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11,13-OXYGENATED-SESQUITERPENE LACTONES FROM *BARTLETTINA KARWINSKIANA*

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Key Word Index—*Bartlettina karwinskiana*; Compositae; Eupatorieae; sesquiterpene lactones; germacrolides; eudesmanolide.

Abstract—Four new sesquiterpene lactones, 11β,13-dihydroxyepitulipinolide, 11β,13-epoxyepitulipinolide, 3β-acetoxy-11β,13-epoxyepitulipinolide and 11β,13-epoxy-8β-acetoxy-α-cyclocostunolide as well as the known lactone epitulipinolide, were isolated from the aerial parts of *Bartlettina karwinskiana*.

INTRODUCTION

Unlike the closely related genus *Eupatorium*, which has been extensively studied, few of the species of the tropical North and South American genus *Bartlettina* have been examined chemically [1]. In the course of our chemotaxonomic studies, we have found that *Bartlettina karwinskiana* contains 6,7-lactonized germacranolides and a eudesmanolide; most of them are 11,13-oxygenated lactones.

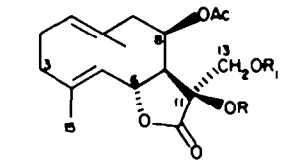
RESULTS AND DISCUSSION

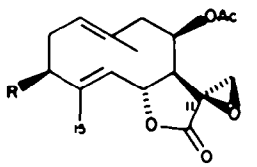
The dichloromethane extract of the aerial parts of *B. karwinskiana* yielded sesquiterpene lactones **1**–**4** and **6**. Epitulipinolide (**6**) was easily identified by comparing its ^{1}H NMR spectrum with published data [2]. The IR spectrum of **1** indicated the presence of a γ-lactone and an acetate group (bands at 1780, 1730 and 1230 cm^{-1}) while the ^{1}H NMR data (Table 1) confirmed the presence of the acetate moiety. In the ^{1}H NMR spectrum, two vinylic methyl signals at δ1.51 (*br s*) and 1.71 (*br s*) and two vinylic proton signals at δ4.87 (*br dd*, J = 3, 10 Hz) and 4.74 (*br d*, J = 10 Hz) suggested a germacrene skeleton similar to that of epitulipinolide (**6**). Since the 11,13-exocyclic methylene signals were replaced by an AB quartet centred at δ3.61 with coupling constants of 12 Hz, an 11,13-diol system was favoured. Spin decoupling experiments confirmed the assignment of all signals except for two which were overlapped. The C-8β-acetoxy orientation was deduced from the H-8 signal at δ5.54 (*br d*) with a coupling constant of 6 Hz. IR (3450 cm^{-1}) and MS (M^+ = 324 for $C_{17}H_{24}O_6$) spectra were in accord with the diol lactone and the well separated ^{13}C NMR signals in both its broad band noise decoupled and single frequency off-resonance decoupled spectra confirmed the structure of **1** as 11,13-dihydroxyepitulipinolide. The 11β-hydroxy configuration assignment was based on the following arguments. When **1** was acetylated to give **5**, the H-7 signal shifted from δ2.57 to 3.13 in the ^{1}H NMR spectra. The significant downfield shift (Δδ0.56) required that H-7 be *cis* to the 13-hydroxyl group, because a *trans* 13-hydroxy-compound produces a much smaller H-7 shift (Δδ0.23 or less) [3, 4].

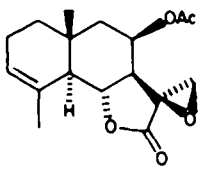
The ^{1}H NMR spectrum of **2** differed from that of **1** only in the AB quartet. The shielding effect (upfield shift from δ3.60 in **1** to 3.01 in **2**) and the change of the coupling constants (12 Hz in **1** and 5 Hz in **2**) indicated an 11,13-epoxy moiety in **2** rather than the diol system in **1**. A

	R	R_1
1	H	H
5	H	Ac

	R
2	H
3	OAc







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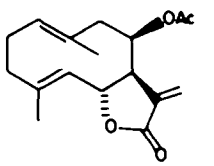

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Table 1. ^{1}H NMR data of compounds **1** (360 MHz) and **5** (200 MHz) ($CDCl_3$, TMS)*

H	1	5
1	4.87 *br dd* (3, 10)	4.87
2	2.29–2.44 *m*	—
5	4.74 *br d* (10)	4.87
6	5.35 *t* (10)	5.37
7	2.57 *d* (10)	3.13
8	5.54 *br d* (6)	5.57
9a	2.18 *br d* (14)	—
9b	2.84 *br dd* (6, 14)	2.80
13a	3.65 *d* (12)	3.71 *s*
13b	3.56 *d* (12)	3.71 *s*
14†	1.51 *br s*	1.53
15†	1.71 *br s*	1.72 *d* (1.2)
OAc†	2.13 *s*	2.14
OAc†	—	2.15 *s*

*Multiplicities and coupling constants (in parentheses) are not repeated if identical with the preceding column.

†Intensity is for 3 protons.

Table 2. ^{1}H NMR data of compounds **2**, **3** and **4** ($CDCl_3$, TMS)*

H	2 (500 MHz)	3 (360 MHz)	4 (360 MHz)
1a	4.86 *br d* (10)	4.95	2.1
1b	—	—	1.46
2a	2.35 *m*	2.35	2.46 *m*
2b	2.22 *m*	2.57	2.27 *m*
3	—	5.24 *dd* (6, 10)	5.34 *br s*
5	4.79 *br d* (10)	4.95	2.65 *d* (10)
6	5.31 *t* (10)	5.33	5.32 *t* (10)
7	2.64 *d* (10)	2.64	2.75 *dd* (2, 10)
8	4.92 *br d* (6)	4.95	4.87 *br d* (6)
9a	2.11	2.1	2.1
9b	2.75 *br dd* (6, 14)	2.75	2.75 *br dd* (6, 14)
13a	3.06 *d* (5)	3.07	3.07 *d* (5)
13b	2.93 *d* (5)	2.94	2.88 *d* (5)
14†	1.47 *br s*	1.52	1.14 *s*
15†	1.75 *br s*	1.75	1.89 *br s*
OAc†	2.08 *s*	2.12	1.89 *br s*
OAc†		2.11 *s*	

*Multiplicities and coupling constants (in parentheses) of **3** are substantially the same as those of **2** except for H-3.

†Intensity is for 3 protons.

Table 3. ^{13}C NMR data of compounds **1**–**5** (22.6 MHz, $CDCl_3$, TMS as internal standard)*

C	1	2	3	5	4 (APT)
1	127.5 *d*	127.3	125.7	127.7	24.4 *t* (*p*)
2	25.5 *t*	25.9	32.1	25.6	36.0 *t* (*p*)
3	38.8 *t*	39.2	78.9 *d*	38.8 *t*	124.2 *d* (*n*)
4	141.2 *s*	142.6	140.1	141.5	145.3 *s* (−)
5	131.0 *d*	131.2	128.3	131.4	50.0 *d* (*n*)
6	74.9 *d*	74.7	73.7	74.8	73.2 *d* (*n*)
7	58.1 *d*	49.2	49.2	53.6	65.5 *d* (*n*)
8	70.0 *d*	69.6	69.5	69.4	67.1 *d* (*n*)
9	43.7 *t*	43.4	43.6	42.1	42.1 *t* (*p*)
10	132.3 *s*	133.4	135.3	132.2	59.6 *s* (*p*)
11	77.3 *s*	57.3	57.1	82.0	57.1 *s* (*p*)
12	175.4 *s*	172.7	172.3	170.5	172.3 *s* (*p*)
13	44.1 *t*	50.7	50.9	44.8	50.6 *t* (*p*)
14	18.9 *q*	18.9	19.2	19.2	19.9 *q* (*n*)
15	16.6 *q*	17.1	12.5	16.8	17.8 *q* (*n*)
1′	169.7 *s*	169.9	169.6	169.9	169.4 *s* (*p*)
2′	21.1 *q*	21.1	21.1	21.0	21.1 *q* (*n*)
1″			170.2 *s*	169.0	
2″			21.2 *q*	21.2	

*Multiplicities are not repeated if identical with those in preceding column. An attached proton test spectrum was also recorded for **4** and the results are given in parentheses in which *p* = positive signal (with two or no protons attached); *n* = negative signal (with one or three protons attached).

^{1}H NMR 2D Cosy spectrum recorded at 500 MHz confirmed the assignments of these signals. Comparison of the ^{13}C NMR data of **2** with those of **1** indicated differences only for the signals of C-7, C-11 and C-13 as expected for an 11,13-epoxy function. From the biosynthetic point of view, the 11,13-diol (**1**) is no doubt derived from the 11,13-epoxy compound (**2**) and therefore an 11β-epoxy stereochemistry could be assigned for **2**. Thus, the structure of **2** can be formulated as 11β,13-epoxyepitulipinolide.

Comparison of the ^{1}H and ^{13}C NMR spectra of **3** with those of **2** indicated one more acetoxy group (at C-3) in **3** relative to **2**. The stereochemistry at C-3 followed from the coupling constants for H-3 (δ5.27 *dd*, J = 6, 10 Hz) [5–7]. All other spectral data were in accord with the structure of **3** as 3β-acetoxy-11β,13-epoxyepitulipinolide.

The ^{1}H NMR data of **4** (Table 2) indicated that it was a eudesmanolide. A C-3,4 double bond rather than a C-4,5 double bond was confirmed by ^{13}C NMR data (Table 3) showing an sp^2 doublet at δ124.2. Spin decoupling experiments confirmed proton assignments. The H-3 signal was in good agreement with reported data for a C-3,4-unsaturated eudesmanolide [8]. The H-6 signal (δ5.31, *t*, J = 10 Hz) confirmed an axial relationship between H-5, H-6 and H-7. The C-8β-acetoxy orientation also followed from the data for H-8 (δ4.87, *br d*, J = 6 Hz). The ^{13}C NMR single frequency off-resonance decoupled spectrum suggested structure **4**. While chemical shifts of most of the signals were in accord with a eudesmanolide [9], the C-7 signal was shifted to a lower field than expected (δ65.5, *d*). The ^{13}C NMR attached proton test spectrum confirmed the multiplicity assignments. The lack of a secondary hydroxy-bearing proton signal in the ^{1}H NMR spectrum and the lack of acetylation (see Experimental) led to the assignment of C-7 appearing at δ65.5, no doubt due to the co-effect of the 11,13-epoxy and the eudesmanolide ring systems causing deshielding. Like **2**, the 11β,13-epoxy configuration was assigned on the basis of biogenetic considerations.

EXPERIMENTAL

Bartlettina karwinskiana (DC) King and H. Robins. (= *Eupatorium karwinskiana* DC) was collected by Douglas Gage and John Norris on Jan. 1, 198[illegible], on Hwy 175 ap-

proximately 33 miles north of Oaxaca, Oaxaca State, Mexico. The material was identified by Douglas Gage, the Department of Botany, the University of Texas at Austin. A voucher specimen is on deposit in the Herbarium of the University of Texas at Austin.

Isolation of the compounds. Dried leaves of *B. karwinskiana* (560 g) were extracted and worked-up in the usual manner [10] to yield 4 g of residue. The residue was added to a silica gel column. The column was eluted with an hexane–EtOAc solvent system. Further separations and purifications were made over Sephadex LH-20 columns (cyclohexane–CH_2Cl_2–MeOH, 7:4:1) and prep. TLC (hexane–EtOAc, 1:1) to give compounds **1**–**4** and **6**.

11β,13-Dihydroxyepitulipinolide (**1**). 85 mg. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 3080, 1670 (C=C), 1780 (γ-lactone), 1730 (OAc), 1230, 1130, 1050, 950; EIMS (probe) 70 eV, *m/z* (rel. int.): 324 $[M]^+$ (1), 282 $[M-43+H]^+$ (7), 246 $[M-HOAc-H_2O]^+$ (3), 230 $[M-C_2H_6O_4]^+$ (3), 43 (100).

Acetylation of **1**. Compound **1** (24 mg) was acetylated with Ac_2O–C_5H_5N in the usual manner. The work-up yielded 22 mg of pure **5**.

11β,13-Epoxyepitulipinolide (**2**). 390 mg. IR ν_{max}^{KBr} cm^{-1}: 3080, 1670 (C=C), 1790 (γ-lactone), 1740 (OAc), 1380, 1320, 1280, 1240, 1130, 1050, 960, 940, 880, 780, 750, 700; EIMS (probe) 70 eV, *m/z* (rel. int.): 247 $[M-OAc]^+$ (4), 246 $[M-HOAc]^+$ (29), 231 $[M-60-Me]^+$ (8), 43 (100).

3β-Acetoxy-11β,13-epoxyepitulipinolide (**3**). 39 mg. EIMS (probe) 70 eV, *m/z* (rel. int.): 364 $[M]^+$ (0.3), 305 $[M-59]^+$ (1), 262 $[M-59-43]^+$ (9), 246 $[M-2\times59]^+$ (13), 244 $[M-2\times HOAc]^+$ (9), 229 $[240-Me]^+$ (5), 43 (100).

11β,13-Epoxy-8β-acetoxy-α-cyclocostunolide (**4**). 60 mg. IR ν_{max}^{KBr} cm^{-1}: 1770 (γ-lactone), 1730, 1230 (OAc), 3020, 1660, (C=C), 1140, 1050, 960, 930, 880, 750; EIMS (probe) 70 eV, *m/z* (rel. int.): 306 $[M]^+$ (0.5), 247 $[M-OAc]^+$ (2), 246 $[M-HOAc]^+$ (3), 43 (100).

Epitulipinolide (**6**). 250 mg. ^1H NMR data were identical to those previously reported [2].

Attempted acetylation of compound **4**. Compound **4** (15 mg) was unchanged when treated with Ac_2O–C_5H_5N even after 10 hr with warming.

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