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Sesquiterpenoids from *Lactuca tatarica*

Xiao-Xiong Wang [a], Xue Gao [b,*], Zhong-Jian Jia [a,*]

[a] State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, PR China
[b] Research Center of Medical Chemistry & Chemical Biology, Chongqing Technology and Business University, Chongqing 400067, PR China

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ABSTRACT

A new guaianolide and a new eudesmanolide were isolated from *Lactuca tatarica*, as well as eight known sesquiterpenoids. The new compounds were elucidated on the basis of spectroscopic methods including IR, HRESIMS, 1D and 2D NMR, and the known compounds were established by comparing their physical data with those of the corresponding compounds in the literature.

1. Introduction

Lactuca tatarica (L.) C. A. Mey (Asteraceae) is a perennial herb mainly distributed in northeast, northwest and southwest of China, Europe, Mongolia, Iran, Afghanistan, and northwest of India. Its whole herb has been used as a folk remedy for the treatment of appendicitis, erysipelas, extravasated blood, abdominal distension and red leucorrhea properties in China [1]. Previous research on *L. tatarica* has resulted in the isolation of several guaianolides and germacrolides [2,3]. In our previous chemical investigations of this plant, triterpenoids and sesquiterpene lactones were the major chemicals. Furthermore, lanostane-type triterpenoids exhibited antibacterial activity and the guaiane-type sesquiterpenoids exhibited significant cytotoxic activity [4]. In the course of our continuing search for naturally occurring sesquiterpenoids from *L. tatarica*, a new guaianolide and a new eudesmanolide together with eight known sesquiterpene lactones were found. In this paper, we report the isolation and identification of these sesquiterpene lactones.

2. Experimental

2.1. General

Optical rotations were obtained on a Perkin-Elmer 341 Polarimeter. Melting point was measured on a Kofler apparatus and was uncorrected. IR spectra were taken on a Nicolet 170SX FT-IR instrument. EIMS and HRESIMS were measured on HP 5988A GC/MS instrument and Bruker APEX II. NMR spectra were recorded with a Varian Mercury-400BB NMR spectrometer. Silica gel 200–300 mesh for column chromatography and silica GF_{254} for TLC were supplied by the Qingdao Marine Chemical Inc., China.

2.2. Plant material

The whole plant of *L. tatarica* was collected in August 2004, in Zhuanglang County, Gansu Province, PR China, and identified by Prof. GuoLiang Zhang, School of Life Science, Lanzhou University. A voucher specimen (No. 20040815) was deposited in the College of Chemistry and Chemical Engineering, Lanzhou University.

2.3. Extraction and isolation

The air-dried whole plant of *L. tatarica* (9.0 kg) was pulverized and extracted at room temperature with MeOH

* Corresponding authors.
E-mail addresses: gaoxue@ctbu.edu.cn (X. Gao), jiazj@lzu.edu.cn (Z.-J. Jia).

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three times (seven days each time). The extract was concentrated under reduced pressure and the residue (930 g) was suspended in hot water (1.8 L). This suspension was successively extracted with petroleum ether (60–90 °C) (1.8 L), EtOAc (1.8 L) and *n*-BuOH (1.8 L). The EtOAc soluble fraction (110 g) was chromatographed on silica gel column (200–300 mesh, 1000 g) eluting with $CHCl_3$–acetone (30:1, 15:1, 7:1, 4:1, 2:1, and 1:1), six crude fractions [Fr.1 (30:1), Fr.2 (15:1), Fr.3 (7:1), Fr.4 (4:1), Fr.5 (2:1) and Fr.6 (1:1)] were obtained on the basis of TLC. Fr.1 (5.5 g) was subjected to repeated silica gel column chromatography (200–300 mesh, 55 g) eluted with $CHCl_3$–EtOAc (10:1) to give compound 8 (2 mg). Fr.3 (1.5 g) was subjected to a silica gel column chromatography (200–300 mesh, 15 g) eluted with $CHCl_3$–CH_3OH (30:1) to give 4 fractions: Fr.3-1–Fr.3-4. Fr.3-1 was chromatographed on silica gel and eluted with $CHCl_3$–CH_3OH (10 : 1) to obtain pure compound 9 (6 mg) and 10 (10 mg). Fr.3-2 (500 mg) was further purified by a preparative TLC with petroleum ether–$CHCl_3$–CH_3OH (5:5:1) to afford compound 2 (4 mg, $R_f = 0.31$). Fr.3-3 (400 mg) was futher purified by preparative TLC with petroleum ether–EtOAc–CH_3OH (1:1:1) to afford compound 6 (10 mg, $R_f = 0.20$). Fr.4 was chromatographed on silica gel and eluted with $CHCl_3$–CH_3OH (7:1) to obtain pure 5 (30 mg).

The *n*-BuOH soluble fraction (90 g) was chromatographed on silica gel column (200–300 mesh, 600 g) eluting with $CHCl_3$–CH_3OH (30:1, 15:1, 7:1, 4:1, 2:1, and 1:1), six crude fractions [Fr.1 (30:1), Fr.2 (15:1), Fr.3 (7:1), Fr.4 (4:1), Fr.5 (2:1) and Fr.6 (1:1)] were obtained on the basis of TLC. Fr.1 (eluted with $CHCl_3$–CH_3OH 10:1; 6.8 g) was purified by repeated silica gel column (68 g): to afford compound 4 (1.2 g) and 3 (1.0 g). Fr.2 (8.1 g) was subjected to a silica gel column chromatography (200–300 mesh, 60 g) eluted with $CHCl_3$–CH_3OH (30:1–5:1) to give 3 fractions: Fr.2-1–Fr.2-3. Fr.2-1 was further purified by the preparative TLC with $CHCl_3$–CH_3OH (20:1) to afford compound 1 (4 mg, $R_f = 0.25$). Compound 7 (600 mg) was recrystallized from Fr.3 in acetone.

11β-hydroxy-11, 13-dihydrolactucin (1), yellow oil; $[\alpha]^{20}{}_D +$ 19 (*c* 0.7, CH_3COCH_3); IR (KBr): 3361, 1775, 1681, 1636 cm^{-1}; ^1H and ^{13}C NMR data: see Table 1; HRESIMS: *m/z* 295.1178 ($C_{15}H_{19}O_6$, calc. 295.1176); EIMS *m/z*: 295 $[M+H]^+$ (3), 206 (2), 188 (3), 159 (6), 91 (18), 77 (16), and 43 (100).

2β-hydroxy-11β, 13-dihydrodouglanin (2), colorless oil; $[\alpha]^{20}{}_D + 63$ (*c* 0.5, CH_3COCH_3); IR (KBr): 3384, 1773, 1654 cm^{-1}; ^1H and ^{13}C NMR data: see Table 1; HRESIMS: *m/z* 289.1412 ($C_{15}H_{22}O_4Na$, calc. 289.1410); EIMS *m/z*: 266 $[M]^+$ (7), 251 (20), 223 (22), 165 (14), 121 (55), 105 (60), 95 (79), 77 (58), 55 (76), and 43 (100).

3. Results and discussion

Compound 1 was obtained as yellow oil, $[\alpha]^{20}{}_D + 19$ (*c* 0.7, CH_3COCH_3). The molecular formula was assigned as $C_{15}H_{18}O_6$ on the basis of ion peak $[M+H]^+$ at *m/z* 295.1178 (calc. 295.1176 for $C_{15}H_{19}O_6$) in its HRESIMS. The IR spectrum showed the presence of hydroxyl (3361 cm^{-1}), γ-lactone (1775 cm^{-1}) and double bond (1636, 1681 cm^{-1}) absorptions. The ^1H NMR spectrum (Table 1) of 1 showed characteristic signals of one olefinic proton at δ_H 6.35 (brs), one oxygenated methylene at δ_H 4.32, 4.80 (each brd, $J = 18.4$ Hz), two oxygenated methines at δ_H 3.94 (m), δ_H 3.90 (*t*, $J =$ 10.1 Hz), and two singlet methyls. Its ^{13}C NMR (DEPT) spectra gave resonances of an α, β-unsaturated ketone at δ_C 194.6 (C), 132.4 (CH) and 174.5 (C), one ester carbonyl at δ_C 176.5 (C), one tetrasubstituted olefin at δ_C 132.6 (C) and 146.7 (C) and four oxygenated carbons at δ_C 74.2 (C), 80.5 (CH), 64.4 (CH) and 62.1 (CH_2). All of these proposed that 1 was a guaianolide with three hydroxyl groups, two double bonds and a ketone similar to that of 11β, 13-dihydrolactucin (4) [5], except that one more hydroxyl group was present in 1. This hydroxyl group has to be located in position C-11 for the singlet methyl in C-13 (δ_H 1.57). The coupling constants $J_{5,6} = J_{6,7} = J_{7,8} =$ 10.1 Hz indicated that these protons were all *trans*-diaxial direction configuration, H-7 and H-5 were in α-orientation, whereas H-6 and H-8 were in β-orientation [5]. In a NOE difference experiment, irradiation at H-13 produced positive NOE effects on H-7 (3.4%), hence H-13 was α-orientated. So, the structure of compound 1 was confirmed as 11β-hydroxy-11, 13-dihydrolactucin (Fig. 1.

Compound 2 was obtained as colorless oil, $[\alpha]^{20}{}_D + 63$ (*c* 0.5, CH_3COCH_3). Its molecular formula was determined as $C_{15}H_{22}O_4$ by HRESIMS, giving a molecular ion peak $[M+Na]^+$ at *m/z* 289.1412 (calc. 289.1410). The IR spectrum showed hydroxyl (3384 cm^{-1}), γ-lactone (1773 cm^{-1}) and double bond

Table 1
^1H and ^{13}C NMR data for compounds 1 and 2 (400 and 100 MHz, $CDCl_3$, *J* in Hz, δ in ppm, TMS as internal standard).

No	1		2	
	δ_C	δ_H	δ_C	δ_H
1	132.6 (C)	–	72.5 (CH)	3.95 (brd, 4.4 Hz, 1H)
2	194.6 (C)	–	80.2 (CH)	3.35 (brd, 4.4 Hz, 1H)
3	132.4 (CH)	6.35 (brs, 1H)	126.1 (CH)	5.36 (brs, 1H)
4	174.5 (C)	–	135.3 (C)	–
5	48.3 (CH)	3.59 (d, 10.1 Hz)	51.0 (CH)	2.28 (d, 11.6 Hz,1H)
6	80.5 (CH)	3.90 (dd, 10.1, 10.1 Hz, 1H)	81.6 (CH)	4.04 (dd, 11.6, 9.6 Hz, 1H)
7	62.9 (CH)	2.23 (dd, 10.1, 10.1 Hz, 1H)	53.7 (CH)	1.62 (m, 1H)
8	64.4 (CH)	3.94 (m, 1H)	22.1 (CH_2)	1.60, 1.38 (m, 2H)
9	48.5 (CH_2)	2.37, 2.81 (m, 2H)	34.8 (CH_2)	2.01, 1.31 (m, 2H)
10	146.7 (C)	–	43.0 (C)	–
11	74.2 (C)	–	40.1 (CH)	2.38 (m, 1H)
12	176.5 (C)	–	178.6 (C)	–
13	22.9 (CH_3)	1.57 (s, 3H)	11.9 (CH_3)	1.12 (d, 7.2 Hz,3H)
14	20.5 (CH_3)	2.36 (s, 3H)	11.5 (CH_3)	0.92 (s, 3H)
15	62.1 (CH_2)	4.32, 4.80 (brd, 18.4 Hz, 2H)	22.6 (CH_3)	1.78 (brs, 3H)

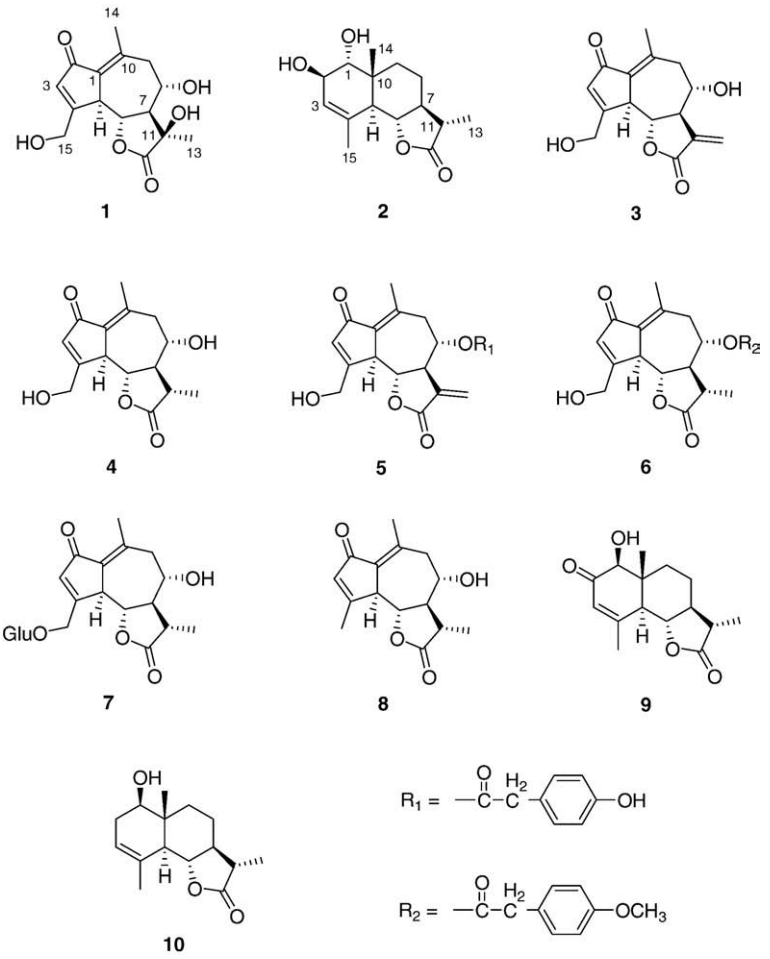

Fig. 1. Structures of compounds 1–10.

(1654 cm^{-1}) absorptions. The NMR spectra (Table 1) of 2 displayed the signals of the three methyls, a vinyl one [δ_H 1.78 (brs), δ_C 22.6], a secondary one [δ_H 1.12 (d, J = 7.2 Hz), δ_C 11.9] and a tertiary one [δ_H 0.92 (s), δ_C 11.5], three oxygenated methines [δ_H 4.04 (dd, J = 11.6, 9.6 Hz), 3.95 (brd, J = 4.4 Hz) and 3.35 (brd, J = 4.4 Hz), δ_C 81.6, 80.2 and 72.5], a trisubstituted olefin [δ_H 5.36 (brs), δ_C 126.1 (CH), 135.3 (C)], and a quaternary carbon [δ_C 43.0]. Above information suggested that compound 2 possessed the eudesmanolide skeleton, just similar to 11β, 13-dihydrodouglanin acetate [6], but the acetyl group was absent, and two hydroxyl groups were present. Linkage of the other hydroxyl with 11β, 13dihydrodouglanin were confirmed by the unit of CH(1)CH(2)CH(3) obtained from ^{1}H–^{1}H COSY results. Stereochemically, $J_{5,6}$ = 11.6 Hz and $J_{6,7}$ = 9.6 indicated that H-7 and H-5 were in α-orientation, whereas H-6 was in β-orientation. Irradiation of H-6 produced NOE enhancement of the H-11 (26.3%) and Me-14 (3.7%) resonance, this suggested that H-11 and Me-14 were both in β-orientation. In the three-dimensional model the protons H-5,-6,-7 and Me-14 should show an axial position. If H-1 was also in an axial position, then irradiation of H-1 could not produce NOE enhancement of the Me-14, but when irradiation of H-1 produced NOE enhancement of the Me-14 (3.6%) resonance, hence H-1 was equatorial oriented. No NOE effect observed between H-1 and H-2 by our NOE experiment, and $J_{1,2}$ (4.4 Hz) resulted in α-orientation of H-2. Thus, the structure of compound 2 was confirmed as 2β-hydroxy-11β, 13-dihydrodouglanin.

The eight known compounds were identified as lactucin (3) [5], 11β, 13-dihydrolactucin (4) [5], lactucopicrin (5) [7], 11β,13-dihydrolactucin-8-*O*-*p*-methoxyphenylacetate (6) [2], cichorioside B (7) [8], deacetylmatricarin (8) [9], 2-oxo-11β, 13-dihydrosantamarin (9) [10], 11β,13-dihydrosantamarin (10) [6] by comparing their physical data (mp., MS, IR, ^{1}H and ^{13}C NMR) with those reported in the literature.

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