Sesquiterpenoids and Other Constituents from *Senecio argunensis*

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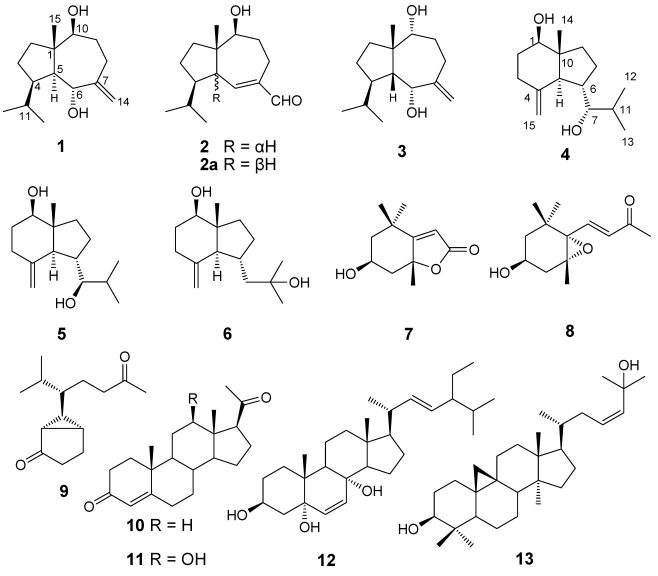
Three new sesquiterpenoids, isodauc-7(14)-en-6α,10β-diol (1), 10β-hydroxyisodauc-6-en-14-al (2), and (7*S)-opposit-4(15)-en-1β,7-diol (4), along with ten known compounds have been isolated from the aerial parts of *Senecio argunensis*. Their structures were established by means of detailed spectroscopic analysis including IR, HR-MS, and 1D NMR and 2D NMR data. The sesquiterpenoids were assayed against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*. Compounds 4 exhibited weak antibacterial activity against *Escherichia coli* and *Bacillus subtilis*.**

Key words *Senecio argunensis*; sesquiterpenoid; isodaucane; oppositane; antibacterial

Senecio argunensis Turcz. (Compositae), a perennial herb, is extensively distributed in north and northeast China, Korea Peninsula, Far East of Russia, and Mongolia. The whole plant of this species is widely used as a traditional Chinese medicine for the treatment of sore throat, and dysentery, *etc*.[1] Mongolian also used it to cure trauma and fracture. Previous phytochemical studies of this plant have led to the isolation of pyrrolizidine alkaloids,[2] flavonoid alkaloids,[3] flavonoid,[4] monoterpene and tetrahydronaphthene derivatives,[5] and cyclohexanone derivatives.[6] As a part of our ongoing study on the finding antibacterial and antifungal sesquiterpenoids from poisonous plants scattered in northeast China, the lesser polar constituents of *S. argunensis* were systematically investigated. As a result, three new sesquiterpenoids, isodauc-7(14)-en-6α,10β-diol (**1**), 10β-hydroxyisodauc-6-en-14-al (**2**), and (7*S**)-opposit-4(15)-en-1β,7-diol (**4**), along with nine known compounds, artabotrol (**3**),[7] (7*R**)-opposit-4(15)-en-1β,7-diol (**5**),[8] opposit-4(15)-en-1β,11-diol (**6**),[9] loliolide (**7**),[10] 5α,6α-epoxy-3β-hydroxymegastigm-7-en-9-one (**8**),[11] chromolaevane dione (**9**),[12] pregn-4-en-3,20-dione (**10**),[13] 12β-hydroxypregn-4-en-3,20-dione (**11**),[14] ergost-6,22-dien-3β,5α,8α-triol (**12**),[15] (23*Z*)-cycloart-23-en-3β,25-diol (**13**)[16] have been isolated from the aerial parts of this plant. This paper deals with the isolation and structure determination of three new constituents. In addition, the antibacterial activity of selected isolates against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis* were also evaluated.



Results and Discussion

Compound **1** was isolated as colorless oil. Its IR spectrum showed the absorption bands of hydroxy group (3384 cm^{-1}) and double bond moiety (1645 cm^{-1}). The molecular formula was determined to be $C_{15}H_{26}O_2$ by the molecular ion peak at *m*/*z* 238.1926 ([M]$^+$, $C_{15}H_{26}O_2^+$; Calcd 238.1933) in high resolution electronic ionization mass spectrometry (HR-EI-MS). The ^{1}H-, ^{13}C-NMR and the distorsionless enhancement by polarization transfer (DEPT) spectra of **1** (Tables 1, 2), obtained with the aid of a ^{1}H-detected heteronuclear multiple quantum coherence spectrum (HMQC), showed signals due to an isopropyl group [δ_H 0.75 (3H, d, J=7.0 Hz, Me-12), 0.84 (3H, d, J=7.0 Hz, Me-13), coupled to a methine group at δ_H 2.06 (1H, m); δ_C 14.5 (C-12), 21.8 (C-13)], an exocyclic double bond group [δ_H 4.90 (2H, br s, H-14); δ_C 114.3 (C-14), 153.1 (C-7)], a tertiary methyl group [δ_H 0.74 (3H, s, Me-15); δ_C 11.7 (C-15)] and two oxygenated methines [δ_H 3.96 (1H, d, J=9.0 Hz, H-6), 3.34 (1H, dd, J=11.5, 5.0 Hz, H-10); δ_C 78.9 (C-6), 81.1 (C-10)], as well as other complicated signals belonging to other methylenes and methines. Detailed analysis of the cross peaks observed in the ^{1}H–^{1}H shift correlation spectroscopy (^{1}H–^{1}H COSY) and heteronuclear multiple bond coherence spectroscopy (HMBC) (Fig. 1) allow to establish the basic skeleton of **1** to be isodaucane sesquiterpenoid, and to confirm the locations of functional groups. The ^{1}H–^{1}H COSY spectrum showed the connectivities of C-2 to C-6, C-8 to C-10, and C-11 to C-12 and C-13 (Fig. 1). In addition, the long rang coupling correlations of H-14 with H-6 and H-8 were also observed, which also confirmed the adjacence of a hydroxy and exocyclic double bond group. In the HMBC spectrum (Fig. 1), the correlations of H_3-15 (δ_H 0.74) to C-1 (δ_C 48.1), C-2 (δ_C 40.2), C-5 (δ_C 49.9) and C-10 (δ_C 81.1), and H-10 to C-2 (δ_C 40.2) and C-5 (δ_C 49.9) suggested the Me-15 was at ring junction and a hydroxy was at C-10. The HMBC correlations of H_3-12 (δ_H 0.75) and H_3-13 (δ_H 0.84) to C-4 (δ_C 50.5) confirmed the position of isopropyl group at C-4. The HMBC correlations of H_2-14 (δ_H 4.90) to C-6 (δ_C 78.9) and C-8 (δ_C 26.9), and H-6

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Table 1. ^{1}H-NMR Data of Compounds **1**, **2**, **4** and **5** (500 MHz, $CDCl_3$, δ in ppm, J in Hz)

No.	1	2	4	5
1	—	—	3.54 (dd, 10.5, 4.0)	3.58 (dd, 11.5, 5.0)
2	1.54 (m)	1.50 (m)	1.75 (m)	1.90 (m)
	1.29 (m)	1.25 (m)	1.44 (m)	1.48 (m)
3	1.51 (m)	1.51 (m)	2.00 (br ddd, 15.5, 13.5, 5.5)	2.12 (ddd, 13.5, 13.5, 5.5)
		1.92 (m)	2.22 (ddd, 15.5, 5.5, 2.0)	2.30 (m)
4	2.04 (m)	2.03 (m)	—	—
5	1.48 (dd, 9.0, 8.5)	2.25 (dd, 11.5, 5.0)	1.94 (br d, 10.5)	1.83 (d, 10.5)
6	3.96 (d, 9.0)	6.60 (ddd, 5.0, 1.8, 0.9)	2.27 (m)	2.32 (m)
7	—	—	3.30 (br dd, 8.5, 2.5)	3.23 (br d, 9.5)
8	2.18 (m)	2.98 (m)	1.58 (m)	1.75 (m)
		1.91 (m)		
9	1.96 (m)	1.79 (m)	1.26 (m)	1.38 (m)
	1.41 (m)	1.26 (m)	1.65 (m)	1.75 (m)
10	3.34 (dd, 11.5, 5.0)	3.49 (dd, 11.5, 4.0)	—	—
11	2.06 (m)	1.63 (m)	1.57 (m)	1.75 (m)
12	0.75 (d, 7.0)	0.90 (d, 7.0)	0.86 (d, 7.0)	0.91 (d, 7.0)
13	0.84 (d, 7.0)	0.89 (d, 7.0)	0.93 (d, 7.0)	0.99 (d, 7.0)
14	4.90 (br s)	9.37 (s)	0.59 (s)	0.66 (s)
15	0.74 (s)	0.74 (s)	4.43 (br d, 2.0)	4.81 (br s)
			4.78 (br d, 2.0)	4.94 (br s)

Table 2. ^{13}C-NMR (DEPT) Data of Compounds **1**, **2**, **4** and **5** (125 MHz, $CDCl_3$, δ in ppm)

No.	1	2	4	5
1	48.1 d	49.3 s	78.0 d	77.9 d
2	40.2 t	39.4 t	30.8 t	30.8 t
3	20.9 t	24.9 t	33.5 t	33.9 t
4	50.5 d	50.2 d	145.3 s	147.9 s
5	49.9 d	49.6 d	51.2 d	55.4 d
6	78.9 d	159.6 d	37.6 d	38.3 d
7	153.1 s	143.6 s	75.4 d	81.7 d
8	26.9 t	19.4 t	19.2 t	25.0 t
9	35.1 t	28.8 t	36.3 t	36.3 t
10	81.1 d	83.2 d	47.3 s	48.5 s
11	29.1 d	32.1 d	32.5 d	30.3 d
12	14.5 q	19.3 q	18.2 q	13.7 q
13	21.8 q	21.5 q	18.6 q	19.5 q
14	114.3 t	193.1 d	10.9 q	11.2 q
15	11.7 q	13.4 q	105.1 t	106.6 d

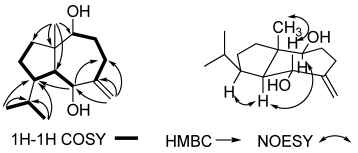

Fig. 1. ^{1}H–^{1}H COSY, Key HMBC and NOESY Correlations for **1**

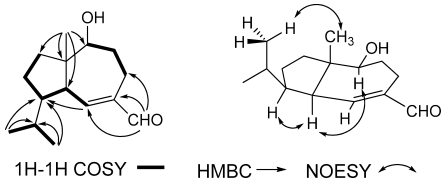

Fig. 2. ^{1}H–^{1}H COSY, Key HMBC and NOESY Correlations for **2**

(δ_H 3.96) to C-4 (δ_C 50.5) and C-14 (δ_C 114.3) permitted the assignment of exocyclic double bond group between C-7 and C-14, and a hydroxy group at C-6. Therefore, the plane structure of **1** was deduced to be isodauc-7(14)-en-6,10-diol, which is same as that of artabotrol (**3**),[7] a closely related isodaucane sesquiterpene isolated at the same time. The significant differences observed between the chemical shifts of **1** (Table 1) and **3** were the results of different stereochemistry.[7] The nuclear Overhauser effect correlation spectroscopy (NOESY) cross peaks observed between H_3-15 and H-6 strongly suggest that Me-15 and H-6 were β orientation, while cross peaks between H-10 and H-5, and H-5 and H-4 indicated the α orientation of H-4, H-5 and H-10 (Fig. 1). The large coupling constants for H-10 (dd, J=11.5, 5.0 Hz) also suggested the β orientation of the hydroxy group at C-10. Thus, the structure of **1** was determined as isodauc-7(14)-en-6α,10β-diol.

Compound **2** was isolated as colorless oil. The molecular formula was deduced to be $C_{15}H_{24}O_2$ by the quasi molecular ion peak at m/z 237.1844 $[M+H]^+$ (Calcd 237.1849) in HR-ESI-MS. Its IR spectrum showed the presence of hydroxy group (3446 cm^{-1}), double bond group (1645 cm^{-1}), and carbonyl group conjugated with double bond (1676 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra of **2** (Tables 1, 2) showed distinctly the presence of two secondary methyl group [δ_H 0.90 (3H, d, J=7.0 Hz, Me-12), 0.89 (3H, d, J=7.0 Hz, Me-13); δ_C 19.3 (C-12), 21.5 (C-13)], a tertiary methyl group [δ_H 0.74 (3H, s, Me-15); δ_C 13.4 (C-15)], an oxygenated methines [δ_H 3.49 (1H, dd, J=11.5, 4.0 Hz, H-10); δ_C 83.2 (C-10)], an trisubstituted double bond moiety [δ_H 6.60 (1H, ddd, J=5.0, 1.8, 0.9 Hz, H-6); δ_C 159.6 (C-14), 143.6 (C-7)], and an aldehyde group [δ_H 9.37 (1H, s, H-14); δ_C 193.1 (C-14)]. Except for minor differences observed between the chemical shifts for C-4, C-5 and C-10, the ^{1}H- and ^{13}C-NMR spectra of **2** were very similar to that of aphanamol II (**2a**).[17] The HMQC, ^{1}H–^{1}H COSY and HMBC spectra (Fig. 2) established the plane structure of **2** as that of 10-hydroxyisodauc-6-en-14-al which is identical with the plane structure of aphanamol II (**2a**).[17] The relative stereochemistry of **2** was deduced by NOESY spectrum (Fig. 2). In this spectrum, H_3-15 and H-5 did not show NOESY correlation, indicating a *trans*-configu-

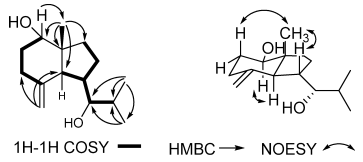

Fig. 3. ^{1}H–^{1}H COSY, Key HMBC and NOESY Correlations for **4**

ration of Me-15 and H-5, while the correlations between H_3-15 and H_3-12, H-5 and H-10, and H-5 and H-4 were observed. These NOESY correlations suggested that Me-15, isopropyl group and the hydroxy group at C-10 were all β orientation, and H-5 and H-10 were α orientation. The large coupling constants for H-10 (dd, J=11.5, 4.0 Hz) also supported the β orientation of the hydroxy group at C-10. From these data, the structure of **2** was established as 10β-hydroxyisodauc-6-en-14-al, a 5-epimer of **2a**.

Compound **4** was isolated as colorless oil. The molecular formula was determined to be $C_{15}H_{26}O_2$ by the quasi molecular ion peak at *m/z* 237.1846 $[M+H]^+$ (Calcd 237.1849) in HR-ESI-MS. Its IR spectrum showed absorptions of hydroxy group 3379 cm^{-1}) and double bond group (1654 cm^{-1}). The ^{1}H- and ^{13}C-NMR (DEPT) spectra of **4** showed the presence of three methyls [δ_H 0.86 (3H, d, J=7.0 Hz, Me-12), 0.93 (3H, d, J=7.0 Hz, Me-13) and 0.59 (3H, s, Me-14); δ_C 18.2 (C-12), 18.6 (C-13) and 10.9 (C-14)], an exocyclic double bond [δ_H 4.43, 4.78 (each 1H, br d, J=2.0 Hz, H-15); δ_C 105.1 (C-15), 145.3 (C-4)] and two oxygenated methines [δ_H 3.54 (1H, dd, J=10.5, 4.0 Hz, H-1), 3.30 (1H, br dd, J=8.5, 2.5 Hz, H-7); δ_C 78.0 (C-1), 75.4 (C-7)]. The remaining signals indicated four methylenes, three methines, and quarternary carbon. Extensive analysis of ^{1}H–^{1}H COSY, HMBC (Fig. 3) and HMQC correlations suggested the plane structure of **4** is same as that of (7*R**)-opposit-4(15)-en-1β,7-diol (**5**) (Table 2).[8] In the NOESY spectrum, the cross peaks observed between H_3-14 and H-6, and H-5 and H-1 suggested a *trans* junction for the two rings, and the relative configuration of the hydroxy at C-1, Me-14 and isobutyl group at C-6 should be β, β and α respectively. These observations were identical to that of compound **5**. Compared with the ^{13}C-NMR chemical shifts of **5**, the highfield shifts of C-5 (from δ_C 55.4 to δ_C 51.2) and C-8 (from δ_C 25.0 to δ_C 19.2), and the lowfield shift of C-12 (from δ_C 13.7 to δ_C 18.2) in **4** were observed, which were only explained to be the different γ-gauche effects arose from the different configurations of 7-hydroxy in these two isomers. Hence, the structure of **4** was determined as (7*S**)-opposit-4(15)-en-1β,7-diol. The absolute configuration of the hydroxy at C-7 was not determined for minor amount. This is the first report of oppositane-type sesquiterpenoid isolated from *Senecio* species.

The antibacterial activity of **1**—**6** was determined against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*, and compared with Chloramphenicol. The zone diameters of growth inhibition against *Escherichia coli* and *Bacillus subtilis* of **4** are 10—12 mm, which indicated that **4** possess weak antibacterial activity. Other tested compounds exhibited no antibacterial activity.

Experimental

General Procedures Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR spectrua were recorded with a Bruker Vertex 70 FT-IR spectrometer in film. ^{1}H-, ^{13}C-NMR (DEPT) and 2D NMR were recorded on Bruker AVANCE 500 spectrometer with tetramethylsilane (TMS) as internal reference. HR-EI-MS spectrum was obtained on Accela UPLC-LTQ Orbitrap Mass spectrometer. HR-ESI-MS spectra were obtained on Bruker APEX II spectrometer using direct insertion probe method. Silica gel (200—300, 300—400 mesh) used for column chromatography (CC) and silica GF_{254} for thin layer chromatography were purchased from Qingdao Marine Chemical Factory in China. Silica gel C-18 used for low pressure CC were purchased from Merck. 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 *Senecio argunensis* were collected in 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 at the herbarium in the Laboratory of Botany, Marine College, Shandong University at Weihai.

Extraction and Isolation The air-dried aerial parts of *S. argunensis* (9.8 kg) were pulverized and extracted with CH_3OH three times (7 d each time) at room temperature. The extract was concentrated under reduced pressure to afford a residue (1.2 kg). This crude extract was suspended in H_2O, and extracted with petroleum ether and $CHCl_3$ to give a dry petroleum ether extract (240 g) and $CHCl_3$ extract (125 g), respectively. The $CHCl_3$ extract was subjected to silica gel column chromatography (CC) with hexane-acetone gradient (10 : 1, 5 : 1, 3 : 1, 1 : 1) to yield four fractions (Fr. A—Fr. D) according to TLC analysis. Fr. A (hexane–acetone 10 : 1; 13.5 g) was subject to silica gel CC with a hexane–EtOAc (15 : 1—0 : 1) gradient to obtained four subfractions (Fr. A1—Fr. A4). Fr. A2 (1.2 g) was isolated by silica gel CC with a hexane–EtOAc (20 : 1—0 : 1) elution, and further purified by low pressure C-18 CC with H_2O–MeOH (2 : 3) elution to obtained **2** (3 mg). Fr. A3 (2.2 g) was isolated by silica gel CC with hexane–acetone (20 : 1—0 : 1) gradient to obtained five subfractions (Fr. A3a—Fr. A3e). Fr. A3a (0.6 g) were purified by low pressure C-18 CC using H_2O–MeOH elution (1 : 2) to give **9** (4 mg) and **10** (26 mg). Fr. A3b (0.8 g) was purified by repeated low pressure C-18 CC eluting with H_2O–MeOH (1 : 1) to yield **13** (3 mg) and **12** (3 mg), respectively. Fr. A3c (120 mg) were isolated by repeated CC with hexane–EtOAc (6 : 1) as eluent to give **1** (5 mg), **3** (8 mg) and **11** (20 mg). Fr. A3d (66 mg) was subjected to a silica gel CC with hexane–acetone (3 : 1) as eluent to afford **5** (14 mg). Fr. B (hexane/acetone 3 : 1; 12.5 g) was subjected to a silica gel CC (150 g) with a hexane–EtOAc (10 : 1—0 : 1) gradient to obtained five fractions (Fr. B1—Fr. B4). Fr. B3 (1.6 g) was isolated by repeated silica gel CC with hexane–acetone (8 : 1—4 : 1) elution, and further purified by low pressure C-18 CC eluting with a H_2O–MeOH gradient (2 : 1, 1 : 1, 2 : 3) to yield **8** (7 mg), **6** (10 mg) and **4** (3 mg), respectively. Fr. B4 (5.2 g) was purified by repeated silica gel CC with hexane–EtOAc (3 : 1) as eluent to yield **7** (25 mg). There is no interesting compound in Fr. C (hexane/acetone 3 : 1; 28 g) and Fr. D (hexane/acetone 1 : 1; 37 g).

By comparing the spectral data with those reported in the literatures, the known compounds were identified.

Isodauc-7(14)-en-6α,10β-diol (**1**): Colorless oil; $[\alpha]_D^{20}$ −89° (c=1.0, $CHCl_3$); IR (Film) ν_{max} 3384, 3064, 2957, 2930, 2868, 1645, 1449, 1382, 1258, 1017, 968, 902 and 800 cm^{-1}. HR-EI-MS *m/z*: 238.1926 ($[M]^+$, Calcd for $C_{15}H_{26}O_2$: 238.1933). ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 1. ^{13}C-NMR (DEPT) (125 MHz, $CDCl_3$): see Table 2.

10β-Hydroxyisodauc-6-en-14-al (**2**): Colorless oil; $[\alpha]_D^{20}$ −69° (c=0.8, $CHCl_3$); IR (Film) ν_{max} 3446, 2961, 2930, 2868, 1676, 1645, 1445, 1187, 1031, 911, and 791 cm^{-1}; HR-ESI-MS *m/z*: 237.1844 ($[M+H]^+$, Calcd for $C_{15}H_{25}O_2$: 237.1849). ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 1. ^{13}C-NMR (DEPT) (125 MHz, $CDCl_3$): see Table 2.

(7*S**)-Opposit-4(15)-en-1β,7-diol (**4**): Colorless oil; $[\alpha]_D^{20}$ −30° (c=0.8, $CHCl_3$); IR (Film) ν_{max} 3379, 3073, 2966, 2930, 2868, 1654, 1467, 1382, 1271, 1080, 1031, 884, and 795 cm^{-1}. HR-ESI-MS *m/z*: 237.1846 ($[M-H]^+$, Calcd for $C_{15}H_{25}O_2$: 237.1849). ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 1. ^{13}C-NMR (DEPT) (125 MHz, $CDCl_3$): see Table 2.

Antibacterial Assay The antibacterial assay was carried out employing the cup–plate method. Chloramphenicol was used as a positive control. Three strain bacteria *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis* were cultured in beef broth and incubated at 37 °C for 24 h. After dilution of beef broth, the three bacteria were cultured in agar medium dishes respectively, six cups (8×10 mm) were put onto the dishes, and each tested compound (20 μl of 100 μg/ml) was respectively added into the cups under aseptic conditions. The dishes were cultured at 37 °C for 24 h. The zone of inhibition of the growth of bacteria, produced by diffusion of the compounds from the cup into the surrounding medium, was measured to

evaluate the antibacterial activity.

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