Synthesis of Larreantin, a Cytotoxic Naphthoquinonoid Sesquilignan from *Larrea tridentata*[1]

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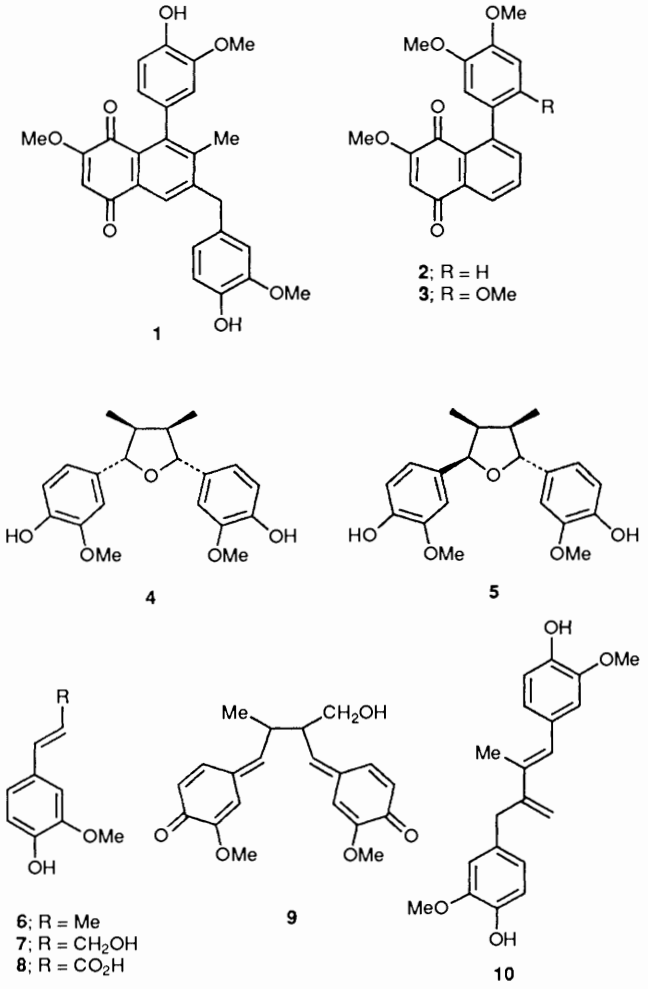
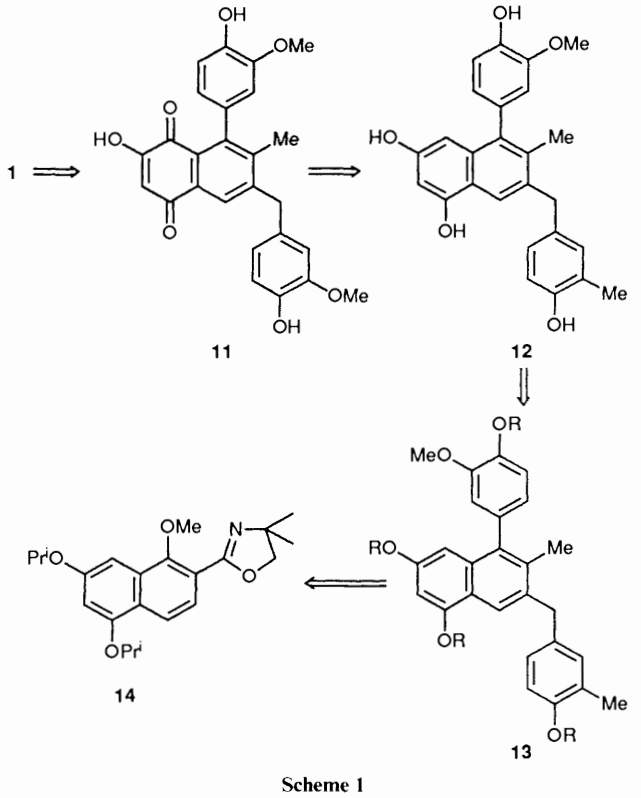
Larreantin [8-(4-hydroxy-3-methoxyphenyl)-6-(4-hydroxy-3-methoxybenzyl)-2-methoxy-7-methylnaphthalene-1,4-dione] **1**, a biogenetically unique cytotoxic naphthoquinonoid sesquilignan has been synthesized by a convergent route. The key intermediate was 4,5-dihydro-2-(5,7-diisopropoxy-1-methoxy-2-naphthyl)-4,4-dimethyloxazole **14** which was elaborated by treatment with 4-isopropoxy-3-methoxyphenylmagnesium bromide **26** and the product of this reaction was lithiated and allowed to react with 4-isoproproxy-3-methoxybenzaldehyde **28**. Subsequent steps then gave larreantin **1**.

The creosote bush, *Larrea tridentata* (DC) Coville (Zygophyllaceae) is native to the south-west of the United States of America and northern Mexico.[2] In continuation of their studies of this plant, Cordell and his co-workers have recently examined a methanol extract of its roots in the search for cytotoxic constituents.[3] Fractionation of this extract by chromatography yielded the naphthoquinone larreantin **1**. This compound, the structure of which was deduced entirely by spectroscopic methods, was shown to have an ED_{50} value of 0.38 μg cm^{-3}, a value which represents cytotoxicity by more than an order of magnitude. Larreantin **1** is an unprecedented type of 1,4-naphthoquinone and its nearest structural relatives are lassumunaquinone 1 **2** and lassumunaquinone 2 **3** which co-occur in *Zingiber cassumunar* Roxb.[4]

The lignans and neolignans are groups of natural products which arise from radical coupling of two oxygenated cinnamyl sub-units. Compounds derived from the coupling of three such phenylpropanoid sub-units have been termed 'sesquilignans' of which larreatin **1** appears to represent an unusual example.[5] The furanoid lignans malabaricanol **4** and 3′,3″-dimethoxylarreatricin **5** have recently been isolated from *Larrea tridentata*[6] and bear substitution patterns similar to larreantin **1**. These lignans probably arise from the radical coupling of two units of isoeugenol **6** and further transformations. If coniferyl alcohol **7** and isoeugenol **6** were to couple in a similar manner to that required for the biosynthesis of compounds **4** and **5** then a possible precursor **9** to larreantin **1** might be produced. Some evidence for this type of transformation comes from the recent work of Umezawa *et al.*[7] Further transformations of intermediate **9** could give the diene **10**. A Diels–Alder reaction, or its biochemical equivalent, of this diene with 2-methoxy-1,4-



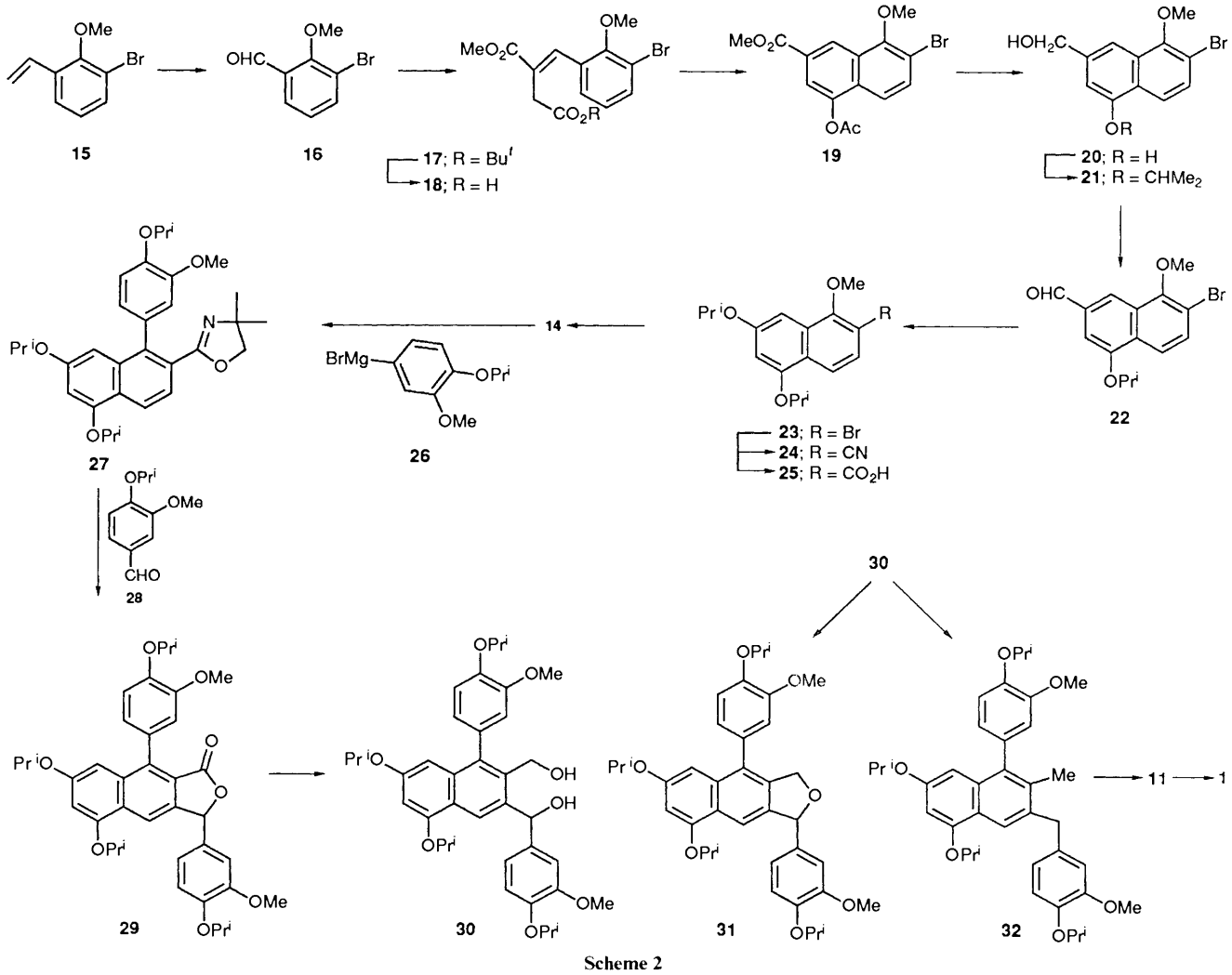


Scheme 1

benzoquinone, derived from three successive side-chain decarboxylations of ferulic acid,[8] would then give larreantin **1**.

We now report the confirmation of the structure of larreantin **1** by a convergent synthesis. Although the synthesis of larreantin **1** by a Diels–Alder reaction is attractive we chose to adopt an approach based on dihydrooxazole chemistry. The immediate precursor to larreantin **1** (see Scheme 1) was perceived to be the 2-hydroxy-1,4-naphthoquinone **11** which should undergo easy methylation since it contains a vinylogous carboxylic acid function. Such a naphthoquinone would be available by aerial oxidation of the 1,3-dihydroxynaphthalene **12**[9] which would arise by deprotection of the precursor **13** in which the protective group R must be capable of removal in the presence of methoxy groups. For this purpose we chose the isopropyl group.[10] The key intermediate which would allow the synthesis of the naphthalene **13** would then be the naphthyldihydrooxazole **14**. Displacement of the methoxy group in the position *ortho* to the dihydrooxazole by the appropriate aryl Grignard reagent would introduce the aryl substituent. Advantage could then be taken of the directive power of the dihydrooxazole moiety in lithiation at the other *ortho*-position and subsequent reaction with an appropriate electrophile would introduce the benzyl group.[11] We thus sought a synthesis of the dihydrooxazole **14** (Scheme 2). Ozonolysis of the known propenylbenzene **15**[12] gave the aldehyde **16**[13] which was caused to react with 2-*tert*-butoxycarbonyl-1-methoxycarbonylethylidene(triphenyl)phosphorane[14] thereby supplying the itaconic ester **17**. This compound on brief treatment with aqueous trifluoroacetic acid gave the acid **18** which underwent ring closure to the naphthoate **19** on boiling with acetic anhydride containing potassium acetate. Reduction of this intermediate with di-isobutyl aluminium hydride then furnished the diol **20** which was selectively converted into the isopropyl ether **21**. Manganese dioxide oxidation now yielded the aldehyde **22** which on Baeyer–Villiger oxidation with *m*-chloroperoxybenzoic acid, hydrolysis of the intermediate formate, and subsequent isopropylation afforded the naphthalene **23**. This was caused to react with copper(I) cyanide and hydrolysis of the resultant nitrile **24** gave the naphthoic acid **25** which converted into the required dihydrooxazole **14** by the standard method.[15]

The dihydrooxazole was now allowed to react with the Grignard reagent **26** which yielded the biaryl **27** (88%). Treatment of a solution of this biaryl in tetrahydrofuran (THF) in the presence of 1 mol equiv. of *N,N,N′N′*-tetramethylethylenediamine (TMEDA) at −78 °C with 1 mol equiv. of *sec*-butyllithium during 1 h gave an orange solution which was then treated with the benzaldehyde **28**. The crude product of this reaction was boiled with aqueous hydrochloric acid in dioxane which brought about hydrolysis, presumably anchimerically assisted, of the hindered dihydrooxazole to give, after chromatography, the phthalide **29** (58%). Reduction of the phthalide with lithium aluminium hydride gave the diol **30**. On catalytic hydrogenation under acidic conditions this diol **30** yielded the 1,3-dihydronaphtho[2,3-*c*]furan **31** but when the reaction was repeated in the presence of trifluoroacetic anhydride and an excess of triethylamine the desired deoxygenated product **32** resulted. Deprotection of this compound



Scheme 2

by treatment with the boron trichloride followed by aerial oxidation of the anion of the resultant tetrol **12** gave the quinone **11** which on selective methylation provided synthetic larreantin **1**.

The spectral properties of this material were entirely in agreement with those recorded for the natural product[3] so that structure **1** is correct.

Experimental

General directions have been given before.[16] *J* Values are given in Hz. Light petroleum is the fraction with b.p. 55–65 °C.

3-Bromo-2-methoxybenzaldehyde **16**.—A solution of (*E*)-3-bromo-2-methoxy-1-prop-1-enylbenzene **15** (38.5 g)[12] in dichloromethane (600 cm^3) and methanol (6 cm^3) was cooled to −78 °C and a stream of ozone was passed through the solution until a blue colour persisted. The excess ozone was removed by passage of nitrogen and then dimethyl sulphide (40 cm^3) was added and the solution was stirred and allowed to warm to room temperature over 12 h. The solvents were removed by evaporation under reduced pressure and the residue was filtered through a column of neutral alumina with 2.5% ethyl acetate–light petroleum as eluent. The *aldehyde* **16** (34.0 g, 93%)[13] crystallized from pentane as rods, m.p. 31–32 °C (Found: C, 44.55; H, 3.4; Br, 37.25%; M^+, 214/216. $C_8H_7BrO_2$ requires C, 44.7; H, 3.25; Br, 37.15%; *M*, 214/216); δ_H(80 MHz) 4.00 (3 H, s, OMe), 7.19 (1 H, ddd, $J_{5,4}$, $J_{5,6}$ 7.6, $J_{5,CHO}$ 0.8, 5-H), 7.81 (2 H, d, $J_{4,5}$, $J_{6,5}$, 7.6, 4- and 6-H) and 10.37 (1 H, br s, CHO).

4-tert-Butyl 1-Methyl (E)-2-(3-Bromo-2-methoxybenzylidene)butanedioate **17**.—A solution of the aldehyde **16** (17.0 g) and 2-*tert*-butoxycarbonyl-1-methoxycarbonylethylidene(triphenyl)phosphorane (44.2 g)[14] in anhydrous benzene (780 cm^3) was stirred and heated under reflux for 20 h. The solvent was removed by evaporation under reduced pressure and the residue was purified by chromatography over silica gel with 1–5% ethyl acetate–light petroleum as eluent to afford the *ester* **17** (26.6 g, 91%) as an oil, b.p. 120 °C at 0.005 mmHg (Found: C, 53.4; H, 5.8; Br, 20.6%; M^+, 384/386. $C_{17}H_{21}BrO_5$ requires C, 53.0; H, 5.5; Br, 20.75%; *M*, 384/386); δ_H(80 MHz) 1.45 (9 H, s, Bu^t), 3.38 (2 H, s, CH_2), 3.77 and 3.84 (each 3 H, s, OMe), 7.00 (1 H, dd, $J_{5,4}$, $J_{5,6}$ 7.7, 5-H), 7.24 (1 H, dd, $J_{6,5}$ 7.7, $J_{6,4}$ 1.5, 6-H), 7.60 (1 H, dd, $J_{4,5}$ 7.7, $J_{4,6}$ 1.5, 4-H) and 7.90 (1 H, s, vinyl-H).

(E)-4-(3-Bromo-2-methoxyphenyl)-3-methoxycarbonylbut-3-enoic Acid **18**.—The ester **17** (14.3 g) was dissolved in 90% aqueous trifluoroacetic acid (140 cm^3) and the solution was stirred for 15 min. The solvent was removed by evaporation under reduced pressure and finally by azeotroping with benzene. The crude product was purified by dissolution in aqueous sodium hydrogen carbonate in the usual manner. The *acid* **18** (11.6 g, 95%) crystallized from dichloromethane–light petroleum as hygroscopic prisms, m.p. 86–87 °C (Found: C, 47.3; H, 3.95; Br, 24.2%; M^+, 328/330. $C_{13}H_{13}BrO_5$ requires C, 47.45; H, 4.0; Br, 24.3%; *M*, 328/330).

Methyl 4-Acetoxy-7-bromo-8-methoxynaphthalene-2-carboxylate **19**.—The acid **18** (24.0 g) and anhydrous potassium acetate (7.0 g) were heated under reflux in acetic anhydride (450 cm^3) for 5 min. The solution was poured into warm water (2 dm^3) and the precipitated solid was filtered off, dissolved in ethyl acetate and washed with aqueous sodium hydrogen carbonate. The crude product crystallized from methanol as needles (21.8 g, 84%) of the *ester* **19**, m.p. 111–112 °C (Found: C, 51.35; H, 3.6; Br, 22.45%; M^+, 352/354. $C_{15}H_{13}BrO_5$ requires C, 51.0; H, 3.7; Br, 22.6%; *M*, 352/354); δ_H(80 MHz) 2.47 (3 H, s, COMe), 3.99 and 4.06 (each 3 H, s, OMe), 7.54 and 7.72 (2 H, AB, $J_{5,6}$ 9.0, 6- and 5-H), 7.87 (1 H, d, $J_{3,1}$ 1.5, 3-H) and 8.77 (1 H, br s, 1-H).

6-Bromo-3-(hydroxymethyl)-5-methoxy-1-naphthol **20**.—A solution of diisobutylaluminium hydride (2 mol dm^{-3}) in hexane (52.5 cm^3) was added dropwise with stirring at −10 °C to a stirred solution of the ester **19** (7.4 g) in anhydrous tetrahydrofuran (THF) (250 cm^3). The solution was stirred for 10 min and excess water was added dropwise followed by acidification with dilute hydrochloric acid. The crude product was isolated by extraction with ethyl acetate and then purified by filtration through a short column of silica gel with 80% ethyl acetate–light petroleum as eluent. The *diol* **20** (5.6 g, 94%) crystallized from ether–light petroleum as pale yellow needles, m.p. 165–167 °C (Found: C, 50.9; H, 3.7; Br, 28.3%; M^+, 282/284. $C_{12}H_{11}BrO_3$ requires C, 50.9; H, 3.9; Br, 28.2%; *M*, 282/284); δ_H[80 MHz; $(CD_3)_2SO$] 3.30 (2 H, br s, 2 × D_2O exchangeable OH), 3.90 (3 H, s, OMe), 4.61 (2 H, s, CH_2OH), 6.92 (1 H, d, $J_{2,3}$ 1.2, 2-H) 7.45 (1 H, br s, 4-H) and 7.51 and 7.80 (2 H, AB, $J_{7,8}$ 8.9, 7- and 8-H).

(7-Bromo-4-isopropoxy-8-methoxy-2-naphthyl)methanol **21**.—The diol **20** (10.0 g), 2-bromopropane (4.8 g) and anhydrous potassium carbonate (4.9 g) were stirred under nitrogen in DMF (120 cm^3) for 4 d. Work-up gave a crude product which was purified by flash chromatography over silica with 20% ethyl acetate–light petroleum as eluent. The *alcohol* **21** (9.4 g, 82%) crystallized from dichloromethane–light petroleum as pale yellow needles, m.p. 87–88 °C (Found: C, 55.5; H, 5.45; Br, 24.85%; M^+, 324/326. $C_{15}H_{17}BrO_3$ requires C, 55.4; H, 5.25; Br, 24.55%; *M*, 324/326); δ_H(80 MHz) 1.44 (6 H, d, Me_2), 3.98 (3 H, s, OMe), 4.76 (1 H, septet, CH), 4.82 (2 H, s, CH_2OH), 6.89 (1 H, d, $J_{3,1}$ 1.2, 3-H), 7.49 and 7.88 (2 H, AB, $J_{5,6}$ 8.2, 6- and 5-H) and 7.54 (1 H, br s, 1-H).

7-Bromo-4-isopropoxy-8-methoxynaphthalene-2-carbaldehyde **22**.—A solution of the alcohol **21** (9.4 g) in dichloromethane (150 cm^3) was stirred with activated manganese dioxide (70 g) for 12 h under argon. Work-up gave the *aldehyde* **22** (8.4 g, 90%) which crystallized from dichloromethane–light petroleum as yellow needles, m.p. 98–99 °C (Found: C, 55.6; H, 4.6; Br, 24.85%; M^+, 322/324. $C_{15}H_{15}BrO_3$ requires C, 55.75; H, 4.7; Br, 24.7%; *M*, 322/324); δ_H(80 MHz) 1.46 (6 H, d, Me_2), 4.06 (3 H, s, OMe), 4.86 (1 H, septet, CH), 7.24 (1 H, br s, 3-H), 7.70 and 7.97 (2 H, AB, $J_{5,6}$ 9.0, 5- and 6-H), 8.16 (1 H, br s, 1-H) and 10.10 (1 H, s, CHO); ν_{max}(KBr)/cm^{-1} 1690 and 1580; λ_{max}(MeOH)/nm 227, 258, 298 and 368 (log ε 4.52, 4.51, 3.86 and 3.78 respectively).

2-Bromo-5,7-diisopropoxy-1-methoxynaphthalene **23**.—A solution of the aldehyde **22** (7.15 g) in dichloromethane (200 cm^3) was stirred and heated under reflux under nitrogen with *m*-chloroperoxybenzoic acid (80%, 9.5 g) for 72 h. The solution was cooled and filtered and the solvent was removed from the filtrate and replaced by ether. The solution was washed in turn with water, aqueous sodium hydrogen carbonate and finally with saturated brine. The crude product was dissolved in methanol (50 cm^3) and methanolic sodium methoxide (0.6 mol dm^{-3}; 40 cm^3) was added and the solution was stirred for 5 min and acidified by the addition of a slight excess of dilute hydrochloric acid. Most of the methanol was removed under reduced pressure and the crude product was isolated by extraction with ether, and next dissolved in DMF (50 cm^3) and stirred with anhydrous potassium carbonate (4.0 g) and 2-bromopropane (4.0 g) under dry nitrogen at 50 C for 72 h. Work-up gave a crude product which was purified by flash chromatography over silica with 1–2% ethyl acetate–light

petroleum as eluent. The *naphthalene* **23** (2.0 g, 26%) crystallized from light petroleum as prisms, m.p. 52–53 °C (Found: C, 58.0; H, 6.2; Br, 22.55%; M^+, 352/354. $C_{17}H_{21}BrO_3$ requires C, 57.8; H, 6.0; Br, 22.6%; *M*, 352/354); δ_H(80 MHz) 1.41 and 1.42 (each 6 H, d, Me_2), 3.95 (3 H, s, OMe), 4.68 (2 H, m, 2 × CH), 6.49 and 6.96 (2 H, AB, $J_{6,8}$ 2.2, 6- and 8-H) and 7.35 and 7.79 (2 H, AB, $J_{3,4}$ 9.0, 3- and 4-H).

5,7-*Diisopropoxy*-1-*methoxynaphthalene*-2-*carbonitrile* **24**.—The bromo compound **23** (2.0 g) and copper(I) cyanide (840 mg) were stirred and heated under reflux in anhydrous DMF (40 cm^3) under dry nitrogen for 12 h. The cooled solution was diluted with aqueous ethylenediamine and extracted with ether. The extract was washed with more aqueous ethylenediamine, water, and finally with saturated brine. The crude product was purified by radial chromatography with 5% ethyl acetate–light petroleum as eluent. The *nitrile* **24** (1.6 g, 95%) crystallized from dichloromethane–light petroleum as pink prisms, m.p. 85–86 °C (Found: N, 4.4%; M^+, 299. $C_{18}H_{21}NO_3$ requires N, 4.7%; *M*, 299); δ_H(80 MHz) 1.42 and 1.44 (each 6 H, d, Me_2), 4.21 (3 H, s, OMe), 4.75 (2 H, m, 2 × CH), 6.60 and 7.03 (each 1 H, d, *J* 2.1, 6- and 8-H), and 7.28 and 7.91 (2 H, AB, $J_{3,4}$ 8.7, 3- and 4-H); ν_{max}/cm^{-1} 2222, 1595 and 1410; λ_{max}(MeOH)/nm 254, 282, 290 and 365 (log ε 4.73, 3.72, 3.72 and 3.55 respectively).

5,7-*Diisopropoxy*-1-*methoxynaphthalene*-2-*carboxylic Acid* **25**.—A solution of the nitrile **24** (1.6 g) in methanol (30 cm^3) and aqueous sodium hydroxide (10%; 10 cm^3) was heated under reflux for 96 h. Most of the methanol was removed and the cooled solution was acidified by the addition of hydrochloric acid. The crude product was isolated by extraction with ether and next crystallized from dichloromethane–light petroleum whereupon it formed needles of the *acid* **25** (1.45 g, 85%), m.p. 136–137 °C (Found: C, 67.6; H, 6.85; M^+, 318. $C_{18}H_{22}O_5$ requires C, 67.9; H, 6.95%; *M*, 318); ν_{max}/cm^{-1} 3480, 1700 and 1675; λ_{max}/nm 214, 244, 288 and 344 (log ε 4.40, 4.57, 3.83 and 3.46 respectively).

4,5-*Dihydro*-2-(5,7-*diisopropoxy*-1-*methoxy*-2-*naphthyl*)-4,4-*dimethyloxazole* **14**.—Oxalyl chloride (270 mm^3) was added to a solution of the acid **25** (500 mg) in dry dichloromethane (20 cm^3) and the solution was stirred under argon for 2.5 h. The solvents were removed under reduced pressure and the residue was dissolved in dry dichloromethane (5 cm^3) and the solution was added dropwise to a stirred solution of 2-amino-2-methylpropan-1-ol (300 mg) in dry dichloromethane (5 cm^3) at 5 °C. After 2 h, the precipitate was filtered off and washed with a little dichloromethane. The filtrate was stirred at 0 °C with thionyl chloride (260 mm^3) and the solution was allowed to warm to room temperature and stirred for 2 h. The solution was next cooled to 0 °C and treated with water, and the crude product was isolated by extraction with dichloromethane and then purified by radial chromatography with 15–40% ethyl acetate–light petroleum as eluent. The *dihydrooxazole* **14** (470 mg, 81%) crystallized from light petroleum as prisms, m.p. 67–68 °C (Found: C, 71.45; H, 7.8; N, 3.7%; M^+, 371. $C_{22}H_{29}NO_4$ requires C, 71.15; H, 7.85; N, 3.75%; *M*, 371); δ_H(80 MHz) 1.41 and 1.43 (each 6 H, d, $CHMe_2$), 1.43 (6 H, s, Me_2), 3.74 (2 H, s, CH_2), 3.95 (3 H, s, OMe), 4.74 (2 H, m, 2 × CH), 6.55 and 7.10 (each 1 H, d, $J_{6,8}$ 2.1, 6- and 8-H) and 7.60 and 7.89 (2 H, AB, $J_{3,4}$ 8.8, 3- and 4-H); ν_{max}/cm^{-1} 1650, 1412 and 1112; λ_{max}(MeOH)/nm 215. 250 and 349 (log ε 4.50, 4.80 and 3.60 respectively).

5-*Bromo*-2-*isopropoxybenzaldehyde*.—A solution of 5-bromo-2-hydroxybenzaldehyde (17.9 g)[17] and 2-bromopropane (13.0 g) in anhydrous DMF (200 cm^3) was stirred at 50 °C under nitrogen with anhydrous potassium carbonate (13.4 g) for 12 h. Work-up gave the *aldehyde* (20.6 g, 95%) as an oil, b.p. 130 °C at 0.1 mmHg (Found: C, 49.55; H, 4.6; Br, 33.1%; M^+, 242/244. $C_{10}H_{11}BrO_2$ requires C, 49.4; H, 4.55; Br, 32.85%; *M*, 242/244); δ_H(80 MHz) 1.40 (6 H, d, Me_2), 4.65 (1 H, septet, CH), 6.89 (1 H, d, $J_{3,4}$ 9.0, 3-H), 7.59 (1 H, dd, $J_{4,3}$ 9.0, $J_{4,6}$ 2.6, 4-H), 7.90 (1 H, d, $J_{6,4}$ 2.6, 6-H) and 10.39 (1 H, s, CHO); ν_{max}(film)/cm^{-1} 2980, 1680 and 1590.

5-*Bromo*-2-*isopropoxyphenol*.—A solution of the foregoing aldehyde (21.0 g) and *m*-chloroperoxybenzoic acid (80%, 30 g) in carbon tetrachloride (300 cm^3) was stirred for 5 h at room temperature. The solution was cooled in ice and the precipitate was filtered off. The filtrate was washed in turn with aqueous sodium hydrogen carbonate, water and finally with saturated brine. The crude product was dissolved in methanol (200 cm^3) and stirred with aqueous potassium hydroxide (10%; 50 cm^3). After 1 min the solution was acidified with dilute hydrochloric acid, and work-up gave the *phenol* as an oil (15.8 g, 79%), b.p. 90 °C at 0.01 mmHg (Found: C, 46.8; H, 4.85; Br, 33.9%; M^+, 230/232. $C_9H_{11}BrO_2$ requires C, 46.8; H, 4.8; Br, 34.56%; *M*, 230/232); δ_H(80 MHz) 1.35 (6 H, d, Me_2), 4.53 (1 H, septet, CH), 5.73 (1 H, br, OH), 6.70 (1 H, d, $J_{3,4}$ 8.4, 3-H) 6.94 (1 H, dd, $J_{4,3}$ 8.4, $J_{4,6}$ 2.1, 4-H) and 7.01 (1 H, d, $J_{6,4}$ 2.1, 6-H).

1-*Bromo*-4-*isopropoxy*-3-*methoxybenzene*.—Methylation of the foregoing phenol (15.5 g) with dimethyl sulphate and potassium carbonate in boiling acetone gave the *bromobenzene* (16.0 g, 97%) as an oil, b.p. 105 °C at 0.05 mmHg (Found: C, 49.0; H, 5.45; Br, 32.4%; M^+, 244/246. $C_{10}H_{13}BrO_2$ requires C, 49.0; H, 5.35; Br, 32.6%; *M*, 244/246).

4,5-*Dihydro*-2-[1-(4-*isopropoxy*-3-*methoxyphenyl*)-5,7-*diisopropoxy*-2-*naphthyl*]-4,4-*dimethyloxazole* **27**.—A solution of 4-isopropoxy-3-methoxyphenylmagnesium bromide **26** [from magnesium (60 mg) and the bromoarene (600 mg)] in anhydrous THF (3 cm^3) was introduced by cannula to a stirred solution of the oxazoline **14** (450 mg) in anhydrous THF (10 cm^3) at room temperature under argon. After 30 min an excess of saturated aqueous ammonium chloride was added and the crude product was isolated by extraction with ethyl acetate and next purified by radial chromatography with 20–30% ethyl acetate–light petroleum was eluent. The *dihydrooxazole* **27** (540 mg, 88%) crystallized from dichloromethane–light petroleum as prisms, m.p. 117–118 °C (Found: C, 73.35; H, 8.05; N, 2.75%; M^+, 505. $C_{31}H_{39}NO_5$ requires C, 73.65; H, 7.75; N, 2.75%; *M*, 505); δ_H(300 MHz) 1.21 and 1.22 (each 3 H, s, Me), 1.26 and 1.27 (each 3 H, d, Me_2), 1.41 and 1.43 (each 3 H, d, Me_2), 1.46 (6 H, d, Me_2), 3.74 (2 H, s, CH_2), 3.82 (3 H, s, OMe), 4.38, 4.62 and 4.71 (each 1 H, septet, CH), 6.52 and 6.58 (2 H, AB, $J_{6,8}$ 2.1, 6- and 8-H), 6.85–6.90 (2 H, m, 2′- and 6′-H), 6.98 (1 H, d, $J_{5',6'}$ 8.1, 5-H), 7.52 (1 H, d, $J_{3,4}$ 8.6, 3-H) and 8.18 (1 H, d, $J_{4,3}$ 8.6, 4-H); λ_{max}(MeOH)/nm 245, 292 and 346 (log ε 4.48, 3.79 and 3.42 respectively).

(±)-3,9-*Bis*(4-*isopropoxy*-3-*methoxyphenyl*)-5,7-*diisopropoxynaphtho*[2,3-c]*furan*-1(3H)-*one* **29**.—A solution of the oxazoline **27** (512 mg) in anhydrous THF (10 cm^3) was stirred and cooled to −78 °C under argon and anhydrous *N,N,N′,N′*-tetramethylethylenediamine (160 mm^3) was added *via* syringe; this was followed by the addition *via* syringe of *sec*-butyllithium (0.42 mol dm^{-3}) in pentane (2.46 cm^3). The solution was stirred at −78 °C for 1 h and then the aldehyde **28** (215 mg)[18] in anhydrous THF (5 cm^3) was added *via* a cannula and the solution was allowed to warm to room temperature over 1 h when water was added dropwise and most of the THF was removed under reduced pressure. The residue was heated under reflux for 0.25 h with dioxane (25 cm^3) and concentrated hydrochloric acid (25 cm^3). The cooled solution was diluted

with water and the crude product was isolated by extraction with ethyl acetate and next purified by radial chromatography with 15% ethyl acetate–light petroleum as eluent. The *furanone* **29** (370 mg, 59%) crystallized from dichloromethane–light petroleum as yellow needles, m.p. 162–163 °C (Found: C, 72.75; H, 7.25%; M^+, 628. $C_{38}H_{44}O_8$ requires C, 72.6; H, 7.05%; *M*, 628); δ_H(300 MHz) 1.26–1.30 (6 H, m, Me_2), 1.37–1.50 (18 H, m, 3 × Me_2), 3.81 and 3.82 (each 1.5 H, s, OMe), 3.85 and 3.86 (each 1.5 H, s, OMe), 4.40 and 4.56 (each 1 H, septet, Me_2), 4.69 (2 H, m, 2 × C*H*Me_2), 6.43 (1 H, br s, 3-H), 6.59 and 6.69 (each 1 H, d, *J* 2.0, 6- and 8-H respectively), 6.83–7.07 (6 H, m, ArH) and 8.09 (1 H, br s, 4-H); ν_{max}(KBr)/cm^{-1} 1770 and 1615; λ_{max}/nm 225, 264 and 385 (log ε 4.64, 4.73 and 3.64 respectively).

(±)-1,3-*Dihydro*-3,9-*bis*(4-*isopropoxy*-3-*methoxyphenyl*)-5,7-*diisopropoxynaphtho*[2,3-c]*furan* **31**.— A solution of the furanone **29** (175 mg) in anhydrous ether (15 cm^3) was added dropwise to a stirred solution of lithium aluminium hydride (60 mg) in anhydrous ether (10 cm^3) at 0 °C. The solution was stirred at room temperature for 2 h and then worked up by the addition of saturated aqueous sodium sulphate to give the diol **30** (175 mg, 99%) as a gum. A solution of the diol **30** (50 mg) in ethyl acetate (10 cm^3) containing concentrated hydrochloric acid (1 drop) was stirred under an atmosphere of hydrogen with palladized charcoal (10%, 20 mg) for 18 h. Work-up gave the *furan* **31** (45 mg, 100%) which crystallized from ether–light petroleum as prisms, m.p. 138–139 °C (Found: C, 74.15; H, 7.6%; M^+, 614. $C_{38}H_{46}O_7$ requires C, 74.25; H, 7.55; *M*, 614); δ_H(300 MHz) 1.28 and 1.29 (each 3 H, d, Me_2), 1.36–1.48 (18 H, m, 3 × Me_2), 3.836 (3 H, s, OMe), 3.844 and 3.848 (each 1.5 H, s, OMe), 4.42 and 4.54 (each 1 H, septet, CH), 4.64 (2 H, m, 2 × CH), 5.06 and 5.18 (1 H, AB, *J* 12.5, 1-CH_2), 5.11 (1 H, br s, 1-CH_2), 6.25 (1 H, br s, 3-H), 6.55 (1 H, d, $J_{6,8}$ 2.1, 6-H), 6.62 (1 H, m, 8-H), 6.86–7.03 (6 H, m, ArH) and 7.83 and 7.85 (each 0.5 H, s, 4-H); ν_{max}/cm^{-1} 1612 and 1505; λ_{max}(MeOH)/nm 220, 249, 283 and 307 (log ε 4.62, 4.76, 4.02 and 3.90 respectively).

1-(4-*Isopropoxy*-3-*methoxyphenyl*)-3-(4-*isopropoxy*-3-*methoxybenzyl*)-5,7-*diisopropoxy*-2-*methylnaphthalene* **32**.—A solution of the diol **30** (210 mg), triethylamine (8 drops) and trifluoroacetic anhydride (0.5 cm^3) in anhydrous THF was stirred under an atmosphere of hydrogen with palladized charcoal (10%, 50 mg) for 18 h. Work-up gave a crude product which was purified by radial chromatography with 10% ethyl acetate–light petroleum as eluent to give the *naphthalene* **32** (160 mg, 80%) as a gum (Found: C, 76.0; H, 8.3. $C_{38}H_{48}O_6$ requires C, 75.95; H, 8.05%); δ_H(300 MHz) 1.21 (6 H, d, Me_2), 1.33–1.45 (18 H, m, 3 × Me_2), 2.06 (3 H, s, Me), 3.79 and 3.80 (each 3 H, s, OMe), 4.12 (2 H, s, CH_2), 4.32, 4.47, 4.61 and 4.66 (each 1 H, septet C*H*Me_2), 6.24 and 6.43 (each 1 H, d, *J* 2.1, 6- and 8-H), 6.64–7.01 (6 H, m, ArH′) and 7.97 (1 H, s, 4-H); ν_{max}(film)/cm^{-1} 1110; *m*/*z* 600 (M^+, 4%), 432 (9) and 137 (100).

8-(4-*Hydroxy*-3-*methoxyphenyl*)-6-(4-*hydroxy*-3-*methoxybenzyl*)-2-*methoxy*-7-*methylnaphthalene*-1,4-*dione* (*Larreantin*) **1**.—A solution of the foregoing naphthalene **32** (100 mg) in anhydrous dichloromethane (5.0 cm^3) was stirred at −10 °C and treated with boron trichloride (592 mg) in dichloromethane (770 mm^3). The solution was next stirred at 0 °C for 8 h and then treated with water and extracted with ethyl acetate. The extract was shaken with ethanolic potassium hydroxide (5%; 10 cm^3) for 2 min whereupon it turned a deep red colour; it was then acidified and worked up. A solution of the crude product in anhydrous DMF (10 cm^3) was stirred with anhydrous potassium hydrogen carbonate (25 mg) and iodomethane (0.5 cm^3) at room temperature for 12 h after which it was worked up. The crude product was purified by radial chromatography using 70% ethyl acetate–light petroleum as eluent to afford synthetic *larreantin* **1** (9.8 mg, 13%) as yellow needles (from methanol), m.p. 189–191 °C (lit.,[2] 204–206 °C) (Found: C, 67.75; H, 5.4%. $C_{27}H_{24}O_7$·H_2O requires C, 67.75; H, 5.5%); δ_H(300 MHz) 2.02 (3 H, s, Me), 3.800, (3 H, s, 2-OMe), 3.827 (3 H, s, 3′-OMe), 3.848 (3 H, s, 3″-OMe), 4.06 (2 H, s, CH_2), 5.54 and 5.64 (each 1 H, s, 4′ and 4″-OH), 6.08 (1 H, s, 3-H), 6.48 (1 H, d, $J_{2',6'}$ 1.9, 2′-H), 6.52 (1 H, dd, $J_{6',5'}$ 7.8, $J_{6',2'}$ 1.9, 6′-H), 6.62 (1 H, dd, $J_{6'',5''}$ 8.0, $J_{6'',2''}$ 1.9, 6″-H), 6.67 (1 H, d, $J_{2'',6''}$ 1.9, 2″-H), 6.85 (1 H, d, $J_{5'',6''}$ 8.0, 5″-H), 6.97 (1 H, d, $J_{5',6'}$ 7.8, 5′-H) and 7.98 (1 H, s, 5-H); δ_C(75.5 MHz) 17.25 (7-Me), 40.35 (7″-CH_2), 55.90 (2-OMe), 55.94 (3′-OMe), 56.28 (3″-OMe), 108.06 (C-3), 110.40 (C-2′), 111.23 (C-2″), 114.50 (C-5′), 114.58 (C-5″), 120.42 (C-6′), 121.52 (C-6″), 127.11 (C-8), 127.25 (C-5), 130.31 (C-1″), 130.72 (C-4a), 132.19 (C-1′), 143.54 (C-7), 143.66 (C-8), 144.26 (C-4″), 144.59 (C-4′), 146.25 (C-6), 146.65 (C-3″), 146.79 (C-3′), 160.62 (C-2), 179.91 (C-1) and 185.23 (C-4); ν_{max}(KBr)/cm^{-1} 3400, 1685, 1645, 1618, 1508, 1340, 1284, 1255, 1236, 1210 and 1082; *m*/*z* 460 (M^+, 100%), 445 (11), 443 (11), 429 (21), 305 (7), 304 (8) and 137 (52).

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