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Short Note

(2*R*,3*R*,4*S*,5*R*,6*S*,8*R*,13*R*,16*S*,17*R*)-11-Ethyl-13-methyl-4,6,8,9,16-pentamethoxy-11-azahexacyclo[7.7.2.1^{2,5}.0^{1,10}.0^{3,8}.0^{13,17}]nonadecane

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Abstract

The *Delphinium albocoeruleum* Maxim is a perennial herbaceous plant of the Ranunculaceae family, genus *Delphinium*. It typically grows in well-drained alpine meadows or shrublands at elevations of 2500–4000 m, which shapes the species' unique environmental adaptation mechanism and endows it with high medicinal value. There are a few reports on the chemical constituents and biological activities of this plant. Therefore, this study focuses on the chemical constituents of the plant in order to discover structurally novel alkaloids. This paper reports on the isolation and structural characterization, using HRMS and 1D and 2D NMR, of a new alkaloid that came from the plant.

Keywords: *Delphinium albocoeruleum* Maxim; *Delphinium*; diterpenoid alkaloids

1. Introduction

Delphinium albocoeruleum Maxim, a perennial herbaceous plant of the genus *Delphinium* in the family Ranunculaceae, is mainly distributed in the high-altitude mountain regions of southwestern China. It typically grows in well-drained alpine meadows or shrublands at elevations of 2500–4000 m, which has shaped the species' unique environmental adaptation mechanism and endows it with high medicinal value [1]. Plants of this genus have been used in folk medicine to treat rheumatic pain, traumatic injuries, and nervous system disorders; however, due to the presence of highly toxic diterpene alkaloids, their medicinal use carries significant risks. Previous chemical studies on *Delphinium* species have shown that C_{19}-diterpene alkaloids [2] are characteristic constituents, exhibiting anti-inflammatory [3], analgesic [4], anti-cancer [5] and multidrug resistance reversal activities [6], yet they possess complex structures and closely related toxicity profiles. To date, no systematic chemical investigation has been conducted on *Delphinium albocoeruleum* Maxim, and its pharmacologically active constituents, as well as the sources of its toxicity, remain unclear. In order to identify the characteristic alkaloids and other non-alkaloidal components of this plant, elucidate its chemical diversity, and provide a material basis for subsequent activity screening and safety evaluation, this study aims to carry out systematic chemical constituent isolation and structural identification from the whole plant of *Delphinium albocoeruleum* Maxim. As a result, a new diterpenoid alkaloid was isolated from *Delphinium albocoeruleum* Maxim and the structure was determined using HRMS, 1D and 2D NMR and reported data.

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2. Results

Compound **1** was obtained as a white amorphous powder. It gave a reddish-brown color upon reaction with Dragendorff's reagent, suggesting that it might be an alkaloid. The molecular formula was determined as $C_{26}H_{43}NO_5$ based on the HRESIMS data (Figure S1), which showed a protonated molecular ion peak at m/z $[M + H]^+$ 450.3216 (calcd for $C_{26}H_{44}NO_5$, 450.3214, error = 0.4 ppm), indicating six degrees of unsaturation. The ^{1}H NMR data (Table 1) of compound **1** displayed a characteristic *N*-ethyl group [δ_H 3.39 (m), 4.05 (dd, J = 12.7, 6.9 Hz), 1.46 (t, J = 7.3 Hz)], a singlet methyl [δ_H 1.17 (3H, s, 13-Me)], and five methoxy groups [δ_H 3.45 (3H, s, -OMe), 3.46 (3H, s, -OMe), 3.49 (3H, s, -OMe), 3.50 (6H, s, 2 × -OMe)]. The ^{13}C NMR data (Table 1*)* further revealed the presence of six methylene groups (one of which is nitrogen-linked) (δ_C 21.7, 27.3, 29.6, 30.2, 34.2, 60.9), eight methine groups (including three oxygenated ones) (δ_C 26.9, 39.0, 45.1, 63.3, 82.8, 84.5, 84.6), and four quaternary carbons (two of which are oxygenated) (δ_C 34.7, 52.4, 81.8, 86.2). Based on these features, compound **1** was preliminarily identified as a C_{19}-diterpenoid alkaloid. Comparison of the 1D NMR spectra (Figures S3 and S4) of compound **1** with those of the known compound tianshanisine C (which was isolated from the same genus, *Delphinium tianshanicum*) [7] revealed close structural similarity. The differences were that the hydroxyl group at C-9 in tianshanisine C was replaced by a methoxy group in compound **1**, and the acetoxy group at C-4 in tianshanisine C was replaced by a methyl group. The structure was further elucidated by the 2D NMR spectroscopic analysis (Figures S5–S8). The ^{1}H–^{1}H COSY correlations of H-2/H-3/H-4/H-5/H_2-19, H-5/H-6/H_2-7, H_2-14/H_2-15/H-16, H-17/H-18 and H_2-21/H_3-22 were identified as well as the HMBC correlations from H_3-20 to C-12, C-13, C-14, C-17; from H_2-12 to C-10, C-13, C-14, C-17, C-20; from H_2-14 to C-13, C-15, C-16, C-17, C-20; from H_2-18 to C-1, C-9, C-10, C-13, C-17; from H-3 to C-1, C-2, C-4, C-5, C-19; from H_2-7 to C-3, C-5, C-6, C-8, C-9; from H-10 to C-17, C-18, C-9, C-8, C-1, C-12; from H-2 to C-17, C-8, C-1, C-19, C-4, C-10; and from H-5 to C-4, C-7, C-10, C-1, C-10, C-20, C-12. The locations of the five methoxy groups were determined by HMBC correlations from 4-OCH_3 to C-4, 6-OCH_3 to C-6, 8-OCH_3 to C-8, 9-OCH_3 to C-9, and 16-OCH_3 to C-16, respectively. Thus, the planar structure of compound **1** was established.

Table 1. ^{1}H NMR and ^{13}C NMR data of compound **1** (δ in ppm, J in Hz).

No	δ_C	δ_H	No	δ_C	δ_H
1	52.4 C	-	16	82.8 CH	3.69 t (3.1)
2	44.4 CH	2.29 m	17	45.3 CH	2.02 t (8.2)
3	39.0 CH	2.52 t (5.7)	18	34.2 CH_2	1.77 m 2.68 dd (15.5, 7.7)
4	84.6 CH	3.75 t (2.7)	19	30.2 CH_2	1.38 dd (13.1, 3.7) 2.26 dd (13.1, 5.8)
5	45.1 CH	2.43 dd (6.9, 4.6)	20	26.9 CH_3	1.17 s
6	84.5 CH	3.41 m			
7	27.3 CH_2	2.19 dd (14.5, 8.4) 2.57 dd (13.8, 7.6)	21	52.6 CH_2	3.39 m 4.05 dd (12.7, 6.9)
8	81.8 C	-	22	11.2 CH_3	1.46 t (7.3)
			4-OCH_3	56.3 CH_3	3.50 s
9	86.2 C	-	6-OCH_3	56.7 CH_3	3.49 s
10	63.3 CH	3.24 s			
12	60.9 CH_2	3.14 s 3.35 s	8-OCH_3	52.8 CH_3	3.50 s
13	34.7 C	-	9-OCH_3	49.8 CH_3	3.45 s
14	29.6 CH_2	1.73 m 1.98 dd (14.8, 5.1)	16-OCH_3	57.7 CH_3	3.46 s
15	21.6 CH_2	1.66 m 2.07 m			

The relative configuration of compound **1** was determined by NOESY experiments. In the NOESY spectrum, correlations were observed between H-16/H-17, H-17/H-2, and H-2/H-4, indicating that H-2, H-4, H-16, and H-17 are cofacial and were assigned as *β*-oriented. Additionally, a cross-peak between H-10 and H-6 demonstrated that H-10 and H-6 share the same orientation, which was defined as *α*-oriented. Hence, the relative configuration of compound **1** was established. This relative configuration is identical to that of the known compound tianshanisine C. Considering the biosynthetic pathway and the absolute configuration of tianshanisine C determined by single-crystal X-ray diffraction, the absolute configuration of compound **1** was determined to be the same as that of tianshanisine C. Compound **1** was determined as shown in Figure 1.

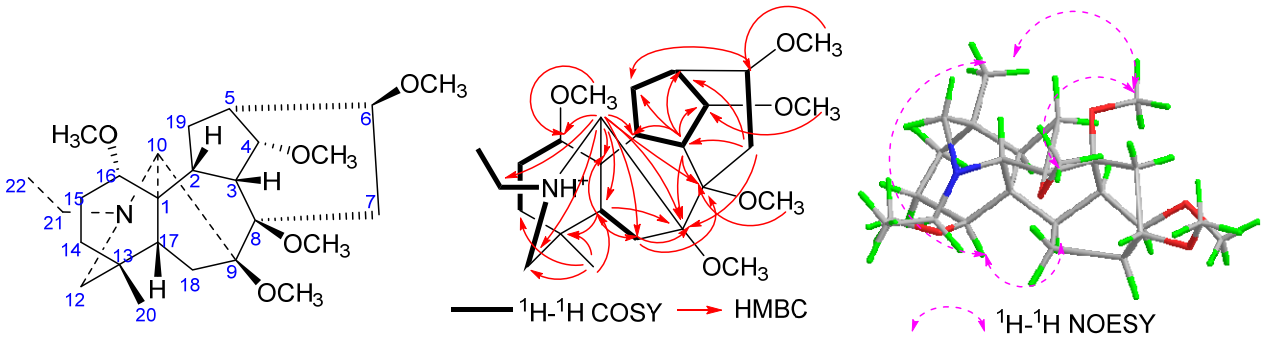


Figure 1. ^{1}H–^{1}H COSY (black bold), key HMBC (red arrows) and NOESY (pink double arrow) correlations of compound **1**.

3. Discussion

One new lycoctonine-type diterpenoid alkaloid was isolated from this plant, and its structures were elucidated by means of IR, HRMS, NMR, and other spectroscopic methods. Furthermore, it was demonstrated that the major active constituents of plants from the genus *Delphinium* are lycoctonine-type diterpenoid alkaloids. This finding enriches the pharmacodynamic material basis of this plant and provides a theoretical foundation for the further development of this plant resource.

4. Materials and Methods

4.1. General Experimental Procedures

The IR data were collected using a VERTEX 70V FT-IR spectrometer (Bruker, Ettlingen, Baden-Württemberg, Germany). The HRESIMS measurements were performed on a Bruker Daltonics APEX II (*m*/*z*) mass spectrometer (Bruker, Karlsruhe, Baden-Württemberg, Germany). NMR analyses—including ^{1}H, ^{13}C, and 2D experiments—were carried out on a Bruker 500 MHz AVANCE NEO spectrometer (Bruker, Karlsruhe, Baden-Württemberg Germany). Silica gel (200–300 mesh, Qingdao Marine Chemical Factory, Qingdao, China) and Sephadex LH-20 (Amersham Pharmacia Biotech, Chicago, IL, USA) served as stationary phases for column chromatography (CC). Semi-preparative HPLC was conducted on a SHIMADZU LC-2030 series pump (Shimadzu, Kyoto, Japan) fitted with a photodiode array detector and an XBridge BEH C18 OBD Prep Column (5 µm, 250 × 10 mm; Waters, Milford, CT, USA). Thin-layer chromatography (TLC) employed fluorescent silica gel GF254 plates (Qingdao Marine Chemical Co., Qingdao, China), with compound visualization achieved under UV light at 254 nm or by spraying with 5% H_2SO_4 in ethanol followed by heating. X-ray diffraction data were acquired on a SuperNova, Dual, Eos diffractometer.

4.2. Plant Material

The whole plant of *Delphinium albocoeruleum* Maxim was collected in Delhi city (37°22′8.7″ N, 97°21′36.4″ E), Haixi Mongol and Tibetan Autonomous Prefecture, Qinghai Province, China, in September 2022 and identified by Professor Sheng Que from Qinghai Normal University. A voucher specimen (No. BLCQ-20220923) was stored at the Institute for the Development of Natural Medicines, Lanzhou Jiaotong University.

4.3. Extraction and Isolation

The collected roots and rhizomes of *Delphinium albocoeruleum* (10.25 kg) were dried, pulverized, and macerated with 95% ethanol (enough to submerge the plant material) three times each for 7 days. The combined ethanol extracts were concentrated under reduced pressure to yield a total crude extract (1.18 kg). Total alkaloids were obtained from the crude extract using an acid–base extraction method: the crude extract was dissolved, and the solution was adjusted to pH 3 with dilute hydrochloric acid, then extracted three times with petroleum ether (2 L each). The aqueous phase was collected, adjusted to pH 9 with sodium hydroxide, and subsequently extracted three times with dichloromethane (2 L each). The organic phases were combined and concentrated under reduced pressure to afford total alkaloids (168 g). The total alkaloids were subjected to macroporous resin column chromatography eluted with methanol–water solution (10:90 to 100:0), yielding five fractions (A–E).

Fraction D (26.42 g) was subjected to normal-phase silica gel column chromatography using a gradient elution system of dichloromethane–methanol solution (130:1 to 0:1, *v*/*v*). The collected fractions were combined based on thin-layer chromatography (TLC) analysis, yielding seven subfractions (Fr. D.1–Fr. D.7). Among these, subfractions Fr. D.3 to Fr. D.6 exhibited well-resolved spots with favorable coloration on TLC plates and were therefore selected for further separation.

Fraction Fr. D.5 (3.58 g) was subjected to column chromatography over Sephadex LH-20, eluting with pure methanol, to yield three subfractions (Fr. D.5.1–Fr. D.5.3). Fr. D.5.1 was then applied to a normal-phase silica gel column and eluted with a gradient of dichloromethane–methanol solution (from 60:1 to 10:1, *v*/*v*), affording four combined subfractions (Fr. D.5.1.1–Fr. D.5.1.4). Subfractions Fr. D.5.1.1 and Fr. D.5.1.2 underwent positive reactions with the Dragendorff reagent. These two subfractions were further separated by isocratic HPLC using a methanol–water solution (1.2:0.8, *v*/*v*) as the mobile phase, yielding compound **1** (7.3 mg).

Compound **1**, white amorphous powder, m.p. 240–242 °C, $[\alpha]_D^{27.8}$ +25.9 (*c* 1.0, MeOH); IR (KBr) νmax 3252, 2943, 2824, 2469, 2226, 1495, 1393, 1217, 1088 cm^{-1}; ^1H NMR (500 MHz, Methanol-d_4) and ^{13}C NMR data (126 MHz, Methanol-d_4), see Table 1; HRESIMS: *m*/*z* 450.3216, $[M + H]^+$ (calcd for $C_{26}H_{44}NO_5$, 450.3214).

Supplementary Materials: The following supporting information is available online. Figure S1: HR-ESI-MS spectrum for **1**; Figure S2: IR spectrum for **1**; Figure S3: ^1H NMR (500 MHz, Methanol-d_4) spectrum for **1;** Figure S4: ^{13}C NMR (126 MHz, Methanol-d_4) spectrum for **1**; Figure S5: HSQC (Methanol-d_4) spectrum for **1**; Figure S6: $^1H-^1H$ COSY (Methanol-d_4) spectrum for **1**; Figure S7: HMBC (Methanol-d_4) spectrum for **1**; Figure S8: NOESY (Methanol-d_4) spectrum for **1**.

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Data Availability Statement: The original contributions presented in this study are included in the Article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

HRESIMS	High-resolution electrospray ionization mass spectrometry
NMR	Nuclear magnetic resonance
2D	Two-dimensional
1D	One-dimensional
TLC	Thin-layer chromatography
TMS	Tetramethyl silane
DMSO	Dimethyl sulfoxide
IR	Infrared absorption

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