Eremophilane-Type Sesquiterpene Derivatives from *Senecio aegyptius* var. *discoideus*

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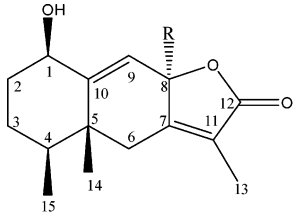
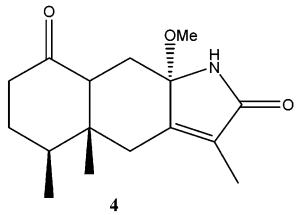
Investigation of a CH_2Cl_2 extract of the aerial parts of *Senecio aegyptius* var. *discoideus* afforded nine eremophilane compounds, of which six are new (**1**−**6**), namely, 1*β*-hydroxy-8α*H*-eremophil-7(11),9-dien-8*β*,12-olide (**1**), 1*β*,8α-dihydroxyeremophil-7(11),9-dien-8*β*,12-olide (**2**), 1*β*-hydroxy-8α-methoxyeremophil-7(11),9-dien-8*β*,12-olide (**3**), 1-oxo-8α-methoxy-10α*H*-eremophil-7(11)-en-8*β*,12-lactam (**4**), 1*β*,10*β*-epoxy-8α-hydroxyeremophil-7(11)-en-8*β*,12-olide (**5**), and 1*β*,10*β*-epoxy-8α-methoxyeremophil-7(11)-en-8*β*,12-olide (**6**). The structures of **1**−**6** were elucidated by spectroscopic methods and by comparison with literature data. The antibacterial activity of the isolated compounds was tested against *Bacillus cereus* and a *Serratia* sp.

Senecio represents the largest genus of the family Asteraceae and has more than 1500 species of herbs, shrubs, vines, and trees.[1] Interest in the chemical investigation of members of this genus is mainly due to the toxicity of its constituents.[2] The most widely studied constituents are sesquiterpenes with a furoeremophilane skeleton and pyrrolizidine alkaloids.[3,4] Previous work on *Senecio aegyptius* L. var. *discoideus* Boiss. led to the isolation of the pyrrolizidine alkaloids integerrimine, otosenine, retrorsine, senecionine, seneciphylline, and senecivernine.[5,6] The essential oil of this species was also investigated for its pyrrolizidine alkaloid composition.[7]

The present study on a CH_2Cl_2 extract of the aerial parts of *S. aegyptius* var. *discoideus* has led to the isolation and identification of nine sesquiterpenes, including six new eremophilanes (**1**−**6**) and three known compounds. The known compounds were identified as istanbulin A and istanbulin B[9] and 1-oxo-10α-hydroxyeremophil-7(11),8-dien-8*β*,12-olide.[10] The latter compound was reported from *Ligularia virgaurea* ssp. *oligocephala* during the preparation of this paper.[10]



1 R = H
2 R = OH
3 R = OMe



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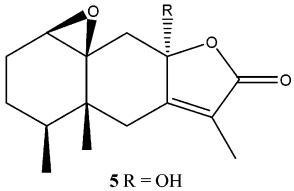

5 R = OH
6 R = OMe

The HREIMS of compound **1** showed a molecular ion peak $[M]^+$ at *m/z* 248.1429, in accord with the molecular formula, $C_{15}H_{20}O_3$. A fragment at *m/z* 230, resulting from the loss of a molecule of water, suggested the presence of a hydroxyl group in the molecule. The IR spectrum showed bands at 3446 cm^{-1} (OH) and 1766 cm^{-1} (C=O). The ^1H NMR spectrum (Table 1) indicated the presence of an olefinic methyl group at δ_H 1.81 (d, J = 1.5 Hz, H-13), a tertiary methyl group at δ_H 1.03 (s, H-14), and a secondary methyl group at δ_H 0.97 (d, J = 7.0 Hz, H-15) that were characteristic of an eremophilenolide derivative.[11] Additionally, a narrow triplet signal at δ_H 4.28 (1H, t, J = 2.8 Hz, H-1) showed, in the $^1H-^1H$ COSY spectrum, correlations with two signals at δ_H 1.59 (1H, m, H-2*β*) and 1.92 (1H, dddd, H-2α) and allylic coupling with a one-proton doublet signal at δ_H 5.77 (H-9). Additionally, H-9 (δ_H 5.77) exhibited a correlation in the $^1H-^1H$ COSY spectrum with a broad singlet at δ_H 5.12 (1H, brs, H-8). The HMBC spectrum gave several important correlations: H-9 with C-5 and C-8; H-1 with C-3; H-6 with C-8, C-10, and C-11; and H-13 with C-7, C-11, and C-12. The stereochemistry of **1** was determined from the observed coupling constants and the NOE effects (Figure S1, Supporting Information). Clear NOE effects were observed between H-14 and H-6*β*, and between H-14 and H-15, indicating the *β*-orientation of these protons. Irradiation of the signal at δ_H 4.28 (H-1) enhanced the signal at δ_H 5.12 (H-8) and suggested the α-orientation of H-1 and H-8. Therefore, compound **1** was assigned as 1*β*-hydroxy-8α*H*-eremophil-7(11),9-dien-8*β*,12-olide.

Compound **2** was obtained as a yellow oil and gave a molecular ion peak $[M]^+$ at *m/z* 264.1381 in the HREIMS, consistent with a molecular formula of $C_{15}H_{20}O_4$. The IR spectrum showed bands at 3420 cm^{-1} (OH) and 1733 cm^{-1} (C=O). The ^1H NMR spectrum was similar to that of **1**, except for the presence of H-9 as a singlet at δ_H 5.76 in **2**,

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Table 1. ^{1}H NMR Spectral Data of Compounds **1**−**6** (400 MHz, $CDCl_3$, δ values, J values in Hz)

position	**1**	**2**	**3**	**4**	**5**	**6**
1	4.28 (t, 2.8)	4.17	4.29		3.17 (br s)	3.11 (br t, 2.4)
2α	1.92 (dddd, 13. 5, 2.9, 2.9, 2.9)	1.90 (m)	1.60 (m)	1.93 (m)	1.64 (m)	2.00
2β	1.59 (m)	1.55 (br t, 12)	1.60 (m)	2.40 (m)	1.44 (m)	1.77
3α	1.77 (m)	1.74 (m)	1.75 (m)	2.25 (dd, 14.0, 3.3)	2.05 (m)	1.36
3β	1.36 (dddd, 13.5, 2.9, 2.9, 2.9)	1.30 (dd, 13.2, 2.8)	1.35 (m)	1.59 (m)	1.90 (m)	1.36
4α	1.52 (m)	1.40 (m)	1.65 (m)	2.00 (m)	1.44 (m)	1.36
6α	2.19 (d, 12.5)	2.08 (br d, 13.2)	2.21 (d, 12.0)	1.93 (d, 13.0)	2.55 (br s)	2.25 (d, 13.8)
6β	2.80 (dd, 12.5, 1.5)	2.70 (br d, 13.2)	2.66 (d, 12.0)	2.56 (d, 13.0)	2.55 (br s)	2.56 (d, 13.8)
8α	5.12 (brs)					
9α	5.77 (d, 2.4)	5.76 (s)	5.86 (s)	1.75 (m)	2.30 (d, 14)	1.83 (d, 14.0)
9β				1.75 (m)	1.80 (d, 14)	2.16 (d, 14.0)
10α				2.74 (dd, 10, 3)		
13	1.81 (d, 1.5)	1.90	1.90	1.80	1.80	1.84
14	0.97 (d, 7)	0.91	0.97	0.98	0.94	0.88
15	1.03 (s)	1.18	1.18	0.50	0.87	0.91
OMe			3.15 (s)	2.97		3.07

compared to a doublet at δ_H 5.77 in **1**, indicating the absence of the H-8 proton in **2**. Additionally, the ^{13}C NMR spectrum showed a signal due to a hemiketal carbon at δ_C 104.0 (C-8), suggesting the γ-hydroxylation of the lactone moiety. The stereochemistry at C-1, C-4, and C-5 was the same as in **1**. The α-orientation of the hydroxyl group at C-8 was determined according to a previous observation of Naya et al.,[12] from the presence of the H-15 signal downfield at δ_H 1.18, compared to the H-14 signal at δ_H 0.91. Compound **2** was assigned as 1β,8α-dihydroxyeremophil-7(11),9-dien-8β,12-olide.

The HRCIMS of compound **3** gave a molecular ion peak $[M]^+$ at *m/z* 279.1548, establishing its molecular formula as $C_{16}H_{22}O_4$. Its IR spectrum showed peaks at 3448 cm^{-1} (OH) and 1766 cm^{-1} (C=O). The ^{1}H NMR spectrum of **3** was closely comparable to that of **2**, except for the presence of a new singlet signal at δ_H 3.15, which integrated for three protons (OMe). The HMBC spectrum was used to place the methoxyl group at δ_H 3.15 and C-8 on the basis of a correlation between its proton signal at δ_H 3.15 and C-8. Other important correlations were observed, namely, H-6 with C-8 and C-10, H-9 with C-1, C-5, and C-11, and H-1 with C-3 and C-5. The stereochemistry of compound **3** was deduced from its chemical shifts and coupling constants and from the analysis of a NOE experiment. Thus, irradiation of the signal at δ_H 0.97 (H-14β) enhanced the signals at δ_H 1.18 (H-15β) and 2.66 (H-6 β), and irradiation of the signal at δ_H 3.15 (OMe) enhanced the signal at δ_H 2.21 (H-6α). Additionally, the absence of any NOE effect between either H-14 (δ_H 0.97) or H-15 (δ_H 1.18) and the methoxyl group at δ_H 3.15 supported the α-orientation of this methoxyl group. Therefore, compound **3** was assigned as 1β-hydroxy-8α-methoxyeremophil-7(11),9-dien-8β,12-olide.

Compound **4** was isolated as a yellow oil, and its molecular formula was established as $C_{16}H_{23}NO_3$ by HREIMS (*m/z* 277.1704) and from its ^{13}C NMR spectrum. Its IR spectrum showed a broad band at 3406 cm^{-1} (NH) and a band at 1710 cm^{-1} (C=O). The ^{13}C NMR spectrum showed a strong shielding of C-8 by 14.8 ppm, compared to C-8 in **3** (Table 2). This was due to the replacement of the oxygen atom in **3** by the less electronegative nitrogen atom in **4**. Therefore, **4** was projected to have a lactam ring, instead of the lactone ring in **3**. The structure of **4** was supported by a HMBC experiment, in which H-6 correlated with C-4, C-8, and C-10, H-14 correlated with C-4, C-5, C-6, and C-10, and H-13 correlated with C-7, C-11, and C-12. The stereochemistry of the methoxyl group at C-8 was assigned as having an α-orientation from a NOE experiment. Thus, irradiation of the methoxyl signal (δ_H 2.97) showed correlations with H-6α (δ_H 1.93) and H-10α (δ_H 2.74), while irradiation of the signal at δ_H 0.98 (H-14β) enhanced the signals at δ_H 0.50 (H-15β) and 2.56 (H-6β) (Figure S1, Supporting Information). Therefore, compound **4** was assigned as 1-oxo-8α-methoxy-10α*H*-eremophil-7(11)-en-8β,12-lactam. To the best of our knowledge, this is the third eremophilane lactam to have been isolated from a natural source. The first two compounds of this type were isolated from the rhizomes of *Petasites hybridus*[13] and *Senecio flavus*,[8] respectively.

Table 2. ^{13}C NMR Spectral Data for Compounds **1**−**6** (400 MHz, $CDCl_3$, δ values)

position	**1**	**2**	**3**	**4**	**5**	**6**
1	73.2	72.0	73.4	211.0	63.6	63.7
2	33.1	32.5	37.7	42.2	23.8	24.0
3	25.4	25.2	25.3	34.2	23.0	23.6
4	44.1	42.7	43.6	41.1	39.7	40.1
5	45.3	45.5	45.8	41.6	38.3	38.8
6	39.2	39.1	33.0	36.7	36.0	36.5
7	159.9	151.6	151.8	150.0	156.0	156.4
8	78.5	104.0	102.8	88.0	102.0	105.7
9	121.9	126.0	122.0	31.2	43.8	43.3
10	150.9	158.2	156.7	53.6	61.9	61.7
11	121.3	125.1	124.8	129.0	122.7	126.0
12	174.8	170.0	169.4	172.0	170.0	171.7
13	8.3	15.4	8.4	7.9	7.6	8.3
14	20.3	18.7	19.8	11.5	17.3	17.6
15	15.4	14.0	15.4	14.7	15.5	15.9
OMe			50.4	49.4		50.5

Compound **5** was assigned the molecular formula $C_{15}H_{18}O_3$, as deduced from its HREIMS ($[M - H_2O]^+$, *m/z* 246.1264). The IR spectrum showed a broad band at 3420 cm^{-1} (OH) and a band at 1733 cm^{-1} (C=O). The ^{1}H (Table 1), ^{13}C (Table 2), DEPT, HMQC, and HMBC NMR spectra were used to determine the functional groups and their positions. The HMBC spectrum gave several important correlations: H-6 correlated with C-7, C-8, C-10, and C-11; H-9 correlated with C-8 and C-10; and H-14 correlated with C-10, suggesting an epoxy moiety at the 1,10-position. The β-orientation of the epoxide was assigned by the absence of any NOE effect between either H-2 and H-14 or H-15. The α-orientation of the hydroxy group at C-8 was assigned by the negative sign of the optical rotation.[14] Therefore, the structure of compound **5** was determined as 1β,10β-epoxy-8α-hydroxyeremophil-7(11)-en-8β,12-olide.

The structure of compound **6** was established by comparison of its NMR data with those of **5**. The appearance of an additional signal in the ^{1}H (δ_H 3.07, s) and ^{13}C NMR (δ_C 50.3, q) spectra supported the presence of a methoxyl group in **6**, compared to a hydroxyl group in **5**. The

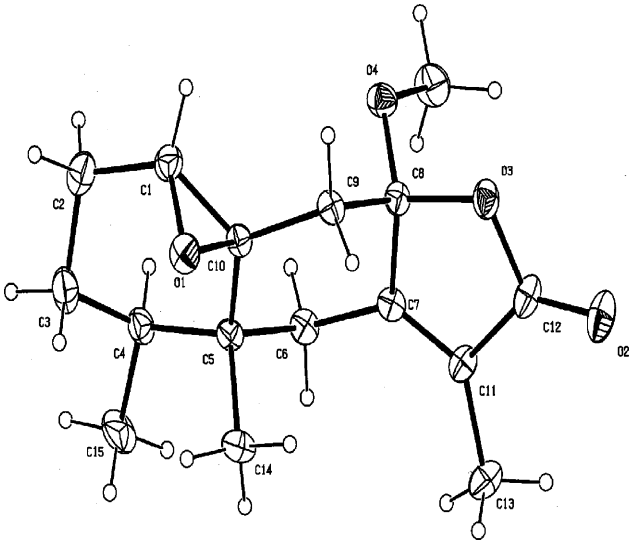

Figure 1. ORTEP diagram of the crystal structure of **6**.

placement of the methoxyl group at C-8 was achieved by a HMBC experiment, in which the methoxyl group (δ_H 3.07, s) showed a correlation with C-8 (δ_C 105.7, s). The other proton and carbon signals were determined from the ^{1}H−^{1}H COSY, HMQC, and HMBC spectra. Finally, the structure of **6** and its relative stereochemistry were confirmed by X-ray analysis (Figure 1). Therefore, compound **6** was assigned as 1β,10β-epoxy-8α-methoxyeremophil-7(11)-en-8β,12-olide. A close analogue of **6** has been reported from *Senecio flavus*.[9]

The antibacterial activity of compounds **1**−**6** was tested against two microorganisms, a Gram-positive bacterium (*Bacillus cereus*, El-U 8180) and a Gram-negative bacterium (*Serratia* sp., El-U 9213), at concentrations of 200 and 400 μg/mL. The growth of both microorganisms was inhibited by compounds **2**, **3**, and **5**. Compounds **1** and **6** inhibited the growth of *B. cereus*, but had no effect on the growth of *Serratia* sp. Compound **4** showed an inhibitory effect on the growth of *B. cereus*, without any effect on the growth of *Serratia* sp.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Perkin-Elmer 241 polarimeter operating at the sodium D line. The IR spectra (KBr) were taken on a Perkin-Elmer FT-IR spectrometer. ^{1}H, ^{13}C, and 2D NMR spectra were measured on a Bruker AMX-400 spectrometer, with TMS as an internal standard. CIMS and HREIMS were recorded on a TSQ-70-triple stage quadrupole mass spectrometer (70 eV).

Plant Material. The aerial parts of *S. aegyptius* var. *discoideus* were collected from a natural population in El-Minia, Egypt, in May 2000. A voucher specimen (A.A. S-112) of the collection was identified by Dr. Mohei Kamel and was deposited in the Department of Botany, El-Minia University.

Extraction and Isolation. Air-dried aerial parts (1 kg) of *S. aegyptius* var. *discoideus* were extracted with methylene chloride at room temperature for 24 h. The extract was concentrated in vacuo to obtain a residue of 20 g. This residue was defatted and chromatographed on a silica gel (500 gm) column (5 × 100 cm) in petroleum ether (bp 40−60 °C) and eluted with a petroleum ether (bp 40−60 °C)−methylene chloride step gradient to give three fractions. The first fraction was separated by TLC (ether−petroleum ether, 4:1) to give compounds **1** (6 mg), **6** (10 mg), and istanbulin B (8 mg). The second fraction was subjected to further purification by passage over Sephadex LH-20 to give compounds 1-oxo-10α-hydroxyeremophil-7(11),8-dien-8β,12-olide (14 mg), **3** (6 mg), **5** (3 mg), and istanbulin A (10 mg). The third fraction (100% methylene chloride) was separated by passage over Sephadex LH-20 (3 × 40 cm, petroleum ether−methylene chloride−methanol, 7:4:0.5) to give compounds **2** (2 mg) and **4** (4 mg).

1β-Hydroxy-8α*H*-eremophil-7(11),9-dien-8β,12-olide (1): yellow oil; $[\alpha]^{25}_D$ +8.5° (*c* 0.36, $CHCl_3$); IR (KBr) ν_{max} 3446, 2927, 1766, 1457, 1266, 1122, 1021, 738 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 248 $[M]^+$ (15), 230 $[M - H_2O]^+$ (9), 219 $[M - HCO]^+$ (24); HREIMS *m/z* 248.1429 (calcd for $C_{15}H_{20}O_3$, 248.1412).

1β,8α-Dihydroxyeremophil-7(11),9-dien-8β,12-olide (2): yellow oil; $[\alpha]^{25}_D$ +3.64° (*c* 0.68, $CHCl_3$); IR (KBr) ν_{max} 3420, 2925, 1733, 1456, 1265, 740 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 264 $[M]^+$ (20), 246 $[M - H_2O]^+$ (45), 231 $[M - (H_2O + CH_3)]^+$ (17); HREIMS *m/z* 264.1381 (calcd for $C_{15}H_{20}O_4$, 264.1361).

1β-Hydroxy-8α-methoxyeremophil-7(11),9-dien-8β,12-olide (3): colorless oil; $[\alpha]^{25}_D$ −27.3° (*c* 0.64, $CHCl_3$); IR (KBr) ν_{max} 3448, 2927, 1766, 1457, 1283, 1100, 751 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2, respectively; CIMS *m/z* 279 $[M + H]^+$ (15), 261 $[M - H_2O]^+$ (8), 247 [*m/z* 261 − CH_3] (43), 219 [*m/z* 247 − H_2O] (50); HRCIMS *m/z* 279.1548 (calcd for $C_{16}H_{22}O_4$, 279.1518).

1-Oxo-8α-methoxy-10α*H*-eremophil-7(11)-en-8β,12-lactam (4): reddish oil; $[\alpha]^{25}_D$ −58.7° (*c* 2.74, $CHCl_3$); IR (KBr) ν_{max} 3406, 2929, 1710, 1457, 1266, 1064, 737 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 277 $[M]^+$ (40), 262 $[M - CH_3]^+$ (22), 246 $[M - (H_2O + CH_3)]^+$ (38); HREIMS *m/z* 277.1704 (calcd for $C_{16}H_{23}NO_3$, 277.1678).

1β,10β-Epoxy-8α-hydroxyeremophil-7(11)-en-8β,12-olide (5): colorless oil; $[\alpha]^{25}_D$ −12.25° (*c* 2.92 $CHCl_3$); IR (KBr) ν_{max} 3420, 2925, 1733, 1457, 1263, 1125, 740 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 246 $[M - H_2O]^+$ (18), 231 $[M - (H_2O + CH_3)]^+$ (6); HREIMS *m/z* 246.1264 (calcd for $C_{15}H_{18}O_3$, 246.1256).

1β,10β-Epoxy-8α-methoxyeremophila-7(11)-en-12,8β-olide (6): colorless crystal; IR (KBr) ν_{max} 2980, 2950, 1765, 1970 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 278 (43), 263 (10), 250 (25), 247 (38), 218 (44), 203 (25), 193 (30), 161 (28), 140 (100), 123 (26), 95 (18), 91 (17); HREIMS *m/z* 278.1515 (calcd for $C_{16}H_{22}O_4$, 278.1518).

X-ray Crystallography of Compound 6. Crystal data: $C_{16}H_{22}O_4$, formula wt 278.34, crystal dimensions 0.25 × 0.20 × 0.10 mm, monoclinic, space group $P2_1$, a = 7.3161(3) Å, b = 12.1600(10) Å, c = 8.4560(4) Å, β = 100.291(4)°, V = 740.18(8) Å^3, Z = 2, D_c = 1.249 g/cm^3, $F(000)$ = 300, GOF = 1.078. The reflection data were collected on a Siemens P4 diffractometer operating in the ω scan mode, using graphite-monochromated Cu Kα radiation (λ = 1.54184 Å). The structure was solved by direct methods using Bruker SHELXS-97[15] and refined by full-matrix least-squares on F^2 using Bruker SHELXL-97.[16] The final R and R_w factors were 0.0473 and 0.0977, respectively. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center (number CCDC 182897). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Bioassay. The antibacterial activity of isolated compounds was determined against a Gram-positive bacterium (*Bacillus cereus,* EL-U 8180) and a Gram-negative bacterium (*Serratia* sp., EL-U 9203), purchased from Adwic Company, Cairo, Egypt, using a filter paper disk diffusion assay method. Filter paper disks were soaked in the tested compounds for 30 s, then placed on the surface of the nutrient agar media cultured with the test bacterium. All plates were incubated at 30 °C for 2 days. Five replicates were performed for each compound, using two concentrations (200 and 400 μg/mL). Ampicillin was used as a control at 200 and 400 μg/mL.

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Supporting Information Available: List of spectroscopic data for the known compounds and figure of selected NOE correlations for compounds **1** and **4**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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