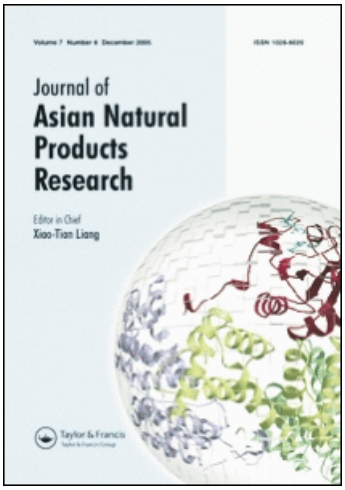

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A novel norditerpenoid alkaloid from *Aconitum macrorhynchum*

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A novel norditerpenoid alkaloid, macrorhynine C (**1**), together with three known compounds, was isolated from *Aconitum macrorhynchum*. The structure of the new alkaloid was elucidated on the basis of spectral analyses as (1α,6α,16β)-3-hydroxy-8-acetyloxy-13-hydroxy-1,6,16-trimethoxy-4-(methoxymethyl)-19-ene-aconitan-14-yl 4-methoxybenzoate (**1**). The novel compound was found to contain the rare C(19)=*N* azomethine group. Compounds **2**–**4** were obtained from this species for the first time.

Keywords: *Aconitum macrorhynchum*; Ranunculaceae; norditerpenoid alkaloid; macrorhynine C

1. Introduction

The genus *Aconitum* (Ranunculaceae) is represented by 208 species in China, mostly growing in the southwestern and northeastern parts of the country on mountains of 1500 m above sea level or higher [1]. *Aconitum* species produce highly toxic norditerpenoid alkaloids that have attracted considerable interest because of their complex structures, interesting chemistry, and noteworthy physiological effects [2]. *Aconitum macrorhynchum* Turcz. ex Ledeb has long been used in Tibetan folk medicine for the treatment of arthralgia, dysmenorrhea, and colic [3]. As a continuation of our studies on medicinal plants of *Aconitum* species growing on the Yunnan–Tibet Plateau [4–7], *A. macrorhynchum* was examined. Our previous work [8] on this species has resulted in the isolation of two new norditerpenoid alkaloids, macrorhynines A and B, and seven norditerpenoid alkaloids from *A. macrorhynchum*. A continuation of our studies on the same plant led to the isolation of a new norditerpenoid alkaloid, named macrorhynine C (**1**), and three known norditerpenoid alkaloids yunaconitine (**2**) [9], 8-deacetyl-yunaconitine (**3**) [10], and 14-*O*-acetyl schaconitine (**4**) [11] (Figure 1). Compounds **2**–**4** were obtained from this species for the first time. Here, we report on the isolation and structural elucidation of **1**.

2. Results and discussion

Macrorhynine C (**1**) was isolated as an optically active amorphous solid. Its molecular formula was determined as $C_{33}H_{44}NO_{11}$ by HR-ESI-MS at *m/z* 630.2936 $[M+1]^+$. The IR spectrum showed characteristic absorptions for an OH (3447 cm^{-1}, br), ester (1717 cm^{-1}),

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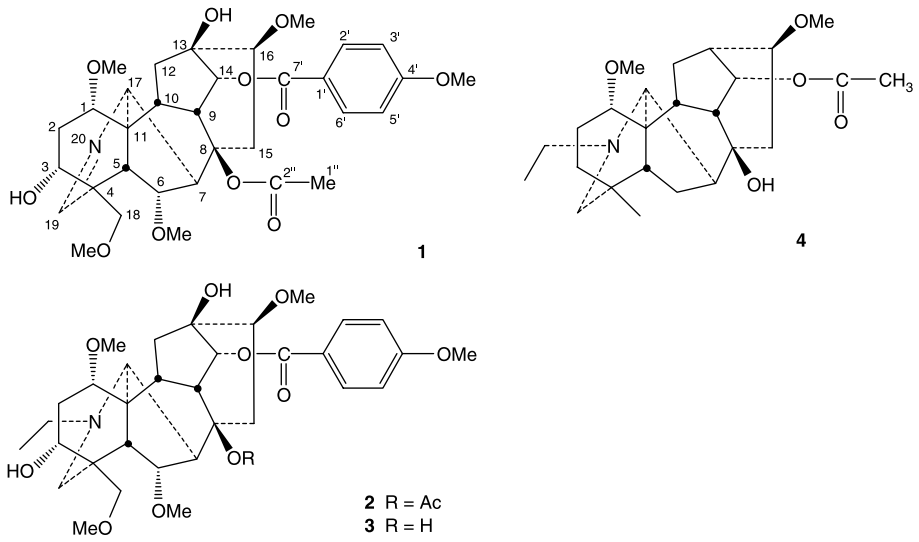

Figure 1. The structures of **1**–**4**.

N=CH (1633 cm^{-1}), and aromatic ring (1606 and 1512 cm^{-1}). The UV absorption maximum at 259 nm is consistent with the presence of a 4-methoxybenzoate unit. The ^{1}H NMR spectrum of **1** (Table 1) showed signals due to an AA′BB′ system for four aromatic protons (δ 8.00, 6.91, each 2H, d, J = 8.8 Hz), five MeO groups (δ 3.85, 3.53, 3.35, 3.21, 3.05, each 3H, s), a strongly shielded MeCO group (δ 1.29, s), and a methine of an *N*=CH group (δ 7.46, s). The ^{13}C NMR spectrum (Table 1) clearly indicated the presence of a norditerpene moiety (C-1 to C-19)

Table 1. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectral data of **1** in $CDCl_3$ (δ in ppm).

No.	^{13}C	^{1}H (J, Hz)	No.	^{13}C	^{1}H (J, Hz)
1	83.5 d	3.95 t (3.9)	16	83.6 d	3.98 t (8.9)
2	33.2 t	1.90 m (H_α),	17	61.8 d	3.92 s
		1.73 m (H_β)	18	78.2 t	4.00 d (8.3, H_α),
3	71.6 d	4.02 t (6.5)			3.81 d (8.3, H_β)
4	50.5 s		19	165.6 d	7.46 s
5	43.5 d	2.68 d (6.4)	1′	122.8 s	
6	80.3 d	4.10 dd (6.4, 1.2)	2′/6′	132.0 d	8.00 d (8.8, 2H)
7	43.8 d	2.75 d (1.2)	3′/5′	114.0 d	6.91 d (8.8, 2H)
8	84.4 s		4′	163.8 s	
9	53.6 d	3.18 dd (4.8, 1.1)	7′	166.3 s	
10	41.1 d	2.23 m	1-MeO	56.1 q	3.05 s
11	51.9 s		6-MeO	59.0 q	3.53 s
12	34.9 t	1.81 d (14.3, H_α),	16-MeO	57.3 q	3.21 s
		2.38 m (H_β)	18-MeO	59.5 q	3.35 s
13	75.1 s		4′-MeO	55.7 q	3.85 s
14	78.7 d	4.89 d (4.8)	1″	21.8 q	1.29 s
15	38.5 t	2.42 dd (15.3, 8.9, H_α),	2″	169.9 s	
		3.27 m (H_β)			

combined with an anisoyl (4-methoxybenzoyl unit, C-1′ to C-7′), five MeO groups, an MeCO group (δ 169.9 and 21.8), and an *N*=CH group (δ 165.6). Its spectral characteristics were similar to those of the known compound yunaconitine (**2**), except for the absence of an *N*-Et group in **1**. The signals at δ_H 7.46 (s) and δ_C 165.6 (d) suggested the presence of an *N*=CH group instead of the *N*-Et or *N*-Me group characteristic of many norditerpenoid alkaloids [12–14]. The ESI-MS of **1** exhibiting a molecular ion at *m/z* 629 ($[M]^+$) compared with *m/z* 659 ($[M]^+$) for **2** is consistent with this argument.

In the HMBC spectrum of **1** (Figure 2), the correlation between H-14 (δ_H 4.89) and C-7′ (δ_C 166.3) suggested that the anisoyl group was located at C-14, while the correlations of H-17 (δ_H 3.92) and H-18 (δ_H 4.00/3.81) with C-19 (δ_C 165.6) suggested the position of the *N*=CH group. The five MeO groups were assigned as 1-MeO, 6-MeO, 16-MeO, 18-MeO, and 4′-MeO, based on the HMQC and HMBC experiments. $^1H-^1H$ COSY correlations of **1** are shown in Figure 2. The relative configuration of **1** was studied by means of a NOESY experiment (Figure 2). The NOEs between H-1/H-10, H-10/H-14, H-14/H-9, and H-9/H-10 indicated β-oriented protons at these locations. The NOE between H-1 and H-3 also suggested the β-oriented proton of C-3. The coupling constant between H-5 and H-6 ($J = 6.4$ Hz) confirmed the β-position of H-6, and NOE of H-6/H-7 established the β-orientation of these protons. Further,

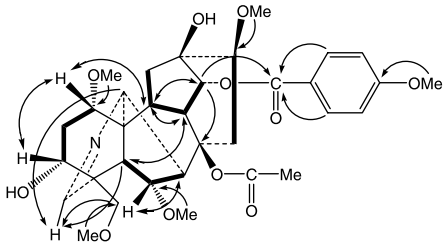

Figure 2. Significant $^1H-^1H$ COSY (▬), HMBC (⟶), and NOESY (⟷) correlations for **1**.

the NOEs between H-17/H_α-15 and H_α-15/H-16 demonstrated the α-position of H-16. The NOEs between H-16/H_α-15, H-17/H_α-12, and H-5/H_β-2 allowed the steric differentiation of the protons of CH_2(2), CH_2(12), and CH_2(15). Therefore, compound **1** was elucidated as (1α,6α,16β)-3-hydroxy-8-acetyloxy-13-hydroxy-1,6,16-trimethoxy-4-(methoxymethyl)-19-ene-aconitan-14-yl 4-methoxybenzoate.

Compounds **2**–**4** were purified from the plant extract. These compounds were obtained from this species for the first time. Their structures were identified by comparing their physical and spectral data with those reported in the literature.

3. Experimental

3.1 General experimental procedures

UV spectra were determined on a UV 210A spectrometer and IR spectra on a Bio-Red FTS-135 spectrometer. Optical rotations were measured on a Jasco-20 C digital polarimeter. 1D and 2D NMR spectra were taken on a Bruker Avance DRX-500 instrument with TMS as the internal reference. EI-MS were recorded on a VG Auto spec-3000 mass spectrometer. Commercial Si gel plates (Qingdao Haiyang Chemical Group Co., Qingdao, China) were used for TLC.

3.2 Plant material

The plant material was collected in Deqin County, Yunnan Province, China, in September 2001, and identified as *A. macrorhynchum* Turcz. ex Ledeb by Mr A. Dou (Deqin Tibetan Hospital). A voucher specimen (No. 01-005) is deposited in the Key Laboratory of Medicinal Chemistry for Natural Resources, Yunnan University, Kunming, China.

3.3 Extraction and isolation

The ground roots (5 kg) of *A. macrorhynchum* were extracted with 95% EtOH

(5 × 20 l) at room temperature. The EtOH extract was evaporated to yield a residue, which was suspended in H_2O and then extracted with petroleum ether, EtOAc, and BuOH, successively. The EtOAc extract (62 g) was subjected to chromatography over silica gel (1.0 kg, 200–300 mesh), eluting with petroleum ether–EtOAc–Et_3N (60:1:0.1 → 0:1:0.1) to afford six fractions (1–6). Fraction 4 was purified by silica gel column chromatography eluted with petroleum ether–EtOAc–Et_3N (3:1:0.1 → 0:1:0) to give compounds **2** (10 mg) and **4** (17 mg). Fraction 6 was purified by silica gel column chromatography eluted with petroleum ether–EtOAc–Et_3N (0:1:0.1 → 1:20:0.1) to give two fractions (A and B). Fraction A was rechromatographed by Sephadex LH-20 eluted with MeOH to yield compounds **1** (5 mg) and **3** (11 mg).

3.3.1 *Compound (**1**)*

(1α,6α,16β)-3-Hydroxy-8-acetyloxy-13-hydroxy-1,6,16-trimethoxy-4-(methoxymethyl)-19-ene-aconitan-14-yl 4-methoxybenzoate. An amorphous solid. $[\alpha]_D^{25}$ −57.5 ($c = 0.186$, $CHCl_3$). UV ($CHCl_3$) λ_{max} (log ε): 235 (4.44), 259 (4.69) nm; IR (KBr film) ν_{max}: 3447, 2963, 2820, 1717, 1633, 1606, 1512, 1461, 1370, 1281, 1261, 1230, 1169, 1097, 1021, 945, 912, 850, 802, 772, 761 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; ESI-MS: *m/z* 629 $[M]^+$(1), 601 (3), 597 (4), 566 (2), 538 (2), 506 (2), 446 (1), 420 (2), 385 (2), 370 (2), 354 (1), 298 (2), 236 (3), 180 (1), 136 (9), 135 (100), 107 (5), 92 (5), 77 (6). HR-ESI-MS: *m/z* 630.2936 $[M+1]^+$ (calcd for $C_{33}H_{44}NO_{11}$, 630.2914).

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