C-15-Functionalized Eudesmanolides from *Mikania campanulata*

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Received April 4, 2007

The aerial parts of *Mikania campanulata* Gardner afforded the nine new eudesmanolides (1*S*,4*S*,5*S*,6*S*,7*S*,10*R*)-1-hydroxy-15-acetoxyeudesm-11(13)-en-6,12-olide (**1**), (1*S*,4*S*,5*S*,6*S*,7*S*,10*R*)-1,4-dihydroxy-15-acetoxyeudesm-11(13)-en-6,12-olide (**2**), (1*R*,4*S*,5*S*,6*S*,7*S*,10*R*)-1,4-dihydroxy-15-acetoxyeudesm-11(13)-en-6,12-olide (**3**), (1*R*,4*S*,5*S*,6*S*,7*S*,10*R*)-1-hydroxy-4,15-diacetoxyeudesm-11(13)-en-6,12-olide (**4**), (1*S*,4*R*,5*S*,6*S*,7*S*,10*R*)-1,15-diacetoxy-4-hydroxyeudesm-11(13)-en-6,-12-olide (**5**), (1*S*,5*S*,6*S*,7*S*,10*R*)-1-hydroxy-15-acetoxyeudesma-4(15),11(13)-dien-6,12-olide (**6**), (1*S*,5*S*,6*S*,7*S*,10*R*)-1,15-dihydroxyeudesma-3,11(13)-dien-6,12-olide (**7a**), (1*S*,2*R*,5*S*,6*S*,7*S*,10*R*)-1,2,15-trihydroxyeudesma-3,11(13)-dien-6,12-olide (**8a**), and (1*R*,6*S*,7*S*,10*R*)-1,15-dihydroxyeudesma-4,11(13)-dien-6,12-olide (**9a**), among which the last three were characterized as their corresponding peracetates (**7b**−**9b**). The structures of **1**−**6** and **7b**−**9b** were elucidated using 1D and 2D NMR measurements, while that of major constituent **1** was confirmed by single-crystal X-ray diffraction analysis, and its absolute configuration evidenced from vibrational circular dichroism measurements, which were compared to results obtained from density functional theory calculations. The chemistry of the large genus *Mikania* is briefly analyzed.

With more than 450 mainly American species, *Mikania* Willdenow is the largest genus in the tribe Eupatoriae (Asteraceae).[1,2] The genus is rapidly characterized by the structure of the head, composed of four florets and an involucre composed of four phyllaries that is subtended by a subinvolucral bract. There is no deviation from this organization. Although it is one of the most distinctive and easily recognized genera of the tribe, species delimitation is sometimes difficult due to the very large number of taxa and the existence of highly polymorphic species complexes.[1−3] Several *Mikania* species, particularly those known under the common name "guaco", are used in Central and South American traditional medicine as anti-inflammatory agents,[4,5] to treat respiratory tract diseases, rheumatism, and influenza, and also as remedies against snake bite.[6] *M. micrantha*, a herbaceous vine native to Central and South America was introduced in Southeast Asia and South Asia, where it has become a noxious weed, being listed as one of the 100 world's worst invasive alien species by the Invasive Species Specialist Group of IUCN.[7,8] So far some 50 *Mikania* species have been investigated chemically, from which two main types of metabolites have been isolated: sesquiterpene lactones and diterpenes. Sesquiterpene dilactones of the mikanolide type and germacranolides functionalized either at C-14 or C-15, or both, are found in nearly 50% of the studied species, while other lactone types such as guaianolides, elemanolides, and eudesmanolides are rare in *Mikania*. Another group of species, constituted mainly by Brazilian representatives, contain *ent*-kaurenoic acid derivatives and occasionally *ent*-labdane and *ent*-pimarane derivatives.[9,10] In about 10% of the studied species, neither sesquiterpene lactones nor diterpenes have been reported.[9]

Continuing our work on Argentinian *Mikania* species[11,12] we report here the isolation of nine new *trans*-lactonized eudesmanolides closed at C-6 and functionalized at C-15 from *M. campanulata* Gardner, a vine found in Brazil[1a] and northeastern Argentina.[1b]

Results and Discussion

Compound **1** showed a terminal absorption at 207 nm (ϵ 9800) in the UV spectrum, while the IR spectrum displayed bands at 3624 and 3514 cm^{-1} (OH), 1766 cm^{-1} (γ-lactone), 1732 cm^{-1} (ester C═O), and 1248 cm^{-1} (C−O). The molecular formula $C_{17}H_{24}O_5$, accounting for six degrees of unsaturation, followed from its HRMS (see Experimental Section). The ^{1}H NMR spectrum of **1** (Table 1) showed two characteristic α-methylene-γ-lactone doublets assigned to H-13a and H-13b at δ 6.06 (J = 3.3 Hz) and 5.40 (J = 3.0 Hz), respectively, whose J values, larger than 3.0 Hz, are indicative of a *trans* lactone ring.[13,14] Resonances for an acetate methyl and a quaternary methyl appeared at δ 2.06 and 0.97, respectively. Other resonances were the AB portion of an ABX system showing a triplet at δ 4.32 (J = 10.4 Hz) and a double doublet at δ 4.03 (J = 10.4, 3.5 Hz) assigned to the C-15 methylene protons, a double doublet at δ 3.94 (J = 11.5 and 10.6 Hz, H-6), a double doublet at δ 3.50 (3.8 and 2.4 Hz, H-1), a multiplet at δ 2.48 (H-7), and a double doublet at δ 2.35 (J = 11.5 and 5.2 Hz, H-5). Collectively this data indicate a 6,12-*trans*-lactonized eudesmanolide with an *O*-acetyl substituent at C-15 and a hydroxy group at C-1, as shown in structure **1**. The relative configuration was established from coupling constants[15,16] for H-1, H-5, H-6, and H-7 and NOESY correlations. In the NOESY spectrum, H-15a (δ 4.32) correlated with H-15b (δ 4.03) and Me-14 (δ 0.97); in turn H-15b correlated with H-15a and H-6 (δ 3.94), while H-6 correlated with Me-14, thus corroborating that the C-4 CH_2OAc group, Me-14, and H-6 are cofacial and β-oriented when assuming that H-7 is α-oriented. Additional support for the relative configuration was obtained by molecular modeling. The minimum energy conformation of **1**, using the PCMODEL program,[17] is in agreement with the observed NOESY correlations.

Further structural evidence for **1** was obtained from the ^{13}C NMR spectrum, which showed the presence of 17 carbons, as shown in Table 2. The assignments were made by DEPT, gHSQC, and gHMBC experiments. The chemical shift of the C-7 resonance (δ 50.5) is also indicative of *trans* lactonization at C-6,[18] since in *cis*

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10.1021/np070154t CCC: $37.00
Published on Web 07/07/2007

Table 1. ^{1}H NMR Data of Compounds **1**−**6** and **7b**−**9b** (300 MHz, $CDCl_3$, TMS as internal standard)

H	1	2	3	4
1	3.50 brdd (3.8,2.4)	3.48 dd (5.7,6.3)	3.36 dd (11.4,3.9)	3.43dd (7.4,6.7)
2α	1.58 m	1.56 m	1.67 m	1.65−1.78 m
2β	1.92 m	2.18 dddd (15,13,5.1,2.5)	1.91 m	
3α	1.88 m	1.85 ddd (14.7,13.0,4.8)	1.52 m	1.63 m
3β	1.60 m	1.54 m	1.80 m	2.87 dt (14.5,3,3)
4	2.41 m			
5	2.35 dd (11.5, 5.2)	2.06 d (11.0)	1.53 d (11.0)	1.87 d (11.0)
6	3.94 dd (11.5,10.6)	4.23 t (11.0)	4.27 t (11.0)	4.25 t (11.0)
7	2.48 m	2.52 ddtd (11.8,11.0, 3.3,3.0)	2.51 tddd (11.0,3.5,3.3,3.0)	2.53 tddd (11.2,4.2, 3.3,3.0)
8α	2.05 m	2.06 m	2.05 m	2.07 m
8β	1.58 m	1.67 m	1.61 m	1.60 m
9α	2.00 m	1.99 m	1.27 m	1.34 brddd (12.8, 12.8,3.8)
9β	1.24 m	1.25 m	2.05 m	2.09 m
13a	6.06 d (3.3)	6.06 d (3.3)	6.08 d (3.3)	6.10 d (3.3)
13b	5.40 d (3.0)	5.39 d (3.0)	5.42 d (3.0)	5.43 d (3.0)
14	0.97 s	1.18 s	1.17 s	1.11 s
15a	4.32 t (10.4)	4.67 d (11.7)	4.66 d (11.7)	4.89 d (11.0)
15b	4.03 brdd (10.4, 3.5)	4.03 d (11.7)	4.01 d (11.7)	4.39 d (11.0)
OAc_1	2.06 s	2.09 s	2.09 s	2.04
OAc_2				2.05
OAc_3				

H	5	6	7b	8b	9b
1	4.69 dd (2.7,2.1)	3.50 t (2.7)	4.68 brs	4.79 t (1.2)	4.82 dd (10.5,5)
2α	1.74−1.86 m	1.70 dddd (13.8,5.8, 2.7,2.0)	2.50 m[a]	5.07 brs	1.7−1.9 m
2β		1.87 tdd (13.8,5.0,2.5)	2.19 m[b]		
3α		2.05 m	5.65 m	5.70 brs	2.20−2.35 m
3β		2.73 ddd (13.8,5,2.0)			
4					
5	2.41 d (12.0)	2.87 brd (11.0)	2.83 brd (11.5)[c]	2.77 brd (11.0)	
6	4.13 dd (12.0,11.0)	4.00 t (11.0)	3.98 dd (11.5, 10.6)	3.98 t (11.0)	4.57 dt (11.4,2.7)
7	2.54 tddd (11.0,4.2,3.3,3.0)	2.58 tddd (11.0,4.3, 3.3,3.0)	2.53 m	2.52 tddd (11.0,3.5, 3.3,3.0)	2.66 tdt (11.4, 3.0, 3,3)
8α	2.11 m	2.08 m	2.08 m	2.06 m	2.11 m
8β	1.61 m	1.59 m	1.67 m	1.60 m	1.61 m
9α	1.74 ddd (12.6,11.0,3.3)	2.09 m	1.69 m	1.74 td (11.7,4.5)	1.44 brddd (13.2, 12.0,4.3)
9β	1.37 dt (12.6,2.7)	1.37 ddd (12.8,3.6,2)	1.44 m	1.53 m	1.88 ddd (13.2, 3.5,2.5)
13a	6.14 d (3.3)	6.08 d (3.3)	6.09 d (3.3)	6.11 d (3.3)	6.18 d (3.3)
13b	5.47 d (3.0)	5.40 d (3.0)	5.41 d (3.0)	5.44 d (3.0)	5.49 d (3.3)
14	1.11 s	0.86 s	0.94 s	1.04 s	1.22 s
15a	4.39 d (12.0)	6.98 t (1.8)	4.70 brs[d]	4.76 brs[d]	5.04 d (12.5)
15b	4.32 d (12.0)		4.70 brs	4.76 brs[d]	4.82 d (12.5)
OAc_1	2.12 s	2.14 s	2.09 s	2.08 s	2.04 s
OAc_2	2.11 s		2.07 s	2.10 s	2.08 s
OAc_3				2.12 s	

[a] 2α,2β = 19.0; 1,2α ≅ 0; 2α,3 = 2α,5 = 3.3; 2α,15a = 2α,15b ≅ 1.5. [b] 1,2β ≅ 0; 2β,3 = 4.2; 2β,5 = 2.4; 2β,15a = 2β,15b = 1.5. [c] 2α,5 = 3.3; 2β,5 = 2.4; 3,5 = 3.0; 5,6 = 11.5; 5,15a ≅ 5,15b = 1.0. [d] Fine splitting.

lactones closed at C-6 the resonance appears in the δ 39−43 range.[19,20] Evaluation of Newman projections looking through the C-1/C-10 bond shows that, in eudesmanolides with an α-OR substituent (R = H, alkyl, acyl) at C-1, the −OR and the C-14 methyl groups have an antiperiplanar disposition, while when the substituent is β-oriented, they have a γ-gauche relationship. Consequently, when a β-oriented −OR grouping is present, the C-14 resonance appears at higher fields (usually in the δ 11.5−14.0[18,19,21−24] range) than when the −OR grouping is α-oriented (δ 17.0−21.0 range).[16,18]

Compound **1** afforded good-quality crystals, which allowed a successful X-ray diffraction analysis. Crystal parameters are given in the Experimental Section, and a molecular view is shown in Figure 1, thus corroborating the relative configuration deduced from NMR data and molecular modeling. The conformation in the solid state was essentially the same as that obtained from MMX molecular modeling.

The atom coordinates derived from the X-ray analysis of **1** were used as input values for a detailed conformational search of the natural product, which was submitted to a Monte Carlo protocol[25] employing the Merck Molecular Force Field (MMFF94) program[26] without any restriction. After applying an energy cutoff of 10 kcal/mol and eliminating duplicate species, 40 conformers were found, which were submitted to B3LYP/6-31G(d) density functional theory (DFT) calculations[27] using the Spartan'04 software. This DFT optimization procedure provided eight conformers in a relative energy range of 1.66 kcal/mol, which account for 94.5% of the conformational population preference of **1**. Each of the remaining 32 conformers has no significant contribution to the conformational population of **1**. The eight minimum energy conformers were further geometry-optimized, and free energy calculations, as well as vibrational frequency calculations, were performed at the B3LYP/6-31G(d,p) DFT level of theory using Gaussian 03 software. The combination of functionals and basis set used for these calculations was selected considering the good agreement with experimental results and reasonable consumption of computer time that this, or even the lower B3LYP/6-31G(d) level of calculation, has shown in the past for vibrational circular dichroism (VCD) studies.[28] The

Table 2. ^{13}CNMR Data of Compounds **1**−**6** and **7b**−**9b** (75 MHz, $CDCl_3$, TMS as internal standard)

C	1	2	3	4	5	6	7b	8b	9b
1	73.5 d	74.4 d	78.6 d	77.7 d	74.6 d	74.4 d	74.3 d	76.2 d	78.7 d
2	24.4 t	24.5 t	26.4 t	26.4 t	23.5 t	29.0 t	29.1 t	68.8 d	23.3 t
3	20.2 t	28.8 t	34.1 t	29.2 t	29.2 t	20.0 t	123.4 d	120.0 d	27.8 t
4	32.5 d	72.8 s	72.8 s	81.9 s	72.4 s	121.1 s	131.8 s	136.7 s	125.8 s
5	43.2 d	45.9 d	52.2 d	50.4 d	51.3 d	45.0 d	43.5 d	43.0 d	134.6 s
6	80.4 d	80.1 d	79.6 d	79.0 d	81.0 d	79.5 d	80.6 d	80.2 d	82.0 d
7	50.5 d	50.4 d	51.0 d	50.8 d	50.6 d	49.4 d	50.6 d	50.6 d	49.3 d
8	21.4 t	21.3 t	21.7 t	21.4 t	21.2 t	21.3 t	20.9 t	20.4 t	22.8 t
9	35.8 t	35.7 t	38.1 t	38.6 t	36.3 t	33.0 t	33.2 t	33.3 t	37.7 t
10	40.0 s	41.2 s	42.6 s	42.3 s	40.6 s	42.7 s	39.2 s	38.3 s	41.2 s
11	139.5 s	139.1 s	139.0 s	138.7 s	137.7 s	139.2 s	138.6 s	138.2 s	138.2 s
12	170.8 s	170.3 s	170.0 s	170.0 s	169.3 s	170.3 s	170.0 s	169.5 s	169.2 s
13	117.0 t	117.0 t	117.5 t	117.4 t	118.4 t	117.0 t	117.1 t	117.6 t	119.2 t
14	20.8 q	20.1 q	13.5 q	13.8 q	19.9 q	18.3 q	17.2 q	17.1 q	19.8 q
15	62.9 t	73.3 t	73.4 t	66.5 t	67.6 t	130.1 d	66.7 t	65.3 t	63.8 t
Ac_1	171.4 s	171.7 s	171.9 s	169.9 s	171.0 s	168.1 s	170.6 s	169.7 s	170.9
	20.9 q	20.8 q	21.0 q	20.9 q	21.2 q	20.8 q	21.3 q	21.1 q	21.0
Ac_2				169.2 s	170.3 s		170.6 s	169.7 s	170.6
				22.1 q	20.9 q		21.0 q	20.9 q	21.2
Ac_3								170.2 s	
								21.0 q	

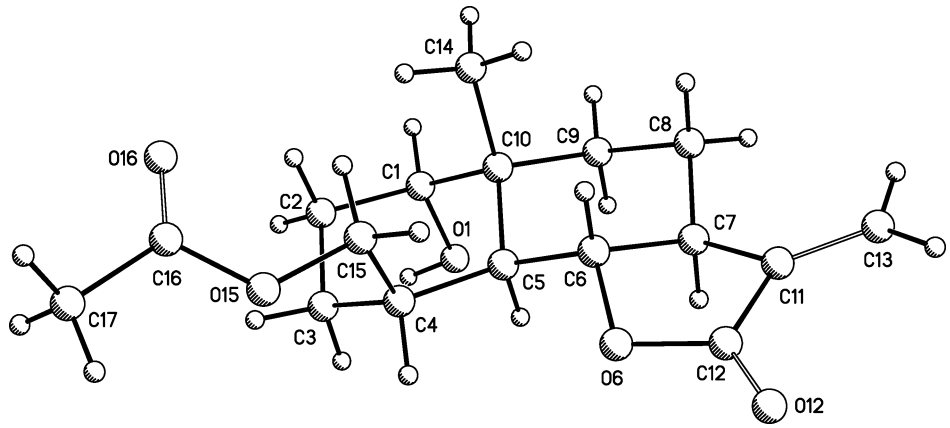


Figure 1. Molecular structure of **1** obtained from single-crystal X-ray diffraction data.

eight lower energy optimized conformers of **1** shown in Figure 2 reveal a rigid *trans*-decalin ring system in which conformers arise by rotation of the C-1 hydroxy group and the C-4 acetoxymethylene group, while their corresponding energy and population data are given in Table 3.

The final calculated VCD spectrum of **1** was obtained weighting the spectra of each conformer considering the equilibrated population, calculated from their relative free energies, using a Boltzmann distribution. The experimental spectrum and the calculated conformational averaged B3LYP/6-31G(d,p) DFT spectrum are shown in Figure 3 and confirm the absolute configuration of **1**, in agreement with many known eudesmanolides.

The HRMS of **2** indicated the molecular formula $C_{17}H_{24}O_6$, which contains one additional oxygen atom compared to compound **1**. Examination of 1D and 2D NMR spectra of **2** and comparison with the data of **1** (Tables 1 and 2) revealed that the two molecules are structurally closely related, the main differences being the multiplicity of the resonances corresponding to H-15a, H-15b, and H-5, which now appear as doublets instead of double doublets, and the δ 0.29, 0.21, and 0.35 deshielding of H-6, Me-14, and H-15a, respectively, indicating that the additional oxygen atom of **2** should be located as a β-oriented hydroxy group at C-4. In the NOESY spectrum, the Me-14 resonance at δ 1.18 showed correlations with H-1 (δ 3.48) and H-6 (δ 4.23), while H-5 exhibited a weak correlation with H-15b (δ 4.03), thus supporting the relative configuration of **2**.

Lactone **3** was isolated as a gum. Its molecular formula $C_{17}H_{24}O_6$ followed from the HRMS. Inspection of the 1D and 2D NMR spectra indicated that **3** was the C-1 epimer of **2**, as deduced from the coupling values[18,19,22−24] for H-1. Lactone **3** is a close relative of vahlenin,[29] a C-15 methacrylate analogue of **3**, with unknown configuration at C-4, isolated from *Centaurea hyssopifoplia*.

The structures of **4** and **5** were deduced from the 1D and 2D NMR spectra and comparison with the data of **2** and **3** (Tables 1 and 2). The position of the ester residue in **4** and **5** was secured from gHMBC experiments.

Compound **6** was isolated as a gum. Its molecular formula $C_{17}H_{22}O_5$, accounting for seven degrees of unsaturation, followed from HRMS. A *trans*-6,12-eudesmanolide skeleton having a 4,15-double bond was deduced from the 1D and 2D NMR spectra. The C-15 vinyl proton resonance appeared at δ 6.98 as a triplet allylically coupled to H-5 and H-3α (J = 1.8 Hz), in agreement with the chemical shift expected for protons attached to the α-carbon in enol ethers.[30] The *E*-configuration of the 4,15-double bond was deduced from a NOESY experiment where the following relevant correlations were observed: Me-14 at δ 0.86 correlated with H-6 (δ 4.00), H-1 (δ 3.50), H-8β (δ 1.59), and H-2β (δ 1.87); H-9β (δ 1.37) correlated with Me-14 and H-1; H-7 (δ 2.58) correlated with H-5; H-1 weakly correlated with Me-14; H-6 correlated with Me-14 and H-15 (δ 6.98); and H-15 weakly correlated with H-6. These supported the configuration proposed for **6**.

The most polar fractions of the chloroform extract from *M. campanulata*, which showed the presence of significant hydroxy absorption and the absence of acetate absorption in the 1740−1730 cm^{-1} region of the IR spectrum, were acetylated using Ac_2O in pyridine to provide a mixture of lactones, which was processed by

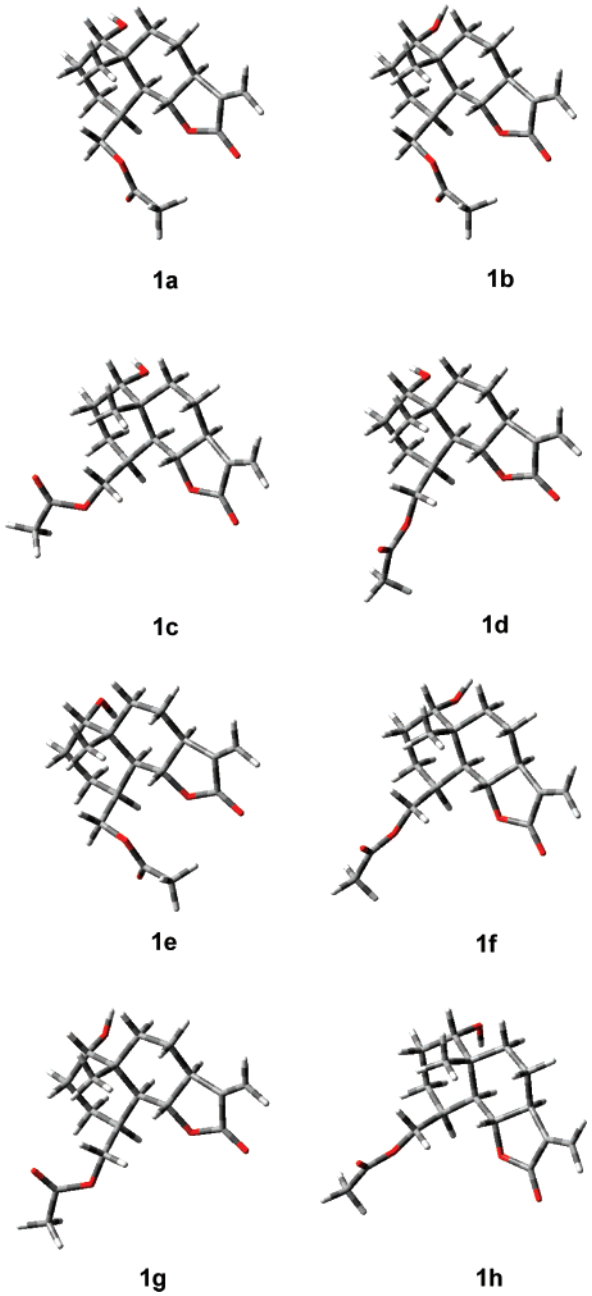


Figure 2. B3LYP/6-31G(d,p)/DFT-optimized structures of the eight more stable conformers of **1**. For relative energies and abundances, see Table 3.

RP-HPLC to yield compounds **7b**, **8b**, and **9b**. HRMS measurements showed that **7b** and **9b** were isomers with a molecular formula of $C_{19}H_{24}O_6$ (see Experimental Section). Examination of 1D and 2D NMR spectra of **7b** showed that the acetate attached to C-1 was α-oriented and the double bond was located between C-3 and C-4. In lactone **9b**, the large coupling constants for H-1 dictated a *β*-orientation for the C-1 acetate. The HRMS of lactone **8b** showed a quasi-molecular ion $[M + NH_4]^+$ at *m/z* 429.1523, in agreement with the molecular formula $C_{21}H_{26}O_8$. Examination of ^1H and ^{13}C NMR spectra of **8b** indicated it to be a derivative of **7b** possessing an additional *O*-acetyl residue at C-2. The relative configuration was established from the coupling constants and NOESY correlations.

In addition to the new constituents, several common plant metabolites were isolated from the hexane extract of *M. campanulata*, which include 1-hexadecanol, 1-octadecanol, 1-eicosanol, *β*-amyrin, 24-methylcholesta-5,22-dien-3*β*-ol, 24-methylcholest-5-en-3*β*-ol, stigmasterol, and sitosterol.

Table 3. Calculated Relative Energies (kcal/mol) and Abundances (%) of the Eight More Stable Conformers of **1**, Using MMFF94 Systematic Search and B3LYP/6-31G/DFT Levels of Theory[a]

conf	ΔE_{MMFF}[b]	$\%_{MMFF}$[b]	ΔE_{DFT}[c]	$\%_{DFT}$[c]	ΔE_{OPT}[d]	$\%_{OPT}$[d]
1a	0.29	23.17	0.00	37.42	0.00	41.58
1b	1.52	1.77	0.58	13.98	0.48	17.88
1c	0.66	12.29	0.68	11.96	0.74	11.73
1d	0.00	37.65	0.73	10.98	0.79	10.55
1e	2.18	0.95	0.91	8.02	0.97	7.69
1f	1.52	2.89	1.13	5.58	1.27	4.54
1g	2.35	0.71	1.29	4.27	1.36	4.08
1h	2.10	1.09	1.66	2.26	1.78	1.95

[a] Conformers are arranged according to their optimized energy. [b]Calculated with Spartan'04 using MMFF94. [c]Calculated with Spartan'04 using B3LYP/6-31G(d)/DFT. [d]Calculated with Gaussian 03W using DFT B3LYP/6-31G(d,p)/DFT optimization.

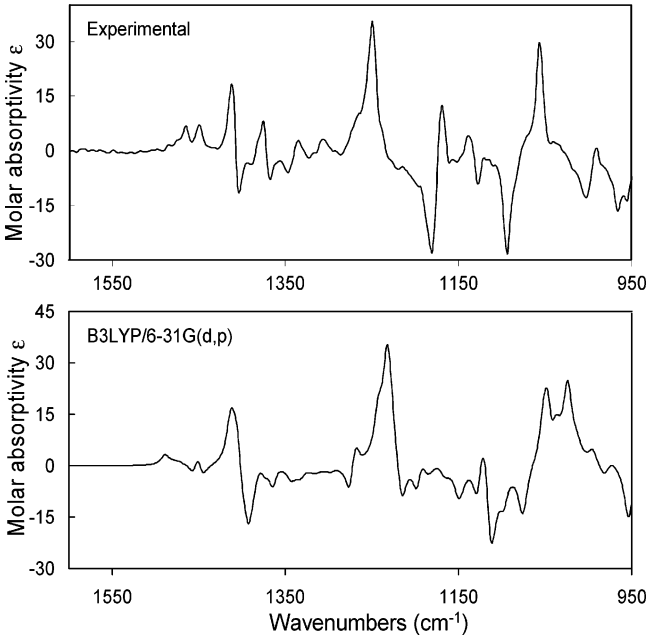
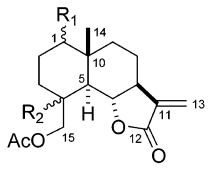
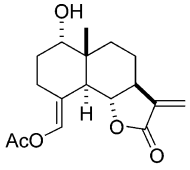


Figure 3. Experimental (top) and calculated (bottom) VCD spectra of **1**. The bottom spectrum is a weighed plot of the eight lowest energy conformers of **1** obtained from B3LYP/6-31G(d,p) DFT calculations. Frequencies are scaled by a factor of 0.97.[28a]

Eudesmanolides oxygenated at C-15 are uncommon in nature. They have been found in *Onopordon* species,[21,31] *Centaurea* species,[29,32] *Sonchus macrocarpus*,[33,34] *Dimerostemma* species,[35−38] *Vernonia pectoralis*,[39] and *Mikania cynanchifolia*.[40] The latter species, besides several isabelin and miscandenin relatives, produces a 6,15,8,12-dilactonized eudesmanolide, named mikacynancholide,[40] which is based on a *cis*-fused decalin ring system and is biogenetically related to mikanolide.[9] On the other hand, a eudesmanolide closed toward C-8 has been reported from *Mikania goyazensis* and *M. pohlii*,[41] while three eudesmanolides closed toward C-6 have been found in a collection of *M. guaco* from Costa Rica.[42] In a more recent study on the latter species, also collected from Costa Rica,[43] only lactones with a germacranolide skeleton have been isolated.

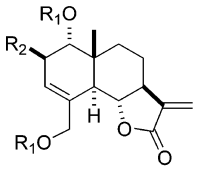
Sesquiterpene lactones and diterpenes are the two groups of metabolites dominating the chemistry of the genus *Mikania*, and they rarely co-occur in the same plant.[9] Several subgeneric classifications have been proposed for this very large genus, but so far, none has gained widespread acceptance since the infrageneric groupings have been designed mainly to facilitate species identification, rather than to reflect phylogenetic relationships.[3,44] This circumstance impedes drawing sound conclusions on the correlation between chemistry and phylogeny.

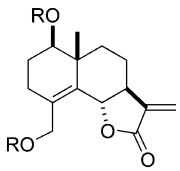




	R_1	R_2
1	α-OH	α-H
2	α-OH	β-OH
3	β-OH	β-OH
4	β-OH	β-OAc
5	α-OAc	α-OH

6





	R_1	R_2
7a	H	H
7b	Ac	H
8a	H	OH
8b	Ac	OAc

	R
9a	H
9b	Ac

Experimental Section

General Experimental Procedures. Optical rotations were performed on a Perkin-Elmer 341 polarimeter. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrophotometer. UV spectra were determined on a Perkin-Elmer Lambda 12 UV/vis spectrophotometer. NMR measurements were recorded on two Varian Mercury spectrometers, one operating at 300 MHz for hydrogen and the other one at 75 MHz for carbon, using 5 mm sample tubes in $CDCl_3$ solutions containing TMS as internal standard. Low-resolution MS were done on a Varian Saturn 2000 spectrometer, while HRMS were recorded on an Agilent LCTOF instrument at the UCR Mass Spectrometry Facility, University of California, Riverside, CA. The VCD spectrum was measured on a dualPEM Chiral*IR* FT-VCD spectrophotometer (BioTools, Inc, Jupiter, FL). A sample of 10 mg of **1** was dissolved in 20 μL of $CDCl_3$ and placed in a BaF_2 cell with a path length of 100 μm, and data were acquired at a resolution of 4 cm^{-1} during 9 h. For separation of mixtures, HPLC with a differential refractometer detector was used. The column employed was a Phenomenex Maxsil 10 C_8 (10 μm, 10 × 250 mm). Retention times were measured from the solvent peak. For column chromatography, Si gel Merck 70−230 or 230−400 mesh ASTM was used.

Plant Material. Aerial parts of *M. campanulata* were collected in August 2003 at Predio Guaraní, Departamento Guaraní, Misiones Province, Argentina. The species was identified by Lic. Sara Tressens. A voucher specimen is deposited in the herbarium of the Instituto de Botánica del Nordeste (IBONE) (Tressens & *al*. CTES 6846), Corrientes, Argentina.

Extraction and Isolation. Ground aerial parts (255 g) were extracted with $CHCl_3$ (3 × 2.0 L) at room temperature for 5 days. Evaporation at reduced pressure furnished 12.6 g of crude extract, which was suspended in EtOH (180 mL) at 60 °C, diluted with H_2O (135 mL), and extracted successively with hexane (3 × 200 mL) and $CHCl_3$ (3 × 150 mL).

Evaporation of the hexane fraction at reduced pressure furnished 4.49 g of residue, which was chromatographed over Si gel (70−230 mesh, 185 g) using hexane with increasing amounts of EtOAc (0−50%) to give 107 fractions, which were reunited according to their TLC profiles. Fractions 35−44 (125 mg) and fractions 47−50 (68 mg), which showed spots with R_f values similar to β-amyrin and cholesterol, respectively, were combined. A portion of fractions 35−44 (76 mg) was saponified in the usual way, and the unsaponifiable material was processed by HPLC using a C18 column (MeOH, 1.5 mL min^{-1}) to give 4 mg of 1-hexadecanol, 5 mg of 1-octadecanol, 3 mg of β-amyrin, and 1.0 mg of 1-eicosanol. Fractions 47−50, containing phytosterols, were combined and saponified. The unsaponifiable material was processed by HPLC, as before, to yield 1.5 mg of 24-methylcholest-5,22-dien-3β-ol, 14 mg of stigmasterol, 2.0 mg of 24-methylcholest-5-en-3β-ol, and 4.8 mg of sitosterol, all of which were identified by GC-MS and co-injection with authentic samples.

Evaporation of the $CHCl_3$ extract at reduced pressure furnished 4.04 g of residue, which was column chromatographed over Si gel (165 g, 70−230 mesh) using $CHCl_3$ and increasing amounts of EtOAc (0−100%) to afford 86 fractions. These were grouped according to their TLC profiles and monitored by IR spectroscopy. Only fractions showing γ-lactone absorption in the 1770−1760 cm^{-1} range were processed. Fractions 3−4 (489 mg) were reunited and rechromatographed on Si gel (230−400 mesh, 15 g) to give 62 mg of **5**. Fractions 10 and 11 (234 mg) were combined, and a portion (100 mg) was processed by HPLC using a C18 column (MeOH−H_2O, 57:43, 1.5 mL min^{-1}) to give 55 mg of **1** (t_R 13 min) and 4.6 mg of **6** (t_R 18 min). Fractions 25−26 (78.4 mg) were combined and processed by HPLC as above with MeOH−H_2O (1:1), at 1.5 mL min^{-1} to give 30 mg of **4** (t_R 14 min). Fractions 27−29 (185 mg) were reunited and rechromatographed on Si gel (230−400 mesh; 6 g) using $CHCl_3$−EtOAc (17:3) to yield 25 mg of **2**. Flash chromatography of fractions 31−34 (429 mg) on Si gel (230−400 mesh, 20 g) gave 10 mg of **3**. Fractions 38−44 (243 mg) were rechromatographed over Si gel (230−400 mesh; 15 g) with $CHCl_3$−EtOAc (1:3) to give 101 mg of a mixture of polar sesquiterpene lactones. Analysis of this mixture revealed the presence of significant hydroxy absorption and the absence of acetate absorption in the 1740−1730 cm^{-1} region of the IR spectrum, and therefore the mixture was acetylated in the usual way with Ac_2O in pyridine. The worked-up mixture (75 mg) was processed by HPLC (C-18, MeOH−H_2O, 11:9, 1.5 mL min^{-1}) to yield 5.8 mg of **8b** (t_R 32.5 min), 3.4 mg of **7b** (t_R 34.5 min), and 7.6 mg of **9b** (t_R 58.5 min).

(1*S*,4*S*,5*S*,6*S*,7*S*,10*R*)-1-Hydroxy-15-acetoxyeudesm-11(13)-en-6,-12-olide (1): colorless flakes from chloroform−hexane, mp 99−101 °C; $[\alpha]_{589}$ +94, $[\alpha]_{578}$ +97, $[\alpha]_{546}$ +110, $[\alpha]_{436}$ +184, $[\alpha]_{365}$ +279 (*c* 1.21, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 207 (9800) nm; IR ($CHCl_3$) ν_{max} 3624, 3514, 1766, 1732, 1248 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int): 309 $[M + H]^+$ (1), 291 (3), 266 (11), 248 (24), 230 (100), 220 (10), 215 (28), 202 (26), 187 (15), 163 (12), 159 (11), 145 (12), 119 (13), 43 (13); HRESIMS (NH_3) *m*/*z* 326.1964 (calcd for $[C_{17}H_{24}O_5 + NH_4]^+$ 326.1967).

(1*S*,4*S*,5*S*,6*S*,7*S*,10*R*)-1,4-Dihydroxy-15-acetoxyeudesm-11(13)-en-6,12-olide (2): gum; $[\alpha]_{589}$ +29, $[\alpha]_{578}$ +30, $[\alpha]_{546}$ +34, $[\alpha]_{436}$ +58, $[\alpha]_{365}$ +86 (*c* 1.58, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 206 (10 800) nm; IR ($CHCl_3$) ν_{max} 3596, 3490, 1764, 1732, 1248 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int) 307 $[M - OH]^+$ (8), 264 (3), 251 (42), 233 (63), 215 (99), 197 (20), 187 (100), 170 (30), 145 (23), 43 (40); HRESIMS (NH_3) *m*/*z* 342.1909 (calcd for $[C_{17}H_{24}O_6 + NH_4]^+$ 342.1917).

(1*R*,4*S*,5*S*,6*S*,7*S*,10*R*)-1,4-Dihydroxy-15-acetoxyeudesm-11(13)-en-6,12-olide (3): gum; $[\alpha]_{589}$ +15, $[\alpha]_{578}$ +16, $[\alpha]_{546}$ +18, $[\alpha]_{436}$ +30, $[\alpha]_{365}$ +43 (*c* 0.82, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 205 (11 300) nm; IR ($CHCl_3$) ν_{max} 3596, 3478, 1766, 1736, 1240 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int) 307 $[M - OH]^+$ (31), 282 (3), 264 (5), 251 (70), 248 (27), 234 (52), 230 (27), 216 (93), 206 (23), 197 (15), 188 (100), 173 (25), 170 (46), 160 (31), 146 (42), 131 (17), 105 (21), 43 (43); HRESIMS (NH_3) *m*/*z* 342.1916 (calcd for $[C_{17}H_{24}O_6 + NH_4]^+$ 342.1917).

(1*R*,4*S*,5*S*,6*S*,7*S*,10*R*)-1-Hydroxy-4,15-diacetoxyeudesm-11(13)-en-6,12-olide (4): gum; $[\alpha]_{589}$ +20, $[\alpha]_{578}$ +21, $[\alpha]_{546}$ +23, $[\alpha]_{436}$ +38, $[\alpha]_{365}$ +58 (*c* 2.2, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 207 (9900) nm; IR ($CHCl_3$) ν_{max} 3622, 3512, 1766, 1732, 1240 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int) 307 $[M - AcO]^+$ (9.4), 264 (24), 251 (100), 246 (62), 234 (12), 233 (64), 228 (27), 215 (65), 205 (19), 187 (58), 173 (18), 169 (31), 159 (20), 145 (26), 131 (17), 119 (16), 105 (19), 83 (46), 43 (86); HRESIMS (NH_3) *m*/*z* 384.2016 (calcd for $[C_{19}H_{26}O_7 + NH_4]^+$ 384.2022).

(1*S*,4*R*,5*S*,6*S*,7*S*,10*R*)-1,15-Diacetoxy-4-hydroxyeudesm-11(13)-en-6,12-olide (5): gum; $[\alpha]_{589}$ +55, $[\alpha]_{578}$ +58, $[\alpha]_{546}$ +68, $[\alpha]_{436}$ +112, $[\alpha]_{365}$ +172 (*c* 0.72, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 208 (12 400) nm; IR ($CHCl_3$) ν_{max} 3570, 1770, 1736, 1244 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int) 349 $[M - OH]^+$ (31), 293 (25), 233 (100), 215 (79), 197 (19), 187 (98), 169 (21), 159 (17), 145 (19), 43 (46); HRESIMS (NH_3) *m*/*z* 384.2021 (calcd for $[C_{19}H_{26}O_7 + NH_4]^+$ 384.2022).

(1*S*,5*S*,6*S*,7*S*,10*R*)-1-Hydroxy-15-acetoxyeudesma-4(15),11(13)-dien-6,12-olide (6): gum; $[\alpha]_{589}$ +88, $[\alpha]_{578}$ +90, $[\alpha]_{546}$ +105, $[\alpha]_{436}$ +173, $[\alpha]_{365}$ +261 (*c* 0.41, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 208 (12 200) nm; IR ($CHCl_3$) ν_{max} 3624, 3514, 1766, 1232 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int) 306 $[M]^+$ (10.5), 264 (100), 246 (90), 228 (30), 217 (51), 200 (40), 185 (28), 171 (19), 148 (76), 133 (26), 43 (19); HRESIMS (NH_3) *m*/*z* 307.1545 (calcd for $[C_{17}H_{22}O_5 + H]^+$ 307.1545).

(1*S*,5*S*,6*S*,7*S*,10*R*)-1,15-Diacetoxyeudesma-3,11(13)-dien-6,12-olide (7b): gum; $[\alpha]_{589}$ +127, $[\alpha]_{578}$ +133, $[\alpha]_{546}$ +151, $[\alpha]_{436}$ +261, $[\alpha]_{365}$ +416 (*c* 0.42, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 201 (12 100) nm; IR ($CHCl_3$) ν_{max} 1770, 1732, 1248 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int): 289 $[M - AcO]^+$ (3), 255 (2), 246 (10), 229 (34), 228 (90), 213 (72), 210 (25), 200 (29), 199 (39), 195 (13), 185 (33), 183 (100), 172 (20), 171 (37), 169 (23), 167 (26), 157 (35), 156 (28), 143 (44), 119 (25), 105 (29), 91 (30), 77 (19), 43 (81); HRESIMS *m*/*z* 371.1469 (calcd for $[C_{19}H_{24}O_6 + Na]^+$ 371.1470).

(1*S*,2*R*,5*S*,6*S*,7*S*,10*R*)-1,2,15-Triacetoxyeudesma-3,11(13)-dien-6,-12-olide (8b): gum; $[\alpha]_{589}$ +26, $[\alpha]_{578}$ +27, $[\alpha]_{546}$ +30, $[\alpha]_{436}$ +47, $[\alpha]_{365}$ +62 (*c* 0.52, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 201 (15 900) nm; IR ($CHCl_3$) ν_{max} 1768, 1740, 1240 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int) 304 $[M - AcOH - CH_2CO]^+$ (12.5), 271 (15), 262 (42), 245 (21), 244 (100), 227 (48), 226 (19), 199 (18), 183 (11), 171 (10), 159 (8), 145 (10), 135 (19), 91 (10), 43 (47); HRESIMS *m*/*z* 429.1523 (calcd for $[C_{21}H_{26}O_8 + Na]^+$ 429.1525).

(1*R*,6*S*,7*S*,10*R*)-1,15-Diacetoxyeudesma-4,11(13)-dien-6,12-olide (9b): gum; $[\alpha]_{589}$ +17, $[\alpha]_{578}$ +18, $[\alpha]_{546}$ +21, $[\alpha]_{436}$ +42 (*c* 0.75, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 206 (12 700) nm; IR ($CHCl_3$) ν_{max} 1774, 1736, 1242 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* (rel int) 288 $[M - AcOH]^+$ (4), 246 (38), 229 (42), 228 (100), 217 (13), 213 (62), 210 (29), 201 (19), 200 (39), 199 (43), 167 (16), 159 (14), 157 (33), 156 (19), 145 (19), 143 (34), 131 (20), 119 (19), 105 (23), 91 (28), 85 (26), 83 (38), 43 (92); HRESIMS *m*/*z* 371.1472 (calcd for $[C_{19}H_{24}O_6 + Na]^+$ 371.1470).

X-ray Diffraction Analysis of 1. A colorless flake-shaped crystal of **1**, measuring 0.40 × 0.36 × 0.18 mm, was mounted on a Bruker Smart 6000 CCD diffractometer, and data were collected at 293 K using Mo Kα radiation ($\lambda = 0.71073$ Å). It revealed $C_{17}H_{24}O_5$; $M = 308.36$; monoclinic, space group $P2_1$; $a = 7.2710(2)$ Å, $b = 9.6910(3)$ Å, $c = 11.7480(4)$ Å, $\beta = 93.725(1)°$, $V = 826.05(4)$ $Å^3$, $Z = 2$; $\rho = 1.24$ mg/mm^3. Unit cell refinements were done using the SHELXTL software. A total of 1321 frames were collected with a scan width of 0.3° and an exposure time of 10 s/frame. The frames were processed with the SAINT software package, provided by the diffractometer manufacturer. The structure was solved by direct methods using the SHELXS-97 program included in the WinGX v1.64.05 crystallographic software package. For the structural refinement, the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. It provided $\mu = 0.082$ mm^{-1}, reflections: total = 3100, unique 3089 (R_{int} 0.01%), observed 2780, final *R* indices [$I > 2\sigma(I)$] R1 = 4.0%, wR2 = 9.1%, for all data R1 = 4.7%, wR2 = 9.5%. Crystallographic data (excluding structure factors) have been deposited under CCDC deposition number 646076 at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 IEZ, UK. Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

Computational Methods. The conformational optimizations of **1** were carried out using the MMFF94[26] force-field calculations as implemented in the Spartan'04 software package employing the Monte Carlo protocol.[25] All conformers found in a 10 kcal/mol relative energy range were reoptimized using density functional theory (DFT) calculations[27] at the B3LYP/6-31G(d) level of theory. For the obtained conformations within a 1.66 kcal/mol relative energy gap, which account for 94.5% of the conformational population, further DFT optimization, vibrational frequency, and free energy calculations were carried out at the B3LYP/6-31G(d,p) level of theory using the Gaussian 03W software package. Typical calculations required around 35 h of computational time per conformer when using a desktop personal computer (PC) with 2 Gb RAM operated at 3 GHz. Calculated dipole and rotational strengths were converted to molecular absorptivities (M^{-1} cm^{-1}) and then plotted as Lorentzian bands with half-widths of 6 cm^{-1}.

Acknowledgment. Work in Tucumán was supported by grants from CONICET-Argentina (Grant PIP 5176/04) and Agencia Nacional de Promoción Científica y Tecnológica-Universidad Nacional de Tucumán (PICTO 2004 No. 503). Stimulating support from CYTED (Spain) is also acknowledged. We are grateful to Lic. Sara Tressens of Instituto de Botánica del Nordeste, Corrientes, Argentina, for collecting and identifying the plant material. Work in Mexico was supported in part by CONACYT-México.

Supporting Information Available: Atom coordinates for the crystal structure of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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NP070154T