Sesquiterpenoids from *Senecio argunensis*

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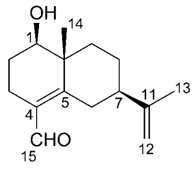
Investigation of unpolar extracts from the aerial parts of *Senecio argunensis* afforded two new sesquiterpenoids, 1β-hydroxyeudesma-4,11-dien-15-al (**1**) and 4(15)-cadinene-5α,10α-diol, (**2**) as well as six known compounds, **3**–**8**. The structures of all isolates were elucidated on the basis of extensive analyses of spectroscopic data and comparison with literature data.

Introduction. – *Senecio* is a genus of the daisy family (Asteraceae), with *ca.* 160 species widely distributed in China, of which several species are used as traditional Chinese medicine (TCM). *Senecio argunensis* TURCZ. is a perennial herb mainly occurring in north and northeast China, Mongolia, Korea Peninsula, and Russia [1]. Its roots and aerial parts are used for the treatment of sore throat, conjunctivitis, dysentery, and snake bites, *etc.* [2]. Earlier phytochemical investigations of this species mainly focused on its polar constituents, such as pyrrolizidine alkaloids [3], flavonoid alkaloids [4], and biflavonoid [5], monoterpene [6], and tetrahydronaphthalene derivatives [6]. During our systematic investigation of *Senecio* species scattered in northeast China, we have examined the unpolar extracts from the aerial parts of *S. argunensis*. Recently, several cyclohexanone derivatives were isolated by our research group [7]. Here, we report the isolation and structure elucidation of two new and six known sesquiterpenoids.

Results and Discussion. – Through the sequential purification of $CHCl_3$-soluble parts of MeOH extracts of *S. argunensis*, two new sesquiterpenoids, 1β-hydroxyeudesma-4,11-dien-15-al (**1**) and 4(15)-cadinene-5α,10α-diol (**2**), as well as six known sesquiterpenoids, 10α-hydroxycardin-4-en-15-al (**3**) [8], eudesm-4(15)-ene-1β,5α-diol (**4**) [9], eudesm-4(15)-ene-1β,6α-diol (**5**) [10], eudesm-4(15)-ene-1β,7α-diol (**6**) [11], 10α-hydroxyoplopan-4-one (**7**) [12], and aromadendrane-4β,10β-diol (**8**) [13], were isolated from the aerial parts of this plant. The known isolates were identified by comparison of their spectroscopic data with those reported in the literature.

Compound **1** was obtained as colorless oil. The IR spectrum showed absorption bands of OH (3446 cm^{-1}), C=C (1662 cm^{-1}), and C=O (1720 cm^{-1}). The molecular formula was determined to be $C_{15}H_{22}O_2$ by the *quasi*-molecular-ion peak at *m/z* 235.1693 ($[M+H]^+$) in the HR-ESI-MS. The ^{1}H-NMR spectrum (*Table*) displayed signals of two tertiary Me groups at δ(H) 1.77 (br. *s*) and 1.18 (*s*), of one characteristic



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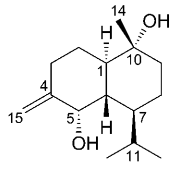

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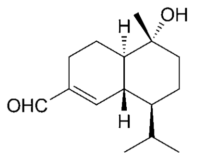

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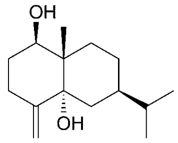

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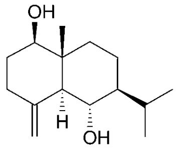

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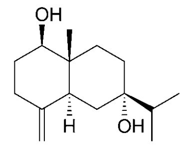

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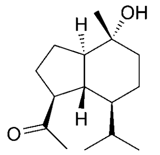

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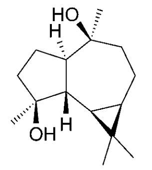

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Table. *^{1}H- and ^{13}C-NMR* (DEPT) *Data of* **1** *and* **2**[a]). δ in ppm, J in Hz.

	1			**2**	
	δ(H)	δ(C)		δ(H)	δ(C)
H−C(1)	3.51 (*dd*, J = 12.0, 3.5)	76.9	C(1)	1.65 (*ddd*, J = 12.0, 11.5, 3.5)	44.9
$\mathrm{H_a}$−C(2)	1.62–1.68 (*m*)[b])	26.0	$\mathrm{CH_2}$(2)	1.00–1.06 (*m*), 1.95–2.01 (*m*)	27.3
$\mathrm{H_b}$−C(2)	1.34–1.43 (*m*)				
$\mathrm{H_a}$−C(3)	2.52–2.57 (*m*)	22.6	$\mathrm{H_a}$−C(3)	2.14 (*ddd*, J = 13.5, 3.5, 3.0)	29.4
$\mathrm{H_b}$−C(3)	1.76–1.83 (*m*)		$\mathrm{H_b}$−C(3)	2.28–2.35 (*m*)	
C(4)		131.4	C(4)		150.7
C(5)		162.2	H−C(5)	4.22 (br. *d*, J = 2.0)	71.6
$\mathrm{H_a}$−C(6)	3.41 (br. *d*, J = 13.5)	29.1	H−C(6)	1.14 (*ddd*, J = 11.5, 11.0, 2.0)	45.8
$\mathrm{H_b}$−C(6)	2.15–2.19 (*m*)				
H−C(7)	2.11–2.16 (*m*)	46.5	H−C(7)	1.43–1.49 (*m*)	42.0
$\mathrm{CH_2}$(8)	1.62–1.70 (*m*)[b])	26.6	$\mathrm{H_a}$−C(8)	1.54–1.61 (*m*)	21.1
			$\mathrm{H_b}$−C(8)	0.96–1.00 (*m*)	
$\mathrm{H_a}$−C(9)	2.02–2.08 (*m*)	38.2	$\mathrm{H_a}$−C(9)	1.71 (*ddd*, J = 12.5, 3.5, 3.0)	42.2
$\mathrm{H_b}$−C(9)	1.55–1.61 (*m*)		$\mathrm{H_b}$−C(9)	1.36 (*ddd*, J = 12.5, 12.5, 3.5)	
C(10)		41.4	C(10)		72.9
C(11)		148.7	H−C(11)	2.01–2.06 (*m*)	25.5
$\mathrm{CH_2}$(12)	4.77 (br. *s*)	109.4	Me(12)	0.70 (*d*, J = 7.0)	15.4
Me(13)	1.77 (br. *s*)	20.6	Me(13)	0.88 (*d*, J = 7.0)	21.6
Me(14)	1.18 (*s*)	17.6	Me(14)	0.99 (*s*)	21.0
H−C(15)	10.18 (*s*)	190.5	$\mathrm{H_a}$−C(15)	4.68 (br. *s*)	109.6
			$\mathrm{H_b}$−C(15)	4.76 (br. *s*)	

[a]) Recorded in $\mathrm{CDCl_3}$ at 500 MHz for ^{1}H-NMR and at 125 MHz for ^{13}C-NMR and DEPT. [b]) Overlapping signals.

terminal olefinic $\mathrm{CH_2}$ group at δ(H) 4.77 (br. *s*), of an O-bearing CH group at δ(H) 3.51 (*dd*, J = 12.0, 3.5), and of an aldehyde H-atom at δ(H) 10.18 (*s*). The ^{13}C-NMR (DEPT) spectrum of **1** (*Table*) showed the presence of 15 C-atoms, including an aldehyde CO group (δ(C) 190.5), two terminal olefinic C-atoms (δ(C) 148.7 (*s*) and 109.4 (*t*)), two tetrasubstituted olefinic C-atoms (δ(C) 131.4 (C(4)) and 162.2 (C(5))), and an O-bearing CH group (δ(C) 76.9 (*d*)). By comparison of the above data with those of a very similar sesquiterpenoid, 2α-hydroxyeudesma-4,11-dien-15-al [14], compound **1** was determined as 1β-hydroxyeudesma-4,11-dien-15-al.

Careful examination of the HMBCs supported the basic C-framework of **1** as an eudesmane-type sesquiterpenoid (*Fig. 1*). The locations of the functional groups were confirmed as follows: the HMBC δ(H) 10.18 (H−C(15))/δ(C) 131.4 (C(4)) suggested conjugation of the tetrasubstituted C=C bond with the aldehyde CO group. The correlations δ(H) 1.18 (Me(14))/δ(C) 162.2 (C(4)), 38.2 (C(9)), 76.9 (C(1)), and 41.4 (C(10)) confirmed the position of a tetrasubstituted C=C bond between C(4) and C(5), and the location of an OH group at C(1). The correlations δ(H) 1.77 (Me(13))/δ(C) 148.7 (C(11)), 109.4 (C(12)), and 46.5 (C(7)) indicated the terminal C=CH_2 bond to be located between C(11) and C(12). The configuration of **1** was determined on the basis of the analysis of NOESY correlations and coupling constants (*Fig. 1*). The NOESY correlations observed between Me(14) and H_a−C(6) demonstrated that these groups are positioned on the same face of the molecule. The NOESY correlation peaks H−C(1)/H_b−C(9) and H_b−C(9)/H−C(7) suggested that the relative configurations of H−C(1) and H−C(7) are both α. Furthermore, the large coupling constant of H−C(1) with H−C(2) ($J(1\alpha,2\beta) = 12.0$) also suggested H−C(1) to be in an axial orientation, which means that the OH group at C(1) has β orientation. From these data, the structure of **1** was established as 1β-hydroxyeudesma-4,11-dien-15-al. The absolute configuration of **1** was not determined.

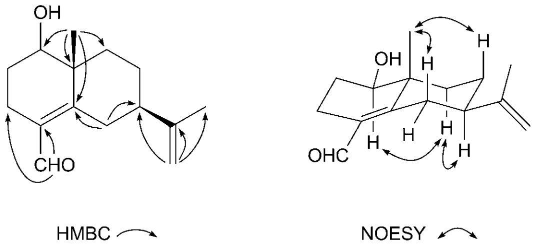

Fig. 1. *Key HMBC and NOESY correlations for* **1**

The HR-ESI-MS of compound **2** showed a *quasi*-molecular-ion peak at *m/z* 256.2277 ($[M+NH_4]^+$), in accord with the molecular formula $C_{15}H_{26}O_2$. The IR spectrum showed absorption bands of OH (3375 cm^{-1}) and C=C (1654 cm^{-1}). In the ^{1}H-NMR spectrum (*Table*), the signals of two secondary Me groups at δ(H) 0.70 (*d*, $J = 7.0$) and 0.88 (*d*, $J = 7.0$), coupled to a CH group at δ(H) 2.01 – 2.06 (*m*), suggested the presence of an ^{i}Pr group. The ^{1}H-NMR signals at δ(H) 4.68 (br. *s*) and 4.76 (br. *s*), and the corresponding C-atom signals at δ(C) 109.6 (*t*) and 150.7 (*s*) were assigned to an exocyclic C=CH_2 group. In addition, the ^{1}H-NMR spectrum (*Table*) also showed the presence of a tertiary Me group (δ(H) 0.99 (*s*)), and an O-bearing CH group (δ(H) 4.22 (br. *d*, $J = 2.0$)). The quaternary C-atom signal at δ(C) 72.9 in the ^{13}C-NMR spectrum indicated the presence of a quaternary OH group. Detailed analysis of 2D-NMR (*Fig. 2*) enabled us to establish the structure of **2** as 4(15)-cadinene-5α,10α-diol.

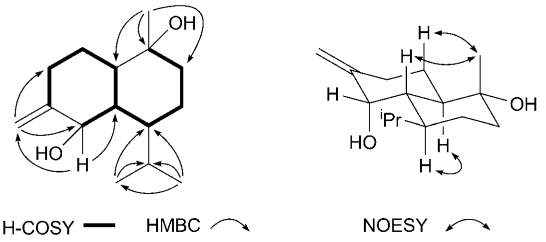

Fig. 2. *Partial structure resolved by ^{1}H,^{1}H-COSY, key HMBC, and NOESY correlations for* **2**

Two closely related sesquiterpenoids, 4(15)-cadinene-10β-ol (millecrol B) [15] and 4(15)-cadinene-6β,10α-diol (isocalamenediol) [16], have been previously reported as natural products.

The chemical shifts of each H-bearing C-atom and the corresponding H-atoms were unambiguously assigned by HMQC (*Table*). The ^{1}H,^{1}H-COSY spectrum indicated the connectivities of C(1) to C(3), and C(5) to C(9) (*Fig. 2*). The ^{1}H,^{1}H-COSY correlation H–C(1)/H–C(6) and allylic coupling correlation CH_2(15)/CH_2(3) were also observed. The *singlet* of the Me group at δ(H) 0.99 (*s*) and the HMBCs δ(H) 0.99 (Me(14))/δ(C) 44.9 (H–C(1)), 72.9 (C(10)), and 42.0 (CH_2(9)) suggested that both Me(14) and quaternary OH group are located on the quaternary C-atom (C(10)). The HMBCs δ(H) 4.68 (H_a–C(15))/δ(C) 71.6 (H–C(5)), δ(H) 4.76 (H_b–C(15))/δ(C) 71.6 (H–C(5)), and δ(H) 4.22 (H–C(5))/δ(C) 29.4 (CH_2(3)), 44.9 (H–C(1)), 109.6 (CH_2(15)) confirmed the OH group to be attached to C(5). In the ^{1}H-NMR spectrum (*Table*), the large coupling constants of H–C(1) with H–C(6) ($J(1\alpha,6\beta) = 11.5$), and H–C(6) with H–C(7) ($J(6\beta,7\alpha) = 11.0$) suggested axial orientations of H–C(1), H–C(6), and H–C(7). Therefore, the two rings are *trans*-fused with the ⁱPr moiety in β orientation (*Fig. 2*), which was further confirmed by the NOESY correlation H–C(1)/H–C(7). The NOESY correlation peak observed between H–C(6) and Me(14) indicated that both H–C(6) and Me(14) were in β orientation (*Fig. 2*). The α configuration of the OH group at C(5) was deduced from the small coupling constant of H–C(5) with H–C(6) ($J(5\beta,6\beta) = 2.0$) [16]. The constitutional formula of **2** is the same as that of 5α,10α-dihydroxymuurol-4(15)-ene [17]. The differences of chemical shifts in the ^{1}H- and ^{13}C-NMR spectra between these two compounds result from the different relative configurations. In the structure of 5α,10α-dihydroxymuurol-4(15)-ene, the H-atoms at the ring junction are *cis* to each other [17], in contrast to the *trans*-junction in **2**. The absolute configuration of **2** was not determined due to the small amount of isolated material.

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Experimental Part

General. TLC: silica gel *GF*$_{254}$ (*Qingdao Marine Chemical Factory*, P. R. China). Column chromatography (CC): silica gel *G* (SiO_2; 200–300 and 300–400 mesh, *Qingdao Marine Chemical Factory*, P. R. China); silica gel *C-18* (*Merck*). Optical rotations: *Perkin-Elmer 341* polarimeter. IR

Spectra: *Bruker Vertex 70* FT-IR spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR (DEPT), and 2D-NMR Spectra: *Bruker AVANCE 500* spectrometer; δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-ESI-MS: *Bruker APEX-II* spectrometer.

Plant Material. The aerial parts of *S. argunensis* were collected from Changbai Mountain, Tonghua, 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. CB200810) was deposited with the herbarium in the Laboratory of Botany, Marine College, Shandong University at Weihai.

Extraction and Isolation. The air-dried aerial parts of *Senecio argunensis* (9.8 kg) were powdered and extracted with MeOH three times (7 d each time) at r.t. The solvent was evaporated, and the residue (1.2 kg) was suspended in hot H_2O (60°, 4 l). This suspension was extracted successively with hexane and $CHCl_3$. The $CHCl_3$-soluble fraction was concentrated to afford a residue (125 g), which was subjected to CC (SiO_2, 200 – 300 mesh, 1400 g; hexane/acetone 10 : 1, 5 : 1, 3 : 1, and 1 : 1): *Frs. 1 – 4*. *Fr. 1* (with hexane/acetone 10 : 1; 13.5 g) was subjected to CC (SiO_2, 300 – 400 mesh, 150 g; hexane/AcOEt 15 : 1, 10 : 1, 5 : 1, and 2 : 1) to afford subfractions f_1 – f_4. *Subfr.* f_1 (hexane/AcOEt 15 : 1; 3.0 g) was subjected to CC (SiO_2; hexane/$CHCl_3$ 3 : 1) to yield a mixture, which was further purified by low-pressure CC (*C-18*; MeOH/H_2O 3 : 2) to give **1** (6 mg) and **3** (8 mg). *Subfr.* f_2 (hexane/AcOEt 10 : 1; 1.2 g) was purified by CC (hexane/AcOEt 6 : 1) and prep. TLC ($CHCl_3$/acetone 9 : 1) to yield **4** (R_f 0.42; 12 mg). *Subfr.* f_3 (hexane/AcOEt 5 : 1; 2.2 g) was separated by CC (hexane/acetone 8 : 1) and low-pressure CC (*C-18*; MeOH/H_2O 1 : 1) to give **5** (25 mg). *Subfr.* f_4 (hexane/AcOEt 2 : 1; 1.0 g) was purifed by CC (hexane/acetone 6 : 1) and low-pressure CC (*C-18*; MeOH/H_2O 1 : 1) to give **7** (12 mg). *Fr. 2* (with hexane/acetone 5 : 1; 12.5 g) was subjected to CC (SiO_2, 300 – 400 mesh, 150 g; hexane/AcOEt 8 : 1, 4 : 1, 2 : 1, and 1 : 1) to afford subfractions f_5 – f_8. *Subfr.* f_5 (hexane/AcOEt 8 : 1; 2.2 g) was subjected to CC (SiO_2; hexane/AcOEt 6 : 1), and further purified by low-pressure CC (*C-18*; MeOH/H_2O 1 : 1) to give **2** (3 mg). *Subfr.* f_7 (hexane/AcOEt 2 : 1; 1.6 g) was purified by repeated CC (hexane/acetone 8 : 1, 4 : 1) to afford **6** (9 mg) and **8** (4 mg). There is no interesting compound in *Fr. 3* (with hexane/acetone 3 : 1; 28 g) and *Fr. 4* (with hexane/acetone 1 : 1; 37 g).

1β-Hydroxyeudesma-4,11-dien-15-al (= rel-*(4*R*,4a*R*,7*R*)-2,3,4,4a,5,6,7,8-Octahydro-4-hydroxy-4a-methyl-7-(1-methylethenyl)naphthalene-1-carbaldehyde*; **1**): Colorless oil. $[\alpha]_D^{20} = +88$ ($c = 0.4$, $CHCl_3$). IR (film): 3446, 3081, 2926, 2855, 1720, 1662, 1614, 1453, 1364, 1026, 884, 800. ^{1}H- and ^{13}C-NMR: see *Table*. HR-ESI-MS: 235.1690 ($[M + H]^+$, $C_{15}H_{23}NO_2^+$; calc. 235.1693).

4(15)-Cadinene-5α,10α-diol (= rel-*(1*R*,4*S*,4a*S*,5*S*,8a*R*)-Decahydro-1-methyl-6-methylidene-4-(1-methylethenyl)naphthalene-1,5-diol*; **2**): Colorless oil. $[\alpha]_D^{20} = -81$ ($c = 0.2$, $CHCl_3$). IR (film): 3375, 3064, 2926, 2859, 1654, 1467, 1373, 1258, 1031. ^{1}H- and ^{13}C-NMR: see *Table*. HR-ESI-MS: 256.2277 ($[M + NH_4]^+$, $C_{15}H_{30}NO_2^+$; calc. 256.2271).

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