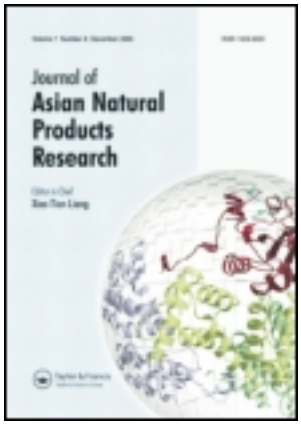

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Shao-Hua Wu [a b], Xiao-Dong Luo [a], Yun-Bao Ma [a], Xiao-Jiang Hao [a] & Da-Gang Wu [a]

[a] Laboratory of Phytochemistry, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, Yunnan, 650204, China

[b] The Key Laboratory for Microbiol Resources of Ministry of Education, Yunnan Institute of Microbiology, Yunnan University, Kunming, 650091, China

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MONOTERPENOID DERIVATIVES FROM *PAEONIA DELAVAYI*

SHAO-HUA WU[1,2], XIAO-DONG LUO[1,*], YUN-BAO MA[1], XIAO-JIANG HAO[1] and DA-GANG WU[1]

[1]*Laboratory of Phytochemistry, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, Yunnan, 650204, China*
[2]*The Key Laboratory for Microbiol Resources of Ministry of Education, Yunnan Institute of Microbiology, Yunnan University, Kunming, 650091, China*

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Three new monoterpene glycosides, 4-*O*-ethylpaeoniflorin (**1**), 6′-*O*-benzoyl-4″-hydroxy-3″-methoxy-paeoniflorin (**2**), 6′-*O*-benzoylalbiflorin (**3**), and a new monoterpenoid, 9-hydroxy-paeonilactone-A (**4**) were isolated from the root cortex of *Paeonia delavayi*. Their structures were elucidated on the basis of spectral methods.

Keywords: *Paeonia delavayi*; Paeoniaceae; Monoterpene glycosides; Monoterpenoid

INTRODUCTION

The genus *Paeonia* (Paeoniaceae) is rich in monoterpene glycosides, which are established as the main biologically active constituents [1–5]. The root cortex of *Paeonia delavayi* Franch, as one of the main sources of Chinese traditional medicine "mudanpi," is an important herb known to be an analgesic, sedative, and anti-inflammatory agent. It is also frequently used as a remedy for female diseases in traditional oriental medicine [6–8]. Previous studies on this plant led to the isolation of a new monoterpene glycoside, paeonivayin 1 [9]. Further investigation on the chemical constituents of the same plant resulted in the isolation of three new monoterpene glycosides, 4-*O*-ethylpaeoniflorin (**1**), 6′-*O*-benzoyl-4″-hydroxy-3″-methoxy-paeoniflorin (**2**), 6′-*O*-benzoylalbiflorin (**3**), and a new monoterpenoid, 9-hydroxy-paeonilactone-A (**4**). In this paper, the isolation and structural elucidation of these new compounds are described.

RESULTS AND DISCUSSION

The molecular formula of compound **1** was determined as $C_{25}H_{32}O_{11}$ by negative HRFABMS ($[M-1]^-$ m/z 507.1822, calcd. 507.1866), in which the molecular ion was

*Corresponding author. Tel.: +86-0871-5223421. Fax: +86-0871-5150227. E-mail: x_dluo@hotmail.com

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28 amu greater than that of paeoniflorin. The ^{1}H and ^{13}C NMR spectra of **1** were very similar to those of paeoniflorin [10,11] except for the additional signals at δ_H 3.75 (2H, q) and 1.14 (3H, t) in the ^{1}H NMR spectrum, which were in correspondence with the signals at δ_C 59.6 (CH_2) and 15.8 (CH_3) in the ^{13}C NMR spectrum based on the HMQC experiment. The HMBC spectrum showed the cross peaks between the methylene protons at δ_H 3.75 to C-4 (δ_C 108.3, s), and the $^{1}H-^{1}H$ COSY spectrum showed that these methylene protons at δ_H 3.75 (2H, q, $J = 7.0$ Hz) were correlated with the methyl protons at δ_H 1.14 (3H, t, $J = 7.0$ Hz). Thus, compound **1** has a $-OCH_2CH_3$ group attached to C-4 instead of a hydroxyl group in paeoniflorin. The structure of compound **1** was thus determined as 4-*O*-ethylpaeoniflorin. Compound **1** may be an artifact from paeoniflorin and ethanol formed during extraction procedure.

Compound **2** gave a quasi-molecular ion peak at *m/z* 629 $[M-1]^-$ by FAB-MS spectroscopy. Its molecular formula was established as $C_{31}H_{34}O_{14}$ by HRFABMS at *m/z* 629.1831. Comparing with the reference data [6], the ^{1}H NMR spectrum of **2** showed the signals of a monoterpene moiety: two methylenes at δ_H 2.28 and 2.46 (d, $J = 12.3$ Hz) (H_2-3), and δ_H 2.27 (d, $J = 10.8$ Hz) and 2.86 (dd, $J = 10.8$, 6.8 Hz) (H_2-7), a methine at δ_H 3.04 (d, $J = 6.8$ Hz) (H-5), a methylene bearing an acyloxy functionality at δ_H 5.02 and 5.16 (d, $J = 12.1$ Hz) (H-8), a methine adjacent to two heteroatoms at δ_H 5.88 (s) (H-9) and a methyl at δ_H 1.68 (s) (H-10). The remaining ^{1}H and ^{13}C NMR signals disclosed the presence of a glucose, a benzoyloxy unit, and a 4-hydroxy-3-methoxybenzoyloxy unit (Tables I and II). The determination of these two acyloxy groups was further supported by the fragment ion peaks at *m/z* 121 and 167, respectively. The locations of these esterifying units were confirmed by the HMBC spectrum, in which long-range correlations were observed from

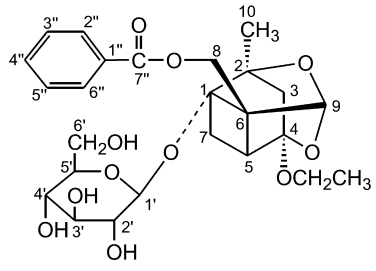
TABLE I ^{1}H NMR spectral data for compounds **1**–**3** (400 MHz)*

H	**1**	**2**	**3**
3α	2.19 (s)	2.46 (d, 12.3)	2.34 (dd, 12.5, 6.0)
3β		2.28 (d, 12.3)	2.12 (d, 12.5)
4α			4.45 (*dt*, 7.2, 6.0)
5α	3.03 (d, 6.8)	3.04 (d, 6.8)	3.13 (*m*)
7α	2.83 (dd, 11.0, 6.8)	2.86 (dd, 10.8, 6.8)	3.08 (dd, 10.5, 7.0)
7β	2.17 (d, 11.0)	2.27 (d, 10.8)	2.28 (d, 10.5)
8a	5.09 (d, 12.1)	5.02 (d,12.1)	5.12 (d, 12.0)
8b	5.17 (d, 12.1)	5.16 (d, 12.1)	5.24 (d, 12.0)
9α	5.81 (s)	5.88 (s)	
10	1.64 (s)	1.68 (s)	1.66 (s)
1′	5.12 (d, 7.7)	5.12 (d, 7.8)	5.03 (d, 8.0)
2′	3.99 (t, 8.9)	4.01 (t, 8.8)	4.03 (t, 8.0)
3′	4.15 (t, 8.9)	4.18 (t, 8.8)	4.15 (t, 8.0)
4′	4.14 (t, 8.9)	4.07 (t, 8.8)	4.07 (t, 8.0)
5′	3.89 (*m*)	4.10 (dd, 8.8, 5.3)	4.08 (dd, 8.0, 5.0)
6′	4.28 (dd, 11.7, 5.8)	4.95 (dd, 11.6, 6.9)	5.15 (dd, 11.5, 5.0)
	4.52 (dd, 11.7, 2.4)	5.22 (dd, 11.6, 1.8)	5.21 (d, 11.5)
2″	8.16 (d, 7.5)	7.91 (d, 1.9)	8.26 (dd, 8.7, 3.1)
3″	7.31 (t, 7.5)		7.03 (d, 8.7)
4″	7.45 (t, 7.5)		
5″	7.31 (t, 7.5)	7.21 (d, 8.1)	7.03 (d, 8.7)
6″	8.16 (d, 7.5)	7.98 (dd, 8.1, 1.9)	8.26 (dd, 8.7, 3.1)
2‴, 6‴		8.10 (dd, 7.4, 1.2)	8.22 (d, 7.8)
3‴, 5‴		7.28 (t, 7.4)	7.25 (t, 7.8)
4‴		7.43 (t, 7.4)	7.56 (t, 7.8)
$-OCH_2CH_3$	3.75 (q, 7.0)		
$-OCH_2CH_3$	1.14 (t, 7.0)		
$-OCH_3$		3.78 (s)	

* All compounds were measured in pyridine-d_5; chemical shift are in parts per million, with TMS as internal standard.

TABLE II ^{13}C NMR spectral data for compounds **1**–**4** (pyridine-d_5, 100 MHz)

C	**1**	**2**	**3**	**4**
1	88.7 s	88.9 s	91.7 s	73.4 s
2	86.2 s	86.1 s	86.3 s	42.0 t
3	42.3 t	44.8 t	41.8 t	75.3 d
4	108.3 s	106.0 s	67.5 d	37.3 d
5	41.5 d	43.9 d	41.3 d	38.5 t
6	71.1 s	71.5 s	55.8 s	211.2 s
7	23.5 t	23.1 t	27.7 t	49.0 d
8	61.4 t	61.4 t	61.7 t	177.5 s
9	101.9 d	101.7 d	175.8 s	59.9 t
10	19.9 q	19.8 q	20.7 q	25.1 q
1′	100.5 d	100.3 d	100.2 d	
2′	75.0 d	74.9 d	74.8 d	
3′	78.5 d	78.3 d	78.2 d	
4′	71.9 d	71.9 d	71.8 d	
5′	78.6 d	75.4 d	75.2 d	
6′	63.0 t	65.0 t	64.5 t	
1″	130.7 s	121.9 s	121.6 s	
2″	130.0 d	113.7 d	132.6 d	
3″	128.9 d	148.5 s	116.2 d	
4″	133.5 d	153.4 s	163.8 s	
5″	128.9 d	116.3 d	116.2 d	
6″	130.0 d	124.9 d	132.6 d	
7″	166.7 s	166.4 s	166.7 s	
1‴		130.7 s	130.8 s	
2‴, 6‴		129.9 d	130.1 d	
3‴, 5‴		128.8 d	128.7 d	
4‴		133.3 d	133.2 d	
7‴		166.6 s	166.5 s	
$-OCH_2CH_3$	59.6 t			
$-OCH_2CH_3$	15.8 q			
$-OCH_3$		56.1 q		



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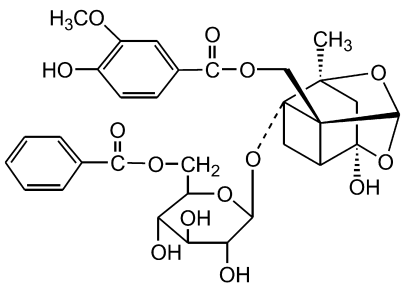

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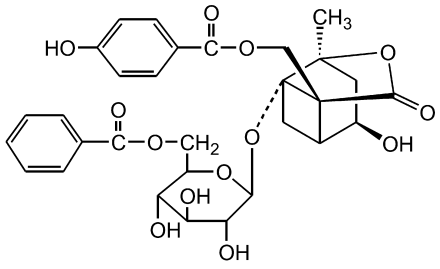

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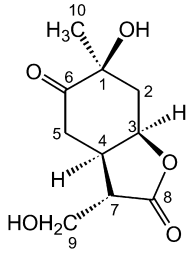

4

H-1′ (δ_H 5.12, d, $J = 8.8$ Hz) to C-1 (δ_C 88.9, s), H_2-8 (δ_H 5.02 and 5.16, d, $J = 12.1$ Hz) to C-7″ (δ_C 166.4, s), H_2-6′ [δ_H 4.95 (dd, $J = 11.6$, 6.9 Hz), 5.22 (dd, $J = 11.6$, 1.8 Hz)] to C-7‴ (δ_C 166.6, s), H-2″ (δ_H 7.91, d, $J = 1.9$ Hz) to C-1″ (δ_C 121.9, s), C-3″ (δ_C 148.5, s) and C-7″, the methoxyl proton (δ_H 3.78, s) to C-3″, and H-2‴, H-6‴ (δ_H 8.10, dd, $J = 7.4$, 1.2 Hz) to C-1‴ (δ_C 130.7, s) and C-7‴. The assignments of the other signals were confirmed by ^{1}H–^{1}H COSY, HMQC, HMBC, and NOESY experiments. Therefore, the structure of the compound **2** was elucidated as 6′-*O*-benzoyl-4″-hydroxy-3″-methoxy-paeoniflorin.

Compound **3** was indicated to have a molecular formula of $C_{30}H_{32}O_{13}$ by negative HRFABMS at *m/z* 599.1742 $[M - 1]^-$. Comparison of the NMR spectra of **3** with those of albiflorin [11] suggested that the compound **3** was made up of the same monoterpene nucleus as albiflorin, a 4-hydroxybenzoyloxy group and a benzoyloxy group. The positions of these two benzene rings were differentiated by the HMBC spectrum, in which the long-range couplings were observed between H-8/C-7″, H-2″/C-7″, H-6″/C-7″, H-6″/C-7‴, H-2‴/C-7‴, and H-6‴/C-7‴. Thus, the 4-hydroxybenzoyloxy group was attached to C-8 of the monoterpene nucleus and the benzoyloxy group was attached to C-6′ of the glucose moiety. The structure of compound **3** was thus established to be 6′-*O*-benzoylalbiflorin.

Compound **4** possessed a molecular formula of $C_{10}H_{14}O_5$ based on the HREIMS, in which the molecular ion (*m/z* 214.0847) was 16 amu greater than that of paeonilactone-A. The IR spectrum showed the presence of hydroxyl group (3331 cm^{-1}) and two carbonyl groups (1751 and 1731 cm^{-1}). Further study showed that the ^{1}H and ^{13}C NMR spectra of **4** were very similar to those of paeonilactone-A [12], indicating the same skeleton for these two compounds. The only difference was that the compound **4** has an oxygenated methylene (δ_C 59.9, t), instead of a methyl group at C-9 in paeonilactone-A. The HMBC spectrum showed the long-range correlations for H-9 [δ_H 4.35 (dd), 4.06 (dd)] to C-7 (δ_C 49.0, d) and C-8 (δ_C 177.5, s). In the NOESY spectrum, NOE enhancement was observed between H-5α and H-4, H-10, and between H-4 and H-3, H-9. Therefore, the structure of compound **4** was determined as 9-hydroxy-paeonilactone-A.

EXPERIMENTAL SECTION

General Experimental Procedures

Optical rotations were measured with a Horiba SEAP-300 spectropolarimeter. Ultraviolet spectra were taken on a Shimadzu double-beam 210A spectrophotometer. Infrared spectra were obtained on a Bio-Rad FTS-135 infrared spectrophotometer with KBr pellets. ^{1}H NMR, ^{13}C NMR, and two-dimensional-NMR spectra were recorded on Bruker AM-400 MHz and DRX-500 spectrometers with TMS as an internal standard. Mass spectrometry data were recorded on a VG Autospec-3000 spectrometer.

Plant Material

The root cortex material of *Paeonia delaviyi* was collected in the Lijiang area of Yunnan Province, in August 1998, and identified by Prof. Zhen-Wei Lu, Kunming Institute of Botany, The Chinese Academy of Sciences, Kunming, Yunnan, where a voucher specimen is deposited.

Extraction and Isolation

Dried and powdered root cortex of *Paeonia delavayi* (5 kg) was extracted with EtOH three times at room temperature. The extract was concentrated under vacuum to afford a residue, which was suspended in water, and partitioned with EtOAc. The EtOAc extract was concentrated *in vacuo* to give a residue (53 g), which was chromatographed on a silica gel column (200–300 mesh, 1 kg) and eluted with a $CHCl_3$–MeOH mixture containing an increasing amount of MeOH. The fractions were combined after monitoring by TLC. Fractions 5–8 (4.8 g) were further submitted to repeated Si gel ($CHCl_3$–MeOH 9:1) and RP-18 gel column (MeOH–H_2O 6:4) chromatography to give compounds **1** (27 mg), **2** (56 mg), **3** (10 mg), and **4** (14 mg).

4-O-Ethylpaeoniflorin (1)

White foam; $[\alpha]_D^{25}$ − 9.5 (*c* 0.39, MeOH); UV (MeOH) λ_{max} (log ε) 202.5 (4.08), 229.0 (4.06), 273.5 (2.38), 280.5 (2.73) nm; IR (KBr) ν_{max} 3434, 2976, 2928, 1714, 1600, 1451, 1345, 1313, 1276, 1224, 1176, 1050, 958, 825, 714 cm^{-1}; ^1H NMR spectral data, see Table I; ^{13}C NMR spectral data, see Table II; negative-ion FAB-MS *m/z* $[M - 1]^-$ 507 (5), 403 (4), 325 (4), 121 (100), 77 (10); negative-ion HRFABMS *m/z* $[M - 1]^-$ 507.1822 (calcd for $C_{25}H_{32}O_{11}$, 507.1866).

6′-O-Benzoyl-4″-hydroxy-3″-methoxy-paeoniflorin (2)

White foam; $[\alpha]_D^{17}$ − 14.0 (*c* 0.43, MeOH); UV (MeOH) λ_{max} (log ε) 202.5 (4.36), 222.0 (4.34), 262.5 (4.02), 292.0 (3.67) nm; IR (KBr) ν_{max} 3430, 1711, 1599, 1514, 1450, 1428, 1383, 1345, 1284, 1222, 1179, 1115, 1073, 1025, 823, 763, 714 cm^{-1}; ^1H NMR spectral data, see Table I; ^{13}C NMR spectral data, see Table II; negative-ion FAB-MS *m/z* $[M - 1]^-$ 629 (100), $[M–CH_3]^-$ 615 (4), 507 (7), 311 (9), 209 (6), 167 (34), 121 (56); negative-ion HRFABMS *m/z* $[M - 1]^-$ 629.1831 (calcd for $C_{31}H_{34}O_{14}$, 629.1870).

6′-O-Benzoylalbiflorin (3)

Amorphous white powder; $[\alpha]_D^{17}$ − 22.7 (*c* 0.31, MeOH); UV (MeOH) λ_{max} (log ε) 203.0 (4.41), 227.5 (4.38), 259.0 (3.59) nm; IR (KBr) ν_{max} 3420, 2923, 2860, 1749, 1712, 1605, 1513, 1452, 1381, 1278, 1167, 1116, 1070, 942, 771, 714 cm^{-1}; ^1H NMR spectral data, see Table I; ^{13}C NMR spectral data, see Table II; negative-ion FAB-MS *m/z* $[M - 1]^-$ 599 (100), 325 (15), 255 (10); negative-ion HRFABMS *m/z* $[M - 1]^-$ 599.1742 (calcd. for $C_{30}H_{32}O_{13}$, 599.1765).

9-Hydroxy-paeonilactone-A (4)

Amorphous white powder; $[\alpha]_D^{24}$ − 11.4 (*c* 0.42, MeOH); UV no absorption; IR (KBr) ν_{max} 3331, 2979, 2915, 1751, 1731, 1464, 1375, 1340, 1174, 1150, 994 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ 1.50 (3H, s, H-10), 2.48 (2H, d, $J = 6.6$ Hz, H-2), 2.91 (1H, dd, $J = 15.6$, 6.9 Hz, H-5β), 2.97 (1H, dd, $J = 15.6$, 3.4 Hz, H-5α), 3.01 (1H, m, overlap, H-7), 3.59 (1H, m, H-4), 4.06 (1H, dd, $J = 10.9$, 3.3 Hz, H-9β), 4.35 (1H, dd, $J = 10.9$, 4.1 Hz, H-9α), 5,14 (1H, dd, $J = 14.9$, 6.7 Hz, H-3α); ^{13}C NMR spectral data, see Table II; EIMS *m/z* $[M]^+$ 214 (3), 186 (36), 171 (39), 168 (31), 125 (31), 114 (78), 97 (85), 87 (96), 55 (100); HREIMS *m/z* $[M]^+$ 214.0847 (calcd. for $C_{10}H_{14}O_5$, 214.0841).

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