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REVISION OF THE STRUCTURE OF AN EUDESMANOLIDE ISOLATED FROM *LASIOLAENA SANTOSII*

M. LUZ CARDONA, ISABEL FERNÁNDEZ, BEGOÑA GARCÍA, and JOSÉ R. PEDRO*

Department of Organic Chemistry, Faculty of Chemistry, University of Valencia, 46100-Burjassot, Valencia, Spain

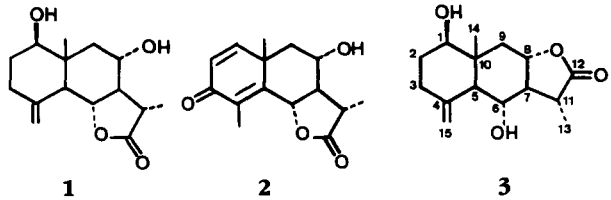
ABSTRACT.—Deacetyl-11β,13-dihydro-β-cyclopyrethrosin [**3**] was synthesized from pyrethrosin [**4**]. The ^{1}H-nmr spectrum of the synthesized product revealed that structure **1**, assigned to an eudesmanolide isolated from *Lasiolaena santosii*, should be revised to **3**.

A few years ago, Bohlmann *et al.* isolated various sesquiterpene lactones from *Lasiolaena santosii* (1) and *Mikania goyazensis* (2); one of these lactones was assigned the structure 8α-hydroxy-11β,13-dihydroreynosin [**1**] on the basis of ^{1}H-nmr spectral data. Later, our group (3) synthesized compound **1** from artemisin [**2**] and found the ^{1}H-nmr spectrum reported for the natural product not to coincide with that obtained for its synthetic counterpart. In particular, the signals of protons H-6 and H-8 were reversed: at δ 4.05 and 3.96 for the synthetic product (3) and δ 3.99 and 4.01 for the natural product (1) in $CDCl_3$, and at δ 3.38 and 3.13 for the former and δ 3.36 and 3.43 for the latter in C_6D_6.

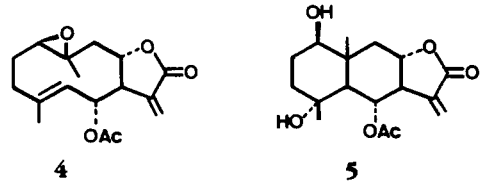
In view of the ^{1}H-nmr data provided by the two products (natural and synthetic), we believe the correct structure of the natural product isolated from *L. santosii* and *M. goyazensis* to be deacetyl-11β,13-dihydro-β-cyclopyrethrosin [**3**]. The aim of this work was to confirm the new structure assigned to this natural product by synthesizing it from pyrethrosin [**4**].

The first step of the synthesis involved an acid treatment (4–6) of pyrethrosin [**4**], which converted the germacrane skeleton to its eudesmane counterpart. Compounds **5**, **6**, and **7** were obtained in variable proportions depending on the reaction conditions used; thus, diol **5** was obtained virtually quantitatively when the reaction was carried out using $BF_3 \cdot OEt_2$ in $CHCl_3$. The 4β position of the hydroxy group was established by the observed nOe between H-14, H-15, and H-6. Compound **5** was recently isolated from *Cassinia subtropica* (7), and the properties of the natural and synthetic products are identical.

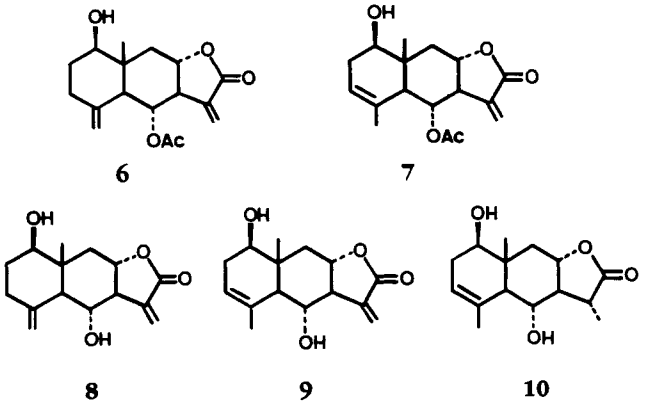
The tertiary hydroxyl group in diol **5** was readily dehydrated with *p*-toluenesulfonic acid adsorbed on Si gel (8) in toluene, where it yielded a mixture of double bond isomers with simultaneous hydrolysis of the C-6 acetate to give compounds **8** (51%) and **9** (12%), in ad-



1 **2** **3**



4 **5**



dition to 7% of a 1:1 mixture of **6** and **7**. Compound **6**, named β-cyclopyrethrosin, has been isolated from *Chrysanthemun cinerariaefolium* (9). The ^{1}H-nmr spectral data for this compound are included in Table 1 as no high-field spectrum has so far been reported. Compound **8** was isolated from *Mikania pohlii* (2) and *Brocchia cinerea* (10), and the properties of the natural and synthetic product are perfectly coincident.

In view of these findings, we treated pyrethrosin [**4**] directly with *p*-toluenesulfonic acid adsorbed on Si gel in toluene, which gave rise to simultaneous cyclization of the germacrane skeleton, dehydration of the resulting hydroxyl at C-4, and hydrolysis of the acetate at C-6 to give product **8** in a yield of 43%.

Finally, the α-methylenelactone function of products **8** and **9** was reduced with $NaBH_4$/MeOH (11), yielding products **3** and **10**, respectively. The ^{1}H-nmr spectral data of compound **3** in $CDCl_3$ and C_6D_6 are fully coincident with those of eudesmanolide **1**, isolated from *L. santosii* (1) and *M. goyazensis* (2), so the structure of this natural product should be revised to **3**.

The products synthesized throughout

TABLE 1. ^{1}H-nmr Chemical Shifts of Eudesmanolides **6–10** (200.1 MHz, $CDCl_3$, δ values).

Proton	Compound				
	6	**7**	**8**[a]	**9**	**10**
H-1 . . .	3.56 dd (4.9,11.2)	3.70 dd (9.5,9.8)	3.48 dd (4.8,11.0)	3.70 br t (7.6)	3.69 br t (7.6)
H-2 . . .		2.3–2.5 m	1.78 dddd (2.4,4.8,5.2,15.4)	2.4–2.6 m	
H-2′ . . .		1.8–2.0 m	1.4–1.6 m	1.9–2.1 m	
H-3 . . .	1.8–2.1 m	5.35 br s	1.8–2.1 m	5.38 br s	5.35 br d (2.2)
H-3′ . . .	2.30 ddd (1.8,5.4,12.9)	—	2.23 ddd (2.0,5.2,12.1)	—	—
H-5 . . .	2.14 d (10.4)	2.10 d (10.3)	1.90 br d (9.8)	2.06 br d (11.5)	2.01 br d (10.5)
H-6 . . .	5.49 t (10.4)	5.44 t (10.3)	4.04 br t (9.8)	4.04 t (11.5)	3.91 br t (10.5)
H-7 . . .	2.72 ddt (3.0,10.4,11.8)	2.68 ddt (3.0,10.3,11.8)	2.40 ddt (3.0,10.0,11.5)	2.4–2.6 m	
H-8 . . .	4.04 dt (3.8,11.8)	4.12 dt (3.8,11.8)	3.92 td (3.6,11.5)	4.05 dt (3.8,11.8)	4.06 td (3.8,11.6)
H-9 . . .	2.56 dd (3.8,11.8)	2.53 dd (3.8,11.8)	2.42 dd (3.6, 11.7)	2.43 dd (3.8,11.8)	2.46 dd (3.8,11.6)
H-9′ . . .		1.43 t (11.8)	1.43 t (11.8)	1.43 t (11.8)	
H-11 . . .	—	—	—	—	2.52 dq (6.8,12.2)
H-13 . . .	6.11 d (3.0)	6.01 d (3.0)	5.94 dd (1.0,3.0)	6.15 d (3.0)	1.38 d (6.8)
H-13′ . .	5.41 d (3.0)	5.41 d (3.0)	5.88 dd (1.0,3.0)	5.93 d (3.0)	
H-14 . . .	0.83 s	0.90 s	0.75 s	0.87 s	0.87 s
H-15 . . .	4.86 br s	1.64 br s	4.91 d (1.1)	1.92 s	1.89 br s
H-15′ . .	4.58 br s		4.73 d (1.1)		
OAc . . .	2.04 s	2.10 s			

[a]In $CDCl_3$/$(CD_3)_2CO$.

this work were characterized by ^{13}C-nmr spectroscopy. The results (Table 2) were interpreted on the basis of distortionless enhancement by polarization transfer (DEPT) experiments. However, some resonances could not be assigned unequivocally. This was not the case with compound **8**, whose resonances were assigned unequivocally by heteronuclear ^{1}H-^{13}C correlation. We should also note that the ^{13}C-nmr data for product **3** were obtained both in $CDCl_3$ and in $CDCl_3$/$(CD_3)_2CO$ because C-5 and C-7 gave a single signal at δ 57.0 in the former solvent and two at δ 57.0 and 55.9 in the latter.

EUDESM-11-EN-8,12-OLIDE [**5**].—To a solution containing 200 mg (0.653 mmol) of pyrethrosin [**4**] in 8 ml of anhydrous $CHCl_3$ was added 660 μl of 43% $BF_3 \cdot OEt_2$. The reaction mixture was stirred at room temperature for 15 min, after which it was diluted with EtOAc, washed with aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation to dryness and filtration through Si gel [CH_2Cl_2-MeOH (100:5)] there was obtained 199 mg (94%) of compound **5**, with the following features: mp 193–196° (hexane/EtOAc) [lit. (6) 190–195°]; ms *m/z* (rel. int.) $[M-H_2O]^+$ 306 (0.3), $[M-HOAc]^+$ 264 (0.3), $[M-H_2O-HOAc]^+$ 246 (7.8); ^{13}C nmr see Table 2.

CONVERSION OF PYRETHROSIN [**4**] TO 6α-ACETOXY-1β,4α-DIHYDROXY-5,7αH,8βH-EUDESM-11-EN-8,12-OLIDE [**5**], β-CYCLOPYRETHROSIN [**6**], AND α-CYCLOPYRETHROSIN [**7**].—A solution containing 100 mg (0.326 mmol) of pyrethrosin [**4**] in 4 ml of anhydrous C_6H_6 was treated with 88 μl of 43% $BF_3 \cdot OEt_2$ at room temperature for 15 min. Usual workup followed by cc over Si gel yielded 14 mg (14%) of a 2:1 mixture of compounds **6** and **7** [eluent CH_2Cl_2-MeOH (100:2)] and 83 mg (78%) of compound **5** [eluent CH_2Cl_2-MeOH (100:6)]. Compound **6** had the following features: mp 167–168° (hexane/EtOAc) [lit. (9) 166–167°]; ms *m/z* (rel. int.) $[M]^+$ 306 (1.1), $[M-HOAc]^+$ 264 (0.9), $[M-H_2O-HOAc]^+$ 246 (3.4); ^{1}H nmr see

TABLE 2. ^{13}C-nmr Data of Compounds **3–9** (50.3 MHz, $CDCl_3$, δ values).

Carbon	Compound							
	3	**3**[a]	**4**[a]	**5**	**6**	**7**	**8**[a]	**9**[a]
C-1	78.3	77.0	72.2[c]	77.9	78.3	75.47[c]	77.9	74.1[c]
C-2	31.5	30.6	22.6[d]	27.9[c]	31.5	29.7[d]	31.8	32.2[d]
C-3	34.5	33.9	46.6[d]	43.2[c]	34.5	123.2	35.0	121.2
C-4	144.3	143.5	139.4	72.4	142.4	132.4	144.4	133.5
C-5	57.0[b]	57.0[c]	125.6	57.2[d]	54.3[c]	54.4[e]	57.2	55.3[e]
C-6	68.6	67.6	65.7[c]	69.7	68.0	69.9	67.4	68.1
C-7	57.0[b]	55.9[c]	51.4	53.6[d]	53.1[c]	50.9[e]	54.9	53.0[e]
C-8	76.1	75.6	77.4[c]	76.4	76.4	75.45[c]	77.1	76.0[c]
C-9	40.1	39.4	36.5[d]	41.5	40.0	32.9[d]	40.7	38.4[d]
C-10	42.6	41.8	58.1	41.7	42.6	40.6	43.1	39.9
C-11	41.5	40.4	136.3	136.6	136.2	136.2	139.0	138.0
C-12	179.1	178.3	169.4[e]	170.4[e]	170.9[d]	171.0[f]	170.6	169.0
C-13	14.3[c]	13.4[d]	125.5	119.0	119.6	119.6	118.9	117.0
C-14	13.8[c]	12.8[d]	17.2[f]	16.3	13.7	12.6	13.9	11.6
C-15	108.6	107.7	17.6[f]	23.8	108.9	22.4	108.9	22.4
MeCOO	—	—	168.9[e]	169.8[e]	169.8[d]	169.9[f]	—	—
CH_3COO	—	—	20.9	21.5	21.0	21.7	—	—

[a]In $CDCl_3/(CD_3)_2CO$.
[b]Overlapped signals.
[c–f]Chemical shifts denoted by the same letter in each column are interchangeable.

EXPERIMENTAL

The melting points of the products were measured in capillary tubes by using a Büchi apparatus and were used uncorrected. Ir spectra were recorded on a Perkin-Elmer 281 spectrometer, while ^{1}H-nmr and ^{13}C-nmr spectra were run at 200.1 and 50.3 MHz, respectively, on a Brucker AC-200 instrument. Mass spectra were recorded at 70 eV on a Varian MAT-311A spectrometer.

Table 1; ^{13}C-nmr see Table 2. Compound **7** was an oil with ms *m/z* (rel. int.) $[M]^+$ 306 (1.4), $[M-HOAc]^+$ 264 (0.8), $[M-H_2O-HOAc]^+$ 246 (4.7); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

CONVERSION OF COMPOUND **5** TO DEACETYL-β-CYCLOPYRETHROSIN [**8**] AND DEACETYL-α-CYCLOPYRETHROSIN [**9**].—To a suspension of 318 mg of *p*-toluenesulphonic acid on Si gel (7) in 4.5 ml of anhydrous benzene was added 50 mg (0.185 mmol) of compound **5**. The resulting mixture was stirred at room temperature for 8 h. The reaction mixture was filtered through Si gel with mixtures of CH_2Cl_2/MeOH of increasing polarity. Eluting with CH_2Cl_2-MeOH (99:1) yielded a 1:1 mixture of compounds **6** and **7** (4 mg, 7%), while eluting with CH_2Cl_2-MeOH (99:1 to 98:2 and 98:2) yielded compounds **8** (25 mg, 51%) and **9** (6 mg, 12%), respectively. Compound **8** had the following features: mp 280° (dec) (hexane/EtOAc); ms *m/z* (rel. int.) $[M]^+$ 264 (8.2), $[M-H_2O]^+$ 246 (6.5), 228 (6.1), 108 (65.4); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2. Compound **9** featured the following properties: mp 235° (dec) (hexane/EtOAc); ms *m/z* (rel. int.) $[M]^+$ 264 (9.0), 213 (2.1), 189 (2.0), 97 (100); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

CONVERSION OF PYRETHROSIN [**4**] TO DEACETYL-β-CYCLOPYRETHROSIN [**8**].—To a suspension of 520 mg of *p*-toluenesulfonic acid on Si gel (7) in 5 ml of anhydrous toluene was added 100 mg (0.326 mmol) of pyrethrosin [**4**]. The resulting mixture was stirred at room temperature for 21 h, after which it was filtered through Si gel and eluted with Me_2CO. The reaction mixture was chromatographed over Si gel and eluted with hexane/Et_2O mixtures of increasing polarity. Eluting with hexane-Et_2O (3:7) yielded compounds **7** (18 mg, 18%) and **6** (28 mg, 28%), while eluting with hexane-Et_2O (2:8) yielded compounds **9** (8 mg, 9%) and **8** (37 mg, 43%).

REDUCTION OF DEACETYL-β-CYCLOPYRETHROSIN [**8**] TO DEACETYL-11β,13-DIHYDRO-β-CYCLOPYRETHROSIN [**3**].—A solution containing 14 mg (0.052 mmol) of compound **8** in 10 ml of anhydrous MeOH was cooled to 0°, and 78 mg (2 mmol) of $NaBH_4$ was added. The resulting mixture was stirred at 0° for 10 min, after which 10 ml of 20% HOAc was added. Usual workup and cc over Si gel using Et_2O as eluent yielded 11 mg (79%) of compound **3**, a colorless oil with the following features: ms *m/z* (rel. int.) $[M]^+$ 266 (6.4), $[M-H_2O]^+$ 248 (4.2), 230 (5.0); ^{13}C nmr see Table 2.

REDUCTION OF DEACETYL-α-CYCLOPYRETHROSIN [**9**] TO DEACETYL-11β,13-DIHYDRO-α-CYCLOPYRETHROSIN [**10**].—A solution containing 6 mg (0.022 mmol) of compound **9** in 4.5 ml of anhydrous MeOH was cooled to 0°, and 33 mg (0.88 mmol) of $NaBH_4$ was added. The resulting mixture was stirred at 0° for 10 min, after which 9 ml of 20% HOAc was added. Usual workup and preparative tlc using 3 elutions of hexane-Et_2O (7:3) yielded 4.4 mg (74%) of compound **10** and 1.4 mg (22%) of recovered starting product **9**. Compound **10** was a colorless oil with the following features: ms *m/z* (rel. int.) $[M]^+$ 266 (3.0), $[M-H_2O]^+$ 248 (1.2), 230 (3.2); ^{1}H nmr see Table 1.

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