Chemical Constituents of *Ligusticum sinensis* OLIV.

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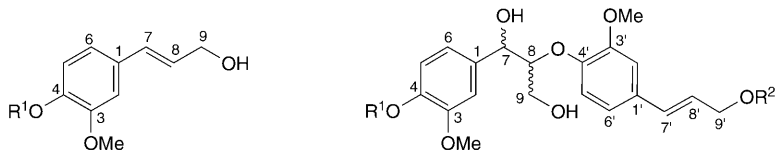
The new phenylpropanoid diglycoside ligusinenoside A (**1**), and the two new 8,4′-oxyneolignan ('8-*O*-4′-neolignan') diglycosides ligusinenosides B (**2**) and C (**3**), together with nine known compounds, were isolated from the rhizomes of *Ligusticum sinensis* OLIV. The structures of **1**–**3** were elucidated on the basis of spectroscopic analyses.

Introduction. – The rhizome of *Ligusticum sinensis* OLIV. (Umbelliferae) is known as '*Gaoben*' in traditional Chinese medicines and used for the treatment of headache, rheumatic arthralgia, diarrhea, etc. [1]. Previous studies revealed two new sesquiterpenes from this plant, ligustilone [2] and ligustiphenol [3]. Furthermore, numerous phthalides [4], coumarins [5], monoterpenes [6], and phenylpropanoids [7] were obtained from plants of the *Ligusticum* genus. Recently, *Huang et al.* reported that aqueous extracts of *L. sinensis* could inhibit melanogenesis in murine B16/F10 melanoma cells [8]. Our phytochemical investigation of the title plant led to the isolation of twelve compounds, including a new phenylpropanoid diglycoside, ligusinenoside A (**1**), and the two new 8,4′-oxyneolignan ('8-*O*-4′-neolignan') diglycosides, ligusinenosides B (**2**) and C (**3**). In this paper, we report the isolation and structural elucidation of the new diglycosides **1**–**3**.



1 R^1 = Api(1→6)Glc
1a R^1 = Api(1→2)Glc

2 (7*R*,8*R*), $R^1 = R^2$ = Glc
3 7,8-*threo*, R^1 = H, R^2 = Api(1→6)Glc

Glc = β-D-glucopyranosyl, Api = β-D-apiofuranosyl

Results and Discussion. – Ligusinenoside A (**1**) was obtained as white amorphous powders. Its HR-ESI-MS gave a molecular formula $C_{21}H_{30}O_{12}$ ($[M+Na]^+$ at m/z 497.1665). Under acid hydrolysis, **1** gave D-glucose and D-apiose as sugar moieties.

Table 1. *^{1}H-NMR Data* (400 MHz) *of* **1**–**3**[1]). δ in ppm, J in Hz.

	1 (CD_3OD)	**2** (C_5D_5N)	**3** (CD_3OD)
H–C(2)	7.06 (*d*, *J* = 1.7)	7.59 (br. *s*)	7.02 (*d*, *J* = 1.5)
H–C(5)	7.09 (*d*, *J* = 8.5)	7.60 (*d*, *J* = 8.3)	6.75 (*d*, *J* = 8.1)
H–C(6)	6.97 (*dd*, *J* = 8.3, 1.7)	7.39 (*dd*, *J* = 8.5, 2.0)	6.85 (*dd*, *J* = 8.0, 1.6)
H–C(7)	6.54 (*d*, *J* = 15.6)	5.57 (*d*, *J* = 5.4)	4.82 (*d*, *J* = 5.9)
H–C(8)	6.28 (*dt*, *J* = 15.8, 6.1)	4.96 (*q-like*, *J* = 4.8)	4.30 (*q*, *J* = 5.5)
CH_2(9)	4.20 (*dd*, *J* = 6.0, 1.2)	4.38 (*dd*, *J* = 11.7, 4.2), 4.02 (*dd*, *J* = 11.7, 5.8)	3.73 (*dd*, *J* = 12.1, 4.1), 3.46 (*dd*, *J* = 11.9, 5.4)
MeO–C(3)	3.86 (*s*)	3.69 (*s*)	3.81 (*s*)
H–C(2′)		7.05 (*d*, *J* = 2.0)	7.06 (*d*, *J* = 1.7)
H–C(5′)		7.42 (*d*, *J* = 8.3)	6.99 (*d*, *J* = 8.4)
H–C(6′)		6.94 (*dd*, *J* = 8.3, 1.8)	6.92 (*dd*, *J* = 8.2, 1.5)
H–C(7′)		6.70 (*d*, *J* = 15.9)	6.60 (*d*, *J* = 15.9)
H–C(8′)		6.37 (*dt*, *J* = 15.9, 5.8)	6.25 (*dt*, *J* = 15.7, 6.1)
CH_2(9′)		4.74 (*dd*, *J* = 12.5, 5.8), 4.46 (*dd*, *J* = 12.1, 5.4)	4.47 (*dd*, *J* = 13.3, 5.9), 4.29 (*dd*, *J* = 13.5, 5.5)
MeO–C(3′)		3.71 (*s*)	3.87 (*s*)
Glc-1			
H–C(1″)	4.84 (*d*, *J* = 7.5)	5.65 (*d*, *J* = 7.1)	4.34 (*d*, *J* = 7.6)
H–C(2″)	3.47 (*dd*, *J* = 8.5, 7.6)	4.32–4.36 (*m*)	3.22 (*dd*, *J* = 8.9, 7.8)
H–C(3″)	3.45 (*t*, *J* = 8.5)	4.04–4.09 (*m*)	3.33–3.36 (*m*)
H–C(4″)	3.32–3.36 (*m*)	4.32–4.36 (*m*)	3.28 (*t*, *J* = 9.1)
H–C(5″)	3.54–3.58 (*m*)	4.32–4.36 (*m*)	3.38–3.42 (*m*)
CH_2(6″)	3.99 (br. *d*, *J* = 10.0), 3.60 (*dd*, *J* = 10.4, 6.6)	4.48 (*dd*, *J* = 12.1, 2.4), 4.39 (*dd*, *J* = 12.1, 5.6)	3.99 (*dd*, *J* = 11.2, 1.6), 3.62 (*dd*, *J* = 11.1, 6.0)
Glc-2 or Api			
H–C(1‴)	4.97 (*d*, *J* = 2.3)	4.97 (*d*, *J* = 7.7)	5.03 (*d*, *J* = 2.5)
H–C(2‴)	3.90 (*d*, *J* = 1.8)	4.11 (*t*, *J* = 7.7)	3.92 (*d*, *J* = 2.4)
H–C(3‴)	–	3.95–3.98 (*m*)	–
H–C(4‴) or CH_2(4‴)	3.95 (*d*, *J* = 9.9), 3.74 (*d*, *J* = 9.9)	4.25–4.28 (*m*)	3.98 (*d*, *J* = 9.7), 3.76 (*d*, *J* = 9.6)
H–C(5‴)	3.57 (*s*)	4.25–4.28 (*m*)	3.57 (*s*)
CH_2(6‴)		4.57 (*dd*, *J* = 11.9, 2.2), 4.40 (*dd*, *J* = 12.1, 5.6)	

The detail NMR studies (*Tables 1* and *2*) allowed us to elucidate the structure of **1** as coniferyl alcohol 4′-*O*-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside[1]).

The ^{1}H-NMR spectrum of **1** (*Table 1*) displayed signals for two anomeric protons due to a β-D-glucopyranosyl (δ 4.84 (*d*, *J* = 7.5 Hz)) and a β-D-apiofuranosyl (δ 4.97 (*d*, *J* = 2.3 Hz)), one 1,3,4-trisubstituted[1]) aromatic ring (δ 7.09 (*d*, *J* = 8.5 Hz, 1 H), 7.06 (*d*, *J* = 1.7 Hz, 1 H), and 6.97 (*dd*, *J* = 8.3, 1.7 Hz, 1 H)), one MeO (δ 3.86, *s*)), and a 3-substituted prop-2-en-1-ol unit (δ 6.54 (*d*, *J* = 15.6 Hz, 1 H), 6.28 (*dt*, *J* = 15.8, 6.1 Hz, 1 H), and 4.20 (*dd*, *J* = 6.0, 1.2 Hz, 2 H)), indicating a phenylpropanoid diglycoside, which was consistent with the ^{13}C-NMR data (*Table 2*). Compared to the ^{13}C-

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

Table 2. *^{13}C- NMR Data* (100 MHz) *of* **1**–**3** [a])[1]). δ in ppm.

	1	**2**	**3**		**1**	**2**	**3**
C(1)	134.0	137.0	134.2	C(1′)		131.2	133.3
C(2)	111.7	112.3	112.1	C(2′)		110.5	111.8
C(3)	151.2	149.8	149.3	C(3′)		150.9	152.1
C(4)	148.0	147.2	147.6	C(4′)		149.3	149.9
C(5)	118.4	115.8	116.3	C(5′)		117.2	119.1
C(6)	121.2	120.0	121.2	C(6′)		120.1	121.5
C(7)	131.7	72.8	74.5	C(7′)		132.2	134.2
C(8)	129.2	86.5	87.4	C(8′)		124.8	125.7
C(9)	64.1	61.5	62.4	C(9′)		69.9	71.5
MeO–C(3)	57.1	55.8	56.8	MeO–C(3′)		55.8	57.0
Glc-1				Glc-2 or Api			
C(1″)	103.1	102.4	103.7	C(1‴)	111.4	103.8	111.5
C(2″)	75.2	74.9	75.6	C(2‴)	77.4	75.2	78.5
C(3″)	78.4	78.7	78.5	C(3‴)	80.9	78.6	81.0
C(4″)	72.0	71.1	72.2	C(4‴)	75.3	71.6	75.5
C(5″)	78.2	78.5	77.4	C(5‴)	65.9	78.6	66.0
C(6″)	69.1	62.2	69.1	C(6‴)		62.8	

[a]) **1** and **3** dissolved in CD_3OD, **2** in C_5D_5N.

NMR data of **1a** [9], the most important differences were the downfield shift of the C(6″) signal and the upfield shift of the C(2″) signal ($\Delta\delta = +8.6$ and -1.6, resp., in different solvents), suggesting **1** to have the same aglycone as **1a** and the glycone moiety β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranose. This structure was confirmed by HMBC correlations, *i.e.*, MeO/C(3), H-C(1″)/C(4), H-C(7)/C(1), and H-C(1‴)/C(6″).

Compound **2** had the molecular formula $C_{32}H_{44}O_{17}$ as deduced from the HR-ESI-MS ($[M+Na]^+$ at m/z 723.2491). The IR spectrum showed characteristic absorptions for OH groups (3415 cm^{-1}) and aromatic moieties (1630 and 1512 cm^{-1}). The acid hydrolysis and GC analysis, together with NMR signals (see *Tables 1* and *2*: δ(H): 5.65 (*d*, $J = 7.1$ Hz) and 4.97 (*d*, $J = 7.7$ Hz); δ(C): 102.4, 78.7, 78.5, 74.9, 71.1, 62.2; and 103.8, 78.6, 78.6, 75.2, 71.6, 62.8), revealed two individual β-D-glucopyranosyl moieties in the molecule of **2**. The structure of **2** was determined to be (7*R*,8*R*)-4,9′-bis(β-D-glucopyranosyloxy)-3,3′-dimethoxy-8,4′-oxyneolign-7′-ene-7,9-diol[1]) on the basis of 1D- and 2D-NMR analyses.

The ^{1}H-NMR signals for the aglycone of **2** were attributed to two 1,3,4-trisubstituted[1]) phenyl moieties (δ 7.60 (*d*, $J = 8.3$ Hz, 1 H), 7.59 (br. *s*, 1 H), and 7.39 (*dd*, $J = 8.5$, 2.0 Hz, 1 H); 7.42 (*d*, $J = 8.3$ Hz, 1 H), 7.05 (*d*, $J = 2.0$ Hz, 1 H) and 6.94 (*dd*, $J = 8.3$, 1.8 Hz, 1 H)), a 3-substituted (2*E*)-prop-2-en-1-ol (δ 6.70 (*d*, $J = 15.9$ Hz, 1 H), 6.37 (*dt*, $J = 15.9$, 5.8 Hz, 1 H), 4.74 (*dd*, $J = 12.5$, 5.8 Hz, 1 H) and 4.46 (*dd*, $J = 12.1$, 5.4 Hz, 1 H)), two oxygenated CH (δ 5.57 (*d*, $J = 5.4$ Hz, 1 H), and 4.96 (*q-like*, $J = 4.8$ Hz, 1 H)), one O-bearing CH_2 (δ 4.38 and 4.02, $^2J = 11.7$ Hz), and two MeO groups (δ 3.71 and 3.69, each *s*), indicating a citrusin A-like 8,4′-oxyneolignan diglucopyranoside [10]. The HMBC experiment substantiated the connectivities of the two MeO groups with C(3) and C(3′), and of the two glucopyranosyloxy groups with C(4) and C(9′). The coupling constant $J(7,8) = 5.4$ Hz and the negative CD absorption

at 210–250 nm demonstrated the relative 7,8-*threo*-configuration and the absolute configuration (8*R*) [11].

The ESI-MS of **3** exhibited quasi molecular ion peaks at *m*/*z* 693.3 ($[M+Na]^+$) and 669.3 ($[M-H]^-$), corresponding to the molecular formula $C_{31}H_{42}O_{16}$. The acid hydrolysis of **3** yielded D-apiose and D-glucose. Its ^{1}H- and ^{13}C-NMR (*Tables 1* and *2*) displayed signals for a 3,3′-dimethoxy-8,4′-oxyneolign-7′-ene-4,7,9-triol and a β-apiofuranosyl-(1 → 6)-β-glucopyranosyloxy moiety, just like a combination of the aglycone of **2** and the glycone of **1**. In the HMBC spectrum, significant correlations C(9′)/H–C(1″), and C(6″)/H–C(1‴) were observed, confirming a β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyloxy group at C(9′) of the aglycone. The $J(7, 8) = 5.9$ Hz of **3** demonstrated the relative 7,8-*threo* configuration [11]. However, noise-like signals appearing at 200–300 nm in the CD spectrum made the determination of the absolute configuration at C(8) uncertain. Therefore, the relative structure of **3** was elucidated to be *threo*-9′-[β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyloxy]-3,3′-dimethoxy-8,4′-oxyneolign-7′-ene-4,7,9-triol[1]).

The known compounds: baihuaqianhuoside [12], 4-[β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyloxy]-3-(methoxyphenyl)propiophenone [13], (7*R*,8*S*)-dehydrodiconiferyl alcohol 4,9-di-*O*-β-D-glucopyranoside [14], dehydrodiconiferyl alcohol 4-*O*-β-D-glucopyranoside [15], scopolin [16], hymexelsin [17], 3-butyl-4,5,6,7-tetrahydro-3,6,7-trihydroxyphthalide [18], benzyl alcohol O-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside [19], and sucrose [20], were identified by comparison of their ^{1}H- and ^{13}C-NMR, MS, and physical data with those reported in the literature.

Experimental Part

General. Column chromatography (CC): silica gel (200–300 or 400 mesh; *Qingdao Haiyang, Co*., China), *ODS-A* gel (*Greenherbs Science & Technology Development Co., Ltd*., Beijing, China), *D-1400* macroporous resin (*Yangzhou Pharmaceutical Factory,* China), and *Sephadex LH-20* (*Pharmacia Biotech AB,* Uppsala, Sweden). GC Analyses: *Perkin-Elmer Sigma-115* gas chromatograph. Anal. and prep. HPLC: *Varian* HPLC system, *Prepstar-SD-1* pump, *UV-VIS-320*, detector, column: *Merck*, 5 μm, i.d. 4.6×250 mm; and *ODS*-A, 12 μm, i.d. 25×250 mm, resp. Optical rotation: *Perkin-Elmer 341* polarimeter. IR Spectra: *Nicolet Magna-750-FTIR* spectrometer, KBr pellets; in cm^{-1}. NMR Spectra: *Bruker DRX-400* instrument; at 400 (^{1}H) or 100 MHz (^{13}C); in (D_4)methanol or (D_5)pyridine; δ in ppm rel. to $SiMe_4$, *J* in Hz. ESI-MS and HR-ESI-MS: *LCQ-Deca* and *Q-Tof-Ultima* mass spectrometers, resp.

Plant Material. The rhizome of *L. sinensis* OLIV. was purchased from *Huanghe Crude Drug Market* in Lanzhou, Gansu Province, China, in October 2004, and identified by Prof. *D.-Y. Zhu*. The voucher specimens (No.20041014) are deposited in the Herbarium of our institute.

Extraction and Isolation. Dried chopped rhizomes of *L. sinensis* (10 kg) were extracted with 95% EtOH (3×). After removal of the solvents by evaporation, the extract was suspended in H_2O and then partitioned successively with petroleum ether, $CHCl_3$, and BuOH. The BuOH-soluble part (280 g) was subjected to CC (macroporous resin (i.d. 10×80 cm), EtOH/H_2O (*v*/*v*) 0, 10, 30, 50, 75, 95%): *Frs. A–F. Fr. C* (30% EtOH fraction, 15 g) was separated by CC (SiO_2, $CHCl_3$/MeOH 100 : 0 → 0 : 100): *Frs.C.1–C.16. Fr. C.8* yielded solid scopolin (13 mg). *Fr. C.5* supplied baihuaqianhuoside (28 mg) and *Fr. C.6* furnished 3-butyl-4,5,6,7-tetrahydro-3,6,7-trihydroxyphthalide (26 mg) after repeated CC (SiO_2, $CHCl_3$/MeOH 15 : 1). The 4-[β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyloxy]-3-(methoxyphenyl)propiophenone (4 mg) and hymexelsin (28 mg) were obtained from *Fr. C.11* after two CC (1. *LiChrospher RP-18*, MeOH/H_2O 1 : 2; 2. *Sephadex LH-20*, MeOH). *Fr. C.13* provided **1** (23 mg), dehydrodiconiferyl alcohol 4,9-di-*O*-β-D-glucopyranoside (25 mg), and **3** (13 mg) after purification by CC (1. *LiChrospher RP-18*, MeOH/H_2O 1 : 3; 2. *Sephadex LH-20*, MeOH/H_2O 10 : 1; 3. prep. HPLC, MeOH/H_2O 1 : 3 for

3). *Fr. C.14* afforded **2** (7 mg), (7*R*,8*S*)-dehydrodiconiferyl alcohol 4,9-di-O-*β*-D-glucopyranoside (31 mg), benzyl alcohol *O*-*β*-D-apiofuranosyl-(1 → 6)-*β*-D-glucopyranoside (20 mg) and sucrose (30 mg) after following CC (1. *LiChrospher RP-18*, MeOH/H_2O 1:3; 2. *Sephadex LH-20*, MeOH/H_2O 10:1; 3. prep. HPLC, MeOH/H_2O 12:88 for **2**).

Ligusinenoside A (= *Coniferyl Alcohol 4′*-O-*β*-D-*Apiofuranosyl-(1 → 6)-β*-D-*glucopyranoside* = *4-(3-Hydroxyprop-1-enyl)-2-methoxyphenyl 6*-O-D-*Apio-β*-D-*furanosyl-β*-D-*glucopyranoside*; **1**): White amorphous powder. $[\alpha]_D^{21} = -101$ ($c = 0.49$, MeOH). IR: 3423 (OH), 1629, 1512. ^{1}H- and ^{13}C- NMR: *Tables 1* and *2*. ESI-MS (pos./neg.): 497.2 ($[M+Na]^+$), 971.4 ($[2M+Na]^+$), 473.0 ($[M-H]^-$). HR-ESI-MS: 497.1665 ($[M+Na]^+$, $C_{21}H_{30}O_{12}Na^+$; calc. 497.1635).

Ligusinenoside B (= *(7*R*,8*R*)-4,9′-Bis(β*-D-*glucopyranosyloxy)-3,3′-dimethoxy-8,4′-oxyneolign-7′-ene-7,9-diol* = *3-{4-{(1*R*,2*R*)-2-[4-(β*-D-*Glucopyranosyloxy)-3-methoxyphenyl]-2-hydroxy-1-(hydroxymethyl)ethoxy}-3-methoxyphenyl}prop-2-enyl β*-D-*Glucopyranoside*; **2**): White amorphous powder. $[\alpha]_D^{21} = -27$ ($c = 0.32$, MeOH). CD ($c = 0.40$ g l^{-1}, MeOH): 3400000 (207 nm), −3200000 (212 nm), −600000 (230 nm), −980000 (282 nm). IR: 3415 (OH), 1630, 1512. ^{1}H- and ^{13}C- NMR: *Tables 1* and *2*. ESI-MS (pos./neg.): 723.3 ($[M+Na]^+$), 561.3 ($[M-Glc+Na]^+$), 699.5 ($[M-H]^-$), 537.2 ($[M-Glc-H]^-$). HR-ESI-MS: 723.2491 ($[M+Na]^+$, $C_{32}H_{44}O_{17}Na^+$; calc. 723.2476).

Ligusinenoside C (= threo-*9′-[β*-D-*Apiofuranosyl-(1 → 6)-β*-D-*glucopyranosyloxy]-3,3′-dimethoxy-8,4′-oxyneolign-7′-ene-4,7,9-triol* = rel-*3-{4-[(1*R*,2*R*)-2-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-1-(hydroxymethyl)ethoxy]-3-methoxyphenyl}prop-2-enyl 6*-O-D-*Apio-β*-D-*furanosyl-β*-D-*glucopyranoside*; **3**): White amorphous powder. $[\alpha]_D^{21} = -53$ ($c = 0.33$, MeOH). IR: 3396 (OH), 1605, 1510. ^{1}H- and ^{13}C- NMR: *Tables 1* and *2*. ESI-MS (pos./neg.): 693.3 $[M+Na]^+$, 669.3 $[M-H]^-$. HR-ESI-MS: 693.2329 ($[M+Na]^+$, $C_{31}H_{42}O_{16}Na^+$; calc. 693.2371).

Acid Hydrolysis of Compounds **1**–**3**. A soln. of **1**–**3** (each 2 mg) in 2M HCl/dioxane 1:1 (*v*/*v*; 2 ml) was heated under reflux for 2 h. After cooling, the mixture was neutralized with $NaHCO_3$, then filtrated to remove the solid. The soln. was subjected to CC (*Sephadex LH-20*, MeOH/H_2O 1:1) to afford a sugar fraction. This sugar fraction and standard D-glucose and D-apiose (*Sigma*, USA) were each treated with L-cysteine methyl ester hydrochloride (2 mg) in pyridine (1 ml) at 60° for 1 h. Then the soln. was treated with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (0.02 ml) at 60° for 1 h. Subsequently, the supernatant was subjected to GC analysis (*Supelco*, 230°, flow rate 15 ml/min). D-Glucose (standard: t_R 24.1 min; **1**: t_R 24.1 min; **2**: t_R 24.2 min; **3**: t_R 24.1 min) was detected in the sugar fractions from **1**–**3**, and D-apiose (standard: t_R 14.3 min; **1**: t_R 14.2 min; **3**: t_R 14.3 min) in that from **1** and **3**.

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