Cyclohexanone derivatives from *Senecio argunensis*

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A new cyclohexanone derivative, methyl 5α,6α-epoxy-1-hydroxy-2-methoxy-4-oxocyclohexanacetate, along with five known cyclohexanones were isolated from the aerial parts of *Senecio argunensis*. Their structures were elucidated on the basis of spectroscopic methods, including IR, EI-MS, HR-ESI-MS, 1D NMR and 2D NMR.

Keywords: Compositae, *Senecio argunensis*, cyclohexanone

The genus of *Senecio* (Compositae), consisting of more than 1000 species, is widely distributed in China.[1] *Senecio argunensis* Turcz. is a perennial herb mainly growing in northeast and northwest China and is extensively used as a folk medicine in China for the treatment of sore throat, conjunctivitis, dysentery, snake bite, *etc*.[2] The constituents of this plant have been previously investigated and several types of natural products, such as pyrrolizidine alkaloids,[3] flavonoid alkaloids,[4] biflavonoid,[5] monoterpene and tetrahydronaphthene derivatives,[6] have been isolated. As a part of our investigations on the phytochemical constituents of *Senecio* species distributing in northeast China, the aerial parts of *S. argunensis* collected in Changbai Mountains, northeast China have been re-examined. We now report the isolation and structural elucidation of a new cyclohexanone derivative, methyl 5α,6α-epoxy-1-hydroxy-2-methoxy-4-oxocyclohexanacetate (**1**), and five known ones (Fig. 1), methyl 1-hydroxy-2,6-dimethoxy-4-oxocyclohexanacetate (**2**),[7] Jacaranone (**3**),[7] methyl 2-[2,2-dimethyl-6-oxo-7-dihydro-1,3-benzodioxol-3(6H)-yl]acetate (**4**),[8] methyl 1-hydroxy-2-methoxy-5-ene-4-oxocyclohexanacetate (**5**),[9] methyl 1-hydroxy-4-oxocyclohexanacetate (**6**).[10] Jacaranone (**3**), a neurotoxic agent, is quite widely distributed in *Senecio* species and is active in several biological systems and moderately toxic to many organisms.[11] Compound **4** is probably an artifact arising from the use of acetone in the course of chromatographic separation.

Compound **1** was obtained as colourless oil. Its molecular formula was deduced to be $C_{10}H_{14}O_6$ by the quasi-molecular ion peak at *m/z* 253.0689 ([M+Na]$^+$) in the HR-ESI-MS. The IR spectrum of **1** displayed absorption bands of hydroxyl at 3469 cm^{-1} and carbonyl at 1727 cm^{-1}. The ^{1}H NMR spectrum of compound **1** showed the presence of two methoxyl groups at δ_H 3.36 (3H, s) and 3.75 (3H, s), and three oxygenated methenyl protons at δ_H 3.77 (1H, dd, J = 5.0, 7.5), 3.37 (1H, d, J = 4.0) and 3.69 (1H, d, J = 4.0). The chemical shifts of a pair of doublets at δ_H 3.37 and 3.69 (d, J = 4.0), together with two typical oxygenated methine carbons at δ_C 59.3 (CH) and 55.0 (CH) suggested the presence of a epoxy group.[12] Apart from the carbon signals for two methoxyl groups and two oxygenated methine carbons, the ^{13}C NMR and DEPT spectra showed the presence of a ketone carbonyl at δc 201.9 (C), an ester carbonyl at δc 171.0 (C), an oxygenated quaternary carbon at δc 70.8 (C) and an oxygenated methine carbon at δc 78.7 (CH). The above data of compound **1** was very similar to those of

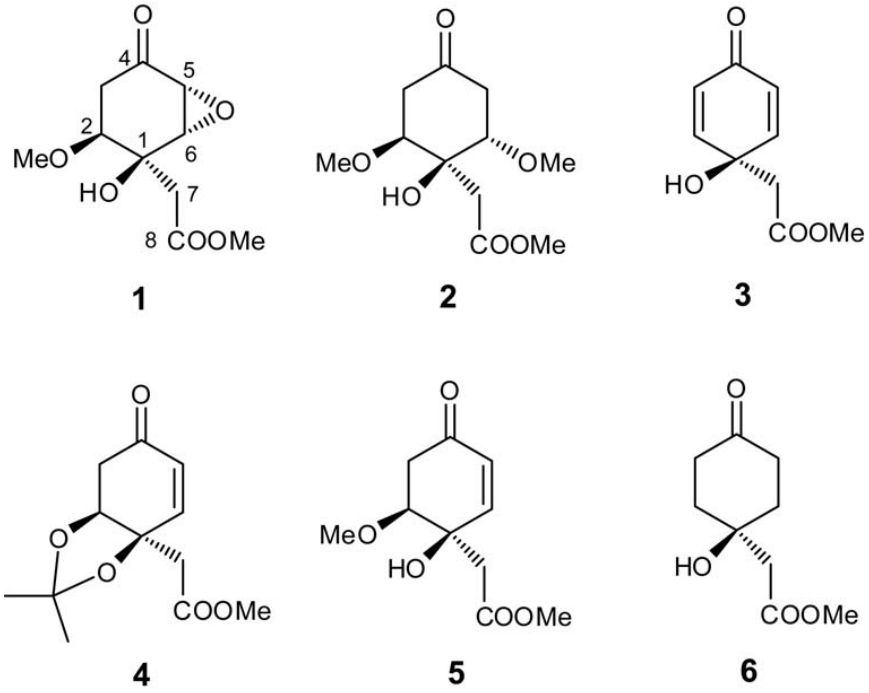

Fig. 1 The structures of compounds **1–6**.

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the known compound **5**. The only difference occurred at C-5 and C-6, where an epoxy was attached to C-5 and C-6 in compound **1** instead of an *α,β*-unsaturated double bond in compound **5**. The presence of epoxy group could be further verified by HMBC correlations (Table 1). The correlations of H-5/C-3,C-4,C-6 and H-6/C-1,C-2,C-5 suggested that the epoxy was attached to C-5 and C-6. Furthermore, the correlations between 2-OMe/C-2, H-2/C-1,C-3,C-4,C-6,2-OMe, H-7/C-1,C-2,C-6,C-8 and 8-OMe/C-8 further confirmed the position of methoxyl group and carbonyl group of compound **1**. In the NOESY spectrum, the correlation between H-5 and H-3*β* suggested that H-5 and H-6 were both *β*-orientations. Therefore, the structure of compound **1** was assigned as methyl 5*α*,6*α*-epoxy-1-hydroxy-2-methoxy-4-oxocyclohexanacetate.

Experimental

IR spectra were taken on Vertex 70 Ft-IR spectrometer in KBr. Optical rotation was measured on a Perkin-Elmer 341 polarimeter. ^{1}H, ^{13}C NMR (DEPT) and 2D NMR spectra were recorded on a Bruker Avance 500 spectrometer with TMS as internal standard. HR-ESI-MS spectrum was obtained on Bruker APEX II spectrometers. Silica gel (200–300 and 300–400 mesh) used for column chromatography (CC) and silica GF_{254} for TLC were supplied by Qingdao Marine Chemical Factory in China. Spots were detected on TLC under UV light at 254 and 365 nm or by heating after spraying with 5% H_2SO_4 in C_2H_5OH.

Plant material

The aerial parts of *S. argunensis* were collected from Changbai Mountains, Jilin Province, P. R. China in September 2008, and identified by Associate Prof. Hong Zhao, Marine College, Shandong University at Weihai. A voucher specimen (No. CB 2008010) is deposited in the Laboratory of Botany, Marine College, Shandong University at Weihai.

Extraction and isolation

The air-dried and powered aerial parts of *Senecio argunensis* (9.8 kg) were extracted with MeOH three times (7 days each time) at room temperature. The MeOH extract was concentrated under reduced pressure and the residue (1.2 kg) was suspended in hot water (60˚C, 4 L). This suspension was extracted with petroleum ether, $CHCl_3$ and n-butanol successively. The $CHCl_3$-soluble fraction was concentrated under reduced pressure to give a residue (125 g), which was chromatographed on silica gel column (200–300 mesh, 1,400 g) with a gradient of hexane/acetone (10:1, 5:1, 3:1, 1:1) as an eluent. Four crude fractions (Fr1–Fr4) were collected according to their TLC analysis. Fr1 (with hexane/acetone 10:1, 13.5 g) was isolated by silica gel column chromatography using hexane/ethyl acetate (15:1, 10:1, 5:1, 2:1) as eluent to yield four fractions: f_1–f_4. Fraction f_1 (3.0 g) was chromatographed over silica gel with a gradient of hexane/acetone (15:1–5:1) to give compound **2** (60 mg) and compound **3** (80 mg). Fraction f_2 (1.2 g) was chromatographed over silica gel with a gradient of hexane /acetone (15:1–8:1) to give compound **6** (20 mg). Fraction f_3 (2.2 g) was chromatographed over silica gel with a gradient of hexane/acetone (8:1) and purified by preparative TLC eluting with $CHCl_3$/acetone (10:1) to yield compound **1** (R*f* 0.42, 5 mg) and compound **5** (R*f* 0.38, 15 mg). Fr2 (with hexane/acetone 5:1, 13.5 g) was isolated by silica gel column chromatography using hexane/ethylacetate (8:1, 4:1, 2:1) as eluent and preparative TLC to yield three fractions: f_a–f_c. Fraction f_a (2.2 g) was chromatographed over silica gel with a gradient of hexane/acetone (8:1–4:1) to give compound **4** (50 mg).

Methyl 5α,6α-epoxy-1-hydroxy-2-methoxy-4-oxocyclohexanacetate (**1**): Colourless oil; $[\alpha]_D^{18}$ –4 (*c* 0.039, $CHCl_3$). IR (KBr) ν_{max}/cm^{-1}: 3469, 2959, 1727, 1441, 1261, 1099, 892, 803. HR-ESI-MS: *m/z*: 253.0689 ([M+Na]$^+$, $C_{10}H_{14}NaO_6^+$; Calcd 253.0683). ^{1}H, ^{13}C NMR and DEPT spectral data see Table 1.

Methyl 1-hydroxy-2,6-dimethoxy-4-oxocyclohexanacetate (**2**): $C_{11}H_{16}O_6$, Colourless crystal, m.p. 83–84°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.68 (3H, s, 8-OMe), 3.59 (1H, dd, *J* = 3.5, 4.0 Hz, H-6), 3.47 (1H, dd, *J* = 6.0, 10.0 Hz, H-2), 3.29 (3H, s, 2-OMe), 3.23 (3H, s, 6-OMe), 2.86 (1H, d, *J* = 14.5 Hz, H-7a), 2.83 (1H, dd, *J* = 4.0, 14.5 Hz, H-5*β*), 2.66 (1H, ddd, *J* = 1.5, 6.0, 12.5 Hz, H-3*α*), 2.63 (1H, dd, *J* = 10.0, 12.5 Hz, H-3*β*), 2.62 (1H, d, *J* = 14.5 Hz, H-7b), 2.52 (1H, ddd, *J* = 1.5, 3.5, 14.5 Hz, H-5*α*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 207.1 (C-4), 173.2 (C-8), 81.3 (C-2), 79.3 (C-6), 73.5 (C-1), 57.3 (2-OMe), 56.9 (6-OMe), 51.8 (8-OMe), 41.9 (C-7), 39.7 (C-3), 38.1 (C-5).

Jacaranone (**3**): $C_9H_{10}O_4$; Colourless crystal, m.p. 79–81°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.07 (2H, d, *J* = 10.0 Hz, H-3, H-5), 6.08 (2H, d, *J* = 10.0 Hz, H-2, H-6), 3.63 (3H, s, 8-OMe), 2.89 (brs, 4-OH), 2.77 (2H, s, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 184.7 (C-1), 169.2 (C-8), 150.5 (C-3, C-5), 127.2 (C-2, C-6), 67.0 (C-4), 51.0 (8-OMe), 44.7 (C-7).

Methyl 2-[2,2-dimethyl-6-oxo-7-dihydro-1,3-benzodioxol-3(6H)-yl]aceate (**4**): $C_{12}H_{16}O_5$; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.59 (1H, d, *J* = 10.0 Hz, H-5), 6.00 (1H, d, *J* = 10.0 Hz, H-6), 4.67 (1H, dd, *J* = 2.5, 5.5 Hz, H-3), 3.71 (3H, s, 8-OMe), 2.89 (1H, dd, *J* = 5.5, 17.5 Hz, H-2*β*), 2.80 (2H, s, H-7), 2.78 (1H, dd, *J* = 2.5, 17.5 Hz, H-2*α*), 1.37 (3H, s, H-10), 1.36 (3H, s, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 195.1 (C-1), 169.1 (C-8), 127.8 (C-5), 147.5 (C-6), 109.1 (C-9), 77.1 (C-3), 76.1 (C-4), 52.0 (8-OMe), 41.1 (C-7), 38.0 (C-2), 27.3 (C-10), 26.7 (C-11).

Methyl 1-hydroxy-2-methoxy-5-ene-4-oxocyclohexanacetate (**5**): $C_{10}H_{14}O_5$; Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.79 (1H, d, *J* = 10.0 Hz, H-6), 5.98 (1H, d, *J* = 10.0 Hz, H-5), 4.56 (brs, 1-OH), 3.76 (3H, s, 8-OMe), 3.74 (1H, dd, *J* = 4.0, 9.5 Hz, H-2), 3.45 (3H, s, 2-OMe), 2.93 (1H, d, *J* = 16.5 Hz, H-7a), 2.91 (1H, dd, *J* = 4.0, 17.0 Hz, H-3*β*), 2.60 (1H, d, *J* = 16.5 Hz, H-7b), 2.43 (1H, dd, *J* = 9.5, 17.0 Hz, H-3*α*); ^{13}C NMR (125 MHz $CDCl_3$,) δ_C 196.8 (C-4), 172.9 (C-8), 150.7 (C-6), 128.9 (C-5), 81.8 (C-2), 72.3 (C-1), 58.2 (2-OMe), 52,1 (8-OMe), 39.4 (C-7), 38.1 (C-3).

Methyl 1-hydroxy-4-oxocyclohexanacetate (**6**): $C_9H_{14}O_4$; Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.84 (1H, brs, 4-OH), 3.75 (3H, s, 8-OMe), 2.80 (2H, ddd, *J* = 6.0, 14.0, 14.0 Hz, H-2*β*, H-6*β*), 2.57 (2H, s, H-7), 2.24 (2H, ddd, *J* = 2.5, 5.0, 14.0 Hz, H-2*α*, H-6*α*), 2.11 (2H, ddd, *J* = 2.5, 6.0, 13.5 Hz, H-3*α*, H-5*α*), 1.77 (2H, ddd, *J* = 5.0, 13.5, 14.0 Hz, H-3*β*, H-5*β*).

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Table 1 ^{1}H, ^{13}C and DEPT data for compound **1** ($CDCl_3$, δ in ppm, TMS)[a]

No.	δ_H	δ_C	HMBC (H→C)
1	-	70.8 (s)	–
2	3.77 (dd, J = 7.5, 5.0, 1H)	78.7 (d)	C-1,C-3,C-4,C-6,-OMe
3*α*	2.98 (dd, J = 17.5, 5.0, 1H)	36.6 (t)	C-1, C-2, C-4
3*β*	2.26 (dd, J = 17.5, 7.5, 1H)		C-1, C-2, C-4, C-5
4	–	201.9 (s)	–
5	3.37 (d, J = 4.0, 1H)	55.0 (d)	C-3, C-4, C-6
6	3.69 (d, J = 4.0, 1H)	59.3 (d)	C-1, C-2, C-5, C-7
7a	2.82 (d, J = 16.0, 1H)	36.8 (t)	C-1,C-2, C-6,C-8
7b	2.54 (d, J = 16.0, 1H)		
8	–	171.0 (s)	–
2-OMe	3.36 (s, 3H)	56.8 (q)	C-8
8-OMe	3.75 (s, 3H)	51.1 (q)	C-2
1-OH	4.06 (brs, 1H)	–	–

[a] Measured at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR.

References

1 Y.L. Chen, *Flora Reipublicae popularis Sinicae*, Science Press, Beijing, 1999, pp. 77.
2 State Administration of Medicine and Drug of People's Republic of China, *Zhonghua Bencao*, Shanghai Science and Technology Press, 1999, vol.2, pp. 492.
3 K. Liu and E. Roder, *Phytochemistry*, 1991, **30**, 1301.
4 N. Li, L. Shao, C.F. Zhang and M. Zhang, *J. Nat. Prod.*, 2008, **10**,1143.
5 N. Li, C.F. Zhang and M. Zhang, *J. Chin. Pharm. Univ.*, 2008, **39**, 20.
6 C.F. Zhang, N. Li, L. Li and M. Zhang, *Chin. Chem. Lett.*, 2009, **20**, 598.
7 P. Torres, C. Grande, J. Anaya and M. Grande, *Fitoterapia*, 2000, **71**, 91.
8 E. Akbar, H.R. Nawaz and A. Malik, *Zeitschrift. Fuer. Naturforschung*, 2001, **56b**, 842.
9 M. Tori, H. Fukuyama, K. Nakashima and M. Sono, *Lett. Org. Chem.*, 2005, **2**, 262.
10 F. Bohlmann, C. Zdero, R.M. King and H. Robinson, *Phytochemistry*, 1981, **20**, 2425.
11 H. Xu, N. Zhang and J.E. Casida, *J. Agr. Food Chem*., 2003, **51**, 2544.
12 J.A. Marco, J.F. Sanz, E. Falco, J. Jakupovic and J. Lex, *Tetrahedron*, 1990, **46**, 7941.