Two New Lignans from *Schisandra henryi*

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Two new lignans, henricines A (1) and B (2), were isolated along with the eight known lignans, ganshisandrine (3), wulignan A_2 (4), epiwulignan A_1 (5), deoxyschisandrin (6), wulignan A_1 (7), epischisandrone (8), schisantherin A (9), and schisandrol A (10), from the stems of *Schisandra henryi*. The structures of the new compounds were elucidated based on the spectral analysis, including 1D and 2D NMR experiments.

Key words *Schisandra henryi*; lignan; henricine A; henricine B

Schisandra henryi Clarke is widely distributed in southwest of China. Its fruits were used as the substitute for the FRUCTUS SCHISANDRAE CHINENSIS (Wuweizi), and its stems were used in folk medicine for the treatment of rheumatism, traumatic injury, ulcer with pyogenic infections, stomachache and irregular menstruation.[1)] Previous phytochemical investigation revealed that lignans are the bioactive constituents of this plant, and demonstrated potential activities in the antitumor, antiviral, antihepatotoxic, and antioxidant aspects.[2—10)] In the course of searching for the new bioactive natural products from the stems of this plant, ten lignans, henricine A (**1**), henricine B (**2**), ganshisandrine (**3**),[3)] wulignan A_2 (**4**),[4)] epiwulignan A_1 (**5**),[4)] deoxyschisandrin (**6**),[5)] wulignan A_1 (**7**),[4)] epischisandrone (**8**),[4)] schisantherin A (**9**),[6,7)] and schisandrol A (**10**),[11)] were isolated from the petroleum ether extract and $CHCl_3$ extract of the stems of *S. henryi*. Among them, henricines A (**1**) and B (**2**) were new compounds. Herein, we report the isolation and extensive structure elucidation of the new compounds.

Results and Discussion

Henricine A (**1**) was obtained as white flakes, $[\alpha]_D^{20}$ +77.3 (c=0.075, $CHCl_3$). The molecular formula was established as $C_{23}H_{30}O_7$ by HR-EI-MS at m/z 418.1977 (Calcd for $C_{23}H_{30}O_7$: 418.1992). The UV spectrum showed λ_{max} (MeOH) ($\log \varepsilon$) at 208 (4.48), 232 (4.29), and 279 (3.78) nm. The IR spectrum showed the presence of a hydroxyl (3548 cm^{-1}) and aromatic (1589, 1517, 1466 cm^{-1}) groups. The ^{1}H- and ^{13}C-NMR spectra (Table 1) of **1** revealed the presence of two methyl groups at δ_H 0.97 (3H, d, J=6.8 Hz), 1.33 (3H, d, J=6.8 Hz), and δ_C 8.4, 20.0; two methane signals at δ_H 2.48 (1H, m), 4.89 (1H, d, J=10.0 Hz), and δ_C 48.7, 87.7; five methoxyl groups at δ_H 3.25, 3.89, 3.90, 3.92, 3.93 (each 3H, s), and δ_C 50.3, 55.8, 55.9, 56.0, 56.0 (overlap). In addition, the ^{1}H-NMR spectrum of **1** showed two ABX systems on the basis of the coupling constants, and the ^{13}C-NMR spectrum of **1** exhibited four oxygenated aromatic carbons at δ_C 148.8, 148.9, 149.2, and 149.3, which indicated that the aromatic rings each had a 1,3,4-trisubstitution pattern. According to the ^{1}H- and ^{13}C-NMR data, tetrahydrofuran lignan was deduced to the structure of **1**, which was similar to the known compound ganshisandrine.[3)] But significant differences between them were the signals of H-7′ and H-8′ disappeared in the ^{1}H-NMR spectrum of **1**, as well as the signals of C-7′ and C-8′ were downshifted from δ_C 84.8 and 47.6 in ganshisandrine to δ_C 111.8 and 82.3 in the ^{13}C-NMR spectrum of **1**, which indicated the H-7′ and H-8′ of **1** were replaced. These were also confirmed by the cross peaks at δ_H 2.48/0.97 (H-8/H_3-9) and 2.48/4.89 (H-8/H-7) in the ^{1}H–^{1}H COSY spectrum of **1**. Ob-

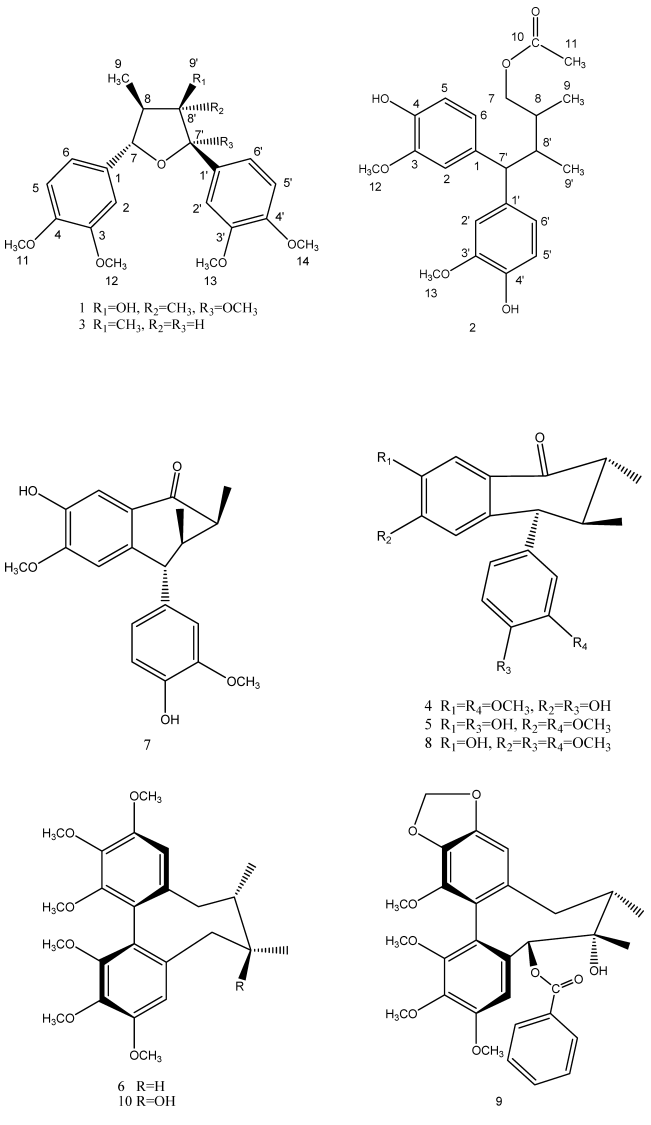

Fig. 1. Structures of Compounds **1**—**10**

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Table 1. ^{1}H- (400 MHz) and ^{13}C-NMR (100 MHz) Data of Compounds **1** ($CDCl_3$) and **2** (CD_3OD)

No.	**1**		**2**	
	δ_H	δ_C	δ_H	δ_C
1		133.8		138.3
2	7.03 (1H, br s)	110.3	6.78 (1H, d, 1.6)	113.0
3		149.3		149.0
4		148.9		145.8
5	6.87 (1H, d, 8.0)	110.7	6.61 (1H, d, 8.0)	116.3
6	6.97 (1H, d, 8.0)	120.3	6.69 (1H, dd, 1.6, 8.0)	121.4
7	4.89 (1H, d, 10.0)	87.7	3.70 (1H, d, 11.2) 4.04 (1H, dd, 4.8, 10.8)	67.2
8	2.48 (1H, dd, 6.8, 10.0)	48.7	1.82 (1H, m)	34.5
9	0.97 (3H, d, 6.8)	8.4	0.88 (3H, d, 7.2)	17.2
1′		128.2		137.8
2′	7.14 (1H, br s)	110.8	6.75 (1H, d, 1.6)	112.8
3′		149.2		148.9
4′		148.8		145.8
5′	6.91 (1H, d, 8.0)	110.7	6.59 (1H, d, 8.0)	116.2
6′	7.12 (1H, br s)	120.3	6.65 (1H, dd, 1.6, 8.0)	121.3
7′		111.8	3.52 (1H, d, 11.6)	57.3
8′		82.3	2.26 (1H, m)	42.1
9′	1.33 (3H, s)	19.9	0.69 (3H, d, 6.8)	13.6
10	3.25 (3H, s)	50.3		173.1
11	3.92 (3H, s)	56.0	1.90 (3H, s)	30.0
12	3.89 (3H, s)	55.8	3.72 (3H, br s)	56.5
13	3.92 (3H, s)	55.9	3.72 (3H, br s)	56.5
14	3.93 (3H, s)	56.0		

vious cross peaks at δ_H 0.97/δ_C 48.7, 82.3, 87.7 (H_3-9/C-8, C-8′, C-7), δ_H 1.33/δ_C 48.7, 82.3, 111.8 (H_3-9′/C-8, C-8′, C-7′), δ_H 3.25/δ_C 111.8 (H_3-10/C-7′) were observed in the HMBC spectrum (Fig. 2), which further indicated H-7′ and H-8′ were replaced by a methoxyl and a hydroxyl groups, respectively. As previously reported,[12] the signal at δ_H 4.89 (1H, d, J=10.0 Hz) for H-7 indicates that this hydrogen is in *trans* configuration with the adjacent H-8, additionally, the obvious cross peaks at δ_H 0.97/4.89 (H_3-9/H-7), δ_H 1.33/2.48 (H_3-9′/H-8), δ_H 1.33/7.12 (H_3-9′/H-6′), and δ_H 3.25/7.03 (H_3-10/H-2) in the NOESY spectrum (Fig. 3) confirmed the relative configuration of **1**. The absolute configuration of **1** was established on the basis of the circular dichroism (CD) curve from 220 to 400 nm in its CD spectrum, which was similar to those of *d*-epigalbacin.[13] Thus, the structure of **1** was established as 7*S*-(3,4-dimethoxyphenyl)-8*R*,8′*R*-dimethyl-8′*R*-hydroxyl-7′*R*-methoxyl-7′*R*-(3′,4′-dimethoxyphenyl)-tetrahydrofuran (Fig. 1).

Henricine B (**2**) was obtained as yellow gum, $[\alpha]_D^{20}$ −4.0 (c=0.10, $CHCl_3$). It possessed the molecular formula $C_{22}H_{28}O_6$, as derived from its HR-EI-MS at m/z 388.1874 (Calcd for $C_{22}H_{28}O_6$: 388.1886). The ^{1}H- and ^{13}C-NMR spectra of **2** (Table 1) were very closely to those of the known compound 4,4-di(4-hydroxy-3-methoxyphenyl)-2,3-dimethyl butanol,[14] which indicated **2** was an analogue of it. The ^{1}H-NMR and ^{1}H–^{1}H COSY spectra indicated two separate ABX systems (H-5 (δ_H 6.61, 1H, d, J=8.0 Hz), H-6 (δ_H 6.69, 1H, dd, J=1.6, 8.0 Hz), and H-2 (δ_H 6.78, 1H, d, J=1.6 Hz); H-5′ (δ_H 6.59, 1H, d, J=8.0 Hz), H-6′ (δ_H 6.65, 1H, dd, J=1.6, 8.0 Hz), H-2′ (δ_H 6.75, 1H, d, J=1.6 Hz)) in two aromatic rings, according to the heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bonding connectivity (HMBC) spectra, the carbons signals were assigned respectively. The ^{1}H- and ^{13}C-NMR spectra revealed the presence of one methyl groups at δ_H 1.90 (3H, s), δ_C 30.0; one ester carbonyl group δ_C 173.1, while the molecular ion m/z 388 was 42 units greater than that of 4,4-di(4-hydroxy-3-methoxyphenyl)-2,3-dimethyl butanol (m/z 346), indicating that the hydroxyl group in 4,4-di(4-hydroxy-3-methoxyphenyl)-2,3-dimethyl butanol was esterified by acetic acid. The HMBC spectrum (Fig. 2) of **2** showed cross peaks at δ_H 1.90/δ_C 173.1 (H_3-11/C-10), δ_H 3.70/δ_C 173.1 (H-7a/C-10), δ_H 4.04/δ_C 173.1 (H-7b/C-10), which further confirmed that the acetoxy group was located at C-7. The proton chemical shifts of CH_2OH (C-7) in 4,4-di(4-hydroxy-3-methoxyphenyl)-2,3-dimethyl butanol were δ_H 3.22, 3.69, whereas the proton chemical shifts of CH_2OAc (C-7) in compound **2** were δ_H 3.70, 4.04, and the chemical shifts were low-field shifted because the effects of esterification. Additionally, obvious cross peaks at δ_H 0.88/δ_C 67.2 (H_3-9/C-7), δ_H 1.82/δ_C 17.2, 67.2 (H-8/C-9, C-7), δ_H 0.69/δ_C 57.3 (H_3-9′/C-7′) and δ_H 2.26/δ_C 13.6, 34.5, 57.3 (H-8′/C-9′, C-8, C-7′), were observed in the HMBC spectrum (Fig. 2), which assigned the location of δ_H 1.82 (H-8), δ_C 34.5 (C-8) and δ_H 2.26 (H-8′), δ_C 42.1(C-8′), respectively. Therefore, the structure of **2** was established as 7′,7′-di(4-hydroxy-3-methoxyphenyl)-8,8′-dimethylbutyl acetate depicted in Fig. 1.

The known compounds **3**—**10** were determined by comparison of their spectral data with literature values, including tetrahydrofuran lignans ganshisandrine (**3**); aryltetralin lignans, wulignan A_2 (**4**), epiwulignan A_1 (**5**), wulignan A_1 (**7**), epischisandrone (**8**), and dibenzocyclooctadiene lignans, deoxyschisandrin (**6**), schisantherin A (**9**), schisandrol A (**10**). They all are previously isolated from the genus *Schisandra*. According to our previous research,[15] we deduce that aryltetralin lignans are the major constituents of the aerial parts of *S. henryi*.

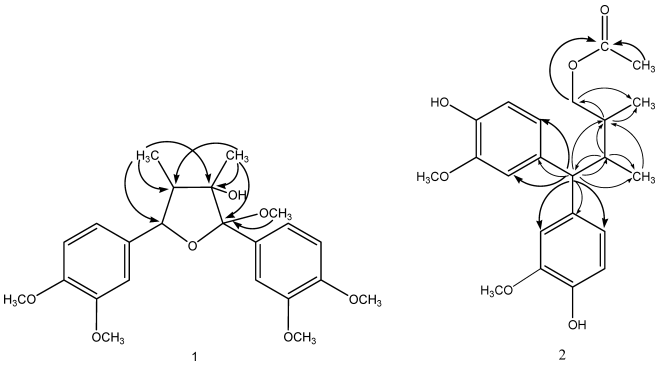

Fig. 2. Key HBMC Correlations of Compounds **1** and **2**

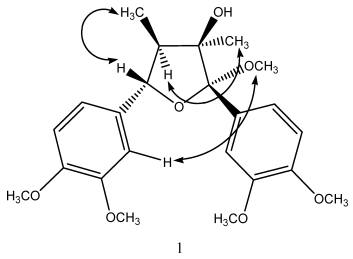

Fig. 3. Key NOESY Correlations of Compound **1**

Experimental

General CD spectra were recorded on a spectropolarimeter (JASCO-815). Optical rotations were performed on a Perkin-Elmer 341 digital polarimeter. IR spectra were run on a Shimadzu FTIR-8400S infrared spectrometer recorded as KBr patches. UV spectra were measured on a Shimadzu UV-2550 UV–VIS recording spectrometer in methanol. EI- and HR-EI-MS spectra were measured with an Autospec Ultima-TOF spectrometer. NMR spectra were measured on a Bruker AV 400 spectrometer with TMS as an internal standard. Silica gel (300—400 mesh) and silica gel GF254 sheets (0.20—0.25 mm) (both from Qingdao Haiyang Chemical Group Co., Shandong Province, People's Republic of China) were used for column chromatography and TLC, respectively.

Plant Material The stems of *S. henryi* was collected at Shennongjia, Hubei Province, People's Republic of China, in January 2007, and identified by Prof. Ce-Ming Tan, Institute of Forest Science, Jiujiang, Jiangxi Province, People's Republic of China. A voucher specimen (070105) has been deposited in the Herbarium of the Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College.

Extraction and Isolation The dried stems of *S. henryi* (4.8 kg) were pulverized and extracted with 95% EtOH under reflux (2 h each ×3). The ethanolic extract was concentrated *in vacuo* to yield a residue (998.0 g), 885.5 g of which was suspended in water and successively partitioned with petroleum ether (PE), $CHCl_3$, and EtOAc. The solvent was evaporated under vacuum to afford a PE extract (119.1 g), a $CHCl_3$ extract (58.0 g), and an EtOAc extract (56.0 g). The PE extract (107.0 g) was chromatographed on silica gel using a gradient system of PE–EtOAc, The fractions obtained were further purified by repeated column chromatography and Sephadex LH-20, to give compounds **1** (45 mg), **2** (12 mg), **3** (10 mg), **4** (27 mg), **5** (376 mg), **6** (9 mg). The $CHCl_3$ extract (58.0 g) was chromatographed on silica gel column using the system of PE–Me_2CO, the fractions obtained were further purified by repeated column chromatography and Sephadex LH-20, to give compounds **7** (53 mg), **8** (21 mg), **9** (6 mg), **10** (8 mg).

Henricine A (**1**): White flakes; $[\alpha]_D^{20}$ +77.3 (c=0.075, $CHCl_3$); UV λ_{max} (MeOH) nm (log ε): 208 (4.48), 232 (4.29), 279 (3.78); IR (KBr) cm^{-1}: 3549, 2964, 2937, 1589, 1518, 1466, 1410, 1292, 1263, 1221, 1161, 1142, 1134, 1076, 1024, 995, 974, 872, 803, 764; CD (c=0.00144, MeOH) [θ] (nm): 5381.1 (220), 1566.6 (230), 6314.9 (240), 324.7 (254), 3670.2 (280), −16.7 (292); EI-MS m/z: 418 $[M]^+$, 287, 207, 197, 179, 165, 151; HR-EI-MS m/z: 418.1977 $[M]^+$ (Calcd for $C_{23}H_{30}O_7$: 418.1992); The ^{1}H- and ^{13}C-NMR data ($CDCl_3$): see Table 1.

Henricine B (**2**): Yellow gum; $[\alpha]_D^{20}$ −4.0 (c=0.10, $CHCl_3$); UV λ_{max} (MeOH) nm (log ε): 207 (4.49), 239 (3.94), 282 (3.68); IR (KBr) cm^{-1}: 2955, 2916, 2848, 1670, 1464, 1365, 1215, 761; EI-MS m/z: 388 $[M]^+$, 259; HR-EI-MS m/z: 388.1874 $[M]^+$ (Calcd for $C_{22}H_{28}O_6$: 388.1886); The ^{1}H- and ^{13}C-NMR data (CD_3OD): see Table 1.

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