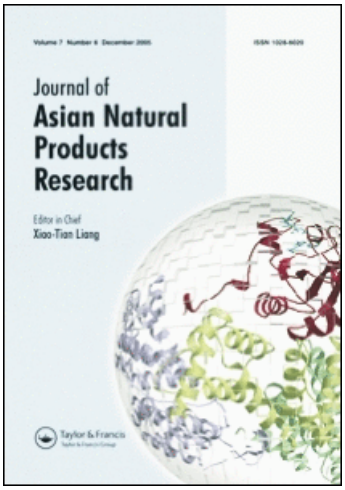

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NEW GUAIANOLIDES FROM *ARTEMISIA SELENGENSIS*

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A new guaianolide artselenin (**1**) and a new dimeric guaianolide artselenoid (**2**), along with 10 known compounds, were isolated from the aerial parts of *Artemisia selengensis*. Their structures were elucidated by spectroscopic methods. Two-dimensional NMR techniques were used to make complete assignments for the ^{1}H- and ^{13}C-NMR chemical shifts of the two new guaianolides.

Keywords: *Artemisia selengensis*; Compositae; Guaianolide; Dimeric guaianolide; Artselenin; Artselenoid; Structure elucidation

INTRODUCTION

Artemisia (Compositae) is a world wide genus of approximately 500 species, about 260 of which have been investigated in the fields of phytochemistry, biochemistry, pharmacology, etc. [1]. *Artemisia selengensis* Turcz, "Hong-Chen-Ai" in Chinese, is a species of the well-known traditional Chinese medicine "Liu-Ji-Nu" [2,3]. It is growing wild in the southwestern part of China and used locally for anti-inflammation, hemostasis, invigorating the blood circulation and relieving dysmenorrhea. Several groups [4–6] carried out chemical investigations of *A. selengensis*, and the anti-tumor and immunomodulating activities of its polysaccharide fractions have been reported [7]. Although *Artemisia* genus is rich in normal sesquiterpenoids [8], no sesquiterpenoid except for a bisabolene endoperoxide [6] has been reported in these previous works. As part of our phytochemical investigations on

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Chinese *Artemisia* species [9,10], we now report the isolation and structural elucidation of a new guaianolide artselenin (**1**) and a new dimeric guaianolide arselenoid (**2**) together with 10 known compounds identified as spiroketal enol ethers (**3**) and (**4**), nonacosanol (**5**), n-butanoic acid nonacosyl ester (**6**), scopoletin (**7**), esculetin (**8**), β-sitosterol(**9**), β-sitosterol-3-O-β-D-glucoside (**10**), stigmasterol-3-O-β-D-glucoside (**11**) and 1,5-dehydroadonitol (**12**) from the ethanolic extract of the aerial parts of *A. selengensis*. The structures of the two new guaianolides were determined by their spectral data, including 2D NMR (^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY, HMBC) techniques.

RESULTS AND DISCUSSION

Compound **1** (artselenin) was obtained as colorless powders, mp 165–166°C, $[\alpha]_D^{20}$ −92(c 0.1, Me_2CO). The IR spectrum showed the presence of hydroxyl (3460 cm^{-1}), γ-lactone (1780 cm^{-1}), acetoxyl (1735, 1037 cm^{-1}), and double bond (1631 cm^{-1}) groups. The EIMS showed a clear molecular ion at *m/z* 322, the peaks at m/z 304(M^+-18), 262(M^+-60) and 244(M^+-60-18) were in agreement with the presence of hydroxyl and acetoxyl groups. The HREIMS *m/z* 322.1413 afforded a formula of $C_{17}H_{22}O_6$ (calcd. 322.1416).

The ^{1}H-NMR spectrum of **1** was similar to that of matricarin and its derivatives [11,12]. A triplet at δ5.96 (J = 2.8 Hz) was assigned to the olefinic H-3 and a doublet (J = 2.8 Hz), centered at δ3.85 geminal to a hydroxyl, was attributed to H-2. The broad double doublets (J = 10.1, 2.8 Hz) with long range allylic coupling centered at δ3.04 was assigned to H-5. These proposed assignments were supported by ^{1}H–^{1}H COSY spectrum, in which the low-field H-3 was coupled with H-2 and H-5. The hydroxyl at C-2 was determined to have β-configuration by comparison with the splitting pattern and coupling constant of the known compounds 2α, 8α- and 2β, 8α-diacetoxy-1α, 10α-epoxyguaia-3, 11(13)-dien-12, 6α-olide [12].

A proton bonded to the carbon bearing the lactonic oxygen was observed as a sharp triplet (J = 10.1, 10.1 Hz) at δ4.48 which was characteristic for a C-6 oriented guaianolide lactone, the C-6α trans-orientation was deduced from the large coupling constants (10.1 Hz). The double triplet at δ5.35 was clearly ascribed to the proton bonded to the acetoxyl carrying carbon at C-8α. The location of the acetoxyl was also determined by HMBC spectrum, a clear ^{3}J interaction between the carbonyl carbon at δ170.42 and the H-8 was observed.

A methyl singlet at δ1.46 was assigned to Me-14 bonded to an oxygen bearing carbon. Furthermore, two quarternary carbons at δ80.17 and 69.62

in the ^{13}C-NMR spectrum determined by DEPT experiments, suggested that **1** contained a C-1/C-10 epoxide ring. Spatial assignment of the epoxide ring was assigned to an α-orientation based on biogenetic considerations and NOEDS. Clear enhancements were observed between H-6 and H-14 (5%), H-8 and H-14 (5%).

A doublet ($J=7.2$ Hz) at δ1.21 showed the presence of a methyl group at C-11. The all-trans-axial disposition of H-5, H-6, H-7, H-8 and H-11 followed from the observed large vicinal couplings ($J_{5,6}=J_{6,7}=J_{7,8}=J_{7,11}=10.1$ Hz), a quartet ($J=10.1$ Hz) at δ2.23 was assigned for H-7α. Inspection of the Dreiding model of the proposed structure of **1**, requires an 11β-H, and this was further supported by NOEDS experiment. Clear effects were observed between H-6 and H-8 (7%), H-6 and H-11 (5%), as well as H-8 and H-11 (6%). The NOEDS also supported the α-configuration of H-2 and H-5, due to a clear effect between H-2 and H-5 (5%). So the structure of **1** was elucidated to be 2β-hydroxy-1α, 10α-epoxymatricarin, and its ^{1}H- and ^{13}C-NMR chemical shifts (Tables I and II) were completely assigned by detailed ^{1}H–^{1}H, ^{13}C–^{1}H COSY and HMBC experiments.

Compound **2**(artselenoid) was obtained as colorless amorphous powders, mp 185–186°C, $[\alpha]_D^{20}+125$(c 0.1, MeOH). The IR spectrum exhibited absorption bands due to hydroxyl (3435 cm^{-1}), g-lactone (1764 cm^{-1}) and double bond (1648, 1635, 1456 cm^{-1}) groups. The molecular formula $C_{30}H_{40}O_6$ of **2** was deduced from the data of ESIMS (*m/z* 519[M+Na]$^+$, 535[M+K]$^+$) and its ^{1}H, ^{13}C(DEPT) NMR.

The ^{13}C-NMR and DEPT spectra displayed the presence of 6 methyl, 4 methylene, 12 methenyl and 8 non-protonated carbons (Table II). The

TABLE I ^{1}H-(500 MHz), ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY and HMBC data for **1** (Acetone-d$_6$)

Proton	δppm, mult., *J*(Hz), int.	^{1}H–^{1}H COSY	C–H (δc) *correlation*	*Observed long-range correlations* (HMBC *spectrum*)
H-2α	3.85, d, 2.8, 1H	H-3	79.72	C-4, C-5, C-15
H-3	5.96, t, 2.8, 1H	H-2α, -5α	127.18	C-1, C-5
H-5α	3.04, dd, 10.1, 2.8, 1H	H-3, H-6β	59.39	C-1, C-2, C-3, C-4, C-7
H-6β	4.48, t, 10.1, 1	H-5α, H-7α	77.26	C-4, C-8
H-7α	2.23, q, 10.1, 1H	H-6β, H-8β, -11β	58.75	C-5, C-6, C-8, C-9, C-11, C-13
H-8β	5.35, ddd, 10.1, 10.4, 5.4, 1H	H-7α, H-9α, H-9β	72.51	C-7, C-10, C-11, O=C(OAc)
H-9α	2.06, dd, 14.8, 10.4, 1H	H-8β, H-9β	46.00	C-7, C-8, C-10, C-14
H-9β	1.89, dd, 14.8, 5.4, 1H	H-8β, H-9α	46.00	C-7, C-8, C-10
H-11β	2.61, dq, 10.1, 7.2, 1H	H-7α, H-13	41.49	C-7, C-8, C-12, C-13
H-13	1.21, d, 7.2, 3H	H-7α	15.26	C-12
H-14	1.46, s, 3H		29.94	
H-15	1.26, s, 3H		21.46	
OAc	2.04, s, 3H		21.19	

TABLE II ^{13}C-(125MHz) NMR data for **1** (Acetone-d_6) and **2** (CD_3OD)

No.	*δ (DEPT)*		*No.*	*δ (DEPT)*		*No.*	*δ (DEPT)*
	1	**2**		**1**	**2**		**2**
C-1	80.17(C)	47.87(CH)	C-11	41.49(CH)	42.92(CH)	C-6′	83.33(CH)
C-2	79.12(CH)	59.96(CH)	C-12	178.89(C)	181.02(C)	C-7′	50.62(CH)
C-3	127.18(CH)	47.17(CH_2)	C-13	15.26(CH_3)	12.99(CH_3)	C-8′	25.55(CH_2)
C-4	152.54(C)	63.93(C)	C-14	29.94(CH_3)	13.96(CH_3)	C-9′	45.97(CH_2)
C-5	59.39(CH)	76.51(C)	C-15	21.46(CH_3)	22.42(CH_3)	C-10′	73.93(C)
C-6	77.26(CH)	84.90(CH)	C-1′		74.80(CH)	C-11′	43.03(CH)
C-7	58.75(CH)	47.69(CH)	C-2′		46.57(CH)	C-12′	181.56(C)
C-8	72.51(CH)	28.59(CH_2)	C-3′		61.76(CH)	C-13′	12.42(CH_3)
C-9	46.00(CH_2)	126.19(CH)	C-4′		137.28(C)	C-14′	26.48(CH_3)
C10	69.62(C)	143.10(C)	C-5′		145.62(C)	C-15′	18.46(CH_3)
OAc				170.42(C)			
				21.19(CH_3)			

^{13}C-NMR spectrum further indicated the presence of three quaternary olefinic carbons (δ137.28, 143.10, 145.62), one trisubstituted olefinic carbon (δ126.19) and two lactone carbonyl carbons (δ181.02, 181.56). Although the molecular ion was not observed in the EIMS, the largest and prominent fragment at *m/z* 248 might be due to the presence of two similar moieties $C_{15}H_{20}O_3$. Comparison of the NMR data (Tables II and III) as well as mass spectroscopic pattern of **2** with those of **1**, absinthin [13] and artanomaloide [14], supported that **2** should be a dimeric guaianolide with a molecular formula of $C_{30}H_{40}O_6$. Only a few natural-occurring dimeric guaianolides have been found in several *Artemisia* species by the French [13] and German scientists [14].

The ^{1}H-NMR spectrum showed signals for six methyls, two being doublets, two olefinic, and two singlets. A broad singlet centered at δ5.57 (1H, brs) characteristic for an olefinic proton, was assigned to H-9 (δC-9, 126.19, CH). This was in agreement with the presence of an allylic methyl signed at δ1.65 with a coupling constant $J = 1.4$ Hz. Thus, this olefinic methyl group should be linked at C-10. The two doublets at δ4.55 (1H, d, $J = 10.9$ Hz) and 4.61 (1H, brd, $J = 10.6$ Hz were easily assigned to the lactone oxygen bearing methine protons at C-6 (δ84.90, CH) and C-6′ (δ83.33, CH), respectively. The H-6′ was broadened by homoallylic coupling with Me-15′ at δ1.80, so a second double bond was assigned to C-4′ (5′) (δ137.28, C-4′; δ145.62, C-5′). The large coupling between H-6 and H-7 (10.9 Hz), as well as H-6′ and H-7′ (10.6 Hz) indicated that they were trans-diaxially related, which was in accord with a trans-fusion of the C-6 (6′)/C-7 (7′) lactone. The two doublet methyl signals at δ1.12 and 1.19 or Me-13 and Me-13′ were quite similar to that of **1**.

TABLE III ^{1}H-(500 MHz, ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY and HMBC data for **2** (CD_3OD)

Proton	*δ, mult., J* (Hz), *int.**	^{1}H–^{1}H COSY(δH)	^{13}C–^{1}H COSY (δC)	*Observed long-range correlations HMBC* (δC)
H-1	3.00, t, 3.4, 1H	2.89, 5.57	47.87	63.93, 143.10
H-2	2.33, m, 1H	2.89, 3.17	59.96	
H-3	1.67, m, 2H		47.17	63.93
H-6	4.55, d, 10.9, 1H	1.97	84.90	28.59, 47.69, 63.93
H-7	1.97, m, 1H	1.35, 1.91, 2.30, 4.55	47.69	
H-8	1.35, m, 1H	1.91, 1.97	28.59	
	1.91, m, 1H	1.35, 1.97	28.59	126.19, 143.10
H-9	5.57, brs, 1H	1.65, 3.00	126.19	47.87
H-11	2.30, m, 1H	1.97, 1.19	42.92	12.99, 47.69
H-13	1.19, d, 6.9, 3H	2.30	12.99	42.92, 47.69, 181.02
H-14	1.65, d, 1.4, 3H	5.57	13.96	126.19, 143.10
H-15	0.84, s, 3H		22.42	47.17, 61.76, 76.51
H-1′	2.00, brs, 1H		74.80	26.48, 46.57, 61.76, 73.93
H-2′	2.89, m, 1H	2.33, 3.00, 3.17	46.57	
H-3′	3.17, brd, 8.3, 1H	2.33, 2.89	61.76	22.42, 46.57, 137.28, 145.62
H-6′	4.61, brd, 10.6, 1H	1.75	83.33	145.62
H-7′	1.75, m, 1H	1.29, 1.77, 2.25, 4.61	50.62	
H-8′	1.29, m, 1H	1.55, 1.75, 1.77, 1.81	25.55	
	1.77, m, 1H	1.29, 1.55, 1.75, 1.81	25.55	
H-9′	1.55, m, 1H	1.29, 1.77, 1.81	45.97	
	1.81, m, 1H	1.29, 1.55, 1.77	45.97	
H-11′	2.25, m, 1H	1.75, 1.12	43.03	12.42
H-13′	1.12, d, 6.8, 3H	2.25	12.42	43.03, 50.62, 181.56
H-14′	1.03, s, 3H		26.48	45.97, 73.93, 74.80
H-15′	1.80, brs, 3H	4.61	18.46	61.76, 137.28, 145.62

*Long-range W-coupling between H-1 (δ3.00) and H-2′ (δ2.89), between H-2 (δ2.33) and H-3′(δ3.17); Long-range allylic coupling between H-1 and H-9 (δ5.57), between H-9 and H-14 (δ1.64), as well as a long-range homoallylic coupling between H-6′ (δ4.61) and H-15′ (δ1.80).

TABLE IV NOE difference spectrum of **2**

Saturation (δ)	(%) *Observed* NOE (δ)
H-1α(3.00)	H-7α(1.97)(9)
	H-2′α(2.89)(7)
H-2(2.33)	H-3(1.67)(6)
H-6β(4.55)	H-11β(2.30)(5)
H-2′α(2.89)	H-1α(3.00)(6)
	H-1′α(2.00)(9)
	H-3′α(3.17)(6)
H-3′α(3.17)	H-2′α(2.89)(6)
H-6′α(4.61)	H-11′α(2.25)(5)
H-15(0.84)	H-15′(1.80)(5)
H-14′(1.03)	H-6′(4.61)(8)

The ^{1}H-NMR spectrum showed the presence of two singlet methyl signals. HMBC analysis showed that the methyl group with δ1.03 (3H, s, Me-14) should be linked to the oxygenated quarternary C-10′ (δ73.93, C), and two neighbouring methylenes should be placed between C-7′ and C-10′.

The other angular methyl (δ0.84) should be at C-4 and cis to the hydroxyl at C-5, because of a gauche effect between the two groups causing the Me-15 shifted lowfield to δ22.42 in the ^{13}C-NMR spectrum. The ^{13}C–^{1}H COSY revealed the correlations between the carbons and the geminal protons (Table III). The ^{1}H–^{1}H COSY and HMBC spectra (Table III) showed that C-2 (δH:2.33; δC: 59.96, CH), C-4 (δC: 63.93, C), C-2′ (δH: 2.89; δC: 46.57, CH) and C-3′ (δH: 3.17; δC: 61.76, CH) should be the linkage positions of the two guaianolides. Inspection of a Dreiding model showed that the structure of artselenoid was suggested as **2**. This was supported by the NOEDS experiment (Table IV). It must be pointed out that there is an unusual NMR phenomenon in these dimeric guaianolides [13,14]. The particular feature is that the ^{1}H-NMR signal of H-1′ showed an upfield shift and, on the contrary, the ^{13}C-NMR signal of C-1′ was in downfield region (δH-1′: 2.00 ppm, but δC-1′: 74.80 ppm) which was confirmed by ^{13}C–^{1}H COSY. The relative configuration of **2** was determined by NOE difference spectra listed in Table IV.

EXPERIMENTAL SECTION

General Experimental Procedures

All NMR spectra were measured on a Bruker AM-500 spectrometer using TMS as internal standard; IR spectra were recorded on a Perkin-Elmer 683 spectrometer; EIMS and HREIMS were taken on an Analytical VG ZAB-2F and on a Zabspec mass spectrometer, respectively; ESIMS was obtained from a VG Platform II mass spectrometer; Optical rotations were determined on a Perkin-Elmer 241 polarimeter; Melting points were taken on a Kofler apparatus and are uncorrected; Silica gel (200–300 mesh) for column chromatography (CC), TLC using precoated Si gel (0.25 mesh) F_{254}. Spots were detected by UV light (254 nm) and spraying with 5%H_2SO_4–EtOH.

Plant Materials

The aerial parts of *A. selegeasis* were collected from Peng county, Sichuan province of China, in November 1990, and identified by Prof. Y.H. Chen of Department of Botany of our Institute. A voucher specimen was deposited at the herbarium of Institute of Chinese Herb of Peng County, Sichuan, China.

Extraction and Isolation

The dried and pulverized aerial parts (5 kg) of *A. selengensis* were extracted with petroleum ether (60–90°C) in a percolator and the defatted material

was exhaustively extracted with hot 95% EtOH (10 L). The ethanolic extract was concentrated under reduced pressure to give a black residue (300 g), 120 g of which was suspended in 0.5 L of boiling H_2O and filtered, then the aqueous filtrate was extracted with petroleum ether (60–90°C), EtOAc and n-BuOH, respectively. The petroleum ether extract (400 mg) was chromatographed on a silica gel column (200–300 mesh, 120 g) eluted with petroleum ether–EtOAc gradient solvent. The eluent was monitored by TLC and combined to give 9 fractions. Compound **3** (10 mg) and **4** (15 mg), compound **5** (20 mg) and **6** (25 mg), and compound **9** (10 mg) were obtained from fraction 2, fraction 3 and fraction 6, respectively. The EtOAc extract (8 g) was chromatographed on a silica gel column 200–300 mesh, 250 g) eluted with $CHCl_3$–MeOH gradient solvent. The eluent was combined to give 11 fractions. Compounds **1** (10 mg) and **2** (8 mg) were obtained from fraction 8($CHCl_3$–MeOH, 8 : 1) and were purified with CC and by preparative TLC, compounds **7** (5 mg) and **8** (6 mg) were obtained from fraction 2 and fraction 3, compounds **10** and **11** were obtained as a mixture (30 mg) from fraction 5, compound **12** (20 mg) was obtained from fraction 11 and purified by Sephadex LH-20 column (MeOH).

Artselenin (**1**) Colorless powders; mp 165–166°C; appearing red-black to 5% H_2SO_4-EtOH reagent; $[\alpha]_D^{20}$ – 92(c0.1, Me_2CO); IR(KBr) ν_{max} 3460, 2972, 2883, 1780, 1735, 1631, 1371, 1276, 1166,1037,970 cm^{-1}; EIMS m/z (rel.int.): 322($[M]^+$, 5), 304($[M-H_2O]^+$, 7), 279($[M-CH_3CO]^+$, 5), 262($[M-HOAc]^+$, 8), 244($[M-HOAc-H_2O]^+$, 33), 229(11), 201(17), 173 (15), 145 (14), 128 (14), 105 (11), 91(21), 85(9), 69 (13), 57(12), 43(100); HR-EIMS m/z: 322.1413(M^+); ^{1}H-NMR and ^{13}C-NMR (see Tables I and II).

Artselenoid(**2**): Colorless amorphous powders; mp 185–186°C; appearing light-purple to 5%H_2SO_4–EtOH reagent; $[\alpha]_D^{20}$ + 125(c0.1, MeOH); IR (KBr) ν_{max} 3435, 2927, 2846, 1764, 1648, 1635, 1456, 1201, 1180, 1105 cm^{-1}; ESIMS m/z (rel.int.): 519 ($[M+Na]^+$, 100), 535($[M+K]^+$, 62); EIMS m/z (rel.int.): 248(1/2$[M]^+$,17), 233(1/2$[M-Me]^+$,9), 230(1/2$[M-H_2O]^+$,100), 215(1/2$[M-H_2O-Me]^+$,65), 205(11), 187(13), 185(39), 169(32), 157(85), 141(75), 128(68), 115(67), 105(27), 91(74), 77(32), 65(14), 55(25), 43(60); ^{13}C-NMR and ^{1}H-NMR see Tables II and III, respectively.

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