Phytochemistry, Vol. 24, No. 12, pp. 2967–2971, 1985.
Printed in Great Britain.

0031–9422/85 $3.00+0.00

SESQUITERPENE LACTONES AND DITERPENES FROM *MIKANIA PERIPLOCIFOLIA*

ALICIA B. GUTIERREZ*, JUAN C. OBERTI*, PALANIAPPAN KULANTHAIVEL† and WERNER HERZ†

* Instituto Multidisciplinario de Biología Vegetal, CONICET and Facultad de Ciéncias Químicas, Universidad Nacional de Córdoba, 5016 Córdoba, Argentina; † Department of Chemistry, The Florida State University, Tallahassee, FL 32306, U.S.A.

(*Received* 24 *January* 1985)

Key Word Index—*Mikania periplocifolia*; Compositae; Eupatorieae; sesquiterpene lactones; mikanolide analogs; diterpenes; geranylnerol derivatives.

Abstract—The aerial parts of two collections of *Mikania periplocifolia* gave, in addition to mikanolide, miscandenin and several other known sesquiterpene dilactones related to them, the new dilactones 3β-hydroxy-11βH,13-dihydroisabelin, 11βH,13-dihydrodeoxymikanolide and mikaperiplocolide and three new geranylnerol derivatives.

INTRODUCTION

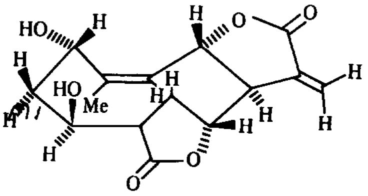
The chemistry of the large genus *Mikania* (Compositae, tribe Eupatorieae) has been reviewed briefly [1]. Sesquiterpene dilactones of the mikanolide and miscandenin group appear to be characteristic constituents of several species although various other sesquiterpene lactone types have been encountered and diterpenes are relatively common. We now report on the constituents of *Mikania periplocifolia* Hook et Arn. which produces a variety of mikanolide type dilactones as well as some new derivatives of geranylnerol.

RESULTS AND DISCUSSION

A collection of *M. periplocifolia* from the province of Córdoba, Argentina, gave a complex mixture of dilactones which were very difficult to separate. Compounds identified were mikanolide (**1**) [2–4] and 3β-hydroxyisabelin (**3**) [5] which were the main lactone constituents, deoxymikanolide (**2a**) [2, 6], scandenolide (**2b**) [2, 3, 6], 3-acetoxy-11βH,13-dihydroisabelin (**4b**) [5], miscandenin (**7**) [2–5], 1,2-epoxymiscandenin (**8**) [5] and mikacynanchifolide (**9**) [5]. New compounds were the dilactone **10a** as well as the geranylnerol derivatives **11a** and **11e** or **11f**. A collection of *M. periplocifolia* from Entre Rios province gave a rather similar mixture in which **1**, **2a**, **2b**, dihydromikanolide (**6**) [2–4] the new dilactones **4a** and **5**, **11a** and its acetate **11b** could be identified.

The structure of 3β-hydroxy-11βH,13-dihydroisabelin (**4a**) was evident from the ^{1}H NMR spectrum (Table 1) which resembled that of **4b** [5] except for the diamagnetic shift of the H-3 resonance. Signal assignments and coupling constants leading to the stereochemistry shown were determined by the usual decoupling procedure. The magnitude of $J_{7,11}$ (13 Hz) shows that the methyl group attached to C-11 is α. Similarly, that **5** was the 11βH,13-dihydro derivative of deoxymikanolide could be deduced from the NMR spectrum (Table 1, $J_{7,11}$ = 13 Hz) and its comparison with that of **2a** [6]‡.

The molecular formula ($C_{15}H_{16}O_6$ by high resolution MS) and the ^{1}H NMR spectra of dilactone **10a**, which we have called mikaperiplocolide, and its diacetate **10b** led to the structures illustrated. Sequential decoupling identified sequences H-1 through H-3 and H-5 through H-9 which had to be linked as shown because of the allylic couplings involving H-3 and H-5 and H-9a and H-14 ($J_{3,5}$ = $J_{9a,14}$ = 1.5 Hz). Small couplings between H-2a, b and H-3 (3.5 and 3 Hz) and a large coupling (9.5 Hz) between H-1 and H-2a ($J_{1,2b}$ was nearly zero) indicated α- and β-orientation of the hydroxyl groups at C-1 and C-3, respectively. The NOE difference spectrum of **10b** (Table 2) confirmed the stereochemistry at these and the other centres and the conformation shown in A below. Particularly significant are the large NOEs involving H-1 and H-8 and the NOE involving H-9 and H-14 which show that the 9,10-double bond is *Z*, like that of tulirinol (**12**) [7].

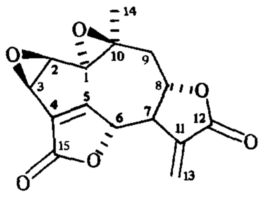


A

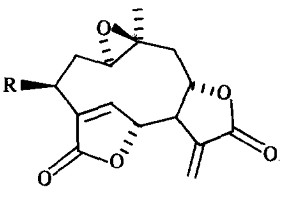
The structure of diacetoxytriol **11a** was established by extensive decoupling on the derived aldehydes **11c** and **11d** (Tables 3 and 4). The *Z*-stereochemistry assigned to the 2,3-double bond is based on the chemical shifts of H-20 (δ9.67 and 9.64) in the ^{1}H NMR spectra of **11c** and **11d**. Similarly the *E*-stereochemistry assigned to the 14,15-double bond is based on the chemical shifts of H-16 (δ9.40) and H-14 (δ6.46) in the ^{1}H NMR spectrum of **11c**. That the single vinyl methyl group of **11a** was C-17 rather

---

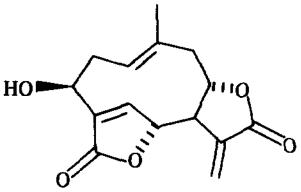
‡In ref. [6] there is a misprint for the H-5 resonance of **2a** which is found at δ7.20; the resonances of H-2a, b and H-3a, b are found in multiplets at δ2.5, 2.3 and 1.61.



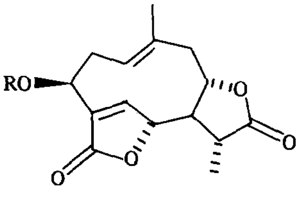
1



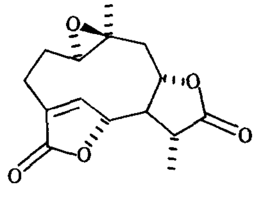
2a R = H
2b R = OH



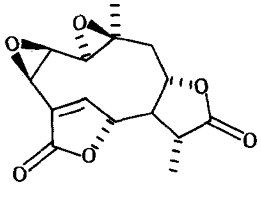
3



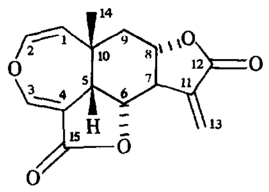
4a R = H
4b R = Ac



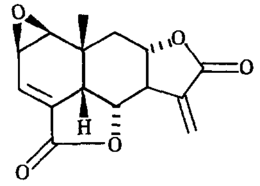
5



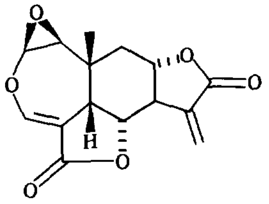
6



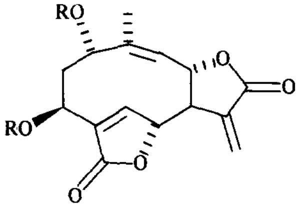
7



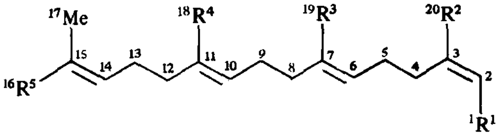
9



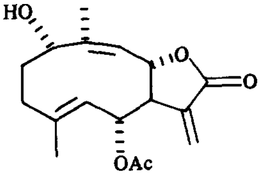
8



10a R = H
10b R = Ac



11a $R^1, R^2, R^5 = CH_2OH$; $R^3, R^4 = CH_2OAc$
11b $R^1, R^5 = CH_2OH$; $R^2, R^3, R^4 = CH_2OAc$
11c $R^1, R^2, R^5 = CHO$; $R^3, R^4 = CH_2OAc$
11d $R^1, R^2 = CHO$; $R^3, R^4 = CH_2OAc$ $R^5 = CH_2OH$
11e $R^1, R^2, R^5 = CH_2OH$; $R^3 = Me$; $R^4 = CH_2OAc$
11f $R^1, R^2, R^5 = CH_2OH$; $R^3 = CH_2OAc$; $R^4 = Me$



12

Table 1. ^{1}H NMR spectra of compounds **4a**, **5** and **10a**, **b** (270 MHz, $CDCl_3$)

H	**4a***	**5***	**10a**	**10b**
1	5.22 *ddq* (13, 3, 1.5)	2.75 *m*	4.70 *br d* (9.5)	5.59 *br d* (9.5)
2a	2.80 *dt* (4, 13)	2.5 *c*–2.1 *c*	2.65‡	2.71 *ddd* (13, 9.5, 3.5)
2b	2.32 *br d* (13)	1.6 *m*	1.95 *dd* (13, 3)	2.05 *dd* (13, 3)
3	4.98 *m*		4.73 *m*	5.76 *dddd* (3.5, 3, 2, 1.5)
5	7.28 *br t* (1.5)	7.45 *br t*	7.39 *t*	7.33 *t*
6	5.11 *m* ($W_{1/2}$ = 5 Hz)	5.09 *br*	5.42 *m*	5.45 *ddd* (2, 1.5, 1.2)
7	2.39 *br dd* (13, 10)	2.48 *br dd*	3.23 *dddd* (10, 3.5, 3, 1.2)	3.29 *dddd*
8	4.46 *ddd* (11, 10, 4)	4.48 *ddd*	5.01 *t* (10)	4.97 *t*
9a	3.03 *br d* (14)	2.22 *dd* (14, 4)	5.13 *br d* (10)	5.26 *dq* (10, 1.5)
9b	1.84 *dd* (14, 11)	2.01 *dd* (14, 11)	—	—
11	2.67 *dq* (7, 13)	2.74 *dq*	—	—
13a	1.43 *d*† (7)	1.42 *d*†	6.35 *d* (3.5)	6.39 *dd* (3.5, 0.7)
13b	—	—	5.70 *d* (3)	5.69 *dd* (3, 0.7)
14†	1.58 *br*	1.22	1.81 *d* (1.5)	1.80 *d*
Ac†	—	—	—	2.22 2.02

*In $CDCl_3$ and three drops of DMSO-d_6.

†Intensity three protons.

‡Partially obscured.

Table 2. NOE difference spectrum of compound **10b**

Irradiated	Observed (%)
H-1	H-8 (26.9)
H-5	H-6 (7.1) H-8 (7.1)
H-6	H-5 (7.6) H-7 (12.4) H-13b (4.8)
H-8	H-1 (2.7) H-5 (8.2)
H-9	H-7 (12.5) H-14 (8.8)

than C-18 or C-19 was easily deduced from the observed allylic coupling between the vinyl methyl signal and the resonance of vinylic H-14 in **11c**. This was also apparent from the upfield shift (δ4.5) of the C-17 resonance of **11c** compared with the C-17 resonances of **11a** and **11d** (Table 4). Triacetoxydiol **11b**, which was not obtained in pure form, differed from **11a** only in carrying an acetate on C-20 as evidenced by the paramagnetic shift of the H-20 signal (see Table 3).

The third new geranylnerol derivative was a monoacetoxytriol **11e** or **11f** whose ^{1}H NMR spectrum (Table 3) showed that one of the two CH_2OAc functions of **11a** on C-7 or C-11 was replaced by a methyl group. A decison between the two alternatives **11e** and **11f** was not possible on the available evidence.

EXPERIMENTAL

Extraction of Mikania periplocifolia. Aerial parts (0.6 kg) of *M. periplocifolia* Hook & Arn., collected in March 1984 in La Calera, District Colón, Province of Córdoba, Argentina and identified by Dr. Luis Ariza, Museo Botánico, Universidad Nacional de Cordoba, were extracted with $CHCl_3$ and worked up in the usual fashion [8]. The crude gum (7.07 g) was chromatographed on 250 g of silica gel packed in $CHCl_3$, 100 ml fractions being collected as follows. Fr. 1–5 $CHCl_3$, 6–10 $CHCl_3$–1 % MeOH, 11–14 $CHCl_3$–2 % MeOH, 15–24 $CHCl_3$–3 % MeOH, 25–30 $CHCl_3$–4 % MeOH.

Fr. 20 on standing deposited 0.413 g of solid material which on recrystallization from MeOH afforded 0.215 g of **1** identified by comparison with authentic material. Fr. 21 on standing deposited 1.6 g of solid material which on recrystallization from MeOH

Table 3. ^{1}H NMR spectra of compounds **11a–e** (270 MHz, $CDCl_3$)

	11a	**11b***	**11c**	**11d**	**11e** (or **11f**)
H-1	4.16 *br d* (7)	4.18 *br d*	10.26 *d* (7)	10.23 *d*	4.18 *br d* (7)
2	5.76 *br t* (7)	5.70 *br t*	6.55 *br d* (7)	6.52 *br t*	5.69 *br t* (7)
4	2–2.3	2–2.3 *c*	2.77 *br t* (7)	2.75 *br t*	2.0–2.6 *c*
5			2.29 *br q*	2.30 *br q*	
6	5.38 *m*	5.39 *m*	5.41 *br t*† (7)	5.35 *br t*	5.09 *br t*† (7)
8	2–2.3 *c*	2–2.3 *c*	2.17 *br t* (7)	1.9–2.2 *c*	2.0–2.6 *c*
9			2.06†		
10	5.38 *m*	5.38 *m*	5.38 *br t* (7)	5.35 *br t*	5.40 *br t*† (7)
12	2–2.3 *c*	2–2.3 *c*	2.24 *bt t* (7)	1.9–2.2 *c*	2.0–2.6 *c*
13			2.49 *br q* (7)		
14	5.38 *m*	5.38 *m*	6.46 *tq* (7, 1.5)	5.35 *br t*	5.40 *br t* (7)
16	3.97 *br*	3.97 *br*	9.40	3.97 *br*	3.99 *br*
17‡	1.65 *br*	1.66 *br*	1.75 *br*	1.69 *br*	1.66 *br*
18	4.58 *br*	4.58 *br*	4.62 *br*	4.57 *br*	4.59 *br*
19	4.59 *br*	4.60 *br*	4.52 *br*	4.50 *br*	1.60 *br*‡
20	4.05 *br*	4.52 *br*	9.67 *br*	9.64 *br*	4.08 *br*
Ac‡	2.05 2.05	2.08 2.06 2.06	2.08 2.06	2.04 2.03	2.07

*From spectrum of mixture.

†Assignments may be interchanged.

‡Intensity three protons.

afforded 0.785 g of a mixture containing **1**, **2a**, **2b** and **4b** (NMR analysis). The gummy material from the mother liquors of fr. 20–21 was rechromatographed (silica gel, C_6H_6 and C_6H_6–Me_2CO mixtures, 25 ml fractions). Fr. 5–7 from the rechromatogram (C_6H_6–5% Me_2CO) gave after recrystallization from Me_2CO–petrol 7 mg of **7** identified by comparison with authentic material. Prep. TLC (C_6H_6–Me_2CO, 4:1) of the material from fr. 8–9 (C_6H_6–5% Me_2CO) gave 8 mg of a 1:1 mixture of **8** and **9** identified by NMR spectrometry. Fr. 10–12 (C_6H_6–5% Me_2CO) of the rechromatogram afforded 110 mg of **1**, fr. 14–17 (C_6H_6–10% Me_2CO) after prep. TLC (C_6H_6–Me_2CO, 9:1) gave 9 mg of a 4:1.5:1 mixture, mp 224°, of three compounds containing mainly **4b** which was identified by NMR spectrometry and fr. 18–22 (C_6H_6–10% Me_2CO) followed by recrystallization from MeOH, gave 147 mg of a 2:1 mixture, mp 175–177°, of **2a** and **2b** identified by NMR spectrometry.

Fr. 22 of the original chromatogram on rechromatography (C_6H_6–15% Me_2CO) yielded 225 mg of **3** identified by its NMR spectrum; fr. 23–24 on rechromatography (C_6H_6–15% Me_2CO) gave 5 mg of a 4:1 mixture of **10a** and an unidentified compound. Rechromatography of the mixture gave essentially pure **10a** whose ^{1}H NMR spectrum is listed in Table 1; MS *m/z* (rel. int.): 293 $[M+1]^+$ (1.1), 292 $[M]^+$ (0.9), 274 (4.2), 256 (4.3) and 95 (100). [Calc. for $C_{15}H_{18}O_6$: M_r 292.0945. Found: M_r (MS), 292.0953.] Acetylation (Ac_2O–pyridine) gave the diacetate **10b** whose ^{1}H NMR spectrum is listed in Table 1.

Fr. 25–30 on rechromatography (C_6H_6–20% Me_2CO) gave first 25 mg of **11e** (or **11f**) and then 65 mg of **11a** as oils whose ^{1}H NMR spectra are listed in Table 3; ^{13}C NMR spectrum of **11a** in Table 4; MS of **11a** *m/z* (rel. int.): 360 $[M-78]^+$ (0.2), 342 (0.2), 318 (0.3), 300 (0.6), 282 (0.6) and 43 (100); MS (CI) *m/z* (rel. int.): 439 $[M+1]^+$ (2.7), 421 (21.5), 379 (4.1), 361 (15.1), 343 (29.8), 319 (5.8), 301 (42.4) and 283 (100). Compound **11e** (or **11f**) decomposed on standing and did not give a satisfactory MS. A solution of *ca* 150 mg of **11a** in 10 ml of $CHCl_3$ was stirred with 0.60 g of MnO_2 for 84 hr at room temp. Filtration, evaporation of the organic layer at red. pres. and prep. TLC of the crude product ($CHCl_3$–MeOH–EtOAc, 19:1:1) afforded 16 mg of **11c** and 95 mg of **11d** whose ^{1}H NMR and ^{13}C NMR spectra are listed in Tables 3 and 4, respectively. Trialdehyde **11c** had IR bands (neat) at 1730, 1675 and 1640 cm^{-1}; MS *m/z* (rel. int.): 433 $[M+1]^+$ (0.2), 432 $[M]^+$ (0.1), 373 (1), 312 (1) and 43 (100). Dialdehyde **11d** had IR bands (neat) at 3450 br, 1725 and 1675 cm^{-1}; MS (CI) *m/z* (rel. int.): 435 $[M+1]^+$ (0.6), 417 (8.8), 375 (11.8), 357 (39.0), 341 (3.5), 339 (4.8), 315 (23.5), 297 (100), 279 (22.2), 269 (9.9), 257 (15.8), 251 (5.5), 241 (4.7), 239 (8.2).

A second collection of *M. periplocifolia* (1.40 kg), collected on April 19, 1984 in Is. Nuñez, District Victoria, Province of Entre Rios gave 20.40 g of crude gum which was chromatographed on 250 g of silica gel packed in C_6H_6, 100 ml fractions being collected as follows. Fr. 1–4 (C_6H_6), fr. 5–16 (C_6H_6–Me_2CO, 19:1), fr. 17–22 (C_6H_6–Me_2CO, 9:1), fr. 23–28 (C_6H_6–Me_2CO, 17:3), fr. 29–34 (C_6H_6–Me_2CO, 4:1), fr. 35–37 (C_6H_6–Me_2CO, 7:3), 38–40 (C_6H_6–Me_2CO, 1:1), 41–42 (C_6H_6–Me_2CO, 3:7) and 44–50 ($CHCl_3$–MeOH, 9:1).

Rechromatography ($CHCl_3$) of the solid material (90 mg) from

Table 4. ^{13}C NMR spectra of compounds **11a**, **c**, **d** (67.89 MHz, $CDCl_3$)

C	**11a**	**11c**	**11d**
1	58.48*	191.36	191.38
2	125.08	141.11	141.08
3	141.12	153.51	151.53
4	28.16	24.04	24.01*
5	26.95†	27.53	27.22*
6	130.60‡	128.41	128.32
7	133.79§	135.79	135.84†
8	35.16‖	35.09	35.12‡
9	26.29†	26.30	26.29§
10	130.32‡	130.96	129.99
11	133.65§	133.07	134.02
12	34.78‖	33.69	34.74‡
13	26.29†	27.25	26.22§
14	125.08	153.43	125.16
15	135.13	139.68	135.19†
16	68.45*	195.07	68.70
17	13.69	9.25	13.64
18	61.97¶	61.59†	61.77‖
19	61.86¶	61.32†	61.37‖
20	65.86*	194.82	194.84*
Ac	171.36 (2) 20.98 (2)	171.03, 170.80 20.91, 20.83	170.91, 170.78 20.89 (2)

*Assignment by selective decoupling.

†‡§‖¶Assignments with the same sign in each column may be interchanged.

fr. 12–16 yielded 48 mg of **7**. Recrystallization of the solid material from fr. 17–22 from MeOH afforded 1.60 g of a mixture of **1**, **2a**, **2b** and **6** which could be separated by further chromatography into **1**, a mixture of **1** and **6** and a mixture of **2a** and **2b**. Recrystallization of fr. 23–24 gave 0.16 g of a mixture containing primarily **2a** and **2b**. Repeated rechromatography (C_6H_6–Me_2CO, 9:1) of fr. 25–27 (0.53 g) gave complex mixtures and 10 mg of gummy **5** whose ^{1}H NMR spectrum is listed in Table 1. [Calc. for $C_{15}H_{18}O_5$: M_r 278.1155. Found: M_r (MS), 278.1147.] Rechromatography (C_6H_6 and C_6H_6–Me_2CO, 9:1) of fr. 28–29 (1.2 g) gave 380 mg of **3**. Rechromatography of fr. 30–32 (0.42 g) gave complex mixtures and a fraction partially soluble in $CHCl_3$. The insoluble substance was **4a** (60 mg) whose ^{1}H NMR spectrum is listed in Table 1; MS *m/z* (rel. int.): 278 (7.2), 260 (2.8), 250 (0.8), 232 (1.3), 210 (30.8), 208 (7.5), 192 (5.8), 181 (2.6), 164 (2.9), 152 (26.1), 136 (7.5), 121 (6.6) and 112 (100). [Calc. for $C_{15}H_{18}O_5$: M_r, 278.1155. Found: M_r (MS), 278.1161.] Rechromatography of fr. 33–36 (0.7 g) gave 0.15 g of an oil approximately half of which was **11b** (for ^{1}H NMR spectrum see Table 3), fr. 37–40 (0.88 g) consisted mainly of **11a** and rechromatography of fr. 41–60 (2.23 g) afforded 0.590 g of pure **11a**.

REFERENCES

1. Herz, W. and Kulanthaivel, P. (1985) *Phytochemistry* **24**, 1761.
2. Herz, W., Subramaniam, P. S., Aota, K. and Hall, A. (1970) *J. Org. Chem.* **35**, 1453.
3. Cox, P. J., Sim, G. A., Roberts, J. S. and Herz, W. (1973) *J. Chem. Soc. Chem. Commun.* 428.
4. Cox, P. J. and Sim, G. A. (1974) *J. Chem. Soc. Perkin Trans.* 2, 1355.
5. Bohlmann, F., Tsankova, E., King, R. M. and Robinson, H. (1984) *Phytochemistry* **23**, 1099.
6. Herz, W. and Govindan, S. V. (1981) *Phytochemistry* **20**, 1740.
7. Doskotch, R. W., Fairchild, E. H., Huang, C.-T., Wilton, J. H., Beno, M. A. and Christoph, G. G. (1980) *J. Org. Chem.* **45**, 1441.
8. Herz, W. and Högenauer, G. (1962) *J. Org. Chem.* **27**, 905.