Lignans from *Schisandra propinqua* var. *propinqua*

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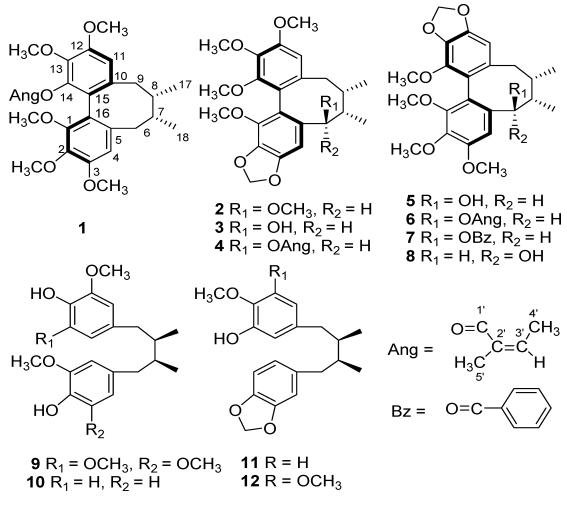
Two new dibenzocyclooctadiene lignans angeloyl-(+)-gomisin K_3 (1) and methylisogomisin O (2), together with six known ones, isogomisin O, angeloylisogomisin O, gomisin O, angeloygomisin O, benzoylgomisin O, epigomisin O, and four 1,4-bis(phenyl)-2,3-dimethylbutane type lignans, pregomisin, meso-dihydroguaiaretic 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 K_3; 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 K_3 (**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 ($CHCl_3$–Me_2CO 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 K_3 (**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 $C_{28}H_{36}O_7$. 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 ^{1}H-, ^{13}C- 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 K_3 with a *R*-biphenyl configuration.[5)] Most signals in the ^{13}C-NMR spectrum of **1** (Table 1) were similar to that of (+)-gomisin K_3 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 K_3 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 K_3 to δ_C 143.3 in **1**, respectively. These changed signals were almost the same as that of the monoacetate derivative of (+)-gomisin K_3.[5)]

In the ^{1}H- and ^{13}C-NMR spectra of **1** (Table 1), two secondary methyl group signals (δ_H 0.77, d, J=7.0 Hz, H_3-17; 0.98, d, J=7.2 Hz, H_3-18) 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, H_3-4′; 1.72, s, H_3-5′; 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

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Table 1. ^{1}H- and ^{13}C-NMR Data of Compounds **1** and **2** (500 MHz for ^{1}H 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_2O			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 K_3 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 $C_{24}H_{30}O_7$, as derived from its HR-ESI-MS (*m/z* 453.1885, $[M+Na]^+$, Calcd 453.1889) and spectroscopic data (Table 1). The 1D-NMR of **2** showed the signals due to an octa-substitued biphenyl moiety [^{1}H-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 exihibited 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 H_3-OMe (δ_H 2.97) to C-6 (Fig. 1). Key HMBC correlations from H-6 to C-7 (δ_H 1.81, m; δ_C 39.5, d), from H_3-18 (δ_H 0.85, overlapped, δ_C 17.2, q, Me-18) to C-6, and from H_2-9 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-6α (Fig. 2). The cyclooctadiene ring of **2** was indicated to be a twist-boat-chair (TBC) conformation by the NOESY correlations between H-4/H_3-18 and H-9β/H-11.

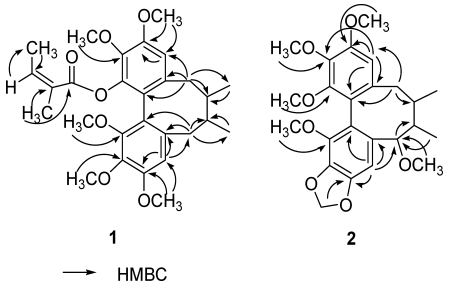

Fig. 1. Selected HMBC Correlations of **1** and **2**

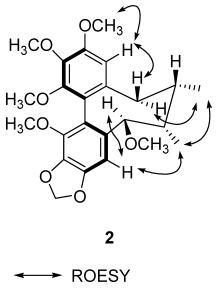

Fig. 2. Partial ROESY Correlations of **2**

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) spectropolarimetre. 1D- and 2D-NMR spectra were run on a Brucker 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 Institue 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. Me_2CO (4×15 l, 3d, each) at room temperature and concentrated *in vacuo* to give a crude extract (560 g), which was dissolved in H_2O and then extracted successively with PE and EtOAc. The EtOAc part (250 g) was chromatographed on silica gel column eluting with $CHCl_3$–Me_2CO (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 H_2O 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 K_3 (**1**): Amorphous powder; $[\alpha]_D^{19.5}$ +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. ^{1}H- and ^{13}C-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 ($[M+H]^+$, $C_{28}H_{37}O_7^+$, Calcd 485.2539).

Methylisogomisin O (**2**): Prism crystals, mp 148—150 °C; $[\alpha]_D^{28.3}$ +46.7° (c=0.40, MeOH); UV λ_{max} (MeOH) nm (log ε): 216.8 (4.51); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 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. ^{1}H- and ^{13}C-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 ($[M+Na]^+$, $C_{24}H_{30}O_7\,Na^+$, Calcd 453.1889).

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