Four New Lignan Glycosides from *Osmanthus fragrans* LOUR. var. *aurantiacus* MAKINO

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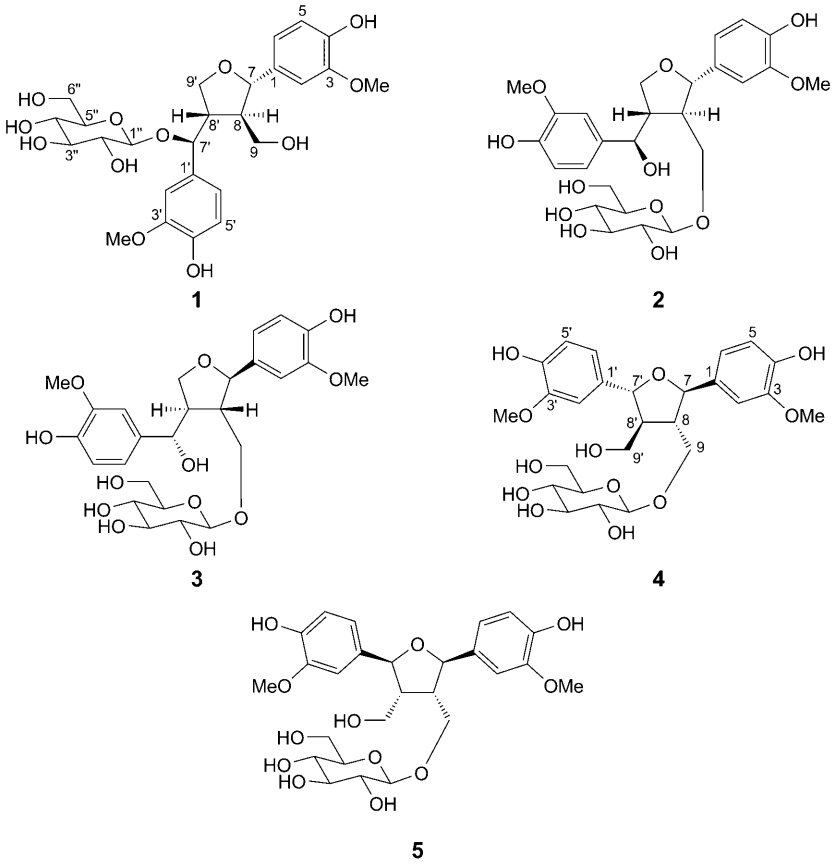
Four new tetrahydrofuranoid lignan glycosides, (7*S*,8*R*,7′*R*,8′*S*)-4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-*O*-*β*-D-glucopyranoside (**2**), (7*R*,8*S*,7′*S*,8′*R*)-4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-*O*-*β*-D-glucopyranoside (**3**), (7*R*,8*S*,7′*R*,8′*S*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9-*O*-*β*-D-glucopyranoside (**4**), and *rel*-(7*R*,8*S*,7′*S*,8′*R*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9-*O*-*β*-D-glucopyranoside (**5**), and ten known lignan glycosides, **1** and **6**–**14**, were isolated from the leaves of *Osmanthus fragrans* LOUR. var. *aurantiacus* MAKINO. Their structures were established on the basis of spectral and chemical studies.

Introduction. – *Osmanthus fragrans* LOUR. var. *aurantiacus* MAKINO belongs to the Oleaceae family. This family is a rich source of iridoid, secoiridoid, phenylpropanoid, and lignan glycosides [1]. As part of our continuing studies on the constituents of oleaceous plants, we previously reported the isolation and identification of three new phenylpropanoids, two new secoiridoid glycosides, along with 24 known compounds from the leaves of this plant [2–4]. The flower of this plant has been used in China as a herbal drug against toothache and as gargle [5]. In the course of further studies on the constituents of this plant, four new tetrahydrofuranoid lignan glycosides (7*S*,8*R*,7′*R*,8′*S*)-4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-*O*-*β*-D-glucopyranoside[1]) (**2**), (7*R*,8*S*,7′*S*,8′*R*)-4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-*O*-*β*-D-glucopyranoside[1]) (**3**), (7*R*,8*S*,7′*R*,8′*S*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9-*O*-*β*-D-glucopyranoside[1]) (**4**), and *rel*-(7*R*,8*S*,7′*S*,8′*R*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9-*O*-*β*-D-glucopyranoside[1]) (**5**), and ten known lignan glycosides, **1** and **6**–**14**, have been isolated. This article deals with the structural elucidation and identification of these compounds.

Results and Discussion. – The MeOH extract of the fresh leaves of *O. fragrans* LOUR. var. *aurantiacus* MAKINO was partitioned with $CHCl_3$, AcOEt, BuOH, and H_2O. The BuOH-soluble fraction was separated by a combination of chromatographic procedures to afford four new tetrahydrofuranoid-lignan glycosides, **2**–**5**, and ten known lignan glycosides, **1** and **6**–**14**[2]). The known compounds **1** and **6**–**14** were identified as tanegoside A (**1**) [6], (+)-lariciresinol 4-*O*-*β*-D-glucopyranoside (**6**) [7],

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

[2]) For formulae, see corresponding references.



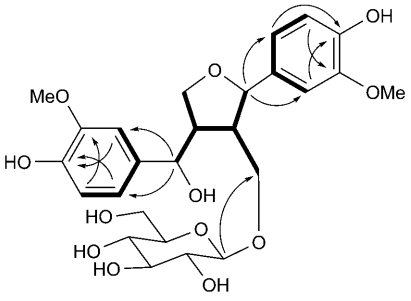
(+)-lariciresinol 4′-*O*-*β*-D-glucopyranoside (**7**) [7], (−)-olivil 4-*O*-*β*-D-glucopyranoside (**8**) [8], (−)-olivil 4′-*O*-*β*-D-glucopyranoside (**9**) [8][9], (+)-8-hydroxypinoresinol 8-*O*-*β*-D-glucopyranoside (**10**) [10], (7*S*,8*R*)-dehydrodiconiferyl alcohol 4-*O*-*β*-D-glucopyranoside (**11**) [11], (7*R*,8*S*)-dehydrodiconiferyl alcohol 9-*O*-*β*-D-glucopyranoside (**12**) [12], (+)-isolariciresinol 6-*O*-*β*-D-glucopyranoside (**13**) [13][14], and (+)-isolariciresinol 9′-*O*-*β*-D-glucopyranoside (**14**) [14][15] by comparison of their spectroscopic data with those described in the literature. This is the first time of the identification of **1** and **6**–**14** in this plant.

Compound **2** was obtained as an optically active hygroscopic amorphous powder. The molecular formula of **2**, $C_{26}H_{34}O_{12}$, was deduced from HR-FAB-MS (*m*/*z* 561.1944 ($[M+Na]^+$)). In the ^{1}H-NMR spectrum of **2** (*Table 1*), two sets of 1,3,4-trisubstituted benzene ring signals at δ(H) 7.00 (*d*, *J* = 2.0, H−C(2′)), 6.83 (*dd*, *J* = 8.1, 2.0, H−C(6′)), 6.77 (*d*, *J* = 8.1, H−C(5′)), 6.91 (*d*, *J* = 2.0, H−C(2)), 6.82 (*dd*, *J* = 8.1, 2.0, H−C(6)), and 6.75 (*d*, *J* = 8.1, H−C(5)), two MeO signals at δ(H) 3.84 (*s*, MeO−C(3)) and 3.87 (*s*, MeO−C(3′)), and an anomeric H-atom signal at δ(H) 4.26 (*d*, *J* = 7.6, H−C(1″)) were observed. Furthermore, the ^{1}H-NMR spectrum exhibited signals attributable to

two O-bearing CH groups at δ(H) 4.65 (*d*, $J = 8.3$, H−C(7)) and 4.54 (*d*, $J = 8.5$, H−C(7′)), two O-bearing CH_2 groups at δ(H) 3.98 (*dd*, $J = 10.0, 5.1$, H_B−C(9)), 3.65 (*dd*, $J = 10.0, 5.3$, H_A−C(9)), 3.76 (*dd*, $J = 9.3, 5.6$, H_B−C(9′)), and 3.70 (*dd*, $J = 9.3, 6.3$, H_A−C(9′)), and two aliphatic CH groups at δ(H) 2.82 (br. *ddd*, $J = 8.3, 6.3, 5.6$, H−C(8′)) and 2.38 (br. *dd*, $J = 8.3, 5.3, 5.1$, H−C(8)). Acid hydrolysis of **2** yielded D-glucose, which was identified on the basis of retention time (HPLC) and optical rotation. The ^{1}H,^{1}H-COSY experiment of **2** in combination with the HMQC spectrum revealed the partial structures shown by the bold lines in *Fig. 1*. The ^{1}H-NMR data (*Table 1*) of **2** were similar to those of **1** (tanegoside A = (7*S*,8*R*,7′*S*,8′*S*)-4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 7′-*O*-*β*-D-glucopyranoside = (*S*)-(4-hydroxy-3-methoxyphenyl)-[(3*S*,4*R*,5*S*)-tetrahydro-5-(4-hydroxy-3-methoxyphenyl)-4-(hydroxymethyl)-3-furanyl]methyl *O*-*β*-D-glucopyranoside) [6], except for the chemical shifts due to H−C(8), CH_2(9), H−C(7′), and H−C(8′). The ^{13}C-NMR spectra (*Table 1*) of **2** were also similar to those of **1**, except for significant upfield shifts of C(8) (δ(C) 50.5, −2.80 ppm) and C(7′) (δ(C) 77.5, −3.80 ppm), and downfield shifts of

Table 1. *^{1}H- and ^{13}C-NMR Data* (400 and 100 MHz, resp.; in CD_3OD) *of* **1** *and* **2**[1]). δ in ppm, J in Hz.

	1		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
C(1)	–	134.3	–	134.2
H−C(2)	6.95 (*d*, $J = 2.0$)	111.4	6.91 (*d*, $J = 2.0$)	111.2
C(3)	–	149.3	–	149.1
C(4)	–	147.3	–	147.2
H−C(5)	6.76 (*d*, $J = 8.1$)	116.0	6.75 (*d*, $J = 8.1$)	115.9
H−C(6)	6.84 (*dd*, $J = 8.1, 2.0$)	120.7	6.82 (*dd*, $J = 8.1, 2.0$)	120.7
H−C(7)	4.59 (*d*, $J = 7.8$)	85.4	4.65 (*d*, $J = 8.3$)	85.5
H−C(8)	1.97 (br. *ddd*, $J = 10.2, 7.8, 5.6$)	53.3	2.38 (br. *ddd*, $J = 8.3, 5.3, 5.1$)	50.5
CH_2(9)	3.17 (*dd*, $J = 11.2, 5.6$), 3.26 (overlapped)	62.1	3.65 (*dd*, $J = 10.0, 5.3$), 3.98 (*dd*, $J = 10.0, 5.1$)	70.5
*Me*O−C(3)	3.86 (*s*)	56.6	3.84 (*s*)	56.5
C(1′)	–	132.0	–	136.4
H−C(2′)	7.02 (*d*, $J = 1.7$)	112.3	7.00 (*d*, $J = 2.0$)	111.6
C(3′)	–	149.0	–	149.0
C(4′)	–	147.6	–	147.3
H−C(5′)	6.73 (*d*, $J = 8.1$)	115.8	6.77 (*d*, $J = 8.1$)	115.9
H−C(6′)	6.77 (*dd*, $J = 8.1, 1.7$)	122.2	6.83 (*dd*, $J = 8.1, 2.0$)	120.9
H−C(7′)	4.81 (*d*, $J = 8.5$)	81.3	4.54 (*d*, $J = 8.5$)	77.5
H−C(8′)	2.62 (br. *ddd*, $J = 8.5, 4.6, 4.1$)	49.8	2.82 (br. *ddd*, $J = 8.3, 6.3, 5.6$)	53.0
CH_2(9′)	3.88 (*dd*, $J = 9.0, 4.6$), 4.31 (*dd*, $J = 9.0, 4.1$)	71.6	3.70 (*dd*, $J = 9.3, 6.3$), 3.76 (*dd*, $J = 9.3, 5.6$)	71.0
*Me*O−C(3′)	3.83 (*s*)	56.4	3.87 (*s*)	56.4
H−C(1″)	4.06 (*d*, $J = 7.6$)	100.4	4.26 (*d*, $J = 7.6$)	104.8
H−C(2″)	3.26 (overlapped)	75.2	3.30 (overlapped)	75.3
H−C(3″)	3.26 (overlapped)	78.0	3.30 (overlapped)	78.3
H−C(4″)	3.26 (overlapped)	72.0	3.30 (overlapped)	71.6
H−C(5″)	3.10 (*ddd*, $J = 8.8, 6.3, 2.2$)	78.0	3.30 (overlapped)	78.1
CH_2(6″)	3.66 (*dd*, $J = 11.9, 6.3$), 3.87 (*dd*, $J = 11.9, 2.2$)	63.0	3.70 (overlapped), 3.86 (overlapped)	62.8



2 and **3**

Fig. 1. *^{1}H,^{1}H-COSY Correlations* (—) *and key HMBCs* (H → C) *of* **2** *and* **3**

C(9) (δ(C) 70.5, +8.4 ppm) and C(8′) (δ(C) 53.0, +3.2 ppm). These findings suggested that β-D-glucopyranosyloxy group in **2** is attached to C(9) of 4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan, and not to C(7′). Detailed analyses of the ^{1}H- and ^{13}C-NMR (*Table 1*) signals of **2** were undertaken with the aid of ^{1}H,^{1}H-COSY, HMQC, and DEPT experiments, and the constitutional structure of **2** was identified as 4,4′,9,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-*O*-β-D-glucopyranoside by the HMBC experiment (*Fig. 1*). In the NOESY spectrum (*Fig. 2*), H−C(8) showed NOE correlations with 2 H−C(2,6) and H−C(7′), whereas H−C(8′) showed NOE correlations with H−C(7), H_A−C(9), and 2 H−C(2′,6′). These NOE correlations of **2** were very similar to those of **1**; however, no NOE correlation between H−C(8) and 2 H−C(2′,6′) was observed. The coupling constant of H−C(7′) (J = 8.5 Hz) in **2** revealed an antiperiplanar orientation of H−C(7′) and H−C(8′). Enzymatic hydrolysis of each **1** and **2** afforded the aglycones **1a** and **2a**, and the NOE correlations of **1a** and **2a** were the same as those of **1** and **2**, respectively. The comparison of the ^{1}H-NMR chemical shifts of **1a** and **2a** reveal shift changes for H−C(8), CH_2(9), and CH_2(9′). The signals of H−C(8) (δ(H) 2.29), CH_2(9) (δ(H) 3.63, 3.74), and CH_2(9′) (δ(H) 3.58, 3.65) of **2a** were shifted downfield (+0.31 ppm), downfield (+0.23, +0.34 ppm), and upfield (+0.54, +0.42 ppm) with respect to those of **1a**, respectively. These shifts are attributed to the anisotropic effect of the aromatic group at C(7′) in (*Fig. 3*), suggesting that the aglycone parts of **1** and **2** are epimers at C(7′). On the other hand, the CD spectrum of **2** showed two positive *Cotton* effects ($\Delta\varepsilon$ +15.2 (206 nm), +3.5 (235 nm)) similar to those of **1** ($\Delta\varepsilon$ +17.6 (210 nm), +4.6 (237 nm)) and of analogous compound (tinosposide B = (7*S*,8*R*,7′*S*,8′*S*)-4,9,7′-trihydroxy-3,3′,4′-trimethoxy-7,9′-epoxylignan 4-*O*-β-D-glucopyranoside) [16] indicating that C(7), C(8), and C(8′) in **2** have (*S*)-, (*R*)-, and (*S*)-configurations, respectively. Therefore, the remaining stereogenic center at C(7′) of **2** is (*R*)-configurated. Consequently, the structure of **2** was determined to be (7*S*,8*R*,7′*R*,8′*S*)-4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-*O*-β-D-glucopyranoside.

Compound **3** was obtained as an optically active hygroscopic amorphous powder. The molecular formula of **3**, $C_{26}H_{34}O_{12}$, was determined by HR-FAB-MS and was the same as that of **2**. Acid hydrolysis of **2** yielded D-glucose, which was identified as described above. Its ^{1}H- and ^{13}C-NMR spectra (*Table 2*) were very similar to those of **2**. The ^{1}H,^{1}H-COSY and HMBC (*Fig. 1*) experiments of **3** led to the same planar

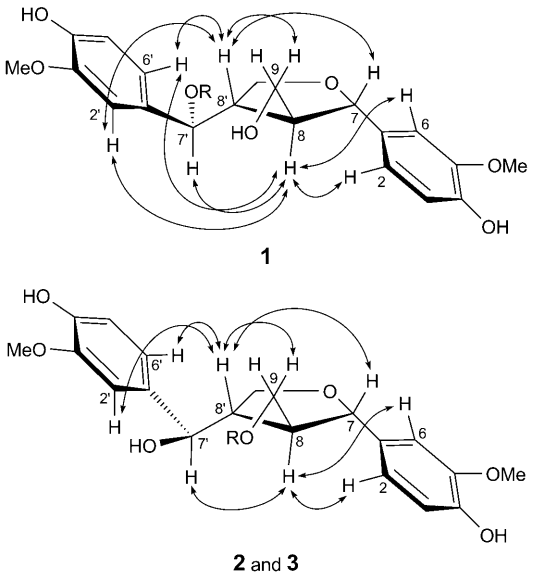


Fig. 2. *NOESY Correlations* (H↔H) *of* **1**, **2**, *and* **3** (R = β-D-glucopyranosyl)

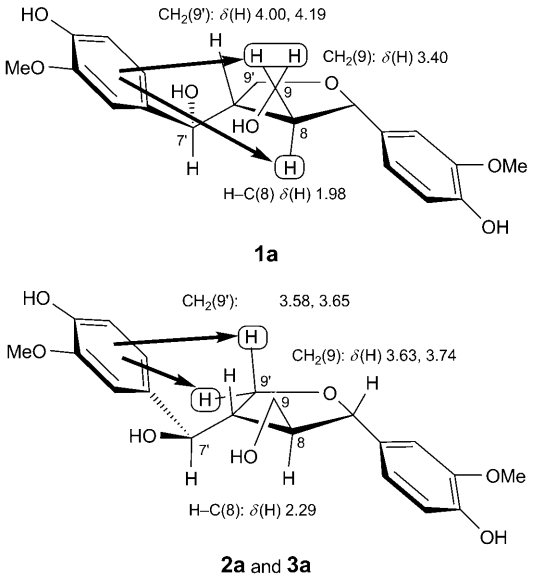


Fig. 3. *Magnetic anisotropy effects of the aromatic group at C(7′) of* **1a**, **2a**, *and* **3a**

structure as the one of **2**. The NOE correlations of **3** (*Fig. 2*) were also the same as those of **2**. On the other hand, the CD curves of **2** and **3** were symmetrical opposites (**2**: $\Delta\varepsilon + 15.2$ (206 nm), $+3.5$ (235 nm); **3**: $\Delta\varepsilon$ -12.9 (205 nm), -2.5 (234 nm)).

Enzymatic hydrolysis of **3** afforded an aglycone, **3a**, and the spectral data of **3a** were in agreement with those of **2a**, except for the signs of the optical rotations (**2a**: $[\alpha]_D = +35.1$; **3a**: $[\alpha]_D = -35.7$) and the CD curves (**2a**: $\Delta\varepsilon + 20.0$ (206 nm), $+5.8$ (234 nm); **3a**: $\Delta\varepsilon$ -20.3 (205 nm), -5.2 (235 nm)). Therefore, the aglycone parts of **2** and **3** were deduced to be enantiomers. Consequently, the structure of **3** was determined to be (7*R*,8*S*,7′*S*,8′*R*)-4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-*O*-*β*-D-glucopyranoside.

Table 2. *^{1}H- and ^{13}C-NMR Data* (400 and 100 MHz, resp.; in CD_3OD) *of* **3**[1]). δ in ppm, J in Hz.

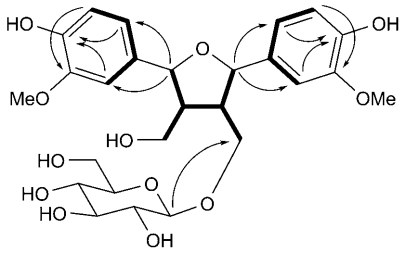
	δ(H)	δ(C)
H−C(1)	–	134.3
H−C(2)	6.93 (*d*, *J* = 2.0)	111.3
C(3)	–	149.1
C(4)	–	147.3
H−C(5)	6.75 (*d*, *J* = 8.1)	115.9
H−C(6)	6.81 (*dd*, *J* = 8.1, 2.0)	120.6
H−C(7)	4.70 (*d*, *J* = 7.8)	85.7
H−C(8)	2.41 (br. *ddd*, *J* = 8.5, 7.8, 5.1)	51.0
CH_2(9)	3.61 (*dd*, *J* = 9.8, 5.1), 4.10 (*dd*, *J* = 9.8, 5.4)	70.9
*Me*O−C(3)	3.85 (*s*)	56.5
C(1′)	–	136.4
H−C(2′)	6.99 (*d*, *J* = 1.8)	111.6
C(3′)	–	149.0
C(4′)	–	147.2
H−C(5′)	6.77 (*d*, *J* = 8.3)	115.9
H−C(6′)	6.83 (*dd*, *J* = 8.3, 1.8)	121.0
H−C(7′)	4.51 (*d*, *J* = 8.8)	77.7
H−C(8′)	2.68–2.71 (*m*)	53.0
CH_2(9′)	3.66 (overlapped), 3.74 (*dd*, *J* = 9.1, 5.1)	71.1
*Me*O−(3′)	3.87 (*s*)	56.4
H−C(1″)	4.29 (*d*, *J* = 7.8)	104.8
H−C(2″)	3.22 (*dd*, *J* = 9.0, 7.8)	75.2
H−C(3″)	3.30 (overlapped)	78.2
H−C(4″)	3.30 (overlapped)	71.7
H−C(5″)	3.30 (overlapped)	78.1
CH_2(6″)	3.73 (overlapped), 3.86 (overlapped)	62.8

Compound **4** was obtained as an optically active hygroscopic amorphous powder. The molecular formula of **4**, $C_{26}H_{34}O_{12}$, was deduced from HR-FAB-MS. In the ^{1}H-NMR spectrum of **4** (*Table 3*), two sets of 1,3,4-trisubstituted benzene ring signals at δ(H) 7.04 (*d*, *J* = 2.0, H−C(2)), 7.02 (*d*, *J* = 2.0, H−C(2′)), 6.91 (*dd*, *J* = 8.1, 2.0, H−C(6)), 6.89 (*dd*, *J* = 8.1, 2.0, H−C(6′)), 6.79 (*d*, *J* = 8.1, H−C(5)), and 6.78 (*d*, *J* = 8.1, H−C(5′)), two O-bearing CH group signals at δ(H) 4.99 (*d*, *J* = 9.0, H−C(7)), 4.98 (*d*, *J* = 9.0, H−C(7′)), an anomeric H-atom signal at δ(H) 4.24 (*d*, *J* = 7.8, H−C(1″)), two O-bearing CH_2 group signals at δ(H) 4.03 (*dd*, *J* = 10.0, 4.1, H_B−C(9)), 3.78 (*dd*, *J* = 11.5, 4.1, H_B−C(9′)), 3.71 (*dd*, *J* = 10.0, 4.1, H_A−C(9)), and 3.61 (*dd*, *J* = 11.5, 4.3, H_A−C(9′)), two MeO signals at δ(H) 3.88 (*s*, MeO−C(3), MeO−C(3′)), and two CH group signals at δ(H) 2.51 (br. *ddd*, *J* = 9.0, 4.3, 4.1, H−C(8)) and 2.39 (br. *ddd*, *J* = 9.0,

Table 3. *^{1}H- and ^{13}C-NMR Data* (400 and 100 MHz, resp.; in CD_3OD) *of* **4** *and* **5**[1]). δ in ppm, J in Hz.

	4		**5**	
	δ(H)	δ(C)	δ(H)	δ(C)
C(1)	–	135.0	–	134.8
H–C(2)	7.04 (*d*, *J* = 2.0)	111.4	7.04 (*d*, *J* = 2.0)	111.5
C(3)	–	149.1	–	149.1
C(4)	–	147.4	–	147.4
H–C(5)	6.79 (*d*, *J* = 8.1)	116.1	6.79 (*d*, *J* = 8.1)	116.1
H–C(6)	6.91 (*dd*, *J* = 8.1, 2.0)	120.6	6.91 (*dd*, *J* = 8.1, 2.0)	120.6
H–C(7)	4.99 (*d*, *J* = 9.0)	84.4	4.83 (*d*, *J* = 6.7)	84.2
H–C(8)	2.51 (br. *ddd*, *J* = 9.0, 4.3, 4.1)	51.9	2.66–2.73 (*m*)	50.2
CH_2(9)	3.71 (*dd*, *J* = 10.0, 4.3), 4.03 (*dd*, *J* = 10.0, 4.1)	70.0	3.68 (overlapped), 4.24 (*dd*, *J* = 10.0, 7.6)	68.4
*Me*O–C(3)	3.88 (*s*)	56.5	3.85 (*s*)	56.5
C(1′)	–	134.9	–	134.7
H–C(2′)	7.02 (*d*, *J* = 2.0)	111.3	7.02 (*d*, *J* = 1.7)	111.5
C(3′)	–	149.1	–	149.1
C(4′)	–	147.4	–	147.3
H–C(5′)	6.78 (*d*, *J* = 8.1)	116.0	6.79 (*d*, *J* = 8.1)	116.1
H–C(6′)	6.89 (*dd*, *J* = 8.1, 2.0)	120.6	6.93 (*dd*, *J* = 8.1, 1.7)	120.4
H–C(7′)	4.98 (*d*, *J* = 9.0)	84.3	4.81 (*d*, *J* = 7.8)	84.1
H–C(8′)	2.39 (br. *ddd*, *J* = 9.0, 4.3, 4.1)	55.1	2.51–2.58 (*m*)	52.8
CH_2(9′)	3.61 (*dd*, *J* = 11.5, 4.3), 3.78 (*dd*, *J* = 11.5, 4.1)	61.2	3.68 (overlapped), 3.86 (overlapped)	60.6
*Me*O–C(3′)	3.88 (*s*)	56.5	3.84 (*s*)	56.4
H–C(1″)	4.24 (*d*, *J* = 7.8)	104.7	4.29 (*d*, *J* = 7.8)	104.4
H–C(2″)	3.18 (*dd*, *J* = 9.5, 7.8)	75.2	3.19 (*dd*, *J* = 9.4, 7.8)	75.2
H–C(3″)	3.32 (overlapped)	78.2	3.32 (overlapped)	78.3
H–C(4″)	3.32 (overlapped)	71.6	3.32 (overlapped)	71.7
H–C(5″)	3.32 (overlapped)	78.1	3.32 (overlapped)	78.2
CH_2(6″)	3.66 (*dd*, *J* = 12.0, 5.3), 3.86 (*dd*, *J* = 12.0, 1.7)	62.8	3.66 (overlapped), 3.85 (overlapped)	62.9

4.3, 4.1, H–C(8′)) were observed. The ^{13}C-NMR spectrum of **4** (*Table 3*) was similar to that of **3**, except for the chemical shifts of C(7′) (δ(C) 84.3, +6.6 ppm) and C(9′) (δ(C) 61.2, −9.9 ppm). These data indicated a 2,5-diaryl-tetrahydofuranoid type of neolignan glycoside [17]. The complete assignments of the ^{1}H- and ^{13}C-NMR signals of **4** were confirmed by the ^{1}H,^{1}H-COSY, HMQC, HMBC (*Fig. 4*), and NOESY (*Fig. 5*) experiments. On enzymatic hydrolysis, **4** gave an aglycone, **4a**, and D-glucose, which was identified as described above. Compound **4a** was identified as (+)-neoolivil (=(7*R*,8*S*,7′*R*,8′*S*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan) by the comparison of its optical rotation value ($[\alpha]_D = +44.8$), ^{1}H-NMR spectrum, and EI-MS data [18]. Furthermore, the CD spectrum of **4** ($\Delta\varepsilon$ + 15.0 (208 nm), +7.8 (238 nm)) showed two positive *Cotton* effects similar to those of an analogous compound ((7*R*,8*S*,7′*R*,8′*S*)-(+)-neoolivil-4-*O*-β-D-glucopyranoside; $\Delta\varepsilon$ + 11.8 (211 nm), +6.7 (236 nm)) [19], indicating (*R*)-configurations at C(7) and C(7′). From the above data, the structure of **4** was determined to be (7*R*,8*S*,7′*R*,8′*S*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9-*O*-β-D-glucopyranoside.



4 and **5**

Fig. 4. *$^1H,^1H$-COSY Correlations* (—) *and key HMBCs* (H → C) *of* **4** *and* **5**

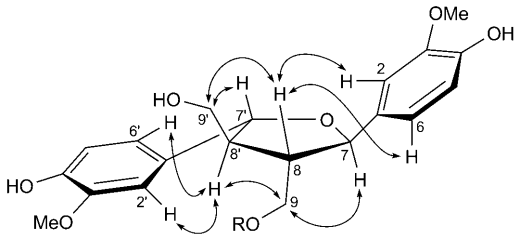


Fig. 5. *NOESY Correlations* (H ↔ H) *of* **4** (R = *β*-D-glucopyranosyl)

This structure had already been assigned to a compound previously isolated from the bark of *O. asiaticus* by one of the authors (*M. K.*) [20]. However, the NMR chemical shifts of **4** and those of the compound previously isolated are not identical. After re-examining the previous spectral data, we found that the structure previously designated as (7*R*,8*S*,7′*R*,8′*S*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9-*O*-*β*-D-glucopyranoside from *O. asiaticus* should be revised to **1**.

Compound **5** was obtained as an optically active hygroscopic amorphous powder. The molecular formula of **5**, $C_{26}H_{34}O_{12}$, was deduced from HR-FAB-MS. The ^{1}H- and ^{13}C-NMR (*Table 3*) spectral data of **5** closely resembled those of **4**, except for the chemical shifts due to C(7), C(8), C(9), C(7′), C(8′), and C(9′) positions. The ^{1}H,^{1}H-COSY and HMBC experiments (*Fig. 4*) of **5** led to the same planar structure as the one of **4**. On the other hand, the NOE correlations (2 H−C(2,6)/H−C(8), 2 H−C(2′,6′)/H−C(8′), H−C(7)/CH_2(9), H−C(7′)/CH_2(9′), and H−C(8)/H−C(8′)) of **5** (*Fig. 6*) indicated that the relative configurations between C(7) and C(8), and C(7′) and C(8′)

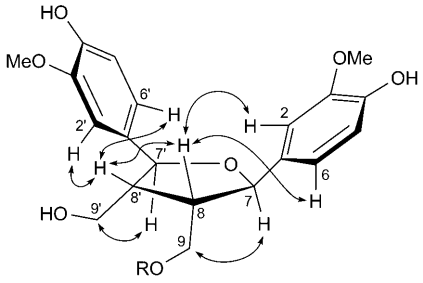


Fig. 6. *NOESY Correlations* (H ↔ H) *of* **5** (R = *β*-D-glucopyranosyl)

were established as *trans*, and between H–C(8) and H–C(8′) as *cis*. From the above data, the aglycone of **5** has a symmetrical structure and a *meso*-configuration. Enzymatic hydrolysis of **5** afforded an aglycone, **5a**. The symmetrical structure and a *meso*-configuration of the aglycone of **5** was also confirmed by the optical rotation ($[\alpha]_D = \pm 0$), CD data (no *Cotton* effect), and ^{1}H-NMR signals (a set of signals for two phenylpropanoid units) of **5a** [21]. The position of the β-D-glucopyranosyl unit could not be determined (at C(9) *or* C(9′)). Consequently, the structure of **5** was determined to be *rel*-(7*R*,8*S*,7′*S*,8′*R*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9-*O*-β-D-glucopyranoside.

We thank Mrs. *S. Sato* and *T. Matsuki* of Tohoku Pharmaceutical University for NMR and MS measurements.

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 230–400 mesh; *Merck*) and *Sephadex LH-20* (*Pharmacia Fine Chemicals*). HPLC: *Tosoh HPLC 8020* apparatus; *TSKgel-ODS-120T* column (10 μm, 7.8 mm i.d. × 30 cm; *Tosoh*), *TSKgel-ODS-80TM* column (5 μm, 6.0 mm i.d. × 15 cm; *Tosoh*), and *Cosmosil-5SL* column (5 μm, 10 mm i.d. × 25 cm; *Nacalai tesque*); t_R in min. Optical rotation: *Jasco-DIP-360* digital polarimeter. CD Spectra: *Jasco J-720* spectropolarimeter; λ_{max} ($\Delta\varepsilon$) in nm. UV Spectra: *Beckman-DU-64* spectrometer; λ_{max} (log ε) in nm. NMR Spectra: *Jeol JNM-LA 400* spectrometer; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-, HR-EI-, FAB-, and HR-FAB-MS: *Jeol JMS-DX 303* mass spectrometer; with glycerol as matrix for FAB; in *m*/*z* (rel. %).

Plant Material. Leaves of *O. fragrans* LOUR. var. *aurantiacus* MAKINO were collected in October 2007, in Sendai, Miyagi prefecture, Japan, and identified by *M. K.* A voucher specimen (2007-10-KM2) was deposited with the laboratory of *M. K.*

Extraction and Isolation. Fresh leaves of *O. fragrans* var. *aurantiacus* (1.3 kg) were extracted with MeOH (8 l) at r.t. for three weeks. The MeOH extract was concentrated under reduced pressure, and the residue (195 g) was suspended in H_2O. This suspension was successively extracted with $CHCl_3$ (3 × 600 ml), AcOEt (3 × 600 ml), BuOH (3 × 600 ml), and H_2O. The BuOH-soluble fraction was concentrated under reduced pressure to produce a residue. The extract (60 g) was subjected CC (SiO_2; $CHCl_3$/MeOH/H_2O 30:10:1), and the eluate was separated into *Frs. 1–4*. *Fr. 3* was chromatographed on a *Sephadex LH-20* column using 50% MeOH, and the eluate was separated into *Frs. 3.1–3.13*. *Fr. 3.6* was subjected to prep. HPLC (*TSK gel ODS 120T*; MeOH/H_2O 4:7; flow rate, 1.5 ml/min; 40°; UV detection at 205 nm) to give ten *Peaks 3.6.1–3.6.10*. *Peak 3.6.1* was subjected to prep. HPLC (*TSK gel ODS 80TM*; MeOH/H_2O 4:11; flow rate, 1.0 ml/min; 40°, UV detection at 205 nm) to give nine *Peaks 3.6.1.1–3.6.1.9*. *Peak 3.6.1.3* was subjected to prep. HPLC (*Cosmosil 5SL*; CH_2Cl_2/MeOH/H_2O 70:10:1; flow rate, 1.5 ml/min; r.t., detection at 225 nm) to give **9** (28.0 mg; t_R 56.4) and **1** (30.5 mg; t_R 59.4). *Peak 3.6.1.4* was subjected to prep. HPLC (*TSK gel ODS 80TM*; MeOH/H_2O 1:5; flow rate, 1.0 ml/min; 40°; detection at 205 nm) to give two *Peaks 3.6.1.4.1–3.6.1.4.2*. *Peak 3.6.1.4.1* was subjected to prep. HPLC (*Cosmosil 5SL*; CH_2Cl_2/MeOH/H_2O 70:10:1; flow rate, 1.5 ml/min; r.t.; detection at 225 nm) to give **4** (20.0 mg; t_R 60.9) and **8** (18.0 mg; t_R 73.2). *Peak 3.6.1.4.2* was subjected to prep. HPLC (*Cosmosil 5SL*; CH_2Cl_2/MeOH/H_2O 70:10:1; flow rate, 1.5 ml/min; r.t.; detection at 225 nm) to give **5** (13.5 mg; t_R 58.8) and **13** (22.5 mg; t_R 64.8). *Peak 3.6.1.5* was subjected to prep. HPLC (*TSK gel ODS 80TM*; MeOH/H_2O 1:5; flow rate, 1.0 ml/min; 40°; detection at 205 nm) to give **2** (18.5 mg; t_R 54.5) and **3** (15.0 mg; t_R 60.0). *Peak 3.6.1.7* was subjected to prep. HPLC (*Cosmosil 5SL*; CH_2Cl_2/MeOH/H_2O 70:10:1; flow rate, 1.5 ml/min; r.t.; detection at 225 nm) to give **7** (38.0 mg; t_R 42.6). *Peak 3.6.1.8* was subjected to prep. HPLC (*Cosmosil 5SL*; CH_2Cl_2/MeOH/H_2O 70:10:1; flow rate, 1.5 ml/min; r.t.; detection at 225 nm) to give **14** (23.0 mg; t_R 88.2). *Peak 3.6.1.9* was subjected to prep. HPLC (*Cosmosil 5SL*; CH_2Cl_2/MeOH/H_2O 70:10:1; flow rate, 1.5 ml/min; r.t.; detection at 225 nm) to give **6** (35.0 mg; t_R 38.4) and **11** (26.0 mg; t_R 46.8). *Peak 3.6.3* was subjected to prep. HPLC (*Cosmosil*

5SL; CH_2Cl_2/MeOH/H_2O 60:10:1; flow rate, 1.5 ml/min; r.t.; detection at 225 nm) to give **12** (35.0 mg; t_R 37.8). *Peak 3.6.4* was subjected to prep. HPLC (*Cosmosil 5SL*; CH_2Cl_2/MeOH/H_2O 60:10:1; flow rate, 1.5 ml/min; r.t.; detection at 225 nm) to give **10** (43.0 mg; t_R 30.0).

*(7S,8R,7′S,8′S)-4,9,4′,7′-Tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 7′-O-β-*D*-Glucopyranoside* (= *Tanegoside A* = *(S)-(4-Hydroxy-3-methoxyphenyl)[(3S,4R,5S)-tetrahydro-5-(4-hydroxy-3-methoxyphenyl)-4-(hydroxymethyl)furan-3-yl]methyl O-β-*D*-Glucopyranoside*; **1**). Hygroscopic amorphous powder. $[\alpha]_D^{25} = -28.8$ ($c = 0.12$, MeOH). UV (MeOH): 209 (4.1), 231 (4.1), 280 (3.8). CD ($c = 1.5 \times 10^{-4}$ M, MeOH): +17.6 (210), +4.6 (237), +1.8 (285). ^{1}H- and ^{13}C-NMR (CD_3OD): *Table 1*. FAB-MS: 561 ($[M+Na]^+$). HR-FAB-MS: 561.1960 ($[M+Na]^+$, $C_{26}H_{34}NaO_{12}^+$; calc. 561.1948).

Enzymatic Hydrolysis of **1**. An aq. soln. (5.0 ml) containing **1** (5.0 mg) and cellulase (10 mg) was incubated at 40° for 4 d. The mixture was extracted with $CHCl_3$ and concentrated to dryness to afford *(7S,8R,7′S,8′S)-4,4′,9,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan* (**1a**; 2.2 mg).

Data of **1a**. Hygroscopic amorphous powder. $[\alpha]_D^{25} = +40.0$ ($c = 0.15$, MeOH). UV (MeOH): 203 (4.5), 228 (4.0), 278 (3.6). CD ($c = 3.9 \times 10^{-5}$ M, MeOH): +19.9 (205), +3.3 (235), +1.4 (280). ^{1}H-NMR ($CDCl_3$): 1.94–2.01 (*m*, H–C(8)); 2.54–2.59 (*m*, H–C(8′)); 3.40 (br. *d*, *J* = 5.8, CH_2(9)); 4.00 (*dd*, *J* = 9.2, 7.7, H_A–C(9′)); 4.19 (*dd*, *J* = 9.2, 4.9, H_B–C(9′)); 3.84 (*s*, MeO–C(3)); 3.83 (*s*, MeO–C(3′)); 4.47 (*d*, *J* = 8.2, H–C(7)); 4.64 (*d*, *J* = 7.2, H–C(7′)); 6.77–6.89 (*m*, H–C(2,5,6,2′,5′,6′)). EI-MS: 376 (M^+). HR-EI-MS: 376.1526 (M^+, $C_{20}H_{24}O_7^+$; calc. 376.1522).

*(7S,8R,7′R,8′S)-4,4′,9,7′-Tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-O-β-*D*-Glucopyranoside* (= *{(2S,3R,4S)-Tetrahydro-4-[(R)-hydroxy(4-hydroxy-3-methoxyphenyl)methyl]-2-(4-hydroxy-3-methoxyphenyl)furan-3-yl}methyl β-*D*-Glucopyranoside*; **2**). Hygroscopic amorphous powder. $[\alpha]_D^{25} = -16.7$ ($c = 0.13$, MeOH). UV (MeOH): 205 (4.4), 229 (4.1), 278 (3.7). CD ($c = 6.8 \times 10^{-5}$ M, MeOH):, +15.2 (206), +3.5 (235). ^{1}H- and ^{13}C-NMR (CD_3OD): *Table 1*. FAB-MS: 561 ($[M+Na]^+$). HR-FAB-MS: 561.1944 ($[M+Na]^+$, $C_{26}H_{34}NaO_{12}^+$; calc. 561.1948).

Enzymatic Hydrolysis of **2**. An aq. soln. (5.0 ml) containing **2** (4.0 mg) and cellulase (10 mg) was incubated at 40° for 4 d. The mixture was extracted with $CHCl_3$, and concentrated to dryness to afford *(7S,8R,7′R,8′S)-4,4′,9,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan* (**2a**; 2.2 mg).

Data of **2a**. Hygroscopic amorphous powder. $[\alpha]_D^{25} = +35.1$ ($c = 0.15$, MeOH). UV (MeOH): 204 (4.5), 230 (4.0), 279 (3.6). CD ($c = 4.5 \times 10^{-5}$ M, MeOH): +20.0 (206), +5.8 (234). ^{1}H-NMR ($CDCl_3$): 2.25–2.32 (*m*, H–C(8)); 2.53–2.62 (*m*, H–C(8′)); 3.58 (br. *d*, *J* = 9.2, H_A–C(9′)); 3.63 (*dd*, *J* = 10.6, 5.7, H_A–C(9)); 3.65 (*dd*, *J* = 9.2, 5.8, H_B–C(9′)); 3.74 (*dd*, *J* = 10.6, 3.4, H_B–C(9)); 3.89 (*s*, MeO–C(3)); 3.90 (*s*, MeO–C(3′)); 4.36 (*d*, *J* = 9.2, H–C(7)); 4.49 (*d*, *J* = 9.6, H–C(7′)); 6.80–6.93 (*m*, H–C(2,5,6,2′,5′,6′)). EI-MS: 376 (M^+). HR-EI-MS: 376.1519 (M^+, $C_{20}H_{24}O_7^+$; calc. 376.1522).

*(7R,8S,7′S,8′R)-4,4′,9,7′-Tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-O-β-*D*-Glucopyranoside* (= *{(2R,3S,4R)-Tetrahydro-4-[(S)-hydroxy(4-hydroxy-3-methoxyphenyl)methyl]-2-(4-hydroxy-3-methoxyphenyl)furan-3-yl}methyl β-*D*-Glucopyranoside*; **3**). Hygroscopic amorphous powder. $[\alpha]_D^{25} = -12.0$ ($c = 0.13$, MeOH). UV (MeOH): 204 (4.3), 229 (4.0), 278 (3.6). CD ($c = 7.9 \times 10^{-5}$ M, MeOH): −12.9 (205), −2.5 (234). ^{1}H- and ^{13}C-NMR (CD_3OD): *Table 2*. FAB-MS: 561 ($[M+Na]^+$). HR-FAB-MS: 561.1945 ($[M+Na]^+$, $C_{26}H_{34}NaO_{12}^+$; calc. 561.1948).

Enzymatic Hydrolysis of **3**. An aq. soln. (5.0 ml) containing **3** (4.0 mg) and cellulase (10 mg) was incubated at 40° for 4 d. The mixture was extracted with $CHCl_3$, and concentrated to dryness to afford *(7R,8S,7′S,8′R)-4,4′,9,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan* (**3a**; 2.0 mg).

Data of **3a**. Hygroscopic amorphous powder. $[\alpha]_D^{25} = -35.7$ ($c = 0.10$, MeOH). UV (MeOH): 204 (4.5), 229 (4.0), 278 (3.6). CD ($c = 4.5 \times 10^{-5}$ M, MeOH): −20.3 (205), −5.2 (235). ^{1}H-NMR ($CDCl_3$): 2.25–2.32 (*m*, H–C(8)); 2.53–2.62 (*m*, H–C(8′)); 3.58 (br. *d*, *J* = 9.2, H_A–C(9′)); 3.63 (*dd*, *J* = 10.6, 5.7, H_A–C(9)); 3.65 (*dd*, *J* = 9.2, 5.8, H_B–C(9′)); 3.74 (*dd*, *J* = 10.6, 3.4, H_B–C(9)); 3.89 (*s*, MeO–C(3)); 3.90 (*s*, MeO–C(3′)); 4.36 (*d*, *J* = 9.2, H–C(7)); 4.49 (*d*, *J* = 9.6, H–C(7′)); 6.80–6.93 (*m*, H–C(2,5,6,2′,5′,6′)). EI-MS: 376 (M^+). HR-EI-MS: 376.1519 (M^+, $C_{20}H_{24}O_7^+$; calc. 376.1522).

*(7R,8S,7′R,8′S)-4,9,4′,9′-Tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9-O-β-*D*-Glucopyranoside* (= *[(2R,3S,4S,5R)-Tetrahydro-2,5-bis(4-hydroxy-3-methoxyphenyl)-4-(hydroxymethyl)furan-3-yl]methyl O-β-*D*-Glucopyranoside*; **4**). Hygroscopic amorphous powder. $[\alpha]_D^{25} = -18.2$ ($c = 0.12$, MeOH). UV (MeOH): 205 (4.5), 231 (4.1), 279 (3.7). CD ($c = 5.5 \times 10^{-5}$ M, MeOH): +15.0 (208), +7.8 (238). ^{1}H-

and ^{13}C-NMR (CD_3OD): *Table 3*. FAB-MS: 561 ($[M+Na]^+$). HR-FAB-MS: 561.1960 ($[M+Na]^+$, $C_{26}H_{34}NaO_{12}^+$; calc. 561.1948).

Enzymatic Hydrolysis of **4**. An aq. soln. (5.0 ml) containing **4** (5.0 mg) and cellulase (10 mg) was incubated at 40° for 3 d. The mixture was extracted with $CHCl_3$ and concentrated to dryness to afford *(7*R*,8*S*,7′*R*,8′*S*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan* (**4a**; 2.0 mg).

Data of **4a**. Hygroscopic amorphous powder. $[\alpha]_D^{25} = +44.8$ ($c = 0.10$, MeOH). UV (MeOH): 204 (4.5), 231 (4.0), 280 (3.6). CD ($c = 4.7 \times 10^{-5}$ M, MeOH): +10.4 (208), +5.2 (238). ^{1}H-NMR ($CDCl_3$): 2.26–2.32 (*m*, H–C(8), H–C(8′)); 3.66 (*dd*, *J* = 10.6, 8.7, H_A–C(9), H_A–C(9′)); 3.80 (*dd*, *J* = 10.6, 2.9, H_B–C(9), H_B–C(9′)); 3.89 (*s*, MeO–C(3), MeO–C(3′)); 4.74 (*d*, *J* = 9.2, H–C(7), H–C(7′)); 6.85 (*dd*, *J* = 8.2, 2.0, H–C(6), H–C(6′)); 6.90 (*d*, *J* = 8.2, H–C(5), H–C(5′)); 6.94 (*d*, *J* = 2.0, H–C(2), H–C(2′)). EI-MS: 376 (M^+). HR-EI-MS: 376.1519 (M^+, $C_{20}H_{24}O_7^+$; calc. 376.1522).

rel-*(7*R*,8*S*,7′*S*,8′*R*)-4,9,4′,9′-Tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan 9*-O-*β*-D-*Glucopyranoside* (= rel-[*(2*R*,3*S*,4*R*,5*S*)-Tetrahydro-2,5-bis(4-hydroxy-3-methoxyphenyl)-4-(hydroxymethyl)furan-3-yl]-methyl* O-*β*-D-*glucopyranoside*; **5**). Hygroscopic amorphous powder. $[\alpha]_D^{25} = -20.0$ ($c = 0.15$, MeOH). UV (MeOH): 205 (4.4), 229 (4.0), 278 (3.7). CD ($c = 6.6 \times 10^{-5}$ M, MeOH): −1.6 (206), −0.5 (232), −0.4 (272). ^{1}H- and ^{13}C-NMR (CD_3OD): *Table 3*. FAB-MS: 561 ($[M+Na]^+$). HR-FAB-MS: 561.1944 ($[M+Na]^+$, $C_{26}H_{34}NaO_{12}^+$; calc. 561.1948).

Enzymatic Hydrolysis of **5**. An aq. soln. (5.0 ml) containing **5** (5.0 mg) and cellulase (10 mg) was incubated at 40° for 3 d. The mixture was extracted with $CHCl_3$, and concentrated to dryness to afford rel-*(7*R*,8*S*,7′*R*,8′*S*)-4,9,4′,9′-tetrahydroxy-3,3′-dimethoxy-7,7′-epoxylignan* (**5a**; 2.2 mg).

Data of **5a**. Hygroscopic amorphous powder. $[\alpha]_D^{25} = \pm 0.0$ ($c = 0.10$, MeOH). UV (MeOH): 206 (4.6), 231 (4.2), 279 (3.8). CD ($c = 4.0 \times 10^{-5}$ M, MeOH): +2.5 (204). ^{1}H-NMR ($CDCl_3$): 2.52–2.61 (*m*, H–C(8), H–C(8′)); 3.79 (*dd*, *J* = 11.6, 2.9, H_A–C(9), H_A–C(9′)); 3.87 (*s*, MeO–C(3), MeO–C(3′)); 3.92 (*dd*, *J* = 11.6, 7.7, H_B–C(9), H_B–C(9′)); 4.62 (*d*, *J* = 7.7, H–C(7), H–C(7′)); 6.90 (*dd*, *J* = 8.2, 2.4, H–C(6), H–C(6′)); 6.94 (*d*, *J* = 8.2, H–C(5), H–C(5′)); 6.97 (*d*, *J* = 2.4, H–C(2), H–C(2′)). EI-MS: 376 (M^+). HR-EI-MS: 376.1520 (M^+, $C_{20}H_{24}O_7^+$; calc. 376.1522).

Determination of the Absolute Configuration of the Sugar Residues in Compounds **2**–**5**. Each of the compounds (*ca.* 1.0 mg) was refluxed with 1M HCl (1 ml) for 5 h. The mixture was neutralized with Ag_2CO_3 and filtered. The soln. was concentrated *in vacuo* and dried to give a sugar fraction. The sugar fraction was analyzed by HPLC (*TSKgel Amide-80*; 10 μm, 7.8 mm i.d. × 30 cm; *Tosoh* column; temp., 45°; MeCN/H_2O 4 : 1; flow rate 1.0 ml/min; chiral detection (*Jasco OR-2090*)). Identification of D-glucose present in the sugar fraction was carried out by the comparison of the t_R and $[\alpha]_D$ values with those of an authentic sample; t_R [min] 39.0 (D-glucose, pos. $[\alpha]_D$).

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