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Four New Eremophilane-Type Alcohols from *Cremanthodium helianthus* Collected in China

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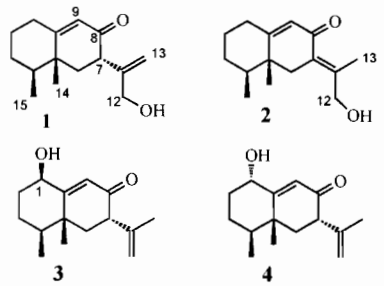
Four new eremophilane-type sesquiterpenoid alcohols were isolated from *Cremanthodium helianthus* collected in China and their structures established on the basis of spectroscopic analyses. All of them had 9-en-8-one partial structures with one more double bond either Δ^{11}, $\Delta^{11(13)}$, or $\Delta^{7(11)}$. Two of them had a hydroxy group at C-1 position.

Keywords: *Cremanthodium helianthus*, Asteraceae, Eremophilane, Sesquiterpenes.

The area of Hengduan Mountains in China is very interesting from the view point of plant diversity. We are investigating both inter- and intra-specific diversity of *Ligularia* species collected in this area and have reported some results [1-8]. The genus *Cremanthodium* (Asteraceae) is close to *Ligularia* [9,10]. They are small in plant size with tiny flowers and grow in the higher mountains than *Ligularia*. It is not so easy to collect a lot of samples at one time. However, we are studying intra-specific diversity and use just one individual plant in each case, which is enough for us to analyze the chemical constituents. Some reports appeared to isolate hydrocarbons and aromatic compounds as well as bisaborane- and oplopane-type sesquiterpenoids from four *Cremanthodium* species [11-19]. We had oppotunities to collect *C. helianthus* in 2008 and 2009 in China. We found four new eremophilane-type sesquiterpenoids, **1-4**, as well as known compounds **5-9**. Now we report our results of this study in detail.

Compound **1** showed a quasi molecular ion peak at *m/z* 235 and its molecular formula was determined to be $C_{15}H_{22}O_2$ by HRCIMS spectrum. The IR spectrum indicated the presence of a hydroxy (3437 cm^{-1}) and a carbonyl (1672 cm^{-1}) group, which was supported by the ^{13}C NMR data (δ 66.5, 199.4). The ^1H NMR spectrum showed the presence of a doublet methyl group (δ 0.55, J = 6.1 Hz), a singlet methyl group (δ 0.63), oxymethylene protons (δ 4.19, 4.26, each dd with J = 12.7, 5.5 Hz), an olefinic proton (δ 5.71), and exomethylene protons (δ 4.87, 5.22) (Table 1). The ^{13}C NMR and HSQC spectra suggested the presence of two methyl, six methylene, three methine, and four quaternary carbon signals. Because the degree of unsaturation was five, this molecule should be bicyclic. The HMBC spectrum indicated correlations between H-15 and C-3 and C-5, between H-14 and C-4, C-5, C-6, and C-10, between H-13 and C-7, between H-12 and C-13, between H-6 and C-8, and between H-9 and C-1 and C-5 (Figure 1), suggesting that the eremophilane skeleton with 9-en-8-one structure for this compound, and that C-12 position is substituted with a hydroxyl function. The stereochemistry was determined by the NOESY spectrum (Figure 1). The NOEs between H-14 and H-7β, between H-1β and H-3β, between H-3β and H-15, and between H-1 α and H-9 were observed. Therefore, the three carbon unit at C-7 should be α and vicinal dimethyl group β. The CD spectrum showed the positive Cotton effect at 237 nm (+20842; EtOH), which was very similar to that of known enone **5** [4,5,7,20], also isolated from this extract (see Experimental). Thus, this compound is established as (4 *S*,5*R*,7*S*)-12-hydroxyeremophila-9,11(13)-dien-8-one.



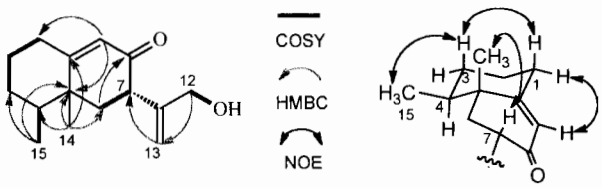


Figure 1: The major COSY, HMBC, and NOESY correlations detected for compound **1**.

Compound **2** had the same molecular formula as that of compound **1**. The ^1H NMR spectrum exhibited the presence of a singlet and a doublet methyl group as well as the one attached to the olefinic carbon (Table 1). An olefinic proton at C-9 appeared at δ 5.88 as a broad singlet, almost the same position as that of compound **1**. The methyl group observed at δ 2.29 as a broad singlet was assigned as H-13, because the chemical shift was almost the same as that of dehydrofukinone (*Z*-methyl group).

Table 1. ^{1}H NMR Data of Compounds **1-4** (500 MHz, measured in C_6D_6) (multi., *J* (Hz))

position	1	2	3	4
1	1.72-1.79 (m)	1.76-1.85 (m)	3.69-3.71 (m)	3.63 (dt, 10.3, 5.1)
	1.72-1.79 (m)	1.76-1.85 (m)	-	-
2	1.37-1.42 (m)	1.36-1.44 (m)	1.68-1.73 (m)	1.66-1.74 (m)
	0.98-1.08 (m)	0.95-1.08 (m)	1.18-1.27 (m)	1.02-1.11 (m)
3	1.07-1.13 (m)	1.07-1.17 (m)	1.68-1.78 (m)	1.66-1.74 (m)
	0.98-1.08 (m)	0.95-1.08 (m)	1.00-1.06 (m)	0.89-1.00 (m)
4	0.97-1.05 (m)	1.07-1.17 (m)	0.97-1.07 (m)	0.89-1.00 (m)
6	1.73 (d, 9.2)	2.70 (d, 13.7)	1.76 (dd, 13.0, 4.7)	1.66-1.74 (m)
	1.73 (d, 9.2)	1.93 (d, 13.7)	1.68 (dd, 14.2, 13.0)	1.66-1.74 (m)
7	3.11 (t, 9.2)	-	3.13 (dd, 14.2, 4.7)	3.01 (dd, 12.7, 6.1)
9	5.71 (s)	5.88 (br s)	5.63 (s)	6.31 (d, 1.7)
12	4.26 (dd, 12.7, 5.5)	3.82-3.87 (m)	5.02 (br s)	5.04 (br s)
	4.19 (dd, 12.7, 5.5)	3.82-3.87 (m)	4.88 (br s)	4.87 (br s)
13	5.22 (br s)	2.29 (br s)	1.85 (br s)	1.89 (br s)
	4.87 (s)	-	-	-
14	0.63 (s)	0.70 (s)	1.05 (s)	0.63 (s)
15	0.55 (d, 6.1)	0.63 (d, 6.6)	0.63 (d, 6.9)	0.51 (d, 6.3)
OH	2.64 (t, 5.5)	-	-	0.80 (d, 5.1)

The proton connectivity for H1-H2-H3-H4-H15 was revealed by the COSY spectrum. The NMR spectrum is similar to that of kanaitzensol, previously isolated from *Ligularia kanaitzensis* [4]. Thus, the planar structure was determined as 9,10-dehydro-kanaitzensol (=12-hydroxyeremophila-7(11),9-dien-8-one). The geometry for $\Delta^{7(11)}$ was *E*, because the NOE between H-12 and H-6β was observed. Therefore, this compound was established as (7(11)*E*)-12-hydroxyeremophila-7(11),9-dien-8-one.

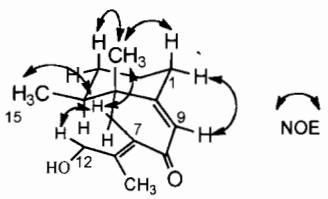


Figure 2: The major NOESY correlations detected for compound **2**.

Compound **3** exhibited the quasi-molecular ion peak at *m/z* 235 and the molecular formula was determined to be $C_{15}H_{23}O_2$ (HRMS). The HMBC spectrum showed the similar correlation peaks as detected in the case of compound **1** (Figure 3), establishing the eremophilane skeleton. The presence of a hydroxy group was indicated by the IR absorption at 3443 cm^{-1}. The position of the hydroxy group was determined at C-1, because the HMBC correlations were detected between H-1 and C-9, C-10, and C-5. The planar structure of this compound should be 1-hydroxy-eremophila-9,11-dien-8-one.

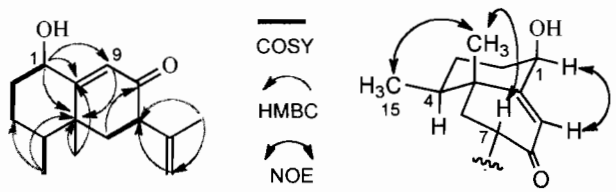
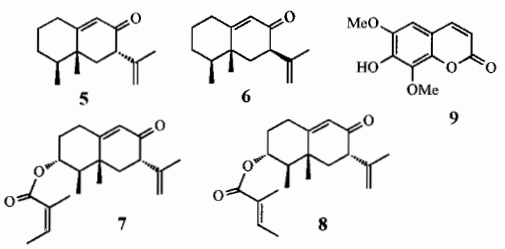


Figure 3: The major COSY, HMBC, and NOESY correlations detected for compound **3**.

The stereochemistry was determined by the NOESY spectrum. As illustrated in Figure 3, the NOE between H-1 and H-9, between H-14 and H-7β, and between H-15 and H-14 was observed. These observations indicate that the hydroxy group of compound **3** is β. The absolute configuration was determined by the CD spectrum (+37156; EtOH (220 nm)) as depicted in the formula.

Compound **4** had the same molecular formula as that of **1-3**. The presence of a hydroxy group was indicated by the IR spectrum (3418 cm^{-1}). The NMR data are very similar to those of compound **3**. The position of the oxymethine proton was determined at C-1 by the HMBC spectrum. This proton (H-1) was observed at δ 3.63 (dt, J = 10.3 and 5.1 Hz), being slightly highfield shifted as compared to that of compound **3**. The structure was determined as 1α-hydroxyeremophila-9,11-dien-8-one. These observations indicate that ring A of both compounds **3** and **4** adopts chair-like conformation and the hydroxy group at C-1 for compound **3** should be β-quasi axial and that for compound **4** α-quasi equatorial.

We have isolated four new eremophilane-type sesquiterpenoids, all of which had 9-en-8-one partial structures with a hydroxy group at C-1 or C-12 position. Compound **2** is considered to be a Δ^9 derivative of kanaitzensol [4]. We assume that 12-hydroxyeremophila-7(11)*E*-en-8-one, such as compound **2** and kanaitzensol, could not cyclize to a furan and remained unchanged in the biosynthetic pathway [21]. Compounds having a hydroxy group at C-1 position, 1-hydroxyeremophila-7(11),9-dien-8-one (both isomers), have been reported by Bohlmann and Knoll [22]. The configuration at C-1 position was discussed that the β-isomer had β-quasi equatorial conformation, while the α-isomer α-quasi axial. However, in our case, compound **3** (β-isomer) adopted β-quasi axial conformation, and compound **4** (α-isomer) α-quasi equatorial, although these compounds had different substitution at C-7 position (*vide supra*). The proton at C-1 of the β-isomer was more shielded, while that of α-isomer more deshielded in Bohlmann's compounds, being completely reversed to ours (Bohlmann's in $CDCl_3$, while ours in C_6D_6) [22]. Sørensen later reported that they isolated Bohlmann's compounds, in the ratio of 1:2 (α:β) [23]. However, the chemical shifts of H-1 of them were δ 3.76 for β-isomer, and 3.71 for α-isomer (in DMSO-d_6), which were similar to our data, not to Bohlmann's. It is interesting to note that a pair of compounds, **3** and **4**, were isolated from this extract. Because Bohlmann and Sørensen also isolated a pair of isomers, it is assumed that the biosynthetic pathway to these compounds may be through a cationic or radical intermediate at C-1. It is also interesting to note that both angelate and tiglate esters of 3α-hydroxyeremophila-7(11),9-dien-8-one, **7** (=petasin) [5,7] and **8** [4,5,7], as well as **5** [4,5,7,20] and **6** [4,5,7,22c,24,25], the major constituents in both samples, were isolated. Oxygenated coumarin **9** was also present in this extract [26].



Experimental

Specific rotations and CD spectra were measured on a JASCO P-1030 and a JASCO J-725 auto recording polarimeter; IR spectra, on a SHIMADZU FT/IR-8400S spectrophotometer; ^{1}H and ^{13}C NMR spectra, on a Varian 500MR (500 MHz and 125 MHz, respectively) spectrometer. Mass spectra, including high-resolution ones, were recorded on a JEOL JMS-700 MStation. Chemcopak

Nucleosil 50-5 (4.6×250 mm) with a solvent system of hexane-ethyl acetate was used for HPLC (JASCO pump system). Silica gel BW-127ZH (100-270 mesh, Fuji Silysia) was used for column chromatography. Silica gel 60 F_{254} plates (Merck) were used for TLC.

The root of the sample 1, *Cremanthodium helianthus*, was collected in Laojunshan, Yunnan (3991 m) in 2008, and the sample 2 in Qianhushan, Yunnan (3666 m) in 2009 (voucher specimen, No. 200856 and 200903, were deposited in the Herbarium of Kunming Institute of Botany). Both were extracted with EtOAc to give extracts (816 and 104 mg, respectively), which were separated by silica-gel column chromatography (hexane:AcOEt, in gradient) followed by HPLC (Nucleosil 50-5, hexane:AcOEt). Compounds isolated from the sample 1 were **1** (0.4 mg), **2** (0.1 mg), **3** (0.1 mg), **4** (0.3 mg), as well as **8** (0.4 mg), and a mixture of **5** and **6** (546.4 mg), and from the sample 2, **7** (1.0 mg), **8** (0.2 mg), a mixture of **5** and **6** (68.6 mg), and **9** (1.0 mg).

Compound 1
$[\alpha]_D$: +80.5 (*c* 0.04, EtOH).
CD [θ] (nm) (EtOH): -2828 (318), +20843 (237).
FTIR (KBr): 3437, 1672 cm^{-1}.
^{13}C NMR (125 MHz, C_6D_6): 15.0 (C15), 15.3 (C14), 26.4 (C2), 30.4 (C3), 32.7 (C1), 39.6 (C5), 41.4 (C6), 43.5 (C4), 47.8 (C7), 66.5 (C12), 113.5 (C13), 124.2 (C9), 148.2 (C11), 169.2 (C10), 199.4 (C8).
MS (CI): *m/z* = 235 $[M+H]^+$, 217 (100), 216.
HRMS (CI *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}O_2$: 235.1698; found: 235.1692.

Compound 2
$[\alpha]_D$: +76.9 (*c* 0.029, EtOH).
MS (CI): *m/z* = 235 $[M+H]^+$, 217 (100), 216.
HRMS (CI) *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}O_2$: 235.1698; found: 235.1694.

Compound 3
$[\alpha]_D$: +100.0 (*c* 0.01, EtOH).
CD [θ] (nm) (EtOH): -1660 (325), -6593 (250), +37156 (220).
FTIR (KBr): 3443, 1666 cm^{-1}.
MS (CI): *m/z* = 235 $[M+H]^+$ (100), 217, 207, 189.
HRMS (CI) *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}O_2$: 235.1698; found: 235.1697.

Compound 4
$[\alpha]_D$: +43.3 (*c* 0.03, EtOH).
CD [θ] (nm) (EtOH): -859 (328), +14262 (239), +4969 (205).
FTIR (KBr): 3418, 1666 cm^{-1}.
MS (CI): *m/z* = 235 $[M+H]^+$ (100), 189.
HRMS (CI) *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}O_2$: 235.1698; found: 235.1691.

Compound 5
$[\alpha]_D^{13}$: +115.9 (*c* 0.58, EtOH).
CD [θ] (nm) (EtOH): +22500 (238).
FTIR (KBr): 1674, 1620 cm^{-1}.
MS (CI): *m/z* = 219 $[M+H]^+$ (100), 218, 135.
HRMS (CI) *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}O$: 219.1749; found: 219.1742.
^1H NMR (400 MHz, C_6D_6): 0.57 (3H, d, *J* = 6.2 Hz, H15), 0.70 (3H, s, H14), 1.00-1.05 (1H, m, H4), 1.05-1.11 (1H, m, H3β), 1.09-1.12 (1H, m, H2β), 1.12-1.16 (1H, m, H3α), 1.39-1.45 (1H, m, H2α), 1.70 (1H, dd, *J* = 13.9, 13.2 Hz, H6α), 1.78 (1H, dd, *J* = 13.2, 4.8 Hz, H6β), 1.78-1.81 (1H, m, H1α), 1.83-1.87 (1H, m, H1β), 1.88 (3H, br s, H13), 3.03 (1H, dd, *J* = 13.9, 4.8 Hz, H7), 4.86 (1H, br s, H12a), 5.02 (1H, quint, *J* = 1.1 Hz, H12b), 5.76 (1H, d, *J* = 1.1 Hz, H9).
^{13}C NMR (100 MHz, C_6D_6): 15.1 (C15), 15.5 (C14), 20.2 (C13), 26.5 (C2), 30.5 (C3), 32.7 (C1), 39.4 (C5), 42.0 (C6), 43.7 (C4), 51.1 (C7), 113.5 (C12), 124.5 (C9), 144.6 (C11), 167.5 (C10), 196.9 (C8).

Compound 6
CD [θ] (nm) (EtOH): -22943 (238).

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