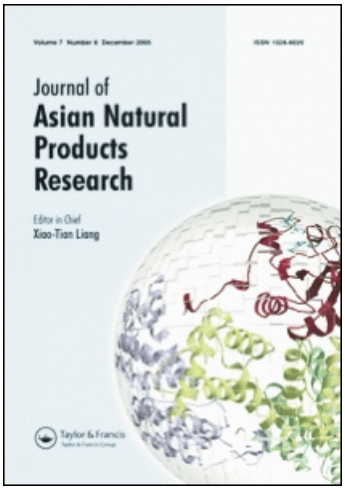

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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To cite this Article Pan, Rui-Le , Chen, Di-Hua , Si, Jian-Yong , Zhao, Xiao-Hong and Shen, Liang-Gang(2004) 'Two new cyclolanostanol glycosides from the aerial parts of *Cimicifuga foetida*', Journal of Asian Natural Products Research, 6: 1, 63 — 67
To link to this Article: DOI: 10.1080/1028602031000135530
URL: http://dx.doi.org/10.1080/1028602031000135530

Journal of Asian Natural Products Research, March 2004, VOL. 6 (1), pp. 63–67

TWO NEW CYCLOLANOSTANOL GLYCOSIDES FROM THE AERIAL PARTS OF *CIMICIFUGA FOETIDA*

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(Received 25 February 2003; Revised 1 April 2003; In final form 10 April 2003)

Two new cyclolanostanol glycosides, cimifoetiside IV (**1**) and cimifoetiside V (**2**) and two known compounds have been isolated from the aerial part of *Cimicifuga foetida* L. On the basis of spectral and chemical evidences, the structures of **1** and **2** were elucidated to be 25-*O*-acetylcimigenol-3-*O*-β-D-glucopyranosyl-(1″ → 2′)-β-D-xylopyranoside (**1**) and cimigenol-3-*O*-β-D-glucopyranosyl-(1‴ → 2″)-β-D-glucopyranosyl-(1″ → 2′)-β-D-xylopyranoside (**2**). The known compounds were identified as 25-*O*-acetylcimigenol-3-*O*-β-D-glucopyranosyl-(1 → 3)-β-D-xylopyranoside (**3**) and 23-*O*-acetylshengmanol-3-*O*-β-D-glucopyranosyl-(1 → 3)-β-D-xylopyranoside (**4**).

Keywords: *Cimicifuga foetida*; Ranunculaceae; Cimifoetiside IV; Cimifoetiside V

INTRODUCTION

The rhizome of *Cimicifuga foetida* L. (Ranunculaceae) has been used as a traditional medicine, as recorded in the Chinese pharmacopoeia (2000 edition). It is used as a cooling and detoxifying agent and for alleviation of fever, pain and inflammation. The chemical constituents of the rhizome have been investigated and more than 20 triterpene or triterpene glycosides have been isolated [1–3]. Recently a few 9,19-cyclolanostane triterpenol saponins from the aerial parts of this plant were reported by our group [4]. As a part of our continuing work, two new glycosides, named cimifoetiside IV (**1**) and V (**2**), were isolated, together with the known triterpene glycosides 25-*O*-acetylcimigenol-3-*O*-β-D-glucopyranosyl(1→3)-β-D-xylopyranoside (**3**), 23-*O*-acetylshengmanol-3-*O*-β-D-glucopyranosyl(1→3)-β-D-xylopyranoside (**4**). This paper deals with the isolation and structural elucidation of the compounds **1** and **2**.

RESULTS AND DISCUSSION

Cimifoetiside IV (**1**) was isolated as an amorphous powder, mp 192–194°C, $[\alpha]_D^{20}$ +11.8 (*c* 0.34, MeOH). Its molecular formula, $C_{43}H_{68}O_{15}$, was deduced from ^{13}C NMR and

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ISSN 1028-6020 print/ISSN 1477-2213 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/1028602031000135530

FABMS data (*m/z* 825 $[M + H]^+$). The IR spectrum showed strong hydroxyl bands at 3700–3040 cm^{-1} and an ester carbonyl band at 1740 cm^{-1}. The ^1H NMR spectrum showed signals due to cyclopropane protons at δ 0.29, 0.54 (each 1H, d, $J = 3.5$ Hz), six methyl singlet signals at δ 1.14, 1.16, 1.17, 1.28, 1.64, 1.66, an acetyl methyl group at δ 1.96 and two anomeric protons at δ 5.38 (1H, d, $J = 8.0$ Hz) and 4.86 (1H, d, $J = 6.5$ Hz). The ^{13}C NMR spectrum exhibited one carbonyl group at 170.2 and 22.3 ppm, and two anomeric carbons at δ 106.2 and 105.5 ppm. All the above evidence suggested that **1** was a 9,19-cyclolanostanol triterpene diglycoside. On acid hydrolysis of **1**, xylose and glucose were detected from the aqueous fraction by comparison of TLC (n-BuOH–AcOH–H_2O, 4:1:1) with authentic samples. Comparing the spectral data of **1** with those of the known compound, 25-*O*-acetylcimigenol-3-*O*-β-D-glucopyranosyl-(1″→3′)-β-D-xylopyranoside (**3**), which has the same formula as compound **1**, showed that they have very similar signals except for the sugar moieties. This suggested that the aglycones of the two compounds are the same.

The TOCSY spectrum of **1** showed one group of xylosyl signals at δ 4.86, 4.30, 4.21, 4.15, 3.63 and one group of glucosyl signals at δ 5.36, 4.47, 4.33, 4.21, 4.12, 4.47, 3.93. Through analysis data of the ^1H–^1H COSY, HMQC, HMBC spectrum, ^1H and ^{13}C signals for compound **1** were fully assigned (Table I). In the HMBC spectrum, significant correlations were observed between δ 4.86 (H-1′) and 88.6 (C-3), and δ 5.36 (H-1″) and 83.1 (C-2′), suggesting the sugar moiety was located at C-3; the glucosyl was connected to C-2′ of the xylosyl.

The relative stereochemistry of **1** was determined on the basis of the coupling constants from the proton and ROESY experiments. In the ROESY spectrum, CH_3-18 at δ 1.14 showed correlations with H-15, H-12, H-20; CH_3-29 at δ 1.16 with H-3 and CH_3-30; and H-8 at δ 1.68 with H-15 and H-19. Based on these observations, H-3 and CH_3-28 were assigned as α-configurations and CH_3-18, H-15, H-8 and H-20 as β-configurations. The configurations of C-23 and C-24 were assigned as *R* and *S*, respectively, by comparing the coupling constants of the C-23 and C-24 proton signals of **1** with those of known 9,19-cyclostanol triterpene glycosides [5]. According to the coupling constants of H-1′ ($J = 6.5$ Hz) and H-1″ ($J = 8.0$ Hz), the glycoside bands were assigned as having β-configurations. Thus, compound **1** was elucidated as (23*R*,24*S*)25-*O*-acetylcimigenol-3-*O*-β-D-glucopyranosyl-(1″→2′)-β-D-xylopyranoside and has been named cimifoetiside IV (Fig. 1).

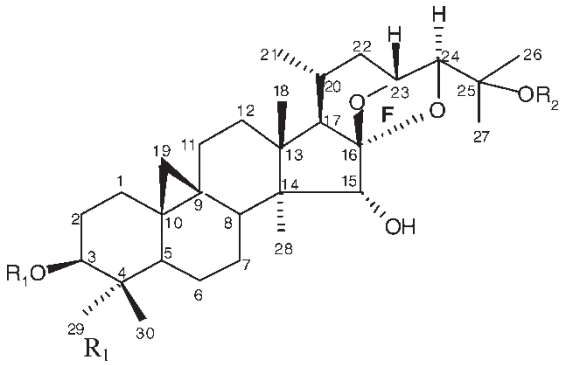
Cimifoetiside V (**2**) was obtained as an amorphous powder, mp 197–99°C, $[\alpha]_D^{20} + 1.79$ (*c* 0.58, MeOH). Its molecular formula was determined as $C_{47}H_{76}O_{19}$ from its ^{13}C NMR and FABMS data (*m/z* 945 $[M + H]^+$). The IR spectrum showed broad hydroxyl bands at 3700–3040 cm^{-1}. The ^1H NMR spectrum shows a cyclopropane methylene at δ 0.26 0.50 (each 1H, d, $J = 4.0$ Hz), six *tert*-methyl groups at δ 1.11, 1.12, 1.16, 1.22, 1.45, 1.48 and three anomeric protons at δ 5.43 (1H, d, $J = 8.0$ Hz), 5.39 (1H, d, $J = 7.5$ Hz), 4.98 (1H, d, $J = 7.0$ Hz). The ^{13}C NMR spectrum exhibited signals of three anomeric carbons at δ 106.5, 104.8 and 103.3. All the above evidence suggested that **2** was a 9,19-cycloartane triterpene triglycoside. This is the only triglycoside to be found in the *Cimicifuga* so far. The ^{13}C NMR data of **2** showed a marked similarity with those of compound **1** for the aglycone, except for the signals of C-24, C-25, C-26, C-27 owing to the presence of a C-25 acetyl substituent in **1**. The aglycone of compound **2** was cimigenol. On acid hydrolysis of **2**, xylose and glucose were detected in the aqueous fraction of a TLC analysis (n-BuOH–AcOH–H_2O, 4:1:1) and confirmed by comparison with authentic samples.

The TOCSY spectrum of **2** showed one group of xylosyl signals at δ 4.98, 4.41, 4.34, 4.30, 4.12, 3.7.3 and two groups of glucosyl signals at δ 5.4.3, 4.4.3, 4.38, 4.28, 4.22, 4.16, 3.85 and δ 5.39, 4.57, 4.30, 4.18, 4.18, 4.10, 3.96. The ^1H and ^{13}C NMR data were assigned with the aid of ^1H–^1H COSY, HMQC, HMBC experiments (Table I). In the HMBC spectrum, correlations between δ 4.98 (H-1′) and 88.7 (C-3); 5.43 (H-1″) and 82.2 (C-2′);

TABLE I NMR spectral data of compounds **1** and **2** (500 Hz for ^{1}H and 125 Hz for ^{13}C in C_5D_5N, δ in ppm, J in Hz)

	1		***2***	
Position	^{13}C	^{1}H	^{13}C	^{1}H
1	32.5	1.21 m, 1.53 m	32.5	1.17 m, 1.53 m
2	30.2	2.30 m,1.94 m	29.9	1.88 m,2.23 m
3	88.6	3.43 (dd, 4.0,11.5)	88.7	3.39 (dd, 4.5,11.5)
4	41.5		41.5	
5	47.6	1.26 m	47.4	1.24 m
6	21.0	0.72 (br q), 1.5 m	21.1	0.70 (br q), 1.48 m
7	26.5	1.05 m, 2.07 m	26.5	1.05 m, 2.05 m
8	48.6	1.68 m	48.6	1.66 m
9	20.1		19.6	
10	26.8		27.2	
11	25.7	1.05 m, 2.07 m	26.7	1.05 m, 2.05 m
12	34.1	1.52 m, 1.64 m	34.2	1.53 m, 1.66 m
13	41.9		42.0	
14	47.3		47.6	
15	80.2	4.25 s	80.2	4.20 s
16	112.5		112.0	
17	59.4	1.44 (d, 11.0)	59.6	1.48
18	19.5	1.14 s	19.6	1.12 s
19	30.9	0.29 (d, 3.5)	30.9	0.26 (d, 4.0)
		0.54 (d, 3.5)		0.50 (d, 4.0)
20	23.9	1.63 m	24.1	1.64 m
21	19.5	0.84 (d, 6.5)	19.4	0.84 (d, 6.5)
22	38.0	0.95 m, 2.24 m	38.2	1.0 m, 2.25 m
23	71.8	4.57 (d, 9.0)	71.9	4.74 (d, 9.0)
24	86.8	4.09 s	90.2	3.76 s
25	83.5		71.0	
26	21.7	1.64 s	25.7	1.22 s
27	23.4	1.66 s	26.8	1.48 s
28	11.5	1.17 s	11.8	1.16 s
29	25.7	1.28 s	25.5	1.45 s
30	15.4	1.16 s	15.4	1.11 s
$COCH_3$	170.2			
$COCH_3$	22.3	1.95 s		
1′	105.5	4.86 (d, 6.5)	104.8	4.98 (d, 6.5)
2′	83.1	4.21	82.2	4.12
3′	78.0	4.26	76.1	4.41
4′	71.0	4.15	77.9	4.30
5′	66.9	3.63, 4.30	65.9	3.73, 4.34
1″	106.2	5.38 (d, 8.0)	106.5	5.43 (d, 8.0)
2″	77.0	4.12	85.4	4.16
3″	77.9	4.21	77.8	4.28
4″	71.9	4.33	71.6	4.22
5″	78.2	3.93	77.9	3.85
6″	62.6	4.47 (2H overlap)	62.8	4.43, 4.38
1‴			103.3	5.39 (d, 7.5)
2‴			76.6	4.10
3‴			77.9	4.18
4‴			71.2	4.18
5‴			79.2	3.96
6‴			62.6	4.32, 4.57

and 5.39 (H-1‴) and 85.4 (C-2″) were observed, suggesting that the connections of sugar moiety were glucopyranosyl-(1‴→2″)-glucopyranosyl-(1″→2′)-xylopyranosyl. According to the coupling constants of H-1′ ($J = 6.5$ Hz), H-1″ ($J = 8.0$ Hz), H-1‴ ($J = 7.5$ Hz), the glycoside bonds has a β-configuration. Thus, compound **2** was elucidated as cimigenol-3-*O*-β-D-glucopyranosyl-(1‴→2″)-β-D-glucopyranosyl-(1″→2′)-β-D-xylopyranoside and named as cimifoetiside IV.



	R_1	R_2
1	β-D-glu-(1″-2′)-β-D-xylopyranoside	Ac
2	β-D-glu-(1‴→2″)-β-D-glu-(1″-2′)-β-D-xylopyranoside	H

FIGURE 1 Structures of compounds **1** and **2**.

The known compounds were confirmed by comparison of their physical and spectral data with those published in the literature [5].

EXPERIMENTAL

General Experimental Procedures

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Perkin-Elmer 983G spectrometer. NMR spectra were measured on a Bruker Am-500 (500 MHz) instrument, and chemical shifts were referenced to TMS. The FABMS data were recorded on a Zabspec instrument.

Plant Material

The aerial parts of *C. foetida* were collected in Ankang, Shannxi Province, China in August 1998 and were identified by one of the authors, Ruile Pan, an Associate Professor. A voucher specimen has been deposited in the Herbarium of the institute.

Extraction and Isolation

The powdered air-dried aerial parts of *C. foetida* (9.5 kg) were extracted exhaustively with boiling 80% EtOH. The alcoholic solution was concentrated *in vacuo* to yield a syrup-like extract (1.1 kg), which was mixed with siliceous earth (80–100 mesh) and eluted with hexane, EtOAc, and 80% EtOH to give three fractions, f_1 (35 g), f_2 (260 g) and f_3 (220 g).

Fraction f_2 was subjected to column chromatography over silica gel (100–200 mesh, 2000 g) and eluted with $CHCl_3$–MeOH (100:0–20:80), yielding fractions 1–10. Fraction 8 (24 g) was rechromatographed on silica gel (100–200 mesh, 400 g), eluted with $CHCl_3$–MeOH (9:1) as solvent, to afford three sub-fractions, 8a (1.2 g), 8b (1.5 g) and 8c (1.0 g), which were then chromatographed on an ODS column with MeOH–H_2O (3:2) as eluent to afford compound **4** (150 mg), compound **1** (200 mg) and compound **3** (100 mg).

Fraction 10 (20 g) was rechromatographed on silica gel (100–200 mesh, 300 g), eluted with $CHCl_3$–MeOH (9:1), to afford five sub-fractions, 10a–10e. Compound **2** (20 mg) was purified from sub-fraction 10e on an ODS column with MeOH–H_2O (3:2) as eluent.

Cimifoetiside IV (1)

White amorphous powder, mp 192–194°C, $[\alpha]_D^{20}$ + 11.8 (*c* 0.34 MeOH). IR (KBr) ν_{max} (cm^{-1}) 3050–3700, 2940, 2880, 1740, 1460, 1380, 1250, 1080, 1040, 900, 840. ^{1}H NMR and ^{13}C NMR see Table I. Positive FAB-MS *m/z*: 825$[M + H]^+$.

Cimioetiside V (2)

White amorphous powder, mp 197–199°C, $[\alpha]_D^{20}$ +1.79 (*c* 0.58 MeOH). IR (KBr) ν_{max} (cm^{-1}): 3040–3700, 2940, 2880, 1460, 1075, 1040, 900, 840. ^{13}C NMR and ^{1}H NMR see Table I. Positive FAB-MS *m/z* 945 $[M + H]^+$.

25-O-Acetylcimigenol-3-O-β-D-glc-(1→3)-β-D-xylopyranoside (3)

White amorphous powder, mp 283–284°C; IR,^{1}H NMR and ^{13}C NMR data are consistent with literature values; [5] positive FAB-MS *m/z*:825 $[M + H]^+$.

23-O-Acetylshengmanol-3-O-β-D-glc-(1→3)-β-D-xylopyranoside (4)

White powder, mp 243–245°C; IR, ^{1}H NMR and ^{13}C NMR data are consistent with literature values [5]; positive FAB-MS *m/z* 825 $[M + H]^+$.

Acid Hydrolysis of Compounds 1 and 2

Compounds **1** and **2** (5 mg of each) were refluxed with 5% HCl in MeOH (5 ml) for 6 h. Each mixture was diluted with H_2O and neutralized with $NaHCO_3$. The neutral hydrolysate revealed the presence of xylose and glucose by TLC (n-BuOH–AcOH–H_2O, 4:1:1) upon comparison with authentic samples that were purchased from the Pfanstienl Chemical Corporation, Waukengan, IL (Lot no, 1279).

Acknowledgements

The authors are grateful to Dr Guangzhong Tu and Miss Dongge An, Beijing Institute of Microchemistry Research, for NMR spectral measurements; to Dr Kaihua Wei, Academy of Military Medical Sciences, Beijing Center of Biomedical Analysis for the FAB mass spectral measurements; and to Mr H. T. Song and Ms Qi Zhang of our Institute for the IR and optical rotation spectral measurements.

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