Total Synthesis of (±)-Porosin, a Neolignan from *Ocotea porosa* and *Urbanodendron verrucosum* (Lauraceae)

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Veratraldehyde was condensed with methyl 2-chloropropanoate to give a glycidic ester. This was hydrolyzed with aqueous sodium hydroxide and the resulting sodium salt was treated with lead(IV) tetraacetate to give 1-acetoxy-1-(3,4-dimethoxyphenyl)propan-2-one (13). Condensation of 13 with dimethyl malonate, followed by acidic hydrolysis and sodium borohydride reduction afforded (2*R,3*S**,4*R**)-4-(3,4-dimethoxyphenyl)-2-methoxycarbonyl-3-methyl-4-butanolide (7a). The γ-lactone 7a was then converted into 5′-demethoxyporosin (10) by means of a series of reactions: Michael reaction with methyl vinyl ketone, elimination of the methoxycarbonyl group, acetalization, allylation, deacetalization, and intramolecular aldol reaction. Introduction of a hydroxyl group at the C-5′ position in 10, followed by methylation with diazomethane afforded racemic porosin. The synthetic porosin was further converted into 5-demethoxymegaphone acetate.**

Key words synthesis; (±)-porosin; neolignan; *Ocotea porosa*; *Urbanodendron verrucosum*

Porosin, a natural neolignan, has been isolated from the heartwood of *Ocotea porosa* (NEES) L. BARR. (Lauraceae)[1] and the branch wood of the shrub *Urbanodendron verrucosum* (NEES) MEZ. (Lauraceae).[2] On the basis of spectroscopic and chemical studies, Aiba *et al.*[3] revised the structure of porosin to $\Delta^{8'}$-4′-oxo-3,4,5′-trimethoxy-1′,4′,5′,6′-tetrahydro-7.*O*.2′,8.1′-neolignan (**1**), which possesses four asymmetric centers in the molecule. Recently, McLaughlin *et al.*[4] reported the isolation of two new neolignans, dysodanthins A (**2**) and B (**3**), together with the known compound, megaphone acetate[5] (**4**), from the roots of *Endlicheria dysodantha* MEZ. (Lauraceae). These natural neolignans (**2**, **3**, **4**) showed biological activities against human lung carcinoma, human breast carcinoma, human colon adenocarcinoma, and crown gall tumors on potato discs, and in the brine shrimp lethality test.[4] Structural similarity of porosin (**1**) to these bioactive neolignans prompted us to study its synthesis. This paper describes the first total synthesis of racemic porosin (**1**) with the desired relative stereochemistry at each of the four asymmetric centers starting from 3,4-dimethoxybenzaldehyde (veratraldehyde) (**6**), and the conversion of **1** into 5-demethoxymegaphone acetate (**5**).

Our retrosynthetic analysis of porosin (**1**) is depicted in Chart 1. Namely, porosin (**1**) would be derived from 5′-demethoxyporosin (**10**), which might be prepared by intramolecular aldol reaction of an allyl derivative **9**. The intermediate **9** possessing the required stereochemistry should be prepared from an oxo-γ-lactone derivative **8**, because the allyl group is expected to be introduced from the opposite side to the C-3 methyl and C-4 aryl groups. The intermediate **8** should be prepared by Michael reaction of methyl vinyl ketone and a γ-lactone ester derivative **7**, which might be derived from 3,4-dimethoxybenzaldehyde (**6**).

The synthesis of (2*R**,3*S**,4*R**)-4-(3,4-dimethoxyphenyl)-2-methoxycarbonyl-3-methyl-4-butanolide (**7a**) was first carried out as follows (Chart 2).

Condensation of **6** with methyl 2-chloropropanoate in benzene in the presence of potassium *tert*-butoxide afforded a glycidic ester (**11**), which was hydrolyzed with aqueous sodium hydroxide in refluxing methanol to give a sodium glycidate (**12**). This was treated with lead(IV) tetraacetate and pyridine in refluxing benzene[6] to give an acetoxy ketone (**13**) in 80.1% overall yield from **6**. The ^{1}H-NMR spectrum of **13** showed the presence of an acetoxyl group at δ 2.10 (3H, s), an acetyl group at δ 2.18 (3H, s), two methoxyl groups at δ 3.89 (6H, s), a benzylic methine proton having an acetoxyl group at δ 5.92 (1H, s), and three aromatic protons at δ 6.88 (1H, br s) and 6.91 (2H, s). Condensation of **13** in dichloromethane with dimethyl malonate in the presence of titanium(IV) tetrachloride and pyridine produced methyl 4-acetoxy-4-(3,4-dimethoxyphenyl)-2-methoxycarbonyl-3-methyl-2-

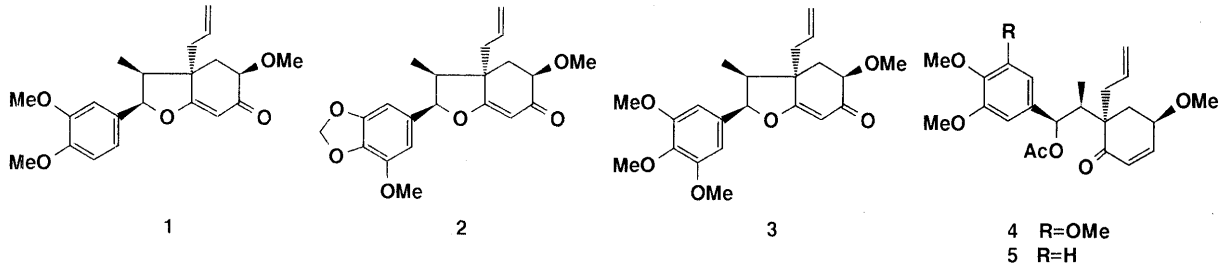

Fig. 1

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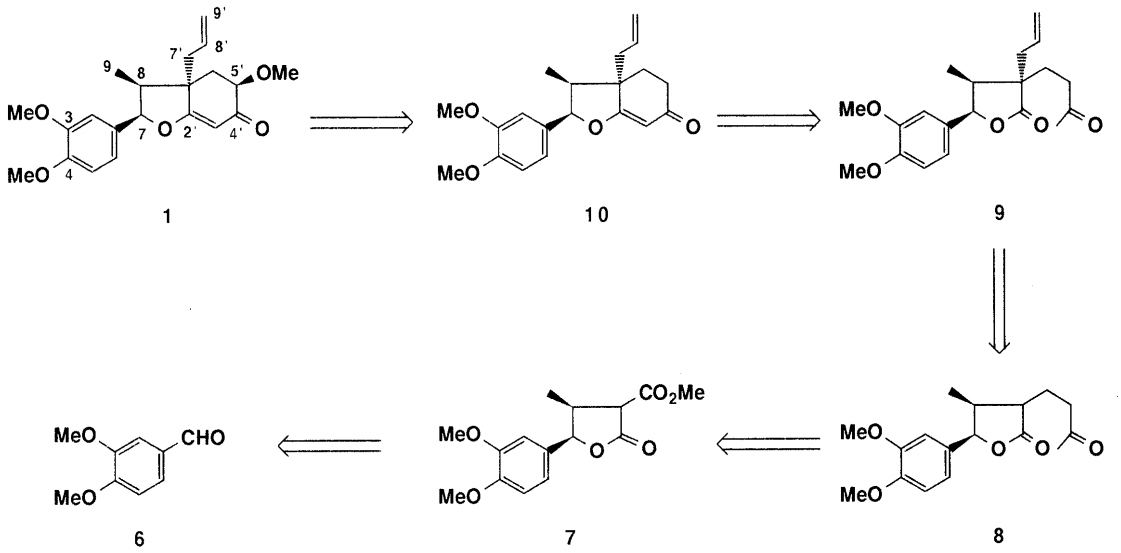
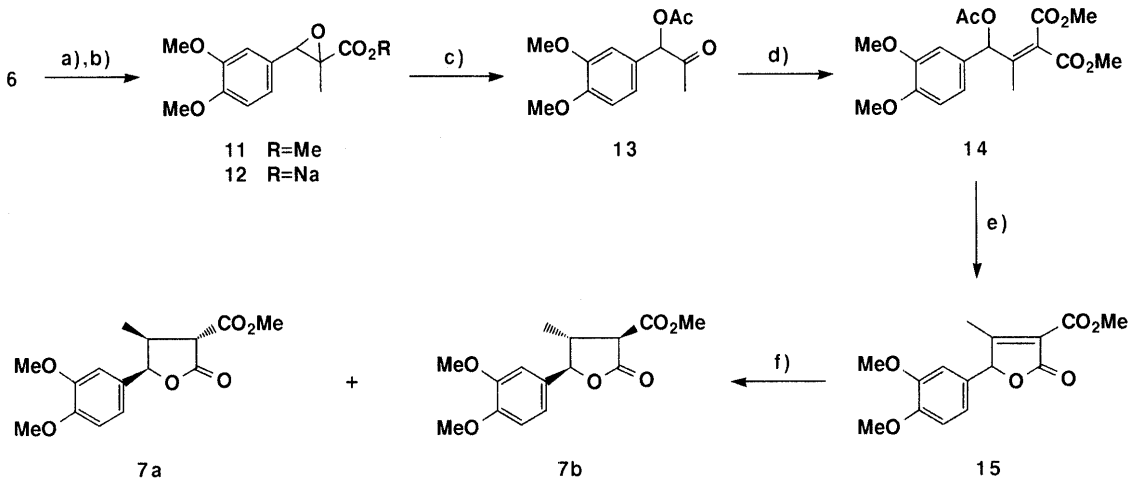


Chart 1. Retrosynthetic Analysis of Porosin (**1**)



reagents a) $CH_3CH(Cl)CO_2Me$, t-BuOK b) NaOH
c) $Pb(OAc)_4$, pyridine (80.1% yield from 6) d) $CH_2(CO_2Me)_2$, $TiCl_4$, pyridine
e) HCl f) $NaBH_4$ (7a:44.6% yield from 13; 7b:3.1% yield from 13)

Chart 2

butenoate (**14**). The butenoate **14** was refluxed with concentrated hydrochloric acid in methanol to give a butenolide ester (**15**), whose IR spectrum showed absorption bands at 1765 (γ-lactone), 1720 (ester), and 1655 cm^{-1} (double bond). The structure of **15** was also supported by its ^{1}H-NMR spectrum, which indicated the presence of a vinyl methyl group at δ 2.23 (3H, s), a methoxycarbonyl group at δ 3.86 (3H, s), and a benzylic methine proton at δ 5.66 (1H, s). The butenolide **15** was then submitted to 1,4-reduction using sodium borohydride in methanol at 0—5 °C to give a saturated compound (**7a**) (44.6% yield from **13**), together with a small amount of its (2*S**,3*R**,4*R**)-stereoisomer (**7b**) (3.1% yield from **13**). The ^{1}H-NMR spectrum of **7a** showed a doublet signal due to the C-3 methyl group at δ 0.79, while that of **7b** showed a corresponding signal at δ 1.18. The appearance of the C-3 methyl signal in **7a** at very high field must be attributable to the shielding effect of the C-4 aromatic ring. Thus, the relative configurations of the methyl and aryl groups in **7a** and **7b** were assigned to be *cis* and *trans*, respectively. In the ^{1}H-NMR spectrum of **7a**, irradiation of the C-3 methyl signal at δ 0.79 resulted in 13.7% and 18.0% enhancements of the signals due to the C-2 proton at δ 3.39 and the C-3 proton at δ 3.22, respectively, whereas no nuclear Overhauser effect (NOE) was observed between the C-3 methyl signal and the C-4 proton signal at δ 5.73. Thus, the relative configurations of the C-3 methyl group and the hydrogens at C-2 and C-4 were assigned as *cis* and *trans*, respectively. On the other hand, irradiation of the C-3 methyl signal at δ 1.18 in the ^{1}H-NMR spectrum of **7b** resulted in 8.4%, 11.3%, and 6.4% enhancements of the signals due to the C-2 proton at δ 3.42, the C-3 proton at δ 2.78—2.97, and the C-4 proton at δ 4.86, respectively. These results also suggested that the relative stereochemistries of the C-3 methyl group and the hydrogens at C-2 and C-4 were all *cis* (Fig. 2).

Subsequently, conversion of **7a** into porosin (**1**) was carried out as follows (Chart 3). Michael reaction of **7a**

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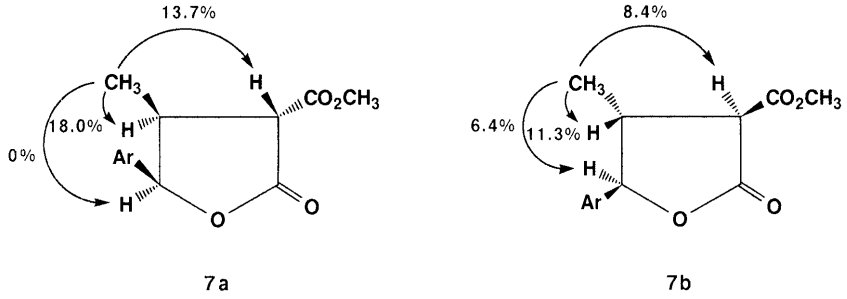
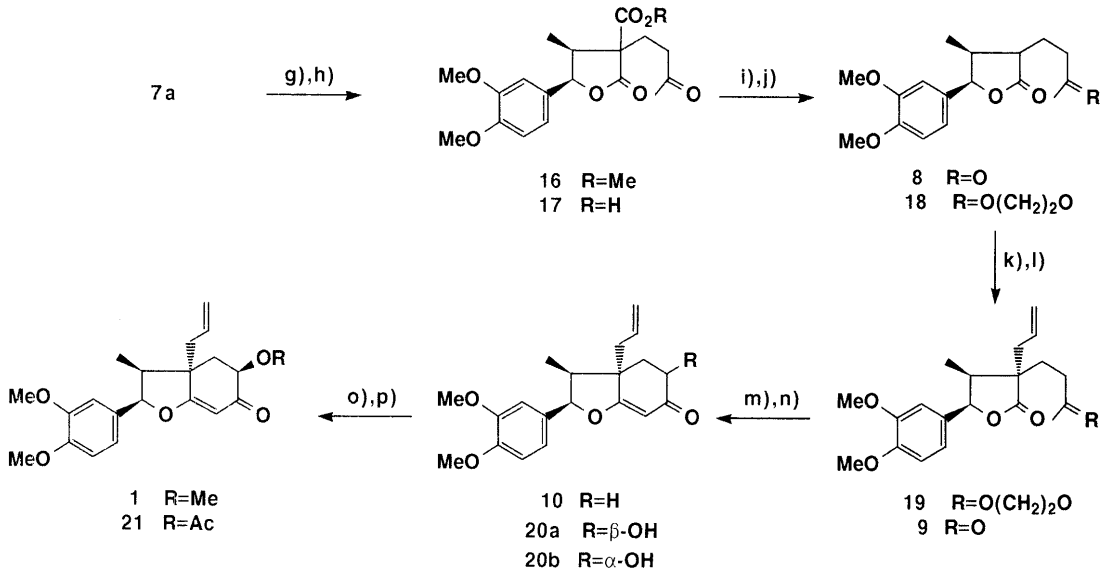


Fig. 2. NOE Spectra of Butanolides, **7a** and **7b**



reagents g) $CH_3COCH{=}CH_2$, Et_3N (82.6% yield) h) NaOH i) HCl (89.0% yield from 16)
j) $HOCH_2CH_2OH$, $CH(OMe)_3$, $BF_3{\cdot}OEt_2$ (98.5% yield)
k) $BrCH_2CH{=}CH_2$, $LiN(i\text{-}Pr)_2$ (76.1% yield) l) HCl (96.5% yield)
m) i) t-BuOK, ii) $p\text{-}TsOH{\cdot}H_2O$ (69.4% yield) n) i) Me_3SiCl, $LiN(SiMe_3)_2$,
ii) $m\text{-}ClC_6H_4CO_3H$, $NaHCO_3$, iii) Bu_4NF (20a:88.1% yield, 20b:11.4% yield)
o) CH_2N_2, SiO_2 (81.2% yield) p) Ac_2O, pyridine (83.5% yield)

Chart 3

in tetrahydrofuran with methyl vinyl ketone in the presence of triethylamine at 0—5 °C produced a single oxo γ-lactone ester (**16**) (82.6% yield), whose IR spectrum showed absorption bands at 1775 (γ-lactone), 1730 (ester), and 1720 cm^{-1} (carbonyl). The ester **16** was hydrolyzed with aqueous sodium hydroxide in refluxing methanol and the resulting acid (**17**) was decarboxylated with dilute hydrochloric acid in refluxing methanol to give a C-2 epimeric mixture (*ca.* 3 : 2) of oxo γ-lactones (**8**) in 89.0% yield. The carbonyl group in **8** was protected by treatment with 1,2-ethanediol, trimethyl orthoformate, and diethyl ether–boron trifluoride (1 : 1) in dichloromethane to give a mixture (*ca.* 3 : 2) of the corresponding acetals (**18**) in 98.5% yield. To introduce an allyl group, the mixture of acetals **18** was treated with allyl bromide and lithium diisopropylamide in tetrahydrofuran under a stream of nitrogen. The resulting single product **19** (76.1% yield) was hydrolyzed with dilute hydrochloric acid in methanol to give an oxo γ-lactone **9** in 96.5% yield. The relative configuration of the C-2 allyl and C-3 methyl groups in **9** was assigned to be *trans* by assuming the introduction of the allyl group from the less hindered side of the molecule. Intramolecular aldol condensation of **9** with potassium *tert*-butoxide in refluxing benzene was carried out and the crude product was immediately refluxed with *p*-toluenesulfonic acid monohydrate in benzene to give an α,β-unsaturated ketone (**10**) in 69.4% yield. Subsequently, the introduction of a hydroxyl group at C-5′ in **10** was carried out as follows. The enone **10** in tetrahydrofuran was treated with chlorotrimethylsilane and lithium bis(trimethylsilyl)amide under a stream of nitrogen to give a silyl enol ether. This was oxidized with *m*-chloroperbenzoic acid in dichloromethane in the presence of sodium hydrogen carbonate and then treated with tetrabutylammonium fluoride to give the desired hydroxy enone (**20a**) and its C-5′ epimer (**20b**) in 88.1% and 11.4% yields, respectively. In the ^{1}H-NMR spectrum of the major alcohol **20a**, a methine proton adjacent to the hydroxyl group exhibits both axial–axial (J = 12.2 Hz) and axial–equatorial (J = 5.4 Hz) vicinal coupling; while the corresponding proton in the minor alcohol **20b** exhibits both equatorial–equatorial (J = 2.0 Hz) and equatorial–

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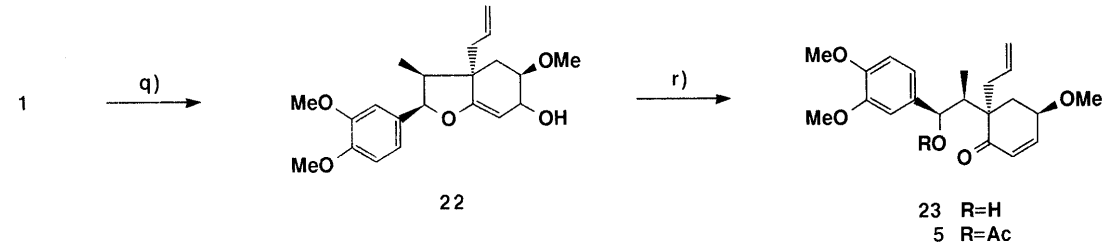

reagents q) AlH(i-Bu)$_2$ r) i) MsCl, Et$_3$N, ii) Et$_3$N, H$_2$O, iii) Ac$_2$O, pyridine (51.0% yield from 1)

Chart 4

axial (J=5.4 Hz) vicinal coupling. Consequently the hydroxyl groups in **20a** and **20b** are equatorial and axial respectively. From these spectral data, the relative configurations of the hydroxyl and allyl groups in **20a** and **20b** were assigned respectively to be *trans* and *cis*. The alcohol **20a** was further characterized as its acetate (**21**) by treatment with acetic anhydride in pyridine. Methylation of **20a** with diazomethane in ether in the presence of silica gel[7] afforded the desired porosin (**1**) in 81.2% yield. The ^{1}H-NMR spectrum of the synthetic **1** was in good agreement with that reported for natural porosin.[1-3] Finally, conversion of the synthetic porosin (**1**) into 5-demethoxymegaphone acetate (**5**) was carried out as follows (Chart 4). Reduction of **1** with diisobutylaluminum hydride in tetrahydrofuran afforded an alcohol (**22**), which was treated with methanesulfonyl chloride and triethylamine in tetrahydrofuran to give a mesylate. This was further treated with a mixture of aqueous tetrahydrofuran and triethylamine, and the resulting hydroxy enone (**23**) was immediately acetylated with acetic anhydride in pyridine to give a desired 5-demethoxymegaphone acetate (**5**) (51.0% overall yield from **1**), whose IR spectrum showed absorption bands at 1730 (acetoxyl) and 1670 cm^{-1} (α,β-unsaturated carbonyl). The ^{1}H-NMR spectrum of **5** showed the presence of a secondary methyl group at δ 0.92 (3H, d), an acetoxyl group at δ 2.11 (3H, s), three methoxyl groups at δ 3.45 (3H, s), 3.85 (3H, s), and 3.92 (3H, s), three olefinic protons on a monosubstituted vinyl group at δ 4.997 (1H, d), 5.003 (1H, d), and 5.57 (1H, m), two olefinic protons on a disubstituted vinyl group at δ 6.00 (1H, dd) and 6.90 (1H, d), a benzylic methine proton having an acetoxyl group at δ 5.70 (1H, s), and three aromatic protons at δ 6.80 (2H, s) and 6.93 (1H, s). These spectral data were very similar to those of megaphone acetate[4] (**4**) except for the absence of the signal of a methoxyl group on an aryl ring.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were measured on a Shimadzu IR-400 spectrometer in chloroform. The mass spectra were recorded on a JEOL JMS-SX102A spectrometer. The ^{1}H-NMR spectra were recorded with a Hitachi R-1500 (60 MHz) or a JEOL JNM EX-400 (400 MHz) spectrometer in deuteriochloroform using tetramethylsilane as an internal standard unless otherwise stated, and the following abbreviations are used: s=singlet, d=doublet, dd=double doublet, ddd=doublet of double doublet, t=triplet, q=quartet, m=multiplet, br= broad. Column chromatography was performed using Merck silica gel (0.063—0.200 mm).

1-Acetoxy-1-(3,4-dimethoxyphenyl)propan-2-one (13) Potassium *tert*-butoxide (21.515 g) was added to a stirred solution of veratraldehyde (**6**) (25.00 g) and methyl 2-chloropropanoate (22.480 g) in dry benzene (375 ml) with cooling in an ice-water bath over a 45-min period. The mixture was stirred at 5—10 °C for 2 h and then at room temperature for 3.5 h, poured into ice-dilute hydrochloric acid, and extracted with benzene. The benzene extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give a crude glycidic ester (**11**) (39.966 g) as an oil. IR: 1725 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.34 (3H, s, –CH$_3$), 3.82 (3H, s, –CO$_2$CH$_3$), 3.89 (6H, s, 2-OCH$_3$), 4.28 (1H, s, –CH(–O–)–), 6.83 (1H, br s), 6.87 (2H, s) (aromatic protons).

A mixture of the crude ester **11** (39.966 g) and aqueous sodium hydroxide (25%, 27 ml) in methanol (510 ml) was refluxed for 30 min. The precipitates were collected by filtration to give a sodium glycidate (**12**) (30.272 g: 77.4% yield from **6**). The filtrate was concentrated *in vacuo* to give additional **12** (4.844 g: 12.4% yield from **6**).

Lead(IV) tetraacetate (purity 91%, 50 g) was added to a stirred suspension of **12** (14.835 g) and pyridine (4.7 ml) in dry benzene (480 ml) over a 10-min period under a stream of nitrogen. The mixture was stirred at room temperature for 20 min, refluxed for 5 h, and then cooled. After the addition of 1,2-ethanediol (8 ml), the mixture was stirred at room temperature for 20 min, washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (140 g), using ether–benzene (3:97) as an eluent, to give **13** (12.827 g: 89.2% yield). IR: 1725 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 2.10 (3H, s, –OCOCH$_3$), 2.18 (3H, s, –CH$_3$), 3.89 (6H, s, 2-OCH$_3$), 5.92 (1H, s, –CH(OAc)–), 6.88 (1H, br s) and 6.91 (2H, s) (aromatic protons). *Anal.* Calcd for C$_{13}$H$_{16}$O$_5$: C, 61.89; H, 6.39. Found: C, 61.71; H, 6.48

Methyl 4-Acetoxy-4-(3,4-dimethoxyphenyl)-2-methoxycarbonyl-3-methyl-2-butenoate (14) A solution of **13** (10.301 g), dimethyl malonate (9.4 ml), and dry pyridine (59.3 ml) in dry dichloromethane (20 ml) was added (over a 25-min period) to a stirred solution of titanium(IV) tetrachloride (26.4 ml) in dry dichloromethane (430 ml) with cooling in an ice-water bath under a stream of nitrogen. The mixture was stirred at this temperature for 10 min and then at room temperature for 4 h, poured into ice-dilute hydrochloric acid, and extracted with dichloromethane. The extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give a crude product (**14**) (16.430 g). Aliquots of the crude **14** (3.024 g) were chromatographed on silica gel (200 g), using ether–benzene (3:97) as an eluent, to give pure **14** as an oil (2.118 g: 76.9% yield). IR: 1720, 1640 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.96, 2.13 (each 3H, s, –CH$_3$, –OCOCH$_3$), 3.78, 3.85 (each 3H, s, 2-CO$_2$CH$_3$), 3.88 (6H, s, 2-OCH$_3$), 6.90—7.07 (4H, m, –CH(OAc)–, three aromatic protons). *Anal.* Calcd for C$_{18}$H$_{22}$O$_8$: C, 59.01; H, 6.05. Found: C, 59.21; H, 6.14.

4-(3,4-Dimethoxyphenyl)-2-methoxycarbonyl-3-methyl-2-buten-4-olide (15) A mixture of the above crude **14** (13.406 g) and concentrated hydrochloric acid (3.8 ml) in methanol (135 ml) was refluxed for 1 h, then concentrated *in vacuo* and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give a crude **15** (12.171 g), which was used without purification in the next reaction. IR: 1765, 1720, 1655 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 2.23 (3H, s, –CH$_3$), 3.86, 3.90, 3.93 (each 3H, s, –CO$_2$CH$_3$, 2-OCH$_3$), 5.66 (1H, s, –CH(–O–)–), 6.64 (1H, br s), 6.87 (2H, s) (aromatic protons).

Reduction of 15 with Sodium Borohydride Sodium borohydride (947 mg) was added to a stirred solution of the above crude **15** (12.171 g) in methanol (150 ml) with cooling in an ice-water bath over a 20-min period. The mixture was further stirred at this temperature for 20 min, acidified with dilute hydrochloric acid, concentrated *in vacuo*, and

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extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was repeatedly chromatographed on silica gel (50—100 times the sample weight in each case), using ether–benzene (3 : 97, 5 : 95) as eluents, to give **7a** (4.372 g: 44.6% yield from **13**) and **7b** (0.306 g: 3.1% yield from **13**).

a): (2*R**,3*S**,4*R**)-4-(3,4-Dimethoxyphenyl)-2-methoxycarbonyl-3-methyl-4-butanolide (**7a**) was recrystallized from a mixture of acetone and hexane, mp 107.5—108.5 °C. IR: 1775, 1735 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.79 (3H, d, J=7.1 Hz, $-CH_3$), 3.22 (1H, m, J=6.9 Hz, C3-H), 3.39 (1H, d, J=6.7 Hz, C2-H), 3.85 (3H, s, $-CO_2CH_3$), 3.89 (6H, s, 2-OCH_3), 5.73 (1H, d, J=6.9 Hz, C4-H), 6.69 (1H, d, J=1.9 Hz), 6.76 (1H, dd, J=1.9, 8.3 Hz), 6.89 (1H, d, J=8.3 Hz) (aromatic protons). *Anal.* Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.09; H, 6.27.

b): (2*S**,3*R**,4*R**)-4-(3,4-Dimethoxyphenyl)-2-methoxycarbonyl-3-methyl-4-butanolide (**7b**) was obtained as an oil. IR: 1775, 1735 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.18 (3H, d, J=6.5 Hz, $-CH_3$), 2.78—2.97 (1H, m, C3-H), 3.42 (1H, d, J=12 Hz, C2-H), 3.85 (3H, s, $-CO_2CH_3$), 3.90, 3.91 (each 3H, s, 2-OCH_3), 4.86 (1H, d, J=9.9 Hz, C4-H), 6.85—6.94 (3H, m, aromatic protons). *Anal.* Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.34; H, 6.31.

Michael Condensation of 7a with Methyl Vinyl Ketone Triethylamine (7.05 ml) was added to a stirred solution of **7a** (1.489 g) and methyl vinyl ketone (6.98 ml) in dry tetrahydrofuran (22.3 ml) with cooling in an ice-water bath. The mixture was allowed to stand in a refrigerator for 20 h, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using ether–benzene (6 : 44) as an eluent, to give an oxo γ-lactone ester (**16**) (1.523 g: 82.6% yield), mp 125.5—127 °C (from acetone). IR: 1775, 1730 sh, 1720 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 0.64 (3H, d, J=7.3 Hz, $-CH_3$), 2.17 (3H, s, $-COCH_3$), 2.28—2.98 (5H, m, C3-H, $-CH_2CH_2-$), 3.76 (3H, s, $-CO_2CH_3$), 3.89 (6H, s, 2-OCH_3), 5.72 (1H, d, J=6.7 Hz, C4-H), 6.82 (3H, s, aromatic protons). *Anal.* Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64. Found: C, 62.43; H, 6.56.

Hydrolysis and Decarboxylation of 16 A mixture of **16** (12.039 g) and 20% aqueous sodium hydroxide (26.5 ml) in methanol (350 ml) was refluxed for 1 h. The mixture was acidified with dilute hydrochloric acid and then refluxed for 40 min. After the methanol had been removed *in vacuo*, the residue was diluted with brine and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (Mallinckrodt CC-4, 150 g), using ether–benzene (5 : 95) as an eluent, to give a mixture of (2*R**,3*S**,4*R**)- and (2*S**,3*S**,4*R**)-4-(3,4-dimethoxyphenyl)-3-methyl-2-(3-oxobutyl)-4-butanolide (**8**) (7.729 g: 76.3% yield). IR: 1760, 1710 cm^{-1}. The ^{1}H-NMR spectrum of the mixture suggested the ratio of the two C-2 epimers to be *ca.* 3 : 2. ^{1}H-NMR (60 MHz) of the major compound δ: 0.76 (3H, d, J=6.5 Hz, $-CH_3$), 1.8—3.2 (6H, m, $-CH_2CH_2-$, C2-H, C3-H), 2.18 (3H, s, $-COCH_3$), 3.88 (6H, s, 2-OCH_3), 5.53 (1H, d, J=6.5 Hz, C4-H). ^{1}H-NMR (60 MHz) of the minor compound δ: 0.58 (3H, d, J=7.0 Hz, $-CH_3$), 1.67—2.19 (2H, m), 2.66—2.89 (4H, m) ($-CH_2CH_2-$, C2-H, C3-H), 2.18 (3H, s, $-COCH_3$), 3.88 (6H, s, 2-OCH_3), 5.45 (1H, d, J=4.1 Hz, C4-H). Further elution with ether–benzene (1 : 9, 3 : 7) afforded an acid (**17**) (2.707 g). IR: 3600—2300, 1765, 1705 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 0.72 (3H, d, J=7.3 Hz, $-CH_3$), 2.18 (3H, s, $-COCH_3$), *ca.* 2.3—3.0 (5H, m, $-CH_2CH_2-$, C3-H), 3.88 (6H, s, 2-OCH_3), 5.82 (1H, d, J=5.9 Hz, C4-H), 6.83 (3H, br s, aromatic protons), 8.22 (1H, br s. $-CO_2H$). The acid **17** (2.707 g) was decarboxylated as described above to give a mixture of the epimers (**8**) (1.291 g: 12.7% yield).

Acetalization of 8 A mixture of **8** (8.548 g), 1,2-ethanediol (20.2 ml), trimethyl orthoformate (38.2 ml), and diethyl ether–boron trifluoride (1 : 1) (2.5 ml) in dichloromethane (195 ml) was stirred at 0—5 °C for 1.5 h. The mixture was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (150 g), using ether–benzene (1 : 9) as an eluent, to give a C-2 epimeric mixture (*ca.* 3 : 2) of acetals (**18**) (9.631 g: 98.5% yield). IR: 1760 cm^{-1}. ^{1}H-NMR (60 MHz) of the major compound δ: 0.75 (3H, d, J=6.5 Hz, $-CH_3$), 1.34 (3H, s, $-CH_3$), *ca.* 1.7—3.0 (6H, m, $-CH_2CH_2-$, C2-H, C3-H), 3.88 (6H, s, 2-OCH_3), 3.96 (4H, s, $-OCH_2CH_2O-$), 5.53 (1H, d, J=6.7 Hz, C4-H), 6.69—6.83 (3H, m, aromatic protons). ^{1}H-NMR (60 MHz) of the minor compound δ: 0.57 (3H, d, J=7.0 Hz, $-CH_3$), 1.34 (3H, s, $-CH_3$), *ca.* 1.6—3.0 (6H, m, $-CH_2CH_2-$, C2-H, C3-H), 3.88 (6H, s, 2-OCH_3), 3.96 (4H, s, $-OCH_2CH_2O-$), 5.46 (1H, d, J=4.4 Hz, C4-H), 6.83 (3H, br s, aromatic protons).

(2*S,3*S**,4*R**)-4-(3,4-Dimethoxyphenyl)-2-(3,3-ethylenedioxybutyl)-3-methyl-2-(2-propenyl)-4-butanolide (19)** A solution of lithium diisopropylamide in hexane (1.5 mol dm^{-3}, 1.05 ml) was added to a stirred solution of **18** (218 mg) in dry tetrahydrofuran (8.0 ml) at −60 °C under a stream of nitrogen. After 15 min, allyl bromide (0.38 ml) was added at −30 °C. The mixture was stirred at −30 °C for 30 min and then at 0—5 °C for 2 h, then the reaction was quenched with 20% aqueous ammonium chloride (8.0 ml), and the whole was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (30 g), using ether–benzene (5 : 95) as an eluent, to give **19** (185 mg: 76.1% yield). This was recrystallized from a mixture of acetone and hexane, mp 70—73 °C. IR: 1760 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 0.66 (3H, d, J=7.3 Hz, $-CH_3$), 1.29 (3H, s, $-CH_3$), 1.4—1.84 (4H, m), 2.5—2.71 (3H, m) (C3-H, $-CH_2CH_2-$, $-C\underline{H}_2CH=CH_2$), 3.89 (10H, s, 2-OCH_3, $-OCH_2CH_2O-$), 5.01—5.81 (4H, m, C4-H, $-CH=CH_2$), 6.7—7.0 (3H, m, aromatic protons). *Anal.* Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.51; H, 7.87.

(2*S,3*S**,4*R**)-4-(3,4-Dimethoxyphenyl)-3-methyl-2-(3-oxobutyl)-2-(2-propenyl)-4-butanolide (9)** A mixture of **19** (385 mg) and 10% hydrochloric acid (0.2 ml) in methanol (4.0 ml) was stirred at room temperature for 3 h. The mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using ether–benzene (5 : 95) as an eluent, to give **9** (330 mg: 96.5% yield), which was recrystallized from methanol, mp 102—102.5 °C. IR: 1755, 1710 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 0.67 (3H, d, J=7.3 Hz, $-CH_3$), 1.6—2.0 (2H, m), 2.4—3.0 (5H, m) ($-CH_2CH_2-$, C3-H, $-C\underline{H}_2CH=CH_2$), 2.16 (3H, s, $-COCH_3$), 3.89 (6H, s, 2-OCH_3), 5.02—5.76 (3H, m, overlap, $-CH=CH_2$), 5.62 (1H, d, J=7.0 Hz, overlap, C4-H), 6.68—6.98 (3H, m, aromatic protons). *Anal.* Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.56; H, 7.36.

(7*R,8*S**,1′*S**)-$\Delta^{8'}$-3,4-Dimethoxy-4′-oxo-1′,4′,5′,6′-tetrahydro-7.*O*.2′,8.1′-neolignan (5′-Demethoxyporosin) (10)** Potassium *tert*-butoxide (437 mg) was added to a stirred solution of **9** (675 mg) in dry benzene (12 ml) with cooling in an ice-water bath. The mixture was stirred at this temperature for 15 min and then refluxed for 3 h. The mixture was cooled, poured into ice-dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give an oily product.

A mixture of the above oily product and *p*-toluenesulfonic acid monohydrate (60 mg) in benzene (12 ml) was refluxed for 1 h, cooled, and diluted with ethyl acetate. The ethyl acetate solution was washed successively with aqueous sodium hydrogen carbonate and brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from methanol to give **10** (219 mg: 34.2% yield), mp 150—152 °C. IR: 1660, 1625 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.52 (3H, d, J=7.8 Hz, $-CH_3$), 1.92—2.03 (2H, m, C6′-H_2), 2.37—2.60 (3H, m, C8-H, C5′-H_2), 2.59 (2H, d, J=7.3 Hz, C7′-H_2), 3.90 (6H, s, 2-OCH_3), 5.28 (1H, d, J=11.7 Hz), 5.28 (1H, d, J=15.6 Hz) ($-CH=C\underline{H}_2$), 5.58 (1H, s, C3′-H), 5.82—5.93 (1H, m, $-C\underline{H}=CH_2$), 5.85 (1H, d, J=5.4 Hz, C7-H), 6.73 (1H, d, J=1.5 Hz, C2-H), 6.80 (1H, dd, J=1.5, 8.1 Hz, C6-H), 6.88 (1H, d, J=8.1 Hz, C5-H). HR-MS *m/z*: Found: 328.1676 (M^+). Calcd for $C_{20}H_{24}O_4$: M, 328.1675. The mother liquor of recrystallization was evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using ether–benzene (1 : 9) as an eluent, to give additional **10** (225 mg: 35.2% yield).

(7*R,8*S**,1′*R**,5′*R**)-$\Delta^{8'}$-3,4-Dimethoxy-5′-hydroxy-4′-oxo-1′,4′,5′,6′-tetrahydro-7.*O*.2′,8,1′-neolignan (20a) and Its (7*R**,8*S**,1′*R**,5′*S**)-Isomer (20b)** A solution of **10** (941 mg) in dry tetrahydrofuran (10 ml) was added to a stirred solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1 mol dm^{-3}, 11.5 ml) at −70 °C under a stream of nitrogen. The solution was stirred at −70 °C for 1 h and then chlorotrimethylsilane (1.64 ml) was added at −70 °C. After having been stirred at room temperature for 1 h, the mixture was poured into saturated aqueous sodium hydrogen carbonate (40 ml) and extracted with hexane. The extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated under vacuum in an atmosphere of nitrogen to give a silyl enol ether, which was used immediately in the next reaction.

To a solution of the above silyl enol ether in dichloromethane (20 ml) were added *m*-chloroperbenzoic acid (purity 80%, 1.052 g) and sodium

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hydrogen carbonate (512 mg) at 4 °C. The mixture was stirred at 4 °C for 2 h and then a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 mol dm^{-3}, 8.3 ml) was added at 4 °C. The whole was stirred at the same temperature for 1 h, then the reaction was quenched with a saturated sodium sulfite solution. The mixture was extracted with chloroform and the extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was repeatedly chromatographed on silica gel (50—100 times the sample weight in each case), using hexane–chloroform (3 : 7) and hexane–ethyl acetate (3 : 2) as eluents, to give **20a** (562 mg: 56.9% yield; 88.1% yield based on the starting material consumed), which was recrystallized from a mixture of tetrahydrofuran and hexane, mp 153—154.5 °C. IR: 3470, 1660, 1625 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.52 (3H, d, J=7.3 Hz, –CH_3), 1.86 (1H, t, J=12.2 Hz), 2.40 (1H, dd, J=5.4, 12.2 Hz) (C6′-H_2), 2.57—2.70 (3H, m, C8-H, C7′-H_2), 3.77 (1H, s, –OH), 3.90 (6H, s, 2-OCH_3), 4.37 (1H, dd, J=5.4, 12.2 Hz, C5′-H), 5.33 (1H, d, J=16.1 Hz), 5.33 (1H, d, J=10.8 Hz) (–CH=C$\underline{H}_2$), 5.66 (1H, s, C3′-H), 5.85—6.04 (1H, m, –C$\underline{H}$=CH_2), 5.90 (1H, d, J=5.4 Hz, C7-H), 6.70 (1H, d, J=2.0 Hz, C2-H), 6.78 (1H, dd, J=2.0, 8.3 Hz, C6-H), 6.88 (1H, d, J=8.3 Hz, C5-H). HR-MS m/z: Found: 344.1639 (M^+). Calcd for $C_{20}H_{24}O_5$: M, 344.1624. Further elution afforded recovered **10** (333 mg) and **20b** (73 mg: 7.4% yield; 11.4% yield based on the starting material consumed). The alcohol **20b** was recrystallized from a mixture of acetone and hexane or ethyl acetate, mp 153—155 °C. IR: 3570, 3300, 1620 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.53 (3H, d, J=7.3 Hz, –CH_3), 2.08 (1H, dd, J=5.4, 14.6 Hz), 2.25 (1H, dd, J=2.0, 14.6 Hz) (C6′-H_2), 2.56—2.66 (2H, m, C8-H, C7′-H), 2.85 (1H, dd, J=6.8, 14.2 Hz, C7′-H), 3.03 (1H, br s, –OH), 3.90 (6H, s, 2-OCH_3), 4.13 (1H, dd, J=5.4, 2.0 Hz, C5′-H), 5.29 (1H, d, J=16.1 Hz), 5.29 (1H, d, J=11.7 Hz) (–CH=C$\underline{H}_2$), 5.64 (1H, s, C3′-H), 5.87 (1H, d, J=5.4 Hz, C7-H), 5.93—6.03 (1H, m, –C$\underline{H}$=CH_2), 6.72 (1H, d, J=2.0 Hz, C2-H), 6.79 (1H, dd, J=2.0, 8.3 Hz, C6-H), 6.88 (1H, d, J=8.3 Hz, C5-H). HR-MS m/z: Found: 344.1613 (M^+). Calcd for $C_{20}H_{24}O_5$: M, 344.1624.

Acetylation of 20a A mixture of **20a** (75 mg) and acetic anhydride (1.0 ml) in pyridine (1.0 ml) was heated at 60 °C for 1.5 h. After the usual work-up, the crude product was chromatographed on silica gel (15 g), using hexane–chloroform (1 : 4) as an eluent, to give an acetate (**21**) (71 mg: 83.5% yield), which was recrystallized from a mixture of acetone and hexane or ethyl acetate, mp 148—150 °C. IR: 1740, 1660, 1625 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.53 (3H, d, J=7.8 Hz, –CH_3), 2.06 (1H, t, J=12.2 Hz), 2.26 (1H, dd, J=5.4, 12.2 Hz) (C6′-H_2), 2.18 (3H, s, –$OCOCH_3$), 2.59—2.69 (3H, m, C8-H, C7′-H_2), 3.90 (6H, s, 2-OCH_3), 5.35 (1H, d, J=10.3 Hz), 5.38 (1H, dd, J=1.5, 15.6 Hz) (–CH=C$\underline{H}_2$), 5.64 (1H, s, C3′-H), 5.64 (1H, dd, J=5.4, 12.2 Hz, C5′-H), 5.85—5.97 (1H, m, –C$\underline{H}$=CH_2), 5.90 (1H, d, J=5.4 Hz, C7-H), 6.71 (1H, d, J=2.0 Hz, C2-H), 6.79 (1H, dd, J=2.0, 8.3 Hz, C6-H), 6.88 (1H, d, J=8.3 Hz, C5-H). HR-MS m/z: Found: 386.1727 (M^+). Calcd for $C_{22}H_{26}O_6$: M, 386.1729.

(±)-Porosin (1) A diazomethane ether solution (*ca.* 150 ml) was prepared from *p*-toluenesulfonyl-*N*-methyl-*N*-nitrosoamide (21.5 g), diethylene glycol monomethyl ether (35 ml), and a solution of potassium hydroxide (6 g) in water (10 ml) at 60—65 °C.

A mixture of **20a** (470 mg) and silica gel (Merck 7729: <0.063 mm) (4.7 g) in dry tetrahydrofuran (20 ml) was stirred at room temperature and freshly prepared diazomethane ether solution (total 360 ml) was added for 26 h at 2—6 h intervals. After having been stirred at room temperature for 33 h, the mixture was filtered to remove silica gel, which was washed with ether. The combined filtrate and washing was washed with dilute hydrochloric acid and brine successively, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (50 g), using hexane–chloroform (3 : 7) as an eluent, to give recovered **20a** (23 mg) and **1** (397 mg: 81.2% yield), which was recrystallized from methanol, mp 139—140 °C. IR: 1660, 1635 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.52 (3H, d, J=7.8 Hz, –CH_3), 1.91 (1H, t, J=12.5 Hz), 2.31 (1H, dd, J=5.2, 12.5) (C6′-H_2), 2.54 (1H, dd, J=7.8, 14.9 Hz), 2.69 (1H, dd, J=6.6, 14.9 Hz) (C7′-H_2), 2.57 (1H, m, C8-H), 3.61 (3H, s, C5′-OCH_3), 3.90 (6H, s, 2-OCH_3), 4.00 (1H, dd, J=5.2, 12.5 Hz, C5′-H), 5.33 (1H, d, J=15.6 Hz), 5.34 (1H, d, J=11.2 Hz) (–CH=C$\underline{H}_2$), 5.58 (1H, s, C3′-H), 5.87 (1H, d, J=4.9 Hz, C7-H), 5.87—5.99 (1H, m, overlap, –C$\underline{H}$=CH_2), 6.71 (1H, d, J=2.0 Hz, C2-H), 6.78 (1H, dd, J=2.0, 8.3 Hz, C6-H), 6.88 (1H, d, J=8.3 Hz, C5-H). HR-MS m/z: Found: 358.1764 (M^+). Calcd for $C_{21}H_{26}O_5$: M, 358.1780. The ^{1}H-NMR spectrum of the synthetic **1** was identical with that of natural porosin[1,2] (lit. mp 133—135 °C).

(±)-5-Demethoxymegaphone Acetate (5) A solution of diisobutylaluminum hydride in hexane (1 mol dm^{-3}, 2.1 ml) was added over 2 min to a stirred solution of the synthetic porosin (**1**) (300 mg) in dry tetrahydrofuran (6.0 ml) with cooling in an ice-water bath under a stream of nitrogen. After the mixture had been stirred at this temperature for 45 min, the following reagents were added successively: saturated aqueous ammonium chloride (0.5 ml), ether (20 ml), ammonium chloride (300 mg), and silica gel (<0.063 mm: 1.5 g). The mixture was stirred at room temperature for 30 min and then filtered. The filtrate was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a crude alcohol (**22**) (329 mg) as an oil. IR: 3590, 3430 cm^{-1}.

Methanesulfonyl chloride (0.26 ml) was added to a stirred solution of the above crude alcohol (**22**) (329 mg) and triethylamine (0.47 ml) in dry tetrahydrofuran (4.0 ml) at −60 °C. After the mixture had been stirred at this temperature for 30 min, a solution of water (1.5 ml), tetrahydrofuran (1.0 ml), and triethylamine (0.5 ml) was added. The whole was stirred at room temperature for 30 min, diluted with ether, and washed with brine. The dried solution was evaporated *in vacuo*. The residue (**23**) was dissolved in acetic anhydride (3.0 ml) and pyridine (3.0 ml), and the solution was allowed to stand at room temperature for 24 h. The mixture was diluted with ether and washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and brine. The dried solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (30 g), using chloroform as an eluent, to give oily **5** (172 mg: 51.0% yield). IR: 1730, 1670 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.92 (3H, d, J=7.3 Hz, –CH_3), 1.89 (1H, dd, J=12.9, 10.0 Hz), 2.31 (1H, ddd, J=12.9, 3.4, 2.0 Hz) (C6′-H_2), 2.11 (3H, s, –$OCOCH_3$), 2.35 (2H, d, J=7.3 Hz, C7′-H_2), 2.55 (1H, q, J=7.3 Hz, C8-H), 3.45 (3H, s, C5′-OCH_3), 3.85, 3.92 (each 3H, s, 2-OCH_3), 4.21 (1H, m, C5′-H), 4.997 (1H, d, J=16.1 Hz), 5.003 (1H, d, J=10.7 Hz) (C9′-H_2), 5.57 (1H, m, C8′-H), 5.70 (1H, s, C7-H), 6.00 (1H, dd, J=10.3, 2.0 Hz, C4′-H), 6.80 (2H, s), 6.93 (1H, s) (aromatic protons), 6.90 (1H, d, J=10.3 Hz, C3′-H). The ^{1}H-NMR spectrum of **5** was very similar to that of megaphone acetate[4] (**4**) except for the absence of the signal of a methoxyl group on an aryl ring. HR-MS m/z: Found: 402.2049 (M^+). Calcd for $C_{23}H_{30}O_6$: M, 402.2042.

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