* - 1,2,3,4 - *tetrahydronaphthalene* (**3A**). LAH (100 mg) was added to a soln of **11** (100 mg) in THF (25 ml), the mixture stirred for 30 min, then worked up in the usual way to give **13** as a colourless oil (82 mg), PMR spectrum: δ ($CDCl_3$) 1.42–2.08 m (4, H-2,3 and two OH), 2.43–2.77 m (2, H-4), 3.25 s (3, C-8 OMe), 3.27–4.05 m (4, two $-CH_2OH$), 3.78 s (9, C-7, 3',4' OMe), 4.18 d (1, poorly resolved, H-1) and 6.57–6.88 m (5, ArH).

This diol **13** (82 mg) was dissolved in dimethylsulphoxide (10 ml), NaH (50 mg, 50% in mineral oil) and MeI (0.2 ml) added and the mixture stirred for 1 hr. The same quantities of NaH and MeI were then added, the mixture stirred for a further 1 hr, then the product isolated by addition of water and ether extraction. Purification by tlc (hexane-ethyl acetate, 2:1, R_f 0.45) gave the 2,3 - *trans* - *bismethoxymethyl ether* (**3A**) as a colourless oil. (Found: M^+ 416.21989. $C_{24}H_{32}O_6$ requires: M^+ 416.21993). PMR spectrum: δ ($CDCl_3$) *ca.* 2.1 br. m (2, H-2,3), *ca.* 2.65 br. m (2, H-4), 3.30 s, 3.35 s and 3.40 s (9, C-8 OMe and two CH_2OCH_3 groups), 3.17–3.48 m (4, two CH_2OCH_3 groups), 3.82 s (9, C-7 OCH_3, 3',4' OMe), 4.51 d (1, J 5 Hz, H-1) and 6.57–7.02 m (5, ArH).

r - 1 - (3',4' - *Dimethoxyphenyl*) - t - 2,t - 3 - *bismethoxymethyl* - 7,8 - *dimethoxy* - 1,2,3,4 - *tetrahydronaphthalene* (**3B**). Compound **12** was reduced with LAH as above to give **14** as a colourless oil. PMR spectrum: δ ($CDCl_3$) 1.45–1.80 m (2, H-2,3), 2.00–2.20 br.s (2, –OH), 2.63–2.97 m (2, H-4), 3.20–3.97 m (4, two CH_2OH), 3.30 s (3, C-8 OMe), 3.80 s (9, C-7, 3',4' OMe), 4.41 d (1, J 2 Hz, H-1), 6.38 dd (1, J 2, 8 Hz, H-6') and 6.62–6.93 m (4, ArH).

Methylation of this diol as above gave the 2,3 - *cis* - *bismethoxymethyl ether* (**3B**) as a colourless oil. (Found: M^+ 416.21911. $C_{24}H_{32}O_6$ requires: M^+ 416.21993). PMR spectrum: δ ($CDCl_3$) 2.0–2.92 m (4, H-2,3,4), 3.25 s, 3.30 s and 3.33 s (9, C-8 and two CH_2OCH_3 groups), 3.12–3.52 m (4, two CH_2OCH_3 groups), 3.82 s (9, C-7, 3',4' OMe groups), 4.55 br.s (1, H-1), 6.37 dd (1, J 1.5, 8 Hz, H-6'), 6.69 d (1, J 1.5 Hz, H-2'), 6.70 d (1, J 8 Hz, H-5') and 6.87 s (2, H-5,6).

Isolariciresinol dimethyl ether (**20**). Methylation of **19** yielded **15**, as tiny needles, m.p. 179.5–180° (lit.[19] m.p. 179–180°), which on LAH reduction gave **20**, m.p. 164–166.5° (lit.[20] m.p. 167–169°).

1β - (3',4' - *Dimethoxyphenyl*) - 2α,3β - *bismethoxymethyl* - 6,7 - *dimethoxy* - 1,2,3,4 - *tetrahydronaphthalene* (**21**). MeI (0.6 g) was added to a stirred soln of **20** (154 mg) in dry dimethylsulphoxide. NaH (0.9 g in 57% oil dispersion) was washed twice with dry ether, covered with dimethylsulphoxide and this added portionwise followed by more MeI (0.5 ml). Afer being stirred at room temp. for 2.5 hr, isolation of the product in the usual way via ether extraction, and crystallization from hexane gave *isolariciresinal tetramethyl ether* (**21**) as beautiful needles (75 mg), m.p. 110–111°, $[\alpha]_D$ – 13° (*c*, 1.5 in $CHCl_3$). (Found: C, 69.50; H, 7.60. $C_{24}H_{32}O_6$ requires: C, 69.21; H, 7.74%). PMR spectrum: δ ($CDCl_3$) *ca.* 1.5–2.4 m (2, H-2,3), *ca.* 2.7–3.0 m (2, H-4), 3.27 s (3, C-2 CH_2OMe), 3.35 s (3, C-3 CH_2OMe), 3.58 s (3, C-7 OMe), 3.80 s, 3.83 s and 3.88 s (9, C-3',4' and 6-OMe), 3.1–3.55 m (4, two CH_2OMe groups), 4.0 d (1, J *ca.* 9 Hz, H-1), 6.25 s (1, H-8) and 6.55–6.85 m (4, ArH).

β-Conidendryl alcohol dimethyl ether (**24**). Treatment of α-conidendrin with NaOMe in MeOH[21] gave **22** as needles, m.p.

213–214°, $[\alpha]_D$ + 29° (lit.[21] m.p. 208–210°, $[\alpha]_D$ + 32.5°). Methylation with dimethyl sulphate gave **23** as needles, m.p. 149–153°, $[\alpha]_D$ 0° (*c*, 0.4 in Me_2CO) (lit. m.p. 154–155°, s 140°, $[\alpha]_D$ 0°) which with LAH gave **24**, m.p. 103–108°.

1*β* - (3',4' - *Dimethoxyphenyl*) - 2*α*,3*α* - *bismethoxymethyl* - 6,7 - *dimethoxy* - 1,2,3,4 - *tetrahydronaphthalene* (**25**). The diol **24** (435 mg) was treated with MeI–NaH-dimethylsulphoxide as for the preparation of **21** above. Three recrystallizations of the product from hexane gave the *cis* - 2,3 - *bismethoxymethyl ether* as irregular prisms (330 mg), m.p. 123–124°, $[\alpha]_D$ + 68° (*c*, 1.5 in $CHCl_3$). (Found: C, 69.37; H, 7.89. $C_{24}H_{32}O_6$ requires: C, 69.21; H, 7.74%) PMR spectrum: *δ* ($CDCl_3$) 2.05–2.50 (2, H-2,3), 2.50–2.95 (2, H-4), 3.25 s (3, C-2 CH_2OMe) 3.32 s (3, C-3 CH_2OMe), 3.68 s (3, C-7 OMe), 3.78 s, 3.82 s and 3.85 s (9, C-3',4' and 6-OMe), *ca.* 3.0–3.53 (4, two CH_2OMe groups), 4.10 d (1, J 4 Hz, H-1) 6.24 s (1, H-8) and 6.45–6.75 m (4, ArH).

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