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Salviskinone A, a diterpene with a new skeleton from *Salvia przewalskii*

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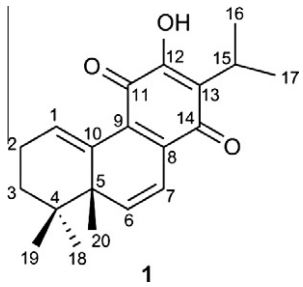
ABSTRACT

A novel compound, named salviskinone A (**1**), was isolated from *Salvia przewarskii*. The compound has a rearranged carbon skeleton with a methyl unit at C-5 from abietane-type diterpene. Its structure and relative stereochemistry were elucidated by detailed spectroscopic analysis, including HREIMS and 2DNMR (COSY, HSQC, HMBC, and NOESY) spectra.

The genus *Salvia* (Lamiaceae) consists of about a thousand species. According to Flora of China,[1] 84 species are found in China, and there are still many taxonomical problems in this genus, especially in Yunnan and Sichuan Provinces. Thus, during the course of our project for the study of plant diversity regarding secondary metabolites,[2] we initiated a study of the chemical constituents of *Salvia* species in that area of China. *Salvia przewalskii* is one of species abundant in the area and is used for the treatment of various cardiovascular diseases.[3] Many abietane[4,5] and icetexane diterpenes[5,6] were isolated as well as compounds having related skeletons such as C_{23} terpenoids,[7] spiro-compound[8] and a dimer.[9] Triterpenes[10] and anthraquinones[11] were also isolated.

Samples of *S. przewalskii* were collected at several locations in Yunnan and Sichuan Providences. TLC analysis showed that a sample collected at Jianzuwanshan in Yajiang County, Sichuan Province,[12] includes a unique compound in comparison with other samples, indicating the presence of chemical diversity in the species. In this Letter, we describe the isolation and structure elucidation of compound **1**, an unprecedented diterpene possessing a rearranged-abietane skeleton.

The roots of *S. prezewalskii* (36.7 g) were crushed and then extracted with MeOH. The MeOH-soluble materials (4.15 g) were separated in an ODS gel column (Wako-gel, 100C18, Wako Ltd) to obtain four fractions (H_2O/MeOH→$CHCl_3$; 40:60, 20:80, 0:100, and $CHCl_3$). The second fraction (910 mg) was further fractionated by silica-gel column (wako-gel C-300, hexane/EtOAc→MeOH) into six fractions. The second fraction (hexane/EtOAc, 60:40, 272 mg) was further subjected to LH-20 column (Sephadex™, GE Health care), silica-gel column (hexane/$CHCl_3$→MeOH) and silica-gel HPLC (hexane/EtOAc, 99.5:0.5, Mightysil Si60, KANTO Chemical, Co. Inc.) to yield compound **1** (1.5 mg), named salviskinone A. The known compounds, tanshinone IIA (**2**),[13] cryptotanshinone (**3**),[14] salvinolone (**4**),[15] and salvilenone (**5**)[16] were also isolated.



1

Salviskinone A[17] (**1**) ($[\alpha]_D^{23}$ −190, *c* 0.016, MeOH) was isolated as an amorphous red solid. The molecular formula, $C_{20}H_{24}O_3$, of **1** was established by HREIMS [M^+, 312.1734 mmu, Δ +0.9]. The IR spectrum of **1** showed the absorption for hydroxy group (3368 cm^{-1}), a quinone moiety (1634, 1545, and 1459 cm^{-1}). The gross structure of **1** was deduced from detailed analysis of the ^1H and ^{13}C NMR data (Table 1) aided by 2D NMR experiments (^1H–^1H COSY, HSQC, and HMBC). The ^{13}C NMR data indicated that compound **1**

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Table 1
^{1}H and ^{13}C NMR data of **1** in $CDCl_3$

No.	δ_H (mult, *J*, Hz)	δ_C (mult)
1	6.85 t, 4.2	137.1, d
2a	2.33 m	24.2, t
2b	2.33 m	
3α	1.27 m	31.8, t
3β	1.88 ddd, 7.4, 10.6, 13.8	
4		33.0, s
5		43.5, s
6	6.43 dd, 0.7[a], 10.0	144.6, d
7	6.66 br d, 10.0	117.5, d
8		133.4, s
9		126.2, s
10		131.6, s
11		183.5, s
12		151.1, s
13		123.3, s
14		185.7, s
15	3.22 hept, 7.1	24.2, d
16	1.24 d, 7.1	19.8, q
17	1.24 d, 7.1	19.9, q
18	1.03 s	24.5, q
19	0.90 br s	25.6, q
20	1.08 s	23.2, q
OH-12	7.39 s	

[a] Long-range coupling with H_3-19.

possessed two sp^3 methylenes, one sp^3 methine, two sp^3 quaternary carbons, three sp^2 methines, four quaternary sp^2 carbons, one oxygenated sp^2 quaternary carbon, two α,β-unsaturated carbonyl groups (1,4-benzoquinone group), and five methyl carbons. Since six of nine unsaturations were accounted for by double-bonds and carbonyl units, it was indicated that **1** contained three

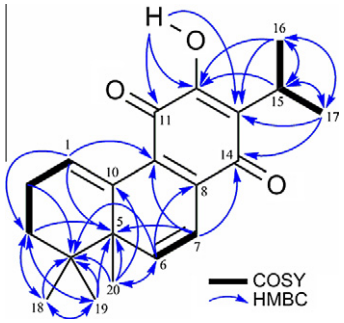


Figure 1. COSY and HMBC correlations of **1**.

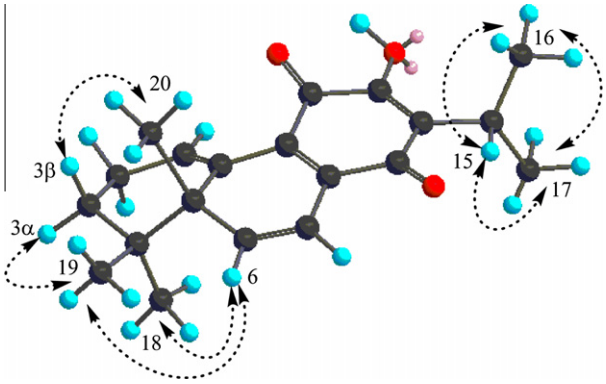
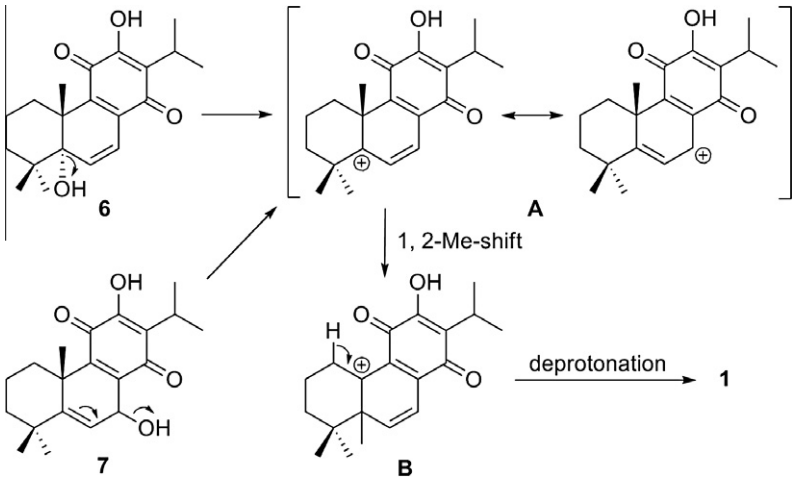


Figure 2. Key NOESY correlations of **1**.

rings including a *p*-benzoquinone ring. The ^{1}H–^{1}H COSY spectrum demonstrated connectivities of C-1 (δ_H 6.85, t; δ_C 137.1) to C-3, C-6 (δ_H 6.43, dd; δ_C 144.6) to C-7 (δ_H 6.66, br d; δ_C 117.5), C-15 to C-16 (δ_H 1.24 d, 3H; δ_C 19.8), and C-17 (δ_H 1.24 d, 3H; δ_C 19.9) (Fig. 1 and Table 1). HMBC correlations were observed: H-1/C-2, C-3, and C-5 (δ_C 43.5), H-2/C-1, C-3, and C-4, H-3/C-2, C-4, and C-5, H-6 (δ_H 6.43, dd)/C-5, C-4, C-7, C-8 (δ_C 133.4), and C-10 (δ_C 131.6), H-7 (δ_H 6.66, br d)/C-6, and C-5. These correlations indicated that compound **1** has a decaline skeleton with $\Delta^{1,10}$, $\Delta^{6,7}$-olefins, and the attachment of dimethyl unit to C-4 was deduced from the HMBC correlations of H_3-19 (δ_H 0.90, br s, 3H)/C-4, C-5 and C-18, H_3-18 (δ_H 1.03, s, 3H)/C-4, C-5, and C-19. However, different from the known abietane diterpenes, an angular methyl unit between rings A and B is located at C-5 as confirmed by the cross peaks of H_3-20 (δ_H 1.08, s, 3H)/C-4, C-5, C-6 (δ_C 144.6), and C-10 (δ_C 131.6). The 1,4-benzoquinone moiety (ring C) is fused with ring B at C-8 and C-9 positions on the basis of the HMBC correlations of H-1/C-9, H-6/C-8, H-7/C-9, and C-14 (quinone-carbonyl group, δ_C 185.7). Furthermore, HMBC correlations of H_3-16 and H_3-17/C-15 (δ_C 24.2) and C-13 (δ_C 123.3), respectively, demonstrated the presence of an isopropyl unit at C-13.

The remaining hydroxy group indicated by the molecular formula and the IR absorption was placed at C-12 (δ_C 151.1) on the basis of the HMBC cross peaks of O*H*-12 (δ_H 7.39, s)/C-11 (quinone-carbonyl group, δ_C 183.5), C-12, and C-13. Therefore, the gross structure of saviskinone A was elucidated as **1**. The NOESY correlations (Fig. 2) of H-3β/H_3-20, H-3α/H_3-19, H_3-18/H-6, and H_3-19/H-6 indicated that the conformation of ring A was a half boat.



Scheme 1. Plausible biogenetic pathway of **1**.

Compound **1** possesses an unprecedented carbon skeleton, a rearranged abietane-type diterpene, in which the methyl group at C-10 in abietane is shifted to the C-5 position. A plausible biogenetic pathway is shown in Scheme 1 supposing that **1** might be derived from an abietane-type diterpenoid. A presumable precursor is hypargenin F (**6**)[18] or its isomer **7**, the former of which has been isolated from the roots of *Salvia* species. A cationic intermediate A, formed by the elimination of the hydroxy group at C-5, presumably undergoes 1,2-methyl shift to give an intermediate B, and the following deprotonation provides **1**. Deprotonation from an intermediate A is impossible because there is no hydrogen that can be eliminated. Although the absolute stereochemistry of **1** has not been determined, this biosynthetic argument allows us to propose that the configuration of C-5, the only asymmetric center, is *R*.

Isolated compounds were evaluated for cytotoxicity against human epithelial carcinoma HeLa and human promyelocytic leukemia HL-60 cell lines. While salvinolone (**4**) and salvilenone (**5**) exhibited significant cytotoxicity against HL-60 cells (IC_{50}, **4**: 6.2, **5**: 3.1 μM), salviskinone (**1**) showed weak activity against HL-60 cell line with IC_{50} 31.0 μM.[19]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.080.

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