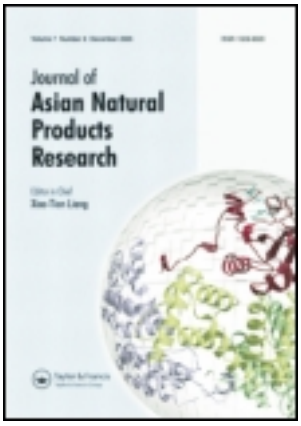

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Two new sesquiterpene lactone glycosides from *Artemisia frigida* Willd.

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The investigation of EtOAc-soluble fraction from the aerial parts of *Artemisia frigida* has led to the isolation of two new sesquiterpene lactone glycosides, named as artemofriginoside A and artemofriginoside B. Their structures were characterized as 3β-(β-D-glucopyranosyloxy)-8β-(*p*-hydroxyphenylacetyloxy)-4(15),10(14),11(13)-guaiatrien-1α,5β,6β,7αH-12,6-olide (**1**) and β-(β-D-glucopyranosyloxy)-8β-(2-hydroxy-3-methylbutanoyloxy)-4(15),10(14),11(13)-guaiatrien-1α,5β,6β,7αH-12,6-olide (**2**), on the basis of 1D and 2D NMR spectral analysis.

Keywords: *Artemisia frigida*; sesquiterpene lactone glycoside; artemofriginoside A; artemofriginoside B

1. Introduction

Artemisia frigida Willd., Agi in Mongolian, is a commonly used medicinal material in Mongolian folk medicine [1–6], distributed throughout Inner Mongolia with occupying 10.38% of its steppe [7]. The aerial parts of *A. frigida* are used as a clinical medicine to treat many diseases, such as hemorrhage, arthrocele, nepropyrexia, rheumatoid, and menoxenia [8–10]. Sesquiterpenoids [11,12], coumarins [13], and flavonoids [14–16] have been reported from *A. frigida*. Recently, we carried out a systematic chemical study on the EtOAc-soluble fraction from the aerial parts of *A. frigida*, which resulted in the isolation of two new sesquiterpene lactone glycosides. This study is concerned with the isolation and structural elucidation of two new sesquiterpene lactone glycosides, artemofriginoside A (**1**) and artemofriginoside B (**2**).

2. Results and discussion

The 95% ethanol extract of *A. frigida* was suspended in water and then partitioned with petroleum ether (PE), $CHCl_3$, EtOAc, and *n*-BuOH. The EtOAc-soluble fraction was separated by chromatography and two new sesquiterpene lactone glycosides, 3β-(β-D-glucopyranosyloxy)-8β-(*p*-hydroxyphenylacetyloxy)-4(15),10(14),11(13)-guaiatrien-1α,5β,6β,7αH-12,6-olide (**1**) and β-(β-D-glucopyranosyloxy)-8β-(2-hydroxy-3-methylbutanoyloxy)-4(15),10(14),11(13)-guaiatrien-1α,5β,6β,7αH-12,6-olide (**2**) were obtained (Figure 1).

Compound **1** was obtained as yellowish solid. It displayed a molecular formula of $C_{29}H_{34}O_{11}$, as established from HR-ESI-MS at *m/z* 557.2026 $[M - H]^-$ and ^{13}C NMR spectrum. The ^1H and ^{13}C NMR spectra showed typical signals of an α-methylene-γ-lactone ring at δ_H 6.03 (d,

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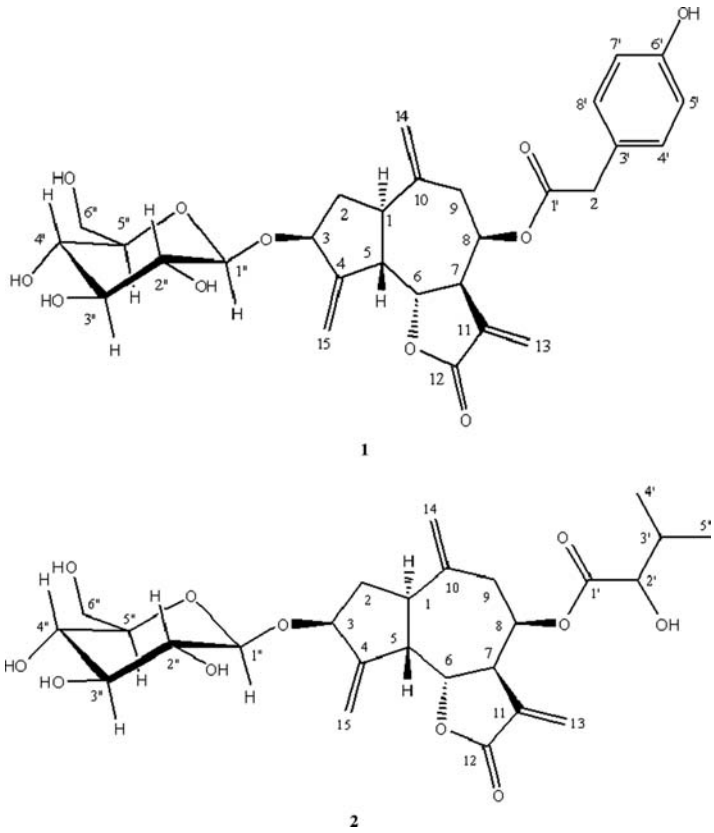

Figure 1. Structures of **1** and **2.**

$J = 3.3$ Hz) and 5.44 (d, $J = 3.3$ Hz) and δ_C 122.3, 136.3, and 169.0 [17]. The α,β-unsaturated carbonyl resonating at δ 169.0 was assigned to C-12 because it showed HMBC correlations with H-13. The ^{1}H and ^{13}C NMR spectra also showed typical signals of two exomethylenes at δ_H 5.06, 4.77, 5.48, 5.33 and δ_C 117.7, 112.5. The carbon signals at δ 150.8 and 112.5 were assigned to C-4 and C-15, respectively, because H_2-15 at δ 5.48 (1H, br s) and 5.33 (1H, br s) showed HMBC correlations with C-4 at δ 150.8 and C-3, H-3 at δ 4.64 (1H, br t, 7.0) showed HMBC correlations with C-4 at δ 150.8 and C-5 at δ 112.5. The anomeric proton at δ 4.46 (1H, d, 7.5) and the anomeric carbon at δ 103.9 were observed in the ^{1}H and ^{13}C NMR spectra of **1**. By analysis of the ^{1}H NMR, ^{13}C NMR, HMQC, and HMBC spectra of **1, 1** was deduced to be a sesquiterpene lactone glycoside. In the NOESY spectrum of **1**, the correlation signals were observed obviously at H-5/H-6β and H-1/H-7α, and thus the configurations of H-5 and H-1 were determined as β and α, respectively. Furthermore, the coupling constant of $J_{H\text{-}6/H\text{-}7}$ (9.3 Hz) showed the presence of the A,B *trans*-fused guaianolide skeleton with *trans*-diaxial disposition of H-6 and H-7 [18]. The strong NOESY correlations between H-8 and H-7α as well as between H-3 and H-7α confirmed the α-configurations of both H-8 and H-3. The presence of 4-hydroxyphenylacetic acid ester was evident from the aromatic A_2B_2 signals at δ 7.00, 6.70 (each 2H, d, $J = 8.4$ Hz) and a benzylic methylene singlet at δ 3.46 [18].

Three oxygenated methines observed at δ 4.64 (1H, br t, 7.0), 4.46 (1H, br t, 9.3), and 5.49 (1H, ddd, 4.8, 2.5, 2.0) were assigned to H-3, H-6, and H-8, respectively. The relative downfield shift of H-8 (δ 5.49) was attributed to the attachment of the ester moiety that was proved by HMBC correlation (Figure 2) between H-8 and the ester carbonyl at δ 172.9. The anomeric proton at δ 4.46 (d, $J = 7.5$ Hz) showed $^{1}H-^{13}C$ long-range correlation with C-3 at δ 81.5, indicating that the glucopyranosyloxy moiety was linked to C-3 position. The β-anomeric configuration for the glucose was determined from their large $^{3}J_{H1,H2}$ coupling constants ($J = 7.5$ Hz). Therefore, the structure of **1** was elucidated as 3β-(β-D-glucopyranosyloxy)-8β-(*p*-hydroxyphenylacetyloxy)-4(15),10(14),11(13)-guaiatrien-1α,5β,6β,7αH-12,6-olide (**1**), named as artemofriginoside A. Some key correlations of HMBC and NOESY were shown in Figures 2 and 3.

Compound **2** was obtained as yellowish solid. The molecular formula of **2** was deduced to be $C_{26}H_{36}O_{11}$ on the basis of its HR-ESI-MS data at *m/z* 523.2161 $[M - H]^-$ and ^{13}C NMR spectrum. The IR and NMR spectra revealed the presence of α-methylene-γ-lactone ring and a β-D-glucosyl moiety similar to that of **1**. The ^{1}H NMR spectrum of **2** was similar to that of **1** except for the absence of the aromatic A_2B_2 signals at δ 7.00, 6.70 (each 2H, d, $J = 8.4$ Hz) and a benzylic methylene singlet at δ 3.46, and the appearance of two methyl signals at δ 0.95 (3H, d, $J = 6.0$ Hz) and 0.88 (3H, d, $J = 6.0$ Hz). The ^{13}C NMR

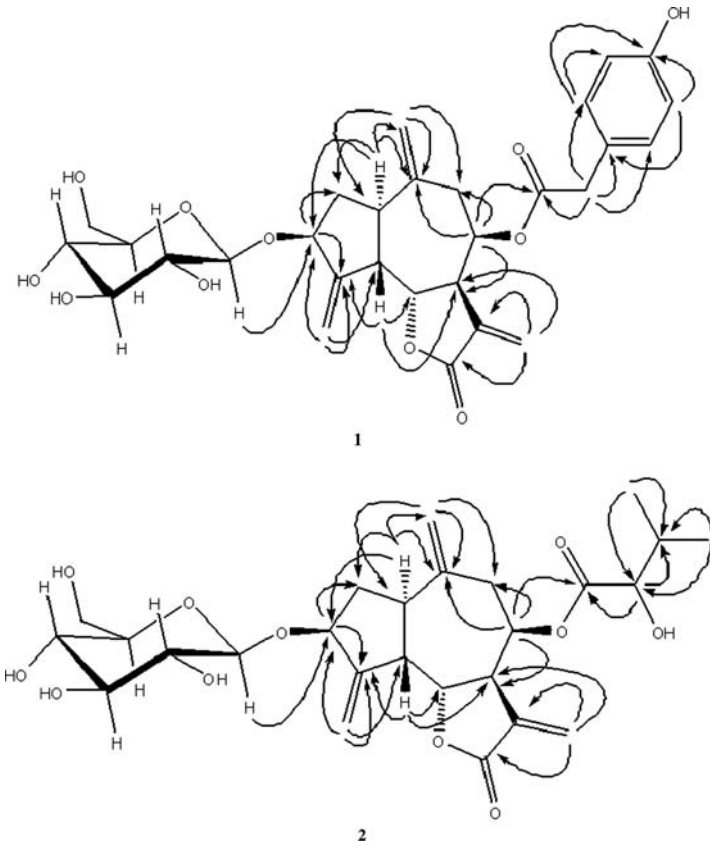

Figure 2. Some key HMBC correlations of **1** and **2**.

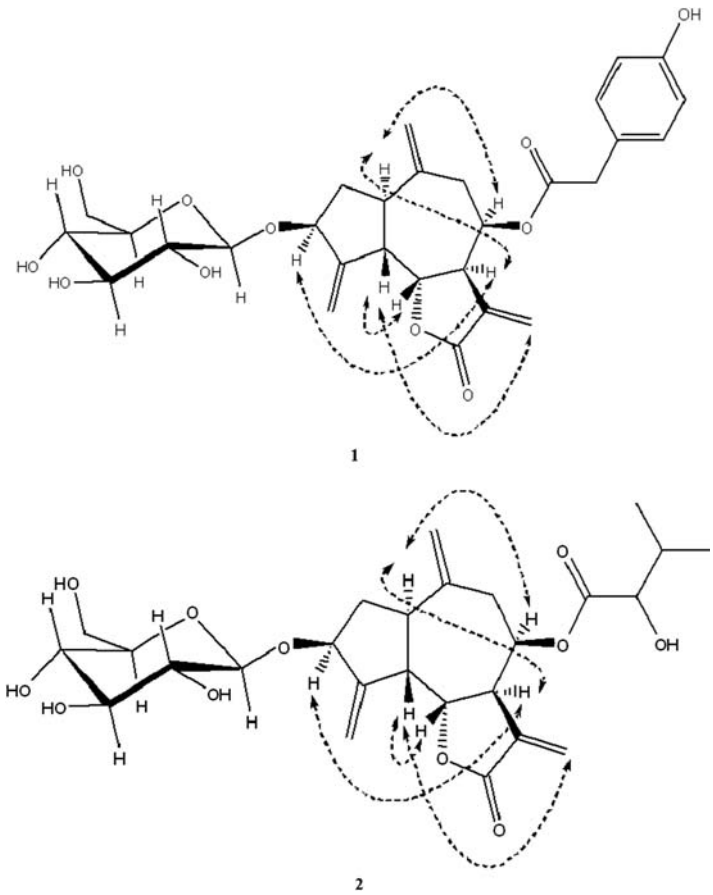

Figure 3. Some key NOESY correlations of **1** and **2**.

spectral data (Table 1) of **2** were also similar to those of **1**, but five additional signals at δ 17.1, 19.3, 33.1, 76.6, and 174.6 were observed. The five signals were the characteristic carbon signals of the 2-hydroxy-3-methylbutanoyloxy unit. In the ^{1}H NMR spectrum, the characteristic proton signals of the 2-hydroxy-3-methylbutanoyloxy unit at δ 3.88 (1H, m), 1.98 (1H, m), 0.95 (3H, d, 6.0), 0.88 (3H, d, 6.0) were also observed. The signals of C-7 and C-9 were shifted upfield to δ49.8, 41.0, and that of C-8 was shifted downfield to δ 69.8, respectively. Thus, compound **2** was assumed to have a C_5 unit ester group at C-8. The HMBC correlations between H-8, H-2′, and C-1′ suggested that the 2-hydroxy-3-methylbutanoyloxy was located at C-8 position. The strong NOESY correlations between H-8 and H-7α as well as between H-3 and H-7α confirmed the α-configuration of both H-8 and H-3. The anomeric proton signal of D-glucosyl moiety at δ 4.46 (1H, d, 7.5) and the anomeric carbon at δ 104.3 were observed in the ^{1}H and ^{13}C NMR spectra of **2**. The β-anomeric configurations for the glucose were determined from their large $^3J_{H1,H2}$ coupling constants ($J = 7.5$). In the HMBC spectrum, the cross-peaks between the anomeric proton signal and the carbon signal at δ 81.6 indicated that the glucopyranosyloxy moiety was linked to C-3 position. Therefore, the structure of **2** was elucidated as β-(β-D-glucopyrano-

Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR spectral data for **1** and **2** in CD_3OD.

	1			**2**	
No.	δ_C	δ_H (*J* in Hz)	No.	δ_C	δ_H (*J* in Hz)
1	45.3	2.95 (1H, br t, 9.3)	1	45.7	3.03 (1H, br t, 9.9)
2	38.5	2.43 (1H, m), 1.98 (1H, m)	2	38.7	2.41 (1H, m), 2.02 (1H, m)
3	81.5	4.64 (1H, br t, 7.0)	3	81.6	4.64 (1H, br t, 9.9)
4	150.8		4	151.0	
5	51.0	2.80 (1H, br t, 9.3)	5	51.4	2.86 (1H, br t, 9.9)
6	80.2	4.46 (1H, br t, 9.3)	6	80.3	4.64 (1H, br t, 9.9)
7	49.0	3.34 (1H, m)	7	49.8	3.34 (1H, m)
8	69.3	5.49 (1H, ddd, 4.8, 2.5, 2.0)	8	69.8	5.64 (1H, ddd, 5.0, 3.0, 2.0)
9	41.4	2.65 (1H, m), 2.52 (1H, m)	9	41.0	2.62 (1H, m), 2.52 (1H, m)
10	144.4		10	144.6	
11	136.3		11	136.9	
12	169.0		12	171.3	
13	122.3	6.03 (1H, d, 3.3), 5.44 (1H, d, 3.3)	13	122.4	6.21 (1H, d, 3.3), 5.61(1H, d, 3.3)
14	117.7	5.06 (1H, br s), 4.77 (1H, br s)	14	118.0	5.16 (1H, br s), 4.95 (1H, br s)
15	112.5	5.48 (1H, br s), 5.33 (1H, br s)	15	113.0	5.48 (1H, br s), 5.38 (1H, br s)
1′	172.9		1′	174.6	
2′	40.0	3.46 (2H, s)	2′	76.6	3.88 (1H, m)
3′	126.1		3′	33.1	1.98 (1H, m)
4′	116.3	7.00 (1H, d, 8.4)	4′	19.3	0.95 (3H, d, 6.0)
5′	131.4	6.70 (1H, d, 8.4)	5′	17.1	0.88 (3H, d, 6.0)
6′	157.6				
7′	131.4	6.70 (1H, d, 8.4)			
8′	116.3	7.00 (1H, d, 8.4)			
1″	103.9	4.46 (1H, d, 7.5)	1″	104.3	4.46 (1H, d, 7.5)
2″	75.3	3.18 (1H, dd, 8.9, 7.5)	2″	75.1	3.18 (1H, dd, 8.9, 7.5)
3″	78.1	3.42 (1H, m)	3″	78.1	3.34 (1H, m)
4″	71.7	3.30 (1H, m)	4″	71.7	3.30 (1H, m)
5″	77.9	3.71 (1H, dd, 9.3, 4.5)	5″	77.9	3.40 (1H, dd, 9.0, 4.4)
6″	62.8	3.85 (1H, m), 3.68 (1H, m)	6″	62.8	3.86 (1H, m), 3.68 (1H, m)

syloxy)-8β-(2-hydroxy-3-methylbutanoyloxy)-4(15),10(14),11(13)-guaiatrien-1α,5β,6β,7αH-12, 6-olide (**2**), named as artemofriginoside B. Some key correlations of HMBC and NOESY were shown in Figures 2 and 3.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured in MeOH at 25°C on a PerkinElmer 241 polarimeter. The IR spectra were recorded in KBr discs on a Thermo Nicolet 200 double beam spectrophotometer. NMR spectra were measured on a Bruker ARX-600 NMR spectrometer with tetramethylsilane (TMS) as the internal reference, and chemical shifts are expressed in δ (ppm). The HR-ESI-MS spectra were measured on a Bruker Daltonics MicrOTOF-Q. Semipreparative HPLC was performed using a Japanese liquid chromatograph equipped with a Zorbax SB-C18 column. Column chromatography was performed using silica gel (200–300 mesh, Marine Chemical Factory, Qingdao, China) and Sephadex LH-20 (Pharmacia, Uppsala, Sweden). Fractions were monitored by TLC (silica gel GF_{254} 10–40 μm, Marine Chemical Factory,

Qingdao, China), and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH.

3.2 Plant material

The aerial parts of *A. frigida*, used as experimental material, were collected in Tongliao, Inner Mongolia of China, in July 2007, and identified by Prof. Buhebateer (Inner Mongolia University for Nationalities). A voucher (No. 20070720) has been deposited in the School of Traditional Mongolian Medicine of Inner Mongolia University for Nationalities.

3.3 Extraction and isolation

The air-dried aerial parts of *A. frigida* (2 kg) were crushed and extracted twice under reflux 95% EtOH. Evaporation of the solvent under reduced pressure delivered the 95% EtOH extract. The extract was partitioned with PE, $CHCl_3$, EtOAc, and *n*-BuOH. The EtOAc-soluble fraction (30.0 g) was isolated by column chromatography on silica gel and gradiently eluted with $CHCl_3$–acetone (80:1 to 5:1) to give 20 fractions (1–20). Fraction 6 [400 mg, $CHCl_3$–acetone (30:1) eluate] was loaded onto a column of silica gel and eluted with $CHCl_3$–acetone (50:1 to 1:1) to give seven fractions (6-1 to 6-7). Fraction 6-4 (60 mg) was further purified by column chromatography on silica gel with $CHCl_3$–acetone (20:1) to give **1** (12 mg) and **2** (10 mg).

3.3.1 3β-(β-D-Glucopyranosyloxy)-8β-(p-hydroxyphenylacetyloxy)-4(15),10(14),11(13)-guaiatrien-1α,5β,6β,7αH-12,6-olide (*1*)

Yellowish solid; $[\alpha]_D$ −20.4 ($c = 0.1$, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3550, 1760, 1740, 1660, 1640; ^1H and ^{13}C NMR spectral data: Table 1; HR-ESI-MS: *m/z* 557.2026 $[M - H]^-$ (calcd for $C_{29}H_{33}O_{11}$, 557.2023).

3.3.2 3β-(β-D-glucopyranosyloxy)-8β-(2-hydroxy-3-methylbutanoyloxy)-4(15),10(14),11(13)-guaiatrien-1α,5β,6β,7αH-12,6-olide (*2*)

Yellowish solid; $[\alpha]_D$ −19.6 ($c = 0.1$, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3402, 1768, 1735, 1515, 1245; ^1H and ^{13}C NMR spectral data: Table 1; HR-ESI-MS: *m/z* 523.2161 $[M - H]^-$ (calcd for $C_{26}H_{35}O_{11}$, 523.2179).

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References

[1] Hasibagen, *Yi Zong Yao Zhi* (Inner Mongolia People's Press, Huhehaote, 1999), p. 499.
[2] W.D.M. Zao, *Compilation of Prescription for the Traditional Mongolian Medicine* (Inner Mongolia Science and Technology Press, Chifeng, 2004), p. 122.
[3] Jigemudedan, and Jinzamusu, *Tong Wa Ga Ji De* (Inner Mongolia People's Press, Huhehaote, 1999), p. 219.
[4] B. Jin, *Lin Zheng Yi Yao Jian* (Inner Mongolia People's Press, Huhehaote, 1977), p. 899.
[5] Guanqigerupanwangbu, *Zhe Dui Pan De Ning Bu* (Inner Mongolia People's Press, Huhehaote, 1987), p. 80.
[6] Namujila, *Aoteqi 5 of Mongolian People* (Inner Mongolia Children Press, Huhehaote, 1993), p. 68.
[7] Y. Liu, J.G. Liu, and L. Tang, *Stud. Trace Elements Health* **25**, 55 (2008).
[8] Q.Y. Bai, *Chinese Medical Encyclopaedia-Mongolian Medicine* (Inner Mongolia Science and Technology Press, Chifeng, 1986), p. 322.
[9] Zanbula, and Daoerji, *Meng Yao Zheng Dian* (Inner Mongolia People's Press, Huhehaote, 1984), p. 260.
[10] M.G. Nei, *Standard of Traditonal Mongolian Medical Material* (Inner Mongolia Science and Technology Press, Chifeng, 1987), p. 342.
[11] Y.L. Liu and T.J. Mabry, *J. Nat. Prod.* **44**, 722 (1981).

[12] Y.L. Liu and T.J. Mabry, *J. Nat. Prod.* **24**, 1009 (1985).
[13] H. Greger, P. Hofer, and W. Robian, *Phytochemistry* **22**, 1997 (1983).
[14] Y.L. Liu and T.J. Mabry, *Phytochemistry* **20**, 309 (1981).
[15] Y.L. Liu and T.J. Mabry, *Phytochemistry* **20**, 189 (1981).
[16] Q.H. Wang and J.H. Wang, *Chin. Tradit. Herb. Drugs* **40**, 1540 (2009).
[17] H. Asada, T. Miyase, and S. Fukushima, *Chem. Pharm. Bull.* **32**, 3036 (1984).
[18] A.M. Helal, N. Nakamura, M.R. Meselhy, A.M. El-Fishawy, M. Hattori, and G.H. Mahran, *Phytochemistry* **45**, 551 (1997).