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裸花紫珠叶中两个新的半日花烷型二萜

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摘要 从裸花紫珠叶子中分离纯化得到 2 个新的半日花烷型二萜化合物 3-氧代-7-羟基-半日花烷-8(17),13*E*-烯-15-酸(**1**)、3-氧代-8-羟基-半日花烷-13*E*-烯-15-酸(**2**)及 5 个已知的萜类化合物, 其结构通过核磁共振(NMR)、高分辨电喷雾电离质谱(HRESIMS)等多种现代波谱技术进行确定, 化合物 **1** 的绝对构型通过单晶衍射确定. 评价了所有化合物对脂多糖(LPS)诱导小鼠巨噬细胞 RAW 264.7 产生一氧化氮(NO)的抑制作用, 结果显示新化合物 **1** 和 **2** 表现出较好的抗炎活性, 其 IC_{50} 值分别为(10.3±0.3)和(12.7±0.4) μmol/L.

关键词 裸花紫珠; 半日花烷型二萜; 倍半萜; 抗炎

Two New Labdane Diterpenoids from the Leaves of *Callicarpa nudiflora*

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Abstract Two new labdane diterpenoids 3-oxo-7-hydroxy-8(17),13*E*-labdadien-15-oic acid (**1**), 3-oxo-8-hydroxy-13*E*-labden-15-oic acid (**2**), and five known terpenoids were obtained from the leaves of *Callicarpa nudiflora* during a systematic phytochemical investigation. The structures were elucidated using comprehensive spectroscopic methods [nuclear magnetic resonance spectroscopy (NMR) and high resolution electrospray ionization mass spectroscopy (HR-ESI-MS)], and the absolute configuration of **1** was established based on single-crystal X-ray diffraction. The inhibitory activity of all the compounds on NO production in lipopolysaccharide-induced (LPS) mouse leukemia cells of monocyte macrophage (RAW 264.7) cells was evaluated. Compounds **1** and **2** showed potential anti-inflammatory activity with IC_{50} values of (10.3±0.3) and (12.7±0.4) μmol/L, respectively.

Keywords *C. nudiflora*; labdane diterpenes; sesquiterpenes; anti-inflammatory

1 Introduction

Callicarpa (Verbenaceae) is a member of a genus with approximately 190 species distributed mainly in tropical and subtropical Asia and Oceanica.[1] *C. nudiflora* Hook et Arn., belonging to *Callicarpa* spp., is a small shrub widely distributed from southern China to Malaysia. *C. nudiflora* is a famous-region drug of Hainan province with a unique position in the treatment of respiratory diseases, it is the only new medicinal decoction pieces in the Chinese Phar-

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macopoeia 2020. *C. nudiflora* as Chinese folk medicine has a long history, its leaves have been used as a famous Li nationality medicine in treating respiratory tract hepatitis, infections, and bleeding in China's Hainan Province.[2]

Previous chemical constituent studies on this plant, led to the isolation of labdane diterpenoids, flavonoids and lignans, some of them showed anti-inflammatory, antibacterial or cytotoxic activities.[3-5] In search for bioactive, and structurally diverse natural products from the Li nationality medicine, two new labdane diterpenoids 3-oxo-7-hydroxy-8(17),13*E*-labdadien-15-oic acid (**1**), 3-oxo-8-hydroxy-13*E*-labden-15-oic acid (**2**) and five known terpenoids were obtained from *C. nudiflora* (Figure 1). Herein, the structure elucidation, and the anti-inflammatory activities of these compounds are reported.

2 Results and discussion

Compound **1** was obtained as colorless crystals. Its molecular formula was defined as $C_{20}H_{30}O_4$ from its high resolution electrospray ionization mass spectroscopy (HR-ESI-MS) ion at *m*/*z* 357.2032 $[M+Na]^+$ (calcd for $C_{20}H_{30}O_4Na$, 357.2036). The ^1H NMR data of **1** (Table 1) contained a deshielded proton at δ_H 5.67 (s, 1H, H-14), an exocyclic double bond at δ_H [4.74 (br s, 1H, H-17α), 5.15 (br s, 1H, H-17β)], three methines at δ_H 2.16 (dd, J=12.8, 3.2 Hz, 1H, H-5), 2.25 (br d, J=11.2 Hz, 1H, H-9), and 4.37 (t, J=2.8 Hz, 1H, H-7), five methylenes at δ_H [1.61～1.64 (m, 1H, H-1α), 2.05～2.11 (m, 1H, H-1β), 2.35～2.42 (m, 1H, H-2α), 2.64～2.73 (m, 1H, H-2β), 1.70～1.75 (m, 1H, overlap, H-6α), 1.77～1.82 (m, 1H, H-6β), 1.61～1.64 (m, 1H, overlap, H-11α), 1.70～1.75 (m, 1H, H-11β), 1.97～2.02 (m, 1H, H-12α), 2.28～2.34 (m, 1H, H-12β), and four high-field methyl groups at δ_H 0.88 (s, 3H, H-20), 1.02 (s, 3H, H-18), 1.07 (s, 3H, H-19), and 2.12 (s, 3H, H-16). The ^{13}C NMR and distortionless enhancement by polarization transfer (DEPT) data of **1** (Table 1) showed 20 carbon resonances, including an α,β-unsaturated carboxylic acid, a ketone group, an exocyclic double bond, and 14 sp^3 carbon atoms (two quaternary carbons, three CH, five CH_2, and four CH_3). The 1D NMR data indicated that **1** was a labdane diterpenoid, and the structure of **1** was similar to that of 3-oxoanticopalic acid from the *Pinus strobus*[6-7], except for the presence of a hydroxyl group in **1**. The attachment of the hydroxyl at C-7 (δ_C 74.2) was supported by the ^1H-^1H COSY correlations of H-5/H-6/H-7 (Figure 2), as well as the heteronuclear multiple bond connectivity (HMBC) correlations (Figure 2) from H_2-6 to C-5, C-7, and C-8, from H_2-17 to C-7, C-8, and C-9, and from H-7 to C-6, C-8 and C-17. Thus, the planar structure of **1** was defined as 7-hydroxy-3-oxoanticopalic acid.

The relative configuration of **1** was assigned by the nuclear over Hauser effect spectroscopy (NOESY) experiment (Figure 3). The NOESY correlations of Me-20 with H-7, H-11 and Me-18 indicated that these protons and methyl groups were cofacial, and they were assigned to be β-oriented, while H-5/H-9 and Me-19 were α-oriented. The *E*-configuration of the $\Delta^{13(14)}$ double bond was defined by the NOESY correlations of H_2-12/H-14. The absolute configuration of **1** was defined as (5*R*,7*R*,9*R*,10*R*) by the X-ray diffraction analysis with a Flack parameter of −0.03(7) (CCDC No.2220395) (Figure 4). Therefore, the structure of **1** was defined as 3-oxo-7-hydroxy-8(17),13*E*-labdadien-15-oic acid.

Compound **2** was obtained as a colorless oil with the molecular formula $C_{20}H_{32}O_4$, as established by HR-ESI-MS data. The ^1H NMR data (Table 1) displayed an olefinic proton at δ_H 5.70 (s, 1H, H-14), two methine signals at δ_H 2.16 (dd, J=12.8, 8.8 Hz, 1H, H-5) and 1.21 (br d, J=4.0 Hz, 1H, H-9), and five high-field signals at δ_H 1.00 (s, 3H, H-20), 1.03 (s, 3H, H-18), 1.09 (s, 3H, H-19), 1.20 (s, 3H, H-17), and 2.13 (s, 3H, H-16) indicating the presence of five methyl groups. The 20 carbon resonances (Table 1) were classified as two carbonyl groups, a trisubstituted olefinic bond, three quaternary carbons, two methines, six methylene and five methyl groups by the ^{13}C NMR and DEPT NMR spectra. Analyses of the ^1H NMR and ^{13}C NMR data suggested that **2** was also a labdane diterpenoid. The 1D NMR data of **2** were similar to those of 3-oxoanticopalic acid,[6-7] the major differences in the ^1H NMR and ^{13}C NMR spectroscopic data were the absence of an exocyclic double bond signals at δ_H [4.59 (br s, 1H, H-17α), 4.93 (br s, 1H, H-17β)] and δ_C 106.4 and 148.4 in 3-oxo-

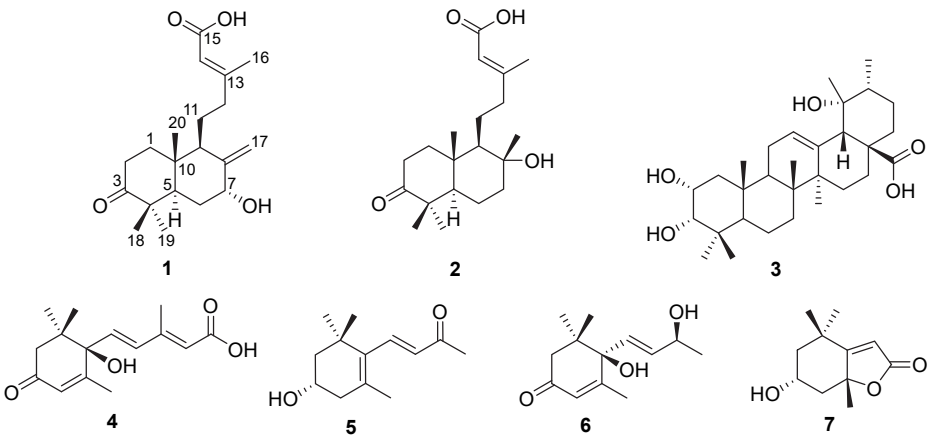

Figure 1 Chemical structures of compounds **1**～**7**

Table 1 ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data for compounds **1** and **2** in MeOD-d_4[a]

No.	Compound **1**		Compound **2**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	1.61～164, m, overlap 2.05～2.11, m	38.5 (CH_2)	1.53～1.62, m 1.92～2.02, m	39.5 (CH_2)
2	2.35～2.42, m 2.64～2.73, m	35.6 (CH_2)	2.37～2.42, m, overlap 2.66～2.72, m	34.9 (CH_2)
3		219.6 (C)		219.6 (C)
4		48.5 (C)		48.5 (C)
5	2.16, dd (12.8, 3.2)	48.6 (CH)	2.16, dd (12.8, 8.8)	56.3 (CH)
6	1.70～1.75, m, overlap 1.77～1.82, m	32.7 (CH_2)	1.47～1.56, m, overlap 1.58～1.66, m	22.3 (CH_2)
7	4.37, t (2.8)	74.2 (CH)	1.47～1.56, m, overlap 1.85～1.91, m	44.3 (CH_2)
8		150.1 (C)		74.5 (C)
9	2.25, br d (11.2)	50.4 (CH)	1.21, br d (4.0)	61.4 (CH)
10		40.4 (C)		39.9 (C)
11	1.61～164, m, overlap 1.70～1.75, m, overlap	22.9 (CH_2)	1.43～1.48, m 1.66～1.75, m	25.2 (CH_2)
12	1.97～2.02, m 2.28～2.34, m	40.2 (CH_2)	2.17, dd (12.8, 4.8) 2.35～2.41, m, overlap	45.1 (CH_2)
13		159.4 (C)		160.0 (C)
14	5.67, s	118.2 (CH)	5.70, s	118.8 (CH)
15		171.5 (C)		171.7 (C)
16	2.12, s	18.9 (CH_3)	2.13, s	19.0 (CH_3)
17	4.74, br s 5.15, br s	110.5 (CH_2)	1.20, s	23.5 (CH_3)
18	1.02, s	22.9 (CH_3)	1.03, s	21.8 (CH_3)
19	1.07, s	26.2 (CH_3)	1.09, s	26.7 (CH_3)
20	0.88, s	13.5 (CH_3)	1.00, s	15.4 (CH_3)

[a] All the compounds were evaluated for their anti-inflammatory activities by inhibiting the lipopolysaccharide (LPS)-induced nitric oxide (NO) release in RAW264.7 cells (Table 2). Compounds **1** and **2** displayed potential anti-inflammatory activity with IC_{50} values of (10.3±0.3) and (12.7±0.4) μmol/L, respectively, which were slightly stronger than the positive control of indometacin [IC_{50}=(19.2±0.4) μmol/L].

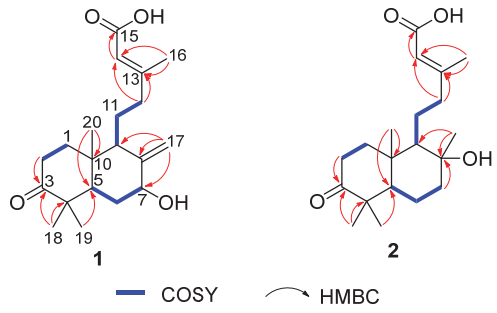

Figure 2 Key HMBC and ^{1}H-^{1}H COSY correlations of compounds **1** and **2**

anticopalic acid, and the presence of a methyl signal at δ_H 1.20 (3H, s)/δ_C 23.5, and an oxygenated quaternary carbon at δ_C 74.5 in **2**, indicating that the exocyclic double bond in 3-oxoanticopalic acid was hydrated in **2**. The HMBC (Figure 2) correlations of H_2-7/C-8 and C-17, and Me-17/C-8, C-9, and C-10, supported the attachment of the methyl and hydroxy groups to C-8. The NOESY correlations of Me-20 with H-11, Me-17 and Me-18, indicated that these protons and methyl groups were cofacial, and they were assigned to be β-oriented, while H-5/H-9 and Me-19 were α-orien-

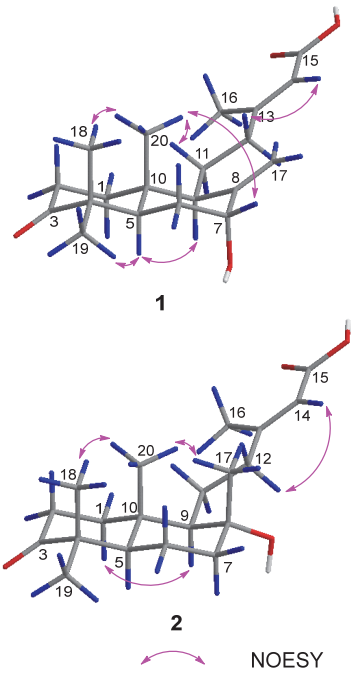

Figure 3 NOSEY correlations of compounds **1** and **2**

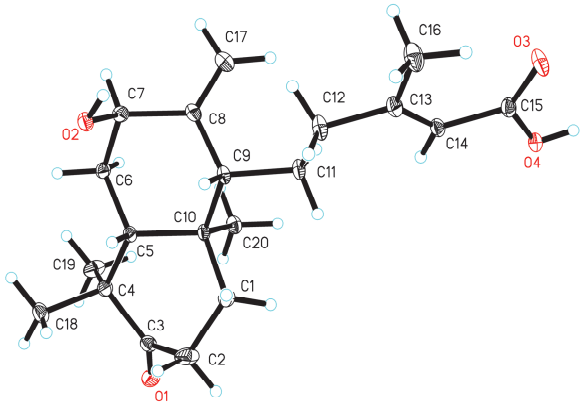

Figure 4 Single-crystal X-ray ORTEP (Oak Ridge thermal ellipsoid plot) drawing of **1**

Table 2 Inhibitory activity of compounds **1**～**7** on NO production in RAW264.7 cells induced by LPS ($\bar{x}\pm s$, $n=3$)

Compd.	IC_{50}/(μmol•L^{-1})
1	10.3±0.3
2	12.7±0.4
3	17.2±0.6
4	21.3±0.5
5	13.7±0.4
6	22.2±0.2
7	29.1±0.3
Indomethacin	19.2±0.4

ted. The absolute configuration of **2** is 5*R*,8*R*,9*R*,10*S* based on the similar specific rotation $[\alpha]_D^{25}$ +22.3 (*c* 0.20, MeOH)] as **1** $[\alpha]_D^{25}$ +17.7 (*c* 0.20, MeOH)] and the biosynthesis pathway. Hence, the structure of **2** was defined as 3-oxo-8-hydroxy-13*E*-labden-15-oic acid.

The known compounds isolated were identified as euscaphic acid (**3**),[8] (2-*trans*,4-*trans*)-abscisic acid (**4**),[9] (*S*)-3-hydroxy-*β*-ionone (**5**),[10] blumenol A (**6**),[11] and (−)-loliolide (**7**)[12] by comparing their spectroscopic data with the reported ones.

3 Conclusions

Two new labdane diterpenoids (**1** and **2**) and five known terpenoids (**3**～**7**) were obtained from the *C. nudiflora* during a systematic phytochemical investigation. The anti-inflammatory activity of RAW 264.7 cells with lipopolysaccharide-induced was evaluated. All the compounds showed potential anti-inflammatory activities with IC_{50} values ranged from 10.3 to 29.1 μmol/L.

4 Experimental section

4.1 General experimental procedures

1D NMR and 2D NMR spectra were obtained with a Bruker AV 400 NMR spectrometer using MeOD-d_4 as a solvent. X-ray crystallographic data were collected at 100 K on a Rigaku Oxford Diffraction Supernova Dual Source with Cu Kα radiation. HR-ESI-MS spectra were performed on an Agilent 6210 ESI/TOF mass spectrometer. Preparative HPLC was performed on an analytic LC equipped with a pump of P230, a DAD detector at 210 and 254 nm wavelengths, and a Waters XBridge C_{18} (250 mm×10 mm, 5 μm) semi-preparative column. C_{18} ODS-A (50 μm, YMC, Japan) and 200～300 mesh silica gel (Qingdao Marine Chemical Plant, Qingdao, China) were used for column chromatography.

4.2 Plant materials

The plants of *Callicarpa nudiflora* Hook. & Arn. were collected from Wu-Zhi-shan Nature Reserve (GPS: 18°68'N; 109°19'E), Hainan Island, China, in October 2018. A voucher specimen (No. HAN20181022) was deposited at the Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, Hainan Normal University.

4.3 Extraction and isolation

The air-dried leaves of the *C. nudiflora* (1.2 kg) were extracted with 75% EtOH (20 L×3, each for 5 d) at room temperature. The solvent was combined and condensed in vacuum to yield a crude extract (210 g). The extract was separated using a silica gel CC (PE/EtOAc and $CHCl_3$/MeOH, V∶V=100∶1 to 1∶100) to generate eight fractions (Frs.1～Frs.8). Fr.3 (14.6 g) was subjected by silica gel CC eluted with PE/acetone (V∶V=20∶1 to 1∶100) to afford five subfractions 3A～3E. Subfraction 3A (3.6 g) was subjected to CC on silica gel using PE/EtOAc (V∶V=10∶1 to 1∶10) and further purified by semi-preparative HPLC using Waters XBridge C_{18} (250 mm×10 mm, 5 μmoL•L^{-1}) with an isocratic solvent system of 48% acetonitrile-water with 0.1% formic acid at a flow rate of 2.0 mL•min^{-1} to afford **5** (4.2 mg, retention time=21.5 min), **6** (6.1 mg, retention time=18.5 min) and **7** (10.2 mg, retention time=26 min). Subfraction 3B (4.7 g) was successively separated by silica gel using CH_2Cl_2/MeOH (V∶V=100∶1 to 1∶100), ODS eluted with MeOH/H_2O (V∶V=1∶100 to 100∶1), to afford four subfractions 3B-1～3B-4. Subfraction 3B-1 was purified by semi-preparative HPLC (Waters XBridge C_{18} 250 mm×10 mm, 5 μm) with 45% acetonitrile-water with 0.1% formic acid at a flow rate of 2.0 mL•min^{-1} to yield **1** (4.3 mg, retention time=17 min) and **2** (3.2 mg, retention time=18 min). Subfraction 3B-2 was also purified by semi-preparative HPLC (Waters XBridge C_{18} 250 mm×10 mm, 5 μm) with 40% acetonitrile-water with 0.1% formic acid at a flow rate of 2.0 mL•min^{-1} to yield **3** (4.6 mg, retention time=16 min) and **4** (2.8 mg, retention time=22 min).

3-Oxo-7-hydroxy-8(17),13*E*-labdadien-15-oic acid (**1**): Colorless crystal. $[\alpha]_D^{25}$ +22.3 (*c* 0.20, MeOH); UV (MeOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 202 (13.2) nm; ^{1}H NMR (400 MHz, MeOD) and ^{13}C NMR (100 MHz, MeOD) data see Table 1. HRESIMS calcd for $C_{20}H_{30}O_4Na$ $[M+Na]^+$ 357.2036, found 357.2032.

X-ray crystallographic analysis of **1**: Crystal data were collected on a Rigaku Oxford Diffraction Supernova Dual

Source X-ray single-crystal diffractometer with Cu Kα radiation (λ=0.154184 nm) at 100 K: $C_{20}H_{30}O_4$ (M_r= 334.44): monoclinic, space group $P2_1$ (No. 4), a = 1.18401(2) nm, b=0.860826(12) nm, c=1.88775(4) nm, β = 102.0928(17)°, V = 1.88136(6) nm^3, Z = 4, T = 100.00(10) K, μ(Cu Kα) = 0.645 mm^{-1}, D_{calc} = 1.181 g/cm^3, 14540 reflections measured (4.788° ≤ 2θ ≤ 147.164°), 6668 unique (R_{int} = 0.0240, R_{sigma} = 0.0299) which were used in all calculations. The final R_1 was 0.0324 [$I>2\sigma(I)$] and wR_2 was 0.0841 (all data). Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Center and allocated with the deposition number: CCDC 2220395. The data can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/deposit.

3-Oxo-8-hydroxy-13*E*-labdadien-15-oic acid (**2**): Colorless oil; $[\alpha]_D^{25}$ +17.7 (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ε/(L•mol^{-1}•cm^{-1})]: 208 (15.3) nm; ^{1}H NMR (400 MHz, MeOD) and ^{13}C NMR (100 MHz, MeOD) data see Table 1; HR-ESI-MS calcd for $C_{20}H_{32}O_4Na$ $[M+Na]^+$ 359.2198, found 359.2193.

4.4 LPS-stimulated NO release in RAW264.7 cell

The RAW264.7 cells in logarithmic growth phase were washed twice with phosphate buffer saline (PBS) and inoculated in 96-well plates at a density of 1×10^4 cells per well, and 100 μL of cell suspension was added to each well. Three compound wells were set in each group and cultured at 37 ℃ and 5% CO_2 for 24 h.[13] Cell maintenance, experimental procedures, and data presentation for the inhibition of NO production and viability assay were the same as previously described.[14] All the compounds were prepared as stock solutions in dimethyl sulfoxide (DMSO) (final solvent concentration less than 0.5% in all assays).

Supporting Information 1D NMR and 2D NMR, HR-ESI-MS of compounds **1** and **2**, and X-ray crystallographic information file (CIF) of **1** are available free of charge via the internet at http://sioc-journal.cn.

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