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SESQUITERPENE LACTONES FROM *CALEA MEGACEPHALA*

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Key Word Index—*Calea megacephala*; Asteraceae; Heliantheae; sesquiterpene lactones; heliangolide.

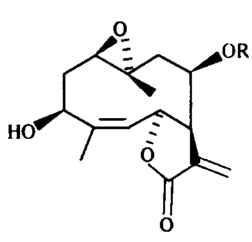
Abstract—Chemical analysis of *Calea megacephala* yielded two new sesquiterpene lactones. The new compounds represent a heliangolide, desacylisovalerylheliangine, and the ternifolin derivative 8β-methacryloyloxyternifolin. Their structures were established by spectroscopic methods.

INTRODUCTION

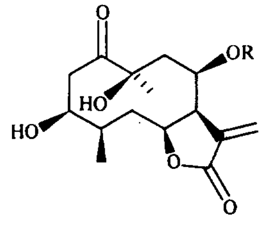
As part of our biochemical systematic investigation of the genus *Calea* (Asteraceae, Heliantheae) [1] we have analysed *Calea megacephala* from Chiapas, Mexico for its sesquiterpene lactone constituents. Its chemical analysis yielded two new sesquiterpene lactones, a heliangolide closely related to heliangine and another germacranolide structurally related to the ternifolins. The structure determinations involved spectroscopic methods which are described below..

RESULTS AND DISCUSSION

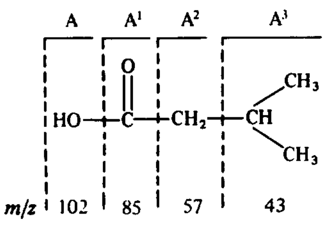
Desacylisovalerylheliangine (**1**), $C_{20}H_{28}O_6$, was a gum with an IR spectrum that indicated the presence of a hydroxyl group (3580 and 3440 cm^{-1}), a γ-lactone (1750 cm^{-1}), a saturated ester (1730 cm^{-1}) and a double bond (1655 cm^{-1}). The α-methylene-γ-lactone was further corroborated by the ^1H NMR spectrum of compound **1** which exhibited two one-proton doublets at δ 6.36 (H-13a) and 5.77 (H-13b) and a one-proton multiplet at 2.86 (H-7). The saturated ester side chain was assigned to an isovalerate group on the basis of the diagnostic ^1H NMR signals (a doublet at δ 2.18, a multiplet at 2.09 and a six-proton doublet at 0.90), together with characteristic mass spectral peaks, a base peak at *m/z* 85 (A^1), and very strong peaks at *m/z* 57 (A^2) and 43 A^3). The assignments of the ^1H NMR signals were deduced from detailed double irradiation experiments, the results being summarized in Table 1. A typical feature of the ^1H NMR spectrum of compound **1** was the presence of H-7 as a very narrow multiplet at δ 2.86. These small coupling constants ($J_{7,13a} = J_{7,13b} = 2.0$ Hz) together with the small value of $J_{6,7} = 2.5$ Hz clearly indicated a 12,6α-lactonized heliangolide with a 4,5-*cis*-double bond [2]. Comparison of the ^1H NMR spectrum of compound **1** with those of heliangine (**2**) and erioflorin (**3**), which were previously isolated from *C. berteriana* [3] and *C. leptocephala* [4], respectively, showed significant differences only in the signals of the side chains. This very close similarity in the chemical

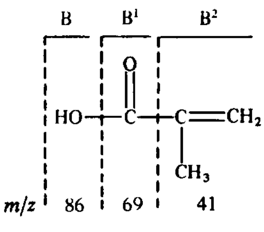


1 R = *i*-valerate
2 R = tiglate
3 R = methacrylate



4 R = methacrylate
5 R = angelate


$HO{-}C(=O){-}CH_2{-}CH(CH_3)_2$


$HO{-}C(=O){-}C(=CH_2){-}CH_3$

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† To whom correspondence should be addressed.

Table 1. ^{1}H NMR spectral data* of compounds **1** and **4**

	1	**4**	
		Benzene-d_6	CDCl$_3$
H-1	2.81 *dd* (10.5; 4.5)	—	—
H-2a	2.46 *dt* (15.0; 4.5)	2.40 *dd* (18.0; 11.0)	3.10 *dd*
H-2b	1.74 *ddd* (15.0; 10.5; 2.8)	2.02 *dd* (18.0; 6.5)	2.83 *dd*
H-3	4.49 *dd* (4.5; 2.5)	3.80 *ddd* (11.0; 6.5; 2.0)	4.28 *ddd*
H-4	—	1.73 *m*†	1.85–2.00†
H-5a	5.29 *dq* (11.0; 1.5)	1.90–2.05 *m*†	2.15–2.30 *m*†
H-5b		0.95–1.20 *m*†	†
H-6	6.62 *dd* (11.0; 2.5)	4.62 *ddd* (10.0; 5.0; 3.0)	4.95 *m*
H-7	2.86 *m*	2.48 *m*	2.64 *m*
H-8	5.19 *m*	5.59 *ddd* (11.0; 4.5; 2.5)	5.47 *m*
H-9a	2.71 *dd* (15.5; 4.5)	2.19 *dd* (15.0; 4.5)	2.35–2.45†
H-9b	1.31 *dd* (15.5; 3.5)	1.67 *dd* (15.0; 11.0)	†
H-13a	6.36 *d* (2.0)	6.06 *d* (2.0)	6.26 *d*
H-13b	5.77 *d* (2.0)	5.04 *d* (2.0)	5.69 *d*
H-14	1.49 *s*	0.80 *s*	1.36 *s*
H-15	1.81 *d* (1.5)	0.76 *d* (6.8)	1.11 *d*
OR	2.18 *d* (7.0)	6.20 *d* (2.0)	6.02 *br*
	2.09 *m*	5.25 *dq* (2.0)	5.56 *br*
	0.90 *d* (7.0)	1.83 *br*	1.87 *br*

*Spectra were run at 200 MHz at ambient temperature and TMS was used as internal standard. Figures in parentheses are coupling constants (J) or line separations in Hz.

†Obscured by other signals.

Table 2. ^{13}C NMR spectral data* of desacylisovalerylheliangine (**1**)

Carbon	δ, multiplicity	Carbon	δ, multiplicity
C-1	60.7 *d*	C-10	58.6 *s*
C-2	32.5 *t*	C-11	141.7 *s*
C-3	74.1 *d*	C-12	169.5 *s*
C-4	137.3 *s*	C-13	124.7 *t*
C-5	126.2 *d*	C-14	22.9 *q*†
C-6	75.5 *d*	C-15	22.2 *q*†
C-7	48.2 *d*	C-1′	172.0 *s*
C-8	72.0 *d*	C-2′	43.3 *t*‡
C-9	43.8 *t*‡	C-3′	25.4 *d*
C-10	58.6 *s*	C-4′	20.0 *q*
		C-5′	19.8 *q*

*Spectra were obtained at 50.32 MHz in CDCl$_3$; peak multiplicity was determined by hereronuclear multipulse programs (DEPT).

†,‡Assignments interchangeable.

shifts and coupling constants of the skeletal signals strongly suggested that all three compounds had the same heliangolide skeleton with a 1,10-epoxide and a 3β-hydroxyl group, and that they differed only in the nature of the side chain attached to C-8. On this basis, the new compound was formulated as shown in structure **1**.

The ^{13}C NMR spectral data (Table 2) corroborated the ^{1}H NMR assignments for compound **1**. Analysis of the spectrum showed four primary, four secondary, seven tertiary and five quaternary carbons, accounting for 20 carbon atoms in the molecule. A triplet at δ43.3 (C-2′), a doublet at 25.4 (C-3′) and two quartets at 20.0 (C-4′) and 19.8 (C-5′) definitively confirmed the isovalerate side chain in compound **1**.

8β-Methacryloyloxyternifolin (**4**), $C_{19}H_{26}O_7$, was a gum showing in the ^{1}H NMR spectrum two one-proton doublets at δ6.26 (H-13a) and 5.69 (H-13b) and a multiplet at 2.64 (H-7) which are characteristic of an α-methylene-γ-lactone moiety. An IR band at 1760 cm^{-1} further corroborated a γ-lactone group. Other IR bands indicated the presence of hydroxyl group(s) (3600 and 3470 cm^{-1}), an unsaturated ester (1720 cm^{-1}), a ketone group (1710 cm^{-1}) and a double bond (1630 cm^{-1}). A pair of one-proton broadened vinylic signals at δ 6.02 (H-3a′) and 5.56 (H-3b′) and a three-proton methyl signal at 1.87 (H-4′), together with strong mass spectral peaks at m/z 69 (**B**^{1}) and 41 (**B**^{2}), clearly indicated the presence of a methacrylate side chain in compound **4**. Detailed spin decoupling experiments in CDCl$_3$ and benzene-d_6 allowed the assignments of the basic ^{1}H NMR signals of compound **4**, as summarized in Table 1.

Based on the above considerations and on the fact that *Calea*-derived sesquiterpene lactones have a C-1 carbonyl and a hydroxyl group at C-10, the new compound could be formulated as a 12,6α-lactonized germacrolide with a carbonyl at C-1, hydroxyl groups at C-3 and C-10 and a methacrylate side chain at C-8 [5]. This was corroborated by comparison of the ^{1}H NMR spectrum of compound **4** with those of ternifolins, which we had previously isolated from *C. ternifolia* var. *calyculata* [5–7]. The new compound showed differences only in the signals arising from the side chain and the absence of a side chain at C-9 in **4**. The great similarity of the chemical shifts and coupling constants of the medium ring proton signals in **4** with those of the known 8β-angeloyloxyternifolin (**5**) [7] was a strong indication that compounds **4** and **5** have the same stereostructure of the medium ring portion. Since the molecular structure of **5** had been established by X-ray analysis [7], we propose structure **4** for 8β-methacryloyloxyternifolin.

EXPERIMENTAL

Calea megacephala Robinson and Greenman was collected in July 1978, in Chiapas, Mexico, 18.2 miles south of the junction of highway 190 and road La Arriaga (L. Urbatsch and J. Pruski, No. 3338, voucher deposited at L.S.U., U.S.A.). The air-dried leaves and stems (350 g) were extracted and worked up by the procedure described earlier [8], providing 1.0 g of the crude terpenoid extract. The crude extract (0.7 g) was fractionated by CC on silica gel with $CHCl_3$–Me_2CO mixtures of increasing polarity, 30 fractions of 100 ml each being collected.

Prep. TLC of fractions 6–8 (78 mg) with $CHCl_3$–Me_2CO (9:1) yielded 42 mg desacylisovalerylheliangine (**1**). Fraction 13 afforded 10 mg 8β-methacryloyloxyternifolin (**4**) after repetitive prep. TLC on silica gel with $CHCl_3$–Me_2CO (9:1).

Desacylisovalerylheliangine (**1**). $C_{20}H_{28}O_6$, gum; UV λ_{max}^{MeOH} nm: strong end absorption; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 3440 (OH), 1750 (γ-lactone), 1730 (saturated ester), 1655 (double bond); EIMS (probe) *m/z* (rel. int.): 262 $[M-\mathbf{A}]^+$ (2.0), 247 $[M-\mathbf{A}-Me]^+$ (1.1), 245 $[M-\mathbf{A}-OH]^+$ (1.4), 244 $[M-\mathbf{A}-H_2O]^+$ (4.2), 219 $[M-\mathbf{A}-Me-CO]^+$ (11.4), 216 $[M-\mathbf{A}-H_2O-CO]^+$ (3.0), 201 $[M-\mathbf{A}-H_2O-Me-CO]^+$ (8.6), 85 $[\mathbf{A}^1]^+$ (100.0), 57 $[\mathbf{A}^2]^+$ (84.5), 43 $[\mathbf{A}^3]^+$ (32.9).

8β-Methacryloyloxyternifolin (**4**). $C_{19}H_{26}O_7$, gum; UV λ_{max}^{MeOH} nm: strong end absorption; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3470 (OH), 1760 (γ-lactone), 1720 (α,β-unsaturated ester), 1710 (ketone), 1630 (double bond); EIMS (probe) *m/z* (rel. int.): 280 $[M-\mathbf{B}]^+$ (0.7), 263 $[M-\mathbf{B}-OH]^+$ (1.1), 262 $[M-\mathbf{B}-H_2O]^+$ (1.7), 247 $[M-\mathbf{B}-H_2O-Me]^+$ (0.8), 245 $[M-\mathbf{B}-H_2O-OH]^+$ (0.8), 244 $[M-\mathbf{B}-2H_2O]^+$ (1.1), 234 $[M-\mathbf{B}-H_2O-CO]^+$ (5.1), 201 $[M-\mathbf{B}-2H_2O-Me-CO]^+$ (2.6), 69 $[\mathbf{B}^1]^+$ (100.0), 41 $[\mathbf{B}^2]^+$ (19.1).

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