

Four New Sesquiterpene Polyol Esters from *Cremanthodium ellisii*

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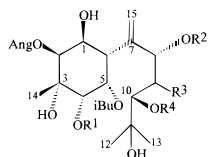
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Esters of four new sesquiterpene polyalcohols (**1–4**) have been isolated from *Cremanthodium ellisii*. Their structures were established on the basis of spectral data interpretation and X-ray crystallographic analysis.

The genus *Cremanthodium* (Compositae) consists of about 55 species distributed in many countries. Some 47 species grow in the People's Republic of China, especially in the northwest and southwest regions.¹ Plants of the *Cremanthodium* genus have long been used as Tibetan traditional medicinal herbs for their anti-inflammatory, detoxification, and pain-relief properties.²

Due to difficulties in their collection (most of the genus *Cremanthodium* grow in areas at an elevation of 3500–5000 m), chemical studies of this genus have not been reported previously. Based on its medicinal value,² we have investigated *Cremanthodium ellisii* Kitam, which grows in northwestern China and have found it to contain four novel bisabolene polyalcohol esters. This paper describes the isolation and structural elucidation of the new compounds **1–4**.



	R1	R2	R3	R4
1	H	iBu	H	H
2	Ac	H	H	iBu
3	Ac	iBu	H	H
4	H	iBu	OH	H

Results and Discussion

The Me₂CO extract of dried and powdered whole plants of *C. ellisii* was subjected to column chromatography over Si gel and fractionated, as described in the Experimental Section, to yield four new compounds: 2 β -angeloyl-5 α ,8-diisobutyryl-1 β ,3 α ,4 α ,10,11-pentahydroxybisabolene (**1**); 4 α -acetyl-2 β -angeloyl-5 α ,10-diisobutyryl-1 β ,3 α ,8,11-tetrahydroxybisabolene (**2**); 4 α -acetyl-2 β -angeloyl-5 α ,8-diisobutyryl-1 β ,3 α ,10,11-tetrahydroxybisabolene (**3**); and 2 β -angeloyl-5 α ,8-diisobutyryl-1 β ,3 α ,4 α ,9,10,11-hexahydroxybisabolene (**4**).

Compound **1** was obtained as colorless needles upon recrystallization from *n*-hexane–EtOAc, mp 179–180 °C, $[\alpha]_D^{25} -80^\circ$ (*c* 0.20, CHCl₃). The ¹³C-NMR spectrum of **1** exhibited the presence of two isobutyryl groups (δ 177.9, 177.0, 2 \times 34.4, 2 \times 19.1, 19.0, 18.8) and one angeloyl group [δ 167.0 (CO), 139.9 (CH), 127.2 (C), 20.6 (CH₃), 15.9 (CH₃)].³ The EIMS of **1** gave an [M – H₂O]⁺

ion peak at *m/z* 540, and the HREIMS gave an [M – H₂O – isobutyric acid]⁺ ion peak at *m/z* 452.2453, with the elemental composition of this fragment being deduced as C₂₄H₃₆O₈ (calcd 452.2410). Thus, the molecular formula of **1** was concluded to be C₂₈H₄₆O₁₁.

The IR spectrum of **1** showed absorption bands for hydroxyl groups (3463 cm⁻¹), ester carbonyl groups (1716 cm⁻¹), and double bonds (1648 cm⁻¹). Except for the three ester groups, the ¹³C-NMR and DEPT spectra exhibited 15 carbons, including three methyls, two methylenes (one olefinic carbon at δ 117.2), seven methines (six oxygenated at δ 75.9, 75.4, 64.8, 76.4, and 70.3), and three quaternary carbons (two oxygenated at δ 72.0 and 74.3). One olefinic carbon was evident at δ 143.9. In turn, the ¹H-NMR spectrum showed three methyl singlets at δ 1.28, 1.13, and 1.11; six oxymethine protons at δ 4.56 (1H, dd, *J* = 2.8, 11.7 Hz), 5.45 (1H, d, *J* = 2.8 Hz), 5.44 (1H, dd, *J* = 2.8, 4.7 Hz), 4.76 (1H, dd, *J* = 1.8, 9.4 Hz), 4.23 (1H, dd, *J* = 5.1, 9.7 Hz), and 3.79 (1H, d, *J* = 4.6 Hz); a methine proton at δ 2.93 (1H, dd, *J* = 2.8, 11.7 Hz); and two olefinic proton singlets at δ 5.11 and 5.21 attributed to an isolated exocyclic double bond. The above data suggested that there was a total of six degrees of unsaturation, and **1** was deduced as being a monocyclic sesquiterpenoid. The ¹H–¹H COSY and ¹H–¹³C COSY spectra of **1** revealed the following partial structures: R–C–2H–C–1H–C–6H–C–5H–C–4H–R and R–C–8H–C–9H₂–C–10H–R (R = nonprotonated carbon atom). A ¹H–¹³C COLOC NMR experiment exhibited cross peaks between C-3 and H-2 and H-4 and H-14 and between C-11 and H-10 and H-12 and H-13; therefore, **1** was deduced as a polysubstituted bisabolene sesquiterpene.^{4,5} The locations of the three ester groups and the five hydroxyl groups were determined from the ¹H–¹³C COLOC NMR spectrum (Figure 1). The configuration of the substituent groups was established from the ¹H–¹H NOESY spectrum of **1**. Confirmation of the structure of **1** was obtained by the application of X-ray crystallographic analysis (Figure 2). The data collection information is listed in the Experimental Section.

Compound **2**, obtained as a white powder, gave an [M – H₂O]⁺ ion peak at *m/z* 582 in the EIMS, while the HREIMS afforded an [M – H₂O – isobutyric acid]⁺ ion peak at *m/z* 494.2491. The elemental composition of this latter peak was analyzed as C₂₆H₃₈O₉, and thus, the molecular formula of **2** was concluded to be C₃₀H₄₈O₁₂. The ¹H-NMR spectrum of **2** was very similar to that of **1**, but some differences were observed. The ¹H-NMR spectrum of **2** showed a signal for an acetyl group [δ

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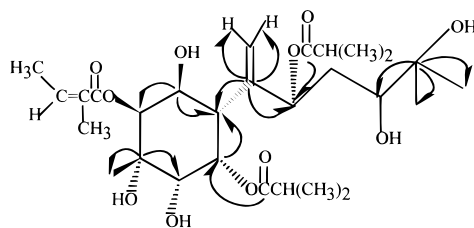


Figure 1. ^1H - ^{13}C long-range COSY of compound **1**.

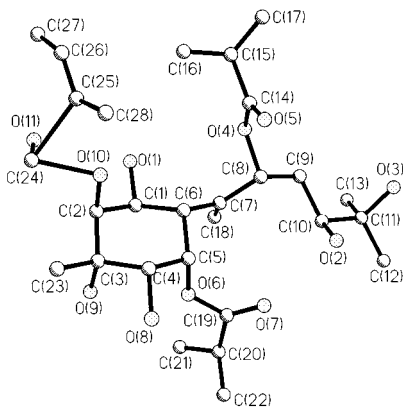


Figure 2. ORTEP representation of **1**.

2.08 (3H, s)]. The doublet at δ 3.79 (H-4) observed in **1** now shifted to δ 5.01. The downfield shift of H-4 by 1.22 ppm in **2** is due to the anisotropic effect of the acetyl carbonyl group. The ^1H - ^{13}C COLOC NMR spectrum showed correlation peaks between C-7 (δ 140.9) and H-8 (δ 3.37) and H-6 (δ 3.04), between δ 169.3 (acetyl-CO) and H-4, and between δ 175.2 (isobutyryl-CO) and H-10 (δ 5.40), indicating an acetyl group at C-4, while a hydroxyl group and an isobutyryl group were affixed to C-8 and C-10, respectively. The complete assignments of the ^1H - and ^{13}C -NMR signals of **2** were based on ^1H - ^1H COSY and ^1H - ^{13}C COSY experiments. The stereochemistry of **2** was deduced on the basis of a ^1H - ^1H NOESY experiment.

Compound **3**, obtained as a white powder, showed IR and EIMS spectral data almost identical to those of **2**. The one significant difference in the ^1H -NMR spectrum of **3**, compared with that of **2**, was that a double doublet occurred at δ 4.92 ($J = 3.0, 9.5$ Hz). Moreover, the double doublet of **2** at δ 5.40 (H-10) now shifted to δ 4.02. The foregoing results clearly indicated that compound **3** was a positional isomer of **2**, but was also a 4 α -acetyl derivative of **1**. The correlation peak between δ 176.0 (isobutyryl-CO) and H-8 in the ^1H - ^{13}C COLOC spectrum of **3** also supported the structure proposed.

The structure of compound **4** clearly followed from the ^1H -NMR data (Table 1), which were closely similar to those of **1**. The major difference in the ^1H -NMR spectrum of **4**, when compared with that of **1**, was that a triplet at δ 4.80 (1H, $J = 5.0$ Hz) replaced the multiplets at δ 1.88 (H-9a) and 1.99 (H-9b). This, therefore, indicated that **4** has a OH substituent at C-9.

Experimental Section

General Experimental Procedures. The melting points were determined on a Kofler melting point apparatus and are uncorrected. Optical rotations were measured in CHCl_3 with a JASCO J-20C automatic recording polarimeter. ^1H - and ^{13}C -NMR spectra were

obtained on a Bruker AM-400 FT-NMR spectrometer with TMS as internal standard. EIMS and HREIMS measurements were carried out on a VG-ZAB-MS mass spectrometer at 70 eV. IR spectra were recorded a Nicolet 170 SX FT-IR instrument. Si gel 200–300 mesh was used for column chromatography.

Plant Material. *C. ellisii* was collected in August 1991, in Zhang County, Gansu Province, People's Republic of China, and identified by Prof. Zexiang Peng, Department of Biology, Lanzhou University, Lanzhou, People's Republic of China. A voucher specimen has been deposited in the Herbarium of the Department of Biology, Lanzhou University.

Extraction and Isolation. The air-dried whole plants of *C. ellisii* (6.5 kg) were powdered and extracted three times (each for five days) with Me_2CO at room temperature, and the solvent was removed under reduced pressure to give a residue (300 g). The extract was subjected to column chromatography over Si gel (1700 g; 200–300 mesh) with petroleum ether (60–90 $^\circ\text{C}$)/ Me_2CO gradient to afford eight fractions. Fraction D (petroleum ether– Me_2CO , 2:1) was further separated on Si gel using *n*-hexane– Me_2CO (2:1) as eluent and purified by preparation TLC with *n*-hexane– Me_2CO (3:1) as developing solvent, to finally yield 12 mg of **1**, 35 mg of **2**, 11 mg of **3**, and 5 mg of **4**.

2 β -Angeloyl-5 α ,8-diisobutyryl-1 β ,3 α ,4 α ,10,11-pentahydroxybisabolene (1): colorless needles (recrystallized from *n*-hexane–EtOAc); mp 179–180 $^\circ\text{C}$; $[\alpha]_D^{25} -80^\circ$ (c 0.20, CHCl_3); IR (KBr) ν max 3463, 3076, 2976, 2936, 2878, 1716, 1649, 1463, 1385, 1359, 1229, 1201, 1153, 1087, 923, 847 cm^{-1} ; ^1H -NMR data, see Table 1; ^{13}C -NMR data, see Table 2; EIMS m/z $[\text{M} - \text{H}_2\text{O}]^+$ 540 (1), 525 (1), 452 (16), 434 (8), 367 (8), 334 (3), 246 (11), 205 (9), 179 (15), 151 (8), 137 (7), 123 (23), 83 (100), 71 (70), 55 (30), 43 (47); HREIMS m/z $[\text{M} - \text{H}_2\text{O} - \text{isobutyric acid}]^+$ 452.2453 ($\text{C}_{24}\text{H}_{36}\text{O}_8$, requires 452.2410).

4 α -Acetyl-2 β -angeloyl-5 α ,10-diisobutyryl-1 β ,3 α ,8,11-tetrahydroxybisabolene (2): white powder; $[\alpha]_D^{25} -41.4^\circ$ (c 0.15, CHCl_3); IR (KBr) ν max 3478, 3089, 2976, 2928, 1728, 1649, 1466, 1376, 1229, 1151, 1059, 919, 848 cm^{-1} ; ^1H -NMR data, see Table 1; ^{13}C -NMR data, see Table 2; EIMS m/z $[\text{M} - \text{H}_2\text{O}]^+$ 582 (1), 567 (1), 541 (5), 523 (5), 512 (11), 494 (14), 453 (30), 436 (17), 408 (10), 365 (7), 353 (10), 264 (5), 247 (10), 205 (20), 177 (15), 141 (13), 123 (8), 83 (100), 71 (20), 55 (8); HREIMS m/z $[\text{M} - \text{H}_2\text{O} - \text{isobutyric acid}]^+$ 494.2491 ($\text{C}_{26}\text{H}_{38}\text{O}_9$, requires 494.2516).

4 α -Acetyl-2 β -angeloyl-5 α ,8-diisobutyryl-1 β ,3 α ,9,10,11-tetrahydroxybisabolene (3): white powder, $[\alpha]_D^{25} -45.5^\circ$ (c 0.17, CHCl_3); IR (KBr) ν max 3484, 3082, 2976, 2935, 2878, 1723, 1649, 1464, 1376, 1229, 1151, 1056, 917, 848 cm^{-1} ; ^1H -NMR data, see Table 1; ^{13}C -NMR data, see Table 2; EIMS m/z $[\text{M} - \text{H}_2\text{O}]^+$ 582 (1), 512 (2), 494 (20), 476 (4), 453 (4), 409 (10), 246 (10), 205 (10) 179 (14), 151 (7), 123 (30), 83 (100), 71 (99), 55 (58); HREIMS m/z $[\text{M} - \text{H}_2\text{O} - \text{isobutyric acid}]^+$ 494.2488 ($\text{C}_{26}\text{H}_{38}\text{O}_9$, requires 494.2516).

2 β -Angeloyl-5 α ,8-diisobutyryl-1 β ,3 α ,4 α ,9,10,11-hexahydroxybisabolene (4): white powder, $[\alpha]_D^{25} -88^\circ$ (c 0.08, CHCl_3); IR (KBr) ν max 3479, 3076, 2976, 2936, 2878, 1716, 1645, 1463, 1385, 1359, 1229, 1201, 1153, 1087, 923, 847 cm^{-1} ; ^1H -NMR data, see Table 1; ^{13}C -NMR data, see Table 2; EIMS m/z $[\text{M} - \text{H}_2\text{O}]^+$ 556 (2), 538 (3), 468 (15), 246 (11), 205 (10), 179 (16), 151

Table 1. ¹H-NMR Data of Compounds 1–4 in CDCl₃

proton	1	2	3	4
H-1	4.56 dd (2.8, 11.7)	4.69 dd (3.0, 11.7)	4.55 dd (2.7, 11.6)	4.70 dd (3.0, 11.4)
H-2	5.45 d (2.8)	5.49 d (3.0)	5.46 d (2.9)	5.36 d (2.7)
H-4	3.79 d (4.7)	5.04 d (3.6)	5.08 d (3.3)	4.12 d (4.9)
H-5	5.44 dd (2.8, 4.7)	5.58 dd (2.7, 3.4)	5.52 dd (2.7, 3.3)	5.36 dd (2.8, 4.9)
H-6	2.93 dd (2.8, 11.7)	3.04 dd (2.7, 12.1)	3.01 dd (2.7, 11.8)	2.84 dd (2.8, 11.5)
H-8	4.76 dd (1.8, 9.4)	3.37 dd (1.6, 9.4)	4.92 dd (3.0, 9.5)	4.95 d (4.8)
H-9	1.88 m	1.66 m	1.64 m	4.80 t (5.0)
H-9'	1.99 m	1.89 m	1.94 m	
H-10	4.23 dd (5.1, 9.7)	5.40 dd (7.1, 7.1)	4.02 dd (2.2, 10.1)	4.12 d (4.9)
H-12	1.11 s	1.20 s	1.21 s	1.13 s
H-13	1.13 s	1.12 s	1.19 s	1.14 s
H-14	1.28 s	1.24 s	1.26 s	1.25 s
H-15	5.11 s	5.28 s	5.08 s	5.07 s
H-15'	5.21 s	5.50 s	5.26 s	5.27 s
angeloyl				
–CH ₃	1.92 br s	2.01 q (1.5)	1.96 q (1.5)	1.94 br
–CH ₃	2.00 dq (7.3, 1.3)	2.05 dq (7.2, 1.5)	2.02 dq (7.2, 1.5)	2.03 dq (7.2, 1.3)
–H	6.14 qq (7.3, 1.3)	6.16 qq (7.2, 1.5)	6.14 qq (7.2, 1.5)	6.14 qq (7.2, 1.3)
2 × isobutyryl				
CH		2.59–2.65 m	2.55–2.66 m	
CH ₃	1.16 d (7.0)	1.19 d (6.8)	1.12 d (6.8)	
CH ₃	1.19 d (6.8)	1.22 d (6.8)	1.21 d (6.8)	1.20 d (6.9)
OAc		2.08 s	2.05 s	

Table 2. ¹³C-NMR Data of Compounds 1–4 in CDCl₃

carbon	1	2	3	4
C-1	64.8	65.3	65.2	64.9
C-2	74.7	76.1	76.1	74.4
C-3	74.3	74.0	74.3	72.8
C-4	70.3	71.7	71.6	71.4
C-5	76.4	70.4	71.4	76.2
C-6	39.9	40.7	41.6	41.2
C-7	143.9	140.9	145.9	144.3
C-8	75.9	75.0	76.7	75.5
C-9	34.1	35.4	35.5	73.2
C-10	75.4	77.5	71.4	71.9
C-11	72.0	72.6	72.2	72.1
C-12	24.7	23.0	25.7	25.7
C-13	26.1	25.7	25.9	25.9
C-14	23.3	22.8	22.8	23.9
C-15	117.2	118.3	114.2	117.7
angeloyl				
		167.0	167.1	
		15.8	20.5	
		20.5	20.5	
		127.3	127.3	
		138.9	139.3	
2 × isobutyryl				
	177.9 (C8–OCO)	176.6 (C10–OCO)	177.7 (C8–OCO)	177.3 (C8–OCO)
	175.2	175.2	176.0	176.7
	34.4	34.5	34.2	34.1
	34.4	34.5	34.2	34.1
	19.1	18.4	18.8	19.1
	19.1	18.8	19.0	19.0
	19.0	19.0	19.0	18.7
	18.8	19.1	19.2	18.9

(7), 137 (7), 123 (24), 83 (100), 71 (80), 55 (31), 43 (48); HREIMS *m/z* [M – H₂O – isobutyric acid]⁺ 468.2343 (C₂₄H₃₆O₉, requires 468.2359).

X-ray Crystal Structure Analysis of Compound

1. Crystal data: C₂₈H₄₆O₁₁, formula wt 558.67, monoclinic, space group *P*2₁, *a* = 11.201 (8), *b* = 11.199 (3), *c* = 12.865 (1) Å, β = 103.34 (6)°, *V* = 1570.3 (7) Å³, *Z* = 2, *D_c* = 1.181 g/cm^{–3}, F(000) = 604, Cu–Kα radiation, λ = 1.541 84 Å. Crystal dimensions 0.32 × 0.12 × 0.08 mm. A total of 2592 reflections with *I* ≥ 3σ(*I*) (1° ≤ θ ≤ 60°) was obtained for the analysis. The structure was solved by the direct method program MULTAN 11/82. All atomic parameters, with anisotropic temperature factors for non-hydrogen atoms and isotropic ones for hydrogen atoms, were refined by full-matrix least-

squares methods. The final *R* value was 0.073. All calculations were carried out on a DEC PDP 11/44 computer using the SDP software package.^{6,7}

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