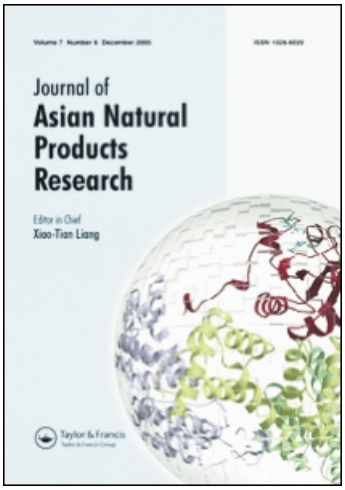

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New Iridoids from *Pedicularis artselaeri*

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NEW IRIDOIDS FROM *PEDICULARIS ARTSELAERI*

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Three new iridoids, named artselaenin I, II and III, were isolated from the whole plants of *Pedicularis artselaeri*, along with 11 known compounds, 8-epiloganic acid, 7-deoxy-8-epiloganic acid, plantarenaloside, mussaenoside, lariciresinol-4-O-β-D-glucoside, lariciresinol-4′-O-β-D-glucoside, alaschaniosideA, cirtusinA, 2-(p-hydroxyphenyl)-ethanol 1-O-β-D-glucopyranoside, 3-methoxy-4-primeverosylacetophenone and adenine. Their structures were identified mainly by spectral evidence.

Keywords: *Pedicularis artselaeri*; Scrophulariaceae; Iridoid; Artselaenin I, II and III

INTRODUCTION

The genus *Pedicularis* comprises about 329 species in China [1]. They are used for the treatment of collapse, exhaustion and senility in folk medicine as cardiac tonics [2], and are usually called 'pseudo-ginseng' by local inhabitants. In previous papers [3–6], we have reported the isolation and structural elucidation of iridoid, phenylpropanoid and neolignan glycosides from *Pedicularis* plants. The chemical constituents of *Pedicularis artselaeri* Maxim. have not been investigated, and we now report the isolation and structural elucidation of three new iridoids, artselaenin I (**1**), II (**2**) and III (**3**) (see Fig. 1), as well as 11 known compounds, from whole plants of *P. artselaeri*.

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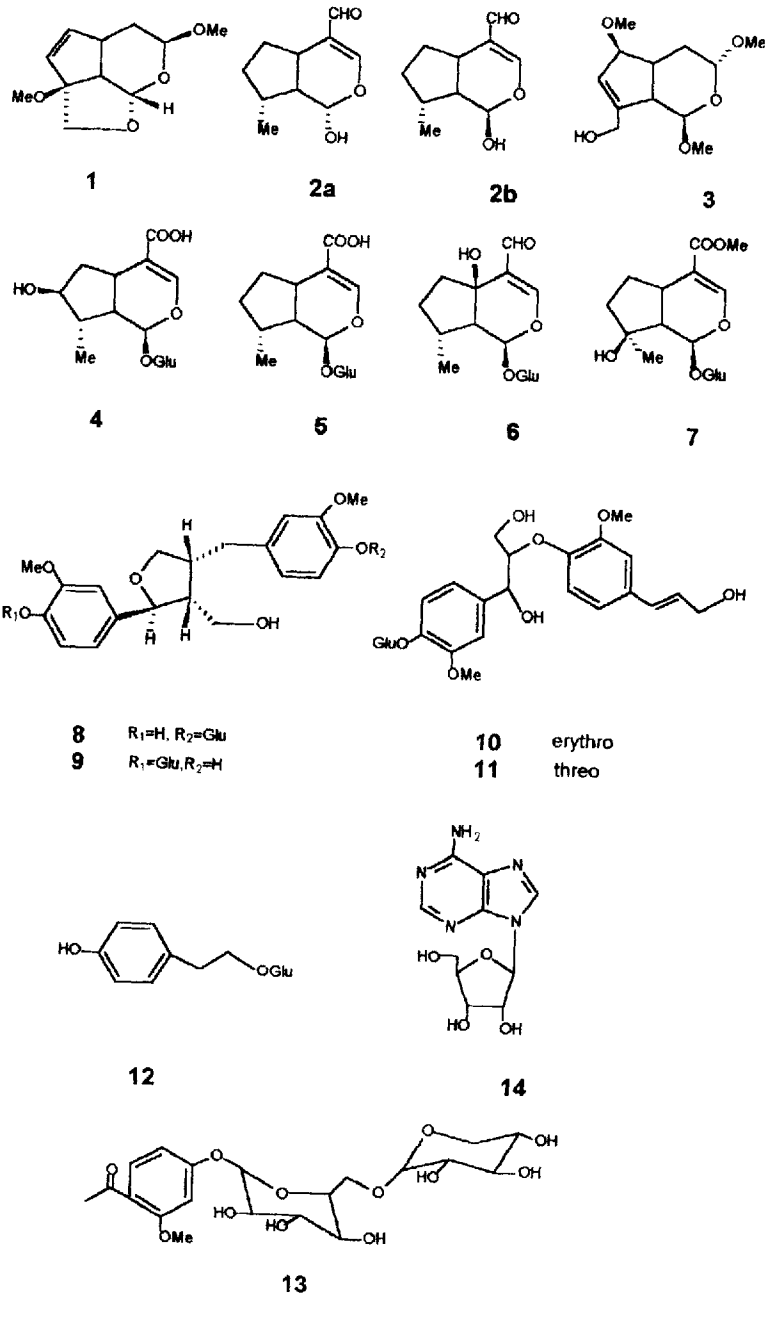

FIGURE 1

RESULTS AND DISCUSSION

Compound **1** was obtained as an amorphous powder, $[\alpha]_D^{25} + 118$ (c 0.15, $CHCl_3$), the UV spectrum showed $\lambda_{max}^{CHCl_3}$ at 202 nm. Its IR spectrum showed the presence of double bond (1674 cm^{-1}) and C–O–C (1098, 1046 cm^{-1}). The EIMS of **1** showed a $[M]^+$ ion at m/z 212, suggesting the molecular formula to be $C_{11}H_{16}O_4$, which was confirmed by the ^{13}CNMR and DEPT data (Table II). Comparison of the ^{1}HNMR spectrum of **1** (see Table I) with usual iridoids showed that the olefinic proton signal due to H-3 was absent in **1**, and instead an additional acetal proton signal at δ 4.71 (1H, dd, $J = 8.0$, 4.4 Hz, H-3) coupled to the methylene protons at C-4 was observed. Two methoxy groups (δ 3.43, 3.18) were also clearly seen. NMR spectral data of **1** were similar to those of gardenogeninA and B [16], suggesting compound **1** to be a tricyclic C-9 iridoid. The signals at δ 3.84 (1H, d, $J = 9.4$ Hz, H-10) and 3.96 (1H, d, $J = 9.4$ Hz, H-10) seem to be due to the C-10 methylene protons from their coupling constants and splitting patterns, this verified C-8 (δ 99.3, C) was a quaternary carbon connected with C-10 (74.3, CH_2) and a methoxy group. The other methoxy group should be at C-3 position according to the ^{1}HNMR (δ 4.71, 1H, dd, $J = 8.0$, 4.4 Hz) and ^{13}CNMR (δ 100.3, CH) data. On the basis of above results, the double bond must be between C-6 and C-7, because both double bond carbons were methines. The relative stereochemistry of **1** has been determined by the NOESY experiment. The correlations of δ 5.54 (H-1) with 3.24 (H-5) and 2.66 (H-9), δ 3.18 (–MeO of C-3) with 2.66 (H-9) and 3.43 (–MeO of C-8), suggested the H-1, H-5, H-9 and two methoxy groups were all β-oriented. Thus, the structure of **1** has been determined, we named it artselaenin I.

TABLE I ^{1}HNMR spectral data of compounds **1**–**4** (400 MHz, $CDCl_3$, δ, ppm, TMS, J = Hz)

H	**1**	**2**	**3**	**4**
1	5.54 (d, 5.8)	5.26 (d, 7.2)	5.67 (d, 3.3)	4.76 (d, 6.0)
3	4.71 (dd, 8.0, 4.4)	7.24 (s)	7.22 (s)	4.91 (t, 5.4)
4	1.96 (dt,14.0, 4.0); 1.76 (ddd, 14.0, 8.0, 4.0)			1.98 (dt, 16.0, 5.4) 1.58 (ddd, 16.0, 6.4, 5.4)
5	3.24 (m)	2.93 (m)	2.85 (m)	2.46 (m)
6	5.70 (dd, 5.6, 2.5)	Overlapped	Overlapped	4.54 (d, 8.0)
7	5.95 (d, 5.6)	Overlapped	Overlapped	5.88 (brs)
8		2.30 (m)	2.28 (m)	
9	2.66 (dd, 8.0, 6.3)	2.19 (m)	2.16 (m)	2.90 (brt, 8.0)
10	3.84 (d, 9.4); 3.96 (d, 9.4)	1.10 (d, 7.2)	1.11 (d, 7.2)	4.22 (brs)
11		9.19 (s)	9.29 (s)	
OMe	3.18, 3.43			3.35, 3.44, 3.51

Compound **2** were obtained as a mixture (yellowish oil) of α- and β-epimers (**2a** and **2b**) at C-1 in a ratio of about 3 : 1, as shown by the integral trace of the corresponding signal multiplicities in their ^{1}HNMR spectra. The UV spectrum showed $\lambda_{max}^{CHCl_3}$ at 244 nm, assigned to an α,β-unsaturated aldehyde function. The IR spectrum (KBr) of **2** showed the presence of hydroxyl group (3370 cm^{-1}) and α,β-unsaturated aldehyde function (2876, 1670, 1627 cm^{-1}). The molecular ion peak at m/z 182 in the EIMS suggested the molecular formula to be $C_{10}H_{14}O_3$, which was confirmed by the ^{13}CNMR and DEPT data (Table II). Most signals in the NMR spectra of the mixture were doubled but due to the different amounts of **2a** and **2b**, it was possible to differentiate the signals of one from another. The NMR spectral data of **2a** and **2b** were very similar to those of boschnaloside [9], however, there were no signals of glucose in the NMR of **2**. The evident difference of **2a** and **2b** is the chemical shifts and coupling constants of H-1 (compound **2a**: $\delta_{H\text{-}1}$ 5.26, $J_{1,9} = 7.2$ Hz; compound **2b**: $\delta_{H\text{-}1}$ 5.67, $J_{1,9} = 3.3$ Hz). This confirmed the hydroxy group at C-1 to be α- and β-oriented [9,17] in **2a** and **2b** respectively. Thus, the structure of **2** were determined.

Compound **3** was obtained as a yellowish oil, $[\alpha]_D^{20} - 52.4$ (c 0.10, $CHCl_3$), the UV spectrum showed $\lambda_{max}^{CHCl_3}$ at 202 nm. The IR (KBr) spectrum of **3** showed the presence of double bond (1652 cm^{-1}) and C–O–C (1096, 1026 cm^{-1}). The EIMS of **3** showed the molecular ion peak at m/z 224, which, together with its ^{13}CNMR and DEPT spectral data (Table II) suggested the molecular formula to be $C_{12}H_{20}O_5$. The ^{1}H and ^{13}CNMR data were similar to those of isonishindaside [18] and 3β-butoxy-3,4-dihydroaucubin [3], however, there were no glucose signals in **3**, but three methoxy groups (δ_H 3.35, 3.44, 3.51: δ_C 55.2, 56.1, 56.4). The methoxy

TABLE II ^{13}CNMR and DEPT spectral data of compounds **1**–**4** (100 MHz, $CDCl_3$, δ, ppm, TMS)

C	1	2	3	4
1	96.4 (CH)	96.1 (CH)	95.8 (CH)	98.9* (CH)
3	100.3 (CH)	162.6 (CH)	162.8 (CH)	99.0* (CH)
4	30.2 (CH_2)	123.7 (C)	124.5 (C)	30.2 (CH_2)
5	45.1 (CH)	36.3 (CH)	36.2 (CH)	40.4 (CH)
6	140.2 (CH)	31.6* (CH_2)	31.5* (CH_2)	89.2 (CH)
7	132.1 (CH)	30.3* (CH_2)	30.8* (CH_2)	126.4 (CH)
8	99.3 (C)	32.4 (CH)	32.8 (CH)	147.9 (C)
9	39.7 (CH)	44.1 (CH)	42.8 (CH)	48.9 (CH)
10	74.3 (CH_2)	16.4 (CH_3)	14.9 (CH_3)	61.1 (CH_2)
11		191.1 (CH)	191.8 (CH)	
MeO	51.9, 55.5			55.2, 56.1, 56.4

* These values in the same column may be interchangeable.

groups at C-1 and C-3 were determined to be β- and α-oriented according to the coupling constants of H-1 (δ 4.76, d, $J = 6.0$ Hz) and H-3 (δ 4.91, t, $J = 5.4$ Hz) [18], respectively. The methoxy group at C-6 was determined to be β-oriented according to the chemical shift of C-6 (δ 89.2) [19]. Thus, the structure of **3** has been established.

Iridoid aglycones have been known as a class of unstable compounds, but compounds **1**–**3** proved to be stable even after storage of three months at room temperature. There is a possibility that compounds **1**–**3** might be artifacts from extraction and isolation procedures. We extracted the same plant (50 g) by EtOH at room temperature, and found compounds **1**–**3** to be still present (by TLC). Thus, **1**–**3** should be genuine natural products.

8-Epiloganic acid (**4**) [7], 7-deoxy-8-epiloganic acid (**5**) [8], plantarenaloside (**6**) [9], mussaenoside (**7**) [10], lariciresinol-4-O-β-D-glucoside (**8**) [11], lariciresinol-4′-O-β-D-glucoside (**9**) [11], alaschaniosideA (**10**) [12], cirtusinA (**11**) [12], 2-(p-hydroxyphenyl)-ethanol 1-O-β-D-glucopyranoside (**12**) [13], 3-methoxy-4-primeverosylacetophenone (**13**) [14] and adenine (**14**) [15] were identified by comparison of their spectral data (FABMS, EIMS, ^{1}H, ^{13}CNMR, DEPT) with those published in the literature.

EXPERIMENTAL SECTION

General experimental procedures IR spectra were recorded on a Nicolet-170 SX spectrometer, UV spectra on a Shimadzu UV-260 visible recording spectrometer, NMR were recorded on a Bruker AM 400 spectrometer and EIMS on a VG ZAB-HS instrument. Optical rotation was measured with a JASCO-20C autorecording polarimeter. HPLC was performed on the Gilson-Model 116 equipped with Whatman Partisil 10 ODS C_{18} (9 × 250 mm) column.

Plant material *P. artselaeri* Maxim. was collected in Zhang county, Gansu province of China in August 1993. It was identified by Prof. Zhang Guo-Liang of Lanzhou University, and a voucher specimen (pv-002) has been preserved at the Herbarium of our Institute of Organic Chemistry.

Extraction and isolation of compounds The dried whole plants (3.2 kg) were extracted with MeOH under reflux (3 × 4 l) for 3 h each time, after concentration of the combined extracts under reduced pressure, the residue was diluted with hot water and the water-insoluble material removed by filtration through Celite. The filtrate was extracted with petroleum ether (60–90°C), EtOAc and n-BuOH.

The EtOAc portion (130 g) was chromatographed over a silica gel column (6.5 × 150 cm, 200–300 mesh, 1500 g) and eluted with $CHCl_3$–MeOH (30 : 1 to 2 : 1), three fractions were obtained. Fraction 1 ($CHCl_3$–MeOH, 18 : 1; 4500–6000 ml) was purified by preparative TLC (20 × 20 cm) eluting with petroleum ether–Me_2CO (4 : 1) to obtain **1** (20 mg, Rf = 0.75), **3** (15 mg, Rf = 0.70) and the mixture of **2a** and **2b** (50 mg, Rf = 0.40). Fraction 2 ($CHCl_3$–MeOH, 8 : 1; 7000–9500 ml) on repeated chromatographic purification over a silica gel column (2.5 × 30 cm) and eluted with $CHCl_3$–MeOH (6 : 1), gave pure compounds **6** (120 mg, 300–450 ml) and **7** (30 mg, 500–580 ml). Fraction 3 ($CHCl_3$–MeOH, 4 : 1; 10 500–14 000 ml) was chromatographed over a silica gel column (1.5 × 20 cm) and eluted with EtOAc–EtOH (4 : 1), gave pure compound **14** (60 mg, 420–550 ml).

The n-BuOH portion (115 g) was chromatographed over a silica gel column (6.5 × 150 cm, 200–300 mesh, 1500 g) and eluted with $CHCl_3$–MeOH (20 : 1 to 2 : 1), four fractions were obtained. Fraction 1 ($CHCl_3$–MeOH, 12 : 1; 5000–8500 ml) on chromatographic purification over a silica gel column (3.2 × 25 cm) and eluted with EtOAc–EtOH (8 : 1), compounds **5** (80 mg, 250–350 ml) and **12** (150 mg, 400–650 ml) were obtained. Fraction 2 ($CHCl_3$–MeOH, 10 : 1; 10 000–13 500 ml) on repeated chromatographic purification over a silica gel column (2.5 × 30 cm) and eluted with $CHCl_3$–MeOH (8 : 1), gave mixture A (300–450 ml) and mixture B (500–600 ml), then the mixtures A and B were purified by HPLC (reverse column: MeOH–H_2O 1 : 4), compounds **8** (20 mg, 250 ml), **9** (25 mg, 300 ml) and **10** (40 mg, 350 ml), **11** (30 mg, 300 ml) to give respectively. Fraction **3** ($CHCl_3$–MeOH, 6 : 1; 16 000–18 500 ml) was chromatographed over a silica gel column (1.5 × 20 cm) eluted with $CHCl_3$–MeOH (6 : 1), to give compound **13** (30 mg, 250–350 ml). Fraction 4 ($CHCl_3$–MeOH, 4 : 1; 19 500–23 500 ml) on repeated chromatographic purification over a silica gel column (3.5 × 50 cm) and eluted with $CHCl_3$–MeOH (6 : 1), gave pure compound **4** (250 mg, 200–550 ml).

Artselaenin I (**1**) IR (KBr) ν_{max} 1674 (double bond), 1098, 1046 (C–O–C), 2929, 2854, 1726, 1452, 1360, 1243, 1017 cm^{-1}; ^{1}HNMR data, see Table I; ^{13}CNMR data, see Table II; EIMS *m/z* $[M]^+$ 212(5), 184(20), 181(82), 168(26), 163(16), 153(124), 152(189), 139(487), 126(210), 125(159), 121(213), 111(203), 109(459), 97(221), 92(403), 77(238), 75(1000), 67(176), 41(236).

Artselaenin II (**2**) IR (KBr) ν_{max} 3370 (hydroxy) 2876, 1670, 1627 (α,β-unsaturated aldehyde function), 2934, 2876, 1457, 1251, 1155, 1073 cm^{-1}; ^{1}HNMR data, see Table I; ^{13}CNMR data, see Table II; EIMS *m/z* $[M]^+$ 182(7), 164(19), 153(43), 149(46), 136(47), 135(22), 125(21), 121(36),

112(36), 109(42), 99(32), 97(24), 94(72), 91(37), 83(44), 81(63), 77(40), 71(100), 67(54), 55(60), 53(51), 41(99), 39(92).

Artselaenin III (**3**) IR (KBr) ν_{max} 1652 (double bond), 1096, 1026 (C–O–C), 3467 (hydroxy), 2924, 1515, 1448, 1381, 1108 cm^{-1}; ^{1}HNMR data, see Table I; ^{13}CNMR data, see Table II; EIMS *m/z* $[M]^+$ 224(2), 194(10), 193(6), 189(100), 181(126), 167(36), 163(23), 153(135), 151(117), 139(686), 126(325), 121(237), 111(298), 109(645), 97(350), 92(529), 81(248), 75(1000), 65(243), 53(235), 45(462).

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