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FIVE MIKANOLIDE DERIVATIVES FROM *MIKANIA CYNANCHIFOLIA* AND THEIR BIOGENETIC RELATIONSHIPS

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Key Word Index—*Mikania cynanchifolia*; Compositae; sesquiterpene lactones; lactones related to mikanolide; biogenetic relationships.

Abstract—The investigation of the aerial parts of *Mikania cynanchifolia* afforded, in addition to miscandenin, five new sesquiterpene lactones, miscandenin-1,2-epoxide, an isomiscandenin and three further dilactones related to mikanolide. The structures of these new compounds were elucidated by high field ^{1}H NMR spectroscopy. The biogenetic relationships of the sesquiterpene lactones are briefly discussed.

INTRODUCTION

So far chemical investigations of representatives of the large genus *Mikania* (tribe Eupatorieae, subtribe Mikaniinae) have shown that highly oxygenated sesquiterpene lactones like mikanolide [1–4] and miscandenin [1] may be characteristic for this genus though also several other sesquiterpene lactones [5–10] and a few different types of diterpenes have been reported from several species. We now have studied the constituents of *Mikania cynanchifolia* Hook. et Arn.. The results are discussed in this paper.

RESULTS AND DISCUSSION

The aerial parts of *M. cynanchifolia* afforded a complex mixture of sesquiterpene lactones which could only be separated by repeated TLC and HPLC. In addition to miscandenin (**6**) [1] five new lactones were obtained, the isabelin derivatives **1** and **2**, the isomer of miscandenin **7**, miscandendin-1β,2β-epoxide (**8**) and the 11β,13-dihydro derivative of 3β-acetoxyisabelin (**9**). The structures of **1** and **2** clearly followed from the ^{1}H NMR spectral data (Table 1) which were close to those of one of the congeners of isabelin [11]. The presence of an additional oxygen function was indicated by low field signals at δ5.08 and 5.95 respectively. Spin decoupling showed that these function were at C-3, while the couplings observed indicated their β-orientation. The ^{1}H NMR spectrum of **9** (Table 1) was close to that of **2**. The presence of an 11β, 13-dihydro derivative followed from the additional methyl doublet at δ1.44 which replaced the methylene signals in the spectrum of **2**. Of course the H-7 signal was also shifted upfield and the additional double quartet at 2.57 was assigned to H-11. The large coupling $J_{7,11}$ clearly showed that the 11-methyl group was α orientated. The ^{1}H NMR spectra of all three isabelin derivatives showed that due to the additional oxygen function at C-3 these lactones are present in only one conformation.

The molecular formula of **7** was $C_{15}H_{14}O_5$ and therefore this lactone was formal an isomer of miscandenin (**6**). Though several ^{1}H NMR signals also were similar to those of **6** (Table 2), signals at δ3.31 and 3.69 required the presence of an epoxide. The chemical shift of an olefinic proton was at δ7.19 and, contrary to the corresponding signal in the spectrum of **6**, this proton had two coupling partners. Spin decoupling showed that it was coupled with the epoxide proton (3.69 *dd*) and with the proton which gave rise to a double doublet at 2.91. As the latter was further coupled with one of the protons under a lactone oxygen, the structure of **7** finally was established. The stereochemistry at C-1 and C-2 was

Table 1. ^{1}H NMR spectral data of compounds **1**, **2** and **9** (400 MHz, $CDCl_3$, TMS as internal standard)

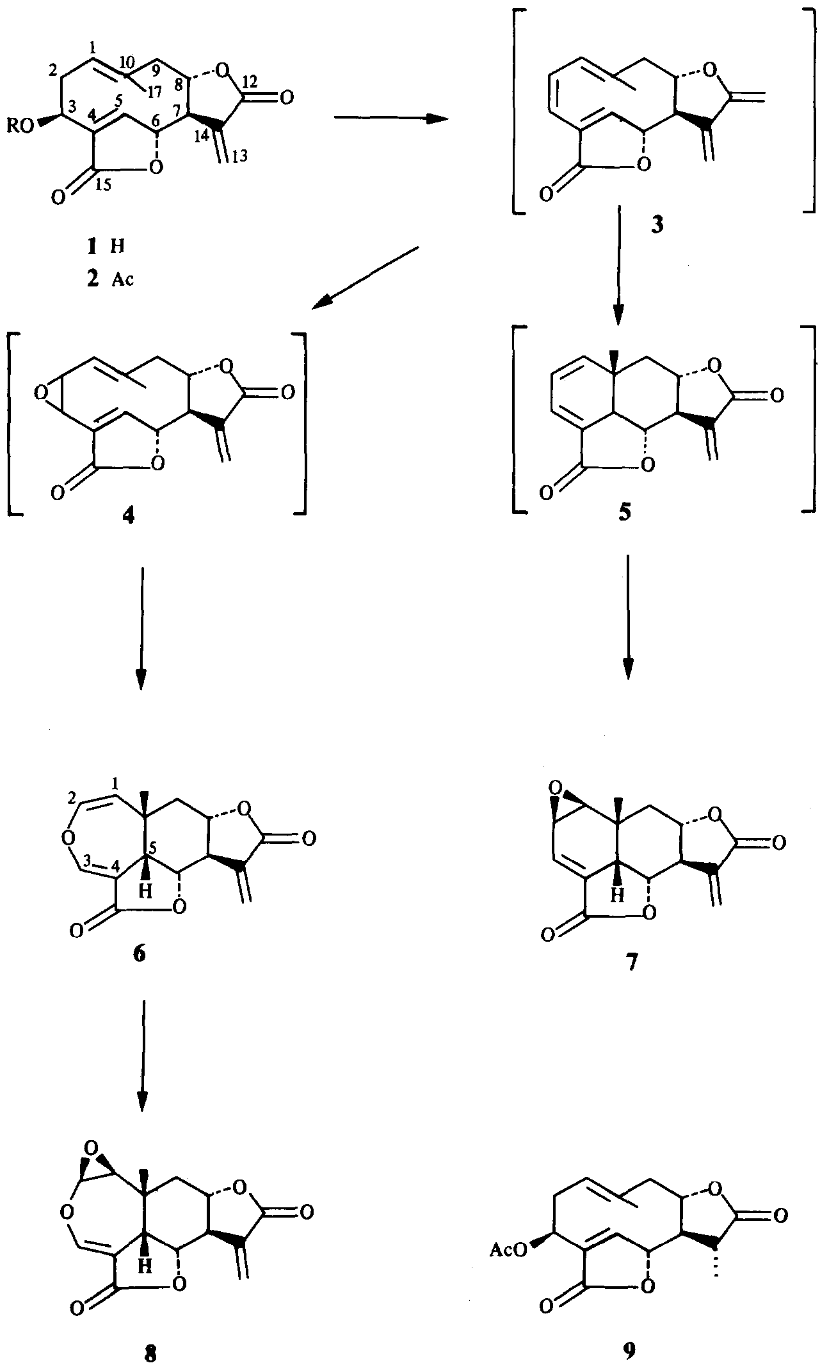
	1	**2**	**9**
H-1	5.24 *br dd*	5.13 *br dd*	5.07 *br d*
H-2	2.80 *ddd*	2.87 *ddd*	2.93 *ddd*
H-2′	2.35 *dd*	2.45 *br d*	2.42 *br d*
H-3	5.08 *ddd*	5.95 *br dd*	5.95 *br dd*
H-5	7.17 *t*	7.00 *t*	7.00 *t*
H-6	5.31 *dd*	5.31 *dd*	5.11 *br d*
H-7	3.28 *dddd*	3.30 *dddd*	2.45 *dd*
H-8	4.49 *ddd*	4.47 *ddd*	4.39 *ddd*
H-9	3.10 *br dd*	3.13 *br dd*	3.09 *br dd*
H-9′	1.93 *dd*	1.96 *dd*	1.89 *dd*
H-11	—	—	2.57 *dq*
H-13	6.48 *d*	6.50 *d*	1.44 *d*
H-13′	5.88 *d*	5.87 *d*	
H-14	1.61 *br s*	1.62 *br s*	1.62 *s br*
OAc	—	2.15 *s*	2.17 *s*

J (Hz): Compounds **1** and **2**: 1, 2 = 12.5; 1, 2′ = 2′, 3 = 2; 2, 2′ = 14; 2, 3 = 4; 3, 5 = 5, 6 = 1.5; 6, 7 = 1.5; 7, 8 = 9; 7, 13 = 3; 7, 13′ = 3; 8, 9 = 4.5; 8, 9′ = 11; 9, 9′ = 14; compound **9**: 1, 2 = 12.5; 1, 2′ = 2′, 3 = 2; 2, 2′ = 14; 2, 3 = 4.5; 3, 5 = 5, 6 = 6, 7 ~ 1.5; 7, 8 = 9, 5; 7, 11 = 13; 8, 9 = 4; 8, 9′ = 11; 9, 9′ = 14; 11, 13 = 7.

deduced from the chemical shift of H-14 which could be explained only by a deshielding effect of a β-orientated oxygen function. We have named **7** mikacynancholide.

The structure of **8**, molecular formula $C_{15}H_{14}O_6$, again followed from the characteristic ^1H NMR spectrum (Table 2) which was in part close to that of **6**. However, again the presence of an epoxide was indicated by a doublet at δ2.93 ($J = 3$ Hz) which was coupled with a doublet at 5.15. As the low field doublet of H-3 still was present (7.23 *d*) the epoxide must be at C-1/C-2. Again the downfield shift of H-14 indicated a β-epoxide. This could be established by epoxidation of **6** which only gave **8** and inspection of a model showed that the *cis*-anellation of the rings strongly favoured a β-attack of the peracid. As the structure of miscandenin was established by X-ray analysis [12] the structure and the configuration of the new epoxide was confirmed.

As shown in Scheme 1 the biogenetic relationships of the lactones present in this *Mikania* species are obvious. Compound **1** is surely formed by allylic oxidation of



Scheme 1.

Table 2. ^{1}H NMR spectral data of compounds **6–8** (400 MHz, $CDCl_3$, TMS as internal standard)

	6	**7**	**8**
H-1	4.80 *d*	3.31 *d*	2.93 *d*
H-2	6.17 *d*	3.69 *dd*	5.15 *d*
H-3	7.53 *d*	7.19 *dd*	7.23 *d*
H-5	3.51 *dd*	2.91 *dd*	3.30 *dd*
H-6	4.76 *dd*	4.93 *dd*	4.80 *dd*
H-7	2.72 *dddd*	2.35 *dddd*	2.66 *dddd*
H-8	4.00 *ddd*	4.07 *ddd*	4.09 *ddd*
H-9	2.22 *dd*	2.16 *dd*	2.26 *dd*
H-9′	1.92 *dd*	1.62 *dd*	1.98 *dd*
H-13	6.23 *d*	6.26 *d*	6.26 *d*
H-13′	5.90 *d*	5.93 *d*	5.91 *d*
H-14	1.31 *s*	1.54 *s*	1.51 *s*

J (Hz): Compound **7**: 1, 2 = 2, 3 = 3, 5 = 3.5; 5, 6 = 7; 6, 7 = 10; 7, 8 = 11; 7, 13 = 7, 13′ = 3; 8, 9 = 3; 8, 9′ = 11; 9, 9′ = 12; compound **8**: 1, 2 = 3, 5 = 3; 5, 6 = 6.5; 6, 7 = 10; 7, 8 = 11; 7, 13 = 7, 13′ = 8, 9 = 3; 8, 9′ = 9, 9′ = 11.5.

isabelin and would lead to **3** by elimination of water. Epoxidation of the 2,3-double bond would give **4**, while Cope-rearrangement of **3** could lead to **5**. Epoxidation of the latter would give mikacynancholide (**7**) and a Cope-rearrangement [1] of **4** would give miscandenin (**6**) as discussed earlier [13].

EXPERIMENTAL

The air dried aerial parts (130 g) (collected in the province Bahia, Brazil, voucher RMK 8913, deposited in the US National Herbarium, Washington) were extracted with Et_2O–petrol, 1:2 (12 hr, room temp.), and the extract obtained was worked-up in the usual fashion. CC fractions (50 ml) were as follows: 1 (petrol), 2 (Et_2O–petrol, 1:10), 3 (Et_2O–petrol, 1:3 and 1:1), 4 (Et_2O and Et_2O–MeOH, 10:1). TLC of fraction 4 (SiO_2, PF 254, Et_2O–petrol, 3:1, detection of zones by UV light, 255 nm) afforded mixtures of **1**, **2** and **6–9** (R_f 0.5) which by TLC (Et_2O–C_6H_6–CH_2Cl_2, 1:1:1) and HPLC (RP 8) (MeOH–H_2O, 3:1) finally gave 5 mg **1** (R_t 4.5 min), 20 mg **2** (R_t 7.5 min), 2 mg **7** (R_t 6.9 min), 3 mg **8** (R_t 6.7 min) and 10 mg **9** (R_t 7.3 min). Quantities were determined by weighing.

3β-Hydroxyisabelin (**1**). Colourless crystals (not sufficient to obtain a sharp mp but homogeneous by TLC in several solvent systems); IR $\nu^{CCl_4}_{max}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone); MS *m/z* (rel. int.): 276.100 $[M]^+$ (5) ($C_{15}H_{16}O_5$), 258 $[M-H_2O]^+$ (2), 112 (100), 97 $[112-Me]^+$ (58).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+4 \quad +4 \quad +2 \quad -11}\,\text{CHCl}_3;\ c = 0.15$$

3β-Acetoxyisabelin (**2**). Colourless crystals, mp 163.5°; IR $\nu^{CCl_4}_{max}$ cm^{-1}: 1775 (γ-lactone), 1750 (OAc); MS *m/z* (rel. int.): 318.110 $[M]^+$ (47) ($C_{17}H_{18}O_6$), 276 $[M-\text{ketene}]^+$ (100), 258 $[M-HOAc]^+$ (14), 206 (44), 164 (56), 119 (52), 111 (56).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+7 \quad +8 \quad +7 \quad -9}\,\text{CHCl}_3;\ c = 0.3$$

Mikacynancholide (**7**). Colourless gum, which could not be induced to crystallize, though no impurities were detectable by TLC in several solvent systems. IR $\nu^{CCl_4}_{max}$ cm^{-1}: 1780 (γ-lactone); MS *m/z* (rel. int.): 274.084 $[M]^+$ (16) ($C_{15}H_{14}O_5$), 256 $[M-H_2O]^+$ (6), 245 $[M-CHO]^+$ (10), 217 $[245-CO]^+$ (9), 69 (100).

1β,2β-Epoxy miscandenin (**8**). Colourless crystals, mp 228.5°; IR $\nu^{CHCl_3}_{max}$ cm^{-1}: 1770 (γ-lactone); MS *m/z* (rel. int.): 290.079 $[M]^+$ (47) ($C_{15}H_{14}O_6$), 261 $[M-CHO]^+$ (100), 246 $[M-CO_2]^+$ (70), 216 (20), 109 (63), 69 (71).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-167 \quad -172 \quad -198 \quad -353}\,\text{CHCl}_3;\ c = 0.2$$

10 mg **6** in 2 ml CH_2Cl_2 were stirred in the presence of a drop of satd $NaHCO_3$ solution for 10 hr with 10 mg *m*-chloroperbenzoic acid. TLC (C_6H_6–Et_2O–CH_2Cl_2, 1:1:1) afforded 7 mg **6** and 2 mg **8**, identical with the natural products (^{1}H NMR, TLC).

3β-Acetoxy-11β,13-dihydroisabelin (**9**). Colourless crystals, mp 236–237°; IR $\nu^{CCl_4}_{max}$ cm^{-1}: 1780 (γ-lactone), 1750 (OAc); MS *m/z* (rel. int.): 320.126 $[M]^+$ (40) ($C_{17}H_{20}O_6$), 278 $[M-\text{ketene}]^+$ (52), 260 $[M-HOAc]^+$ (32), 208 (77), 166 (40), 152 (100), 93 (80).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{0 \quad 6 \quad -10 \quad -14}\,\text{CHCl}_3;\ c = 0.1.$$

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