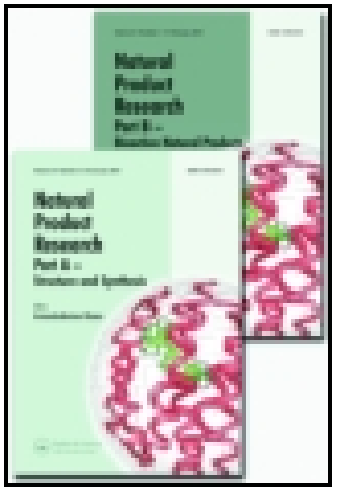

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A new triterpenoid bearing octacosanoate from the stems and roots of Clerodendrum philippinum var. simplex (Verbenaceae)

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A new triterpenoid bearing octacosanoate from the stems and roots of *Clerodendrum philippinum* var. *simplex* (Verbenaceae)

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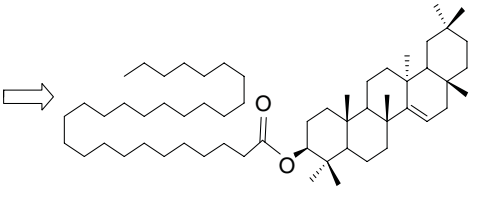

A new triterpenoid bearing octacosanoate, named taraxer-3β-yl octacosanoate (**1**), together with 13 known compounds (**2**–**14**), was isolated from the ethanol extract of the stems and roots of *Clerodendrum philippinum* var. *simplex*. The structure of taraxer-3β-yl octacosanoate (**1**) was elucidated by extensive spectroscopic analysis. Uncinatone (**8**) and clerodenone A (**10**) exhibited inhibition of lipopolysaccharide-induced nitric oxide production in RAW 264.7 macrophages with IC_{50} values of 12.50 and 3.18 μM, respectively.

Keywords: Verbenaceae; *Clerodendrum philippinum* var. *simplex*; taraxer-3β-yl octacosanoate; anti-inflammatory activity; Dai medicine

1. Introduction

The genus *Clerodendrum* (Verbenaceae) is composed of about 400 species, naturally distributing in tropical and subtropical areas. Forty species (34 species and 6 varieties) are distributed in China of which about 10 species have been found in Yunnan Province (Kunming Institute of Botany, Chinese Academy of Sciences 1977). Many species of *Clerodendrum* have been traditionally used as medicines by the indigenous people in India, Thailand, Vietnam and Kenya to treat hypertension and as diabetic, anti-obesity, antimalarial and anti-inflammatory (Panthong et al. 2003; Muthaura et al. 2007; Jadeja et al. 2012; Lokesh & Amitsankar 2012). Previous studies on the chemical constituents of the genus *Clerodendrum* have obtained various bioactive compounds, such as terpenoids (Sannigrahi et al. 2012), diterpenoids (Li et al. 2014; Patel et al. 2014), polyphenolic (Thitilertdecha et al. 2014) and phenyl propanoid glycosides

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(AbouZid et al. 2013). *Clerodendrum philippinum* Schauer var. *simplex* C.Y. Wu & R. C. Fang is a small shrub mainly distributed in south-west of China. Although local inhabitants, especially the Dai minority inhabited in Xishuangbanna, south-west of Yunnan province, and practitioners of minority medicine have used its leaves, stems and roots as a folk medicine an an anti-inflammatory drug such as for treating inflammation, rheumatoid and bronchitis for a long time (Lin et al. 2003; Yunnan Province State Food and Drug Administration 2007; Zhao et al. 2008), there are a few reports to date on the chemical constituents and biological activity of *C. philippinum* var. *simplex* (Na 2006; Zhu et al. 2013). In our continuing chemical studies from local traditional medicinal plants, a new triterpenoid bearing octacosanoate (Khan et al. 2012), named taraxer-3β-yl octacosanoate (**1**), and 13 known compounds (**2**–**14**) were isolated from the ethanol extract of the stems and roots of *C. philippinum* var. *simplex*. Herein, we report on the isolation and structural elucidation of taraxer-3β-yl octacosanoate (**1**) as well as on the inhibitory activities of lipopolysaccharide (LPS)-induced nitric oxide (NO) production of all compounds isolated in RAW 264.7 macrophages.

2. Results and discussion

Compound **1** was obtained as white powder. The molecular formula was established as $C_{58}H_{104}O_2$ by HR-ES-MS at *m/z* 832.8025 $[M]^+$. The IR spectrum (KBr) showed absorption bands due to methylene groups (2917, 2851 cm^{-1}), ester carbonyl groups (1727 cm^{-1}) and olefin groups (1640 cm^{-1}). Its ^1H and ^{13}C NMR spectra showed great similarity to that of taraxerol (**2**) (Sakurai et al. 1986), which was isolated from this plant (See Supplementary Material S9–S14). In the ^1H NMR spectra, eight tertiary methyls at δ 1.09 (3H, s), 0.95 (6H, s), 0.90 (6H, s), 0.87 (3H, s), 0.85 (3H, s) and 0.82 (3H, s) were typical for triterpene; an oxymethine proton at δ 4.47 (1H, dd, J = 10.6, 5.2 Hz, H-3) was observed; a downfield one proton at δ 5.53 (1H, dd, J = 8.0, 2.9 Hz, H-15) indicated the presence of an olefinic bond, and was assigned to the olefinic proton at C-15 of the taraxerol skeleton (Sakurai et al. 2007). Two geminal methylene protons at δ 1.92 (1H, br d, J = 14.0 Hz, H-16a) and 2.03 (1H, br d, J = 12.6 Hz, H-19a) could be discerned in the ^1H NMR spectra. In the ^{13}C NMR, chemical shifts for one oxymethine carbon at δ 80.8 (C-3), olefinic carbon at δ 158.1 (C-14) and 117.1 (C-15) were all observed. Thus, the carbocyclic nucleus of compound **1** proved to be that of a typical taraxerol. Additional signals as one carboxyl carbon at δ 173.8, one terminal methyl carbon at δ 14.3,

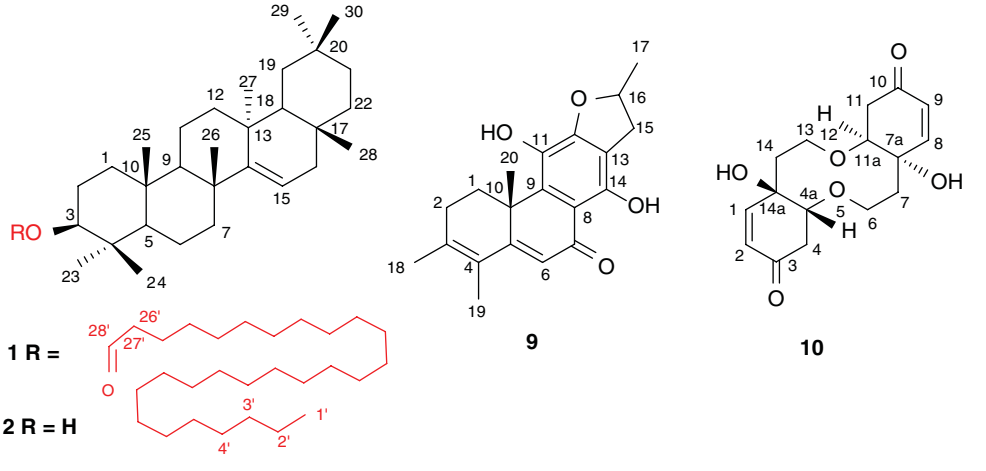

Figure 1. Structure compounds **1**, **2**, **9** and **10**.

multiple methylene carbon signals at δ 29.3–29.7 indicated that the hydroxyl of taraxerol was substituted by a long fatty acid. These observations suggested that **1** was likely a long fatty acid derivative of taraxerol. The HMBC spectrum revealed a strong correlation between the oxymethine proton H-3 (δ 4.47, dd, J = 10.6, 5.2 Hz) and the carboxyl carbon C-28′ (δ 173.8) as well as between methylene protons H-26′ [δ 1.61, (2H)] and the carboxyl carbon C-28′ (δ 173.8). This indicated that the long fatty acid group (A) was connected to oxymethine C-3 (δ 80.0) on the basis of elemental constitution analysis (Figure 2). The relative configuration of **1** was assigned by a ROESY experiment (Figure 2), in which the correlations between H-3/H_3-23, H_3-23/H-9 and H-9/H_3-27 indicated that they were β-oriented. Consequently, the ROESY correlations of H_3-24/H-5, H-5/H_3-25 and H_3-25/H_3-26/H_3-28 showed them to be a-configured. The structure of compound **1** is shown in Figure 1 and named taraxer-3β-yl octacosanoate 1.

The known compounds were identified as taraxerol (**2**) (Tang et al. 2012), myricadiol (**3**) (Kerr et al. 1996), friedelin (**4**) (Klass et al. 1992), quinovic acid 3-β-D-glucopyranoside (**5**) (Matos et al. 1986), clerosterol 3-β-*O*-[β-D-glucoside] (**6**) (Goswami et al. 1996), 22-dehydroclerosterol (**7**) (Kitajima & Tanaka 1993), uncinatone (**8**) (Tian et al. 1993), 11,12,14-trihydroxyabieta-8,11,13-trien-7-one (**9**) (Chang et al. 2005), clerodenone A (**10**) (Liu et al. 2009), 9-hydroxytridecyl docosanoate (**11**) (Chai-Ming & Chun-nan 1994), tetracosanoic acid (**12**) (Zhuang et al. 2009), indolyl-3-carboxylic acid (**13**) (Feng et al. 2007) and clerodenoside A (**14**) (Tian & Sun 1995) by comparing their spectral data to those reported in the literature.

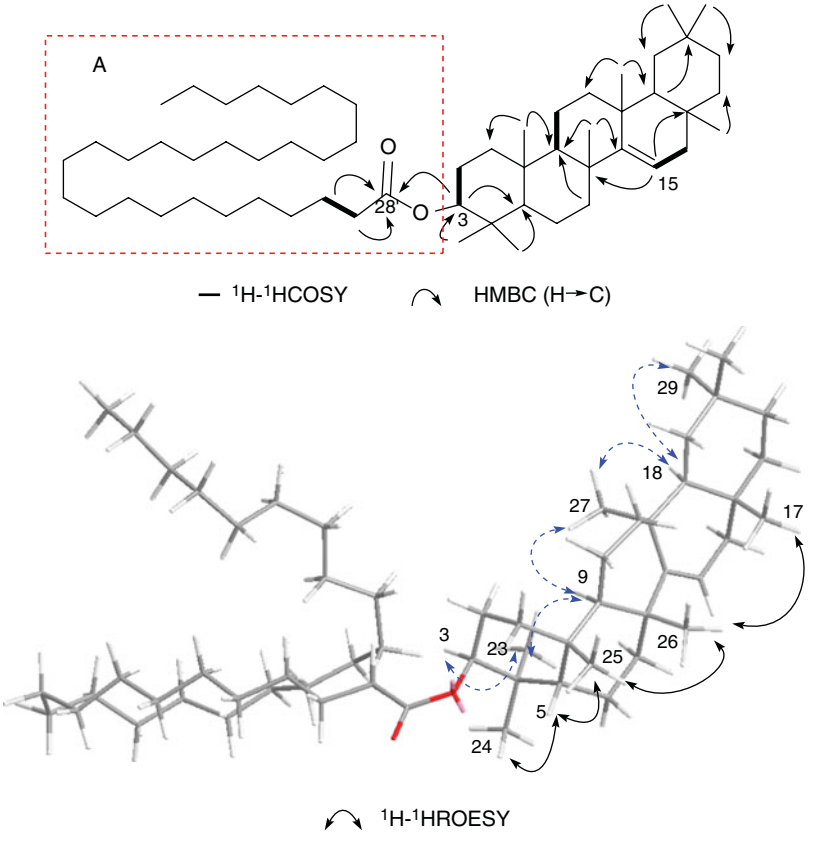

Figure 2. Key COSY, ROESY and HMBC correlations of compound **1**.

Considering the Dai traditional medicine used from stems and roots of *C. philippinum* var. *simplex* as anti-inflammatory, all the compounds isolated were evaluated for their inhibitory effects on NO release in LPS-stimulated RAW 264.7 macrophage cell line. The results showed that compounds **8** and **10** could inhibit NO production with IC_{50} values of 12.50 and 3.18 μM, respectively, comparable to positive control MG132 ($IC_{50} = 0.1$ μM), whereas the other compounds were only weakly active or inactive ($IC_{50} > 25$ μM).

3. Experiments

3.1. *General experimental procedures*

Optical rotations were obtained with a JASCO P-1020 polarimeter equipped with a 1 dm path length cell. IR spectra (KBr) were determined on a Bruker Tensor-27 infrared spectrophotometer. 1D and 2D NMR spectra were recorded on Bruker AM-400 spectrometers with TMS as an internal standard. EI-MS and HR-EI-MS spectra were recorded on an Auto Spec Premier P776 instrument. Silica gel (200–300 mesh, Qingdao Marine Chemical, P.R. China), Lichroprep RP-18 (40–65 μm, Merck, Darmstadt, Germany), MCI (75–150 μm, Mitsubishi Chemical Corporation, Japan) and Sephadex LH-20 (Pharmacia Fine Chemical Co., Ltd.) were used for column chromatography (CC). Fractions were monitored by TLC, and spots were visualised by spraying TLC plates with 10% sulphuric acid in ethanol and heating at 110°C for 5–10 min. All solvents were distilled prior to use.

3.2. *Plant material*

The stems and roots of *C. philippinum* var. *simplex* were collected at Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences, Yunnan Province, in July 2011, and were identified by Xiao Chun-Fen of the Xishuangbanna Tropical Botanical Garden (XTBG), Chinese Academy of Sciences. A voucher specimen (No. Dyla-201107-XTBG) was deposited in the herbarium of XTBG.

3.3. *Extraction and isolation*

The air-dried and powdered stems and roots of *C. philippinum* var. *simplex* (5.0 kg) were extracted three times (each for 6 days) with 95% ethanol at room temperature. The combined extracts were concentrated under reduced pressure to give a semi-solid dark brown ethanol extract (228 g). The ethanol extract was then dispersed in water and fractionated sequentially with petroleum ether, chloroform and butanol to yield petroleum ether fraction (35 g), ethyl acetate fraction (43 g) and butanol fraction (26 g), respectively. The petroleum ether fraction (35 g) was then subjected to silica gel CC eluted with a petroleum ether/ethyl acetate (v/v 8:2 to 1:9) gradient to yield four fractions (Frs 1–4). Fraction 1 (7 g) was subjected to silica gel CC using a gradient solvent system containing petroleum ether/acetone (19:1 to 3:1) to yield **4** (21 mg), **1** (35 mg) and **2** (25 mg). Fraction 2 (4 g) was separated on a silica gel column eluted with petroleum ether/ethyl acetate/acetone (7:3:0 to 1:6:3) to yield **7** (18 mg) and **12** (17 mg). Fr. 3 (10) was separated by a reversed phase (RP-18) silica gel column eluted by water/methanol (20:80 to 0:100) to yield **11** (18 mg) and **14** (12 mg). The ethyl acetate fraction (43 g) was subjected to silica gel CC eluted with chloroform/methanol (9:1 to 2:8) to yield **3** (35 mg), **6** (28 mg), **10** (45 mg) and **8** (125 mg) and sub-fractions Frs 2–5. Frs 2–5 were subjected to Sephadex LH 20 CC using a gradient solvent system containing water/methanol (40:60 to 10:90) to yield **9** (41 mg). The butanol fraction (26 g) was separated by silica gel CC eluted with EtOAc/MeOH (from 10:1 to 3:1) to give two major fractions (Frs b-1–2). Fr. b-1 and Fr. b-2 were

subjected to Sephadex LH 20 CC using a gradient solvent system containing water/methanol (30:70 to 10:90) to yield **13** (15 mg) and **5** (27 mg), respectively.

3.4. *Taraxer-3β-yl octacosanoate (1)*

White solid; $[\alpha]_D^{22.5}$ −29 ($c = 0.25$ MeOH); HR-EI-MS$^+$*m/z*: $[M]^+$832.8025 (calcd. for $C_{58}H_{104}O_2$, 832.8036); EI-MS$^+$*m/z*: 833 [M + H], 805, 791, 749 (25), 625 (25), 446 (8), 409 (20), 218 (28), 204 (100); IR (KBr disc) ν_{max} cm^{-1}: 3432, 2918, 2851, 1727, 1472, 1389, 1376, 1029, 999; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.81 (s, 3H, H-27), 0.85 (s, 3H, H-23), 0.87 (s, 3H, H-25), 0.88 (t, $J = 6.4$ Hz, 4H, H-1′, 5), 0.90 (s, 6H, H-28, 30), 0.95 (s, 7H, H-18, 24, 29), 1.01–1.03 (m, 4H, H-1, 7, 12), 1.09 (s, 3H, H-26), 1.23–1.28 (m, 48H, H-3′-H-25′, H-2, H-22), 1.35 (m, 1H, H-19), 1.43–1.45 (m, 2H, H-9, 11), 1.48 (m, 1H, H-6), 1.55 (m, 1H, H-22), 1.59–1.63 (m, 12H, H-1, 2, 6,11, 12, 16, 21, 2′, 26′), 1.92 (d, $J = 8.0$ Hz, 1H, H-16) 2.03 (d, $J = 12.6$ Hz, 1H, H-19), 2.29 (t, $J = 7.4$ Hz, 2H, H-27′), 4.47 (dd, $J = 10.6$, 5.2 Hz, 1H, H-3), 5.53 (dd, $J = 8.0$, 2.9 Hz, 1H, H-15); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 37.3 (C-1), 22.9 (C-2), 80.8 (C-3), 37.9 (C-4, 16), 55.8 (C-5), 18.9 (C-6), 35.3 (C-7), 38.1 (C-8, 17), 49.3 (C-9), 35.9 (C-10), 17.7 (C-11), 36.8 (C-12), 39.4 (C-13), 158.1 (C-14), 117.1 (C-15), 48.9 (18), 41.4 (19), 29.0 (C-20), 33.9 (C-21), 33.3 (C-22), 28.2 (C-23), 15.6 (C-24), 16.8 (C-25), 26.1 (C-26), 30.1 (C-27), 30.0 (C-28), 33.5 (C-29), 21.4 (C-30), 14.3 (C-1′), 23.7 (C-2′), 32.1 (C-3′), 29.3-29.7 (C-4′-25′), 25.3 (C-26′), 35.0 (C-27′), 173.8 (C-28′).

3.5. *Inhibition of NO production assays*

The assay was performed according to a previously described method (Ji et al. 2014). Each compound was dissolved in DMSO and further diluted in the medium to produce different concentrations with a maximum concentration of 25 μM. The absorbance was measured at 570 nm with a 2104 Envision Multilabel Plate Reader (Perkin-Elmer Life Sciences, Inc., Boston, MA, USA). Cytotoxicity was determined with the MTT assay. MG-132 (Sigma-Aldrich, Foster City, CA, USA) was used as the positive control.

4. Conclusions

In this paper, 14 compounds, including 5 triterpenoids (**1**—**5**) [1 new triterpenoid bearing octacosanoate, named taraxer-3β-yl octacosanoate (**1**)], 2 sterids (**6** and **7**), two diterpens (**8** and **9**), 1 cyclohexylethanoids (**10**), two fatty acids (**11** and **12**) one indole acid (**13**) and one phenylpropanoid (**14**) were isolated from the stems and roots of *C. philippinum* var. *simplex*. The structure of taraxer-3β-yl octacosanoate (**1**) was identified as (3*S*,4*aR*,12*aS*,14*aR*)-4,4,6*a*,8*a*,11,11,12*b*,14*b*-octamethyl-1,2,3,4,4*a*,5,6,6*a*,8,8*a*,9,10,11,12,12*a*,12*b*,13,14,14*a*,14*b*-icosahydropicen-3-yl octacosanoate (**1**) by 1D and 2D NMR spectra and MS. All compounds were isolated for the first time from this plant. Bioassay results showed that uncinatone (**8**) and clerodenone A (**10**) exhibited the inhibitory activities of LPS-induced NO production in RAW 264.7 macrophages with IC_{50} values of 12.50 and 3.18 μM, respectively.

Supplementary material

Supplementary material relating to this article is available online: 1D NMR, 2D NMR, IR and HR-EI-MS spectra of **1** (Figures S1–S8).

Disclosure statement

No potential conflict of interest was reported by the authors.

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