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New diterpenoids from *Semiaquilegia adoxoides*

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Two new *ent*-kaurane-type diterpenoids, *E*-semiaquilegin (**1**) and *Z*-semiaquilegin (**2**), together with eight known compounds (**3–10**) were isolated from the dried roots of *Semiaquilegia adoxoides* (DC.) Makino. The structures of compounds **1** and **2** were elucidated mainly by 2D NMR techniques including ¹H–¹H COSY, HSQC, HMBC, NOESY as 16 α -hydroxy-*ent*-kaurane-17,20-di-(3,4-dihydroxy-*E*-cinnamoyl) ester and its (*Z*)-isomer.

Keywords: *Semiaquilegia adoxoides*; Diterpenoids; *E*-Semiaquilegin; *Z*-Semiaquilegin

1. Introduction

Semiaquilegia adoxoides (DC.) Makino (Chinese name “Tian-Kui-Zi”) is the only species of Genus *Semiaquilegia* (Ranunculaceae). The roots have often been used to treat inflammation, snakebite, bruises and injuries, tonsillitis, mastitis, scrofula, and cancer for their antibacterial, anti-inflammatory and anti-neoplastic activities [1,2]. A literature survey revealed that a flavonoid glucoside was isolated from the aerial parts [3]; four cyano-containing and one nitro-containing compounds [4,5] as well as lithospermoside, griffonilide, magnoflorine [6] were obtained from its roots. In this paper, we report the isolation and structural elucidation of two new diterpenoids *E*-semiaquilegin (**1**) and *Z*-semiaquilegin (**2**), and eight known compounds (+)-pinoresinol (**3**), (+)-syringaresinol (**4**), 7-hydroxycoumarin (**5**), griffonilide (**6**), 2,4-dihydroxybenzoic acid (**7**), (2,4-dihydroxyphenyl) acetic acid methyl ester (**8**), aquilegionolide (**9**) and menisdaurilide (**10**).

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2. Results and discussion

Compound **1** (figure 1) was obtained as a white amorphous powder. It exhibited a molecular formula of $C_{38}H_{46}O_9$, as deduced from HRFAB-MS at m/z 645.3059 $[M - H]^-$. The IR spectrum showed the presence of hydroxyl (3372 cm^{-1}), ester carbonyl (1685 cm^{-1}) and phenyl groups ($2931, 1603, 1519\text{ cm}^{-1}$). The ^1H NMR spectrum of **1** showed signals for two tertiary methyls at δ_{H} 0.91 (3H, s), 0.92 (3H, s), and two caffeoyl groups at δ_{H} 7.59 (1H, d, $J = 16.0\text{ Hz}$), 7.54 (1H, d, $J = 16.0\text{ Hz}$), 7.15 (1H, d, $J = 8.0\text{ Hz}$), 7.13 (1H, d, $J = 8.0\text{ Hz}$), 7.03 (1H, dd, $J = 8.0, 3.0\text{ Hz}$), 7.01 (1H, dd, $J = 8.0, 3.0\text{ Hz}$), 6.86 (1H, d, $J = 3.0\text{ Hz}$), 6.84 (1H, d, $J = 3.0\text{ Hz}$), 6.34 (1H, d, $J = 16.0\text{ Hz}$), 6.28 (1H, d, $J = 16.0\text{ Hz}$). The ^{13}C NMR and DEPT experiments revealed the presence of 38 carbons: two methyls, 11 methylenes, 13 methines and 12 quaternary carbons (including two ester carbonyls at δ_{C} 167.7). The above data were similar to those of known compound **11** (*ent*-16 β ,17-kauranediol) [7] (figure 1) except for the presence of two caffeoyl groups. On analysis of the ^1H - ^1H COSY, HMBC and

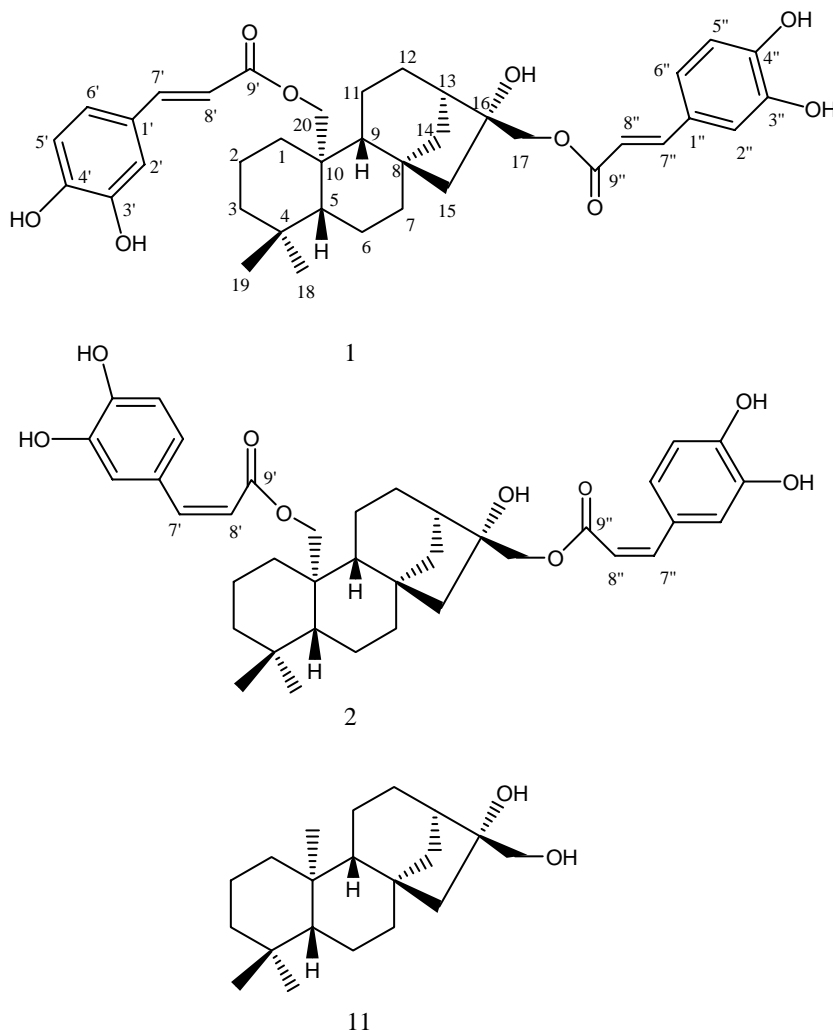


Figure 1. Structures of compounds **1**, **2** and **11**.

HSQC spectra and based on the previous literature [8–11], compound **1** was elucidated to possess a kaurane skeleton. In the ^{13}C NMR spectrum, the C-17 signal and C-20 signal downshifted to δ_{C} 68.9 and 63.9, respectively, which suggested that these positions were esterified. In the HMBC spectrum, correlations between H-17 (δ_{H} 4.32, 2H, d, $J = 12.5$ Hz) and C-9' (δ_{C} 167.7), H-20 (δ_{H} 4.51, 1H, d, $J = 12.5$ Hz; δ_{H} 4.77, 1H, d, $J = 12.5$ Hz) and C-9' (δ_{C} 167.7) confirmed these linkages. Further HMBC, HSQC and ^1H – ^1H COSY experiments enabled full assignments of the ^1H NMR and ^{13}C NMR spectra of **1**. The stereochemistry of **1** was confirmed by a NOESY experiment. In the NOESY spectrum of **1**, correlation between H-5 and H-9 confirmed that the relative configuration of H-5 and H-9 were β . 20 α -Hydroxymethyl (δ 4.51, 4.77, each 1H, d) was established by the correlation with 18 α -methyl. The configuration of C-16 hydroxyl was concluded by the chemical shift values of C-16 and C-17. A literature survey revealed that when C-16 hydroxyl was β , the chemical shift values of C-16 and C-17 were δ 79.6 and 69.8, while C-16 hydroxyl was α , the values were δ 81.6 and 66.0, respectively [7,8]. Comparing compound **1** with **11**, it can be determined that both of the configurations of C-16 hydroxyl were the same, which were α . But the chemical shift values of C-16 and C-17 upshifted and downshifted in compound **1**, respectively, for the linkage of a caffeoyl group. Other key correlations consisted in H-11/H-17, and H-15/H-17, respectively, indicating that C-16 hydroxyl was α . Thus, the structure of **1** was determined to be 16 α -hydroxy-*ent*-kaurane-17,20-di-(3,4-dihydroxy-*E*-cinnamoyl) ester, named *E*-semiaquilegin.

Compound **2** was obtained as a white amorphous powder. Its ESI-MS exhibited (figure 1) the same quasi-molecular ion peak at m/z 645 $[\text{M} - \text{H}]^-$ as that of **1**. The ^1H NMR and ^{13}C NMR chemical shift of **2** were similar to those of **1** except for $J_{7',8'}$, $J_{7'',8''}$ (12.0 Hz), in **2** instead of $J_{7',8'}$, $J_{7'',8''}$ ($J = 16.0$ Hz) in **1**. This fact indicated that compound **2** has the same kaurane skeleton as **1** except for the presence of (*Z*)-caffeoyl groups in **2**. Thus, the structure of compound **2** was elucidated as 16 α -hydroxy-*ent*-kaurane-17,20-di-(3,4-dihydroxy-*Z*-cinnamoyl) ester, named *Z*-semiaquilegin.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured on a Polatronic D polarimeter. Melting points were determined on XT4A melting point apparatus. UV spectra were recorded on a Shimadzu UV-2401 spectrometer. IR spectra were measured on an AVATER-360 spectrometer. ^1H NMR, ^{13}C NMR, DEPT, COSY, HSQC and HMBC spectra were measured on a JEOL JNM-A300 and a Bruker AM-500 spectrometer. ESI-MS and HRFAB-MS spectra were obtained using (MDS SCIEX) QSTAR (ABI, USA) ESI-TOF Mass and APEX II FTICR-MS (Bruker Daltonics) spectrometer, respectively. CC: silica gel (200–300 mesh, Qingdao Marine Chemical Factory); Sephadex LH-20 (Amersham Pharmacia Biotech).

3.2 Plant material

The roots of *Semiaquilegia adoxoides* were collected in Anhui Province, China, during the early summer of 2003 and identified by one of the authors (P.-F.T.). A voucher specimen

(No. TKZ040202) has been deposited at the Herbarium of the Modern Research Centre for Traditional Chinese Medicine, Peking University.

3.3 Extraction and isolation

The air-dried roots of *S. adoxoides* (28 kg) were extracted with 95% EtOH (100 L) three times. After the solvent removal, the combined residue was dissolved in water, and partitioned with EtOAc. The EtOAc-soluble phase was concentrated in vacuum to give a dark-red residue (67 g). The residue was subjected to a silica gel column (200–300 mesh, 1000 g) and eluted with a gradient of CHCl₃/MeOH (100:1 to 1:1, v/v) to provide eight fractions. The selected fractions were separated by column chromatography on silica gel, Sephadex LH-20, repeatedly. Fraction 5 (CHCl₃/MeOH 100:10, v/v) afforded two new diterpenes, *E*-semiaquilegin (**1**, 8 mg) and *Z*-semiaquilegin (**2**, 2 mg). Two lignans, (+)-pinoresinol (**3**, 12 mg) [12] and (+)-syringaresinol (**4**, 15 mg) [12] were obtained from fraction 7 (CHCl₃/MeOH 100:32, v/v). Fraction 4 (CHCl₃/MeOH 100:10, v/v) gave 7-hydroxycoumarin (**5**, 10 mg) [13], as well as griffonilide (**6**, 1.2 g) [6]. 2,4-Dihydroxybenzoic acid (**7**, 13 mg) [14] and (2,4-dihydroxyphenyl) acetic acid methyl ester (**8**, 152 mg) [15] came from fraction 6 (CHCl₃/MeOH 100:16, v/v). Fraction 5 afforded aquilegolide (**9**, 18 mg) [16] and menisdaurilide (**10**, 10 mg) [16], respectively.

3.3.1 *E*-semiaquilegin (1). White amorphous powder, mp 163–165°C; $[\alpha]_D^{25} - 52.7$ (*c* 0.06, CH₃OH); UV (CH₃OH) λ_{\max} nm: 235, 301, 329. IR (KBr) ν_{\max} cm⁻¹: 3372, 2931, 1685, 1603, 1519, 1448, 1272, 1172. ¹H NMR (acetone-*d*₆, 500 MHz) and ¹³C NMR (acetone-*d*₆, 125 MHz) data: see table 1; HRFAB-MS *m/z*: 645.3059 [M – H]⁻ (calcd for C₃₈H₄₅O₉, 645.3068).

3.3.2 *Z*-semiaquilegin (2). White amorphous powder, mp 156–158°C; $[\alpha]_D^{25} - 32.7$ (*c* 0.04, CH₃OH); UV (CH₃OH) λ_{\max} nm: 235, 301, 329. IR (KBr) ν_{\max} cm⁻¹: 3372, 2930, 1685, 1600, 1519, 1448, 1272. ¹H NMR (acetone-*d*₆, 300 MHz) and ¹³C NMR (acetone-*d*₆, 75 MHz) data: see table 1; ESI-MS *m/z*: 645 [M – H]⁻.

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