

Lignans from *Schisandra propinqua* var. *propinqua*

Chun LEI,^{a,b} Sheng-Xiong HUANG,^{a,b} Ji-Jun CHEN,^a Jian-Xin PU,^{a,b} Li-Bin YANG,^{a,b} Yong ZHAO,^{a,b} Jin-Ping LIU,^{a,b} Xue-Mei GAO,^{a,b} Wei-Lie XIAO,^a and Han-Dong SUN*^a

^aState Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences; Kunming 650204, P. R. China; and ^bGraduate School of the Chinese Academy of Sciences; Beijing 100039, P. R. China. Received April 30, 2007; accepted May 15, 2007

Two new dibenzocyclooctadiene lignans angeloyl-(+)-gomisin K₃ (**1**) and methylisogomisin O (**2**), together with six known ones, isogomisin O, angeloylisogomisin O, gomisin O, angeloygomisin O, benzoylgomisin O, epigomisin O, and four 1,4-bis(phenyl)-2,3-dimethylbutane type lignans, pregomisin, meso-dihydroguaiaretic acid, isoanwulignan, and sphenanlignan were isolated from the aerial parts of *Schisandra propinqua* var. *propinqua*. The structures of **1** and **2** were elucidated by spectroscopic methods including extensive 1D- and 2D-NMR techniques.

Key words *Schisandra propinqua* var. *propinqua*; dibenzocyclooctadiene; angeloyl-(+)-gomisin K₃; methylisogomisin O

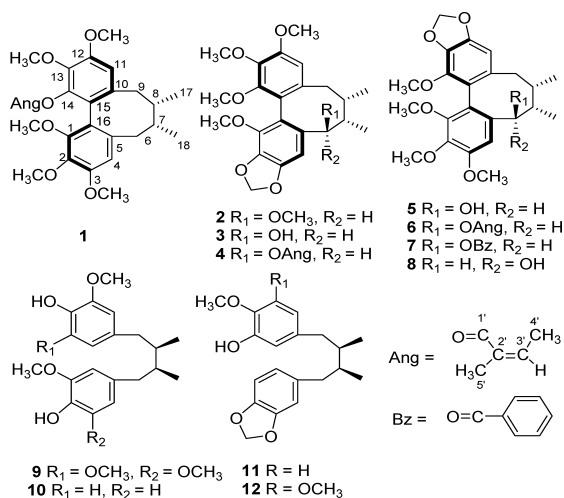
The fruits of *Schisandra* spp. (Schisandraceae) are commonly used in Chinese traditional medicine as tonic, sedative, and astringent agents.¹⁾ Pioneering phytochemical work on them were achieved by Yukinobu Ikeya *et al.* resulting in a series of dibenzocyclooctadiene lignans (“gomisins” in Japanese),^{2–13)} which are then found to possess various biological activities including antihepatitis, antitumor, and antilipid peroxidation effects.^{14–18)} In western China, aerial parts of *Schisandra* genus are also used for the treatment of rheumatic lumbago and traumatic injury and related diseases. In order to investigate the components of the aerial parts and search for potential leads for drug development, phytochemical investigation on the aerial parts of *Schisandra propinqua* var. *propinqua*, a Chinese traditional medicine indigenous to Yunnan province, was carried out in our group. Eight dibenzocyclooctadiene lignans, angeloyl-(+)-gomisin K₃ (**1**), methylisogomisin O (**2**), isogomisin O (**3**),²⁾ angeloylisogomisin O (**4**),²⁾ gomisin O (**5**),³⁾ angeloygomisin O (**6**),²⁾ benzoylgomisin O (**7**),¹⁹⁾ and epigomisin O (**8**),³⁾ and four 1,4-bis(phenyl)-2,3-dimethylbutane type lignans, pregomisin (**9**),⁴⁾ meso-dihydroguaiaretic acid (**10**),⁴⁾ isoanwulignan (**11**),²⁰⁾ and sphenanlignan (**12**)²¹⁾ were isolated from fraction B (CHCl₃–Me₂CO 9 : 1) of EtOAc extract, which are almost the same as the components previously isolated from fruits.

Among them, compounds **1** and **2** were new compounds. Herein, we report the isolation and extensive structure elucidation of the new compounds.

Results and Discussion

Angeloyl-(+)-gomisin K₃ (**1**) was obtained as yellowish powder and showed a molecular ion peak at *m/z* 485.2532 ([M+H]⁺, Calcd 485.2539) in its HR-ESI-MS corresponding to the molecular formula C₂₈H₃₆O₇. The UV spectrum showed λ_{max} (MeOH) values at 215 nm. The IR spectrum showed the presence of an α,β-unsaturated ester (1736 cm⁻¹) and aromatic groups (1597, 1578, 1492 cm⁻¹). The ¹H-, ¹³C- and DEPT-NMR spectra exhibited 18 carbon atoms (including 12 aromatic ones, two methines, two methenes, and two secondary methyls) for the dibenzocyclooctadiene skeleton in addition to one angeloyl and five methoxy groups. Closely investigation on the spectral data (including 1D-NMR and optical rotation data) of **1** showed that it was an angeloyl-derivative of (+)-gomisin K₃ with a *R*-biphenyl configuration.⁵⁾ Most signals in the ¹³C-NMR spectrum of **1** (Table 1) were similar to that of (+)-gomisin K₃ except those of C-11, C-12, C-13, and C-15, which were downshifted from δ_C 107.9, 150.6, 134.0, and 117.0 in (+)-gomisin K₃ to δ_C 113.8, 152.5, 140.5, and 124.9 in **1**, and C-14, which was upshifted from δ_C 146.9 in (+)-gomisin K₃ to δ_C 143.3 in **1**, respectively. These changed signals were almost the same as that of the monoacetate derivative of (+)-gomisin K₃.⁵⁾

In the ¹H- and ¹³C-NMR spectra of **1** (Table 1), two secondary methyl group signals (δ_H 0.77, d, *J*=7.0 Hz, H₃-17; 0.98, d, *J*=7.2 Hz, H₃-18) were assignable to *cis*-oriented Me-17 (δ_C 13.0) and Me-18 (δ_C 21.8),²²⁾ which was then found to be attached to C-8 (δ_H 1.91, m; δ_C 34.7) and C-7 (δ_H 2.28, m; δ_C 41.7), respectively. The presence of an angeloyl group were indicated by signals (δ_H 5.92, m, H-3'; 1.74, d, *J*=6.5 Hz, H₃-4'; 1.72, s, H₃-5'; δ_C 166.2, C-1'; 126.8, C-2'; 137.1, C-3'; 15.4, C-4'; 20.5, C-5')²³⁾ in the 1D-NMR, which was further confirmed by the peak at *m/z* 402 [M–82]⁺ (100) in the EI-MS spectrum. This angeloyl group and those methoxyl groups at δ_C 60.7 (δ_H 3.46, s), 60.7 (δ_H 3.76, s), and 60.6 (δ_H 3.74, s) should be located at C-1, C-2, C-13, or C-14, and the other two methoxyls at δ_C 56.3 (δ_H 3.83, s) and 56.2 (δ_H 3.91, s) should be attributed to C-3 or



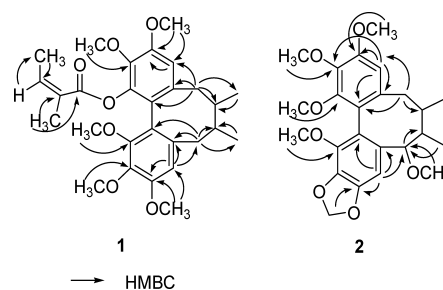
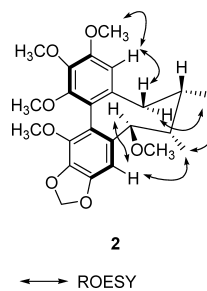
* To whom correspondence should be addressed. e-mail: hdsun@mail.kib.ac.cn

Table 1. ^1H - and ^{13}C -NMR Data of Compounds **1** and **2** (500 MHz for ^1H and 125 MHz for ^{13}C , in CDCl_3)

	1		2	
	δ_{C}	δ_{H}	δ_{C}	δ_{H}
1	152.2 s		142.6 s	
2	140.7 s		137.7 s	
3	154.4 s		148.4 s	
4	108.6 d	6.67 (s)	107.5 d	6.59 (s)
5	139.8 s		133.7 s	
6	35.9 t	1.91 (m) 2.02 (d, 13.0)	90.6 d	3.82 (overlapped)
7	41.7 d	2.28 (m)	39.5 d	1.81 (m)
8	34.7 d	1.91 (m)	37.5 d	1.58 (m)
9	39.6 t	2.50 (br d, 13.5) 2.69 (dd, 13.5, 1.5)	39.3 t	2.37 (m) 1.95 (m)
10	134.6 s		137.2 s	
11	113.8 d	6.88 (s)	107.4 d	6.55 (s)
12	152.5 s		154.1 s	
13	140.5 s		140.8 s	
14	143.3 s		152.9 s	
15	124.9 s		123.5 s	
16	121.9 s		124.5 s	
17	13.0 q	0.77 (d, 7.0)	17.1 q	0.85 (overlapped)
18	21.8 q	0.98 (d, 7.2)	17.2 q	0.85 (overlapped)
OMe-1	60.7 q	3.46 (s)	59.5 q	3.72 (s)
OMe-2	60.7 q	3.76 (s)		
OMe-3	56.3 q	3.83 (s)		
OCH ₂ O			102.1 t	6.03 (br s), 6.01 (br s)
OMe-6			55.9 q	2.97 (s)
OMe-12	56.2 q	3.91 (s)	56.1 q	3.82 (s)
OMe-13	60.6 q	3.74 (s)	60.6 q	3.77 (s)
OMe-14			60.5 q	3.69 (s)
1'	166.2 s			
2'	126.8 s			
3'	137.1 d	5.92 (m)		
4'	15.4 q	1.74 (d, 6.5)		
5'	20.5 q	1.72 (s)		

C-12. By comparison with 1D-NMR signals of monoacetate-(+)-gomisin K₃ and with the help of HMBC (Fig. 1), compound **1** was established as shown.

Methylisogomisin O (**2**) was obtained as prism crystals and possesses a molecular formula of $\text{C}_{24}\text{H}_{30}\text{O}_7$, as derived from its HR-ESI-MS (m/z 453.1885, $[\text{M}+\text{Na}]^+$, Calcd 453.1889) and spectroscopic data (Table 1). The 1D-NMR of **2** showed the signals due to an octa-substituted biphenyl moiety [^1H -NMR, δ_{H} 6.55, 6.59 (1H, each, s), ^{13}C -NMR, δ_{C} 154.1, 152.9, 148.4, 142.6, 140.8, 137.7, 137.2, 133.7, 124.5, 123.5 (1C, each, s); 107.5, 107.4 (1C, each, d)], and the CD spectrum exhibited a strong negative Cotton effect at λ_{max} 241 nm, which indicated that **2** is a dibenzocyclooctadiene lignan with *S*-biphenyl configuration. These data were found to be almost identical to those of isogomisin O.²⁾ Thus, the methylenedioxy group (δ_{H} 6.01 and 6.03, 1H each, br s; δ_{C} 102.1), four methoxy groups (δ_{H} 3.72, 3.82, 3.77, 3.69, 3H each, s; δ_{C} 59.5, 56.1, 60.6, 60.5, 1C each, q), the benzylic methylene group (δ_{H} 2.37, 1.95, 1H each, m; δ_{C} 39.3, t, C-9), the benzylic oxymethine (δ_{H} 3.82, 1H, overlapped; δ_{C} 90.6, d, C-6) were assigned to be in the same place as isogomisin O. The other methoxy group (δ_{H} 2.97, 3H, s; δ_{C} 55.9, q) was placed at C-6, which can be further confirmed by the HMBC correlation from H₃-OMe (δ_{H} 2.97) to C-6 (Fig. 1). Key HMBC correlations from H-6 to C-7 (δ_{H} 1.81,

Fig. 1. Selected HMBC Correlations of **1** and **2**Fig. 2. Partial ROESY Correlations of **2**

m; δ_{C} 39.5, d), from H₃-18 (δ_{H} 0.85, overlapped, δ_{C} 17.2, q, Me-18) to C-6, and from H₂-9 to C-8 (δ_{H} 1.58, m; δ_{C} 37.5, d) confirmed the attribution of the cyclooctadiene as shown in Table 1. The configuration of OMe-6 was deduced as β -orientation by the δ_{C} 90.6 which was similar to that of the 6- β -oriented derivatives of gomisins^{2,3,6,9,10,19)} and was distinct from that of 6- α -oriented components in dibenzocyclooctadiene lignan family,^{2,7-9)} which was further confirmed by the NOESY correlation between H-4/H-6 α (Fig. 2). The cyclooctadiene ring of **2** was indicated to be a twist-boat-chair (TBC) conformation by the NOESY correlations between H-4/H₃-18 and H-9 β /H-11.

The known compounds **3**–**12** were determined to be isogomisin O (**3**), angeloylisogomisin O (**4**), gomisin O (**5**), angeloygomisin O (**6**), benzoylgomisin O (**7**), and epigomisin O (**8**), pregomisin (**9**), meso-dihydroguaiaretic acid (**10**), isoanwulignan (**11**), and sphenanlignan (**12**) by comparison of their spectral data with literature values. They all are previously isolated from the fruits of *Schisandra* genus. Thus, we could deduce that lignans are the main components of the aerial parts of *S. propinqua* var. *propinqua*, just the same as in the fruits of *Schisandra* spp, and dibenzocyclooctadiene lignans are the major constituents of the aerial parts.

Experimental

General Procedure Optical rotations were measured with a HORIBA SEPA-300 High Sensitive. IR spectra were determined on a Bio-Rad FTS-135 spectrophotometer with KBr pellets. Melting point was measured on a Fisher-Johns apparatus and uncorrected. The CD spectrum was recorded on a J-8115 (JASCO) spectropolarimeter. 1D- and 2D-NMR spectra were run on a Bruker AM-400 and DRX-500 instruments with tetramethylsilane (TMS) as an internal standard. EI-MS were recorded on a VG Auto Spec-3000 spectrometer (70 eV). HR-ESI-MS were taken on an API Qstar Pulsar instrument. Column chromatography was performed on silica gel and silica gel H (200–300 mesh, 10–40 μm , Qingdao Marine Chemical Inc. China). Lichroprep RP-18 (43–63 μm , Merck, Darmstadt, Germany) and Sephadex LH-20 (Pharmacia Fine Chemical Co. Ltd.) were also used for column chromatography. Fractions were monitored by TLC and spots were visualized by heating silica gel plates sprayed with 8% H_2SO_4 in EtOH.

Plant Material Plants of *S. propinqua* var. *propinqua* were collected in

Tengchong county, Yunnan province, China, in July 2006, and were identified by Prof. Xi-Wen Li, Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, P. R. China.

Extraction and Isolation The air-dried leaves and stems of *S. propinqua* var. *propinqua* (8 kg) were extracted with 70% aq. Me₂CO (4×151, 3d, each) at room temperature and concentrated *in vacuo* to give a crude extract (560 g), which was dissolved in H₂O and then extracted successively with PE and EtOAc. The EtOAc part (250 g) was chromatographed on silica gel column eluting with CHCl₃-Me₂CO (1:0, 9:1, 8:2, 2:1, 1:1, and 0:1) to afford fractions A—F. Fraction B (75 g) was purified by repeated chromatography over silica gel and RP-18 and then recrystallization to yield compounds **2** (565 mg), **7** (26 mg), and **9** (70 mg). Continuing purification of Fraction B by Sephadex LH-20, silica gel H and then by semi-preparative HPLC with 65—75% MeOH in H₂O as the mobile phase to yield compounds **1** (4 mg), **3** (20 mg), **4** (4 mg), **5** (16 mg), **6** (3 mg), **8** (30 mg), **10** (4 mg), **11** (5 mg), and **12** (2 mg).

Angeloyl-(+)-gomisin K₃ (**1**): Amorphous powder; [α]_D^{19.5} +16.5° (*c*=0.12, MeOH); UV λ_{\max} (MeOH) nm (log ϵ): 215.0 (4.71), 193.4 (4.39); IR (KBr) λ_{\max} cm⁻¹: 2956, 2934, 2872, 1736, 1597, 1578, 1492, 1456, 1401, 1328, 1275, 1127, 1008. ¹H- and ¹³C-NMR: see Table 1; EI-MS: *m/z* (%): 485 [M+H]⁺ (27), 484 [M]⁺ (88), 403 (27), 402 (100), 83 (61), 55 (25); HR-ESI-MS (pos.) *m/z*: 485.2532 [M+H]⁺, C₂₈H₃₇O₇⁺, Calcd 485.2539.

Methylisogomisin O (**2**): Prism crystals, mp 148—150 °C; [α]_D^{28.3} +46.7° (*c*=0.40, MeOH); UV λ_{\max} (MeOH) nm (log ϵ): 216.8 (4.51); CD (MeOH) λ_{\max} nm ($\Delta\epsilon$) 212.6 (+10.09), 219.6 (-10.19), 223.2 (+10.94), 226.8 (+16.16), 241.8 (-95.44), 249.4 (-69.78), 251.6 (-73.13). IR (KBr) λ_{\max} cm⁻¹: 3426, 2969, 2935, 2873, 1620, 1597, 1570, 1466, 1427, 1407, 1329, 1270, 1231, 1194, 1146, 1119, 1098, 1083, 1002. ¹H- and ¹³C-NMR: see Table 1; EI-MS: *m/z* (%): 430 [M]⁺ (85), 398 (100), 383 (15), 312 (33); HR-ESI-MS (pos.) *m/z*: 453.1885 [M+Na]⁺, C₂₄H₃₀O₇ Na⁺, Calcd 453.1889.

Acknowledgments This work was supported by grants from the National Science Foundation of China (No. 20402016), the project of Chinese Academy Sciences (XiBuZhiGuang to W.-L. Xiao), the Natural Science Foundation of Yunnan province (No. 2005XY04), and from the Yong Academic and Technical Leader Raising Foundation of Yunnan Province (2006PY01-47).

References

- Song W. Z., Tong Y. Y., Chen L. S., *Chin. Trad. Herbal Drugs*, **13**, 51—58 (1982).

- Ikeya Y., Ookawa N., Taguchi H., Yosioka I., *Chem. Pharm. Bull.*, **30**, 3202—3206 (1982).
- Ikeya Y., Taguchi H., Yosioka I., Kobayashi H., *Chem. Pharm. Bull.*, **27**, 2695—2709 (1979).
- Ikeya Y., Taguchi H., Yosioka I., Kobayashi H., *Chem. Pharm. Bull.*, **27**, 1583—1588 (1979).
- Ikeya Y., Taguchi H., Yosioka I., *Chem. Pharm. Bull.*, **28**, 2422—2427 (1980).
- Ikeya Y., Taguchi H., Yosioka I., Iitaka Y., Kobayashi H., *Chem. Pharm. Bull.*, **27**, 1395—1401 (1979).
- Ikeya Y., Taguchi H., Yosioka I., Kobayashi H., *Chem. Pharm. Bull.*, **28**, 3357—3361 (1980).
- Ikeya Y., Kanatani H., Hakozaiki M., Taguchi H., Mitsuhashi H., *Chem. Pharm. Bull.*, **36**, 3974—3979 (1988).
- Ikeya Y., Miki E., Okada M., Mitsuhashi H., Chai J. G., *Chem. Pharm. Bull.*, **38**, 1408—1411 (1990).
- Ikeya Y., Sugama K., Okada M., Mitsuhashi H., *Phytochemistry*, **30**, 975—980 (1991).
- Ikeya Y., Taguchi H., Yosioka I., Kobayashi H., *Chem. Pharm. Bull.*, **27**, 1576—1582 (1979).
- Ikeya Y., Taguchi H., Yosioka I., Kobayashi H., *Chem. Pharm. Bull.*, **27**, 1383—1394 (1979).
- Ikeya Y., Taguchi H., Yosioka I., *Chem. Pharm. Bull.*, **30**, 132—139 (1982).
- Kuo Y. H., Li S. Y., Huang R. L., Wu M. D., Huang H. C., Lee K. H., *J. Nat. Prod.*, **64**, 487—490 (2001).
- Kuo Y. H., Huang R. L., Kuo Y. L. K., Chen C. F., *J. Org. Chem.*, **64**, 7023—7027 (1999).
- Peng H. L., Chen D. F., Lan H. X., Zhang X. M., Gu Z., Jiang M. H., *Acta Pharmacol. Sin.*, **17**, 538—541 (1996).
- Zhang X. M., Chen D. F., He X. J., Yang S., Zheng P., Jiang M. H., *Acta Pharmacol. Sin.*, **21**, 373—376 (2000).
- Chang J. B., Reiner J., Xie J. X., *Chem. Rev.*, **105**, 4581—4609 (2005).
- Chen C. C., Shen C. C., Shin Y. Z., Pan T. M., *J. Nat. Prod.*, **57**, 1164—1165 (1994).
- Luo G., Liu J. S., *Acta Chemica Sinica*, **50**, 515—520 (1992).
- Jiang S. J., Wang Y. H., Chen D. F., *Chin. J. Nat. Med.*, **3**, 78—82 (2005).
- Ghera E., Ben D. Y., Becker D., *Tetrahedron Lett.*, **18**, 463—467 (1997).
- Xu L. J., Huang F., Chen S. B., Zhang Q. X., Li L. N., Chen S. L., Xiao P. G., *Planta Med.*, **72**, 169—174 (2006).