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ARTICLE *in* JOURNAL OF NATURAL PRODUCTS · MAY 1990

Impact Factor: 3.8 · DOI: 10.1021/np50069a024

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Journal of Natural Products
Vol. 53, No. 3, pp. 686-691, May-Jun 1990

14,15-DIHYDROXYGERMACRANOLIDES AND OTHER CONSTITUENTS OF *MIKANIA MINIMA*

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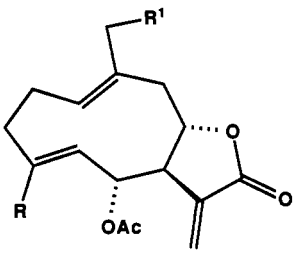
ABSTRACT.—The aerial parts of *Mikania minima* yielded a large amount of 14-acetoxyartemisiifolin-6α-*O*-acetate [**1**], a known lactone, along with two closely related new analogues, 14-hydroxyartemisiifolin-6α-*O*-acetate [**3**] and 11βH-11,13-dihydro-14-hydroxyartemisiifolin-6α-*O*-acetate [**5**]. Several common triterpenes and sterols were also identified. The structures were determined by spectroscopic methods and chemical transformations.

Mikania minima (Bak.) Robinson (Compositae, tribe Eupatorieae) is a rare vine found only in Tucumán province, Argentina. With its small flower heads, hexagonal branches, and typical location of the bractlet, *M. minima* is one of the best marked species of the perplexing *Mikania scandens* complex (1). Sesquiterpene dilactones of the miscandenin and mikanolide group are frequently found in the genus (2–7), although other sesquiterpene lactone types (2,3,6–10), *ent*-kaurene and pimarene diterpenes (3,11,12), and geranylnerol derivatives (2–4) are also relatively common. Recently, bisabolone derivatives were isolated from a newly described *Mikania* species (13). Continuing our work on this genus (5) we report here the chemical composition of *M. minima*.

The main constituent of *M. minima* was a crystalline lactone, mp 110°, identified as 14-acetoxyartemisiifolin-6α-*O*-acetate [**1**]. This lactone has previously been isolated as a gum from two subspecies of *Dicoma anomala* (14). Even though the ^{1}H-nmr spectrum of **1** was reported to give broad signals at room temperature (14), our crystalline sample exhibited quite well-defined signals in $CDCl_3$, which were assigned by spin decoupling and COSY experiments. The signals at higher fields were better resolved in C_6D_6 solution (Table 1). The absence of nOe's between H-1 or H-5 and any of the two proton AB systems of H-14 and H-15 confirmed that the stereochemistry of the 1,10 and 4,5 double bonds was *Z* in both cases. Oxidation of **1** with MnO_2 afforded **4**, the ^{1}H-nmr spectrum of which, in accordance with Herz's rule (15,16), showed the aldehyde proton at 9.98 ppm as a doublet allylically coupled to H-5 at 6.00 ppm (Table 1). The acetate **2** prepared from **1** showed the expected downfield shift for the H-15 protons (Table 1). A



1 R=CH_2OH, R^1=OAc
2 R=CH_2OAc, R^1=OAc
3 R=CH_2OH, R^1=OH
4 R=CHO, R^1=OAc

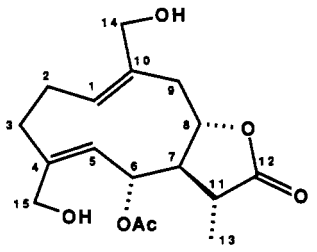


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TABLE 1. ^{1}H-nmr Data of Compounds **1–4**.[a]

Proton	Compound			
	1[b,c] C_6D_6	**2**[c] $CDCl_3$	**3**[c] $CDCl_3$	**4**[d] $CDCl_3$
H-1	4.71 br dd	5.26 br dd	5.34 br dd	5.26 br dd
H-2α	2.14 dddd	2.3–2.45 m	2.1–2.6 m	1.9–3.1 m
H-2β	1.88 m			
H-3α	1.70 ddd	2.15 m		
H-3β	2.37 ddd	2.56 ddd		
H-5	4.43 d	5.04 d	4.87 br d	6.00 dd
H-6	4.86 dd	4.98 dd	5.14 dd	5.61 dd
H-7	2.55 dddd	3.06 dddd	3.07 dddd	3.15 dddd
H-8	4.98 br dd	5.06 br dd	5.10 br dd	5.05 ddd
H-9α	2.04 dd	2.47 dd	2.48 dd	2.66 dd
H-9β	2.72 br d	2.71 br d	2.66 br d	2.39 dd
H-13a	6.37 dd	6.38 dd	6.36 dd	6.42 dd
H-13b	5.53 dd	5.83 dd	5.87 dd	5.88 dd
H-14a	4.55 br d	4.57 br d	4.24 br d	4.35 d
H-14b	4.33 br d	4.40 br d	3.87 br d	4.24 d
H-15a	3.88 d	4.61 d	4.34 d	9.98 d
H-15b	3.78 d	4.55 d	3.98 d	—
Ac_1[e]	1.85 s	2.13 s	2.09 s	2.07 s
Ac_2[e]	1.59 s	2.11 s	—	2.07 s
Ac_3[e]	—	2.08 s	—	—

[a]The spectrum of **4** was recorded at 80 MHz; all other data were obtained at 400 MHz. The numbering is the same in all skeletons.

[b]See Bohlmann *et al.* (14) for $CDCl_3$ data.

[c]Couplings (Hz) **1–3**: $J_{1,2\alpha}=4$, $J_{1,2\beta}=12$, $J_{2\alpha,2\beta}=13$, $J_{2\beta,3\alpha}=10$, $J_{2\beta,3\beta}=5$, $J_{2\alpha,3\alpha}=5$, $J_{2\alpha,3\beta}=2$, $J_{3\alpha,3\beta}=12$, $J_{5,6}=10$, $J_{6,7}=7.5$, $J_{7,13a}=3.5$, $J_{7,13b}=3.1$, $J_{7,8}=7$, $J_{8,9\alpha}=9$, $J_{8,9\beta}\sim 0$, $J_{9\alpha,9\beta}=13$, $J_{13a,13b}=0.8$, $J_{14a,14b}=12.5$, $J_{15a,15b}=13.5$.

[d]Couplings (Hz) **4**: $J_{1,2\alpha}=6.5$, $J_{1,2\beta}=9$, $J_{5,6}=10.5$, $J_{6,7}=7$, $J_{7,8}=7$, $J_{8,9\alpha}=10$, $J_{8,9\beta}=3$, $J_{9\alpha,9\beta}=13$, $J_{7,13a}=3.5$, $J_{7,13b}=3.1$, $J_{13a,13b}=0.7$, $J_{14a,14b}=12.5$.

[e]Intensity 3H.

triacetate reported to have an identical stereoformula (17) was actually a melampolide as noted in a later publication (14).

The previously unreported ^{13}C-nmr data of **1** are listed in Table 2. The proton-bearing carbons were assigned by ^{1}H-^{13}C heteronuclear correlation. The assignment of the signals of the quaternary carbons in the germacradiene ring of **1** was made possible by the regioselective and stereoselective conversion of **1** into the corresponding 4α,5β-epoxide **6** with *m*-chloroperbenzoic acid. NOESY data of **6** (in DMSO-d_6) were consistent with the 4α,5β stereochemistry of the epoxide ring and a conformation with H-6, H-8, H-14, and H-15 above and H-1, H-5, and H-7 below the plane of the ten-membered ring. The dihedral angles measured on a Dreiding model of **6** in this conformation are in excellent agreement with the coupling constants observed (Table 2). The value of $J_{5,6}$ of the epoxide ring (9.5 Hz) of **6** is consistent with literature data for the coupling H-5α–H-6β (9–10 Hz) in structurally related 5α,6β epoxides (18,19). Smaller coupling constants ($J_{5\beta,6\beta}=3$–4 Hz) have been observed in 4β,5α isomers (19,20). The structure of **6** indicates that, under conditions employed for the selective epoxidation of **1**, lactone **1** exists in the $_1D^{14}$, $^{15}D_5$ conformation (21).

Rearrangement of **1** in boiling toluene cleanly produced a 3:7 equilibrium mixture of **1** with the Cope product **7** which is an attractive starting material for the partial syn-

TABLE 2. ^{1}H nmr Data of Compounds **5**–**7**.[a]

Proton	Compound				
	5 $CDCl_3$	**5**[b] C_5D_5N	**6**[c] DMSO-d_6	**6**[d] C_5D_5N	**7**[e,f] $CDCl_3$
H-1	5.12 br dd	5.12 br dd	5.80 br dd	5.83	5.70 dd
H-2α	2.30 m	2.14 m	2.18 br dd	2.25	5.07 d
H-2β	2.54 m	2.61 dddd	2.54 dddd	2.81	5.16 d
H-3α	~2.6	2.72 m	1.03 ddd	1.29	5.02 br s
H-3β	2.09 m	~2.0	2.38 br dd	2.74	5.48 br s
H-5	4.83 d	4.92 d	3.02 d	3.16	2.67 d
H-6	5.03 dd	5.41 dd	4.35 dd	5.08	4.43 dd
H-7	2.21 dddd	2.40 dddd	3.59 dddd	3.67	2.85 dddd
H-8	5.32 ddd	5.86 ddd	4.52 ddd	5.01	5.25 ddd
H-9α	2.47 dd	2.49 dd	2.55 dd	2.70	1.61 dd
H-9β	2.58 br d	3.11 dd	2.45 br d	2.81	2.35 dd
H-11	2.75 dq	2.75 dq	—	—	—
H-13a	1.43[g] d	1.50[g] d	6.19 d	6.48	6.16 d
H-13b			5.77 d	5.81	5.59 d
H-14a	4.29 d	4.42 d	4.78 d	5.06	4.32 d
H-14b	3.91 d	4.39 d	4.54 d	4.91	4.12 d
H-15a	4.34 d	4.36 d	3.56 dd	4.14	4.10 d
H-15b	3.98 d	4.35 d	3.21 br dd	3.90	4.02 d
Ac_1[h]	2.13 s	2.03 s	2.01 s	1.98	2.12 s
Ac_2[h]	—	—	1.99 s	1.92	2.11 s

[a]All data were obtained at 400 MHz. The numbering is the same in all skeletons.

[b]Couplings (Hz) **5** in C_5D_5N: $J_{1,2\alpha}=4.7$, $J_{1,2\beta}=12.5$, $J_{5,6}=10$, $J_{6,7}=9.5$, $J_{7,8}=8.5$, $J_{7,11}=11.5$, $J_{8,9\alpha}=10$, $J_{8,9\beta}=1.5$, $J_{9\alpha,9\beta}=12$, $J_{11,13}=7$, $J_{14a,14b}=12.5$, $J_{15a,15b}=14$.

[c]Couplings (Hz) **6** in DMSO-d_6: $J_{1,2\alpha}=3.6$, $J_{1,2\beta}=12.4$, $J_{2\alpha,2\beta}=12$, $J_{2\beta,3\alpha}=12.5$, $J_{2\beta,3\beta}=4.6$, $J_{2\alpha,3\alpha}=6.5$, $J_{2\alpha,3\beta}=0.7$, $J_{3\alpha,3\beta}=12.5$, $J_{5,6}=9.5$, $J_{6,7}=6.7$, $J_{7,8}=4.3$, $J_{7,13a}=3.4$, $J_{7,13b}=3$, $J_{8,9\alpha}=11.5$, $J_{8,9\beta}=1.5$, $J_{9\alpha,9\beta}=12.3$, $J_{14a,14b}=12.1$, $J_{15a,15b}=12.5$, $J_{15a,OH}=5.4$, $J_{15b,OH}=3.5$; OH δ 5.05 dd.

[d]Multiplicities of all signals are the same as in $CDCl_3$.

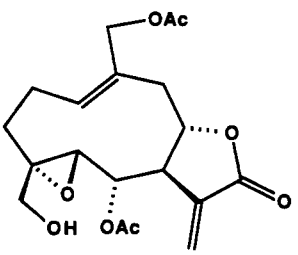
[e]Read 2a, 2b, 3a, 3b instead of 2α, 2β, 3α, 3β.

[f]Couplings (Hz) **7**: $J_{1,2\ cis}=11$, $J_{1,2\ trans}=17.7$, $J_{5,6}=12$, $J_{6,7}=12$, $J_{7,8}=11$, $J_{7,13a}=3$, $J_{7,13b}=3$, $J_{8,9\alpha}=11$, $J_{8,9\beta}=4.3$, $J_{9\alpha,9\beta}=13.5$, $J_{14a,14b}=12$, $J_{15a,15b}=14$.

[g]Intensity 2H.

[h]Intensity 3H.

thesis of the bioactive elemanolides vernomenin and vernolepin (22,23). Dihedral angles measured in a Dreiding model of **7** agree with all observed splitting constants, as does comparison with ^{1}H-nmr data of similar elemanolides in the literature (23–26). If the Cope product had the opposite stereochemistry at C-5 and C-10, H-5 and H-6



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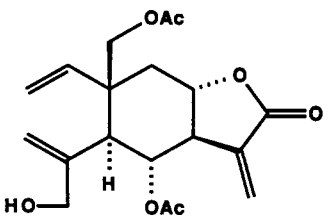

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would be cis and the expected maximum value for $J_{5,6}$ would be 7.5 Hz. The observed value is 12 Hz (Table 2).

Two minor lactones of *M. minima* were the new analogues **3** and **5** whose structures were deduced by ms, extensive ^{1}H-nmr studies to verify coupling constants, ^{13}C nmr, and comparison with the spectral data of **1** (Tables 1–3). Compound **3** was obtained only as a 1:2 mixture with **5**. The chemical shifts and coupling constants showed that both **3** and **5** possessed identical stereochemistry around the 1(10) and 4,5 double bonds and a lactone ring trans fused as in **1**. The C-13 methyl group of **5** had to be α-oriented because of the value of $J_{7,11}$ (11.5 Hz).

Other substances identified in the extract were lupeol, α- and β-amyrin, stigmasterol, sitosterol, and isofucosterol.

TABLE 3. ^{13}C-nmr Data of Compounds **1–7**.[a]

Carbon	Compound						
	1[b] $CDCl_3$	**2** $CDCl_3$	**3**[c] MeOH-d_4	**4** $CDCl_3$	**5** MeOH-d_4	**6** DMSO-d_6	**7** $CDCl_3$
C-1	135.99 d	134.90 d	134.29 d	135.98 d	134.96 d	133.96 d	141.64 d
C-2	26.07 t	25.99 t	26.63 t	25.62 t	26.85 t	26.25 t	114.86 t[e]
C-3	34.23 t	34.53 t	35.01 t	29.93 t	35.24 t	33.08 t	115.77 t[e]
C-4	143.92 s	138.99 s	145.21 s	142.20 s	144.13 s	63.18 s	142.94 s
C-5	129.00 d	130.07 d	130.26 d	145.93 d	130.68 d	64.41 d	50.61 d[f]
C-6	77.02 d	77.05 d	79.23 d	74.63 d	78.08 d	78.83 d	78.36 d
C-7	52.82 d	52.81 d	53.86 d	51.89 d	59.06 d	47.65 d	51.68 d[f]
C-8	72.61 d	72.56 d	74.64 d	72.01 d	74.84 d	72.78 d	69.11 d
C-9	44.97 t	45.24 t	45.58 t	[d]	46.66 t	44.77 t	40.71 t
C-10	129.98 s	131.38 s	137.38 s	131.06 s	136.05 s	128.25 s	44.33 s
C-11	135.26 s	135.94 s	135.37 s	133.65 s	41.42 d	134.09 s	136.53 s
C-12	169.80 s	169.52 s	171.93 s	168.61 s	180.89 s	170.05 s	169.15 s[g]
C-13	125.41 t	125.57 t	125.11 t	125.98 t	17.22 q	124.80 t	120.23 t
C-14	62.04 t	62.19 t	60.25 t[e]	61.89 t	60.08 t[e]	60.16 t[e]	67.23 t[h]
C-15	61.14 t	61.90 t	61.02 t[e]	188.45 d	61.03 t[e]	60.04 t[e]	66.32 t[h]
C-1′	171.06 s	170.86 s	172.05 s	170.22 s	171.72 s	170.24 s	170.03 s[g]
C-2′	21.10 q	21.07 q	21.17 q	20.76 q	21.10 q	20.85 q	20.95 q
C-1″	169.60 s	170.54 s	—	169.44 s	—	168.97 s	170.42 s[g]
C-2″	20.95 q	20.29 q	—	20.65 q	—	20.58 q	21.00 q
C-1‴	—	169.44 s	—	—	—	—	—
C-2‴	—	20.85 q	—	—	—	—	—

[a]The spectrum of **4** was recorded at 20 MHz. All other ^{13}C data were obtained at 100.61 MHz. Multiplicities were determined by DEPT experiments. Carbons 1′–2‴ are acetate carbons. The numbering is the same in all skeletons.

[b]Results of a ^{1}H-^{13}C heteronuclear correlation facilitated the assignment.

[c]From a mixture with **5**.

[d]Signal not observed.

[e–h]Assignments with the same superscript in a column are interchangeable.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—For separation of mixtures we used a Konik-500-A liquid chromatograph with RI detector, a Rheodyne injector (2-ml loop), and, unless stated otherwise, an Alltech RSil C18 column (10 mm i.d. × 50 cm, 10μ).

PLANT MATERIAL.—Aerial parts of *M. minima* were collected in Rio Vipos, Tucuman Province, Argentina, in May 1988. A voucher specimen (CANC #38) has been deposited at the Instituto Miguel Lillo, S.M. de Tucumán.

EXTRACTION OF *M. MINIMA*.—Flower heads and leaves (84 g) were extracted with $CHCl_3$ (2 × 600 ml) at room temperature for 7 days to give 11.1 g of crude extract, which was suspended in EtOH (100 ml) at 50–55°, diluted with H_2O (75 ml), and extracted successively with hexane (3 × 100 ml) and $CHCl_3$ (3 × 100 ml). Evaporation of the hexane extract gave 5.2 g of residue, which was chromatographed over Si gel using hexane and increasing amounts of Et_2O (0–33%), yielding crude triterpenes (234 mg) and crude sterols (81 mg). The triterpene sample was saponified with dilute KOH, and the neutral unsaponifiables were chromatographed over Si gel with hexane-Et_2O (4:1) and gave purified triterpenes (96 mg). Reversed-

phase hplc of part (32 mg) of the purified triterpenes (MeOH, flow rate 3 ml/min) gave crystalline lupeol (3 mg), crystalline β-amyrin (14 mg), and 5.2 mg of α-amyrin contaiminated with an unidentified triterpene. The crude sterol sample, processed in the same way as the crude triterpenes, yielded stigmasterol (14 mg), β-sitosterol (13 mg), and isofucosterol (1.2 mg).

The residue of the $CHCl_3$ extract (4.3 g) was chromatographed over Si gel using C_6H_6 with increasing amounts of EtOAc (20–33%). The separation was monitored by Si gel tlc using C_6H_6-EtOAc mixtures (2:1, 1:1, and 2:3) as developers, and 60 fractions were collected. Fractions 11–33 afforded crystalline **1** [1.48 g, mp 109.5–110.5°, from heptane/EtOAc, R_f 0.50, C_6H_6-EtOAc (1:1)]. Fractions 48–53 were combined (residue 193 mg) and rechromatographed over Si gel C_6H_6-EtOAc (5:3). A 1:2 mixture (50 mg) of **3** and **5** was obtained [unresolved spot on Si gel, R_f 0.28, C_6H_6-EtOAc (2:3)]. Separation by reversed-phase hplc [C8 column (Phenomenex, Palos Verdes, California), 10 mm i.d. × 50 cm, 10μ, MeOH-H_2O (3:2), flow 2 ml/min] gave pure **5**, Rt 5 min, as a gum. Lactone **3** partially decomposed during workup of the column effluent.

IDENTIFICATION OF STEROLS AND TRITERPENES.—All compounds were first tentatively identified on the basis of their relative retention times in gc and hplc. ^1H- and ^{13}C-nmr spectra (run at 400 and 100.61 MHz, respectively) confirmed these assignments. The ^{13}C-nmr spectra showed sitosterol and stigmasterol to be sterically pure (27). This is of interest because it is known, mainly through the work of Akihisa and co-workers (28,29), that 24-alkyl sterols of higher plants are usually mixtures of epimers at C-24.

14-Acetoxyartemisiifolin-6α-O-acetate [**1**].—Mp 109.5–110.5° from heptane-EtOAc (9:1); ir (KBr) ν max cm^{-1} 3445 (OH), 1770 (shoulder) (γ-lactone), 1734 (OAc), 1650, 1233, 1222, 1035, 999; cims (reagent gas CH_4) *m/z* (rel. int.) $[C_{19}H_{24}O_7+H]^+$ 365 (44), 347 (38), 333 (42), 323 (58), 305 (15), 245 (100), 227 (99).

14-Acetoxy-4α,5β-epoxyartemisiifolin-6α-O-acetate [**6**].—To **1** (182 mg) in CH_2Cl_2 (3 ml) and 0.5 M $NaHCO_3$ (1.25 ml) cooled in ice was added with magnetic stirring *m*-chloroperbenzoic acid (135 mg) in small portions. The progress of the reaction was followed by tlc. The reaction was complete in 5 h. The organic layer was diluted with CH_2Cl_2 (15 ml) and extracted with 10% aqueous $Na_2S_2O_3$ (2 × 2 ml), 1 M NaOH (3 × 2 ml), and H_2O (2 × 2 ml). After drying and solvent evaporation the residue **6** was shown to be impure by hplc and tlc. Recrystallization from heptane-EtOAc (1:4) gave pure **6** (98 mg): mp 207–209°; ir (KBr) ν max cm^{-1} 3445, 1745, 1736, 1650, 1382, 1290, 1269, 1244, 1226, 1161, 1042, 1024, 1008, 968, 952, 923; cims (reagent gas CH_4) *m/z* (rel. int.) $[C_{19}H_{24}O_8+H]^+$ 381 (61), 363 (39), 349 (51), 339 (75), 321 (20), 261 (90), 243 (100).

14-Acetoxyartemisiifolin-6α,15-di-O-acetate [**2**].—Ac_2O (0.30 ml) was added to **1** (90 mg) in pyridine (3 ml). After the usual workup the product was purified by cc over Si gel to give **2** (49 mg) as a gum: ir (KBr) ν max cm^{-1} 1766, 1742, 1651, 1374, 1239, 1145, 1023, 961. The ms sample of **2** decomposed prior to analysis.

6α,14-Diacetoxy-15-oxo-(Z)1(10),(Z)4-germacradien-8α,12-olide [**4**].—To **1** (50 mg) in $CHCl_3$ (50 ml) was added active MnO_2 (300 mg) at room temperature and with magnetic stirring. The progress of the reaction was monitored by tlc. It was complete after 2 h. Filtration and solvent evaporation yielded **4** (42 mg) as a gum. This aldehyde was very unstable, and most of it had decomposed after one day at room temperature.

6α,14-Diacetoxy-15-hydroxyeleman-8α,12-olide [**7**].—Compound **1** (30 mg) was refluxed in toluene (6 ml) under N_2. The progress of the reacton was monitored by tlc. Only one product could be detected. The equilibrium was reached in about 5 h. Preparative Si gel tlc [EtOAc-C_6H_6 (4:3), two developments] gave **7** (gum, 18.2 mg) and **1** (8.3 mg). Compound **7**: ir (film) ν max cm^{-1} 3570 (OH), 1770 (γ-lactone), 1740 (OAc), 1674, 1642, 1372, 1245, 1143, 1041, 992, 974, 924, 757.

14-Hydroxyartemisiifolin-6α-O-acetate [**3**].—Compound **3** was obtained as the minor component of a 1:2 mixture with **5**. It partially decomposed during workup after hplc separation from **5**. The ^1H spectrum of this material indicated that one of the components was 13-methoxy-11,13-dihydro-14-hydroxyartemisiifolin-6α-*O*-acetate, probably produced by 1,4-addition of MeOH to the α,β-unsaturated γ-lactone **3** catalyzed by traces of acid present in the $CHCl_3$ used for extraction. Mixture of **3** and **5**: ir (KBr) ν max cm^{-1} 3480, 3430, 1750, 1710, 1652; cims (reagent gas CH_4) *m/z* (rel. int.) $[C_{17}H_{24}O_6+H]^+$ 325 (30), $[C_{17}H_{22}O_6+H]^+$ 323 (11). Compound **5** could be isolated pure (see below) and was properly identified. Subtraction of the corresponding signals in the high field ^{13}C and ^1H spectra permitted assignment of all signals corresponding to **3**.

11βH-11,13-Dihydro-14-hydroxyartemisiifolin-6α-O-acetate [**5**].—Gum, ir (KBr) ν max cm^{-1} 3430, 1760, 1720, 1655, 1414, 1380, 1260, 1220, 1035, 957; cims (reagent gas CH_4) *m/z* (rel. int.) $[C_{17}H_{24}O_6+H]^+$ 325 (36), 307 (77), 283 (21), 265 (19), 205 (61), 187 (100).

ACKNOWLEDGMENTS

We thank the Consejo Nacional de Investigaciones Científicas y Técnicas de la República Argentina and the Consejo de Investigaciones de la Universidad Nacional de Tucumán for financial support.

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Received 29 December 1989