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Five novel oligostilbenes from the roots of *Caragana sinica*

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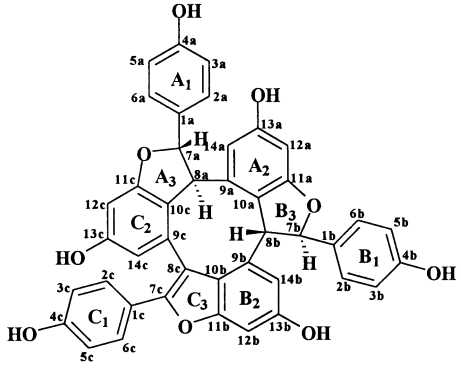
Abstract—One novel resveratrol trimer, caraphenol A (**1**), and four novel resveratrol dimers, (+)-isoampelopsin F (**2**), caraphenol B (**3**), C (**4**), (−)-ampelopsin F (**5**) were isolated from the roots of *C. sinica*. Their structures and stereochemistry were elucidated by means of spectroscopic evidence, especially HMBC and NOE experiments. The pharmacological activities in anti-HIV of all compounds and stimulation of osteoblast growth tests of the EtOAc extract of the roots of *C. sinica* have been determined.

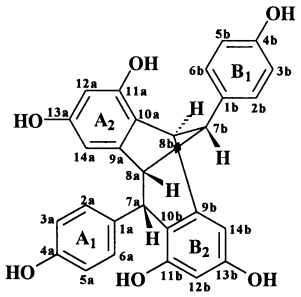
1. Introduction

The dried roots of *Caragana sinica* (Buc'hoz) Rehd. (Leguminosae) have been used in China as a folk medicine (Chinese name: Jinquegen) for the treatment of asthenia syndrome, vascular hypertension, leukorrhagia, bruises and contused wounds. In our study, we found that the EtOAc extract of the roots of *C. sinica* showed the effects of stimulating the proliferation, differentiation and maturation of cultured osteoblasts in vitro and contained many oligostilbenes which have been found to have multi-faceted bioactivities.[1–7] Few studies on bioactive oligostilbenes from the roots of *C. sinica* have been performed.[8,9] We now report on the isolation and structure elucidation of five novel oligostilbenes (**1**–**5**) besides (+)-α-viniferin (**6**), miyabenol C (**7**), pallidol (**8**) and kobophenol A (**9**) reported earlier[10] (Scheme 1) from the EtOAc extract of the roots of *C. sinica*. Compounds **3** and **4** are the first resveratrol dimers with a C-7 carbonyl group.



1 H-7c and H-8c = dedihydro

6 H-7c (α)and H-8c (β) = dihydro



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2. Results and discussion

Caraphenol A (**1**) was obtained as a yellowish amorphous powder, $[\alpha]_D^{20}$=+35.1 (*c* 0.343, MeOH). Its molecular formula of $C_{42}H_{28}O_9$ was established by HRFAB-MS *m/z* 677.1804 $[MH]^+$ ($C_{42}H_{29}O_9$ requires 677.1812) together with its ^{1}H NMR spectral data which suggested that **1** could be a resveratrol trimer. The UV spectrum (λ_{max}: 326 nm) revealed the presence of a strong conjugated system in the structure. The ^{1}H NMR spectrum exhibited signals for the three 4-hydroxy-1-substituted benzyl moieties at δ 7.26 (2H, d, *J*=8.7 Hz) and 6.75 (2H, d, *J*=8.7 Hz), δ 7.24 (2H, d, *J*=8.6 Hz) and 6.80 (2H, d, *J*=8.6 Hz), δ 7.05 (2H, d, *J*=8.6 Hz) and 6.71 (2H, d, *J*=8.6 Hz); three 3,5-dihydroxy-1,2-disubstituted benzyl moieties at δ 6.94 (1H, d, *J*=1.8 Hz) and 6.81 (1H, d, *J*=1.8 Hz), δ 6.54 (1H, d, *J*=1.8 Hz) and 6.25 (1H, d, *J*=1.8 Hz), δ 6.52 (1H, d, *J*=2.1 Hz) and 6.32 (1H, d, *J*=2.1 Hz); four aliphatic protons of two dihydrobenzofuran rings at δ 5.92 (1H, br s) and 4.87 (1H, br s), δ 5.91 (1H, br s) and 4.31 (1H, br s). The ^{13}C NMR spectrum exhibited the presence of four aliphatic carbons (δ 95.17 and 54.06, δ 87.92 and 45.71) besides 38 aromatic carbons. The ^{1}H NMR and ^{13}C NMR features were similar to those of

Keywords: *Caragana sinica*; leguminosae; caraphenol A, B, C, (+)-isoampelopsin F; (−)-ampelopsin F; oligostilbene; resveratrol; trimer; dimer.

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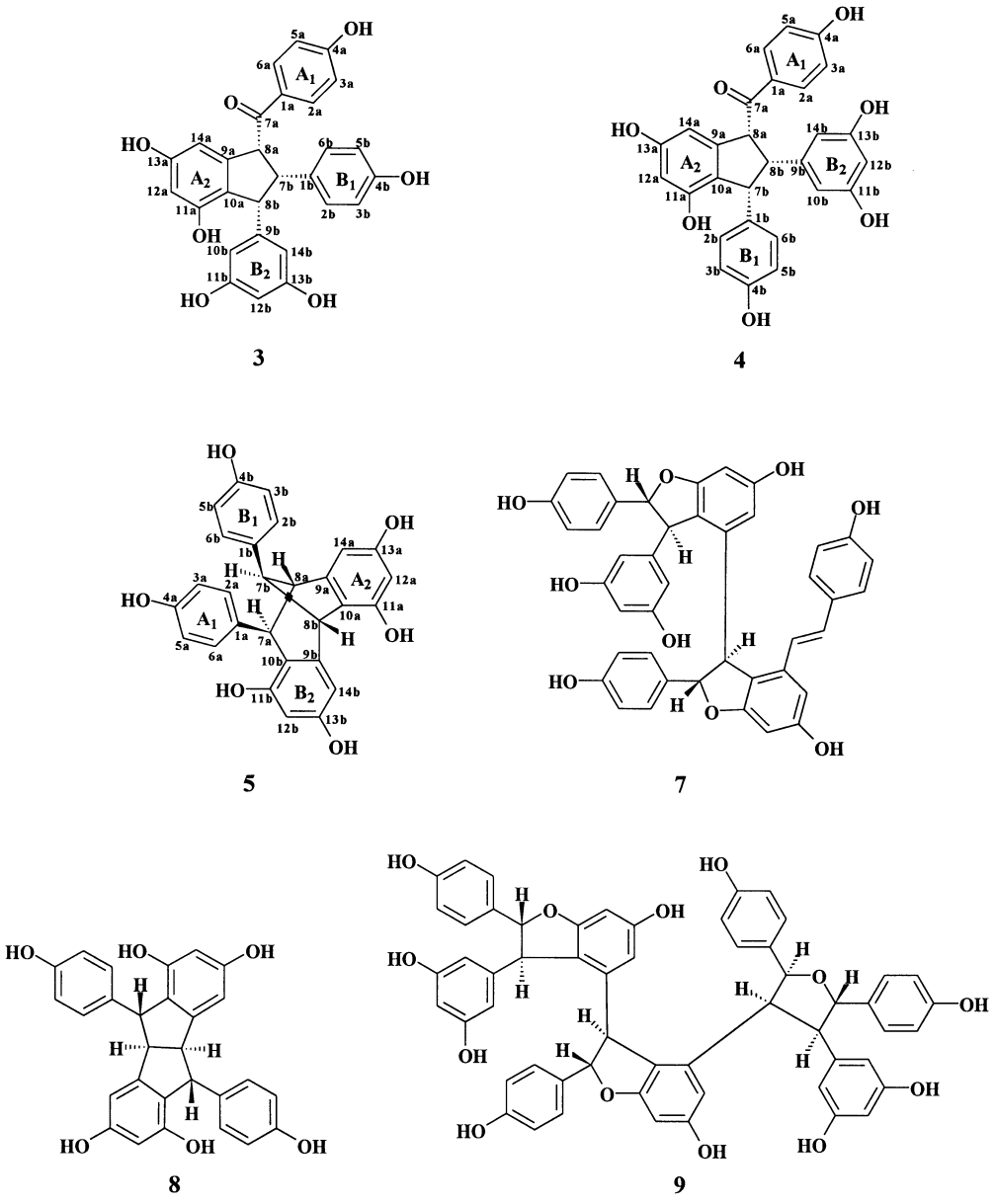

Scheme 1.

(+)-α-viniferin[8] except that **1** showed only four aliphatic protons for two dihydrobenzofuran moieties in the ^{1}H NMR spectrum and two quaternary carbon signals more than (+)-α-viniferin in the ^{13}C NMR spectrum, which meant that one dihydrobenzofuran moiety was changed into an unsaturated benzofuran moiety in **1**. Thus the planar structure of caraphenol A was as shown in **1**, which was confirmed by long-range correlations in HMBC spectrum (Fig. 1b).

The stereochemistry of **1** was established on the basis of the ^{1}H NMR and NOSEY spectra. In the ^{1}H NMR spectrum, that the coupling constants found in H-7a and H-8a, H-7b and H-8b approximate 0 Hz suggesting that the bond angles between H-7a and H-8a, H-7b and H-8b approximate 90°. So it revealed two *trans* orientations of H-7a and H-8a, H-7b and H-8b according to the structural model of **1**. That the NOE enhancement between H-8a and H-8b was not observed in the NOESY spectrum (Fig. 1a) indicated a *trans* orientation of H-8a and H-8b. Thus, the relative stereochemistry of caraphenol A was determined as **1**.

(+)-Isoampelopsin F (**2**) was obtained as a yellowish amorphous powder, $[\alpha]_D^{20}=+30.6$ (*c* 0.766, MeOH). HRFAB-MS *m/z* 455.1485 $[MH]^+$ ($C_{28}H_{23}O_6$ requires 455.1495) gave a molecular formula of $C_{28}H_{22}O_6$, which in combination with ^{1}H NMR and ^{13}C NMR of **2** suggested that it could be a resveratrol dimer. The ^{1}H NMR spectrum exhibited signals for one 4-hydroxy-1-substituted benzyl moiety at δ 6.97 (2H, d, *J*=8.5 Hz) and 6.64 (2H, d, *J*=8.5 Hz); two 3,5-dihydroxy-1,2-disubstituted benzyl moieties at δ 6.44 (1H, d, *J*=2.5 Hz) and 6.14 (1H, d, *J*=2.5 Hz), δ 6.04 (1H, d, *J*=1.9 Hz) and 5.20 (1H, d, *J*=1.9 Hz); four aromatic protons each a double-doublet at δ 7.32 (1H, dd, *J*=2.2, 8.2 Hz), δ 6.80 (1H, dd, *J*=2.6, 8.2 Hz), δ 6.37 (1H, dd, *J*=2.6, 8.4 Hz) and 5.83 (1H, dd,

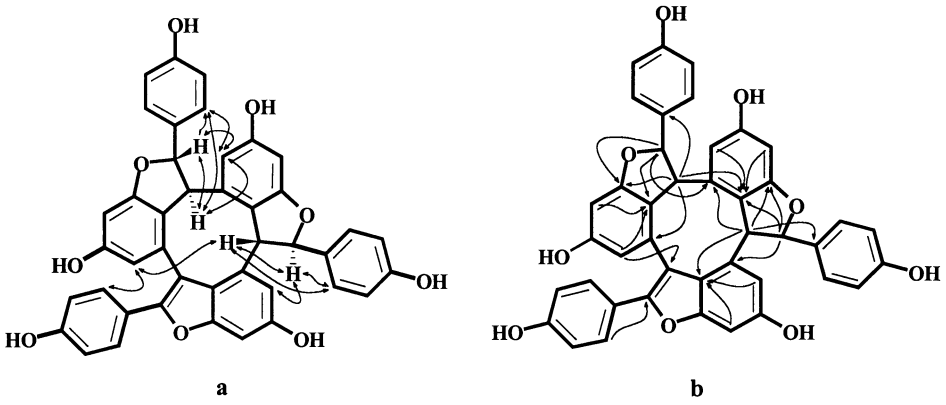

Figure 1. Significant NOE interactions in the NOESY spectrum (a) and long-range CH correlations in the HMBC spectrum (b) of **1**.

J=2.2, 8.4 Hz); four aliphatic methine protons at δ 4.51 (1H, d, J=5.5 Hz) and 3.39 (1H, d, J=5.5 Hz), δ 4.03 (1H, br s) and 3.58 (1H, br s). The ^{1}H NMR and ^{13}C NMR spectra of **2** were the same as those of isoampelopsin F[11] isolated from *Parthenocissus tricuspidata*, so **2** has the same relative structure as isoampelopsin F; however, its optical rotation was opposite to that of isoampelopsin F.

Caraphenol B (**3**) was obtained as a yellowish amorphous powder, $[\alpha]_D^{20}$=+27.9 (*c* 0.384, MeOH). HRFAB-MS *m/z* 471.1479 $[MH]^+$ ($C_{28}H_{23}O_7$ requires 471.1444) gave a molecular formula of $C_{28}H_{22}O_7$, which in combination with ^{1}H NMR and ^{13}C NMR suggested that **3** was a resveratrol dimer. The ^{1}H NMR spectrum exhibited signals for two 4-hydroxy-1-substituted benzyl moieties at δ 7.90 (2H, d, J=8.8 Hz) and 6.92 (2H, d, J=8.8 Hz), δ 7.08 (2H, d, J=8.6 Hz) and 6.72 (2H, d, J=8.6 Hz); one 3,5-dihydroxy-1-substituted benzyl moiety at δ 6.15 (2H, d, J=2.2 Hz) and 6.18 (1H, t, J=2.2 Hz); one 3,5-dihydroxy-1,2-disubstituted benzyl moiety at δ 6.26 (1H, d, J=1.4 Hz) and 5.99 (1H, d, J=1.4 Hz); three aliphatic methine protons at δ 5.12 (1H, d, J=8.7 Hz), δ 4.24 (1H, d, J=8.7 Hz) and 3.95 (1H, t, J= 8.7 Hz). The ^{13}C NMR spectrum revealed the presence of one carbonyl carbon (δ 198.58) and three aliphatic carbons (δ 60.25, 59.81 and 57.31) besides 24 aromatic carbons, and all protonated carbons were assigned from the HMQC spectrum. In the HMBC spectrum of **3** (Fig. 2b), long range correlations between H-2(6)a and C-7a (δ 198.58), H-8a and C-7a, indicated that ring A_1 was attached to C-8a through C-7a carbonyl group; long range correlations between H-2(6)b and C-7b (δ 59.81), H-10(14)b and C-8b (δ 57.31), indicated that ring B_1 was attached to C-7b and ring B_2 was attached to C-8b. Therefore, the planar structure of caraphenol B was concluded to be as shown in **3**.

The stereochemistry of **3** was established on the basis of a NOESY experiment. The NOE enhancements between H-8a and H-7b, H-7b and H-8b, H-8a and H-8b, suggested that H-8a, H-7b and H-8b were situated in a *cis* orientation. Thus, the relative configuration of caraphenol B was as shown in **3**. Caraphenol B was the first naturally occuring resveratrol dimer with a C-7 carbonyl group.

Caraphenol C (**4**) was obtained as a yellowish amorphous powder, $[\alpha]_D^{20}$=+19.3 (*c* 0.329, MeOH). HRFAB-MS *m/z* 471.1423 $[MH]^+$ ($C_{28}H_{23}O_7$ requires 471.1444) gave a molecular formula of $C_{28}H_{22}O_7$, which in combination with ^{1}H NMR and ^{13}C NMR suggested that **4** was a resveratrol dimer. The ^{1}H NMR and ^{13}C NMR spectra of **4** were similar to that of **3**. The ^{1}H NMR spectrum also exhibited signals for two 4-hydroxy-1-substituted benzyl moieties at δ 7.93 (2H, d, J=8.4 Hz) and 6.96 (2H, d, J= 8.4 Hz), δ 6.94 (2H, d, J=8.3 Hz) and 6.70 (2H, d, J= 8.3 Hz); one 3,5-dihydroxy-1-substituted benzyl moiety at δ 6.24 (2H, d, J=1.9 Hz) and 6.17 (1H, t, J=1.9 Hz); one 3,5-dihydroxy-1,2-disubstituted benzyl moiety at δ 6.26 (1H, d, J=1.3 Hz) and 6.00 (1H, d, J=1.3 Hz); three aliphatic methine protons at δ 5.10 (1H, d, J=8.2 Hz), δ 4.36 (1H, d, J=8.2 Hz) and 3.81 (1H, t, J=8.2 Hz). The ^{13}C NMR spectrum also revealed the presence of one carbonyl

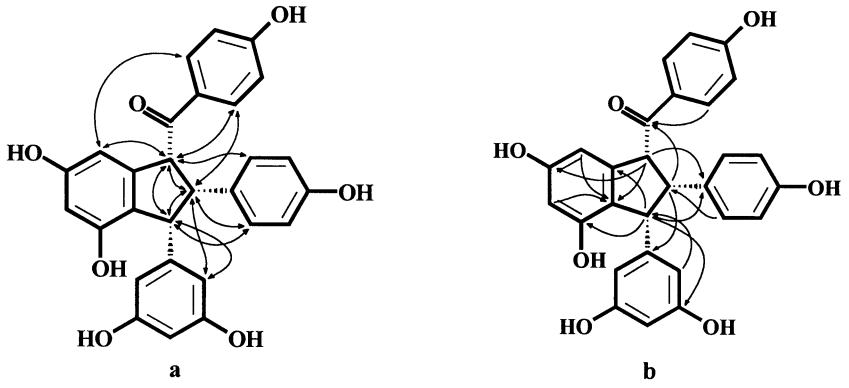

Figure 2. Significant NOE interactions in the NOESY spectrum (a) and long-range CH correlations in the HMBC spectrum (b) of **3**.

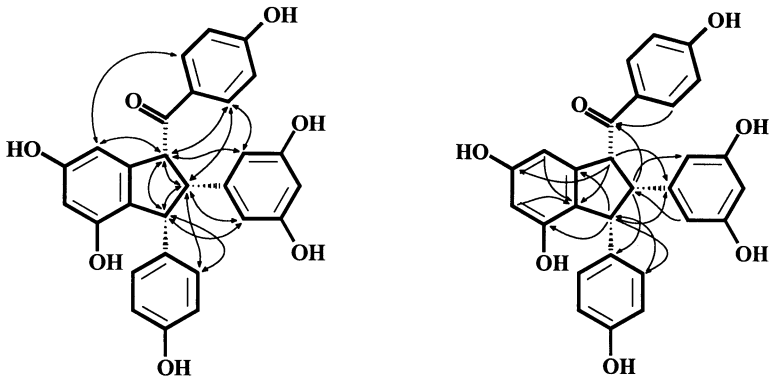

Figure 3. Significant NOE interactions in the NOESY spectrum (a) and long-range CH correlations in the HMBC spectrum (b) of **4**.

carbon (δ 197.77) and three aliphatic carbons (δ 60.60, 59.87 and 56.23) besides 24 aromatic carbons. In the HMBC spectrum of **4** (Fig. 3b), H-8a showed long range coupling with C-9b, which was different from that of **3** (In the HMBC spectrum of **3**, H-8a showed long range coupling with C-1b). Thus, the locations of ring B_1 and ring B_2 were interchanged compared with those of **3**. In the NOESY spectrum of **4** (Fig. 3a), the NOE enhancements between H-8a and H-8b, H-7b and H-8b, H-8a and H-7b were observed, which indicated that H-8a, H-8b and H-7b were situated in a *cis* orientation. Therefore, the relative configuration of caraphenol C was determined as **4**.

(−)-Ampelopsin F (**5**) was obtained as a yellowish amorphous powder, $[\alpha]_D^{20}=-4.56$ (*c* 0.14, MeOH). HRFAB-MS *m/z* 455.1472 $[MH]^+$ ($C_{28}H_{23}O_6$ requires 455.1495) gave a molecular formula of $C_{28}H_{22}O_6$, which in combination with ^{1}H NMR and ^{13}C NMR of **5** suggested that it could be a resveratrol dimer. The ^{1}H NMR spectrum exhibited signals for two 4-hydroxy-1-substituted benzyl moieties at δ 7.08 (2H, d, J=8.5 Hz) and 6.76 (2H, d, J=8.5 Hz), δ 6.78 (2H, d, J=8.5 Hz) and 6.58 (2H, d, J=8.5 Hz); two 3,5-dihydroxy-1,2-disubstituted benzyl moieties at δ 6.51 (1H, d, J=1.9 Hz) and 6.07 (1H, d, J=1.9 Hz), δ 6.44 (1H, d, J=2.4 Hz) and 6.17 (1H, d, J=2.4 Hz); four aliphatic methine protons at δ 4.18 (1H, d, J=1.5 Hz) and 3.34 (1H, br s), δ 4.12 (1H, br s) and 3.64 (1H, br s). The ^{13}C NMR spectrum showed the presence of four aliphatic carbons and 24 aromatic carbons. The ^{1}H NMR and ^{13}C NMR spectra of **5** were the same as those of ampelopsin F[12] isolated from *Ampelopsis brevipeduncu-lata var. hancei*, so **5** has the same relative structure as ampelopsin F; however, its optical rotation was opposite to that of ampelopsin F.

Of compounds **1**–**9**, the activities of anti-HIV were tested, but unfortunately, all of them were inactive. In the tests of stimulation of osteoblast growth of the EtOAc extract, the methods of MTT,[13] PNPP[14] and ARS[15] were used to observe the proliferation, activity of ALP and the number of mineral nodes of osteoblasts cultured in vitro.[16] It was found that the EtOAc extract had the effects of stimulating the proliferation (the reproduction rates of cultured osteoblasts were raised 11–37% in different concentration (10^{-10}–10^{-4} g/ml) than that of the control group (0 g/ml)), enhancing the ALP activities and increasing the number of mineral nodes of cultured osteoblasts (the number of mineral nodes of cultured osteoblasts were increased 7.8–13.5% in different concentration (10^{-8}–10^{-6} g/ml) than that of the control group (0 g/ml)). At 10^{-6} g/ml concentration, the effects were greater.

3. Experimental

3.1. General procedure

Melting points were determined on a Kofler micro melting point apparatus and are uncorrected. UV spectra were obtained on a Shimadzu UV-240 spectrophotometer. IR spectra were recorded as KBr pellets on a Perkin–Elmer 783 infrared spectrophotometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. FAB-MS were measured with a VG AutoSpec 3000 mass spectrometer. The NMR spectra were carried out on a Bruker AM-400 spectrometer using TMS as internal standard.

3.2. Plant material

The roots of *C. sinica* (Buc'hoz) Rehd. were purchased from Zhongxiang County, Hubei Province. The original plant was identified by Professor Zhi-Jian Feng, Department of Biology, Shanghai East China Normal University.

3.3. Isolation of 1–5

Dry roots of *C. sinica* (Buc'hoz) Rehd. (60 kg) were pulverized and extracted by macerating with 95% ethanol at room temperature. The solvent was evaporated in vacuo to yield 4 kg residue that was partitioned between H_2O and petroleum ether, $CHCl_3$, and EtOAc, successively. The EtOAc extract (1 kg) was subjected to a silica gel column eluted with $CHCl_3$–MeOH to give A (100:7), B (100:8), C (100:9), D (100:11) and E (100:13) fractions. Fraction A (20 g) was divided into A_1 and A_2 by a polyamide column eluted with MeOH–H_2O (7:3 and 8:2). A_2 was subjected to a YWG-C_{18} column eluted with MeOH–H_2O (1:1) to afford **1** (60 mg). Compound **1** was further purified by a silica gel (200–300 mesh) column eluted with $CHCl_3$–EtOAc–MeOH (100:9:4.5). Fraction C (4 g) was applied to a silica

Table 1. ^{1}H NMR spectral data for compounds **1**–**5** (400 MHz, in acetone-d_6)

Position	1	2	3	4	5
2a	7.24 (d, 8.6)	5.83 (dd, 2.2, 8.4)	7.90 (d, 8.8)	7.93 (d, 8.4)	7.08 (d, 8.5)
3a	6.80 (d, 8.6)	6.37 (dd, 2.6, 8.4)	6.92 (d, 8.8)	6.96 (d, 8.4)	6.76 (d, 8.5)
5a	6.80 (d, 8.6)	6.80 (dd, 2.6, 8.2)	6.92 (d, 8.8)	6.96 (d, 8.4)	6.76 (d, 8.5)
6a	7.24 (d, 8.6)	7.32 (dd, 2.2, 8.2)	7.90 (d, 8.8)	7.93 (d, 8.4)	7.08 (d, 8.5)
7a	5.91 (br s)	4.51 (d, 5.5)			4.18 (d, 1.5)
8a	4.31 (br s)	3.39 (d, 5.5)	5.12 (d, 8.7)	5.10 (d, 8.2)	3.34 (br s)
12a	6.25 (d, 1.8)	6.04 (d, 1.9)	6.26 (d, 1.4)	6.26 (d, 1.3)	6.07 (d, 1.9)
14a	6.54 (d, 1.8)	5.20 (d, 1.9)	5.99 (d, 1.4)	6.00 (d, 1.3)	6.51 (d, 1.9)
2(6)b	7.05 (d, 8.6)	6.97 (d, 8.5)	7.08 (d, 8.6)	6.94 (d, 8.3)	6.78 (d, 8.5)
3(5)b	6.71 (d, 8.6)	6.64 (d, 8.5)	6.72 (d, 8.6)	6.70 (d, 8.3)	6.58 (d, 8.5)
7b	5.92 (br s)	3.58 (br s)	3.95 (t, 8.7)	4.36 (d, 8.2)	3.64 (br s)
8b	4.87 (br s)	4.03 (br s)	4.24 (d, 8.7)	3.81 (t, 8.2)	4.12 (br s)
10b			6.15 (d, 2.2)	6.24 (d, 1.9)	
12b	6.81 (d, 1.8)	6.14 (d, 2.5)	6.18 (t, 2.2)	6.17 (t, 1.9)	6.17 (d, 2.4)
14b	6.94 (d, 1.8)	6.44 (d, 2.5)	6.15 (d, 2.2)	6.24 (d, 1.9)	6.44 (d, 2.4)
2(6)c	7.26 (d, 8.7)				
3(5)c	6.75 (d, 8.7)				
12c	6.52 (d, 2.1)				
14c	6.32 (d, 2.1)				

gel (10–40 μ) low pressure column eluted with $CHCl_3$–EtOAc–MeOH (100:12:6) and then was subjected to a YWG-C_{18} column eluted with MeOH–H_2O to afford **2** (45 mg, 30:70), **3** (25 mg, 27.5:72.5), and **4** (10 mg, 22.5:77.5). Fraction D (6 g) was applied to a silica gel (10–40 μ) low pressure column eluted with $CHCl_3$–EtOAc–MeOH (100:14:7) and then was subjected to a YWG-C_{18} column eluted with MeOH–H_2O (25:75) to afford **5** (70 mg).

Table 2. ^{13}C NMR spectral data for compounds **1**–**5** (100 MHz, in acetone-d_6)

Position	1	2	3	4	5
1a	133.51	135.29	130.56	130.79	138.42
2a	127.37	130.32	132.28	132.29	129.83
3a	116.01	114.96	116.18	116.24	115.55
4a	158.02	156.56[a]	163.26	163.02	156.18[b]
5a	116.01	115.54	116.18	116.24	115.55
6a	127.37	130.50	132.28	132.29	129.83
7a	95.17	46.88	198.58	197.77	47.15
8a	54.06	57.18	60.25	59.87	58.28
9a	140.95	145.10	145.82	145.80	147.24
10a	122.79[c]	126.38	122.71	122.95	127.72
11a	159.79	153.16	155.22	155.28	153.10
12a	97.64	102.00	102.77	102.91	101.73[d]
13a	159.17	157.59	159.14	159.21	158.53
14a	108.75[e]	107.01	103.50	103.75	104.01
1b	132.49	135.68	134.47	136.03	135.36
2(6)b	128.34	129.65	129.58	129.72	129.18
3(5)b	115.85	115.84	115.97	115.72	115.44
4b	158.21	156.71[a]	156.88	156.67	156.11[b]
7b	87.92	59.20	59.81	56.23	50.45
8b	45.71	50.46	57.31	60.60	49.66
9b	139.67	147.63	147.66	146.65	147.56
10b	120.56	114.60	107.20	107.03	113.23
11b	155.22	158.05	159.07	159.34	157.79
12b	96.36	102.19	101.54	101.84	101.68[d]
13b	157.20	157.27	159.07	159.34	157.08
14b	108.71[e]	106.31	107.20	107.03	105.54
1c	122.71[c]				
2(6)c	128.15				
3(5)c	116.18				
4c	158.29				
7c	149.27				
8c	114.50				
9c	135.32				
10c	118.93				
11c	163.49				
12c	98.32				
13c	160.72				
14c	109.65				

Superscripts a–e are interchangeable.

3.3.1. Caraphenol A (1). Yellowish amorphous powder; mp: 178–180°C; $[\alpha]_D^{20}=+35.1$ (c 0.343, MeOH); HRFAB-MS m/z 677.1804 $[MH]^+$ (calcd for $C_{42}H_{29}O_9$, 677.1812); UV (MeOH) λ_{max}: 298 nm (log ε=4.27), 326 nm (log ε=4.40). IR (KBr) ν_{max}: 3338, 1615, 1593, 1515, 1430, 1364, 1243, 1173, 1111, 992 and 834 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1 and 2.

3.3.2. (+)-Isoampelopsin F (2). Yellowish amorphous powder; mp: 185–187°C; $[\alpha]_D^{20}=+30.6$ (c 0.766, MeOH); HRFAB-MS m/z 455.1485 $[MH]^+$ (calcd for $C_{28}H_{23}O_6$, 455.1495); UV (MeOH) λ_{max}: 281 nm (log ε= 4.11). IR (KBr) ν_{max}: 3306, 1612, 1513, 1457, 1367, 1236, 1172, 1119,1014, 989 and 828 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1 and 2.

3.3.3. Caraphenol B (3). Yellowish amorphous powder; mp: 117–119°C; $[\alpha]_D^{20}=+27.9$ (c 0.384, MeOH); HRFAB-MS m/z 471.1479 $[MH]^+$ (calcd for $C_{28}H_{23}O_7$, 471.1444); UV (MeOH) λ_{max}: 283 nm (log ε=4.22). IR (KBr) ν_{max}: 3348, 1656, 1600, 1515, 1451, 1336, 1170, 977 and 838 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1 and 2.

3.3.4. Caraphenol C (4). Yellowish amorphous powder; mp: 136–138°C; $[\alpha]_D^{20}=+19.3$ (c 0.329, MeOH); HRFAB-MS m/z 471.1423 $[MH]^+$ (calcd for $C_{28}H_{23}O_7$, 471.1444); UV (MeOH) λ_{max}: 284 nm (log ε=4.24). IR (KBr) ν_{max}: 3333, 1650, 1602, 1514, 1367, 1220 and 840 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 2.

3.3.5. (−)-Ampelopsin F (5). Yellowish amorphous powder; mp: 164–166°C; $[\alpha]_D^{20}=-4.56$ (c 0.14, MeOH); HRFAB-MS m/z 455.1472 $[MH]^+$ (calcd for $C_{28}H_{23}O_6$, 455.1495); UV (MeOH) λ_{max}: 282 nm (log ε=4.03). IR (KBr) ν_{max}: 3318, 1612, 1512, 1458, 1366, 1239, 1118,

1014 and 840 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 2.

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