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Jasomontanone, a Novel Bicyclic Sesquiterpene from the Leaves of *Jasonia montana*

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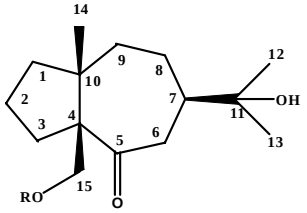
A novel rearranged eudesmane sesquiterpene with a new 5/7 membered bicyclic-ring-system, jasomontanone, was isolated from *Jasonia montana*. Its structure was determined as (3a*R**, 6*R**, 8a*R*)-3a-(hydroxymethyl)-6-(2-hydroxy-propan-2-yl)-8a-methyl-octahydrazulen-4(5*H*)-one by analysis of spectroscopic data (IR, HR-MS, ^{1}H and ^{13}C NMR), including 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC and NOESY), chemical transformation, and biogenetic consideration.

Keywords: *Jasonia montana*, Asteraceae, jasomontanone, bicyclic sesquiterpene.

Jasonia (Asteraceae) is a small genus with about five species and mainly distributed in the Mediterranean region [1]. Some species of this genus exhibit a number of biological activities such as hypoglycemic, antidiabetic [2], antiprotozoal [3], anti-inflammatory [4], antibacterial and antimicrobial [5,6]. Previous chemical studies on this genus revealed that the characteristic constituents are sesquiterpenes and sesquiterpene lactones, including highly oxygenated eudesmane alcohols [3,7-13], eudesmanoic acids [14], germacranes [15], guaianolides and pseudoguaianolides [5]. In our previous work on this genus, we isolated a rare tricyclic eudesmane sesquiterpene together with six other new sesquiterpenes [10] and two new flavonoids from the leaves of *J. candicans* [16], while the aerial parts afforded some new sesquiterpene lactones possessing antimicrobial activity [5]. In a continuation of our phytochemical study of this genus and the search for new constituents, we reinvestigated the extract of the leaves of *J. montana* and report herein the isolation and structural elucidation of jasomontanone (**1**), a novel rearranged eudesmane sesquiterpene with a new 5/7 membered bicyclic-ring-system.

The CH_2Cl_2-MeOH (1:1) extract of the leaves of *J. montana* was concentrated under reduced pressure and chromatographed successively on columns of silica gel and Sephadex LH-20, and by preparative TLC to afford jasomontanone **1**.

Jasomontanone (**1**) was isolated as a colorless gum {$[\alpha]_D25$ + 27.0^o (c 0.4, MeOH)}. The molecular formula was determined as $C_{15}H_{26}O_3$ by high resolution positive-ion CIMS, which showed a [M+H$^+$] peak at *m/z* 255.19497; calcd 255.19602. This formula was confirmed by ^{13}C NMR and DEPT spectroscopic analysis, which indicated the existence of three degrees of unsaturation. The fragmentation pattern of the mass spectrum exhibited two ion peaks at *m/z* 237 [M-18+H$^+$] (100%) and 219 [M-36+H$^+$] (95%), corresponding to loss of one and two water molecules, respectively. This indicated that two of the oxygen-containing functionalities were hydroxyl groups.



1 : R = H
1a: R = Ac

The IR spectrum supported this result by a strong absorption at ν = 3450 cm^{-1} (O-H). The remaining oxygen given by the formula was deduced to be a non-conjugated ketonic carbonyl group from the ^{13}C NMR resonance at δ 214.7 and by the IR absorption at ν = 1705 cm^{-1}. The ^{13}C NMR spectral data of compound **1** (Table 1) revealed 15 carbon atoms, while their multiplicities were assigned by DEPT 135° and 90° analysis. The carbons were assigned as three CH_3, seven CH_2, including one bearing oxygen (δ 66.5), one CH (δ 49.8), three non-protonated C, including one bearing oxygen (δ 72.7), and one C=O (δ 214.7). Taking into account the presence of this keto group (δ 214.7), with the absence of any olefinic carbon signal in the ^{13}C NMR spectrum, the remaining two degrees of unsaturation were, therefore, attributed to a bicyclic skeleton. All the above data assumed **1** to be a dihydroxy derivative of a bicyclic sesquiterpene ketone. The ^{1}H NMR spectrum of **1** (Table 1) confirmed the characteristic features for three tertiary methyl groups [δ 1.24 (s), 1.19 (s) and 1.15 (s)], an AB spin system of two protons linked to an oxygen-bearing carbon [δ 4.02 (1H, d, *J* = 11.0 Hz) and 3.57 (1H, d, *J* = 11.0 Hz)], and two aliphatic protons, most probably adjacent to a keto group [δ 2.72 (1H, dd, *J* = 11.5, 10.5 Hz) and 2.54 (1H, ddd, *J* = 11.5, 3.0, 1.3 Hz)], while the remaining signals were assigned to aliphatic methine and methylene protons (11H, δ 1.80–1.48). The assignments of all these protons in **1** and their connectivities to adjacent protons and carbons could be substantiated from the results of the 2D ^{1}H-^{1}H COSY and HMQC spectra. Careful inspection of these established the presence of two proton sequences (Figure 1).

The first sequence, A [-$C(1)H_2$-$C(2)H_2$-$C(3)H_2$-], was followed from the C-1 methylene protons (δ 1.60 and 1.52), which showed ^{1}H-^{1}H spin correlations with the C-2 methylene protons (δ 1.58), and this further exhibited vicinal couplings with the C-3 methylene protons (δ 1.80 and 2.43). The second sequence, B [-$C(6)H_2$-C(7)H(R)-$C(8)H_2$-$C(9)H_2$-], was traced from the C-6 methylene protons (δ 2.54 and 2.72), which exhibited ^{1}H-^{1}H COSY interactions with the methine proton C-7 (δ 1.61), which in turn showed vicinal couplings with the C-8 methylene protons (δ 1.48 and 1.72), and this further exhibited ^{1}H-^{1}H COSY interactions with the C-9 methylene protons (δ 1.61 and 1.51). The presence of a hydroxyisopropyl group at C-7 of the sesquiterpene skeleton was indicated by the two methyls at δ 1.19 (H-12) and 1.24 (H-13), which showed long-range HMBC correlations with their corresponding carbons, C-12 (δ 26.3) and C-13 (δ 27.9), in addition to a similar set of correlations with the neighboring carbons, δ 72.7 (C-11) and δ 49.8 (C-7). The second hydroxyl group was assumed to be a part of an angular hydroxymethylene group that was established from the characteristic AB spin system of two oxymethylene protons at δ 4.02 (1H, d, *J* = 11.0 Hz) and 3.57 (1H, d, *J* = 11.0 Hz). Furthermore, these protons showed, in the HMQC spectrum, correlations with an oxymethylene carbon at δ 66.5. The complete structure of **1** from the partial structures (A and B) and groups deduced from the spectral data was established from the HMBC experiments (Figure 1). The HMBC correlations observed between the methyl group H-14 at δ 1.15 with the carbon signals at δ 45.8 (C-1), 65.5 (C-4), 40.3 (C-9) and 43.5 (C-10) established the attachment of this methyl at C-10. Moreover, the HMBC correlations observed between the hydroxymethylene protons H-15a (δ 4.02) and H-15b (δ 3.57) with the carbons C-3 (δ 31.6), C-4 (δ 65.5), C-5 (δ 214.7) and C-10 (δ 43.5) located the hydroxyisopropyl group at C-7. From all these HMBC correlations (Figure 1), it was evident that the partial sequence A was connected to the partial sequence B through the quaternary carbons C-4 and C-10; also, the methyl group H-14 was connected to the hydroxymethylene

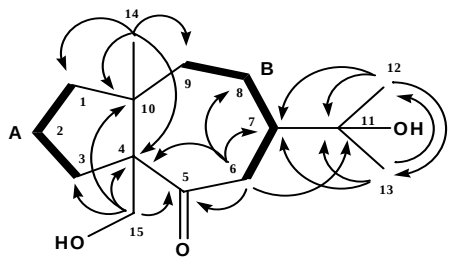


Fig.1 ^{1}H-^{1}H COSY HMBC

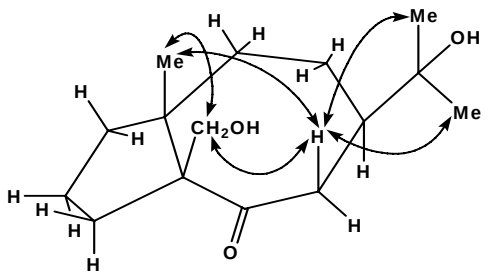
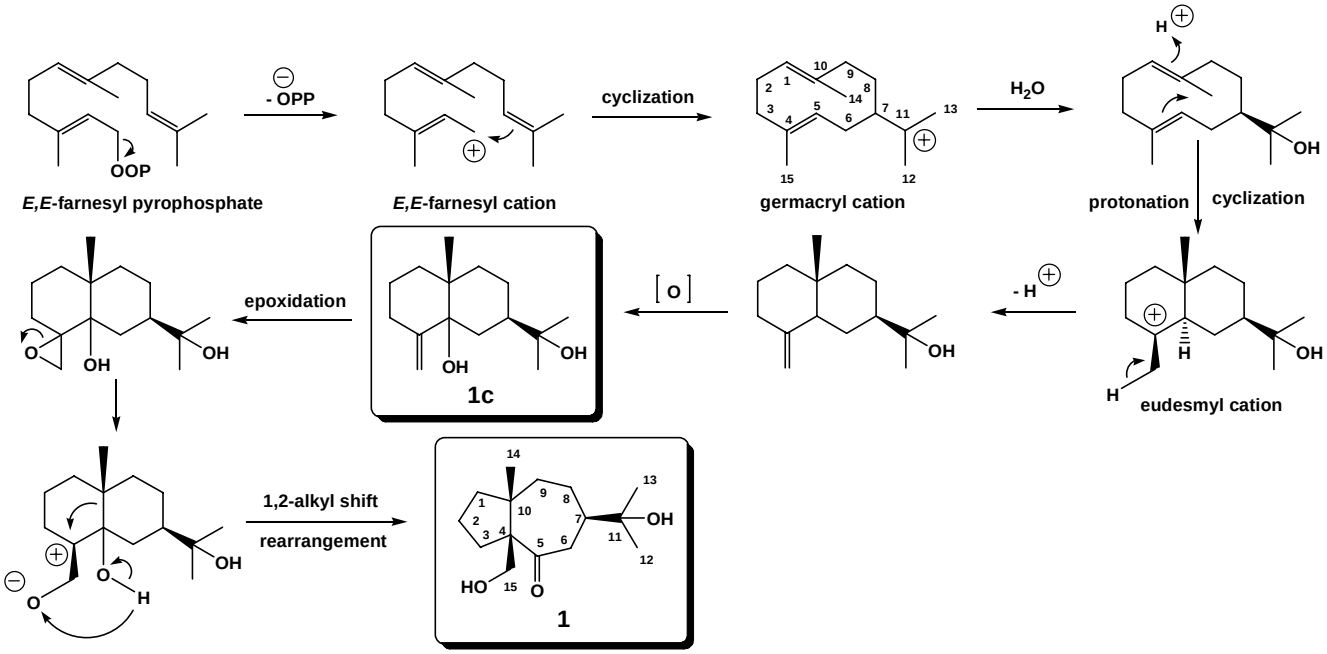


Fig. 2 NOEs oserved in 1

group CH_2-15 through the same carbons C-4 and C-10, which established the presence of a 5/7 membered bicyclic-ring-system and confirmed structure **1**. The position of the keto group (δ 214.7) was assigned to C-5 from the chemical shifts of the methylene protons H-6α and H-6β at δ 2.54 and 2.72, respectively, and from the HMBC correlations to H-3, H-6, H-7, H-15a and H-15b. The relative stereochemistry of **1** was deduced from analysis of the NOESY experiments (Figure 2), by inspection of the Dreiding model, and from biogenetic consideration. To be consistent with all the previously isolated bicyclic sesquiterpenes from the same species and genus [3, 7-14], which showed that the β-stereochemistry of CH_3-14 is characteristic for these compounds, and based on the biogenetic correlation between **1** and sesquiterpenes of this genus, we proposed the same (β) stereochemistry for the methyl group at C-10 (CH_3-14) in **1**. In this case, the strong NOEs observed between this methyl group (CH_3-14) and H-6 at δ 2.72 indicated the β-orientation of this proton. This H-6β resonated as a doublet of doublets and showed geminal coupling with H-6α (J = 11.5 Hz) and *trans* diaxial coupling with the methine proton H-7 at δ 1.61 (J = 10.5 Hz). The diaxial coupling permitted us to establish an α-stereochemistry for H-7 and consequently the β-configuration for the hydroxyisopropyl group at C-7, the same stereochemistry observed in the common sesquiterpenes of this genus [3, 7-15]. This result was further supported by the NOESY spectrum, which showed a strong NOE between H-6β and the methyl groups CH_3-12 and CH_3-13. Furthermore, the strong NOEs observed between H-6β and the angular methyl group at C-10 (CH_3-14) and H-15a of the hydroxymethylene proton at C-4; and between CH_3-14 with the methylene protons H-15a and H-15b, as well as H-6β, indicated, by inspection of the Dreiding model, that CH_3-14, -CH_2-15, CH_3-12 and CH_3-13 have the same (β) configurations. The proposed biosynthetic route of **1** (Scheme 1) agreed with the structure of **1**. Finally, acetylation of **1** gave the monoacetate derivative **1a,** which had the molecular formula $C_{17}H_{29}O_4$ ($M+H^+$), while its ^1H NMR spectral data (Experimental) confirmed the structure of **1** by the downfield shifts of H-15 and H-15' at δ 4.45 and 4.08 (each 1H, d, J = 11.0 Hz).

It is known that the common sesquiterpenes possessing a 5/7 membered bicyclic-ring-system (guaiane skeleton) are formed via a 1/5 cyclization process of the germacrane skeleton [17-19]. However, jasomontanone (**1**) was found to possess a new 5/7 membered bicyclic-ring-system. Most likely it is formed via rearrangement (1,2-alkyl shift and ketonization) of the epoxide derivative of the common eudesmane alcohol (**1c**) in this genus [3, 7-14]. The proposed biosynthetic route of **1** starting from the fundamental sesquiterpene precursor, farnesyl pyrophosphate (FPP) [17-19], is shown in Scheme 1.



Scheme 1. Proposed biosynthetic pathway of jasomontanone (**1**) from *E,E*-fernysyl PP via rearrangement of the eudesmane **1c**

Experimental

General procedure for isolation and purification of jasomontanone: *Jasonia montana* (Vahl) Botsch. was collected in May 2001, at North Sinai, Egypt. Dry leaves (600 g) were extracted with CH_2Cl_2-MeOH (1:1) at room temperature. The extract was concentrated to give a dark residue (12 g), which was chromatographed by flash chromatography on silica gel and eluted with *n*-hexane-CH_2Cl_2 (step-gradient). The CH_2Cl_2 fraction was further separated on a Sephadex LH-20 column eluted with *n*-hexane-CH_2Cl_2-MeOH, with increasing polarity. The *n*-hexane-CH_2Cl_2-MeOH (4:7:1) fraction was further purified by prep. TLC (*n*-hexane-Et_2O-MeOH) (1:3:0.25) to give **1** (15 mg).

Jasomontanone [(3a*R,6*R**,8a*R**)-3a-(hydroxyl methyl)-6-(2-hydroxypropan-2-yl)-8a-methyl-octahydrazul-en-4(5*H*)-one (1)]**

Colorless oil.
$[\alpha]_D$: + 27.0 (*c* 0.4, MeOH).
Rf = 0.6 (*n*-hexane:Et_2O:MeOH, 1:3:0.1).
IR (film, $CHCl_3$): 3450 (OH), 1705 (C=O), 970 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): 1.15 (3H, s, Me, H-14), 1.19 (3H, s, Me, H-12), 1.24 (3H, s, Me, H-13), 1.48 (1H, m, H-8α), 1.51 (1H, m, H-9β), 1.52 (1H, m, H-1β), 1.58 (2H, m, H-2α, H-2β), 1.60 (1H, m, H-1α), 1.61 (2H, m, H-7α, H-9α), 1.72 (1H, m, H-8β), 1.80 (1H, m, H-3α), 2.43 (1H, ddd, *J* = 13.0, 8.0, 4.0 Hz), 2.54 (1H, ddd, *J* = 11.5, 3.0, 1.3 Hz, H-6α), 2.72 (1H, dd, *J* = 11.5, 10.5 Hz, H-6β), 3.57 (1H, d, *J* = 11.0 Hz, H-15b), 4.02 (1H, d, *J* = 11.0 Hz, H-15a).
^{13}C NMR (125 MHz $CDCl_3$): 21.7 (CH_2, C-2), 22.2 (CH_3, C-14), 24.8 (CH_2, C-8), 26.3 (CH_3, C-12), 27.9 (CH_3, C-13), 31.6 (CH_2, C-3), 40.3 (CH_2, C-9), 40.6 (CH_2, C-6), 43.5 (C, C-10), 45.8 (CH_2, C-1), 49.8 (CH, C-7), 65.5 (C, C-4), 66.5 (CH_2, C-15), 72.7 (C, C-11).
HMBC: H-3α / C-2, C-5, C-10; H-3β / C-1, C-2, C-4, C-5, C-15; H-6α and H-6β / C-4, C-5, C-7, C-8, C-11; H-12 / C-7, C-11, C-13; H-13 / C-7, C-11, C-12; H-14 / C-1, C-4, C-5, C-10; H-15a and H-15b / C-3, C-4, C-5, C-10.
MS (CI): m/z (%) 255 [M+H^+] (15), 237 [M-H_2O+H^+] (100), 219 [M-2H_2O+H^+] (95), 207 (38), 201 (22), 191 (13).
HRMS-CI: m/z [M + H^+] calcd. for $C_{15}H_{26}O_3$ 255.19602; found: 255.19497

***Acetylation of 1*:** Compound **1** (6 mg) was refluxed in 2 ml of Ac_2O-C_5H_5N (2:1) for 6h. The mixture was worked up by standard methods to give the monoacetate **1a** (4.5 mg).

Colorless oil.
IR (film, $CHCl_3$): 3450 (OH), 1750, 1705 (2 x C=O), cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): 1.19 (6H, s, 2 Me, H-12, H-14), 1.23 (3H, s, H-13), 1.40-1.75 (11H, m), 2.00 (3H, s, 4 x OAc), 2.47 (1H, ddd, *J* = 11.0, 3.5, 1.5 Hz, H-6α), 2.64 (1H, t, *J* = 11.0, 11.5 Hz, H-6β), 4.08 (1H, d, *J* = 11.0 Hz, H-15b), 4.45 (1H, d, *J* = 11.0 Hz, H-15a).
^{13}C NMR (125 MHz $CDCl_3$): 20.8 (CH3, -OCO$\underline{CH_3}$), 22.0 (CH_2, C-2), 22.7 (CH_3, C-14), 24.8 (CH_2, C-8), 26.2 (CH3, C-12), 28.0 (CH_3, C-13), 31.7 (CH_2, C-3), 40.2 (CH_2, C-9), 40.3 (CH_2, C-6), 43.6 (C, C-10), 45.8 (CH_2, C-1), 50.1 (CH, C-7), 62.8 (C, C-4), 68.0 (CH_2, C-15), 72.6 (C, C-11), 171 (C, -O$\underline{CO}CH_3$), 212.2 (C, C-5).
HMBC: H-6α and H-6β / C-4, C-5, C-7, C-8, C-11; H-12 / C-7, C-11, C-13; H-13 / C-7, C-11, C-12; H-14 / C-1, C-4, C-5, C-10; H-15a and H-15b / C-3, C-4, C-5, C-10.
MS (Positive ion CI): m/z (%) 297 [M+H^+] (15), 279 [M-H_2O+H^+] (20), 261 (7), 207 (38), 237 (15), 219 (18)
HRMS-CI: m/z [M + H^+] calcd. for $C_{17}H_{29}O_4$ 297.20658; found: 297.20549.

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