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Short Note

1β, 6α-Dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide

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Abstract

1β, 6α-dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide is a natural eudesmane sesquiterpene lactone isolated from the aerial parts of *Inula nervosa* Wall. In this paper, we report the X-ray crystallography of the compound **1** for the first time, along with the 1D/2D NMR spectra.

Keywords: *Inula nervosa* Wall.; sesquiterpenoid; 1β, 6α-dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide; isolation

1. Introduction

Natural products have long been a vital source for drug discovery and development, offering unique advantages for creating innovative therapeutics due to their structural diversity and remarkable biological activities [1]. Particularly, Chinese herbal medicines, widely used in traditional medical practices, represent a valuable reservoir for identifying bioactive lead compounds [2]. In this context, plants from the genus *Inula* have attracted considerable interest owing to their applications in both traditional and modern research [3]. For instance, *Inula nervosa* Wall., commonly known as "Xiǎo Hēi Yào" (Little Black Medicine) in Chinese folk medicine, particularly in regions like Yunnan, is used for a variety of purposes based on traditional experience, including wind-cold cough, phlegm-fluid retention, chest and diaphragmatic fullness, and vomiting with belching. Modern pharmacological studies further indicate that this genus exhibits promising activities, including antitumor [4], anti-inflammatory [5], and antioxidant effects [6], primarily attributed to its abundant secondary metabolites such as sesquiterpenes, diterpenes, and triterpenes. To further elucidate its pharmacologically active constituents, we conducted a systematic phytochemical investigation on *I. nervosa*, leading to the isolation of a sesquiterpene compound identified as 1β, 6α-dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide (**1**). This paper details the isolation and purification process of this compound and confirms its absolute configuration via X-ray single-crystal diffraction analysis.

2. Results and Discussion

A systematic phytochemical investigation of the ethanolic extract from the aerial parts of *Inula nervosa* led to the isolation of an eudesmane-type sesquiterpene lactone (**1**) shown in Figure 1. The structure was elucidated as 1β, 6α-dihydroxy-5αH-eudesma-3(4), 11(13)-dien-12, 8β-olide through comprehensive spectroscopic analyses, including high-resolution electrospray ionization mass spectrometry (HRESIMS), nuclear magnetic resonance (NMR)

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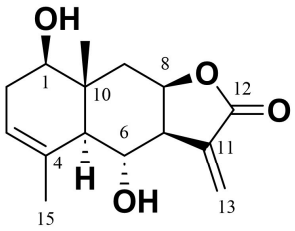
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spectroscopy, and X-ray single-crystal diffraction. Its spectral data showed high consistency with those reported for 1β, 6α-dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide [7]. The detailed process of structural elucidation will be discussed in the following section.



Inula nervosa Wall. ex DC.

Isolation



1*β*, 6*α*-dihydroxy-5*αH*-eudesma-3(4), 11(13)-dien-12, 8*β*-olide

Figure 1. Structure of 1β, 6α-dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide (**1**) isolated from *Inula nervosa* Wall.

2.1. Determination of Molecular Formula and Basic Physical Properties

Compound **1** was obtained as colorless needle-shaped crystals and was characterized as a eudesmane-type sesquiterpene. Its molecular formula was determined to be $C_{15}H_{20}O_4$ from the quasimolecular ion peak observed at *m*/*z* 265.1434 $[M + H]^+$ (calcd for $C_{15}H_{21}O_4$, 265.1434) in the HRESIMS analysis, corresponding to six degrees of unsaturation.

2.2. Structural Elucidation Based on NMR Spectroscopic Data

The ^{1}H NMR spectrum displayed an olefinic proton signal [δ_H 5.37 (1H, s, H-3)]; a terminal methylene group [δ_H 6.16 (1H, s, H-13α), 5.85 (1H, s, H-13β)]; and two methyl singlets [δ_H 0.83 (3H, s, H-14), 1.88 (3H, s, H-15)]. The ^{1}H and ^{13}C NMR spectra of compound **1** were analyzed in detail (data provided in Materials and Methods). The ^{13}C NMR spectra revealed the presence of 15 carbon signals, comprising a lactone carbonyl carbon (δ_C 172.6, C-12); two pairs of olefinic carbons [δ_C 135.6 (C-4), 123.7 (C-3); δ_C 141.7 (C-11), 122.9 (C-13)]; two oxygenated carbons [δ_C 76.4 (C-1), 71.2 (C-6)]; one oxygenated methine carbon (δ_C 79.7, C-8); along with two methyl carbons [δ_C 12.1 (C-14), 25.3 (C-15)]; two methylene carbons [δ_C 32.6 (C-2), 36.9 (C-9)]; two methine carbons [δ_C 51.1 (C-5), 51.1 (C-7)]; and one quaternary carbon [δ_C 40.0 (C-10)]. All proton and carbon signals were unambiguously assigned with the aid of HSQC, ^{1}H—^{1}H COSY, and HMBC experiments. The spectral data of compound **1** closely matched those reported for the known compound 1β, 6α-dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide [7].

2.3. Structural Confirmation by X-Ray Diffraction

The structure of compound **1** was initially deduced from spectroscopic data, while its complete relative configuration, precise molecular geometry, crystal system, and unit cell parameters were unambiguously confirmed by X-ray single-crystal diffraction analysis (Figure 2). Specifically, compound **1** crystallizes in the orthorhombic system with unit cell parameters: a = 6.9234(3) Å, b = 10.0147(4) Å, c = 20.6838(8) Å, unit cell volume V = 1434.39(9) Å^3, Z = 4, and T = 293.81(10) K; the diffraction data were collected with Cu Kα radiation (μ = 0.804 mm^{-1}), yielding 7004 measured reflections and 2714 unique reflections (R_{int} = 0.0216, R_{sigma} = 0.0217), which were used for structure calculations with final refinement parameters R1 = 0.0309 (I > 2σ(I)), wR2 = 0.0862 (all data), and Flack parameter = −0.02 (9) (data from Table S1). Its core structure consists of two fused six-membered rings (Ring A: C1-C2-C3-C4-C5-C10; Ring B: C5-C6-C7-C8-C9-C10) and one γ-lactone ring (Ring C: C7-C8-O1-C11-C12), where Ring A adopts a half-chair conformation, Ring B exhibits a chair conformation, and lactone Ring C is a nearly planar five-membered

ring. Detailed geometric parameters of compound **1**, including all bond lengths and bond angles with their corresponding estimated standard deviations (ESDs), are provided in Table S2. These parameters are consistent with the typical structural characteristics of eudesmane-type sesquiterpene lactones, further verifying the accuracy of the structure elucidation. This X-ray diffraction analysis not only validated the initially deduced structure but also established the relative configurations of all chiral centers (1β, 5α, 6α, 8β), thereby fully confirming the structure of compound **1** as depicted in Figure 2. Crystallographic data for compound **1** have been deposited at the Cambridge Crystallographic Data Centre.

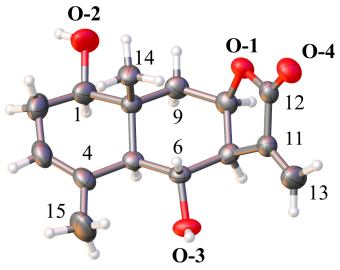


Figure 2. X-ray crystal structure of 1β, 6α-dihydroxy-5α*H*-eudesma-3(4),11(13)-dien-12, 8β-olide (CCDC: 2408916).

3. Materials and Methods

3.1. Plant Materials

The aerial parts of *I. nervosa* Wall. were collected in October 2022 from Kunming City of Yunnan province, China. The plant was authenticated by Professor Jun-Mian Tian, kept dry and ventilated. A voucher specimen (TJJ-20221011) was stored in a cool and dry environment of Shaanxi Key Laboratory of Natural Products & Chemical Biology, Northwest A&F University.

3.2. Extraction and Isolation

The dried aerial parts of *I. nervosa* Wall. (135 kg) were extracted with 95% EtOH (200 L × 2 h × 3). The combined extracts were then concentrated under reduced pressure to obtain a residual extract, which was further suspended in water and partitioned with petroleum ether, CH_2Cl_2, and ethyl acetate, successively. The EtOAc-soluble fraction (2 kg) was chromatographed on a silica gel column eluting with a CH_2Cl_2/MeOH (100: 0–1: 1 v/v) gradient to obtain fourteen fractions. After repeated column chromatography of fraction Fr. 3, subfraction Fr.3.7.1.9.5 (259.5 mg) was purified by semipreparative HPLC (CH_3CN-H_2O, 20%, 2 mL/min) to afford this natural product (5.6 mg, t_R = 33.6 min).

1β, 6α-dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide (**1**): white amorphous powder. The physicochemical properties were consistent with those reported in the literature for the same compound [7]: white amorphous powder, m.p. 155.7–158.2 °C; $[\alpha]^{20}$_D – 21.5 (c 0.1, MeOH); IR (KBr) ν_{max} 3423, 2922, 1757, 1635, 1400, 1130 cm^{-1}. The compound was soluble in common organic solvents such as methanol and dimethyl sulfoxide. ^{1}H NMR (400 MHz, CD3OD, *J*/Hz) δ 3.46 (1H, m, H-1), 2.25 (1H, m, H-2α), 1.93 (1H, m, H-2β), 5.37 (1H, s, H-3), 2.00 (1H, m, H-5), 3.46 (1H, m, H-6), 2.82 (1H, t, *J* = 7.2, H-7), 4.74 (1H, m, H-8), 2.48 (1H, dd, *J* = 15.6, 1.6, Hα-9), 1.51 (1H, dd, *J* = 16.0, 5.2, Hβ-9), 6.16 (1H, s, H-13α), 5.85 (1H, s, H-13β), 0.83 (3H, s, H-14), 1.88 (3H, s, H-15); ^{13}C NMR (100 MHz, CD3OD, J/Hz) δ 76.4 (C-1), 32.6 (C-2), 123.7 (C-3), 135.6 (C-4), 51.1 (C-5), 71.2 (C-6), 51.1 (C-7), 79.7 (C-8), 36.9 (C-9), 40.0 (C-10), 141.7 (C-11), 172.6 (C-12), 122.9 (C-13), 12.1 (C-14), 25.3 (C-15). Colorless X-ray-quality crystals of this natural product were grown by the slow cooling of a sample dissolved in methanol.

3.3. X-Ray Structure of 1β, 6α-Dihydroxy-5αH-eudesma-3(4), 11(13)-dien-12, 8β-olide (**1**)

Suitable crystals were selected and analyzed on a XtaLAB Synergy R, DW system, HyPix diffractometer (Rigaku, Tokyo, Japan). The crystal was kept at 296(4) K during data collection. Using Olex2, the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization. The crystal data are as follows: $C_{15}H_{22}O_5$ (M = 282.32 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 6.9234(3) Å, b = 10.0147(4) Å, c = 20.6873(8) Å, V = 1434.39(9) Å^3, Z = 4, T = 293.81(10) K, μ(Cu Kα) = 0.804 mm^{-1}, *Dcalc* = 1.307 g/cm^3, 7004 reflections measured ($8.548^\circ \leq 2\Theta \leq 139.74^\circ$), 2714 unique ($R_{int}$ = 0.0216, R_{sigma} = 0.0217) which were used in all calculations. The final R_1 was 0.0309 ($I > 2\sigma(I)$) and wR_2 was 0.0862 (all data). Flack parameter = −0.02 (9). Crystallographic data for compound **1** have been deposited at the Cambridge Crystallographic Data Center with the number CCDC-2408916.

4. Conclusions

This study led to the isolation of an eudesmane-type sesquiterpene lactone from the medicinal plant *Inula nervosa* Wall. Its structure was unequivocally identified as 1β, 6α-dihydroxy-5α*H*-eudesma-3(4), 11(13)-dien-12, 8β-olide through a combination of spectroscopic techniques (HRESIMS and NMR) and X-ray crystallographic analysis. The X-ray diffraction study confirmed the molecular structure and definitively established the absolute configuration of all chiral centers. The successful isolation and structural elucidation of this compound enrich the chemical database of the *Inula* genus and lay a foundation for further investigation into its biological activities.

Supplementary Materials: The following supporting information can be downloaded online: Figure S1: ^{1}H-NMR spectrum of compound **1**; Figure S2: ^{13}C DEPT spectrum of compound **1**; Figure S3: ^{1}H-^{1}H COSY spectrum of compound **1**; Figure S4: HSQC spectrum of compound **1**; Figure S5: HMBC spectrum of compound **1**; Figure S6: ^{1}H-^{1}H NOESY spectrum of compound **1**; Figure S7: ESI mass spectrum of compound **1**; Figure S8: HPLC chromatogram of compound **1**; CIF file for compound **1**; Table S1: Crystal data and structure refinement for compound **1**; Table S2: The key bond distance and bond angle of compound **1**.

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Data Availability Statement: CCDC 2408916 contains the Supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures (10 December 2024).

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

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