New Lignans from the Aerial Parts of *Rudbeckia laciniata*

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Three new furofuran lignans, (+)-4,4′-*O*-diangeloylpinoresinol (**1**), (+)-4,4′-*O*-diangeloylmedioresinol (**2**), and (+)-4,4′-*O*-diangeloylsyringaresinol (**3**), together with the known compound (+)-syringaresinol, were isolated from the MeOH extract of *Rudbeckia laciniata*. The structure elucidation of these compounds were based on 1D- and 2D-NMR, and HR-ESI-MS data. The additional structural evidence was obtained from alkaline hydrolysis of the compounds.

Introduction. – Three *Rudbeckia* species, *R. bicolor*, *R. hirta*, and *R. laciniata*, are widespread in Korea [1]. Extracts from the plants have been used as traditional Chinese medicine in the treatment of the common cold and urinary diseases [2]. Various phytochemical constituents, *i.e.*, sesquiterpene esters [3–7], sesquiterpene lactones [8–11], lignans [10], flavonoids [3][12][13], polyacetylenes [14], and carotenoids [15], have been reported from the genus *Rudbeckia*, and a wide range of biological activities, including antitumour [2–4], antioxidant [16], antibacterial, and antifungal [17–19] properties, have been investigated.

In our continuing search for bioactive constituents from the Korean Asteraceae medicinal plants, we performed a phytochemical investigation of the MeOH extract from the aerial parts of *R. laciniata*. By repeated column chromatographic separation of the extract, three new furofuran lignans, **1**–**3**, along with one known lignan were isolated. The structures were determined using spectroscopic methods including 1D- and 2D-NMR (COSY, HMQC, HMBC, and NOESY). Here, we describe the structure elucidation of the new compounds **1**–**3** (*Fig. 1*).

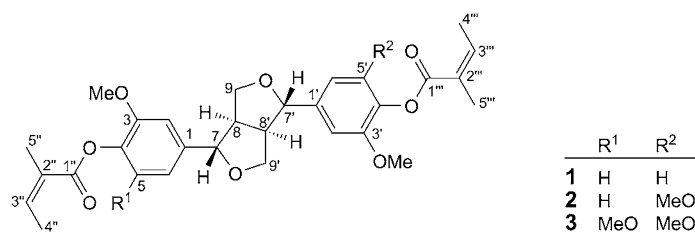

Fig. 1. *Compounds* **1**–**3**, *isolated from* R. laciniata

Results and Discussion. – Compound **1** was obtained as a colorless gum. The molecular formula of **1** was determined as $C_{30}H_{34}O_8$ from the molecular-ion peak

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$[M + Na]^+$ at m/z 545.2163 in the positive-ion-mode HR-ESI-MS. The IR spectrum of **1** showed absorption bands at 3358 and 1650 cm^{-1} ascribable to a OH and a C=O group, respectively. The ^{1}H-NMR spectrum (*Table*) of **1** showed signals of two H-atoms of a 1,3,4-trisubstituted benzene at δ(H) 7.03 (*d*, $J = 8.5$, H–C(5,5′)), 7.00 (*d*, $J = 1.5$, H–C(2,2′)), and 6.89 (*dd*, $J = 8.5$, 1.5, H–C(6,6′)), of two O–CH H-atoms at δ(H) 4.80 (*d*, $J = 4.0$, H–C(7,7′)), of two OCH_2 H-atoms at δ(H) 4.28 (*dd*, $J = 9.0$, 7.0, H–C(9a,9′a)), and 3.94 (*dd*, $J = 9.0$, 3.5, H–C(9b,9′b)), and of two CH H-atoms at δ(H) 3.07–3.13 (*m*, H–C(8,8′)), and two MeO signals at δ(H) 3.87 (*s*). In the ^{13}C-NMR spectrum (*Table*), ten C-atom signals for a symmetrical structure appeared at δ(C) 54.4 (CH), 71.9 (CH_2O), 85.6 (OCH), 109.9, 117.9, 122.9, 139.2, 139.8, and 151.6

Table. *^{1}H- and ^{13}C-NMR* (500 and 125 MHz, resp.) *Data of Compounds* **1**–**3**. Recorded in $CDCl_3$; δ in ppm, J in Hz.

Position	**1**		**2**		**3**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
C(1)		139.8		139.9		139.4
H–C(2)	7.00 (*d*, $J = 1.5$)	109.9	7.01 (*d*, $J = 1.5$)	109.9	6.62 (*s*)	102.3
C(3)		151.6		151. 6		152.4
C(4)		139.2		139.2		128.0
H–C(5)	7.03 (*d*, $J = 8.5$)	122.9	7.05 (*d*, $J = 8.5$)	122.9		152.4
H–C(6)	6.89 (*dd*, $J = 8.5$, 1.5)	117.9	6.92 (*dd*, $J = 8.5$, 1.5)	117.9	6.62 (*s*)	102.3
H–C(7)	4.80 (*d*, $J = 4.0$)	85.6	4.83 (*d*, $J = 4.0$)	85.9	4.80 (*d*, $J = 4.0$)	85.9
H–C(8)	3.07–3.13 (*m*)	54.4	3.08–3.11 (*m*)	54.5	3.09–3.11 (*m*)	54.4
CH_2(9)	4.28 (*dd*, $J = 9.0$, 7.0), 3.94 (*dd*, $J = 9.0$, 3.5)	71.9	4.31 (*dd*, $J = 9.0$, 7.0), 3.97 (*dd*, $J = 9.0$, 3.5)	72.0	4.32 (*dd*, $J = 9.0$, 7.0), 3.96 (*dd*, $J = 9.0$, 3.5)	72.1
*Me*O–C(3)	3.87 (*s*)	55.6	3.85 (*s*)	56.0	3.84 (*s*)	56.3
*Me*O–C(5)					3.84 (*s*)	56.3
C(1′)		139.8		139.3		139.4
H–C(2′)	7.00 (*d*, $J = 1.5$)	109.9	6.63 (*s*)	102.3	6.62 (*s*)	102.3
C(3′)		151.6		152.7		152.4
C(4′)		139.2		128.0		128.0
H–C(5′)	7.03 (*d*, $J = 8.5$)	122.9		152.7		152.4
H–C(6′)	6.89 (*dd*, $J = 8.5$, 1.5)	117.9	6.63 (*s*)	102.3	6.62 (*s*)	102.3
H–C(7′)	4.80 (*d*, $J = 4.0$)	85.6	4.79 (*d*, $J = 4.0$)	85.6	4.80 (*d*, $J = 4.0$)	85.9
H–C(8′)	3.07–3.13 (*m*)	54.4	3.08–3.11 (*m*)	54.3	3.09–3.11 (*m*)	54.4
CH_2(9′)	4.28 (*dd*, $J = 9.0$, 7.0), 3.94 (*dd*, $J = 9.0$, 3.5)	71.9	4.31 (*dd*, $J = 9.0$, 7.0), 3.95 (*dd*, $J = 9.0$, 3.5)	71.9	4.32 (*dd*, $J = 9.0$, 7.0), 3.96 (*dd*, $J = 9.0$, 3.5)	72.1
*Me*O–C(3′)	3.87 (*s*)	55.6	3.83 (*s*)	56.3	3.84 (*s*)	56.3
*Me*O–C(5′)			3.83 (*s*)	56.3	3.84 (*s*)	56.3
C(1″)		166.0		166.0		165.8
C(2″)		127.2		127.3		127.3
H–C(3″)	6.20–6.25 (*m*)	139.9	6.18–23 (*m*)	140.0	6.17–6.21 (*m*)	139.3
H–C(4″)	2.06 (*d*, $J = 1.5$)	15.9	2.08 (*d*, $J = 1.5$)	15.9	2.08 (*d*, $J = 1.5$)	15.9
H–C(5″)	2.05 (*d*, $J = 1.5$)	20.7	2.07 (*d*, $J = 1.5$)	20.7	2.07 (*d*, $J = 1.5$)	20.7
C(1‴)		166.0		165.8		165.8
C(2‴)		127.2		127.2		127.3
H–C(3‴)	6.20–6.25 (*m*)	139.9	6.18–23 (*m*)	139.9	6.17–6.21 (*m*)	139.3
H–C(4‴)	2.06 (*d*, $J = 1.5$)	15.9	2.08 (*d*, $J = 1.5$)	15.9	2.08 (*d*, $J = 1.5$)	15.9
H–C(5‴)	2.05 (*d*, $J = 1.5$)	20.7	2.07 (*d*, $J = 1.5$)	20.7	2.07 (*d*, $J = 1.5$)	20.7

(benzene C), including MeO signals at δ(C) 55.6. These spectral data implied that **1** was a furofuran-type lignan [20]. Additionally, the ^{1}H-NMR spectrum of **1** showed the H-atom signals for the two angeloyl groups at δ(H) 6.20 – 6.25 (*m*, H–C(3′,3″)), 2.06 (*d*, *J* = 1.5, H–C(4′,4″)), and 2.05 (*d*, *J* = 1.5, H–C(5′,5″)). The corresponding C-atom resonances of the two angeloyl groups were observed at δ(C) 166.0, 139.9, 127.2, 20.7, and 15.9 in the HMQC spectrum. The ^{1}H- and ^{13}C-NMR data of **1** were very similar to those of pinoresinol [21], except for the signals for additional two angeloyl groups [22]. The two angeloyl groups were at C(4) and C(4′), respectively, based on the comparison of ^{13}C-NMR chemical shifts of **1** with those of pinoresinol (δ(C) 151.6 (C(3,3′)), 139.2 (C(4,4′)), 122.9 (C(5,5′)) in **1**; 146.7 (C(3,3′)), 145.3 (C(4,4′)), 114.3 (C(5,5′)) in pinoresinol). The configuration of **1** was deduced to be same as that of (+)-pinoresinol [20][23][24] based on the NOESY correlations (*Fig. 2*) and by comparison of the coupling constants and optical rotation. Final evidence was obtained by alkaline hydrolysis. Treatment of **1** with 0.1M KOH at room temperature afforded (+)-pinoresinol, which was identified by comparison of its optical rotation value ($[\alpha]_D^{25}$ = +5.0), and ^{1}H-NMR and MS data [21]. Thus, the structure of **1** was determined as (+)-4,4′-*O*-diangeloylpinoresinol.

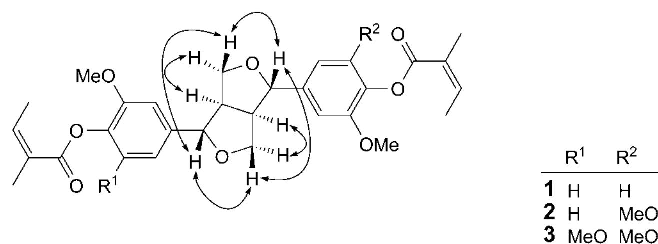

Fig. 2. *Key NOE* (H ↔ H) *correlations of compounds* **1** – **3**

Compound **2** was obtained as a colorless gum. The molecular formula of **2** was determined as $C_{31}H_{36}O_9$ from the molecular-ion peak $[M + Na]^+$ at *m/z* 575.2259 in the positive-ion-mode HR-ESI-MS. The IR spectrum of **2** showed absorption bands at 3357 and 1660 cm^{-1} ascribable to a OH and a C=O group, respectively. The ^{1}H- and ^{13}C-NMR spectra of **2** were similar to those of **1** (*Table*). The main differences were the additional NMR signals (δ(H) 6.63 (*s*, H–C(2′,6′)) and 3.83 (*s*, MeO–C(3′,5′)); δ(C) 152.7 (C(3′,5′)), 139.3 (C(1′)), 128.0 (C(4′)), 102.3 (C(2′,6′)), and 56.3 (MeO–C(3′,5′))) in **2**, impling that **2** has one 1,3,4-trisubstituted and one 1,3,4,5-tetrasubstituted benzene ring. The additional MeO group was at C(5′) as deduced from the HMBC between the MeO signal at δ(H) 3.83 and δ(C) 152.7 (C(5′)) (*Fig. 3*). The ^{1}H- and ^{13}C-NMR spectral data (*Table*) of **2** were similar to those of medioresinol [21], except for the presence of signals for the two angeloyl groups. The configuration of **2** was assumed to be same as that of (+)-medioresinol [20][21][25] by comparison its coupling constants and optical-rotation value, and confirmed by NOESY correlations (*Fig. 2*). Alkaline hydrolysis of **2** afforded (+)-medioresinol, which was identified by comparison of its optical-rotation value, and ^{1}H-NMR and MS data [21]. Thus, the structure of **2** was determined as (+)-4,4′-*O*-diangeloylmedioresinol.

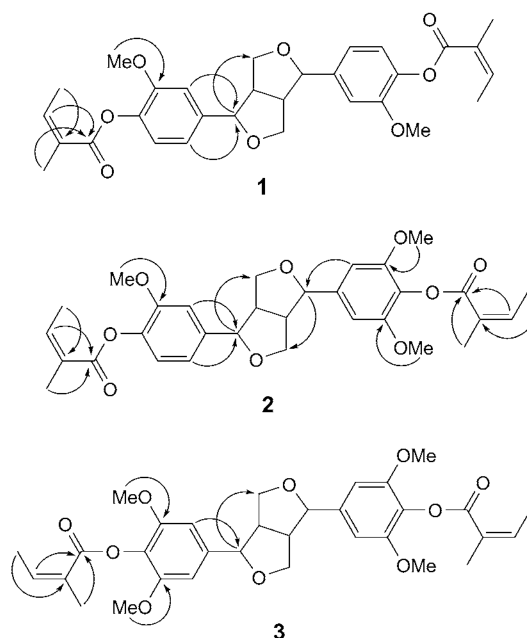

Fig. 3. *Key HMBCs* (H → C) *of compounds* **1**–**3**

Compound **3** was obtained as a colorless gum. The molecular formula of **3** was determined as $C_{32}H_{38}O_{10}$ from the molecular-ion peak $[M + Na]^+$ at m/z 605.2377 in the positive-ion-mode HR-ESI-MS. The IR spectrum of **3** showed an absorption bands at 3357 and 1660 cm^{-1} ascribable to a OH and a C=O group, respectively. The ^{1}H- and ^{13}C-NMR spectra of **3** were similar to those of (+)-syringaresinol (*Table*), except for the signals of the additional two angeloyl groups. The configuration of **3** was assumed to be same as that of (+)-syringaresinol [20][21][25] by comparison its coupling constants and optical rotation value, and verified by NOESY correlations (*Fig. 2*). Alkaline hydrolysis of **3** yielded (+)-syringaresinol, which was identified by comparison of its optical-rotation value, and ^{1}H-NMR and MS data [21]. Thus, the structure of **3** was determined as (+)-4,4′-*O*-diangeloylsyringaresinol.

Sesquiterpene lactons with angeloyl moieties had been already isolated from this plant [7], but lignans attached to short organic-acid moieites had not been reported. Furofuran lignans containing the angeloyl groups were reported from *Ligularia* [26] and *Cremanthodium* species [27].

The structure of the known compound was identified as (+)-syringaresinol by comparing its spectroscopic data with those in the literature [21].

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 230–400 mesh; *Merck*, Germany), *Lichroprep RP$_{18}$* gel (40–60 μm, *Merck*, DE-Darmstadt), and *Sephadex LH-20* (*Amersham Pharmacia Biotech*, UK). TLC: SiO_2 *60 F$_{254}$* and *RP-18 F$_{254s}$* SiO_2 plates (*Merck*, Germany); detection under UV light and by spraying with 10% aq. H_2SO_4 soln., followed by heating at 120° for 1 min. HPLC: Prep. HPLC *Gilson 306* pump, *Gilson-101* RI detector, *Phenomenex-Luna-C$_{18}$-(2)* column (250 mm × 10.00 mm i.d., 5 μm); t_R in min. UV Spectra: *Jasco P-1020* polarimeter in $CHCl_3$; λ_{max} (log ε) in nm. IR Spectra: *Bruker IFS-66/S* FT-IR spectrometer; KBr pellets; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Varian UNITY INOVA 500* FT-NMR instrument; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI- and HR-ESI-MS: *VG BIOTECH* platform LC/MS spectrometer; in *m/z*.

Plant Material. The aerial parts of *R. laciniata* (7.0 kg) were collected at the Taebaek Mountain in Gangwon-Do Province, Korea, in May 2009, and the plant was identified by one of the authors (*K. R. L.*). A voucher specimen of the plant (SKK-09-06) was deposited with the School of Pharmacy in Sungkyunkwan University.

Extraction and Isolation. Half-dried aerial parts of *R. laciniata* (Asteraceae) (7.0 kg) were extracted with 80% MeOH three times at r.t. (6 × 12 l, overnignt). The resulting MeOH extracts (400 g) were suspended in dist. H_2O (800 ml × 4), and then successively partitioned with hexane, $CHCl_3$, AcOEt, and BuOH, yielding residues of 37, 1, 5, and 30 g, resp. The hexane-soluble extract (37 g) was subjected to CC (*RP-18* (400 g), 90% MeOH): *Frs. 1–7. Fr. 2* (2 g) was subjected again to CC (SiO_2 (20 g); hexane/$CHCl_3$/MeOH 2.5 : 3 : 0.1): *Frs. 2.1–2.7. Fr. 2.4* was purified by prep. HPLC (*RP-C$_{18}$*; MeOH/H_2O 85 : 15; 2 ml/min): **1** (t_R 20 min; 5 mg). *Fr. 2.5* (1 g) was subjected to CC (*Sephadex LH-20* (100 g); 100% MeOH): *Frs 2.5.1–2.5.2. Fr. 2.5.2* (40 mg) was purified by prep. HPLC (*RP-C$_{18}$*; MeOH/H_2O 85 : 15; 2 ml/min): **2** (t_R 19 min; 5 mg) and **3** (t_R 18 min; 5 mg). *Fr.* 2.9 was purified by prep. HPLC (*RP-C$_{18}$*, MeOH/H_2O 60 : 40; 2 ml/min): *(+)-syringaresinol* (t_R 15 min; 5 mg).

(+)-4,4′-O-Diangeloylpinoresinol (*=(1*S*,3a*R*,4*S*,6a*R*)-Tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan-1,4-diylbis-[2-methoxybenzene-4,1-diyl] Bis[(2*Z*)-2-methylbut-2-enoate)*; **1**). Colorless gum. $[\alpha]_D^{25} = +14.0$ ($c = 0.17$, $CHCl_3$). UV (MeOH): 216 (4.0), 276 (3.9). IR (KBr): 3358, 2942, 2833, 1650, 1453, 1122, 1033. ^1H- and ^{13}C-NMR: *Table.* HR-ESI-MS: 545.2163 ($[M+Na]^+$, $C_{30}H_{34}NaO_8^+$; calc. 545.2151).

(+)-4,4′-O-Diangeloylmedioresinol (*=2,6-Dimethoxy-4-[(1*S*,3a*R*,4*S*,6a*R*)-4-(3-methoxy-4-{[(2*Z*)-2-methylbut-2-enoyl]oxy}phenyl)tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan-1-yl]phenyl (2*Z*)-2-Methylbut-2-enoate*; **2**). Colorless gum. $[\alpha]_D^{25} = +52$ ($c = 0.15$, $CHCl_3$). UV (MeOH): 223 (4.0), 275 (4.1). IR (KBr): 3357, 2945, 2832, 1660, 1451, 1118, 1031. ^1H- and ^{13}C-NMR: *Table.* HR-ESI-MS: 575.2259 ($[M+Na]^+$, $C_{31}H_{36}NaO_9^+$; calc. 575.2257).

(+)-4,4′-O-Diangeloylsyringaresinol (*=(1*S*,3a*R*,4*S*,6a*R*)-Tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan-1,4-diylbis-[2,6-dimethoxybenzene-4,1-diyl] Bis[(2*Z*)-(2-Methylbut-2-enoate]*; **3**). Colorless gum. $[\alpha]_D^{25} = +71.0$ ($c = 0.15$, MeOH). UV (MeOH): 216 (4.0), 272 (3.9). IR (KBr): 3357, 2945, 2832, 1660, 1451, 1116, 10311. ^1H- and ^{13}C-NMR: *Table.* HR-ESI-MS: 605.2377 ($[M+Na]^+$, $C_{32}H_{38}NaO_{10}^+$; calc. 605.2363).

Alkaline Hydrolysis of **1**–**3**. Compound **1** (1.7 mg) was hydrolyzed with 0.1M KOH (1 ml) at r.t. for 3 h. After adding H_2O (3 ml), the mixture was extracted with $CHCl_3$ three times, and the $CHCl_3$ extract was evaporated *in vacuo*. The $CHCl_3$ extract was purified through a SiO_2 *Waters Sep-pak Vac 12cc* cartridge (Milford, MA, USA; with $CHCl_3$/MeOH 20 : 1) to give (+)-pinoresinol, which was identified by ^1H-NMR, MS, and optical-rotation data. Compounds **2** (1.0 mg) and **3** (1.0 mg) were treated by the same method. The $CHCl_3$ extract was purified through a SiO_2 *Waters Sep-pak Vac 12cc* cartridge to give (+)-medioresinol, and (+)-syringaresinol, which were identified by ^1H-NMR, MS, and optical-rotation data.

(+)-Pinoresinol. $[\alpha]_D^{25} = +5.0$ ($c = 0.03$, $CHCl_3$). ^1H-NMR ($CDCl_3$, 500 MHz): 6.89 (*d*, $J = 2.0$, H–C(2,2′)); 6.88 (*d*, $J = 8.0$, H–C(5,5′)); 6.82 (*dd*, $J = 8.0$, 2.0, H–C(6,6′)); 4.74 (*d*, $J = 4.0$, H–C(7,7′)); 4.24 (*dd*, $J = 9.0$, 7.0, H–C(9a,9a′)); 3.91 (*s*, MeO–C(3,3′)); 3.88 (*dd*, $J = 9.0$, 3.5, H–C(9b,9b′)); 3.09–3.11 (*m*, H–C(8,8′)). ESI-MS: 357 ($[M-H]^-$).

(+)-Medioresinol. $[\alpha]_D^{25} = +20.0$ ($c = 0.01$, $CHCl_3$). ^1H-NMR ($CDCl_3$, 500 MHz): 6.87 (*d*, $J = 2.0$, H–C(2)); 6.86 (*d*, $J = 8.0$, H–C(5)); 6.83 (*dd*, $J = 8.0$, 2.0, H–C(6)); 6.54 (*s*, H–C(2′,6′)); 4.74 (*d*, $J = 4.0$, H–C(7)); 4.70 (*d*, $J = 4.0$, H–C(7′)); 4.24 (*dd*, $J = 9.0$, 7.0, H–C(9a,9a′)); 3.91 (*s*, MeO–C(3)); 3.88 (*s*,

MeO–C(3′,5′)); 3.88 (*dd*, $J = 9.0$, 3.5, H–C(9b)); 3.85 (*dd*, $J = 9.0$, 3.5, H–C(9b′)); 3.08–3.11 (*m*, H–C(8, 8′)). ESI-MS: 387 ($[M - H]^-$).

(+)-Syringaresinol. $[\alpha]_D^{25} = +56.0$ ($c = 0.01$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 500 MHz): 6.58 (*s*, H–C(2,6,2′,6′)); 4.74 (*d*, $J = 4.0$, H–C(7,7′)); 4.24 (*dd*, $J = 9.0$, 7.0, H–C(9a,9a′)); 3.90 (*s*, MeO–C(3,5,3′,5′)); 3.88 (*dd*, $J = 9.0$, 3.5, H–C(9b,9b′)); 3.10–3.13 (*m*, H–C(8, 8′)). ESI-MS: 417 ($[M - H]^-$).

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