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Foetidinol, a new trinor-triterpenoid with a novel carbon skeleton, from a Chinese crude drug "Shengma" (*Cimicifuga foetida* L.)

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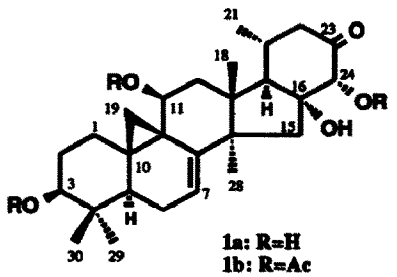
Summary: Foetidinol (**1a**), trinor-triterpenoid with a novel carbon skeleton, has been isolated from the rhizoma of *Cimicifuga foetida* L., and its structure was determined based on the 2D NMR spectroscopy including HMBC.

During our investigation on biologically active substances from Chinese medicinal plants, a new trinor-triterpenoid, foetidinol (**1a**), was isolated from the methanol extract of "Shengma" (rhizoma of *Cimicifuga foetida* L. Ranunculaceae).[1] This paper deals with the structure elucidation of foetidinol (**1a**).

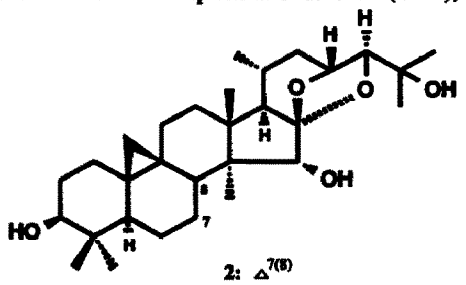
The dried rhizoma of *Cimicifuga foetida* L. (4 kg) was extracted with boiling MeOH. The MeOH extract was concentrated *in vacuo* and the aqueous suspension was partitioned with *n*-hexane, EtOAc, *n*-BuOH, respectively. Repeated silica gel column chromatography of the EtOAc-soluble fraction afforded foetidinol (**1a**) (0.0004%).

Foetidinol (**1a**), colorless needles (hexane-EtOAc), mp 255-256 °C, $[\alpha]_D$ -93.5° (*c*=0.12, $CHCl_3$:MeOH=1:1), has the molecular formula $C_{27}H_{40}O_5$ (M^+ 444.2909, calcd. 444.2873) and its IR spectrum (KBr) showed absorptions at 3450 (OH), 1718 (C=O), and 1620 cm^{-1}. The ^1H- and ^{13}C-NMR[2] spectra of **1a** indicated the presence of a carbonyl (δ_C 211.3), a double bond (δ_H 5.25; δ_C 114.0, 149.3), three hydroxy-bearing methine (δ_H 3.63, 4.50, and 4.62; δ_C 78.0, 82.0, and 63.6), a cyclopropyl methylene (δ_H 1.08 and 2.04; δ_C 18.8), four *tert*-methyl groups (δ_H 1.21, 1.29, 1.30, and 1.62; δ_C 13.9, 21.2, 26.4, and 28.2), a secondary methyl group (δ_H 0.93; δ_C 20.7), and six quaternary sp^3 carbons (δ_C 27.5, 29.5, 40.5, 46.3, 50.9, and 82.4). These data coupled with the detailed analyses of the ^1H-^1H and ^1H-^{13}C COSY spectra suggested that **1a** has the partial structures shown in Chart 1a. The ^1H- and ^{13}C-NMR data showed fewer methine and methyl groups than usual triterpenoid, but the chemical shift for five methyl groups at C-18, C-21, C-28, C-29, and C-30 of **1a** were similar to those of **2**.[3] Hence, it was assumed that the basic structure of **1a** was similar to that of **2**, but the total number of carbons was less than that of common triterpenoid. Also, the cyclopropane methylene protons (δ_H 1.08 and 2.04) of **1a** revealed a marked downfield shift compared with those of **2** (δ_H 0.55 and 1.09) and **3**[4] (δ_H 0.36 and 0.64), which led us to suppose displacement of 11-H by a hydroxyl group.

Acetylation of **1a** gave an amorphous triacetate (**1b**), and it showed IR absorption at 1725 cm^{-1} (C=O), and



1a: R=H
1b: R=Ac



2: $\Delta^{7(8)}$
3

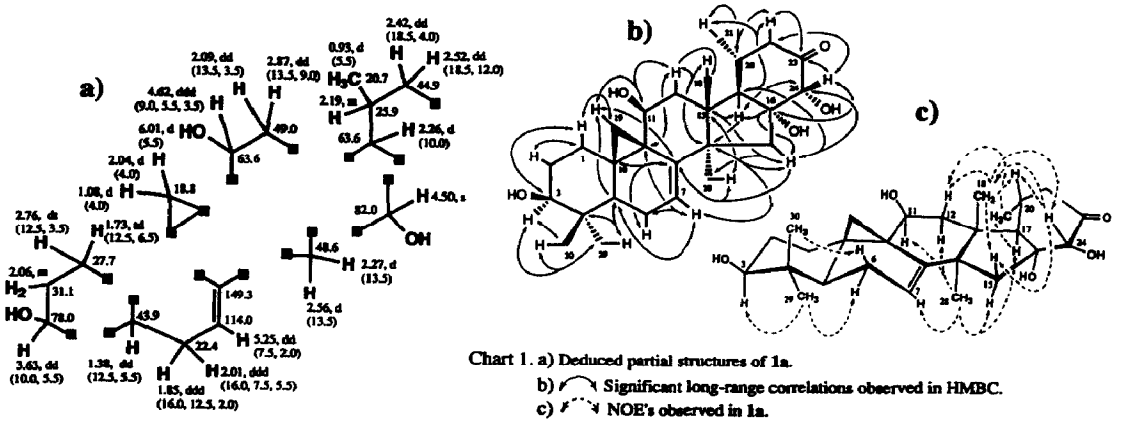


Chart 1. a) Deduced partial structures of **1a**.
b) Significant long-range correlations observed in HMBC.
c) NOE's observed in **1a**.

three acetyl methyl signals at δ_H 2.03, 2.07, and 2.24 in ^{1}H-NMR spectrum. The positive ion FAB-MS exhibited a *quasi*-molecular ion peak at *m/z* 571 $(M+H)^+$. Therefore, all these spectral informations of **1a** and **1b** suggested that **1a** must contain a *tert*-hydroxyl and three secondary hydroxyl groups.

Then, we measured the HMBC spectrum of **1a** in order to clarify the connectivities of the partial structures. As shown by arrows in Chart 1b, the carbon signal at δ_C 27.5 (C-9) is correlated with the proton signals at δ_H 2.87 (12-Hβ) and 5.25 (7-H) in terms of long-range correlation, while the quaternary carbon signal at δ_C 43.9 (C-5) with the protons at δ_H 1.08, 2.04 (19-H), and 5.25 (7-H). Thus, the structure of foetidinol was assigned to the formula in Chart 1b, in which other significant long-range correlations observed are also shown by arrows.

The relative stereochemistry was elucidated on the basis of the coupling constants of each proton and the results of NOE experiments. Irradiation at 18-H$_3$ enhanced the signal intensity of the 15-Hβ, 20-Hβ, and 24-Hβ. Similarly, signal intensities of 15-Hβ, 18-H$_3$ and 20-Hβ were increased on irradiating at 24-Hβ. These findings with other pertinent NOE enable us to determine the stereostructure of foetidinol to be **1a** as depicted in Chart 1c.

The absolute configuration of foetidinol was determined as **1a** based on the negative Cotton effect due to the optically active ketone chromophore in the CD spectrum and it was also supported by ORD spectrum.

Our present result provided the first example of trinor-triterpenoid having a novel carbon skeleton.[5] This compound is of interest from a biogenetic viewpoints. The biological activities are now under examination.

REFERENCES AND NOTE

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2. **1a**: ^{1}H-NMR (400MHz, pyridine-d_5): δ_H 0.93 (3H, d, *J*=5.5 Hz, 21-H$_3$), 1.08 (1H, d, *J*=4.0 Hz, 19-H), 1.21 (3H, s, 30-H$_3$), 1.29 (3H, s, 18-H$_3$), 1.30 (3H, s, 29-H$_3$), 1.38 (1H, dd, *J*=12.5, 5.5 Hz, 5-H), 1.62 (3H, s, 28-H$_3$), 1.73 (1H, td, *J*=12.5, 6.5 Hz, 1-H), 1.85 (1H, ddd, *J*=16.0, 12.5, 2.0 Hz, 6-Hβ), 2.01 (1H, ddd, *J*=16.0, 7.5, 5.5 Hz, 6-Hα), 2.04 (1H, d, *J*=4.0 Hz, 19-H), 2.06 (2H, m, 2-H$_2$), 2.09 (1H, dd, *J*=13.5, 3.5 Hz, 12-Hα), 2.19 (1H, m, 20-H), 2.26 (1H, d, *J*=10.0 Hz, 17-H), 2.27 (1H, d, *J*=13.5 Hz, 15-Hα), 2.42 (1H, dd, *J*=18.5, 4.0 Hz, 22-H), 2.52 (1H, dd, *J*=18.5, 12.0 Hz, 22-H), 2.56 (1H, d, *J*=13.5 Hz, 15-Hβ), 2.76 (1H, dt, *J*=12.5, 3.5 Hz, 1-H), 2.87 (1H, dd, *J*=13.5, 9.0 Hz, 12-Hβ), 3.63 (1H, dd, *J*=10.0, 5.5 Hz, 3-H), 4.50 (1H, s, 24-H), 4.62 (1H, ddd, *J*=9.0, 5.5, 3.0 Hz, 11-H), 5.25 (1H, dd, *J*=7.5, 2.0 Hz, 7-H), 6.00 (1H, d, *J*=5.5 Hz, 11-OH); ^{13}C-NMR (100MHz, pyridine-d_5): δ_C 13.9 (q, C-30), 18.8 (t, C-19), 20.7 (q, C-21), 21.2 (q, C-18), 22.4 (t, C-6), 25.9 (d, C-20), 26.4 (q, C-29), 27.5 (s, C-9), 27.7 (t, C-1), 28.2 (q, C-28), 29.5 (s, C-10), 31.1 (t, C-2), 40.5 (s, C-4), 43.9 (d, C-5), 44.85 (t, C-22), 46.3 (s, C-13), 48.6 (t, C-15), 49.0 (t, C-12), 50.9 (s, C-14), 63.6 (d, C-11 and 17), 78.0 (d, C-3), 82.0 (d, C-24), 82.4 (s, C-16), 114.0 (d, C- 7), 149.3 (s, C-8), 211.3 (s, C-23); CD (*c*=0.61 mM, MeOH): $[\theta]_{213}$ -47870, $[\theta]_{284}$ -17700; ORD (*c*=2.55 mM, MeOH) [M](nm): -1.19 x 10^4 (230), +0.93 x 10^4 (264), -1.14 x 10^4 (303).
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