Aromatic Constituents from the Heartwood of *Santalum album* L.

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A phytochemical investigation of the polar constituents in the heartwood of Indian *Santalum album* L. resulted in the isolation of three new neolignans (1—3) and a new aromatic ester (4), along with 14 known components. The structures of the new compounds (1—4) were established using spectroscopic methods.

Key words *Santalum album*; Santalaceae; sandalwood; benzodioxane; dihydrobenzo[*b*]furan; 8.*O*.4′-type neolignan

Santalum album LINN. (Santalaceae) is a mid-sized evergreen parasitic tree widely distributed in India, Malaysia, and Australia; it is commonly known as sandalwood. The essential oil of sandalwood is usually prepared by steam distillation from chips and billets cut from the heartwood and is used in perfumes, cosmetics, and sacred unguents.[1] Sandalwood oil has various biological activities, such as antiviral and chemopreventive effects.[2—5] Previous phytochemical studies of *S. album* revealed triterpenoids,[6,7] phenylpropanoids,[8] and sesquiterpenoids,[9—12] represented by α- and β-santalol.[13,14] Recent investigations found that the major sesquiterpene, α-santalol, was responsible for the pharmacological effects of sandalwood oil.[15—19] As part of our continuing search for novel bioactive natural products, we investigated an ethyl acetate extract of heartwood chips of East Indian (Mysore) *S. album* L. and isolated four new compounds (**1**—**4**, Fig. 1), together with 14 known metabolites. Here, we describe the structure elucidation of these new compounds.

Results and Discussion

Successive column and preparative layer chromatographic purification of the ethyl acetate-soluble fraction of the methanolic extract of *S. album* led to the isolation and characterization of three new neolignans (**1**—**3**) and a new benzoic acid derivative (**4**), along with 14 known constituents. The known compounds were identified as 7,8-*erythro*- and 7,8-*threo*-4,9,9′-trihydroxy-3,3′-dimethoxy-8.*O*.4′-neolignans (**5**, **6**),[20] dihydrodehydrodiconiferyl alcohol (**7**),[21] (7*S*,8*S*)-3-methoxy-3′,7-epoxy-8,4′-oxyneoligna-4,9,9′-triol (**8**),[22] (7′*S*,8*R*,8′*R*)-lyoniresinol (**9**),[23] 2,3-bis[(4-hydroxy-3,5-dimethoxyphenyl)-methyl]-1,4-butanediol (**10**),[24] (−)-secoisolariciresinol (**11**),[25] ω-hydroxypropioguaiacone,[26] 3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone,[27] *C*-veratroylglycol,[28] syringic acid, vanillic acid, isovanillic acid, and vanillic acid 4-*O*-neohesperidoside[29] from comparisons of their physicochemical and spectroscopic data (^{1}H-, ^{13}C-NMR, 2D NMR, and MS) with those of authentic samples and reference data. These polar phenolic constituents were first isolated from *S. album* heartwood.

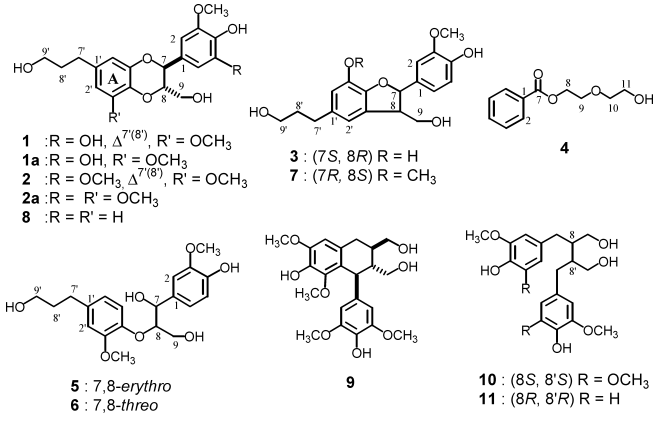

Fig. 1

Compound **1** was obtained as a colorless oil, $[\alpha]_D^{20}$ +8.0° (MeOH). Its molecular formula was determined to be $C_{20}H_{22}O_8$ using positive high-resolution (HR) fast atom bombardment (FAB)-MS, which showed a pseudomolecular ion peak at *m*/*z* 391.1379 $[M+H]^+$. The ^{1}H-NMR spectrum of **1** (Table 1) in CD_3OD showed two sets of *meta*-coupled signals at δ_H 6.73 (1H, d, *J*=1.8 Hz, H-2′)/6.67 (1H, d, *J*=1.8 Hz, H-6′) and 6.62 (1H, d, *J*=1.8 Hz, H-2)/6.60 (1H, d, *J*=1.8 Hz, H-6), indicating the presence of two 1,3,4,5-tetrasubstituted aromatic rings. The spectrum also included signals attributable to *trans* olefinic protons [δ_H 6.52 (1H, br d, *J*=16.2 Hz, H-7′) and 6.27 (1H, dt, *J*=16.2, 5.4 Hz, H-8′)], a hydroxymethyl proton [δ_H 4.24 (2H, dd, *J*=5.4, 1.8 Hz, H-9′)], and two methoxyl groups [δ_H 3.92 (3H, s) and 3.89 (3H, s)]. In addition to these proton signals, the ^{1}H–^{1}H correlated spectroscopy (COSY) spectrum of **1** revealed aliphatic AMXY-type signals [δ_H 4.84 (1H, d, *J*=8.4 Hz, H-7), 4.03 (1H, ddd, *J*=8.4, 4.8, 3.0 Hz, H-8), 3.76 (1H, dd, *J*=12.6, 3.0 Hz, H-9), and 3.56 (1H, dd, *J*=12.6, 4.8 Hz, H-9)]. The deshielded benzylic oxymethine proton at δ_H 4.84 (H-7) and the doublet of double doublets at δ_H 4.03 (H-8) implied the linkage of two phenylpropanoid units *via* a 1,4-dioxane bridge.[30,31] Recently, several studies have demonstrated that the location of the side chain on the A-ring (C-1′ or C-2′) of benzodioxane-type neolignans is difficult to determine using heteronuclear multiple bond connectivity (HMBC).[31,32] In order to overcome this problem, NMR measurement techniques, such as long-range selective proton decoupling (LSPD), and a selective insensitive nuclei enhanced using a polarization transfer (INEPT) technique had to be applied to elucidate the structure of the neolignans and a flavonolignan.[30,31,33] The linkage point of the substituent on the 1,4-dioxane moiety in **1** was determined unambiguously from HMBC and nuclear Overhauser and exchange spectroscopy (NOESY) spectra using pyridine-d_5 as the solvent, which gave clear correlations of the H-7/C-5′ and H-2′,9/C-4′ (Fig. 2). In addition, long-

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Table 1. NMR Data for Compound **1**

Position	δ_H [a] (mult., J Hz)	δ_H [b] (mult., J Hz)	δ_C [a]	δ_C [b]	HMBC correlations	NOESY
1			128.6	128.1		
2	6.62 (d, 1.8)	7.00 (d, 1.8)	104.0	103.7	C-1,[a] 3,[c] 4,[b] 6,[c] 7[c]	H-3[c] (OCH_3), 7,[c] 8[c]
3			149.8	149.5		
4			135.9	136.6		
5			146.8	148.0		
6	6.60 (d, 1.8)	7.36 (d, 1.8)	109.3	111.1	C-2,[c] 4,[c] 5,[c] 7[c]	H-7,[b] 8[b]
7	4.84 (d, 8.4)	5.44 (d, 7.8)	77.7	77.3	C-1,[c] 2,[c] 6,[c] 8,[c] 5′[b]	H-2,[c] 6,[b] 8,[c] 9[c]
8	4.03 (ddd, 8.4, 4.8, 3.0)	4.35 (m)	80.1	80.0	C-7[c]	H-2,[c] 6,[b] 7,[c] 9[c]
9	3.76 (dd, 12.6, 3.0)	4.23 (dd, 12.6, 2.4)	62.1	61.5	C-7,[c] 8[b]	H-7,[c] 8,[a] 9[c]
	3.56 (dd, 12.6, 4.8)	3.95 (dd, 12.6, 3.6)			C-4′,[b] 7[c]	H-7,[c] 8,[a] 9[c]
1′			134.2	129.6		
2′	6.73 (d, 1.8)	6.87 (d, 1.8)	103.9	103.5	C-1′,[c] 3′,[c] 4′,[b] 5′,[a] 6′[a]	H-3′[c] (OCH_3), 8′[c]
3′			150.2	150.0		
4′			131.1	134.1		
5′			145.8	145.5		
6′	6.67 (d, 1.8)	7.03 (d, 1.8)	109.2	108.6	C-1′,[c] 2′,[c] 4′,[b] 5′,[b] 7′[a]	H-7′[c]
7′	6.52 (br d, 16.2)	6.88 (br d, 15.6)	131.6	130.3	C-2′,[c] 6′,[a] 9′[c]	H-2′,[a] 6′,[c] 9′[c]
8′	6.27 (dt, 16.2, 5.4)	6.62 (dt, 15.6, 5.4)	128.5	129.9	C-7′,[c] 9′[c]	H-2′,[c] 6′,[a] 9′[c]
9′	4.24 (dd, 5.4, 1.8)	4.57 (dd, 5.4, 1.8)	63.7	63.1	C-7′,[a] 8′[c]	H-7′,[c] 8′[c]
OCH_3-3	3.89 (s)	3.76 (s)	56.7	56	C-3′[c]	H-2′[c]
OCH_3-3′	3.92 (s)	3.82 (s)	56.7	55.9	C-3[c]	H-2[c]

a) Observed in CD_3OD. *b*) Observed in C_5D_5N. *c*) Observed in both CD_3OD and C_5D_5N.

range correlations between each of the two methoxyl signals (δ_H 3.92, 3.89) and aromatic carbons at δ_C 150.2 and 149.8, respectively, indicated the position of the methoxyl groups at C-3 and C-3′. The coupling constant ($J_{7,8}$=8.4 Hz) between H-7 and H-8, and the NOE correlations between H-8/H-6 and H-7/H-9 clearly indicated a *threo* configuration of the chiral centers on the dioxane ring.[34,35] The absolute configurations at C-7 and C-8 were determined by the circular dichroism (CD) spectral comparison with the analogous neolignans, eusiderins, whose absolute configurations were determined based on the CD comparison with synthetic analogs[36] as follows. To remove a contribution of a double bond conjugated with the A-ring in **1**, a dihydro-derivative **1a** which has similar chromophoric system to those of the reference compounds was prepared by catalytic hydrogenation over PtO_2. The observed CD spectrum of **1a** ($[\theta]_{226}$ −1800, $[\theta]_{238}$ +4806, $[\theta]_{299}$ −1010) allowed the assignment of 7*S*,8*S* configurations.[36] Consequently, compound **1** was represented by structure **1**.

Compound **2** was isolated as a colorless oil, $[\alpha]_D^{20}$ −16.0° (MeOH). The electrospray ionization (ESI)-MS of **2** showed a pseudomolecular ion peak at *m/z* 422 $[M+NH_4]^+$, which was 14 mass units larger than **1**, and its molecular formula, $C_{21}H_{24}O_8$, was confirmed using HR-ESI-MS. The ^{1}H- and ^{13}C-NMR spectra of **2** were very similar to those of **1**, except for the presence of an extra methoxyl signal [δ_H 3.90 (3H, s), δ_C 54.1] and a magnetically equivalent 2H-singlet (δ_H 6.78) instead of the two *meta*-coupled aromatic signals in **1**. Compound **2** was regarded as the 5-*O*-methyl congener of **1**. The 7*S*,8*S*-configuration of **2** was also evidenced by the similar CD spectrum of its dihydro-derivative **2a** to that of **1a**. Although the racemic mixture of **2** (nitidanin) was reported as a constituent from the bark of *Xanthoxylum nitidum*,[30] this is the first isolation of the 7*S*,8*S* enatiomer from a natural source.

Compound **3** was obtained as a yellowish oil, $[\alpha]_D^{20}$ −5.3° (MeOH). The HR-ESI-MS of **3** had a molecular ion peak at *m/z* 364.1778 $[M+NH_4]^+$, consistent with the molecular formula $C_{19}H_{22}O_6$. The 1D ^{1}H-NMR and ^{1}H–^{1}H COSY spectra of **3** indicated the presence of five aromatic protons [δ_H 7.02 (1H, d, J=2.4 Hz, H-2), 6.89 (1H, d, J=8.4, 2.4 Hz, H-6), 6.80 (1H, d, J=8.4 Hz, H-5), 6.65 (1H, br s, H-2′), and 6.61 (1H, br d, J=1.8 Hz, H-6′)], a hydroxypropyl group [δ_H 3.60 (2H, t, J=6.0 Hz, H-9′), 2.60 (2H, br t, J=7.2 Hz, H-7′), and 1.83 (2H, m, H-8′)], two methines [δ_H 5.53 (1H, d, J=6.0 Hz, H-7), 3.49 (1H, dd, J=12.6, 6.0 Hz, H-8)], a hydroxymethyl [δ_H 3.87 (1H, m, H-9), and 3.79 (1H, dd, J=10.8, 7.2 Hz, H-9)], and a methoxyl group [δ_H 3.86 (3H, s)]. In addition to the methoxyl carbon signal, 18 skeletal carbon resonances appeared in the ^{13}C-NMR spectrum. These spectral features indicated that **3** was a dihydro[*b*]benzofuran-type neolignan formed by two phenylpropanoid units.[37] The methoxyl group was located at C-3, based on the HMBC and NOESY (δ_H 3.86/H-2) correlations (Fig. 2). The *threo* relationship between H-7 and H-8 was inferred from their coupling constant ($J_{7,8}$=6 Hz), which is similar to that reported in the analogs based on X-ray analysis.[38,39] This arrangement was verified by the NOE correlations between H-7 and H-9 and between H-8 and H-2, 6 (Fig. 2). The absolute structures of many dihydrobenzo[*b*]furan-type neolignans have been assigned[21,40—43] on the basis of the CD results of Achenbach *et al.*[44] However, Antus *et al.*[45] re-

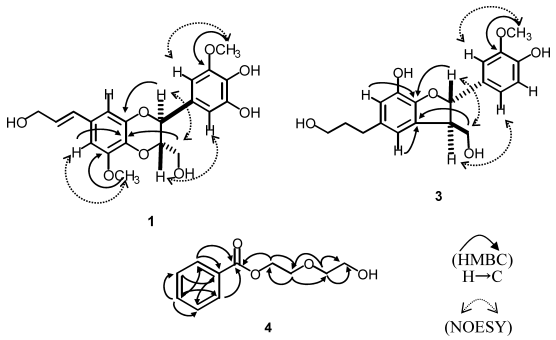

Fig. 2. HMBC and NOESY Correlations for Compounds **1**, **3** and **4**

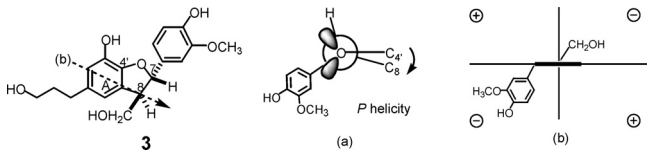

Fig. 3. Projection for ^1L_b (a) and ^1L_a (b: Projection in the Direction of Arrow, Wedge Represents the Plane of the A-Ring) Transitions

cently claimed that several published configurational assignments for those neolignans are incorrect and should be revised based on the correlation between *P*/*M* helicity of the *O*-heterocyclic ring in chiral 7,8-dihydrobenzo[*b*]furan and their ^1L_b band (270—300 nm) CD data. This helicity rule is controlled by the presence of oxygen function at C-5′, which leads to the positive sign of the ^1L_b band CD for the predicted *P* helicity, while the negative sign for the *M* helicity. Examined data for many natural neolignans confirmed the validity of this helicity rule.[45] The CD spectrum of **3** showed a positive Cotton effect at 295 nm ([θ] +643), indicating that the absolute configuration of **3** was the 7*S*,8*R*-configuration. On the other hand, we found that the aromatic quadrant rule for the ^1L_a transition (220—240 nm)[46] is validly applicable to the configurational assignment of a chiral benzylic C-8 position upon examining the neolignans reported in the literature.[45] The 8*R*-configuration in **3** was thus supported by the negative Cotton effect ($[\theta]_{229}$ −1550) for the ^1L_a transition (Fig. 3). Compound **3** was previously reported from *Sambucus nigra* without assigning the absolute configurations at C-7 and C-8.[47] There are also reports of glycosides of **3** from *Juniperus communis*,[48] *Pinus silvestris*,[49] and its enantiomer (cedrusin; $[\alpha]_D$ +4.39°) from *Cedrus deodara*.[50] Accordingly, compound **3** is the first example isolated as the 7*S*,8*R*-form.

Compound **4** was shown to have the molecular formula $C_{11}H_{14}O_4$ by the molecular ion peak at *m*/*z* 211.0964 $[M+H]^+$ in HR-FAB-MS. The ^{1}H-NMR spectrum of **4** (Experimental) displayed a monosubstituted benzene signal (δ_H 8.08—7.52) and four oxymethylene protons (δ_H 4.51, 3.88, 3.73, 3.67, each multiplet). In addition to the ^{13}C-NMR resonances owing to these functionalities, an ester carbonyl carbon was observed at δ_C 168.1 (Experimental). The HMBC correlations (Fig. 2) indicated that compound **4** was a benzoyl ester with a diethylene glycol group. This is also the first isolation from a natural source, although it was previously reported as a synthetic compound.[51]

Experimental

General Optical rotations were measured with a Jasco DIP-4 digital polarimeter. The UV spectra were obtained with a Hitachi U-2000 spectrophotometer, and the CD spectra were run on a Jasco J-720W spectrometer. The ^{1}H- and ^{13}C-NMR data (including HSQC, HMBC, NOESY, and ^{1}H–^{1}H COSY) were measured on a Varian Unity Inova AS600NB instrument operating at 600 and 150 MHz, respectively. The chemical shifts are given in δ (ppm) values relative to those of the solvent [CD_3OD (δ_H 3.35; δ_C 49.0), C_5D_5N (δ_H 7.20; δ_C 123.5)] and tetramethylsilane (TMS). The HR-ESI-MS and ESI-MS were obtained on a Micromass AutoSpec OA-Tof spectrometer (solvent: 50% MeOH containing 0.1% $AcONH_4$; flow rate: 0.02 ml/min), and FAB-MS using 3-nitrobenzyl alcohol as the matrix agent, including high-resolution mass spectra, were performed on a Micromass AutoSpec OA-Tof spectrometer. Normal phase HPLC was conducted on a YMC-Pack SIL A-003 column (4.6 mm i.d.×250 mm; YMC Co., Ltd.) and was developed at room temperature with *n*-hexane/EtOH/formic acid (75 : 24 : 1) as the solvent (flow rate: 1.5 ml/min; detection: UV 254 nm). Reversed-phase HPLC was carried out on a YMC-Pack ODS A-302 column (4.6 mm i.d.×150 mm; YMC Co., Ltd.) and was developed at 40 °C with 10 mM H_3PO_4/10 mM KH_2PO_4/MeCN (4 : 4 : 2, flow rate: 1.0 ml/min). Column chromatography was performed with Toyopearl HW-40 (coarse grade; Tosoh Co.), YMC GEL ODS AQ 120-50S (YMC Co., Ltd.), MCI GEL CHP-20P (Mitsubishi Kasei Co.), and Sephadex LH-20 (Pharmacia Fine Chemicals Co., Ltd.). Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} plates (0.2 mm layer thickness, Merck), and the spots were detected by ultraviolet irradiation (254, 366 nm) and by spraying with 10% H_2SO_4 reagent.

Plant Material Chips of *S. album* L. wood collected in Mysore district of India were used. The wood was officially imported from India under a special treaty between India and Japanese governments to sculpture a Buddhist image in a Japanese temple with a long and distinguished history.

Extraction and Isolation The heartwood of *Santalum album* (1.53 kg) was extracted with MeOH at room temperature. The combined crude MeOH extract (73.1 g) was suspended in 20% MeOH (2 l) and then partitioned with *n*-hexane (3×2 l) and EtOAc (3×2 l), to afford dried *n*-hexane- (16.4 g), EtOAc- (27.1 g), and H_2O-soluble (17.5 g) residues. The fractionation was achieved by monitoring the eluate using normal- and reversed-phase HPLC. Part (7.0 g) of the EtOAc extract was chromatographed over a Toyopearl HW-40 column (coarse grade; 2.2 cm i.d.×65 cm) with H_2O containing increasing amounts of MeOH in a stepwise gradient mode. The 40% MeOH eluate was subjected to column chromatography over a YMC GEL ODS AQ 120-50S column (1.1 cm i.d.×41 cm) with aqueous MeOH, to yield vanillic acid 4-*O*-neohesperidoside (3.6 mg). The 50% MeOH eluate was submitted to a combination of chromatography over Sephadex LH-20 (1.1 cm i.d.×43 cm) (with EtOH), YMC GEL ODS AQ 120-50S (1.1 cm i.d.× 41 cm) (with aqueous MeOH), and preparative HPLC (YMC-Pack ODS A-302, 4.6 mm i.d.×150 mm) with 20% aqueous MeCN to yield vanillic acid (0.8 mg), isovanillic acid (1.0 mg), syringic acid (1.8 mg), compound **4** (12.6 mg, t_R 12.8 min), 7,8-*erythro*-4,9,9′-trihydroxy-3,3′-dimethoxy-8.*O*.4′-neolignan **5** (0.9 mg, t_R 8.7 min), 7,8-*threo*-4,9,9′-trihydroxy-3,3′-dimethoxy-8.*O*.4′-neolignan **6** (4.8 mg, t_R 7.9 min), *ω*-hydroxypropioguaiacone (3.2 mg, t_R 3.4 min), 3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (5.0 mg, t_R 4.9 min), and *C*-veratroylglycol (1.9 mg, t_R 5.2 min). Similarly, the 60% MeOH eluate was chromatographed over Sephadex LH-20 (1.1 cm i.d.×43 cm) and YMC GEL ODS AQ 120-50S (1.1 cm i.d.×41 cm), followed by preparative HPLC (YMC-Pack ODS A-302, 4.6 mm i.d.×150 mm) using 20% aqueous MeCN to afford pure compounds **1** (12.9 mg, t_R 9.8 min), **2** (3.7 mg, t_R 17.4 min), and **3** (2.7 mg, t_R 5.8 min); dihydrodehydrodiconiferyl alcohol (**7**) (4.7 mg, t_R 15.4 min); (7*S*,8*S*)-3-methoxy-3′,7-epoxy-8,4′-oxyneoligna-4,9,9′-triol (**8**) (8.2 mg, t_R 20.4 min); (7′*S*,8*R*,8′*R*)-lynoniresinol (**9**) (10.4 mg, t_R 5.4 min); 2,3-bis[(4-hydroxy-3,5-dimethoxyphenyl)-methyl]-1,4-butanediol (**10**) (1.3 mg, t_R 6.0 min); and (−)-secoisolariciresinol (**11**) (7.0 mg, t_R 12.84 min). The eluate with 70% MeOH from the Toyopearl HW-40 (2.2 cm i.d.×65 cm) was further fractionated by column chromatography on Sephadex LH-20 (1.1 cm i.d.×43 cm) and YMC GEL ODS AQ 120-50S (1.1 cm i.d.×41 cm) with aqueous MeOH to afford a mixture of compounds **1**, **2**, **7**, and **8**, each of which was finally purified by preparative HPLC (YMC-Pack SIL A-003, 4.6 mm i.d.×250 mm) developed with *n*-hexane/EtOH (75 : 25), to yield additional quantities of compounds **1** (5.8 mg), **2** (2.7 mg), **7** (10.7 mg), and **8** (19.1 mg).

Compound (**1**): Colorless oil, $[\alpha]_D^{20}$ +8.0° (*c*=1.0, MeOH). UV λ_{max} MeOH nm (log ε): 223 (2.43), 273 (2.00). CD (MeOH; [θ]) nm 224 (−2437), 237 (+2480), 282 (+2549). FAB-MS *m*/*z* 391 $[M+H]^+$. HR-FAB-MS *m*/*z* 391.1379 $[M+H]^+$ (Calcd for $C_{20}H_{22}O_8$+H, 391.1392). ^{1}H- and ^{13}C-NMR data: Table 1.

7*S*,8*S*-Nitidanin (**2**): Colorless oil, $[\alpha]_D^{20}$ −16.0° (*c*=0.5, MeOH). UV λ_{max} MeOH nm (log ε): 224 (2.45), 273 (1.98). CD (MeOH; [θ]) nm 225 (−1312), 236 (+1646), 288 (+1684). ^{1}H-NMR (CD_3OD): δ 6.78 (2H, s, H-2, 6), 6.74 (1H, d, *J*=1.8 Hz, H-2′), 6.69 (1H, d, *J*=1.8 Hz, H-6′), 6.53 (1H, br d, *J*=15.6 Hz, H-7′), 6.28 (1H, dt, *J*=15.6, 5.4 Hz, H-8′), 4.93 (1H, d, *J*=8.4 Hz, H-7), 4.24 (2H, dd, *J*=5.4, 1.8 Hz, H-9′), 4.08 (1H, ddd, *J*=8.4, 4.8, 3.0 Hz, H-8), 3.93 (3H, s, MeO-3′), 3.90 (6H, s, MeO-3, 5), 3.77 (1H, dd, *J*=12.6, 3.0 Hz, H-9), 3.55 (1H, dd, *J*=12.6, 4.8 Hz, H-9); ^{13}C-NMR (CD_3OD) δ 147.5 (C-1), 146.7 (C-3, 5), 143.1 (C-5′), 134.6 (C-4), 131.6 (C-4′), 128.9 (C-8′), 128.8 (C-1), 128.4 (C-1′), 125.9 (C-7′), 106.5 (C-6′), 103.3 (C-2,6), 101.3 (C-2′), 77.4 (C-8), 75.2 (C-7), 61.0 (C-9′), 59.4 (C-9), 54.1 (C-3, 5 MeO), 54.0 (C-3′ MeO). ESI-MS *m*/*z* 422 $[M+NH_4]^+$. HR-ESI-MS *m*/*z* 422.1827 $[M+NH_4]^+$ (Calcd for $C_{21}H_{24}O_8$+NH_4, 422.1815).

Hydrogenation of 1 and 2 To solution of **1** (6.0 mg) [or **2** (2.0 mg)] in EtOH were added PtO_2 (**1**, 6.0 mg; **2**, 2.0 mg). A mixture was subjected to catalytic hydrogenation for 2 h with stirring under monitoring the reaction

process by reversed-phase HPLC (20% aqueous MeCN). The reaction mixture was filtered and concentrated to give the pure dihydro-derivatives, **1a** (t_R 10.2 min; 5.9 mg) and **2b** (t_R 18.5 min; 1.8 mg).

1a: Colorless oil, $[\alpha]_D^{20}$ −6.3° (c=1.0, MeOH); UV λ_{max} MeOH nm (log ε): 224 (2.40), 271 (1.95); CD (MeOH; [θ]) nm 226 (−1800), 238 (+4806), 299 (−1010); FAB-MS m/z 393 $[M+H]^+$. ^{1}H-NMR (CD_3OD) δ 6.62 (1H, d, J=1.8 Hz, H-2′), 6.59 (1H, d, J=1.8 Hz, H-6′), 6.51 (1H, d, J=1.8 Hz, H-2), 6.41 (1H, d, J=1.8 Hz, H-6), 4.82 (1H, d, J=7.8 Hz, H-7), 3.99 (1H, ddd, J=7.8, 4.8, 2.4 Hz, H-8), 3.90 (3H, s, MeO-3′), 3.89 (3H, s, MeO-3), 3.74 (1H, dd, J=12.6, 2.4 Hz, H-9), 3.60 (2H, t, J=6.0 Hz, H-9′), 3.57 (1H, dd, J=12.6, 4.8 Hz, H-9), 2.62 (2H, br t, J=7.8 Hz, H-7′), 1.85 (2H, m, H-8′).

2a: Colorless oil, $[\alpha]_D^{20}$ −9.3° (c=0.5, MeOH); UV λ_{max} MeOH nm (log ε): 224 (2.38), 270 (1.91); CD (MeOH; [θ]) nm 223 (−6498), 235 (+11478), 291 (−1885); FAB-MS m/z 407 $[M+H]^+$. ^{1}H-NMR (CD_3OD) δ 6.76 (2H, s, H-2′,6′), 6.52 (1H, d, J=1.8 Hz, H-2′), 6.47 (1H, d, J=1.8 Hz, H-6′), 4.93 (1H, d, J=7.8 Hz, H-7), 4.04 (1H, ddd, J=7.8, 4.8, 2.4 Hz, H-8), 3.90 (6H, s, MeO-3), 3.89 (3H, s, MeO-3′), 3.75 (1H, dd, J=12.6, 2.4 Hz, H-9), 3.60 (2H, t, J=6.6 Hz, H-9′), 3.54 (1H, dd, J=12.6, 4.8 Hz, H-9), 2.63 (2H, br t, J=7.8 Hz, H-7′), 1.85 (2H, m, H-8′).

(7*S*,8*R*)-Dihydro-3′-hydroxy-8-hydroxy-methyl-7-(4-hydroxy-3-methoxyphenyl)-1′-benzofuranpropanol (**3**): Yellowish oil, $[\alpha]_D^{20}$ −5.3° (c=1.0, MeOH). UV λ_{max} MeOH nm (log ε): 212 (3.10), 257 (1.58), 282 (1.97). CD (MeOH; [θ]) nm 229 (−1550), 295 (+643). ^{1}H-NMR (CD_3OD): δ 7.02 (1H, d, J=2.4 Hz, H-2), 6.89 (1H, dd, J=8.4, 2.4 Hz, H-6), 6.80 (1H, d, J=8.4 Hz, H-5), 6.65 (1H, br s, H-2′), 6.61 (1H, br d, J=1.8 Hz, H-6′), 5.53 (1H, d, J=6.0 Hz, H-7), 3.87 (1H, m, H-9), 3.86 (3H, s, MeO-3), 3.79 (1H, dd, J=10.8, 7.2 Hz, H-9), 3.60 (2H, t, J=6.0 Hz, H-9′), 3.49 (1H, dd, J=12.6, 6.0 Hz, H-8), 2.60 (2H, br t, J=7.2 Hz, H-7′), 1.83 (2H, m, H-8′). ^{13}C-NMR (CD_3OD) δ 149.1 (C-3), 147.4 (C-4), 146.5 (C-4′), 141.9 (C-3′), 136.7 (C-1′), 135.1 (C-5′), 129.8 (C-1), 119.7 (C-6), 117.0 (C-6′), 116.7 (C-2′), 116.1 (C-5), 110.5 (C-2), 88.7 (C-7), 65.2 (C-9), 62.3 (C-9′), 56.4 (C-3 MeO), 55.8 (C-8), 35.8 (C-8′), 32.7 (C-7′). ESI-MS m/z 364 $[M+NH_4]^+$. HR-ESI-MS m/z 364.1778 $[M+NH_4]^+$ (Calcd for $C_{19}H_{22}O_6+NH_4$, 364.1760).

Diethylene Glycol Monobenzoate (**4**): Colorless oil, UV λ_{max} MeOH nm (log ε): 210 (1.60), 228 (2.30). ^{1}H-NMR (CD_3OD): δ 8.08 (2H, m, H-2, 6), 7.65 (1H, m, H-4), 7.52 (2H, m, H-3, 5), 4.51 (2H, m, H-8), 3.88 (2H, m, H-9), 3.73 (2H, m, H-11), 3.67 (2H, m, H-10). ^{13}C-NMR (CD_3OD): δ 168.1 (C-7), 134.3 (C-4), 131.4 (C-1), 130.6 (C-2, 6), 129.6 (C-3, 5), 73.8 (C-10), 70.2 (C-9), 65.4 (C-8), 62.2 (C-11). FAB-MS m/z 211 $[M+H]^+$. HR-FAB-MS m/z 211.0964 $[M+H]^+$ (Calcd for $C_{11}H_{14}O_4+H$, 211.0970).

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