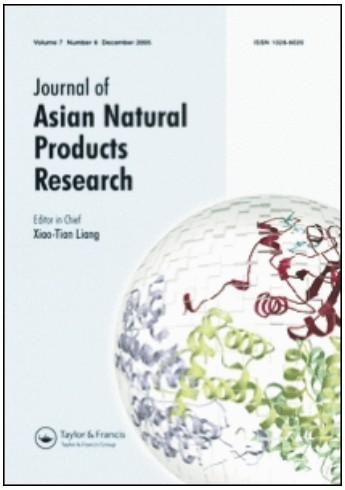

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Four new compounds from *Paeonia albiflora*

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Studies on the chemical constituents of the roots of *Paeonia albiflora* Pall. led to the isolation of four new compounds named (3*R*,4*S*)-3-methyl-3,4-dihydro-5,6,7-trihydroxy-4-(3′-methoxy-4′-hydroxyphenyl)-1H-[2]-benzopyran-1-one (**1**), 5-hydroxy-6-methyl-1H-indole-3-carbaldehyde (**2**), *trans*-5-hydroxy-2-methoxy-6-methyl-2,3-dihydrobenzofuran-3-yl methyl benzoate (**3**) and *cis*-5-hydroxy-2-methoxy-6-methyl-2,3-dihydrobenzofuran-3-yl methyl benzoate (**4**), and two known ones, (7*S*,8*S*)-3-methoxy-3′,7-epoxy-8,4′-oxyneligna-4,9,9′-triol (**5**) and (7*S*,8*R*)-dihydrodehydrodiconifery alcohol (**6**). Their structures were determined mainly by spectroscopic techniques including 2D-NMR (HSQC, HMBC, NOESY), MS, and CD experiments.

Keywords: *Paeonia albiflora* Pall.; Ranunculaceae; (3*R*,4*S*)-3-methyl-3,4-dihydro-5,6,7-trihydroxy-4-(3′-methoxy-4′-hydroxyphenyl)-1H-[2]-benzopyran-1-one; 5-hydroxy-6-methyl-1H-indole-3-carbaldehyde; dihydrobenzofuran

1. Introduction

Paeonia albiflora Pall. (Shaoyao) is an important ornamental and medicinal plant in China. Chemical studies on *P. albiflora* Pall. have been carried out since 1969 [1] and the presence of monoterpene glucoside [2,3], triterpene [4], tannin [5], catechin [6], and aromatic acid [7] has been reported. Various biological activities such as inhibiting platelet aggregation [8], anti-hepatic fibrosis [9], anti-inflammatory [10] as well as improvement on learning, spatial resolution, and delaying senility [11] led us to investigate the constituents of this plant. Here, we report the isolation of four new compounds named (3*R*,4*S*)-3-methyl-3,4-dihydro-5,6,7-trihydroxy-4-(3′-methoxy-4′-hydroxyphenyl)-1H-[2]-benzopyran-1-one (**1**), 5-hydroxy-6-methyl-1H-indole-3-carbaldehyde (**2**), *trans*-5-hydroxy-2-methoxy-6-methyl-2,3-dihydrobenzofuran-3-yl methyl benzoate (**3**) and *cis*-5-hydroxy-2-methoxy-6-methyl-2,3-dihydrobenzofuran-3-yl methyl benzoate (**4**), along with the two known ones, (7*S*,8*S*)-3-methoxy-3′,7-epoxy-8,4′-oxyneoligna-4,9,9′-triol (**5**) [12] and (7*S*,8*R*)-dihydrodehydrodiconifery alcohol (**6**) [13].

2. Results and discussion

Compound **1** was obtained as colorless oil. Its molecular formula was determined to be $C_{17}H_{16}O_7$ using HR-ESI-MS, which showed a pseudo-molecular ion peak at *m/z* 355.0798 $[M+Na]^+$. The ^1H NMR spectrum of **1** contained a typical ABX aromatic proton system at δ_H 6.49 (1H, dd, $J = 2.0$, 8.1 Hz), 6.66 (1H, d, $J = 8.1$ Hz), and 6.70 (1H, d, $J = 2.0$ Hz), one penta-substituted aromatic ring with a proton signal at δ_H 7.14 (1H, s), one methyl at δ_H 1.42 (3H, d, $J = 6.6$ Hz), and one methoxyl group at δ_H 3.75 (3H, s). The ^{13}C NMR spectrum of **1** confirmed the

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presence of the two aromatic rings and one ester carbonyl group at δ_C 167.6. The HMBC spectrum of **1** showed long-range correlations from H-4 to C-5 and C-10, H-3 to C-1 and C-10, and H-8 to C-1, C-6, and C-10. By analyzing the above data and comparing with the related literature data [14], the structure of **1** was deduced as a 3,4-dihydroisocoumarin derivative.

The HMBC correlations from H-2′ to C-3′, C-4′, and C-6′, H-5′ to C-1′ and C-3′, and from the methoxyl group to C-3′ indicated that **1** contained a 3′-methoxy-4′-hydroxyphenyl group. The HMBC correlation from H-4 to C-1′ confirmed that the 3′-methoxy-4′-hydroxyphenyl group was connected to C-4. Furthermore, the methyl group showed correlation with C-3 in the HMBC spectrum. The above data led to the assignment of **1** as 3-methyl-3,4-dihydro-5,6,7-trihydroxy-4-(3′-methoxy-4′-hydroxyphenyl)-1H-[2]-benzopyran-1-one.

The NOE correlations between H-3 and H-2′, H-6′, and that between H-4 and the methyl group indicated that H-3 and H-4 were in a *trans*-orientation. The CD spectrum of **1** showed a positive Cotton effect at 288 nm indicating that methyl group was in an α-axial orientation and accordingly the absolute configuration at C-3 was *R* [15]. Thus, the absolute configuration of compound **1** was 3*R*,4*S* (Figure 1).

Compound **2** was isolated as white crystal. The HR-ESI-MS of **2** had a molecular ion peak at *m/z* 198.0534 $[M+Na]^+$, consistent with the molecular formula $C_{10}H_9NO_2$. The ^{13}C NMR spectrum displayed 10 carbons including eight aromatic carbons and one carbonyl carbon. The ^1H NMR spectrum displayed one methyl at δ_H 2.20 (3H, s) and three aromatic protons at δ_H 7.17 (1H, s), 7.49 (1H, s), and 8.03 (1H, s). The structural assignment was achieved by HSQC, HMBC, and NOESY spectra. The HSQC correlation from H-10 to carbonyl indicated the appearance of an aldehyde group. In the HMBC spectrum, the methyl group had cross-peaks with C-5, C-6, and C-7, H-2 with C-3, C-9, and C-10, H-4 with C-3, C-5, C-6, and C-8, H-7 with C-5 and C-9, and the methyl, aldehyde groups with C-2, C-3, and C-9. The NOEs between H-2 and the aldehyde group and that between the methyl and H-7 indicated that the methyl was attached to C-6 and the aldehyde group was attached to C-3. From the above spectral data, compound **2** was deduced to be 5-hydroxy-6-methyl-1H-indole-3-carbaldehyde (Figure 2).

Compound **3** was obtained as colorless oil. The HR-ESI-MS of **3** showed a quasi-molecular ion $[M+Na]^+$ at *m/z* 337.1053. Taking into account the 18 carbons displayed in its ^{13}C NMR spectrum, the molecular formula was established as $C_{18}H_{18}O_5$. The ^1H NMR spectrum of **3** indicated the presence of one methyl group at δ_H 2.16 (3H, s), one methoxyl group at δ_H 3.49 (3H, s), one acetal proton at δ_H 5.48 (1H, d, $J = 1.8$ Hz), aromatic protons at δ_H 6.60 (1H, s) and 6.74 (1H, s), and five characteristic protons attributable to one single-substituted benzene at δ_H 7.47 (2H, t, $J = 8.1$ Hz), 7.61 (1H, t,

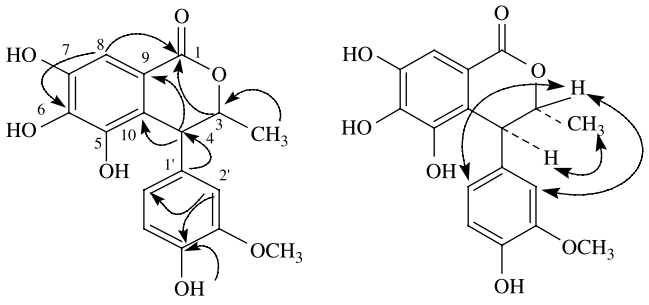

Figure 1. Key HMBC and NOESY correlations of **1**.

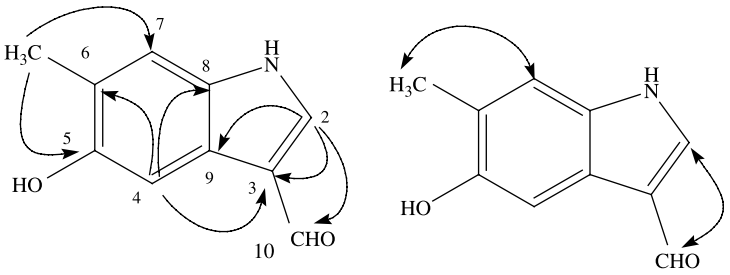

Figure 2. Key HMBC and NOESY correlations of **2**.

$J = 8.1$ Hz), and 7.97 (2H, d, $J = 8.1$ Hz). The ^{13}C NMR spectrum evidenced the presence of two benzene rings and one ester carbonyl carbon at δ_C 167.7. The structure of **3** was determined by the analysis of NMR spectral data including HSQC, HMBC, and NOESY experiments. The HMBC correlations from H-3 to C-2, C-8, C-3a, and C-7a, H-2 to C-3, C-8, C-3a, and C-7a, H-7 to C-3a, C-7a, and C-5, and H-4 to C-5, C-6, and C-7a could be observed. By comparing the above data with the related literature data [16–18], the structure of **3** was deduced as 2,3-dihydrobenzofuran derivative. The long-range correlations from the methoxyl group to C-2, from the methyl group to C-5, C-6, and C-7, and H-8 (H-8a and H-8b) to C-3a, C-3, and C-2 showed that the methoxyl group was attached to C-2, the methyl group to C-6, and the methylenoxy to C-3. The HMBC experiment revealed long-range correlations from H-8 to C-7′, and from both H-2′ and H-6′ to C-7′, demonstrating that compound **3** contained a benzoyl group and the benzoyl group was located at C-8. The relative stereochemistry of the dihydrofuran ring was elucidated by a NOESY experiment. The strong NOEs between H-2 and H-8, between H-3 and the methoxyl group indicated a *trans*-2/3 configuration. So, the structure of **3** was determined as *trans*-5-hydroxy-2-methoxy-6-methyl-2,3-dihydrobenzofuran-3-yl methyl benzoate (Figure 3).

The HR-ESI-MS of compound **4** also showed a quasi-molecular ion at *m/z* 337.1058 $[M+Na]^+$, which indicated a molecular formula of $C_{18}H_{18}O_5$, in combination with the ^{1}H and ^{13}C NMR spectral data. The ^{13}C NMR spectral data of **4** were similar to those of **3** except for C-3a, C-2, C-3, and C-8 shifting upfield by -1.4, 2.4, 3.7, and 1.8 ppm, respectively, suggesting that **4** had the similar structure with **3**. The structural assignment was confirmed by HSQC, HMBC, and NOESY. The relationship of H-2 and H-3 is *cis*, which was verified by the NOE correlations not only between H-2 and H-3, but also between the methoxyl group and H-8. Accordingly, **4** was deduced to be *cis*-5-hydroxy-2-methoxy-6-methyl-2,3-dihydrobenzofuran-3-yl methyl benzoate (Figure 4).

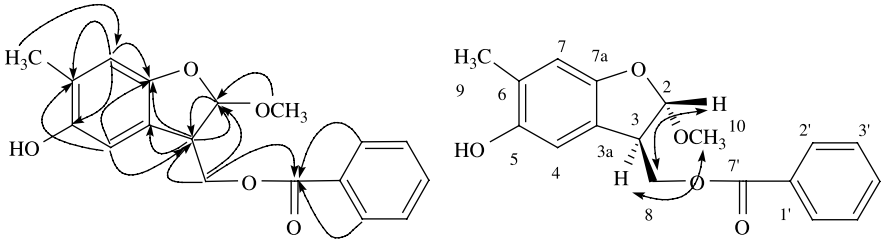

Figure 3. Key HMBC and NOESY correlations of **3**.

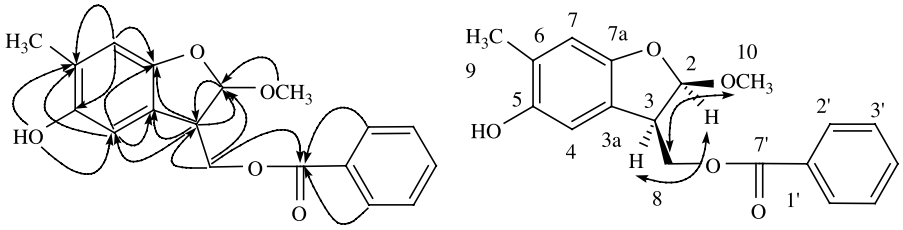

Figure 4. Key HMBC and NOESY correlations of **4**.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter in methanol solution. The UV spectra were measured on a Shimadzu UV-240 instrument. The IR spectra were recorded on a Bruker IFS-55 spectrophotometer in methanol. The ^{1}H, ^{13}C, and 2D NMR spectra (HMQC, HMBC, and NOESY) were recorded on a Bruker ARX-600 NMR spectrometer with TMS as the internal standard. ESI-MS data were measured on Bruker APEX-II mass spectrometer. HR-ESI-MS data were obtained using Autospec Ultima-Tof mass spectrometer. Column chromatography was carried out on silica gel 60 (Qingdao Haiyang Chemical Co., Ltd, Qingdao, China), ODS (40–75 μm, Fuji Silysia Chemical Ltd, Fuji Japan), and Prep. HPLC (Waters-600 chromatograph with ODS C_{18} column and Waters-490 UV detector). All reagents were of analytical grade and purchased from Shenyang Chemical Company (Shenyang, China); the purity of reagents for HPLC was 99.9%.

3.2 Plant material

Roots of *P. albiflora* were purchased from Liaoning Yaocai Co., Liaoning, China, and identified by Prof. Qi-Shi Sun, Department of Natural Products Chemistry, Shenyang Pharmaceutical University. This plant originated from Neimeng Province in China. A voucher specimen (No. 20041120) has been deposited at the herbarium of Shenyang Pharmaceutical University, Shenyang, China.

3.3 Extraction and isolation

The dried roots of *P. albiflora* (6 kg) were repeatedly (×3) extracted with ethanol–water (6:4, v/v) for 2 h. The combined extract was concentrated under vacuum. The residue was suspended in water and partitioned with EtOAc thrice. The EtOAc layer was subjected to silica gel column chromatography with $CHCl_3$:MeOH (100:1, 30:1, 20:1, 10:1, 5:1, 1:1) as eluent to afford 13 fractions (A–M). Fraction F (14 g) was further subjected to silica gel column chromatography with $CHCl_3$:MeCOMe gradient system to give 10 fractions (F1–F10). Fraction F4 was further purified by HPLC (MeOH:H_2O, 6:4) to afford compounds **5** (14 mg) and **6** (12 mg). Fraction F5 was further purified by P-TLC ($CHCl_3$:MeOH, 6:1) to afford compound **2** (35 mg). Fraction G (6 g) was further subjected to silica gel column chromatography with $CHCl_3$:MeCOMe (20:1, 10:1, 5:1, 3:1, 1:1) to give six fractions (G1–G6). Fraction G3 was purified by HPLC (MeOH:H_2O, 7:3) to afford compounds **3** (12 mg) and **4** (10 mg). Fraction H (16 g) was further subjected to silica gel column chromatography with $CHCl_3$–MeOH gradient system to give nine fractions (H1–H9). Fraction H7 was further chromatographed on a C-18 reverse-phase open column to yield subfraction H75, then subfraction H75 was purified by HPLC (MeOH:H_2O, 8:2) to afford compound **1** (15 mg).

3.3.1 Compound **1**

Colorless oil; $[\alpha]_D^{25} + 4.3$ ($c = 0.13$, MeOH). UV λ_{max} (MeOH) 230 nm. IR (KBr) ν_{max} (cm^{-1}): 3362, 2977, 1692, 1602, 1518,

Table 1. ^{1}H NMR spectral data of **1**–**4** (at 300 MHz; δ in ppm, J in Hz).

Position	**1**	**2**	**3**	**4**
2		8.03 (1H, s)	5.48 (1H, d, $J = 1.8$)	5.63 (1H, d, $J = 6.3$)
3	4.87 (1H, m)		3.50 (1H, m)	3.87 (1H, ddd, $J = 5.4, 6.3, 7.5$)
4	4.26 (1H, s)	7.17 (1H, s)	6.74 (1H, s)	6.78 (1H, s)
6				
7		7.49 (1H, s)	6.60 (1H, s)	6.58 (1H, s)
8	7.14 (1H, s)		4.32 (1H, dd, $J = 7.5, 11.7$), 4.46 (1H, dd, $J = 5.4, 11.7$)	4.51 (1H, dd, $J = 7.5, 11.7$), 4.70 (1H, dd, $J = 5.4, 11.7$)
9			2.16 (3H, s)	2.16 (3H, s)
10		9.80 (1H, s)	3.49 (3H, s)	3.49 (3H, s)
2′	6.70 (1H, d, $J = 2.0$)		7.97 (1H, d, $J = 8.1$)	8.08 (1H, dd, $J = 1.5, 8.1$)
3′			7.47 (1H, t, $J = 8.1$)	7.52 (1H, t, $J = 8.1$)
4′			7.61 (1H, t, $J = 8.1$)	7.63 (1H, t, $J = 8.1$)
5′	6.66 (1H, d, $J = 8.1$)		7.47 (1H, t, $J = 8.1$)	7.52 (1H, t, $J = 8.1$)
6′	6.49 (1H, dd, $J = 2.0, 8.1$)		7.97 (1H, d, $J = 8.1$)	8.08 (1H, dd, $J = 1.5, 8.1$)
$-OCH_3$	3.75 (3H, s)			
$-CH_3$	1.42 (3H, d, $J = 6.6$)	2.20 (3H, s)		
−OH		9.05 (1H, brs)		
−NH		11.76 (1H, brs)		

Table 2. ^{13}C NMR spectral data of **1**–**4** (at 75 MHz; δ in ppm).

Position	**1**	**2**	**3**	**4**
1	167.6			
2		137.5	111.1	108.7
3	82.6	123.1	50.3	46.6
3a			124.3	125.7
4	43.0	104.8	112.2	111.9
5	146.2	151.9	150.8	150.8
6	141.4	121.9	126.4	125.7
7	144.3	113.2	112.5	112.5
7a			152.5	152.5
8	108.7	131.2	66.1	64.3
9	121.3	117.9	16.7	16.6
10	121.3	184.4	56.0	56.5
1′	134.9		131.1	131.4
2′	112.5		130.5	130.6
3′	148.0		129.6	129.7
4′	146.2		134.4	134.3
5′	116.0		129.6	129.7
6′	121.2		130.5	130.6
7′			167.7	168.0
$-CH_3$	21.0	16.9		
$-OCH_3$	56.3			

1388, 1031. CD (MeOH): $\Delta\varepsilon_{242\,nm} + 1.02$, $\Delta\varepsilon_{288\,nm} + 0.62$ ($c = 3.61 \times 10^{-4}$ M). ^1H and ^{13}C NMR (in CD_3OD) spectral data: see Tables 1 and 2. HR-ESI-MS (*m/z*): 355.0798 $[M+Na]^+$ (calcd for $C_{17}H_{16}O_7Na$, 355.0794).

3.3.2 *Compound* **2**

White crystal; $[\alpha]_D^{25} - 7.5$ ($c = 0.13$, MeOH). UV λ_{max} (MeOH) 226 nm. IR (KBr) ν_{max} (cm^{-1}): 3390, 2834, 1626, 1528, 1456, 1276, 1055, 1016, 828, 714. ^1H and ^{13}C NMR (in DMSO) spectral data: see Tables 1 and 2. HR-ESI-MS (*m/z*): 198.0534 $[M+Na]^+$ (calcd for $C_{10}H_9NO_2Na$, 198.0531).

3.3.3 *Compound* **3**

Colorless oil; $[\alpha]_D^{25} - 6.2$ ($c = 0.13$, MeOH). UV λ_{max} (MeOH) 232 nm. IR (KBr) ν_{max} (cm^{-1}): 3442, 2952, 1720, 1637, 1450, 1381, 1273, 1016, 713. ^1H and ^{13}C NMR (in CD_3OD) spectral data: see Tables 1 and 2. HR-ESI-MS (*m/z*): 337.1053 $[M+Na]^+$ (calcd for $C_{18}H_{18}O_5Na$, 337.1052).

3.3.4 *Compound* **4**

Colorless oil; $[\alpha]_D^{25} - 12.5$ ($c = 0.15$, MeOH). UV λ_{max} (MeOH) 232 nm. IR (KBr) ν_{max} (cm^{-1}): 3450, 2948, 1719, 1600, 1453, 1275, 1055, 1014, 713. ^1H and ^{13}C NMR (in CD_3OD) spectral data: see Tables 1 and 2. HR-ESI-MS (*m/z*): 337.1058 $[M+Na]^+$ (calcd for $C_{18}H_{18}O_5Na$, 337.1052).

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