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EREMOPHILENOLIDES FROM *PETASITES JAPONICUS*

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Key Word Index—*Petasites japonicus*; Compositae; Senecioneae; sesquiterpene lactones; eremophilenolides; ^{13}C NMR; CD spectra.

Abstract—Chemical investigation of the young flower stalks of *Petasites japonicus* afforded some eremophilenolides, including a mixture of the two new compounds 6β-angeloyloxy-3β,8α-dihydroxyeremophil-7(11)-en-12,8β-olide and 6β-angeloyloxy-3β,8β-dihydroxyeremophil-7(11)-en-12,8α-olide. Their structures were elucidated by chemical and spectroscopic methods. The ^{13}C NMR signals for the carbon atoms of the eremophilenolides were assigned with the help of Beierbeck's parameters. The CD spectra of the compounds are briefly discussed.

INTRODUCTION

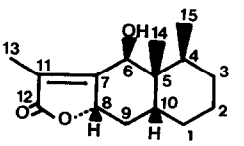
Petasites japonicus, which is used both as a food and a herbal cough remedy, has been previously investigated and shown to contain eremophilane types of sesquiterpenes [1–3], bakkenolide derivatives [4] and pyrrolizidine alkaloids [5, 6]. It has been reported that 6β-hydroxyeremophilenolide (**1**) has anti-histamine activity [7] and that bakkenolide A has cytotoxic activity [8]. We have now investigated the young flower stalks of *P. japonicus* subsp. *giganteus Kitam.* and isolated **1**, a mixture of 6β,8β-dihydroxyeremophil-7(11)-en-12,8α-olide (**2**) and 6β,8α-dihydroxyeremophil-7(11)-en-12,8β-olide (**3**), 6β-hydroxy-8α-methoxyeremophil-7(11)-en-12,8β-olide (**7**), a mixture of 6β-angeloyloxy-3β,8β-dihydroxyeremophil-7(11)-en-12,8α-olide (**8**) and 6β-angeloyloxy-3β,8α-dihydroxyeremophil-7(11)-en-12,8β-olide (**9**), and a mixture of phytosterols. Compounds **8** and **9** are new compounds.

RESULTS AND DISCUSSION

The methanol extract of dried and powdered young flower stalks of this plant was subjected to CC over silica gel to yield the eremophilenolides **1–3** and **7–9**.

Compound **1**, $C_{15}H_{22}O_3$, mp 202–204°, $[\alpha]_D$ +205°, was identified as 6β-hydroxyeremophilenolide [10, 11] on the basis of physical and spectral properties. The IR and the UV spectra showed the presence of an α,β-unsaturated-γ-lactone and a hydroxyl group. The ^1H NMR (Table 1) and ^{13}C NMR (Table 2) spectra were consistent with structure **1**. Compound **1** was converted to eremophilenolide (**13**) using the method of Naya *et al.* [12].

Compounds **2** and **3** could not be separated by CC on silica gel and displayed ^1H NMR signals that were similar to those of **1** with the exception that a proton at the carbon next to a lactone group of **1** was absent. The mass spectrum indicated the presence of two hydroxyl groups, i.e. *m/z* 266 $[M]^+$, 248 $[M-H_2O]^+$, 230 $[M-2H_2O]^+$. The ^{13}C NMR spectrum of the mixture showed the presence of two compounds. The mixture was treated with acetic anhydride–pyridine to afford an epimeric mixture,



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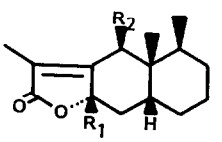
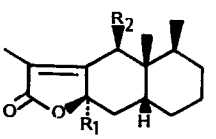
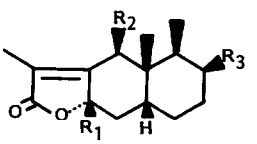


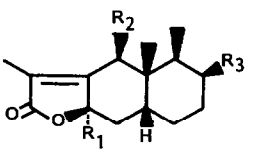
	R_1	R_2
2	OH	OH
4	OAc	OAc
6	OMe	OH



	R_1	R_2
3	OH	OH
5	OAc	OAc
7	OMe	OH



	R_1	R_2	R_3
8	OH	OAng	OH
10	OAc	OAng	OAc



	R_1	R_2	R_3
9	OH	OAng	OH
11	OAc	OAng	OAc

Ang = COC(Me)=CH(Me)cis-

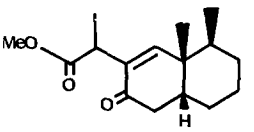
which was then separated by CC on silica gel.

The more polar diacetate **4**, mp 119–122°, $[\alpha]_D$ +62.6°, was analysed for $C_{19}H_{26}O_6$. The mass spectrum of **4** showed the parent ion peak (*m/z* 350) and the loss of two acetic acid molecules (*m/z* 290 and 230). The ^1H NMR spectrum of **4** showed two acetyl methyl groups at δ2.01 and 2.04 and the C-15 methyl group as a doublet at δ0.85 (J = 5.4 Hz) and the C-14 methyl group as a singlet at δ1.01. Naya *et al.* [13] reported that for 8α-methoxy-eremophilenolide derivatives the chemical shifts due to C-14 methyls are downfield from those due to C-15 methyls,

whereas this relationship is reversed in the 8β-series. They also reported that the homoallylic spin-coupling (J = 1.0–1.5 Hz) between H-6α and C-13 methyls found in the 8α-series, is absent in the 8β-series. The value of the optical rotation of the 8β-series, which had a steroidal conformation, was positive, and that of the 8α-series, which has a nonsteroidal conformation, was negative. As mentioned above, the structure of **4** was deduced to be 6β,8β-diacetoxyeremophil-7(11)-en-12,8α-olide.

The less polar diacetate **5**, mp 150–151°, $[\alpha]_D$ −103.0°, had the molecular formula $C_{19}H_{26}O_6$ by high resolution mass spectrometry. The spectral data (IR, UV and MS) of **5** were similar to those of **4**. In the ^{1}H NMR spectrum of **5**, the C-15 methyl doublet (J = 7.3 Hz) at δ1.00 was downfield of the C-14 methyl singlet at δ0.87 and there was homoallylic coupling (J = 1.5 Hz) between the H-6α and C-13 methyl protons. The value of the optical rotation of **5** was negative. Therefore, **5** was deduced to be the 8α-epimer of **4**, and **2** and **3** were deduced to be 6β,8β-dihydroxyeremophil-7(11)-en-12,8α-olide and its 8α-epimer, respectively. Naya *et al.* [11] reported that pure **2** was isolated from *P. japonicus*, but in this study the mixture of **2** and **3** could not be separated.

The mixture of **2** and **3** was treated with sulphuric acid and methanol to afford the epimers of the 8-methoxy derivatives. The major, more polar product **6**, mp 128–129.5°, $[\alpha]_D$ +174°, had the molecular formula $C_{16}H_{24}O_4$ by high resolution mass spectrometry. The ^{1}H NMR spectrum of **6** indicated the presence of a methoxyl group as a singlet at δ3.32. The other physical properties of **6** were identical with those of 6β-hydroxy-8β-methoxyeremophil-7(11)-en-12,8α-olide [11]. The minor, less polar product **7** was deduced to be the 8α-epimer of **6** by comparison of the ^{1}H NMR spectra of **6** and **7**.



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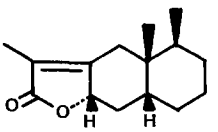

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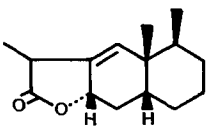

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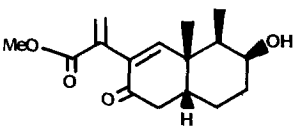

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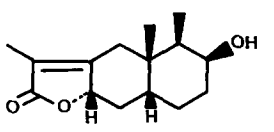

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Compound **7**, mp 160–162°, $[\alpha]_D$ −154°, was also obtained from a natural source. The ^{1}H NMR spectrum of **7** was identical with those of a compound isolated from the mixture obtained on methyl ketalization of **2** and **3**, and

Table 1 ^{1}H NMR data of eremophilenolide derivatives (δ in $CDCl_3$)

H	1*	4†	5†	6†	7†	10*	11‡	13†	16†
3α						4.99 *ddd* (3.0, 3.0, 2.9)	4.98 *ddd* (11, 4.4, 4.4)		3.85 *ddd* (2.9, 2.9, 2.9)
6α	4.69 *s*	5.88 *s*	6.21 *s*	4.52 *d* (10)	4.99 *s* (*br*)	5.77 *s*	6.21 *d* (1.5)	2.91 *d* (15)	2.91 *d* (14)
8β	5.10 *ddq* (11, 7.0, 1.5)							4.68 *m*	4.64 *m*
13	1.85 *d* (1.5)	1.98 *s*	1.92 *d*	1.91 *s*	2.08 *d* (1.5)	1.92 *s*	1.85 *d* (1.5)	1.81 *d* (1.2)	1.81 *s*
14	1.12 *s*	1.01 *s*	0.87 *s*	1.11 *s*	0.82 *s*	1.30 *s*	0.97 *s*	1.04 *s*	1.29 *s*
15	0.78 *d* (6.4)	0.85 *d* (5.4)	1.00 *d* (7.3)	0.78 *d* (4.4)	1.02 *d* (7.1)	0.98 *d* (7.0)	0.96 *d* (6.8)	0.87 *d* (7.3)	1.01 *d* (6.8)
OAc		2.01 *s*	2.08 *s*			2.04 *s*	2.02 *s*		
OAc		2.04 *s*	2.19 *s*			2.08 *s*	2.11 *s*		
OMe				3.32 *s*	3.19 *s*				
OAng						1.91 *quint* (1.2) 2.00 *dq* (7.0, 1.2) 6.12 *dq* (7.0, 1.2)	2.00 *quint* (1.5) 2.08 *dq* (7.3, 1.5) 6.27 *qq* (7.3, 1.5)		
HO-6				2.70 *d* (10)					

Values in parentheses are coupling constants (Hz).
*Measured at 200 MHz.
†Measured at 100 MHz.
‡Measured at 500 MHz.

Table 2. ^{13}C NMR data of eremophilenolide derivatives (δ in C_5D_5N)

C	1	2	3	4	5	6	7	8	9	10	11	13	16
1	26.1	26 0	29 0	25.6	28 4	25.9	28.7*	21.6	27.8	21.7	25.5	26.7	22.3
2	20.2	20.3	20 7	19.9	20.4	20.2	18.9	28.7	29 5	24.7	26.9	20.8	29.1
3	30 9	31 0	29.0	30 5	29.0	31.0	28.9*	71.8	67.5	73.4†	70.3	30.8	70.7
4	30 9	29 4	31.9	28 9	32.5	29 2	31 8	33.4	39.9	32.2	35.1‡	30.0	40.3
5	43.2	43.7	46.1	41.9	44.5	43.7	46.0	42.8	46.6	42.0	45.9	39.7	40.2
6	68 7	70 2	69 6	70.8	71 3	69 3	69 6	70.7	71.8	70.7†	71 7	36.2	37.4†
7	163.8	157 6	163 5	150 2	154 8	156 5	160.9	154.3	158.0	§	154.1	161.4	161.7
8	78 6	105 4	§	104 1	105 3	108 2	107 3	105 6	105 2	104.0	105.1	80 4	80.4
9	35 4	39 9	40 2	38 6	37.2	39.2	38.5	39 8	39.0	38.3	36.3	35 3	35.4
10	34.2	34 5	36 5	35 0	36 3	34 3	36.2	36 3	36.0	35.2	35.9‡	40.1	34 3
11	120.1	123.7	§	129.4	126 3	126.8	126.5	§	128.0	130.1	127.1	120.5	120.2
12	174.8	172 1	173.0	170 7	171 0	171.5	172 0	§	171 8	170.8	171.0	174.7	174.9
13	8 5	8 4	9.2	8 9	8.7	8.7	9.3	8.9	8 1*	9 1	8 4*	8.3	8.4†
14	16.5*	16.6*	18.9	16 3*	19 3	16 7*	15 8	19 6	20.2	18.6†	19.8	21.4	25.4
15	16.4*	16 4*	15 8	15 9*	15.7	16.6*	14.3	13.5	8.1*	12 4†	8 5*	16.0	13.0†
OMe						51.1	49.8						
$O\underline{C}OCH_3$				20 4	20 4					21 0	21.0		
$O\underline{C}OCH_3$				21.6	21 8					21 4	21.8		
$OCO\underline{C}H_3$				169 1	168 4					169.0	168.3		
$OCO\underline{C}H_3$				169 7	170.0					170.1	169.8		
$\underline{C}H_3CH=$								20.8	20.6	20.6	20.6		
$CH_3\underline{C}H=$								139 7	140 7	139.4	140.9		
–COO–								166 0	167 1	166 5	166 0		
$\underline{C}COO–$								127.0	127 1	127 7	126.4		
$\underline{C}H_3–CCOO$								16 0	16 0	16 0	16.0		

*,‡Assignments may be reversed within each column

†Assignments confirmed by selective ^1H decoupling experiments.

§Not observed

Measured as the mixture of **2** and **3**, and of **8** and **9**

deduced to be 6β-hydroxy-8α-methoxyeremophil-7(11)-en-12,8β-olide. Compound **7** may be an artifact by the methanol extraction procedure used to isolate the compounds.

Compounds **8** and **9** also could not be separated. The mass spectrum of the mixture gave a parent ion peak at *m/z* 364 and peaks at *m/z* 346, 264 and 83 (base peak), indicating successive loss of angelic or tiglic acid and one molecule of water. The ^1H NMR spectrum of this mixture showed the presence of an angeloyloxyl group as shown by the typical vinylic proton double doublet at δ6.26 (J = 7.1, 1.2 Hz). The multiplets at δ3.82, 4.50, 5.64 and 6.00 were assigned to the protons attached to a carbon bearing an oxygen atom, respectively. The ^{13}C NMR spectrum of this mixture revealed the presence of two components. The mixture was treated with acetic anhydride–pyridine to afford an epimeric mixture, which was separated by CC on silica gel to give two compounds **10** and **11**.

The less polar diacetate **10**, mp 164.5–165°/174.5–175°, $[\alpha]_D$ +83.6°, was analysed for $C_{24}H_{32}O_8$. The mass spectrum of **10** gave no parent ion peak, however, the ion peaks at *m/z* 388, 328 indicated the loss of two acetic acid molecules. The elimination of 100 mass units and a peak at *m/z* 83 showed the presence of an angeloyloxy or a tigloyloxy group. In the ^1H NMR spectrum of **10**, the two methyl singlets at δ2.04 and 2.08 were assigned to acetyl methyl groups. The presence of the angeloyloxy group was shown by the vinylic methyl quintet at δ1.91 (J = 1.2 Hz), the vinylic methyl doublet quartet at δ2.00 (J = 7.0, 1.2 Hz) and the vinylic proton doublet quartet at δ6.12 (J = 7.0, 1.2 Hz). As the signal of a methine proton next to lactone group could not be observed, C-8 was substituted. As the signal of the proton attached to the C-6 carbon bearing an oxygen atom was observed at δ6.00 before and after acetylation, the angeloyloxyl group was attached to C-6. The signal of a methine proton at C-3 next to the acetoxyl group was observed as a quartet-like signal at δ4.99 (J = 3.0, 3.0, 2.9 Hz) which was of a similar coupling pattern to that of the H-3α signal of 3β-hydroxyeremophilenolide [14]. The signal of the C-14 methyl singlet at δ1.30 was downfield from that of C-15 methyl doublet at δ0.98 (J = 7.0 Hz) and the value of the optical rotation was positive. These facts suggested that **10** is 6β-hydroxy-3β,8β-diacetoxyeremophil-7(11)-en-12,8α-olide.

The more polar diacetate **11**, mp 144.5–146°, $[\alpha]_D$ −92.0°, gave spectral data similar to those of **10**. In the ^1H NMR spectrum of **11**, however, the signal of the C-14 methyl singlet at δ0.97 was very close to that of the C-15 methyl doublet at δ0.96 (J = 6.8 Hz) and homoallylic coupling (J = 1.5 Hz) was observed between H-6α and the C-13 methyl group. A double double doublet at δ4.98 (J = 11, 11, 4.4 Hz) as triplet-like was assigned to the H-3 proton next to the acetoxyl group. In addition to these facts, the negative value of the optical rotation suggested that **11** was the 8α-epimer of **10**, i.e. 6β-angeloyloxy-3β,8α-diacetoxyeremophil-7(11)-en-12,8β-olide.

The mixture of compounds **8** and **9** was converted to

3β-hydroxyeremophilenolide **16** by the method by Naya *et al.* [12]. As the ^{13}C NMR data of eremophilenolide derivatives had been scarcely reported, the signals were assigned by comparison of the data and selective ^{1}H decoupled ^{13}C NMR measurements, etc.

In the case of the derivatives in which no oxygen atom was present on C-3, it was difficult to assign the values from C-1 to C-3. The calculated values from C-1 to C-3 of **6** by Beierbeck's parameters [9] were δ28.6, 22.2 and 31.3 each. Those of **7** were δ26.7, 22.2, 28.6 each. The ^{13}C NMR data of **6** and **7** and another eremophilenolides were assigned by reference to these calculated values.

In the ^{13}C NMR data (Table 2), the chemical shifts of C-1, C-4, C-5, C-7 and C-10 of the 8α-series were down field from those of the 8β-series. The signals of C-13 in eremophilenolides were observed at δ8.00–9.00. The signals of C-14 and C-15 in the 8β-series appeared at nearly δ16. The signals of C-15 in the 8α-series also appeared at nearly δ16. The signals of C-14 in the 8β-series were downfield from those of C-15 in the 8α-series.

The Cotton effects in eremophilenolides obtained in the present works are summarized in Table 3. In the 8β-series the α,β-unsaturated-γ-lactone group has a positive Cotton effect at about 250 nm whereas in the 8α-series it has negative Cotton effect in this region. In the case of **6**, the Cotton effect at 228 nm was so strong that the positive effect at 250 nm was hidden by the absorption at 228 nm.

Table 3 CD maxima (nm) in ethanol

Compound	λ_{max} nm	
13		221 (+4.62)*
1		220 (+8.97)
16		223 (+4 58)
4	249 (+4.97)	229 (−2.27)
		215 (+1.68)
5	246 (−2.58)	225 (+2.49)
6		228 (+11.5)
7	245 (−4.95)	225 (−2.53)
8	248 (+6 24)	226 (+0.95)
9	245 (−2.30)	225 (+2.60)

*Δε values in parentheses.

EXPERIMENTAL

Mps (Kofler hot-stage apparatus): uncorr; ^{1}H NMR: 100, 200 or 500 MHz, $CDCl_3$ or C_5D_5N, TMS as int. standard; ^{13}C NMR: 25 or 50 MHz, C_5D_5N, TMS as int. standard; optical rotations: $CHCl_3$ at room temp; CD: EtOH

Extraction and isolation. Young flower stalks of *P japonicus* collected in April 1983, at Nishino in Sapporo-shi, Hokkaido, Japan were dried, powdered (4.7 kg), and extracted with MeOH (28 l.). The total MeOH extract was filtered and concd *in vacuo*. The crude extract (1 kg) was chromatographed on silica gel using *n*-hexane, EtOAc and Me_2CO The EtOAc fraction (160 g) was rechromatographed on silica gel eluted with a hexane–Me_2CO gradient. Fraction 6 contained a mixture of sterols (22.3 mg) and **7** (39.5 mg) which were separated by further CC on silica gel. Fraction 7 gave **1** (508.6 mg) which was purified by CC (silica gel) Fraction 9 contained a mixture of **2** and **3** (475 mg) and fraction 10 yielded a mixture of **8** and **9** (1.3 g).

Identification of isolated compounds. The mixture of sitosterol, stigmasterol and campesterol was identified by GC/MS (1.5% OV-17 column at 250°) and comparison with authentic samples

6β-Hydroxyeremophilenolide (**1**). Mp 202–204° (EtOH), $[\alpha]_D$ +205° ($CHCl_3$; *c* 0.86). (Found: C, 71.92; H, 8.78. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%.) IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 1740, 1710, 1690 (C=CCOO); UV λ_{max}^{EtOH} nm (ε): 219 (9600); MS (probe) 70 eV, *m/z*: 250 $[M]^+$, 232 $[M-H_2O]^+$, 141, 126 (100), 123, 109.

Alkaline hydrolysis and methylation of **1**. Compound **1** (53.1 mg) was dissolved in 5% KOH–MeOH (8 ml) and the mixture refluxed for 1 hr under N_2. After cooling, the mixture was diluted with 2 M HCl and extracted with Et_2O. The combined Et_2O fractions were washed with satd NaCl soln and dried over Na_2SO_4. The Et_2O fractions were evaporated to give a dienoic acid (38.3 mg) Methylation of the product with ethereal CH_2N_2 followed by the usual work up gave **12** as a viscous oil (52.2 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (COOMe), 1660 (C=CCO); UV λ_{max}^{EtOH} nm (ε): 239 (6700); EIMS (probe) 70 eV, *m/z*: 264 $[M]^+$, 249 $[M-Me]^+$, 232 $[M-MeOH]^+$, 217 $[232-Me]^+$, 204, 177, 162, 135 (100), 107, HRMS *m/z*: Calc. for $C_{16}H_{24}O_3$ 264.1724. Found 264.1719; ^{1}H NMR (100 MHz; $CDCl_3$): δ0.92 (3H, *d*, *J* = 6.9 Hz, H-15), 1.13 (3H, *s*, H-14), 1 27 (3H, *dd*, *J* = 7.1, 1.0 Hz, H-13), 2.27 (1H, *dd*, *J* = 17, 4.4 Hz, H-9β), 2.69 (1H, *ddd*, *J* = 17, 11, 1.5 Hz, H-9α), 3 65 (3H, *s*, OMe), 3.70 (1H, *q*, *J* = 7.1 Hz, H-11), 6.65 (1H, *d*, *J* = 1.5 Hz, H-6), ^{13}C NMR (25 MHz; C_5D_5N): δ27.2 (*t*, C-1), 20.6 (*t*, C-2), 30.3 (*t*, C-3), 35.9, 36.2 (each *d*, C-4, C-10), 39.3 (*s*, C-5), 156.2 (*d*, C-6), 137.1 (*s*, C-7), 197.9 (*s*, C-8), 39.7 (*t*, C-9), 39.0 (*d*, C-11), 174.9 (*s*, C-12), 20.6 (*q*, C-13), 16.7, 15.8 (each *q*, C-14, C-15), 57.7 (*q*, OMe).

$NaBH_4$ *reduction of* **12**. A soln of 110 mg **12** in 7 ml MeOH was reduced with 90 mg $NaBH_4$ by stirring for 30 min at room temp., diluted with 2 M HCl and extracted with Et_2O The washed and dried extract was evaporated and the residue (102.9 mg) was purified by silica gel CC (EtOAc–hexane, 17:83, two developments) The less polar product was **14** (14 6 mg). MS (probe) 70 eV, *m/z*: 234 $[M]^+$, 219 $[M-Me]^+$, 206, 178, 164, 149, 119, 110, 109 (100); ^{1}H NMR (100 MHz; $CDCl_3$): δ0.85 (3H, *d*, *J* = 6.4 Hz, H-15), 0.98 (3H, *s*, H-14), 1.36 (3H, *d*, *J* = 7.6 Hz, H-13), 3.02 (1H, *d*, *J* = 7.6 Hz, H-11), 5.00 (1H, *dd*, *J* = 7.6, 7.6 Hz, H-8), 5.68 (1H, *s* (*br*), H-6); ^{13}C NMR (25 MHz; C_5D_5N): δ28.6 (*t*, C-1), 22.0 (*t*, C-2), 31.0 (*t*, C-3), 36.5 (*d*, C-4), 38.5 (*s*, C-5), 132.8 (*d*, C-6), 79.3 (*d*, C-8), 31.4 (*t*, C-9), 39.2, 40.3 (each *d*, C-10, C-11), 16.3, 19.2, 17.0 (each *q*, C-13, C-14, C-15). The more polar product was eremophilenolide **13** (38 9 mg). MS (probe) 70 eV, *m/z*: 234 $[M]^+$, 161, 123 (100), 110, 81.

The mixture of 6β,8β-dihydroxyeremophil-7(11)-en-12,8α-olide (**2**) *and 6β,8α-dihydroxyeremophil-7(11)-en-12,8β-olide* (**3**). Mp 205–208° (dec) (EtOAc). MS (probe) 70 eV, *m/z*. 266 $[M]^+$, 248 $[M-H_2O]^+$, 230 $[M-2H_2O]^+$, 140, 124, 109 (100); ^{1}H NMR (100 MHz, C_5D_5N): δ0.73 (3H, *d*-like, H-15), 0.98 (3H, *s*, H-14), 1 27 (3H, *s*, H-14), 1.84 (3H, *s*, H-13), 4 80 (1H, *m*, H-8), 5 60 (1H, *s*, H-6).

Acetylation of the mixture of **2** *and* **3**. Acetylation of 37.1 mg of the mixture with Ac_2O–C_5H_5N for 2 days at room temp followed by the usual work up and purification by CC on silica gel (CH_2Cl_2, two developments) gave two products. The minor, less polar product was **5** (17 mg). Mp 150–151° (hexane–EtOAc), $[\alpha]_D$ −103° ($CHCl_3$; *c* 0.52). IR ν_{max}^{Nujol} cm^{-1}: 1770, 1760, 1730, 1690, 1230; UV λ_{max}^{EtOH} nm (ε): 223 (9700); EIMS (probe) 70 eV, *m/z*: 350 $[M]^+$, 308, 290 $[M-HOAc]^+$, 248, 230 $[M-2HOAc]^+$, 182, 140, 109 (100), 43; HRMS *m/z*: Calc. for $C_{19}H_{26}O_6$ 350.1692. Found 350.1710. The major, more polar product was **4** (39.4 mg). Mp 119–122° (Me_2CO–hexane), $[\alpha]_D$ +62.6° ($CHCl_3$; *c* 1.04). (Found: C, 65 03; H, 7.41. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7 48%.) IR ν_{max}^{Nujol} cm^{-1}: 1770, 1750, 1730, 1700, 1240, 990; UV λ_{max}^{EtOH} nm (ε): 226 (7100); MS (probe) 70 eV,

m/z. 350 $[M]^+$, 308, 290 $[M-HOAc]^+$, 248, 230 $[M-2HOAc]^+$, 182, 174, 140, 109 (100), 43.

Methyl ketalization of the mixture of **2** *and* **3**. The mixture (58.8 mg) was dissolved in 3% H_2SO_4–MeOH (10 ml), kept overnight at room temp., and then refluxed for 1 hr. After cooling, the mixture was neutralized by satd $NaHCO_3$ soln and extracted with Et_2O. The extract was washed with 2 M HCl, 5% $NaHCO_3$, satd NaCl soln and dried over Na_2SO_4. Evaporation of the solvent gave a residue (55.2 mg), which was chromatographed on silica gel CC (EtOAc–hexane, 23:77, two developments). The more polar product was **6** (12.1 mg), Mp 128–129.5° (EtOAc–hexane), $[\alpha]_D$ +194° ($CHCl_3$; *c* 0.63). IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 1740, 1680 (C=CCOO); UV λ_{max}^{EtOH} nm (ε): 219 (4200), EIMS (probe) 70 eV, *m/z*: 280 $[M]^+$, 262 $[M-H_2O]^+$, 248 $[M-MeOH]^+$, 156, 140, 124, 109 (100), HRMS *m/z*: Calc. for $C_{16}H_{24}O_4$ 280.1709. Found 280.1692. The minor, less polar product was identical with **7** (^{1}H NMR).

6β-Hydroxy-8α-methoxyeremophil-7(11)-en-12,8β-olide (**7**). Mp 160–162° (Me_2CO–hexane), $[\alpha]_D$ −154° ($CHCl_3$; *c* 1.07). (Found: C, 68.45; H, 8.49. $C_{16}H_{24}O_4$ requires C, 68.54; H, 8.63%.) IR ν_{max}^{Nujol} cm^{-1}: 3400, 3320 (OH), 1750, 1720, 1680 (C=CCOO); UV λ_{max}^{EtOH} nm (ε): 225 (7400); MS (probe) 70 eV, *m/z*: 280 $[M]^+$, 262 $[M-H_2O]^+$, 248 $[M-MeOH]^+$, 156, 140, 124, 109 (100).

The mixture of 6β-angeloyloxy-3β,8β-dihydroxyeremophil-7(11)-en-12,8α-olide (**8**) *and 6β-angeloyloxy-3β,8α-dihydroxyeremophil-7(11)-en-12,8β-olide* (**9**). MS (probe) 70 eV, *m/z*. 364 $[M]^+$, 346 $[M-H_2O]^+$, 264 $[M-$angelic acid$]^+$, 246 $[264-H_2O]^+$, 108, 83 $[C_4H_7CO]^+$ (100); ^{1}H NMR (100 MHz; $CDCl_3$): δ0.95 (3H, *s*, H-14), 1.29 (3H, *d*, *J* = 7.3 Hz, H-15), 1.73 (3H, *s*, H-13), 3.82 (1H, *m*, H-3), 4.50 (1H, *m*, H-3), 5.64 (1H, *m*, H-6), 6.00 (1H, *m*, H-6), 6.29 (1H, *dd*, *J* = 7.1, 1.2 Hz, =CH–Me).

Acetylation of the mixture of **8** *and* **9** Acetylation of 101 mg of the mixture with Ac_2O–C_5H_5N for 2 days at room temp. followed by the usual work up and purification by silica gel CC (EtOAc–hexane, 17:83, two developments) gave two acetates. The less polar product was **10** (31.9 mg). Mp 164 5–165°/174 5–175° (EtOAc–hexane), $[\alpha]_D$ +83.6° ($CHCl_3$; *c* 0.45). (Found: C, 64.08; H, 7.23. $C_{24}H_{32}O_8$ requires C, 64.27; H, 7.19%.) IR ν_{max}^{Nujol} cm^{-1}: 1780, 1750, 1730, 1710, 1650; UV λ_{max}^{EtOH} nm (ε): 228 (11 000); MS (probe) 70 eV, *m/z*: 406 $[M-42]^+$, 388 $[M-HOAc]^+$, 328 $[M-2HOAc]^+$, 306 $[406-$angelic acid$]^+$, 288 $[388-$angelic acid$]^+$, 247, 108, 83 $[C_4H_7CO]^+$ (100). The more polar product was **11** (103 1 mg). Mp 144 5–146° (EtOAc–hexane), $[\alpha]_D$ −92.0° ($CHCl_3$; *c* 0.91). (Found. C, 64.24; H, 7.32. $C_{24}H_{32}O_8$ requires C, 64.27; H, 7.19%.) IR ν_{max}^{Nujol} cm^{-1}: 1770, 1750, 1725, 1700, 1640; UV λ_{max}^{EtOH} nm (ε). 226 (15 000); MS (probe) 70 eV, *m/z*: 406 $[M-42]^+$, 388 $[M-HOAc]^+$, 328 $[M-2HOAc]^+$, 306 $[406-$angelic acid$]^+$, 288 $[388-$angelic acid$]^+$, 247, 228, 174, 108, 83 $[C_4H_7CO]^+$ (100).

Alkaline hydrolysis and methylation of the mixture of **8** *and* **9**. The mixture (52.2 mg) was dissolved in 5% KOH–MeOH (10 ml) and refluxed for 1 hr under N_2. After cooling, the mixture was acidified with 2 M HCl and extracted with Et_2O. The combined Et_2O fractions were washed with satd NaCl soln and dried over Na_2SO_4. Removal of the solvent gave the residue (45.1 mg). To a soln of the residue in 5 ml of Me_2CO (5 ml) under N_2 was added dry K_2CO_3 (30 mg) and MeI (0.4 ml). The reaction was heated at 40° for 5 hr, and every 1 hr additional MeI (0.4 ml) was added. After removal of the solvent, the residue was partitioned between Et_2O (40 ml) and 10% K_2CO_3 soln. The Et_2O layer was separated, and washed with satd NaCl soln and dried over Na_2SO_4. Removal of the solvent gave a crude crystal of **15** (29.1 mg). Mp 116–116.5° (hexane–EtOAc). IR ν_{max}^{Nujol} cm^{-1}: 3500 (OH), 1700, 1670 (C=CCO), 1630, 1610, 920; EIMS (probe) 70 eV, *m/z*: 278 $[M]^+$, 260 $[M-H_2O]^+$, 246 $[M-MeOH]^+$ (100), 228 $[246-H_2O]^+$, 174, 124, 90; HRMS *m/z*: Calc. for $C_{16}H_{22}O$ 278.1528. Found 278.1523; ^{1}H NMR (200 MHz; $CDCl_3$): δ1.01 (3H, *d*, *J* = 7.3 Hz, H-15), 1.29 (3H, *s*, H-14), 2.33, 2 71 (1H each, *dd*, *J* = 17, 3.9 Hz, H-9), 3.73 (3H, *s*, OMe), 3.77 (1H, *ddd*, *J* = 12, 9.3, 4.4 Hz, H-3), 5.66, 6.22 (1H each, *d*, *J* = 1.0 Hz, H-13); ^{13}C NMR (25 MHz; C_5D_5N): δ26.9 (*t*, C-1), 28.7 (*t*, C-2), 70.0 (*d*, C-3), 44.9 (*d*, C-4), 40.5 (*s*, C-5), 157.9 (*d*, C-6), 139.6, 135.9 (each *s*, C-7, C-11), 197.1 (*s*, C-8), 40.7 (*t*, C-9), 36.7 (*d*, C-10), 167.0 (*s*, C-12), 126.3 (*t*, C-13), 24.9 (*q*, C-14), 8.3 (*q*, C-15), 51.9 (*q*, OMe).

$NaBH_4$ *reduction of* **15**. A soln of 75 mg **15** in 20 ml MeOH was reduced with 52.3 mg $NaBH_4$ at 0° for 30 min, then at room temp. for 30 min. After addition of 32.6 mg $NaBH_4$, the mixture was kept at 60° for 1.5 hr, then diluted with 2 M HCl and extracted with Et_2O. The washed and dried extract was evaporated and the residue (50.5 mg) was purified by silica gel CC (EtOAc–hexane, 30:70) to afford **16** (25 mg). Mp 154–154.5° (hexane–EtOAc). EIMS (probe) 70 eV, *m/z*: 250 $[M]^+$, 232 $[M-H_2O]^+$, 217 $[M-Me]^+$, 159, 139, 121 (100), 112; HRMS *m/z* Calc. for $C_{15}H_{22}O_3$ 250 1586. Found 250 1578.

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