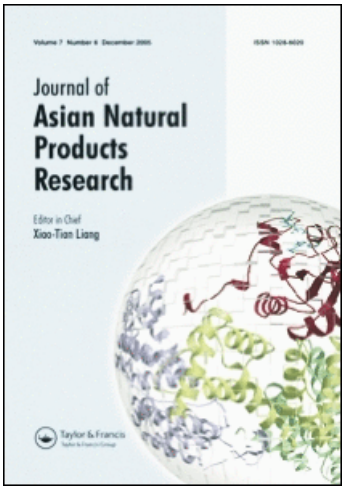

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Two novel sesquiterpenoids from *Ainsliaea fragrans* Champ.

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A new sesquiterpene lactone, 3β-*O*-β-D-glucopyranosyl-8α-hydroxy-11α,13-dihydrozaluzanin C (**1**), and a novel trinorguaiane-type sesquiterpene, 4β,10α-dimethyl-1β,5α-bicycle[3,5,0]dec-6-en-4α,10β-diol (**2**), together with three known compounds, glucozaluzanin C (**3**), 11α,13-dihydrozaluzanin C (**4**), and 8α-hydroxy-11α,13-dihydrozaluzanin C (**5**), were isolated from the whole plant of *Ainsliaea fragrans* Champ. The structures of **1** and **2** were elucidated on the basis of detailed spectral analysis. Structures of the known compounds were identified by comparison of its spectral data with those values in the literature.

Keywords: Compositae; *Ainsliaea fragrans* Champ.; 3β-*O*-β-D-glucopyranosyl-8α-hydroxy-11α,13-dihydrozaluzanin C; 4β,10α-dimethyl-1β,5α-bicycle[3,5,0]dec-6-en-4α,10β-diol

1. Introduction

Ainsliaea fragrans Champ. (Compositae) is widely distributed in the south of China [1]. It has long been used in folk medicine for the treatment of arresting hemorrhages, curing wounds, and dispersing blood clots [2]. Several chemical constituents have been isolated from *A. fragrans* including sesquiterpene lactones [2,3], flavonoids [3,4], and triterpenoids [5]. As a continuation of our search for bioactive principles from the plant, a new sesquiterpene lactone, 3β-*O*-β-D-glucopyranosyl-8α-hydroxy-11α,13-dihydrozaluzanin C (**1**), a novel trinorguaiane-type sesquiterpene, 4β,10α-dimethyl-1β,5α-bicycle[3,5,0]-dec-6-en-4α,10β-diol (**2**), and three known compounds, glucozaluzanin C (**3**) [6], 11α,13-dihydrozaluzanin C (**4**) [2], and 8α-hydroxy-11α,13-dihydrozaluzanin C (**5**) [2], were isolated. This paper is concerned with the isolation and structure determination of the new compounds **1** and **2**.

2. Results and discussion

Compound **1** was obtained as colorless needles. The molecular formula of compound **1** was established to be $C_{21}H_{30}O_9$ by HR-ESI-TOF-MS at *m/z* 449.1775 $[M+Na]^+$. Its IR spectrum suggested the presence of hydroxyl groups (3427 cm^{-1}), a γ-lactone group (1774 cm^{-1}), and double bonds (1664, 1638 cm^{-1}). Its ^1H NMR spectrum showed the characteristics of guaianolide that exhibited two pairs of exocyclic methylene signals at δ 5.33 (1H, d, $J = 1.2$ Hz), 5.17 (1H, d, $J = 1.2$ Hz),

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4.94 (1H, br s), and 4.87 (1H, br s), and a methyl signal at δ 1.14 (3H, d, $J = 7.6$ Hz). Acid hydrolysis of **1** with 1 mol/l HCl afforded glucose that was identified by direct comparison with an authentic sample. The ^{13}C and ^{1}H NMR spectra of **1** also showed the presence of a β-glucopyranosyl moiety by the signals at δ_C 101.9 and δ_H 4.25 (1H, d, $J = 7.7$ Hz). By comparing the ^{13}C NMR spectral data of **1** with those of 8α-hydroxy-11α,13-dihydrozaluzanin C (**5**) [7], the aglycone of **1** showed greater similarity to the latter except that the chemical shifts of C-3 moved downfield to δ 79.2, and those of C-2 and C-4 moved upfield to δ 36.6 and 149.9, respectively. So **1** should be 3β-*O*-β-D-glucopyranosyl-8α-hydroxy-11α,13-dihydrozaluzanin C (Figure 1); it was further proved by the correlated signal between H-1′ at δ 4.25 (1H, d, $J = 7.7$ Hz) and C-3 at δ 79.2 in its HMBC spectrum.

Compound **2** was obtained as colorless needles. Its molecular formula was determined to be $C_{12}H_{20}O_2$ on the basis of HR-ESI-TOF-MS at *m/z* 197.1539 $[M+H]^+$. The IR spectrum showed the absorptions of hydroxyl groups (3385 cm^{-1}) and double bonds (1647 cm^{-1}). EI-MS gave fragment ion peaks at *m/z* 163 ($[M—H_2O—CH_3]^+$) and 145 ($[M—2H_2O—CH_3]^+$) and proved the presence of hydroxyl and methyl groups. The ^{1}H NMR spectrum of **2** showed the presence of two methyl groups at δ 1.19 and 1.26 (each 3H, s) and two olefinic protons at δ 5.74 (1H, br d, $J = 11.0$ Hz) and 5.80 (1H, ddd, $J = 11.0$, 5.3, 2.4 Hz). The ^{13}C NMR and DEPT spectra exhibited 12 carbon signals including two methyls at δ 21.7 and 22.8, four methylenes, four methines (two olefinic carbons at δ 130.1, 131.6), and two oxygen-bearing quaternary carbon signals at δ 75.0 and 80.0. These spectral features (Table 1) suggested that **2** was a trinorguaiane-type sesquiterpene, and were similar to that of nephalbidol [8] except for C-6, C-7, and C-8. Compared with nephalbidol, the chemical shifts of C-6 moved downfield to δ 130.1, and those of C-7 and C-8 moved upfield to δ 131.6 and 23.5, respectively, because of the absence of the isopropyl group at C-7.

Analysis of the $^{1}H-^{1}H$ COSY and HMQC spectra of **2** allowed the establishment of the following fragment: $—CH_2—CH_2—CH=CH—CH—CH—CH_2—CH_2—$. The four remaining carbons were two methyls and two oxygen-bearing quaternary carbons. Since the two methyls appeared as singlets at δ 1.19 and 1.26 (each 3H, s) in the ^{1}H NMR spectrum, they should be linked to the quaternary carbons and be germinal to hydroxyl groups, respectively. The HMBC spectrum was allowed to establish the cyclic system as shown in Figure 1. The relative configuration of **2** was characterized by the ROESY experiment. In this spectrum, no NOESY correlation was observed between two bridgehead protons, which suggested a *trans*-relationship for H-1 and H-5.

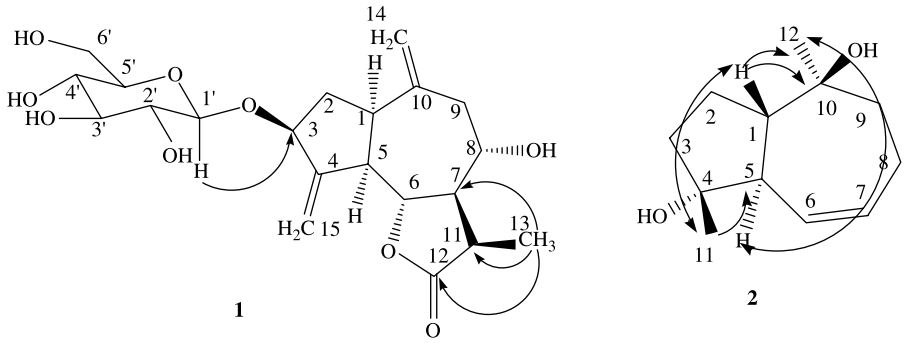


Figure 1. Structures, key HMBC (⟶), and ROESY (⟷) correlations of compounds **1** and **2**.

Table 1. ^{1}H and ^{13}C NMR spectral data of compounds **1** and **2**.

	1[a]			**2**[b]		
No.	δ_C	δ_H (J, Hz)	HMBC (H → C)	δ_C	δ_H (J, Hz)	HMBC (H → C)
1	43.1	2.90 m	C2, C5, C10	50.6	2.05 m	C2, C5, C6, C10, C12
2	36.6	1.71 ddd (7.8, 7.8, 13.2), 2.21 ddd (7.8, 7.8, 13.2)	C1, C3 C5	21.6	1.76 dd (11.7, 6.4), 1.66 dd (11.7, 7.3)	C1, C3, C4, C5, C10
3	79.2	4.44 t (7.8)	C4	40.3	1.70 dd (7.3, 6.4)	C1, C2, C4, C5, C11
4	149.9			80.0		
5	49.1	2.80 m	C1, C4	51.2	2.24 dd (11.5, 2.5)	C6, C7, C10
6	78.7	4.18 dd (10.0, 10.0)	C1, C4, C8	130.1	5.74 br d (11.0)	C1, C4, C5, C8
7	52.0	2.33 ddd (10.0, 10.0, 8.0)	C5, C6, C8, C11, C13	131.6	5.80 ddd (11.0, 5.3, 2.4)	C5, C8, C9
8	68.6	3.52 m		23.5	1.98 m, 2.30 m	C6, C7, C9, C10
9	45.0	2.03 dd (8.5, 13.2), 2.59 dd (4.6, 13.2)	C1, C7, C8, C10, C1, C7, C8, C10, C14	42.7	1.61 ddd (14.0, 9.5, 1.8), 1.83 ddd (14.0, 9.5, 2.0)	C1, C7, C8, C10, C12
10	144.5			75.0		
11	38.0	2.63 dq (8.0, 7.6)	C6, C7, C8, C13	22.8	1.19 s	C3, C4, C5
12	179.0			21.7	1.26 s	C1, C9, C10
13	10.8	1.14 d (7.6)	C7, C11, C12			
14	114.5	4.87 br s, 4.94 br s	C1, C9, C10			
15	112.1	5.17 d (1.2), 5.33 d (1.2)	C3, C5			
1′	101.9	4.25 d (7.7)	C3, C5′			
2′	73.7					
3′	76.9	2.99–3.10 (4H, m)				
4′	70.4					
5′	77.0					
6′	61.4	3.67 br d (11.0), 3.41 m				

Notes: The assignments were based on the DEPT, $^{1}H-^{1}H$ COSY, HMQC, and HMBC experiments.
[a] Measured in DMSO-d_6.
[b] Measured in $CDCl_3$ at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR.

The NOE correlations between H-5 and H-12, H-1 and H-11 could be observed, while the ROESY signals between H-5 and H-11, H-1 and H-12 did not appear in its ROESY spectrum. Thus, CH_3-12 and H-5 were located at the different sides of the fused ring with CH_3-11 and H-1. Therefore, the structure of **2** was determined as 4β,10α-dimethyl-1β,5α-bicyclo[3,5,0]dec-6-en-4α,10β-diol (Figure 1). The possible biogenetic pathways for new sesquiterpenes **1** and **2** were proposed as shown in Scheme 1. Although **1** and **2** have the same precursor – farnesyl pyrophosphate [9,10] – they have different biosynthetic pathways.

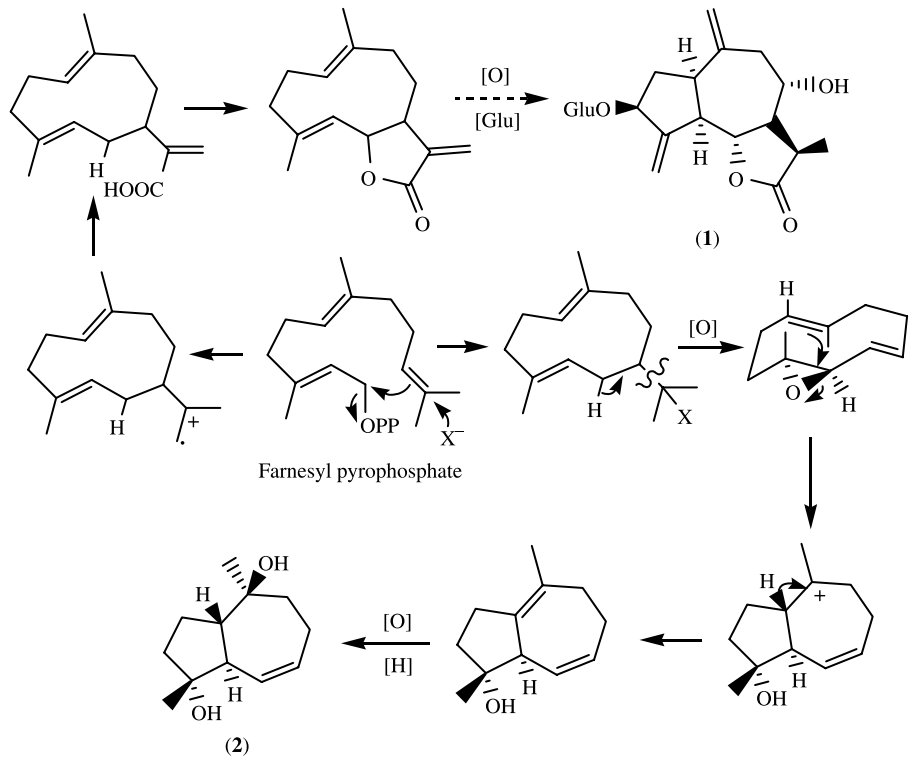
3. Experimental

3.1 General experimental procedures

Optical rotations were performed on a JASCO P-1020 digital polarimeter. Melting points were measured on an X-4 micromelting point apparatus and are uncorrected. The IR spectra were obtained on a Nicolet Impact 410 infrared spectrometer with KBr disk technique. The NMR spectra were recorded on a Bruker ACF-500 NMR instrument (the ^{1}H NMR spectra at 500 MHz and the ^{13}C NMR spectra at 125 MHz). ESI-MS and EI-MS experiments were performed on an Agilent 1100 Series MSD Trap mass spectrometer and a Shimadzu 2010 EI/MSD spectrometer, respectively. HR-ESI-MS were recorded with an Agilent TOF MSD 1946D spectrometer. Silica gel (200–300 mesh) used for column chromatography and silica GF_{254} (10–40 μm) for thin-layer chromatography were supplied by the Qingdao Marine Chemical Factory, Qingdao, China.

3.2 Plant material

The plants of *A. fragrans* Champ. (Compositae) were collected at Ganzhou,



Scheme 1. Proposed biosynthesis of the sesquiterpenes.

Jiangxi Province (China) in 2003, and identified by the fifth author. The specimen (AF20031105) is deposited in the Department of Natural Medicine Chemistry, China Pharmaceutical University, China.

3.3 Extraction and isolation

The air-dried whole plant of *A. fragrans* (14.7 kg) was extracted with 95% EtOH under reflux (2 h × 3). The extract was filtered and concentrated under reduced pressure, and then the residue was suspended in water and partitioned with petroleum ether, EtOAc, and *n*-BuOH, successively. The *n*-BuOH extract (120.0 g) was subjected to silica gel chromatography using a gradient system of $CHCl_3$–MeOH (10:1–0:1 volume ratio), yielding five fractions. Fraction 2 (11.0 g) was repeatedly chromatographed on silica gel column by eluting with a mixture of $CHCl_3$–MeOH (10:1) to obtain compounds **1** (50.0 mg) and **3** (45.0 mg). The EtOAc extract (70.0 g) was also subjected to silica gel column and eluted with petroleum ether–EtOAc (1:0–0:1 volume ratio) to produce fractions AF1–AF8. Compounds **2** (9.5 mg), **4** (15.0 mg), and **5** (35.0 mg) were obtained from AF5 (21.0 g) by Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) after silica gel column by eluting with petroleum ether–acetone (5:1 2 L, 2.5:1 2 L, 1:1 2 L).

3.3.1 3β-O-β-D-Glucopyranosyl-8α-hydroxy-11α,13-dihydrozaluzanin C (*1*)

Colorless needles, mp 143–145°C, $[\alpha]_D^{20}$ + 37.6 (*c* 0.19, MeOH). IR ν_{max} (KBr, cm^{-1}): 3427, 2985, 2974, 2940, 2924, 2891, 2877, 1774, 1664, 1638, 1072, 1064, 1040, 1012; ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) spectral data: see Table 1; ESI-MS *m/z*: 449 $[M+Na]^+$; 444 $[M+NH_4]^+$; HR-ESI-MS *m/z*: 449.1775 $[M+Na]^+$ (calcd for $C_{21}H_{30}O_9Na$, 449.1788).

3.3.2 4β,10α-Dimethyl-1β,5α-bicycle[3,5,0]dec-6-en-4α,10β-diol (*2*)

Colorless needles, mp 108–110°C, $[\alpha]_D^{20}$ −2.2 (*c* 0.23, MeOH). IR ν_{max} (KBr, cm^{-1}): 3385, 2971, 2936, 2850, 1646, 1437, 1373, 1303, 1091, 970, 916, 748, 735, 695; ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectral data: see Table 1; HR-ESI-MS *m/z*: 197.1539 $[M+H]^+$ (calcd for $C_{12}H_{21}O_2$, 197.1542). EI-MS *m/z*: 163, 145, 135, 120, 107, 91, 71, 57.

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