Structure Elucidation of Two Secoiridoid Glucosides from *Jasminum officinale* L. var. *grandiflorum* (L.) KOBUSKI

Takao TANAHASHI,*[,a] Takeshi SAKAI,[a] Yukiko TAKENAKA,[a] Naotaka NAGAKURA,[a] and Cheng-Chang CHEN[b]

Kobe Pharmaceutical University,[a] 4–19–1, Motoyamakita-machi, Higashinada-ku, Kobe 658–8558, Japan and National Kaoshiung Normal University,[b] Kaoshiung, Taiwan, Republic of China.

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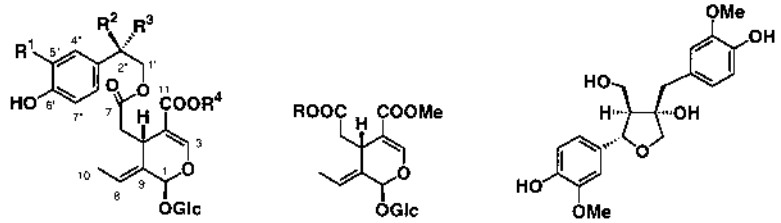
Phytochemical investigation of the dried leaves of *Jasminum officinale* var. *grandiflorum* has led to the isolation of two new secoiridoid glucosides, (2″*R*)-2″-methoxyoleuropein and (2″*S*)-2″-methoxyoleuropein, together with four known secoiridoid glucosides, oleuropein, ligstroside, demethyloleuropein and oleoside dimethyl ester, a lignan, (−)-olivil and *p*-hydroxyphenethyl alcohol. The structures of the new compounds were elucidated from chemical and spectroscopic evidence.

Key words *Jasminum officinale* var. *grandiflorum*; Oleaceae; secoiridoid glucoside; (2″*R*)-2″-methoxyoleuropein; (2″*S*)-2″-methoxyoleuropein; 2-(3,4-dihydroxyphenyl)-2-methoxyethanol

Jasminum officinale L. var. *grandiflorum* (L.) KOBUSKI is an oleaceous plant which is widely cultivated for its fragrant flowers and its leaves are used as a diuretic in Indian folk medicine. In a recent screening of the plant for angiotensin-converting enzyme (ACE) inhibitory activity, oleacein, which could be artificially formed from oleuropein (**1**), was isolated as an active compound along with its genuine glucoside **1**.[1)] In the course of our chemical studies on the secoiridoid glucosides from the family Oleaceae,[2)] we have investigated the constituents of the leaves and twigs of *J. officinale* var. *grandiflorum* and isolated two new secoiridoid glucosides, (2″*R*)-2″-methoxyoleuropein (**2**) and (2″*S*)-2″-methoxyoleuropein (**3**) as well as six known compounds, oleuropein,[3)] ligstroside (**4**),[3)] demethyloleuropein (**5**),[4)] oleoside dimethyl ester (**6**),[3)] (−)-olivil (**7**)[5)] and *p*-hydroxyphenethyl alcohol. Compounds **4**—**7** were isolated for the first time from this species. This paper deals with the isolation and structure elucidation of the novel glucosides.

Compound **2** was isolated as a colorless amorphous powder, $[\alpha]_D$ −172° (MeOH). The high resolution secondary ion mass spectrum (HR-SI-MS) of **2** exhibited a strong $(M-H)^-$ at *m*/*z* 569.1889 indicating a molecular formula of $C_{26}H_{34}O_{14}$. It showed UV maxima at 233 and 281 nm and IR bands at 3422 (OH), 1732 (ester), 1705 and 1630 (α,β-unsaturated ester) and 1522 (aromatic ring) cm^{-1}. Its ^{1}H-NMR spectra (Table 1) showed signals due to an oleoside 11-methyl ester (**8**) moiety [H-3 at δ 7.52, H-8 at δ 6.09 (qd), H_3-10 at δ 1.70 (dd), and a carbomethoxyl group at δ 3.72] as well as an ABX spin system at 6.65, 6.756 and 6.758, indicating that **2** was structurally similar to **1**. However, there were marked differences in the spectra with the aliphatic protons of **2** appearing as an ABX spin system at δ 4.04, 4.10 and 4.27, instead of an ABX_2 system of a $COOCH_2CH_2Ar$ moiety as in **1**. The ^{13}C-NMR signals of **2** (Table 1) were superimposable on those of **1**, except for the presence of an additional methoxyl signal and chemical shifts of C-1″ and C-2″. ^{1}H-Detected heteronuclear multiple-bond connectivity (HMBC) experiments with **2** showed significant correlations between H_2-1″ (δ 4.04 and 4.10) and C-7 (δ 173.0) and between the methoxyl group (δ 3.21) and C-2″ (δ 82.6). These findings indicated that **2** had a 2-(3,4-dihydroxyphenyl)-2-methoxyethanol unit instead of a 2-(3,4-dihydroxyphenyl)-ethanol unit, as in **1**. This was confirmed by the fact that methylation of **2** with CH_2N_2–Et_2O and subsequent methanolysis gave 2-methoxy-2-(3,4-dimethoxyphenyl)ethanol (**9**). Thus, the structure of **2** was established as 2″-methoxyoleuropein except for the absolute configuration of C-2″.

Compound **3** was isomeric with **2**, and showed UV, IR, MS and NMR spectral features closely similar to those of **2**. A significant difference between the two compounds was observed only in the signals of H_2-1″ in the ^{1}H-NMR spectra, suggesting **3** to be a C-2″ epimer of **2**. This assumption was supported by methylation of **3** followed by methanolysis to compound **10**, whose ^{1}H-NMR data were identical to those



1 : R^1 = OH, R^2 = R^3 = H, R^4 = Me
2 : R^1 = OH, R^2 = OMe, R^3 = H, R^4 = Me
3 : R^1 = OH, R^2 = H, R^3 = OMe, R^4 = Me
4 : R^1 = R^2 = R^3 = H, R^4 = Me
5 : R^1 = OH, R^2 = R^3 = R^4 = H

6 : R = Me
8 : R = H

7

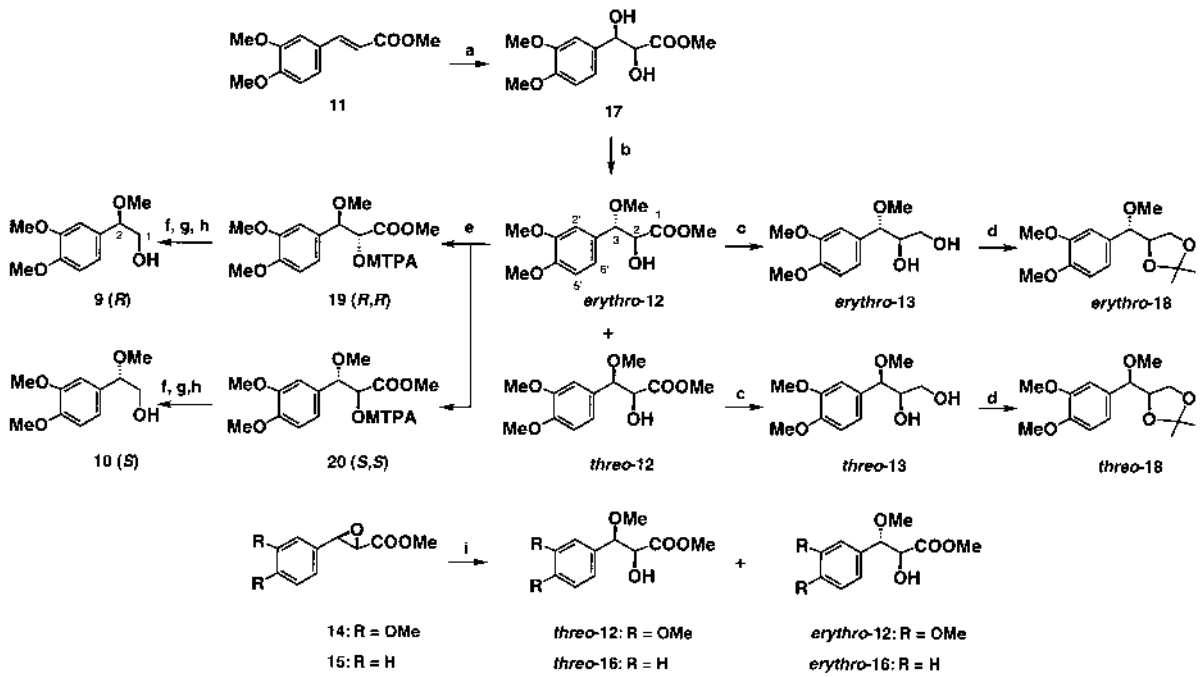
Chart 1

* To whom correspondence should be addressed.

Table 1. ^{1}H- and ^{13}C-NMR Spectral Data of Compounds **2** and **3** in CD_3OD

C	**2**		**3**	
	δ_H	δ_C	δ_H	δ_C
1	5.93 br s	95.2	5.93 br s	95.3
3	7.52 s	155.2	7.53 s	155.2
4	—	109.4	—	109.4
5	3.99 dd (9.5, 5.0)	31.9	3.98 dd (9.0, 5.0)	31.8
6	2.48 dd (14.5, 9.5)	41.1	2.50 dd (14.5, 9.0)	41.1
	2.74 dd (14.5, 5.0)		2.72 dd (14.5, 5.0)	
7	—	173.0	—	173.0
8	6.09 qd (7.0, 1.0)	124.9	6.10 qd (7.0, 1.0)	125.0
9	—	130.55[a)]	—	130.6[c)]
10	1.70 dd (7.0, 1.5)	13.6	1.70 dd (7.0, 1.5)	13.6
11	—	168.7	—	168.7
11-OMe	3.72 s	51.9	3.72 s	51.9
1′	4.81 d (8.0)	100.9	4.80 d (8.0)	101.0
2′	3.3—3.4 m	74.8	3.3—3.4 m	74.8
3′		78.4		78.5
4′		71.5		71.5
5′		78.0		78.0
6′	3.68 dd (12.0, 5.5)	62.8	3.67 dd (12.0, 6.0)	62.8
	3.89 dd (12.0, 1.5)		3.89 dd (12.0, 1.5)	
1″	4.04 dd (11.5, 8.0)	69.2	3.98 dd (11.5, 4.0)	69.1
	4.10 dd (11.5, 4.0)		4.18 dd (11.5, 8.0)	
2″	4.27 dd (8.0, 4.0)	82.6	4.28 dd (8.0, 4.0)	82.5
3″	—	130.60[a)]		130.7[c)]
4″	6.756 d (2.0)	115.0	6.759 d (2.0)	115.0
5″	—	146.62[b)]	—	146.63[d)]
6″	—	146.64[b)]	—	146.66[d)]
7″	6.758 d (8.0)	116.4	6.763 d (8.0)	116.4
8″	6.65 dd (8.0, 2.0)	119.9	6.65 dd (8.0, 2.0)	119.9
2″-OMe	3.21 s	56.9	3.22 s	56.9

Values in parentheses are coupling constants in Hz. *a—d*) Assignments may be interchangeable.



a: 1) OsO_4, Et_2O, Py, 2) $NaHSO_3$, Py, H_2O; b: conc. HCl, MeOH, reflux; c: $LiAlH_4$, Et_2O, reflux; d: 2,2-dimethoxypropane, acetone, *p*-TsOH; e: (*R*)-MTPA, DCC, 4-DMAP, CH_2Cl_2; f: $LiAlH_4$, THF; g: $NaIO_4$, EtOH; h: $NaBH_4$, EtOH, 0 °C; i: BF_3–Et_2O, MeOH, −30 °C.
Compounds **12**—**18** are racemates. Structures of **9**, **10**, **19** and **20** represent the absolute configurations.

Chart 2

of **9**.

The 2-(3,4-dihydroxyphenyl)-2-methoxyethanol unit has so far been found in glucosides such as campneoside II[6] and syringopicroside-C.[7] However, the absolute stereochemistry of the unit has not been determined for these compounds. This situation prompted us to establish the absolute configuration of C-2″ in glucosides **2** and **3** by comparison of compounds **9** and **10** with the authentic (*R*)- and (*S*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanols. These compounds could be chemically prepared from methyl 3,4-dimethoxycinnamate (**11**) *via* methyl 2-hydroxy-3-methoxy-3-(3,4-dimethoxyphenyl)propionates (**12**) and then 3-methoxy-3-(3,4-dimethoxyphenyl)-1,2-propanediols (**13**). An initial attempt to prepare *erythro*-**12** from **11** through the stereospecific ring-opening reaction of oxirane **14**[8] with BF_3–Et_2O in dry MeOH was not successful. Although the oxirane ring of **15**[8] was opened to give mainly *erythro*-**16** (*erythro* : *threo* = 6 : 1) as expected,[9] the reaction of **14** gave a mixture of *erythro*-**12** and *threo*-**12** in a ratio of 1 : 3. Moreover, as methyl 3,4-dimethoxycinnamate (**11**) resists epoxidation with a peracid,[8] an alternative practical synthetic route was developed as follows.

Methyl 3,4-dimethoxycinnamate (**11**) was treated with osmium tetroxide (OsO_4) in pyridine–Et_2O, giving a diol, **17**. Treatment of **17** with conc.HCl in MeOH afforded two methyl ethers, *erythro*-**12** and *threo*-**12**, in a ratio of 17 : 19. The stereochemical relationship of C-2 and C-3 of the two isomers was determined from the following observations: i) when the ^{1}H-NMR data were compared, there were characteristic differences between the *erythro*- and *threo*-isomers in the chemical shift of H-2 (*erythro*-**16**: δ 4.50; *threo*-**16**: δ 4.27; *erythro*-**12**: δ 4.50; *threo*-**12**: δ 4.26) and the coupling constant between H-2 and H-3 (*erythro*-**16**: 4.2 Hz; *threo*-**16**: 3.0 Hz; *erythro*-**12**: 4.2 Hz; *threo*-**12**: 3.3 Hz); ii) the signals of two acetonide methyls in *erythro*-**18**, which was prepared from *erythro*-**12** through reduction with lithium aluminum hydride ($LiAlH_4$) and subsequent treatment of the resulting *erythro*-**13** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid, resonated at δ 1.31 and 1.41, whereas those of *threo*-**18**, derived from *threo*-**12** *via* *threo*-**13**, appeared at δ 1.39 and 1.45.[10]

Next, *erythro*-**12** was esterified with (*R*)-2-methoxy-2-trifluoromethylphenylacetic acid ((*R*)-MTPA) and the resulting esters, **19** and **20**, were separated by preparative HPLC. The absolute configuration of C-2 of each compound was determined by a modification of Mosher's method.[11] Differences in the chemical shifts of the corresponding proton signals between **19** and **20** indicated the absolute configuration of C-2 of **20** to be *S* and so **19** is the (2*R*,3*R*)-isomer, while, on the other hand, **20** is the (2*S*,3*S*)-isomer (Fig. 1). Compound **19** was reduced with $LiAlH_4$ to afford (2*S*,3*R*)-3-methoxy-3-(3,4-dimethoxyphenyl)-1,2-propanediol, which was treated with sodium periodate ($NaIO_4$) and subsequently reduced with sodium borohydride ($NaBH_4$) to yield (*R*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanol ($[\alpha]_D$ −91°). Compound **20** was subjected to a series of the similar reactions as for **19** to give (*S*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanol ($[\alpha]_D$ +92°). The absolute configuration at C-2 of (*R*)- and (*S*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanols was supported by agreement of the sign of their specific optical rotations with those of similar compounds, (*R*)-2-methoxy-2-phenylethanol ($[\alpha]_D$ −107°) and (*S*)-2-methoxy-2-phenylethanol ($[\alpha]_D$ +117°), respectively.[12]

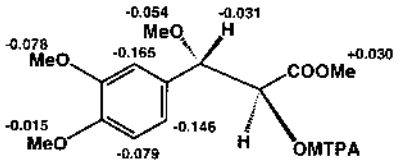


Fig. 1. $\Delta\delta$ Values Obtained from the MTPA Esters, **19** and **20**

Chiral HPLC analysis showed that **9** and **10** derived from natural products were identical with synthetic (*R*)- and (*S*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanols, respectively. These results led us to conclude that compound **2** is (2″*R*)-2″-methoxyoleuropein, while **3** is (2″*S*)-2″-methoxyoleuropein. These glucosides represent the first instance of glucosides with an *O*-function at C-2″ among the oleuropein-type secoiridoid glucosides. No interconversion of the two glucosides **2** and **3** was observed during the separation procedures. However, we could not exclude the possibility that the isolated compounds are artifacts formed from an unknown 2″-hydroxyoleuropein by the same mechanism as previously proposed for related compounds.[13]

Experimental

Melting points were measured on a Yanagimoto microapparatus and are uncorrect. The UV spectra were recorded on a Shimadzu UV-240 spectrophotometer and the IR spectra on a Shimadzu FTIR-8200 infrared spectrophotometer. The optical rotations were measured on a Jasco DIP-370 digital polarimeter. SI-MS, electron impact (EI)-MS, chemical ionization (CI)-MS, HR-SI-MS and HR-EI-MS were obtained with a Hitachi M-4100 mass spectrometer. Glycerol or 3-NOBA was used as the matrix for SI-MS. The NMR experiments were performed with Varian VXR-500 and Varian Gemini-300 spectrometers, with tetramethylsilane as internal standard. HPLC was performed using a Waters system (510 HPLC Pump, 486 Tunable Absorbance Detector). Thin-layer chromatography was performed on precoated Kieselgel 60F_{254} plates (Merck) and spots were visualized under UV light.

Isolation of Glucosides The plant material was collected by the Taiwan Forestry Research Institute, Taipei, Taiwan. A voucher specimen (KPFY-971) has been deposited in the laboratory of Kobe Pharmaceutical University. The dried leaves and stems of *J. officinale* var. *grandiflorum* (115.2 g) were extracted with hot MeOH. The MeOH extract (13.4 g) was suspended in H_2O and successively partitioned with $CHCl_3$ and *n*-BuOH. The *n*-BuOH-soluble fraction was concentrated and the resulting residue (2.0 g) was chromatographed on a Wakogel LP-40C_{18} (Wako Pure Chemical Industries Ltd., Osaka, Japan) column. Elution with MeOH–H_2O mixtures of increasing MeOH content (0—90%) gave five fractions I (H_2O eluate, 66 mg), II (3—10% MeOH eluate, 105 mg), III (10—20% MeOH eluate, 161 mg), IV (25—35% MeOH eluate, 262 mg) and V (35—40% MeOH eluate, 119 mg). Fraction I was further purified by preparative HPLC (μBondasphere 5 μC18—100 Å; MeOH–H_2O, 3 : 17), giving *p*-hydroxyphenethyl alcohol (4.3 mg). The following fractions were also purified by a combination of preparative HPLC (μBondasphere 5 μC18—100 Å; MeOH–H_2O, 1 : 3 or 27 : 73 or MeCN–H_2O, 11 : 39, 1 : 4, 1 : 3 or 3 : 7). Fraction II yielded **6** (5.7 mg) and **7** (6.7 mg); fraction III: **5** (25.5 mg), **6** (3.9 mg) and **7** (5.1 mg); fraction IV: **1** (36.1 mg), **2** (13.1 mg) and **3** (11.0 mg); and fraction V: **4** (10.5 mg).

(2″*R*)-2″-Methoxyoleuropein (2) A white amorphous powder, $[\alpha]_D^{24}$ −172° (c = 1.01, MeOH). UV λ_{max}^{MeOH} nm (log ε): 233 (4.22), 281 (3.50). IR (KBr) cm^{-1}: 3422, 1732, 1705, 1630, 1522, 1078. ^{1}H- and ^{13}C-NMR: Table 1. Significant HMBC correlations: H-1→C-1′, H-3→C-11, H_2-6→C-7, 11-OMe→C-11, H-1′→C-1, H_2-1″→C-7, H-1″ (δ 4.04)→C-2″, H-2″→C-1″, H-2″→C-3″, 2″-OMe→C-2″, H-4″→C-2″. HR negative-mode SI-MS *m/z*: Calcd for $C_{26}H_{33}O_{14}$: 569.1871(M−H)$^-$. Found: 569.1889.

(2″*S*)-2″-Methoxyoleuropein (3) A white amorphous powder, $[\alpha]_D^{25}$ −121° (c = 0.98, MeOH). UV λ_{max}^{MeOH} nm (log ε): 232 (4.15), 281 (3.40). IR (KBr) cm^{-1}: 3393, 1736, 1707, 1630, 1522, 1076. ^{1}H- and ^{13}C-NMR: Table 1. Significant HMBC correlations: H-1→C-1′, H-3→C-11, H_2-6→C-7, 11-

OMe→C-11, H-1′→C-1, H_2-1″→C-7, H-1″ (δ 4.18)→C-2″, H-2″→C-1″, H-2″→C-3″, 2″-OMe→C-2″, H-4″→C-2″. HR negative-mode SI-MS Calcd for $C_{26}H_{33}O_{14}$: 569.1871 $(M-H)^-$. Found: 569.1879.

Methylation of 2 and 3 Followed by the Zemplen Reaction To a solution of **2** (1 mg) in MeOH (1 ml) was added CH_2N_2–Et_2O until the solution showed a persistent yellow color. The reaction mixture was concentrated and dried *in vacuo*, then the residue was dissolved in dry MeOH (1 ml) and 0.1 M NaOMe (1 ml). The solution was stirred at room temperature for 1 h. After neutralization with Amberlite IR-120 (H^+-form), the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated to give **9**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.30 (3H, s, 2-OMe), 3.60 (1H, dd, J=11.6, 4.0 Hz, H-1), 3.69 (1H, dd, J=11.6, 8.0 Hz, H-1), 3.88 (3H, s, 3′- or 4′-OMe), 3.90 (3H, s, 4′- or 3′-OMe), 4.25 (1H, dd, J=8.0, 4.0 Hz, H-2), 6.82—6.88 (3H, m, H-2′, 5′, 6′). EI-MS m/z: 212 (M^+).

Compound **3** (1 mg) was treated in the same way as described above to give **10**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.30 (3H, s, 2-OMe), 3.60 (1H, dd, J=11.5, 4.0 Hz, H-1), 3.69 (1H, dd, J=11.5, 8.0 Hz, H-1), 3.88 (3H, s, 3′- or 4′-OMe), 3.89 (3H, s, 4′- or 3′-OMe), 4.25 (1H, dd, J=8.0, 4.0 Hz, H-2), 6.82—6.90 (3H, m, H-2′, 5′, 6′). EI-MS m/z: 212 (M^+).

Treatment of 14 and 15 with BF_3–Et_2O in MeOH BF_3–Et_2O (3 μl) was added to a stirred solution of oxirane **14** (13.6 mg) in dry MeOH (1 ml) at −30 °C, and the resulting solution was then stirred for 30 min at the same temperature. The mixture was diluted with Et_2O and washed successively with 5% aqueous $NaHCO_3$ and H_2O. The dried Et_2O layer was concentrated *in vacuo* and the residue (13.8 mg) was purified by preparative TLC (Et_2O–*n*-hexane, 2 : 3) to give a mixture (11.6 mg) of *erythro*-**12** and *threo*-**12** (*erythro* : *threo* = 1 : 3).

To a solution of **15** (45.3 mg) in dry MeOH (1 ml) was added BF_3–Et_2O (100 μl) at −30 °C with stirring, and stirring was continued for 2 h at the same temperature. The mixture was worked-up in the same way as described above and purified by preparative TLC (Et_2O–*n*-hexane, 4 : 1) to give *erythro*-**16** (34.3 mg) and *threo*-**16** (5.4 mg). *erythro*-**16**: Colorless crystals, mp 65—66 °C (AcOEt–*n*-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.90 (1H, d, J=7.0 Hz, 2-OH), 3.33 (3H, s, 3-OMe), 3.69 (3H, s, COOMe), 4.50 (1H, dd, J=7.0, 4.2 Hz, H-2), 4.53 (1H, d, J=4.2 Hz, H-3), 7.25—7.40 (5H, m, H-2′, 3′, 4′, 5′, 6′). CI-MS m/z: 211 $(M+H)^+$. *threo*-**16**: Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.95 (1H, d, J=7.0 Hz, 2-OH), 3.29 (3H, s, 3-OMe), 3.80 (3H, s, COOMe), 4.27 (1H, dd, J=7.0, 3.0 Hz, H-2), 4.55 (1H, d, J=3.0 Hz, H-3), 7.30—7.45 (5H, m, H-2′, 3′, 4′, 5′, 6′). CI-MS m/z: 211 $(M+H)^+$.

OsO_4 Oxidation of 11 A mixture of OsO_4 (580 mg), pyridine (0.5 ml) and dry Et_2O (1 ml) was added dropwise to a stirred solution of **11** (500 mg) in dry Et_2O (10 ml). Stirring was continued at room temperature for 29 h, then a mixture of $NaHSO_3$ (1.2 g), pyridine (10 ml) and H_2O (15 ml) was added to the reaction mixture. The whole was stirred for a further 1 h and then the mixture was concentrated *in vacuo*. To the residue was added dil. HCl followed by extraction with $CHCl_3$. The washed and dried organic layer was concentrated *in vacuo* and the resulting residue (631 mg) was chromatographed on silica gel with $CHCl_3$ to give **17** (536 mg, 94%) as colorless crystals, mp 84—85 °C (AcOEt–*n*-hexane). UV λ_{max}^{MeOH} nm (log ε): 231 (3.93), 278 (3.43), 283 sh (3.38). IR (KBr) cm^{-1}: 3485, 3425, 1751, 1516, 1271. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.71 (1H, d, J=6.6 Hz, 3-OH), 3.11 (1H, d, J=6.0 Hz, 2-OH), 3.82 (3H, s, COOMe), 3.88 (3H, s, 3′- or 4′-OMe), 3.89 (3H, s, 4′- or 3′-OMe), 4.36 (1H, dd, J=6.0, 3.0 Hz, H-2), 4.96 (1H, dd, J=6.6, 3.0 Hz, H-3), 6.86 (1H, d, J=8.1 Hz, H-5′), 6.94 (1H, dd, J=8.1, 1.9 Hz, H-6′), 6.97 (1H, d, J=1.9 Hz, H-2′). EI-MS m/z: 256 (M^+).

Methanolysis of 17 A solution of **17** (250 mg) in MeOH (30 ml) and conc. HCl (3 ml) was heated under reflux for 90 min. After neutralization with 5% aqueous $NaHCO_3$, the reaction mixture was concentrated *in vacuo*, diluted with H_2O and extracted with $CHCl_3$. The washed and dried organic layer was concentrated *in vacuo*. The residue (252 mg) was purified by a combination of column chromatography on silica gel and preparative HPLC (μBondasphere 5 μC18—100 Å; MeOH–H_2O, 3 : 7) to yield *erythro*-**12** (91 mg, 34%) and *threo*-**12** (101 mg, 38%). *erythro*-**12**: Colorless needles, mp 121—122 °C (AcOEt–*n*-hexane). UV λ_{max}^{MeOH} nm (log ε): 232 (3.94), 278 (3.42), 284 sh (3.36). IR (KBr) cm^{-1}: 3362, 1713, 1520. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.73 (1H, d, J=7.0 Hz, 2-OH), 3.32 (3H, s, 3-OMe), 3.72 (3H, s, COOMe), 3.88 (6H, s, 3′, 4′-OMe), 4.45 (1H, d, J=4.2 Hz, H-3), 4.50 (1H, dd, J=7.0, 4.2 Hz, H-2), 6.80 (1H, dd, J=8.0, 1.8 Hz, H-6′), 6.85 (1H, d, J=8.0 Hz, H-5′), 6.88 (1H, d, J=1.8 Hz, H-2′). HR-EI-MS Calcd for $C_{13}H_{18}O_6$: 270.1104 (M^+). Found: 270.1081. *threo*-**12**: Colorless crystals, mp 89—90 °C (AcOEt–*n*-hexane). UV λ_{max}^{MeOH} nm (log ε): 232 (4.00), 278 (3.51), 284 sh (3.45). IR (KBr) cm^{-1}: 3493, 1734, 1514. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.95 (1H, d, J=7.0 Hz, 2-OH), 3.28 (3H, s, 3-OMe), 3.80 (3H, s, COOMe), 3.89 (3H, s, 3′- or 4′-OMe), 3.90 (3H, s, 4′- or 3′-OMe), 4.26 (1H, dd, J=7.0, 3.3 Hz, H-2), 4.49 (1H, d, J=3.3 Hz, H-3), 6.86 (1H, d, J=8.0 Hz, H-5′), 6.90 (1H, dd, J=8.0, 1.6 Hz, H-6′), 6.93 (1H, d, J=1.6 Hz, H-2′). HR-EI-MS Calcd for $C_{13}H_{18}O_6$: 270.1104 (M^+). Found: 270.1084.

Reduction of *erythro*-12 and *threo*-12 with $LiAlH_4$ To a soluton of *erythro*-**12** (30 mg) in dry Et_2O (5 ml) was added portionwise $LiAlH_4$ (12 mg) and the mixture was stirred under reflux for 50 min. After addition of Et_2O containing H_2O and then 10% aqueous H_2SO_4, the reaction mixture was extracted with AcOEt. The washed and dried organic layer was concentrated *in vacuo*. The resulting residue was purified by preparative TLC ($CHCl_3$–MeOH, 95 : 5) to afford *erythro*-**13** (12 mg, 45%) as a colorless oil. IR (KBr) cm^{-1}: 3406, 1516, 1263, 1028. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.27 (3H, s, 3-OMe), 3.68—3.78 (3H, m, H_2-1, H-2), 3.89 (3H, s, 3′- or 4′-OMe), 3.90 (3H, s, 4′- or 3′-OMe), 4.23 (1H, d, J=5.7 Hz, H-3), 6.84—6.90 (3H, m, H-2′, 5′, 6′). EI-MS m/z: 242 (M^+).

threo-**12** (35 mg) was worked-up in the same way as for *erythro*-**12** to give *threo*-**13** (18 mg, 58%) as colorless crystals, mp 78—79 °C (AcOEt–*n*-hexane). IR (KBr) cm^{-1}: 3425, 1514, 1265, 1026. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.26 (3H, s, 3-OMe), 3.35 (1H, dd, J=12.0, 4.5 Hz, H-1), 3.55 (1H, dd, J=12.0, 3.3 Hz, H-1), 3.73 (1H, ddd, J=8.0, 4.5, 3.3 Hz, H-2), 3.890 (3H, s, 3′- or 4′-OMe), 3.893 (3H, s, 4′- or 3′-OMe), 4.14 (1H, d, J=8.0 Hz, H-3), 6.82—6.90 (3H, m, H-2′, 5′, 6′). EI-MS m/z: 242 (M^+).

Preparation of the Acetonides *erythro*-18 and *threo*-18 A mixture of *erythro*-**13** (6.8 mg), 2,2-dimethoxypropane (0.1 ml), and *p*-toluenesulfonic acid (0.5 mg) in dry acetone (0.5 ml) was stirred at room temperature for 30 min. After neutralization with 5% aqueous $NaHCO_3$, the reaction mixture was concentrated *in vacuo*, diluted with H_2O and extracted with $CHCl_3$. Removal of the solvent from the $CHCl_3$ layer *in vacuo* gave *erythro*-**18** (7.9 mg, 98%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (3H, s, acetonide-Me), 1.41 (3H, s, acetonide-Me), 3.24 (3H, s, 3-OMe), 3.88 (3H, s, 3′- or 4′-OMe), 3.89 (3H, s, 4′- or 3′-OMe), 4.01 (1H, dd, J=8.4, 6.0 Hz, H-1), 4.04 (1H, d, J=6.8 Hz, H-3), 4.06 (1H, dd, J=8.4, 6.0 Hz, H-1), 4.19 (1H, dt, J=6.8, 6.0 Hz, H-2), 6.84—6.90 (3H, m, H-2′, 5′, 6′). EI-MS m/z: 282 (M^+).

threo-**13** (8.3 mg) was worked-up in the same way as for *erythro*-**13** to give *threo*-**18** (7.9 mg, 81%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (3H, s, acetonide-Me), 1.45 (3H, s, acetonide-Me), 3.25 (3H, s, 3-OMe), 3.50 (1H, dd, J=8.5, 7.8 Hz, H-1), 3.58 (1H, dd, J=8.5, 6.5 Hz, H-1), 3.89 (3H, s, 3′- or 4′-OMe), 3.90 (3H, s, 4′- or 3′-OMe), 4.07 (1H, d, J=7.8 Hz, H-3), 4.30 (1H, td, J=7.8, 6.5 Hz, H-2), 6.82—6.86 (3H, m, H-2′, 5′, 6′). EI-MS m/z: 282 (M^+).

Preparation of the MTPA Esters 19 and 20 To a solution of *erythro*-**12** (45 mg) in dry CH_2Cl_2 (5 ml) were added (*R*)-MTPA (40 mg), 4-dimethylaminopyridine (4-DMAP) (21 mg) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (36 mg), and the whole was stirred at room temperature for 25 h. The reaction mixture was poured into dil. HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was dried and concentrated *in vacuo*. The residue was chromatographed on silica gel to give a mixture (77 mg), which was further purified by preparative HPLC (μBondasphere 5 μC18—100 Å; MeOH–H_2O, 13 : 7) to yield **19** (40 mg, 49%) and **20** (30 mg, 37%). **19**: Colorless oil, $[\alpha]_D^{28}$ −29° (c=0.92, MeOH). UV λ_{max}^{MeOH} nm (log ε): 232 (3.91), 278 (3.38), 283 (3.33). IR (KBr) cm^{-1}: 1751, 1518. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.219 (3H, s, 3-OMe), 3.524 (3H, d, J=1.0 Hz, MTPA-OMe), 3.647 (3H, s, 3′-OMe), 3.764 (3H, s, COOMe), 3.853 (3H, s, 4′-OMe), 4.558 (1H, d, J=6.0 Hz, H-3), 5.524 (1H, d, J=6.0 Hz, H-2), 6.670 (1H, dd, J=8.0, 2.0 Hz, H-6′), 6.698 (1H, d, J=8.0 Hz, H-5′), 6.709 (1H, d, J=2.0 Hz, H-2′), 7.30—7.50 (5H, m, MTPA-Ph). ^{13}C-NMR* (125 MHz, $CDCl_3$) δ: 52.5 (COO<u>Me</u>), 55.5 (3′-OMe), 55.8 (4′-OMe), 56.8 (3-OMe), 75.8 (C-2), 81.5 (C-3), 110.2 (C-2′), 110.4 (C-5′), 120.4 (C-6′), 128.1 (C-1′), 148.9 (C-3′), 149.2 (C-4′), 167.9 (C-1). HR-EI-MS Calcd for $C_{23}H_{25}F_3O_8$: 486.1502 (M^+). Found: 486.1519. **20**: Colorless oil, $[\alpha]_D^{28}$ +59° (c=0.85, MeOH). UV λ_{max}^{MeOH} nm (log ε): 233 (3.95), 278 (3.44), 283 sh (3.40). IR (KBr) cm^{-1}: 1755, 1518. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.273 (3H, s, 3-OMe), 3.404 (3H, br s, MTPA-OMe), 3.725 (3H, s, 3′-OMe), 3.734 (3H, s, COOMe), 3.868 (3H, s, 4′-OMe), 4.589 (1H, d, J=6.0 Hz, H-3), 5.460 (1H, d, J=6.0 Hz, H-2), 6.777 (1H, d, J=8.0 Hz, H-5′), 6.818 (1H, dd, J=8.0, 2.0 Hz, H-6′), 6.874 (1H, d, J=2.0 Hz, H-2′), 7.26—7.40 (5H, m, MTPA-Ph). ^{13}C-NMR* (125 MHz, $CDCl_3$) δ: 52.5 (COO<u>Me</u>), 55.6 (3′-OMe), 55.8 (4′-OMe), 56.9 (3-OMe), 76.1 (C-2), 81.5 (C-3), 110.3 (C-2′), 110.6 (C-5′), 120.8 (C-6′), 128.3 (C-1′), 149.1 (C-3′), 149.4 (C-4′), 167.6 (C-1). HR-EI-MS Calcd for $C_{23}H_{25}F_3O_8$: 486.1502 (M^+). Found: 486.1513. *Compounds **19** and **20** showed additional signals of an MTPA moiety.

Preparation of (*R*)-2-Methoxy-2-(3,4-dimethoxyphenyl)ethanol (9) from 19 To an ice-cooled solution of **19** (40 mg) in dry tetrahydrofuran

(THF, 5 ml) was added portionwise $LiAlH_4$ (6.5 mg) and the mixture was stirred at room temperature for 90 min. After addition of THF containing H_2O and removal of the insoluble portion by filtration, the reaction mixture was concentrated *in vacuo*. The residue was extracted with AcOEt and the washed and dried organic layer was concentrated *in vacuo*. The resulting residue was purified by preparative TLC ($CHCl_3$–MeOH, 95 : 5) to afford (2*S*,3*R*)-**13** (12.2 mg, 61%), $[\alpha]_D^{28}$ −60° (*c*=0.57, MeOH). EI-MS *m*/*z*: 242 (M^+). To a solution of (2*S*,3*R*)-**13** (5.8 mg) in EtOH (1 ml) was added a solution of $NaIO_4$ (5.2 mg) in H_2O (1 ml). The mixture was stirred at room temperature for 30 min, checked by TLC ($CHCl_3$–MeOH, 95 : 5) to make sure that the reaction was complete, and treated with a small portion of $NaBH_4$ for 10 min. After addition of dil. AcOH, the mixture was extracted with $CHCl_3$. Following removal of the solvent *in vacuo*, the residue was recrystallized from AcOEt–*n*-hexane to give (*R*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanol (**9**) (3.7 mg, 79% from (2*S*,3*R*)-**13**) as colorless crystals, mp 52—53 °C, $[\alpha]_D^{25}$ −91° (*c*=0.31, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 231 (4.46), 278 (3.43), 285 sh (3.32). IR (KBr) cm^{-1}: 3337, 1520, 1019, 820. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.30 (3H, s, 2-OMe), 3.60 (1H, dd, *J*=11.6, 4.0 Hz, H-1), 3.69 (1H, dd, *J*=11.6, 8.4 Hz, H-1), 3.88 (3H, s, 3′- or 4′-OMe), 3.89 (3H, s, 4′- or 3′-OMe), 4.25 (1H, dd, *J*=8.4, 4.0 Hz, H-1), 6.83—6.90 (3H, m, H-2′, 5′, 6′). EI-MS *m*/*z*: 212 (M^+).

Preparation of (*S*)-2-Methoxy-2-(3,4-dimethoxyphenyl)ethanol (10) from 20 Compound **20** (26 mg) was worked-up in the same way as for **19** to give (2*R*,3*S*)-**13** (6.8 mg, 52%), $[\alpha]_D^{28}$ +58° (*c*=0.57, MeOH). EI-MS *m*/*z*: 242 (M^+). (2*R*,3*S*)-**13** (3.5 mg) was treated in the same way as described above to give (*S*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanol (**10**) (2.8 mg, 98% from (2*R*,3*S*)-**13**) as a colorless oil, $[\alpha]_D^{26}$ +92° (*c*=0.37, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 231 (3.82), 278 (3.34), 285 sh (3.26). IR (KBr) cm^{-1}: 3444, 1518, 1028, 812. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.30 (3H, s, 2-OMe), 3.60 (1H, dd, *J*=11.6, 4.0 Hz, H-1), 3.69 (1H, dd, *J*=11.6, 8.5 Hz, H-1), 3.88 (3H, s, 3′- or 4′-OMe), 3.90 (3H, s, 4′- or 3′-OMe), 4.25 (1H, dd, *J*=8.5, 4.0 Hz, H-1), 6.83—6.90 (3H, m, H-2′, 5′, 6′). EI-MS *m*/*z*: 212 (M^+).

HPLC Analysis of 9 and 10 Standard (*R*)- and (*S*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanols were separated by chiral HPLC [column, CHIRALCEL OB-H (4.6 i.d.×250 mm, Daicel Chemical Industries, Ltd.); mobile phase, *n*-hexane–2-propanol (22 : 3); flow rate, 0.6 ml/min; detection, 270 nm; retention time, *R*-form (24 min), *S*-form (28 min)]. HPLC analysis under the same conditions demonstrated that compounds **9** and **10**, derived from the natural products, were identical with (*R*)- and (*S*)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanols, respectively.

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