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OXIDATIVE COUPLING OF BROMO- AND IODO-FERULIC ACID DERIVATIVES: SYNTHESIS OF (±)-VERAGUENSIN

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Abstract—The phenolic coupling of halogen-containing ferulic acid and methyl ester derivatives was examined with particular reference to the synthesis of lignans of the aryltetralin and tetrahydrofuran classes. (±)-Isolariciresinol dimethyl ether (**18**) and (±)-veraguensin (**27**) have been synthesized.

The oxidative coupling of the *p*-hydroxycinnamic acids, ferulic acid (**1**) and sinapic acid (**2**) to yield the diaryl dilactones, (**3** and **4**) respectively, has been demonstrated.[1-4] It has also been shown that such dilactones are susceptible to acid-catalyzed rearrangement leading to the corresponding aryl *trans*-1,2-dihydronaphthalene dicarboxylic acids (**5** and **6**). This two-step procedure provided a convenient synthetic route to the unusual aryldihydronaphthalene lignans, thomasidioic acid (**6**) and its major congener, thomasic acid (CH_2OH for CO_2H at C-2 in **6**).

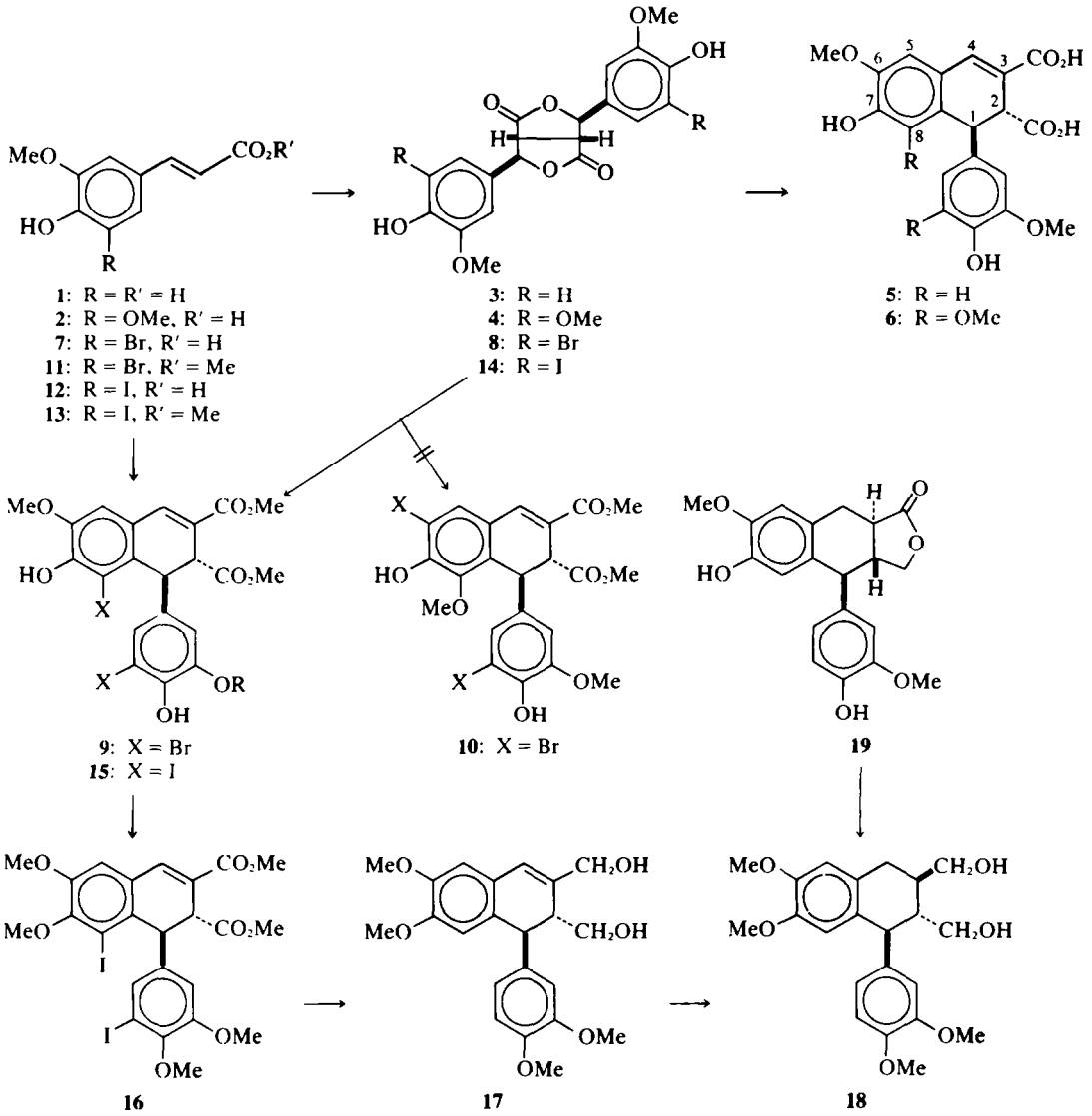
We are currently examining the generality of these procedures and their extension to the synthesis of the more extensively-occurring arylnaphthalene and aryltetrahydronaphthalene lignans. Within this context, we noted that Row *et al.*[5] have isolated from the plant *Phyllanthus niruri* Linn. several lignans, three of which (hypophyllanthin, nirtetralin and phyltetralin) are aryltetralins in which it is postulated that ether functions are located at C-7 and C-8. We sought consequently to effect the oxidation of a *p*-hydroxycinnamic acid with appropriate halogen substituent (e.g. **7**) to the analogous dihalodilactone (**8**). If this were to behave towards methanolic hydrogen chloride in the same manner as **3** and **4**, it would give rise to the diesters **9** and/or **10**, of which the latter would be an excellent intermediate for the synthesis of *Phyllanthus* lignans.

When the known 5-bromoferulic acid (**7**)[2,6] was treated with ferric chloride in aqueous acetone, there precipitated immediately a product shown by the IR spectrum to be a lactone and by the PMR spectrum to have the structure and stereochemical configuration represented by **8**. Treatment of this dihalodilactone (**8**) with methanolic hydrogen chloride then yielded a product whose IR spectrum showed two CO absorption bands (typical of a conjugated and non-conjugated ester), leaving little doubt that a rearrangement to an aryl dihydronaphthalenedicarboxylic acid dimethyl ester had occurred. A distinction between the isomers **9** and **10** for this product was initially made on the basis of the PMR spectrum. Since it is known[7] that a C-8 aryl OMe group is shielded (typically in the range δ 3.60–3.67) by an axial 1-aryl group and even more strongly shielded (*ca.* δ 3.20) by an equatorial 1-aryl group, the absence of this feature (apart from the resonance of C-2 carbomethoxyl group) and the presence of a high field OMe signal (δ 3.96) as expected for a C-6 aryl OMe group, indicated that the rearrangement product had the structure **9**. The same product could be conveniently obtained in only one step from the methyl ester derivative (**11**).

We have also oxidized 5-iodoferulic acid (**12**)[8] to the di-iodo dilactone (**14**) to examine whether the steric requirement of the larger halogen atom would influence the direction of ring closure in the acid-catalyzed rearrangement. The examination of the PMR spectrum of the product so obtained however, indicated the same ring substitution pattern as for the bromo analogue, and the di-iodo diester could accordingly be formulated as **15**. Again, the product **15** could be obtained simply in one step and in good yield by the ferric chloride oxidation of the iodoferulic acid methyl ester (**13**).

Chemical proof for these structures **9** and **15** was achieved by an interconversion to (±)-isolariciresinol dimethyl ether (**18**) of established structure.[9] Thus, treatment of **15** with diazomethane gave the tetramethyl ether dimethyl ester (**16**) which underwent reductive deiodination and ester reduction with LAH to give the diol (**17**), catalytic hydrogenation of which gave (±)-isolariciresinol dimethyl ether (**18**), identified by spectra comparison with the (+)-isomer obtained from α-conidendrin (**19**) by methylation[10] followed by LAH reduction.[11]

Since the result of the oxidation of the methyl esters (**11** and **13**) had been a $\beta\beta$-coupling, followed by cyclization at the position *para* to the OMe group (envisioned as **11** → A → B → C-9, in Chart 1), we sought to examine the oxidation when this particular position was occupied. It was hoped that this would favour cyclization at the position *ortho* to the OMe group (e.g. **21** → D → E as in Chart 2) leaving the guaiacol functionality at C-7 and 8. For this purpose, methyl 2,3-dibromo-4-hydroxy-5-methoxycinnamate (**21**, R = Me) was prepared from 2,3-dibromovanillin (**20**)[12] by the Perkin condensation to the corresponding substituted cinnamic acid (**21**, R = H), followed by methyl esterification. Under the usual ferric chloride oxidation conditions, the course of oxidation of **21** (R = Me) was visibly different, and a precipitate separated from the reaction mixture only after several days. Although the conversion yield was low, starting material suitable for re-oxidation without further purification was readily recovered. Difficulties initially encountered with the reproducibility of this experiment were obviated with the discovery of the beneficial effect of the presence of a



low concentration of hydrochloric acid. This may be attributable to acid catalysis of the conversion of the initial quinone-methide intermediate (e.g. **F**, Chart 2) to phenolic product. It was also noted that higher concentrations of hydrochloric acid retarded the oxidation, probably by lowering the concentration of the phenolate anion substrate.

Under these modified conditions, there was readily

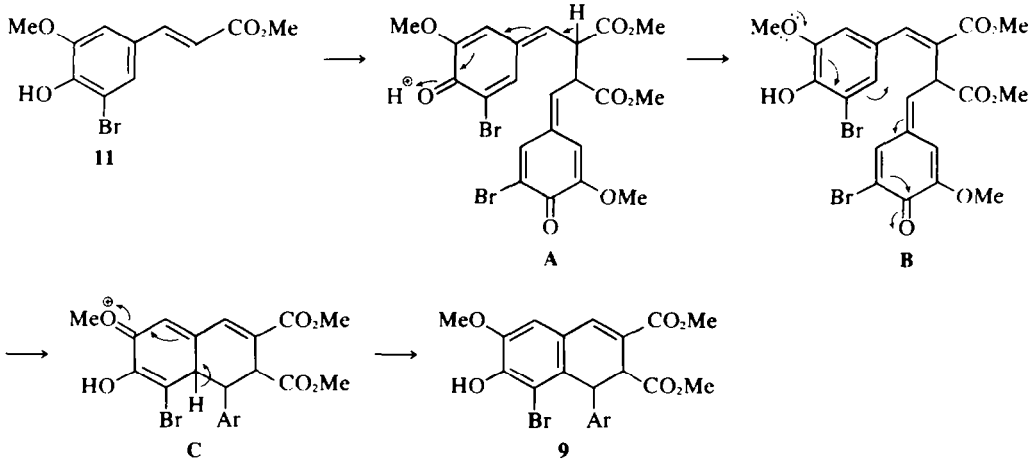


Chart 1.

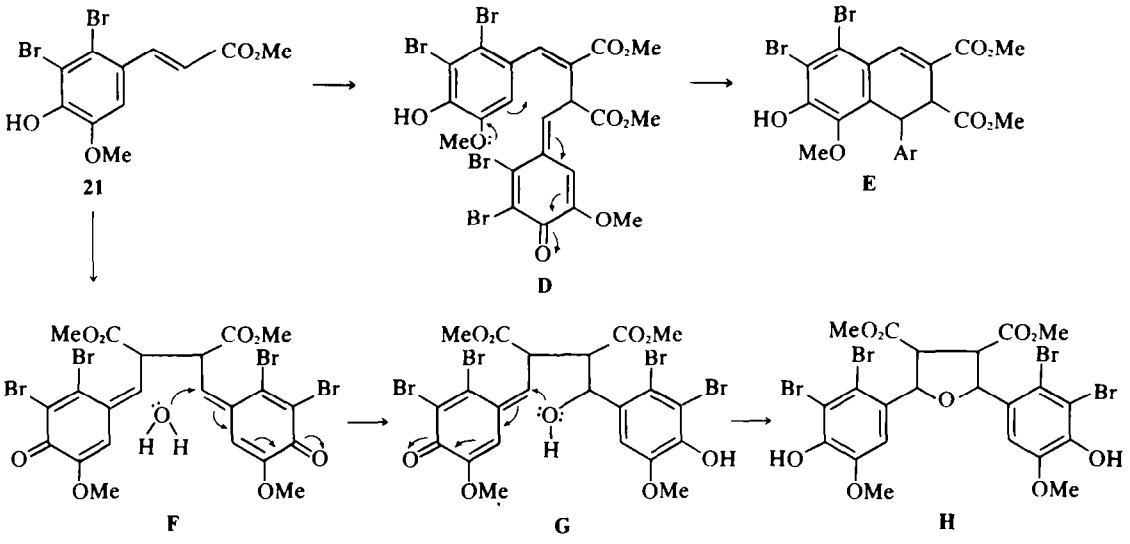
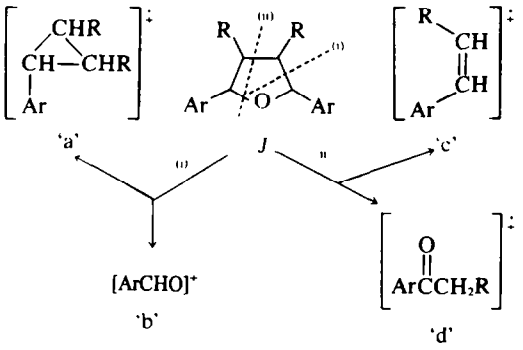


Chart 2.

obtained a "dimeric" oxidation product, whose molecular formula $C_{22}H_{20}Br_4O_9$ (rather than $C_{22}H_{18}Br_4O_8$ required of the aryldihydronaphthalene analogue **E**) indicated a structurally distinct type. An apparent explanation of the additional O atom in the oxidation product lay in the formation of a tetrahydrofuran by a pathway such as **21**→**F**→**G**→**H**. As established in the sequel, we propose the constitution **22** for this oxidation product. It was characterized by formation of a diacetate derivative (**23**), and with diazomethane the tetramethyl ether (**24**).

Mass spectra of simple lignans containing the tetrahydrofuran nucleus have been studied, and in structures of general formula **J** (R = CH_3), two main breakdown pathways, (i) leading to ions "a" and "b" and (ii) leading to ions "c" and "d" were recognized.[13]

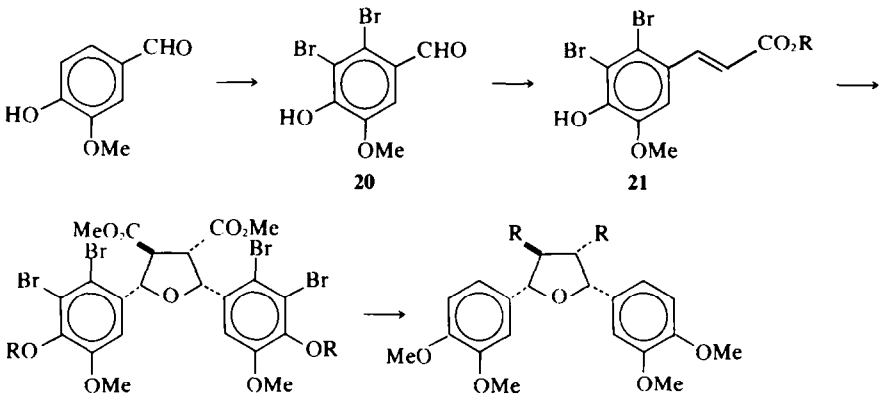


The mass spectrum of the tetrabromotetramethyl ether (**24**) supported this formulation in that, for example, three intense fragments corresponded to the molecular ion (*m/e* 772 for $C_{24}H_{24}Br_4O_9$) and type (i) cleavage ions *m/e* 450 (ion "a"), *m/e* 371 (ion "a"-Br) and *m/e* 321 (ion "b"-H) were apparent.

When subjected to catalytic hydrogenation conditions, the tetrabromide (**24**) underwent reductive debromination to give a tetramethyl ether dimethyl ester (**25**). The mass spectrum of this product further supported the tetrahydrofuran formulation with prominent ion fragments at *m/e* 460 (molecular ion), 294 and 165 (ions "a" and "b-H" by pathway (i)), and 238 and 222 (ions "d" and "c" by pathway (ii)).

With regard to the configuration of the oxidation product **22**, the PMR spectrum allowed the exclusion of four of the six *ab initio* possibilities (**22** a–f; R = CO_2Me, Ar = 2,3-dibromo-4-hydroxy-5-methoxyphenyl). Thus, for example, the presence of four distinct OMe signals in the spectrum of **22** ruled out the *meso* forms (**22a** and **22b**) in the *cis*-R group, and **22d** and **22f**, which have an axis of symmetry, in the *trans*-R group. In addition, the highly shielded location (δ 3.25) of one OMe group indicated the presence of *one* carbomethoxyl group *cis* to an adjacent aryl group in agreement with the remaining possibilities, **22c** and **22e**. To establish the configuration by chemical means, it was decided to convert the oxidation product to the corresponding lignan analogue by methylation to **24**, debromination to **25**, reduction to **26** and hence to **27**. Of the lignan isomers (**27a–f**, R = Me, Ar = 3,4-dimethoxyphenyl), four are known as natural products and well characterized. The *meso* form **27b** is known as galgravin,[14] isolated from *Himantandra belgraveana* bark or as tetrahydrofuroguaiacin-A dimethyl ether[15] from "*lignum vitae*". Both **27b** and the all-*cis* isomer **27a** (tetrahydrofuroguaiacin-B dimethyl ether[15]) have been synthesized.[16] (−)-Galbelgin (**27d**) was later isolated[17] from the same source as galgravin, and (+)-veraguensin (**27e**) has been obtained from the wood of *Ocotea veraguensis*[18] and the leaves of *Trimenia papuana*.[19]

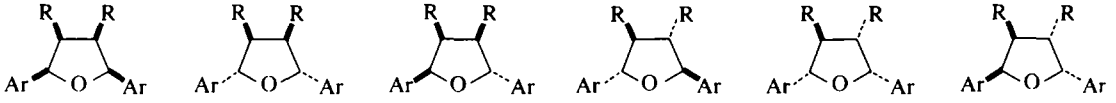
The methyl dibromoferulate oxidation product (**22**) was accordingly converted to the tetramethyl ether (**24**) by diazomethane treatment, and debrominated smoothly by catalytic hydrogenation, using relatively large quantities of Pd–C catalyst, to yield **25**. Conversion of the carbomethoxyl to Me groups was effected by the standard procedure of LAH reduction to give **26** which was converted to the bis-toluenesulphonate ester derivative and again reduced by the same reagent to give (±)-veraguensin (**27** = **27e**), with m.p. and PMR spectrum in excellent agreement with that reported.[20] This lignan was isolated previously in racemic form in low yield as one of the products isolated by enzyme-catalyzed oxidation of (E)- and (Z)-isoeugenol, followed by diazomethane methylation.[20]



20 **21**

22: R = H
23: R = Ac
24: R = Me

25: R = CO_2Me
26: R = CH_2OH
27: R = CH_3



22,27a **22,27b** **22,27c** **22,27d** **22,27e** **22,27f**

EXPERIMENTAL

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

3-Bromo-4-hydroxy-5-methoxycinnamic acid (*5-bromoferulic acid*) (**7**) was prepared from 5-bromovanillin[21] by the Doebner-Knoevenagel reaction as described, and had m.p. 258–263° without recrystallization. Lit m.p. 246°,[2] 257–258°.[6] PMR ($(CD_3)_2CO$) δ 3.97 (3, OMe), 6.43 d (J = 16 Hz, 1, α-vinyl H), 7.35 d (J = 2 Hz, 1, H-6), 7.45 d (J = 2 Hz, 1, H-2) and 7.60 d (J = 16 Hz, 1, β-vinyl H).

Methyl-3-Bromo-4-hydroxy-5-methoxycinnamate (**11**) was prepared by refluxing a solution of **7** in MeOH with a few drops of conc H_2SO_4 for 3 hr, dilution with water to turbidity and allowing to crystallize. Recrystallization from aqueous acetone gave the *ester* as needles, m.p. 106–108°. Lit m.p. 112–113° (hydrate).[22] PMR ($CDCl_3$) 3.79 (3, CO_2Me), 3.92 (3, OMe), 6.28 d (J = 16 Hz, 1, α-vinyl H), 6.97 d (J = 2 Hz, 1, H-6), 7.30 d (J = 2 Hz, 1, H-2) and 7.57 d (J = 16 Hz, 1, β-vinyl H).

r-1H-2c, 6c-Bis-(3'-bromo-4'-hydroxy-5'-methoxyphenyl)-3,7-dioxabicyclo-[3,3,0]-octane-4,8-dione (**8**). A soln of ferric chloride hydrate (2.5 g) in water (40 ml) was added to a stirred soln of 5-bromoferulic acid (2.1 g) in acetone (180 ml). Stirring was continued for 2 hr during which a ppt formed. The mixture was then allowed to stand overnight, filtered, the filtrate suspended in a small volume of acetone, acidified with H_2SO_4 and diluted with water. The white ppt so obtained was collected and recrystallized from acetone-light petroleum to yield the *dilactone* (**8**) as tiny needles, (0.27 g), m.p. 208–210° dec., λ (KBr) 5.65μ (lactone), PMR ($(CD_3)_2CO$) 3.92 (6, OMe), 4.18 d (J = 1 Hz, 2, H-1 and 5), 5.83 br.s. (2, H-2 and 6), 7.10 d (J = 2 Hz, 2, H-6') and 7.21 d (J = 2 Hz, 2, H-2'). (Found: C, 44.11; H, 2.61. $C_{20}H_{16}Br_2O_8$ requires: C, 44.14, H, 2.96%).

Dimethyl 8-Bromo-7-hydroxy-6-methoxy-1-(3'-bromo-4'-hydroxy-5'-methoxyphenyl)-trans-1, 2-dihydronaphthalene-2, 3-dicarboxylate (**9**)

(a) HCl was bubbled through a soln of **4** (R = Br) (90 mg) in MeOH (50 ml) for 20 min, the mixture then heated under reflux for 2 hr, poured into water and the ppt collection. Crystallization from aqueous MeOH gave the *dihydronaphthalene* (**9**) as needles (40 mg), m.p. 196–199°; λ (KBr) 5.76 (C-2 ester) and 5.92μ (C-3 ester). PMR ($CDCl_3$) δ 3.68 (3, C-2 CO_2Me), 3.78 (3, C-3 CO_2Me), 3.80 (3, 5'-OMe), 3.94 (3, 6-OMe), 4.03 d (J = 1.5 Hz, 1, H-2), 5.05 br.s. (1, H-1), 6.53 d and 6.60 d (J = 1.5 Hz, 1, H-2' and 6'), 6.88 (1, H-5) and 7.68 (1, H-4). (Found: C, 46.61; H, 3.73. $C_{22}H_{20}Br_2O_8$ requires: C, 46.17; H, 3.53%).

(b) A soln of ferric chloride hydrate (1.27 g) in water (40 ml) was added dropwise over 30 min to a stirred soln of **11** (1.0 g) in acetone (50 ml) and water (40 ml). The mixture was stirred for a further 10 min, diluted with water (25 ml), acidified with dil H_2SO_4, and concentrated under reduced pressure until a gum separated. The soln was decanted, and the gum crystallized from aqueous MeOH to give a light yellow solid (225 mg, m.p. 160–180°. Two recrystallizations from the same solvent gave **9**, m.p. 195–199°, with same PMR spectrum as in (a).

3-Iodo-4-hydroxy-5-methoxycinnamic acid (*5-Iodoferulic acid*) (**12**)

(a) Prepared as described had m.p. 259–263°. (Lit[8] m.p. 250–251°). PMR ($(CD_3)_2CO$) δ 3.95 (3, OMe), 6.40 d (J = 16 Hz, 1, α-vinyl H), 7.37 d (J = 2 Hz, 1, H-6), 7.57 d (J = 16 Hz, 1, β-vinyl H) and 7.62 d (J = 2 Hz, 1, H-2).

(b) Piperidine (0.4 ml) was added to a soln of 5-iodovanillin (5.0 g) and malonic acid (10.4 g) in pyridine (14 ml), the mixture heated on a steam bath for 1.5 hr, then poured on to ice (35 g)-HCl (20 ml) and the ppt (3.98 g, m.p. 240–248°) collected. Recrystallization from AcOH gave **12** as a yellow solid, m.p. 256–259°.

Methyl 3-Iodo-4-hydroxy-5-methoxycinnamate (**13**). The acid **12** (3.0 g) in MeOH (150 ml) and conc H_2SO_4 (0.5 ml) was heated under reflux for 1 hr, concentrated and worked up in the usual way to give a solid (2.84 g, m.p. 135–138°). Recrystallization from aqueous MeOH gave the *methyl ester* as needles, m.p. 140–143°. (Found: C, 39.37; H, 3.18. $C_{11}H_{11}IO_4$ requires: C, 39.54; H, 3.32%).

r-1H-2c,6c-Bis-(3'-iodo-4'-hydroxy-5'-methoxyphenyl)-3,7-dioxabicyclo-[3,3,0]-octane-4,8-dione (**14**). A soln of ferric chloride hydrate (7 g) in water (200 ml) was added over 20 min to a stirred soln of 5-iodoferulic acid (6.0 g) in acetone (500 ml) and water (400 ml). The product was worked up as for the bromo analogue to yield the *dilactone* (**14**) as rhombs (1.5 g), m.p. 268–271° after recrystallization from MeOH–acetone. λ (KBr) 2.83 (OH) and 5.62μ (lactone). PMR ($(CD_3)_2CO$) δ 3.92 (6, OMe), 4.17 d (J = 1.5, 2, H-1 and 5), 5.82 br.s. (2, H-2 and 6), 7.12 d (J = 2 Hz, H-6') and 7.40 d (J = 2 Hz, H-2'). (Found: C, 37.86; H, 2.96. $C_{20}H_{16}I_2O_8$ requires: C, 37.64; H, 2.53%).

Dimethyl 8-Iodo-7-hydroxy-6-methoxy-1-(3'-iodo-4'-hydroxy-5'-methoxyphenyl)-trans-1,2-dihydronaphthalene-2,3-dicarboxylate (**15**)

(a) HCl was bubbled into a suspension of **14** (R = I) (700 mg) in

MeOH (25 ml) over 15 min during which it dissolved. The mixture was then refluxed for 1 hr during which a crystalline ppt formed. After cooling, this was collected (430 mg, m.p. 208–211°). A further quantity (300 mg) of lesser quality was obtained by aqueous dilution. Recrystallization from MeOH gave the *dihydronaphthalene* (**15**) as rosettes, m.p. 211–212°, λ 2.90 (OH), 5.81 and 5.96μ (CO_2Me). PMR ($CDCl_3$) δ 3.67 (3, C-2 CO_2Me), 3.77 (3, C-3 CO_2Me), 3.78 (3, 5'-OMe), 3.96 (3, 6-OMe), 4.00 d (J = *ca.* 1 Hz, 1, H-2), 4.98 br.s (1, H-1), 6.61 d (J = 2 Hz, 1, H-6'), 6.77 d (J = 2 Hz, 1, H-2'), 6.90 (1, H-5) and 7.63 (1, H-4). (Found: C, 40.09; H, 3.13. $C_{22}H_{20}I_2O_8$ requires: C, 39.67; H, 3.03%).

(b) A soln of ferric chloride (2.0 g) in water (50 ml) was added over 10 min to a soln of **13** (2.0 g) in acetone (60 ml)–water (50 ml), and the mixture stirred overnight at room temp. The resultant ppt was collected, dissolved in chloroform, boiled with carbon, filtered and evaporated to yield a solid (1.5 g) which on crystallization from MeOH yielded **15**, m.p. 212–215°.

Dimethyl 8-Iodo-6,7-dimethoxy-1-(3'-iodo-4',5'-dimethoxyphenyl)-trans-1,2-dihydronaphthalene-2,3-dicarboxylate (**16**). Excess ethereal diazomethane was added to a solution of **15**, (200 mg), in MeOH and the mixture allowed to stand at room temp. overnight. Recrystallization of the product from MeOH gave the *tetramethoxy-dihydronaphthalene* (**16**) as cubes (150 mg), λ 5.71 and 5.84μ (CO_2Me), m.p. 197–198°. PMR ($CDCl_3$) δ 3.68 (3, C-2 CO_2Me), 3.75 (3, C-3 CO_2Me), 3.78 (6, 4' and 5'-OMe), 3.88 (3,7-OMe), 3.92 (3, 6-OMe), 4.03 d (J = 1.5 Hz, 1, H-2), 5.00 br.s. (1, H-1), 6.58 d (J = 2 Hz, 1, H-6'), 6.85 d (J = 2 Hz, 1, H-2'), 6.97 (1, H-5) and 7.63 (1, H-4). (Found: C, 41.66; H, 3.51. $C_{24}H_{24}I_2O_8$ requires: C, 41.52; H, 3.48%).

r-1H-6, 7-Dimethoxy-2c, 3t-bishydroxymethyl-1-(3', 4'-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene ((±)-*isolariciresinol dimethyl ether*) (**18**)

(a) LAH was added in small batches to a soln of **16** until H_2 evolution ceased. The mixture was allowed to stand at room temp. for 30 min and worked up in the usual way to give the non-crystalline diol (**17**), a soln of which (90 mg) in EtOH (75 ml) was stirred at room temp with Pd–C (10%, 30 mg) under an atmosphere of H_2 for 3 hr. Filtration, evaporation and crystallization from EtOH gave (±)-**18**, m.p. 161–164° (lit[9] m.p. 155–158°) with IR spectrum (in $CHCl_3$) and PMR spectrum identical to that obtained from α-conidendrin (see below).

(+)-*Isolariciresinol dimethyl ether* (**18**). Methylation of **19** with Me_2SO_4[23] gave dimethyl α-conidendrin, m.p. 179.5–180° which on reduction as described[11] by LAH in tetrahydrofuran gave (+)-isolariciresinol dimethyl ether, m.p. 164–166.5° (lit.[11] m.p. 167–169°). PMR ($CDCl_3$) δ 3.57, 3.80, 3.83 and 3.87 (four OMe groups), 6.23 (1, H-8), 6.62 br.s. (two ArH) and 6.78 br.s. (two Ar-H).

2,3-Dibromo-4-hydroxy-5-methoxybenzaldehyde (5,6-*dibromovanillin*) (**20**) was prepared by a simplification of the method of Raiford and Hilman.[17] I_2 (200 mg) was added to a refluxing soln of vanillin (27.3 g) in AcOH (250 ml) in a flask equipped with an air condenser surmounted with an acetone–CO_2 condenser. Br_2 (110 g) in AcOH (100 ml) was then added dropwise (2–3 hr) with refluxing continued for a further 2–3 hr. On cooling, a solid separated, was collected and crystallized from AcOH to give the dibromovanillin as off-white needles (33.4 g), m.p. 221–222°. Lit.[12] m.p. 218°. Repeated recrystallization raised the m.p. to 233°. PMR ($CDCl_3$): δ 3.98 (3, OMe), 7.48 (1, ArH) and 10.28 (1, CHO).

2,3-Dibromo-4-hydroxy-5-methoxycinnamic acid. 5,6-dibromoferulic acid (**21**, R = H) was prepared by the Perkin condensation and was obtained as white needles, m.p. 279–283° from aqueous dimethyl sulphoxide. Lit.[24] m.p. 278°. PMR ($(CD_3)_2SO$): δ 3.88 (3, OMe), 6.47 d (J = 16 Hz, 1, α-vinyl H), 7.40 (1, ArH) and 7.87 d (J = 16 Hz, 1, β-vinyl H).

Methyl 2,3-Dibromo-4-hydroxy-5-methoxycinnamate (**21**, R = CH_3) prepared by refluxing the above acid in MeOH with a few drops of conc. H_2SO_4, aqueous dilution and crystallization from MeOH gave the *methyl ester* as small needles, m.p. 148–149°, PMR ($CDCl_3$): δ 3.82 (3, CO_2Me), 3.93 (3, ArOMe), 6.25 d (J = 16 Hz, 1, α-vinyl H), 7.08 (1, ArH) and 8.10 d (J = 16 Hz, 1, β-vinyl H). (Found: C, 35.87; H, 2.68. $C_{11}H_{10}Br_2O_4$ requires: C, 36.09; H, 2.75%).

Oxidative coupling of methyl dibromoferulate. To a soln of **21** (R = CH_3) (2.04 g) in acetone (70 ml)–water (40 ml) was added HCl (2 N, 3 ml), followed by ferric chloride hydrate (4.20 g). The mixture was set aside for several days, then the ppt collected, washed with a little cold aqueous acetone and dried. It was then shaken with chloroform (to remove starting material), and filtered to give *r-2, c-5-bis(2',3'-dibromo-4'-hydroxy-5'-methoxyphenyl)-tetrahydrofuran-t-3, c-4-dicarboxylic acid dimethyl ester* (**22**) (264 mg), m.p. 258–259°. PMR ($(CD_3)_2CO$ + $(CD_3)_2SO$): δ 3.25 (3, C-4 CO_2Me), 3.75, 3.93 and 4.03 (each 3, two ArOMe and one CO_2Me), 3.59 dd and 4.03 dd (J *ca.* 7.5 and 4 Hz, each 1, H-3 and H-4), 5.61 d and 5.63 d (J *ca.* 7.5, each 1, H-2 and H-5), 7.28 (1, ArH) and 7.78 (1, ArH). (Found: C, 35.39; H, 2.59. $C_{22}H_{20}Br_4O_9$ requires: C, 35.33; H, 2.70%). Starting material of good quality is readily recovered by aqueous dilution of the filtrate. In a set of parallel experiments run for 14 days, variation in the volume of added 2 N HCl between 0.10 and 3.00 ml gave yields in the range 100–260 mg. No ppt was obtained with 0.02 or 6.0 ml acid.

r-2, c-5-Bis(2',3'-dibromo-4'-acetoxy-5'-methoxyphenyl)-tetrahydrofuran-t-3, c-4-dicarboxylic acid dimethyl ester (**23**). A soln of **22** (100 mg) in pyridine (10 ml) and Ac_2O (10 ml) was heated for 1 hr at *ca.* 80°, poured on to ice and the ppt filtered off and recrystallized from THF–MeOH to give the *diacetate* as prisms (70 mg), m.p. 220–220.5°. PMR ($CDCl_3$) δ 3.22 (3, C-4 CO_2Me), 3.78, 3.80 and 3.93 (each 3, two ArOMe and one CO_2Me), 3.73 dd and 4.13 dd (J *ca.* 7 and 3 Hz, each 1, H-3 and H-4), 5.61 d and 5.69 d (J = 7 Hz, each 1, H-2 and H-5), 7.23 (1, ArH), 7.83 (1, ArH), 2.35 (3, OAc) and 2.38 (3, OAc). (Found: C, 37.45; H, 2.94. $C_{26}H_{24}Br_4O_{11}$ requires: C, 37.53; H, 2.91%).

r-2, c-5-Bis(2',3'-dibromo-4',5'-dimethoxyphenyl)-tetrahydrofuran-t-3, c-4-dicarboxylic acid dimethyl ester (**24**). A soln of **22** (200 mg) in MeOH (250 ml) was treated batchwise with ethereal diazomethane soln until the yellow colour persisted (about 0.5 hr), concentrated and the product recrystallized from MeOH to give the bis-dibromodimethoxyphenyl ether as prisms (177 mg), m.p. 146.5–147.5°. PMR ($CDCl_3$); δ 3.22 (3, C-4 CO_2Me), 3.77 (3), 3.85 (6), 3.90 (3) and 3.97 (3) (four ArOMe and one CO_2Me), 3.58 dd and 4.08 dd (J = 4 and 7 Hz, each 1, H-3 and H-4), 5.58 d and 5.62 d (J = 7 Hz, each 1, H-2 and H-5), 7.18 (1, ArH) and 7.70 (1, ArH). (Found: C, 36.94; H, 2.92. $C_{24}H_{24}Br_4O_9$ requires: C, 37.14; H, 3.12%). Mass spectrum: *m/e* 772 (86%, M^-), 693 (44%, M-Br), 661 (56%, M-HBr–OCH_3), 633 (56%, M-Br–HCO_2CH_3), 450 (98%, ion "a"), 390 (68%, ion "a"-HCO_2CH_3), 371 (100%, ion "a"-Br), 339 (66%, ion "a"-HBr–OCH_3), 331 (58%), 321 (56%, ion "b"-H), 312 (78%, ion "d"-Br–CH_3), 299 (63%, ion "c"-Br) and 243 (54%, ion "b"-Br).

r-2, c-5-Bis(3',4'-dimethoxyphenyl)-tetrahydrofuran-t-3, c-4-dicarboxylic acid dimethyl ester (**25**). A soln of **24** in EtOH was stirred with 10% Pd–C (*ca.* equal weight) under H_2 at atmospheric pressure for 2 hr. Filtration, solvent evaporation, and crystallization of the residue from ether-light petroleum gave the *tetramethyl ether dimethyl ester* as long soft needles, m.p. 108–109°. PMR ($CDCl_3$): δ 3.25 (3, C-4 CO_2Me), 3.70 (3), 3.87 (6), 3.88 (3) and 3.93 (3), (four ArOMe and one CO_2Me), 5.02 d and 5.28 d (J = 8 Hz, each 1, H-2 and H-5), 6.7–7.25 m (6, ArH) with H-3 and H-4 protons hidden under OMe resonance. (Found: C, 62.32, H, 6.12. $C_{24}H_{28}O_9$ requires: C, 62.60; H, 6.13%.) Mass spectrum: *m/e* 460 (77% M'), 294 (94%, ion "a"), 262 (65%), 261 (71%), 238 (70%, ion "d"), 235 (93%, ion "a"-CO_2CH_3), 234 (100%, ion "a"-HCO_2CH_3), 231 (66%), 222 (90%, ion "c"), 207 (57%, ion "d"-OCH_3), 206 (70%), 203 (54%), 181 (78%), 175 (96%), 165 (86%, ion "b"-H), 160 (70%), 151 (74%, dimethoxybenzyl), 149 (74%) and 115 (65%). Use of catalytic quantities of palladium–carbon gave a mixture of products.

r-2, c-5-Bis(3',4'-dimethoxyphenyl)-t-3, c-4-bishydroxymethyltetrahydrofuran (**26**). Excess LAH was added to a soln of **24** (500 mg) in THF (50 ml) and the mixture allowed to stand at room temp. for 30 min after gas evolution had ceased. It was then worked up in the usual way, with solvent evaporation to give the residual diol; PMR ($CDCl_3$) 3.87 and 3.90 (OMe groups), 4.50 d and 5.12 d (J = 8–9 Hz, each 1, H-2 and H-5) and 6.7–7.1 m (ArH). The same diol was obtained similarly from the debromi-

nated dimethyl ester (**25**), and was used without further purification.

(±)-*Veraguensin* (**27**). *p*-Toluenesulphonyl chloride (1 g) was added to a soln of the crude diol (300 mg) in pyridine (5 ml) at −12°, the mixture allowed to stand overnight at this temp., allowed to come to room temp., diluted with water and extracted with chloroform. Evaporation of the washed and dried extract yielded the crude ditosylate (500 mg), PMR ($CDCl_3$) δ 3.83, 3.85, 3.87 (four OMe), 4.63 d and 5.03 d (J = 8 Hz, each 1, H-2 and H-5) and 6.8–7.85 m (ArH) which was dissolved in THF, and added to a suspension of LAH (500 mg) in the same solvent (40 ml) at 0°. The mixture was heated under reflux for 1 hr, worked up in the usual way and purified by filtration of a benzene soln of the product through a short column of alumina to give, on crystallization from diethyl ether *r*-2,*c*-5-bis(3',4'-dimethoxyphenyl)-*t*-3, *c*-4-dimethyltetrahydrofuran as jagged rhombs, m.p. 121–122°. Lit.[20] m.p. 121–123°. PMR ($CDCl_3$) 0.67 d (J = 7 Hz, 3, C-4 Me), 1.08 d (J = 6 Hz, 3, C-3 Me), 3.85, 3.87, 3.88 and 3.92 (four OMe), 4.43 d (J = 9 Hz) and 5.13 d (J = 8 Hz) (each 1, H-2 and H-5) and 6.8–7.17 m (ArH). This spectrum is in excellent agreement with that reported.[20]

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